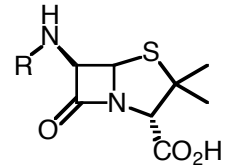


Biochemistry 704  
Problem Set 2  
Due 02/26/2008

1. Natural products are often derived from common building blocks.  
Which two of the 20 amino acids are precursors to penicillin?



penicillin

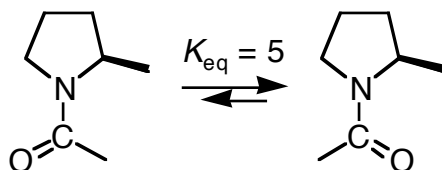
2. Consider an  $\alpha$ -helix and a  $\beta$ -hairpin (*i.e.*,  $\beta$ -strand- $\beta$ -turn- $\beta$ -strand) of equal conformational stability and containing an equal number of amino acid residues.
- a. Which is likely to fold more quickly? Explain briefly.
- b. Which is likely to unfold more quickly? Explain briefly.

3. A wild-type protein has a  $\Delta G^\circ_{\text{unfolding}}$  of 3 kcal/mol. An amino acid residue was replaced. This change had no effect on the free energy of the folded form of the protein, but lowered the free energy of the unfolded form by 5 kcal/mol.

Is the native form of the variant protein more stable or less stable than that of the wild-type protein? Illustrate your answer with a free energy profile that shows the values of  $\Delta G^\circ_{\text{unfolding}}$  for the wild-type and variant proteins.

4. In a typical peptide bond, a protonated nitrogen ( $pK_a \approx -6$ ) is a much stronger acid than a protonated oxygen ( $pK_a \approx 0$ ). Explain this result by applying the concept of “resonance” to the unprotonated and two differently protonated peptide bonds.

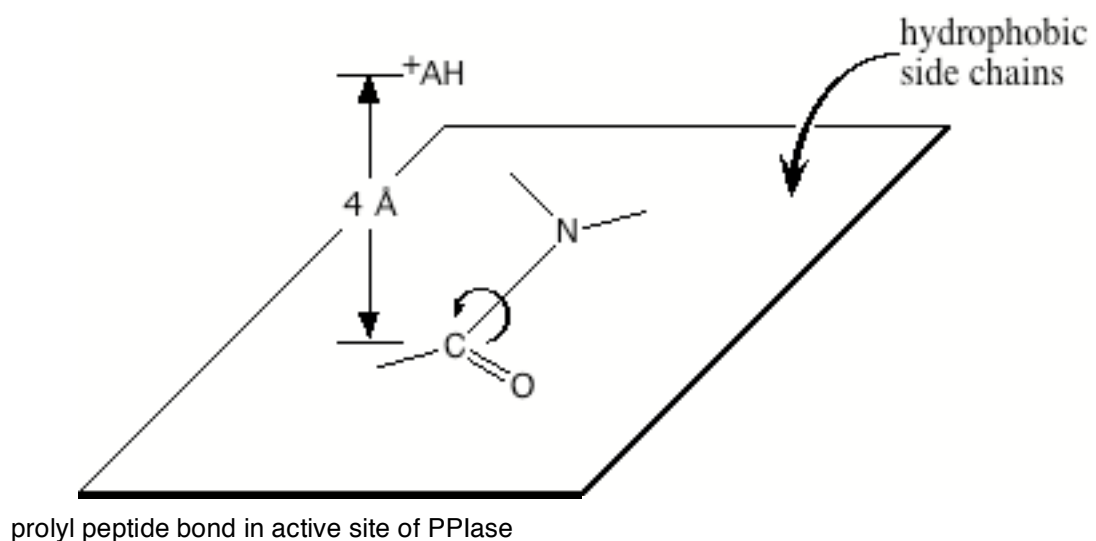
5. The *cis-trans* isomerization of a prolyl peptide bond can limit the rate of protein folding. This process is shown below.



- a. Draw the major resonance structures of a prolyl peptide bond.
- b. Would protonation of the O atom (but not the N atom) of a prolyl peptide bond increase or decrease the rate of isomerization? Explain briefly.
- c. Would protonation of the N atom (but not the O atom) of a prolyl peptide bond increase or decrease the rate of isomerization? Explain briefly.

- d. Collagen contains many 4-hydroxyproline residues. Would you expect a hydroxyl group in the 4-position (*i.e.*, on C<sup>γ</sup>) to increase or decrease the rate of isomerization? Explain briefly.

- e. Peptidyl prolyl isomerase (PPIase) catalyzes the *cis-trans* isomerization of prolyl peptide bonds. The structure of this enzyme has been determined by using NMR spectroscopy and x-ray diffraction analysis. Its active site consists of two types of side chains:
- several hydrophobic side chains in the plane of the prolyl peptide bond.
  - an Arg side chain (<sup>+</sup>AH) 4 Å above the carbon atom of the prolyl peptide bond.



Explain how each of the two types of side chains contribute to catalysis by altering the free energy of the two ground states and/or the transition state. Illustrate your answer with a free energy profile that compares the reaction energetics in water with that in the active site of PPIase.