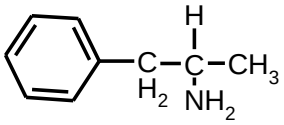
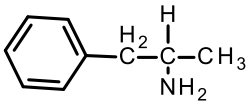
Problem Set 2:

1. The chemical formula and bonding of the drugs Dexedrine and Benzedrine are the same, and shown on the right. Both of these drugs have the identical physical properties, such as melting point, molecular weight, etc. The dose of Dexedrine is 5mg/day, but the dose of Benzedrine is 10 mg/day. Additional side effects are seen when patients take Benzedrine. Please answer the following questions: [Hint: Is there a chiral center in this compound?]



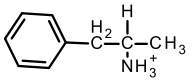
i) Why is twice as much Benzedrine required for the same biological effect.

ii) Why are there reduced side effects with Dexedrine?

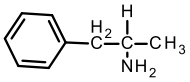


There is a chiral carbon in Dexedrine/Benzedrine. Only one enantiomer has high biological activity – since ½ of much of Dexedrine is required, Dexedrine is a pure enantiomer and Benzedrine is a racemic mixture with only 50% of it active. The other enantiomer found in Benzedrine may be responsible for increased side effects

2. Benzedrine is absorbed more readily in the small intestine, where the pH=8, than in the stomach, where the pH=2.0. Why? Hint. Identify the ionizable group on Benzedrine, consider how its ionization state and charge would differ at the different pH values. Only uncharged molecules can move across the non-polar cell membrane and be absorbed.



Low pH



High pH

There is an amino group – NH_2 on this drug. The pKa of this group is around 8 or 9.

At pH=2 it would be fully protonated with a positive charge (NH_3^+), so it would not pass-through cell membranes in the stomach very effectively.

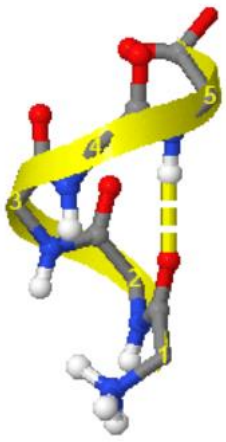
At pH=8, more molecules would be deprotonated, and ***neutral***. This would pass through the cell membranes in the intestines quite readily.

Problem 3 requires you to view a small protein using graphic software called JSmol. There is a tutorial on the software that can be found at:

http://www.andrew.cmu.edu/user/rule/jsmol/jsmol_tutorial.html

Clicking on "Summary" will give you information on how the mouse works.

3. A link to a JSmol page can be found on the course page. Navigate to that page and answer the following questions:



i) Give the primary structure (amino acid sequence of the protein, N to C). Note that you need to identify the amino acid on the basis of its sidechain atoms.

ii) What is the secondary structure of this peptide, α-helical or β-strand? Justify your answer.

iii) What is the geometry of the atoms associated with the peptide bond (N, HN, C, O)? Do these lie in the same plane or are they tetrahedral?

(Note that there are checkboxes below the image to help you understand the structure, click them!)

i)

Residue 1 is Alanine – it has a methyl for a sidechain

Residue 2 is glycine (no sidechain)

Residue 3 is Asparagine (short amide sidechain)

Residue 4 is Phenylalanine

Residue 5 is Valine

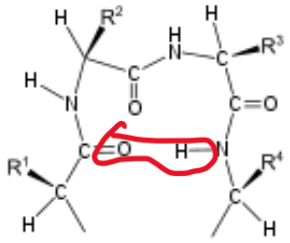
Sequence is: Ala-Gly-Asn-Phe-Val

ii)

It is alpha helical because: i) the backbone atoms trace out a helix (see diagram) and the mainchain H-bond (shown with a dotted line) is parallel to the helix axis.

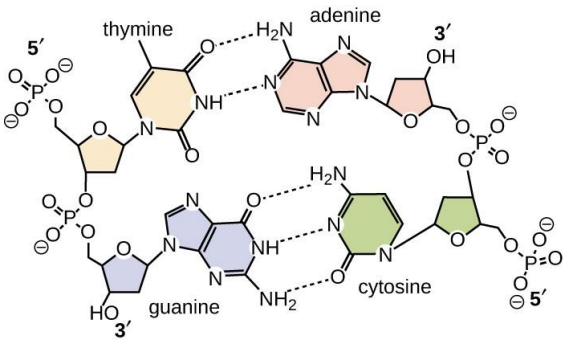
iii) The four atoms are planer – i.e. they all lie on the same page.

4. Beta strands are connected by turns in the protein backbone that are called tight or reverse turns. The diagram of a reverse turn is shown on the right. What favorable interaction would stabilize the geometry of the turn?



There is a hydrogen bond between the C=O and the H-N, indicated on the diagram.

5. Proteins that regulate the expression of DNA in cells generally bind to the DNA by either hydrogen bonding, electrostatic (charge-charge) interactions, or both. These proteins contain a large number of lysine residues. In answering the following, assume that the pKa of the lysine sidechain is 9 and the pKa of the phosphate group in DNA is 2.0. A partial structure of DNA is shown on the right.



i) Explain how the presence of lysine residues would enhance the interaction (binding) of the protein to the DNA by hydrogen bonding. Which groups on the DNA would be involved.

The N-H on the sidechain of lysine can donate an H-bond to the phosphate, or any oxygen on the deoxyribose or the bases.

ii) Explain how the presence of lysine residues would enhance the interaction (binding) of the protein to the DNA by electrostatics. Which groups on the DNA would be involved?

The positive charge on the lysine would interact favorably with the negative charge on the phosphate.

iii) Mutations occur such that the some of the lysine residues on the protein are changed to glutamic acid. Predict how the DNA binding would change, would it get better, worse, or stay the same. Justify your answer.

The change from lysine to glutamic acid would produce a negative charge, this would repel from the negative charge on the phosphate decreasing the affinity.

6. A protein contains a valine that is found in its central core. Please discuss how the following mutations would affect the structure of the protein. You should discuss possible changes in van der Waals, hydrogen bonding, and the hydrophobic effect and whether the mutant would be more stable or less stable.

i) Valine changed to alanine.

ii) Valine changed to threonine.

i) Valine to Alanine: This protein would likely be less stable.

- The smaller alanine would show reduced van der Waals interactions with the other sidechains in the core.
- Alanine is less non-polar than valine, so there would be a smaller hydrophobic effect, i.e. less ordered water would be released when the protein folded. Therefore there is a smaller (less favorable) increase in the entropy of the water when folded.

ii) Valine to Threonine. It is difficult to tell whether this protein would more or less stable.

- Threonine is the same size as valine and would have at least the same van der Waals stabilization. The van der Waals stabilization may be higher because the -OH on threonine would have a permanent charge distribution, while the -CH3 in valine would only have a temporary charge distribution (see example in lecture notes).
- Threonine is more polar than valine, so the hydrophobic effect would be reduced, destabilizing the protein.
- However, threonine could potentially form new hydrogen bonds using its -OH group, which would stabilize the protein.