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5.111 Principles of Chemical Science

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Catalysts of Life: Enzymes

See lecture 35 notes for an introduction to enzyme catalysis.

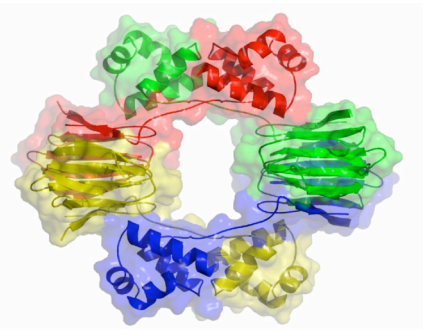
An enzyme is a large protein molecule (typically 20,000 g/mol or more) that is capable of carrying out a specific reaction or series of reactions.

Enzyme catalysis

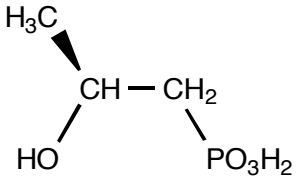
Reactant molecules are called substrates.

Example from Lecture 35 video: Enzyme Catalysis

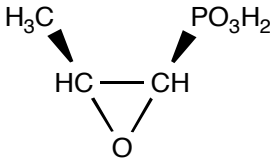
An iron-containing enzyme catalyzes the final step in the biosynthesis of the antibiotic fosfomycin. The structure (shown below) of this enzyme step was reported by the Drennan laboratory at MIT in 2005.



Enzyme (E)



reactant
substrate (S)

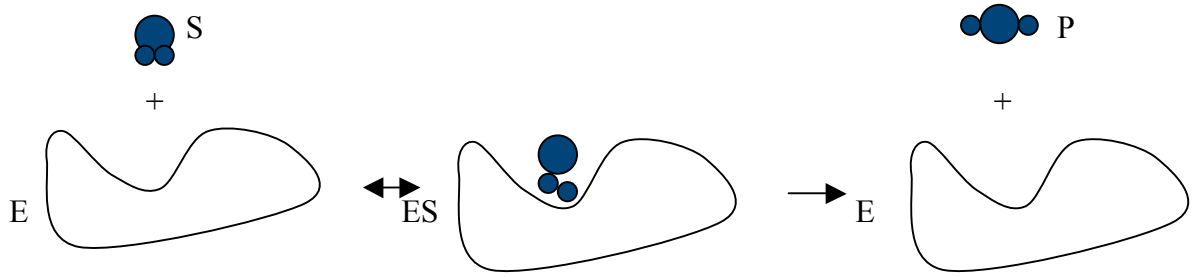


fosfomycin (an antibiotic)
product (P)

With the emergence of antibiotic-resistant bacteria, the development of new antibiotics will be an important problem for future chemists to tackle.

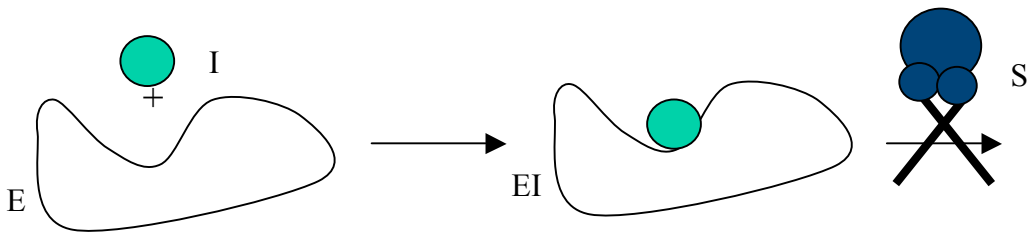
Substrates bind to an active site on the enzyme.

enzyme (E) + substrate (S) ⇔ enzyme-substrate complex (ES) → enzyme (E) + product (P)



Enzyme Inhibition

If an inhibitor is bound in the active site, then substrate can't bind.



Many pharmaceutical drugs work by blocking the action of enzymes. Enzymes catalyze reactions by stabilizing the "transition state" of the reaction.

Compounds that resemble the transition state should bind more tightly to the enzyme than reactants or products. These compounds can therefore serve as enzyme inhibitors (drugs).

Example from page 7 of Lecture 35 notes: HIV Protease Inhibitors

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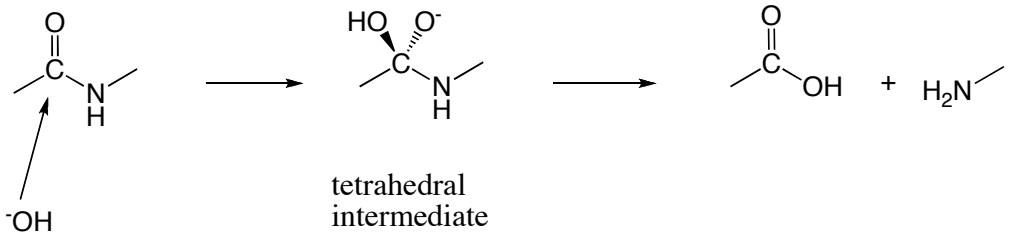
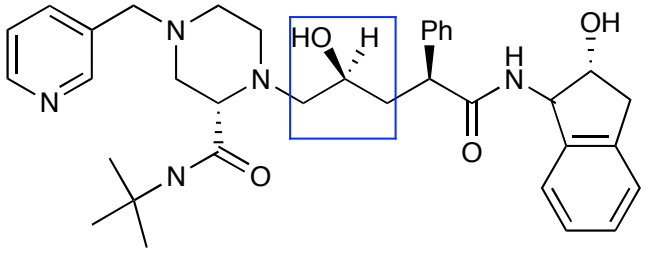
Proteases inhibitors are used in treatment of HIV. Enzymes that cleave peptide bonds are called proteases. The overall mechanism of peptide bond cleavage - a type of displacement reaction- is shown below:



Molecules with a stable tetrahedral atom at cleavage site will resemble the transition state and could bind more tightly to the enzyme than substrate does.

Example of a molecule with a tetrahedral center:

Approved drug for HIV, indinavir sulfate (The New England J. Med. 338, 1285 (1998)). Knowledge of reaction mechanism can lead to design of new therapeutic treatments.



Ph = phenyl

Interesting and important question - why doesn't this compound block all proteases? A second consideration is specificity.

Tight binding is just one facet of drug design. Also must consider specificity and delivery.