Chem 135: First Midterm

September 30th, 2013

Please provide all answers in the spaces provided. You are not allowed to use a calculator for this exam, but you may use (previously disassembled) molecular model kits. Including the title page, there should be **4** total questions spread over **5** pages. There is also a sixth page that should be blank. You can use this last page for scratch paper if you need it, but please remember to copy your answers into the appropriate exam question space.

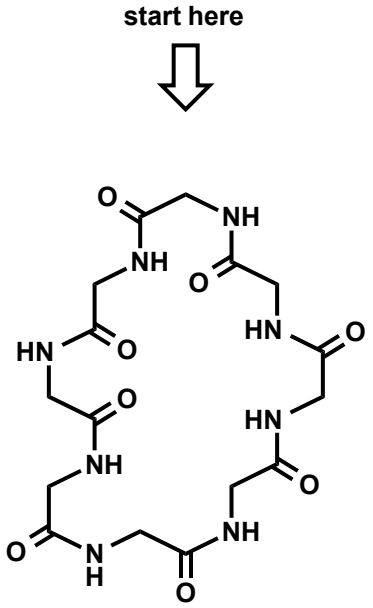
Name: _____

(1)	_____	(22 points)
(2)	_____	(10 points)
(3)	_____	(48 points)
(4)	_____	(20 points)
TOTAL	_____	(100 points)

1. Many organisms produce cyclic peptides, which lack free N- and C-termini. Suppose the following (hypothetical) cyclic peptide has just been discovered. The amino acid sequence, written in the usual direction for a linear peptide analog, is:

VWSRGAEF

a. Starting at the arrow, draw the side chains of this sequence on the backbone template shown below. Draw the ionizable groups in their most prominent protonation state at pH 7 (10 points).

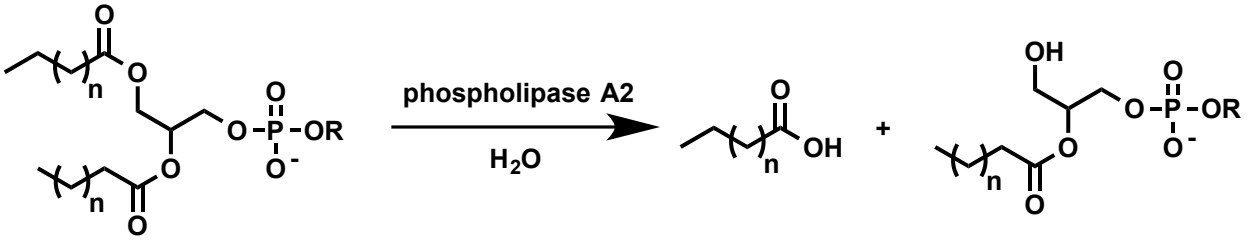


b. If any of the amide bonds in the above structure are in the *cis* conformation, circle them (6 points).

c. In general, polypeptides have the lowest degree of solubility when they have no net charge. Considering a range of 0 to 14, which pH values would this be for the cyclic peptide (6 points)?

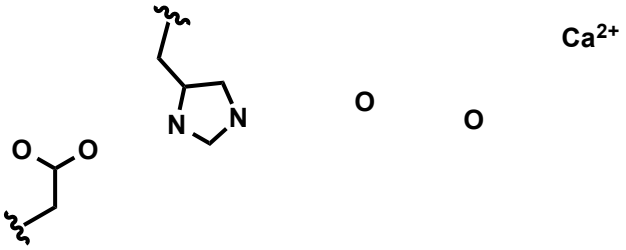
2. In the space below, draw two peptide segments consisting of three amino acids each as they would be found in an *antiparallel* beta sheet. You may abbreviate the side chains as R groups. Clearly indicate the hydrogen bonding pattern between the two strands (10 points).

3. Phospholipases are a class of enzymes that cleave the ester groups of phospholipids. This can be beneficial for digestion and signal transduction mechanisms, but can cause disruption of the plasma membrane if left unchecked. As an example of the latter case, snake venom contains large amounts of these enzymes to destroy the cells of the victim.



a. Assuming that the enzyme remains functional at all pH values, would you expect the solution pH to affect the overall thermodynamics of this reaction? Briefly explain your answer (6 points).

b. Upon analysis of a crystal structure of phospholipase A2, you find evidence of a catalytic array consisting of an asp residue, a his residue, two water molecules (represented below by the "O" atoms), and a calcium ion. However, remember that x-ray structures of proteins normally do not provide the locations of the protons or the double bonds. Fill these in on the following diagram. Next, add the ester group to be hydrolyzed by the enzyme where you think it would be located. Finally, provide a detailed, arrow pushing mechanism to show how this enzyme could hydrolyze the ester to provide the products shown above. You may use R groups to abbreviate the ester structure as you see fit (12 points).



c. Suppose you generate a version of this enzyme in which the asp residue shown above has been replaced by a glu residue. You find that the resulting enzyme has a 5-fold drop in k_{cat}, but the value of K_m is unchanged. What conclusion can you make from this observation (6 points)?

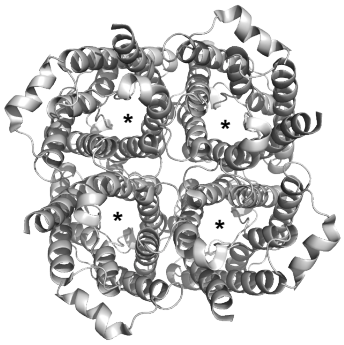
d. On the axes provided below, sketch a graph for *V* vs. [S] for both the normal and the mutant enzymes. Clearly indicate which curve corresponds to which enzyme (6 points).

e. Leaving the glu mutation and its associated drop in the value of k_{cat} intact, is there any way that the enzyme could be improved to achieve the same level of catalytic performance as the natural enzyme at low substrate concentration? What about at high substrate concentration (6 points)?

f. Because phospholipases cleave substrates with long hydrocarbon tails, they have a number of non-polar amino acids in their binding pocket. Using the one-letter codes, give 5 examples of amino acids that you think would be found in this location (6 points).

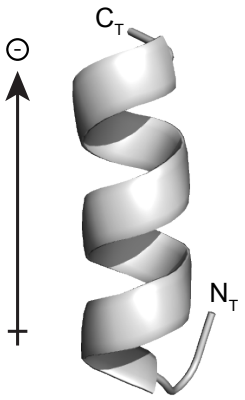
g. These amino acids would be expected to bind the hydrocarbon tails through the hydrophobic effect. Briefly describe the origin of this interaction (6 points).

4. Aquaporins are a class of proteins that allow water to pass through cell membranes, but not protons or other ions. They are critical to the function of many tissues in the body, including the kidneys, the lungs, and the eye. In most cases, four identical copies of these proteins assemble into a tetramer that spans the plasma membrane, as shown in a "top-down" view at right. This provides four pores through which water can freely pass.

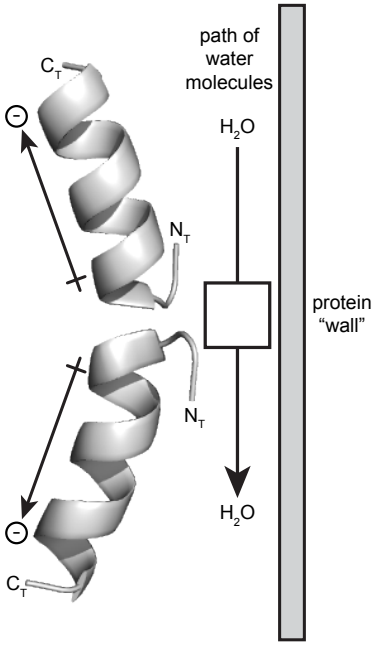


*** = water transport pores**

a. For some time, it has been appreciated that alpha helices possess a large dipole moment that is independent of the specific side chains that are present. The directionality of this dipole is shown for an aquaporin alpha helix on the right. Speculate on the specific structural aspect of the alpha helix that creates this dipole. Note that N_T and C_T refer to the directionality of the polypeptide chain, but there are no free termini because this is a portion of a large protein structure (7 points).



b. All known aquaporins possess two alpha helices that are oriented end-to-end, with their N-terminal regions in direct contact (see figure at right). This brings the positive ends of the helix dipoles together at a point in the channel where only one water molecule can pass through at a time. This location is indicated by the white box in the figure. Sketch how a water molecule would be oriented in this position as it passes through the channel. The "protein wall" is formed by other portions of the biomolecule, and interacts minimally with the water (7 points).



c. A critical feature of aquaporins is their ability to allow water to pass through, but not protons or other cations. Briefly state how this helix-dipole gating mechanism might achieve this selectivity (6 points).

This last page should be blank. You may use it as scratch paper, but if you do be sure to recopy your answers into the exam questions so that we can grade them easily. Nothing on this page will be graded.