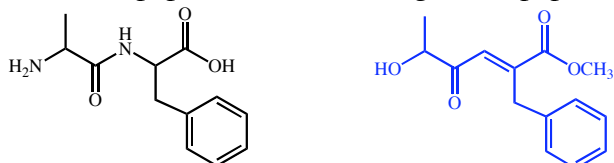


PAGE ONE - VERY SHORT ANSWER QUESTIONS

1. Why are peptides typically not ideal drugs?

Most peptides are rapidly degraded in the human gastrointestinal tract... therefore are not typically orally available. Even if they evade destruction in the GI tract, peptides are prone to degradation by protease enzymes and have poor pharmacokinetic properties.

2. Draw a peptidomimetic analog of the peptide shown below



Your structure should retain key structural features of the peptide (the side chains) and replace the amide bond (the central point of pharmacokinetic instability) and the carboxylic acid and amine groups (charged groups that present potential problems in drug delivery) with bioisosteres. (You saw this in lecture and on question 2 from problem set three, and on the previous exams posted on the course website.)

3. List three "strategies" used by enzymes to catalyze chemical reactions:

Catalysis by proximity

General acid-base catalysis

Strain and distortion

Selective transition state stabilization

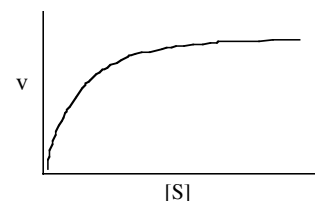
Electrostatic catalysis

4. (a) Draw the general kinetic scheme depicting an enzyme-catalyzed reaction.



(b) Explain why the velocity of enzyme catalyzed reactions reach a plateau (level off) at high substrate concentrations, as shown in the plot below. Refer to your kinetic scheme in 4a, if necessary.

At high substrate concentrations all of the enzyme is in the E·S form. When this point is reached the velocity of the enzyme-catalyzed reaction cannot increase further. The protein catalyst is functioning at full velocity.



5. The DNA-damaging agent chlorambucil is very effective at killing bacterial cells in culture dishes. Why are DNA-damaging agents *not typically used* as antibacterial drugs?

The structure of DNA is essentially identical in bacterial and human cells. Thus, DNA-damaging drugs will cause toxicity to both bacterial and human cells. Too much human-cell toxicity for use as antibacterial agents.

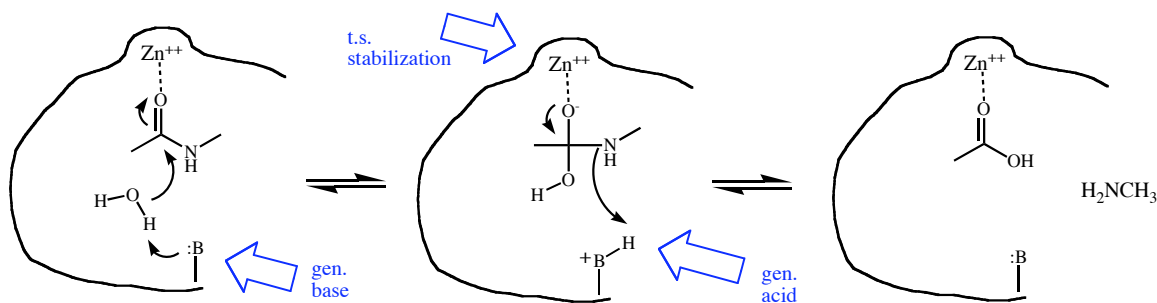
6. Given the bond enthalpies shown below, do you anticipate that a thiyl radical ($\text{RS}\cdot$) will be capable of inducing efficient DNA strand cleavage? Show your reasoning.

bond dissociation energies; RS-H 80 kcal/mol; typical DNA C-H 90 kcal/mol

First, you need to explicitly show the reaction that you are considering:

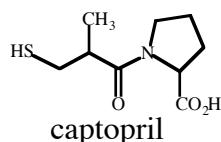
$\text{RS}\cdot + \text{DNA-H} \rightarrow \text{RS-H} + \text{DNA}\cdot$ Then, you should note that DNA radicals ($\text{DNA}\cdot$) lead to strand breaks. Finally, calculate that the cost of bonds broken (90 kcal/mol) exceeds the payoff of bonds formed (80 kcal/mol). The reaction will *not* occur readily because it is estimated to be endothermic by 10 kcal/mol (see problems 5 and 6 on problem set four).

7. As discussed in lecture, angiotensin converting enzyme (ACE) is a protease that carries out the general reaction shown below.



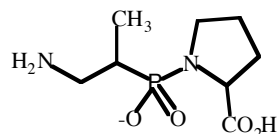
(a) What types of enzymatic catalysis are occurring in the Scheme above? (Point to the relevant locations on the Scheme to clearly connect chemical steps to your answers).

(b) What is the role of the SH group in the ACE inhibitor captopril?



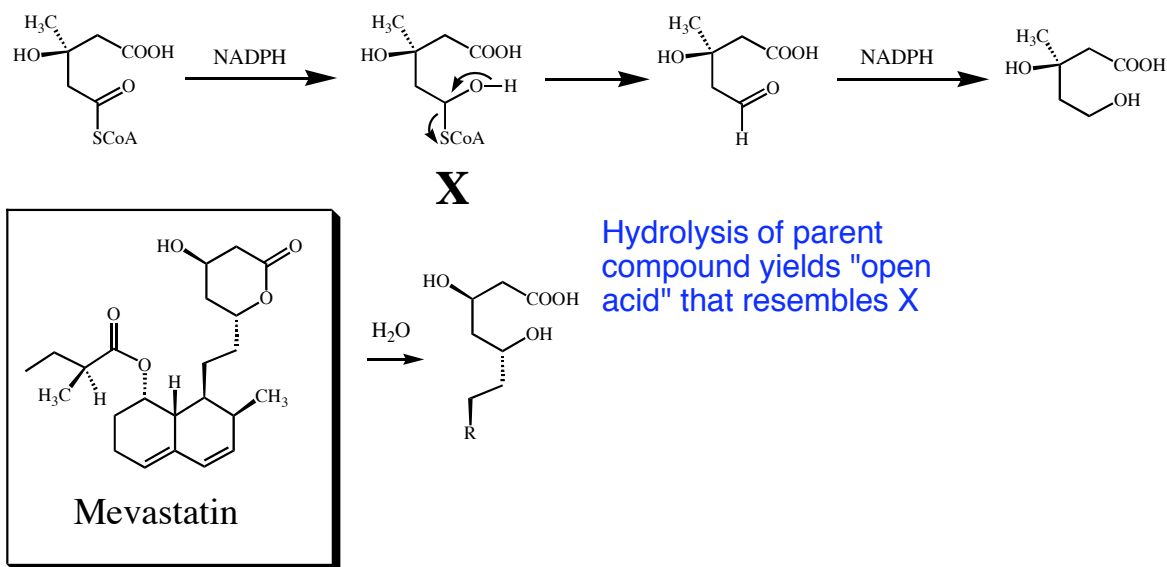
The SH group is a good ligand for the Zn(II) at the active site of the enzyme. This metal-ligand bond makes a large energetic contribution to the array of “weak bonding interactions” that hold the drug at the active site of the enzyme.

(c) What is the role of the phosphoramidate group in the ACE inhibitor shown below?

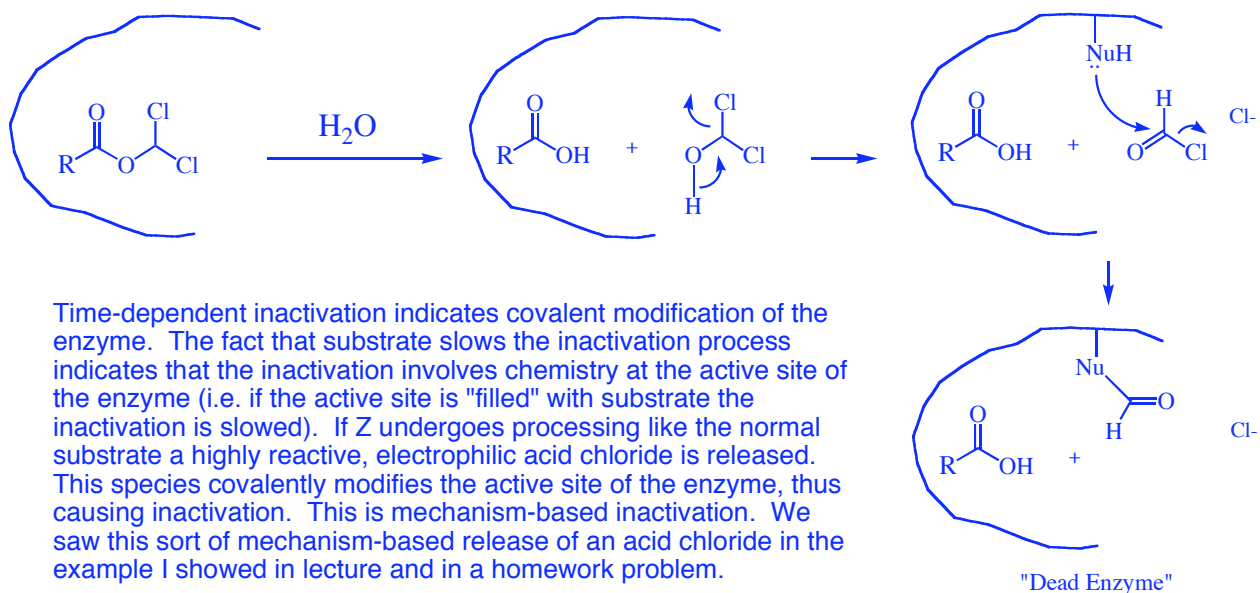


This compound is a transition state analog inhibitor. The installation of the phosphoramidate group into the peptide yields a *stable compound* whose structure resembles the *tetrahedral intermediate* (here, loosely called the “transition state”) generated in the hydrolysis of amide bonds by ACE. Structures that resemble the transition state of enzymatic reactions are often powerful enzyme inhibitors, supporting the early suggestion of Pauling that the transition state should be the most tightly bound structure on any enzymatic reaction pathway. (See lecture notes and problem on previous exam for examples of this type of protease inhibitor).

8. Lipitor and the other "statin" drugs are generally thought to inhibit the enzyme HMG-CoA reductase. The reaction catalyzed by this enzyme is shown below. Some have suggested that the statin drugs, such as mevastatin (shown below), are *transition state analogs* that mimic the structure **X** in the Scheme below. The mevastatin really does not *look* very much like structure **X**... explain how this drug can act as a transition state analog inhibitor of HMG-CoA reductase.



9. The enzyme "esterase 1b1" catalyzes the reaction shown below. Compound **Z** causes a time-dependent inactivation of esterase 1b1. That is, the enzyme activity decreases over a period of about 1-2 hours. The inactivation of esterase 1b1 by compound **Z** occurs is *slowed* by the presence of the normal enzyme substrate (**S**) in the reaction mixture.



(problem 4 on problem set three)

In the space above, explain what is happening here (in words) and provide a chemical mechanism (drawing structures).