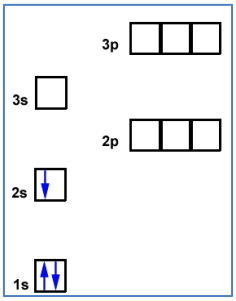
This exam consists of 4 pages and a total of 100 points. Allot 1 min per 2 points. Use the space provided or the back of the preceding page.



1. (5 pts) Please do one of the following two choices

Choice A: A lithium atom has an electronic configuration of $1s^2$ and $2s^1$, i.e. two electrons in the 1s orbital and one in the 2s orbital, as shown on the right. What is the most likely ion that lithium will form? Why?

It will form a +1 ion, because if it loses its 2s electron it will have the same electronic configuration as He, which is a stable configuration.

Choice B: What is the geometric difference between sp^2 hybrid orbitals and sp^3 hybrid orbitals?

- sp^2 orbitals all lie in the same plane and are separated by an angle of 120°
- sp^3 orbitals are tetrahydral in geometry and are separated by an angle of 109° .

2. (4 pts) Why is water a polar molecule?

- The O-H bond is polar because the electronegativity of oxygen is larger than hydrogen
- The water molecule is bent, so that the polarity of the bonds add, instead of cancelling (like O=C=O).

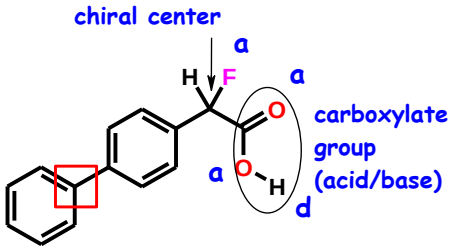
3. (6 pts) The structure of a drug is shown on the right.

i) Add any missing hydrogen atoms to the carbon atom indicated by the box. *Justify your answer.*

There are none to add since carbon forms 4 four bonds and the indicated carbon already has four bonds.

ii) Does this drug have a chiral center? If so, where is it located? Why is it a chiral center?

Yes, as indicated, the carbon has four different groups attached to it, so this carbon is chiral.



4. (3 pts) In what way might a chiral center affect the activity of a drug?

If there is a chiral center, then the molecule exists in two forms which are mirror images of each other (enantiomers). These may have different biological properties.

5. (20 pts total, 12 this page) ***(Part iv of this question is on the next page.)***

i) (6 pts) State the general rule for hydrogen bonds, that is, what are the properties of the three atoms involved in a hydrogen bond.

The general rule is: X-H … Y

Where X and Y are electronegative atoms.

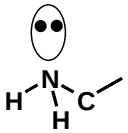
X and Y would have partial negative charges

The hydrogen would have a partial positive charge.

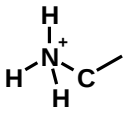
Note:

The nitrogen in an NH group can't always accept a hydrogen bond. A free amino group (such as the amino terminus) can accept a hydrogen bond using its full lone pair orbital. Once it is protonated, it cannot.

lone pair orbital is a good H-bond acceptor

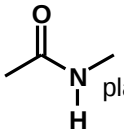


Can't accept an H-bond when protonated



tetrahydral sp^3

P_z orbital is delocalized and not a good H-bond acceptor. The N-H group is a good donor.



planer sp^2

The NH group when the nitrogen is sp^2 hybridized and participating in a delocalized double bond/aromatic system, such as in peptide bonds or as NH groups in nucleobases, does **not** accept a hydrogen bond. A single nitrogen in a ring can accept a hydrogen bond, on the edge of the ring.

ii) (4 pts) Identify all hydrogen bond donors (***d***) and acceptors (***a***) on the drug shown in question 3, add "a" or "d" to the above diagram, as appropriate. A table of electronegativities is on the right.

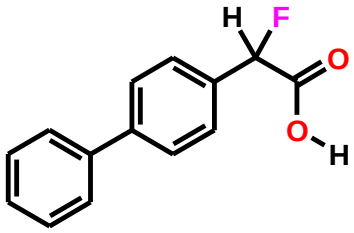
H 2.1						
Li 1.0	**Be** 1.5	**B** 2.0	**C** 2.5	**N** 3.0	**O** 3.5	**F** 4.0

The electronegative atoms are potential hydrogen bond acceptors, this includes the two oxygens and the fluorine. The -O-H is a hydrogen bond donor. These are labeled on the diagram above.

iii) (2 pt) Circle the ionizable group on the drug and state its name. See diagram above, this is a carboxylate.

iv) Please do choice A or B (8 pts)

Choice A: The ionizable group on this drug has a pKa of 3.0. Given that the pH of the small intestine is 8.0, how likely is it for this drug to be able to cross the cell membrane in this environment? *Justify your answer.*



Since the pH is well above the pKa, the group will be completely deprotonated, giving it a negative charge. This will make it difficult for the drug to cross the membrane.

Choice B: Compare the solubility of the drug at pH 1.0 and pH 5.0. At which pH would the solubility be higher? Why?

pH 1.0 – the pH is well below the pKa, so the drug will be completely protonated, and will be neutral and less soluble.

pH 5.0 – the pH is well above the pKa, so the drug will be completely deprotonated, and will have a negative charge, making it more soluble.

6. (10 pts) The drug in question 3 binds to its target protein with an enthalpy of -5 kJ/mol and an entropy of +5 J/mol-deg, giving an overall standard energy ($\Delta G^{o}=\Delta H^{o}-T\Delta S^{o}$) change of -6.5 kJ/mol at 300K.

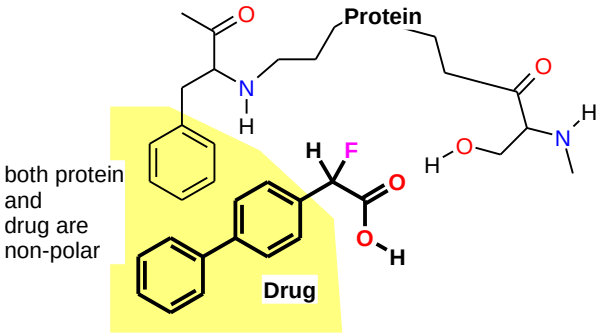
i) Based on the standard energy, what is favored – the unbound drug or the bound drug? Justify your answer. (4pts).

Since the standard energy is negative, the products are lower in energy than the reactants, the bound drug is more stable.

ii) Explain, with reference to functional groups on the drug, why the entropy change due to binding is positive. You may find it useful to look at the bonus question at the end of the exam to help you answer this one. (6 pts)

The drug has a large non-polar section which interacts with a non-polar side chain (Phe) on the target protein. The reactants (unbound drug, unoccupied binding site) will have ordered the water molecules.

When the drug binds the ordered water will be released, increasing the entropy of the system.



7. (12 pts) Pick any two amino acids that are **different** and:

i) Draw the resultant dipeptide that would be formed after the condensation reaction to form the peptide bond (4 pts).

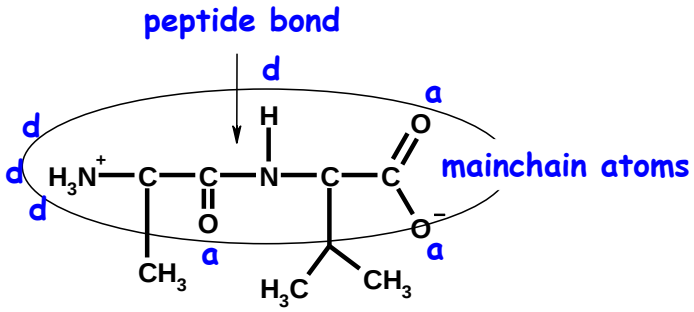
ii) Identify the peptide bond (1 pt).

iii) Circle the mainchain atoms (1 pt).

iv) Identify all hydrogen bond donors and acceptors on the **mainchain** atoms (2 pts).

v) Write the sequence of your peptide (2 pts).

Ala – Val in this example, always begin the sequence starting from the amino terminus.



/30

8. (10 pts) Give **one** example of a secondary structure and:

i) State the force or interaction that stabilizes it (4 pts).

ii) Sketch the structure and indicate on your sketch the location of the stabilizing forces you stated in *part i*, and the location of the sidechains (6 pts).

a - helix – stabilized by mainchain hydrogen bonds.

You should draw a helical structure with the hydrogen bonds parallel to the helix axis and the sidchains projecting out from the helix.

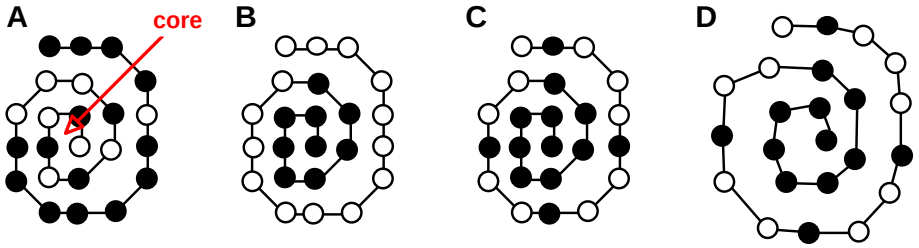
β - stand/sheet – also stabilized by mainchain hydrogen bonds

You should draw two peptide chains running parallel to each other with:

- The hydrogen bonds perpendicular to the strand direction.
- The side-chains pointing up and down on alternative residues. As you cross the sheet, residues on adjacent strands all point the same way, the first row points up, second row points down, etc.

9. (10 pts) Cartoon structures of four different proteins are shown below, the core, or interior of the protein is in the center in all four cases, but only labeled in the first case. In these diagrams:

◯ = polar or charged amino acids • = non-polar amino acids



Given what you know about the location of amino acids in proteins, **and** the forces that stabilize proteins, explain why C is most likely to be a folded protein while the other three are unlikely. **Note**: The order of polar and non-polar amino acids in C and D are identical.

- Proteins have well packed cores to optimize van der Waals interactions. A, B, and C show the same packing so these are acceptable. D is more loosely packed and would have weaker van der Waals, so D is excluded.
- Protein have completely non-polar cores due to the hydrophobic effect, this stabilizes proteins by burying non-polar groups, increasing the disorder of the water. This excludes A, because it has some buried polar residues, but not B, C, or D. Since D is excluded, only B and C are left.
- Proteins have polar, charged, and non-polar residues on their surface. This excludes B, leaving only C.

Alternatively, you could have answered the question this way:

A- has buried polar residues, the core of proteins are completely non-polar due to the hydrophobic effect, so A cannot represent a folded protein.

B –although it has a non-polar core, it is lacking non-polar residues on its surface, most proteins have some non-polar residues on their surface.

D – Is poorly packed compared to C, it lacks good van der Waals contacts, which are found in proteins.

C – Has all the properties of a folded protein:

- non-polar core due to the hydrophobic effect,
- good packing to optimize van der Waals effects,
- All polar/charged residues are on the outside. Some non-polar residues are on the outside.

/20

10. (4 pts) What are the properties of an active site of an enzyme?

It contains amino acid residues that provide:

- A binding site for substrates (responsible for substrate specificity)
- Residues that aid in the chemical reaction.

11. (10 pts) Briefly describe why enzymes increase the rate of reaction.

- The lower the energy of the transition state, reducing the activation energy, thus making it more favorable for substrates to convert to the transition state.
- They do so by pre-ordering reactants, so that there is no large decrease in entropy as the reactants move to the transition state.

12. (6 pts) Compare and contrast a competitive inhibitor to an allosteric inhibitor. Compare and contrast means to give similarities and differences between the two.

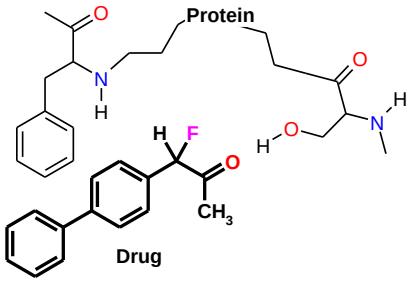
Both bind to the enzyme and reduce its activity.

Competitive inhibitor – binds at the active site and prevents the substrate from binding. It is structurally similar to the substrate.

Allosteric inhibitor – binds elsewhere (not at the active site), causing a change in the structure of the active site that make the enzyme non-active. It is not structurally similar to the substrate.

Bonus (5 pts): A drug bound to its target protein is shown on the right. The drug is in bold. The ability of this drug to cross cell membranes depends on pH. How could you modify the drug to remove this dependence, but still allow binding to its target? [Hint: What functional group on the **drug** would you replace, and what would you replace it with?]

The –O-H group on the carboxylate is the group that ionizes. The carboxylate group could be replaced by any of the following functional groups: aldehyde, ketone, or ester. All of these would retain the C=O that can hydrogen bond to the protein target. The structure of the ketone version is shown in the diagram on the right.



Although the fluorine is an acceptable hydrogen bond acceptor, it is not in an ideal position to accept the hydrogen bond from the –OH group on the protein.

/20 + 5 (bonus)