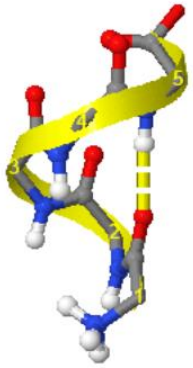
1. Use the Jmol page from the ***previous*** problem set to answer this question.



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

ii) 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)

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.

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

2. 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.

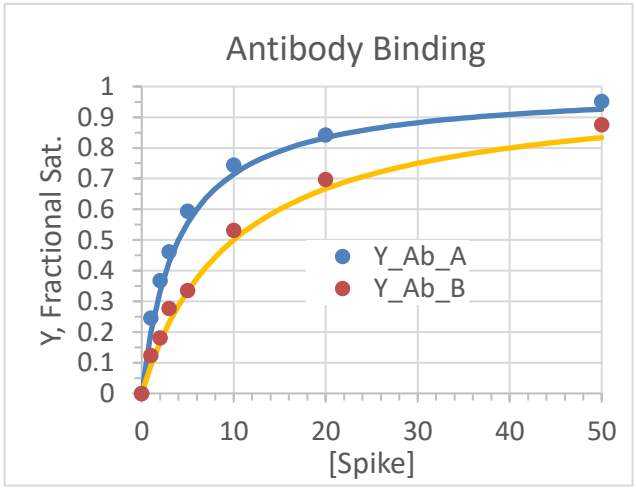
i) Valine: This protein would likely be less stable.

- 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.

ii) 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 could 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.

3. Two different antibodies (Ab_A, Ab_B) are being tested as treatments for Covid-19 infection. Both of these antibodies bind to a surface protein on the virus, the spike protein, preventing the virus from entering the cell (physical blocking). A plot of fractional saturation versus the concentration of the spike protein (in nM) is shown on the right. Please answer the following questions.



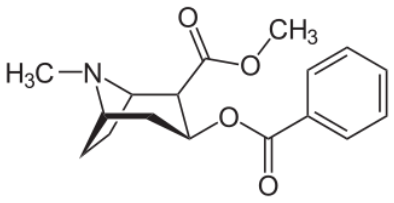
i) What is the K_D for each antibody?

ii) Which of these antibodies will be more effective against Covid-19? You can assume that the concentration of spike protein is 10 nM during an infection. Justify your answer.

i) The Kd is the amount of ligand (spike protein in this case) to ½ saturate the protein. For A, it is about 2 and for B it is about 10.

ii) Antibody A will bind more spike protein at that concentration, 73% versus about 50% for B, so it should be more effective.

4. The Jmol page contains the structure of a complex between an immunoglobulin (antibody) and cocaine. The chemical structure of cocaine is shown on the right. Only the very top part of the immunoglobulin (Fv region) is shown on the Jmol page.



i) Describe the energetics of the interaction between Tryptophan33H and the bound cocaine. Your answer should discuss what stabilizes the bound cocaine, e.g. H-bonds, electrostatics, van der Waals, or the hydrophobic effect.

ii) Describe the interaction(s) between Tyrosine32L and the bound cocaine. Your answer should discuss what stabilizes the bound cocaine, e.g. H-bonds, electrostatics, van der Waals, or the hydrophobic effect.

iii) How would changing tyrosine32L to phenylalanine affect the affinity of cocaine to the antibody? Would the cocaine binding be stronger or weaker? Justify your answer.

https://www.andrew.cmu.edu/user/rule/03_131/Pset/PS03/ps03_jmol_b.html

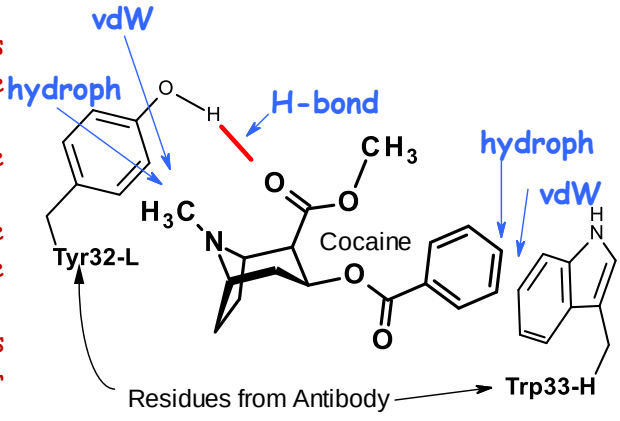
You want to consider if any of the following interactions occur between the bound antigen (cocaine) and the antibody:

H-bonds: Are donors and acceptors present in the appropriate location?

Van der Waals: Is there close contact between the antigen and the amino acid side chains from the antibody.

Hydrophobic effect: Are there non-polar surfaces that would lead to the release of ordered water when the antigen binds?

Electrostatics: Are there complementary (opposite) charges on the antigen and the antibody?

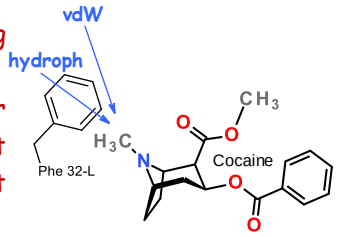


In general, there will always be van der Waals due to shape complementarity, and then one or more of the other three.

i) Tryptophan 33 on the heavy chain is in close contact with the phenyl ring on cocaine, showing van der Waals and the hydrophobic effect.

ii) Tyr32L on the light chain forms an H-bond with cocaine, it also has van der Waals interactions and a hydrophobic interaction with the methyl group on cocaine.

iii) If Tyr32 was replaced by Phe, the -O-H group would be removed, leading to a loss of a hydrogen bond, reducing the affinity.



In summary; The bound cocaine is stabilized by hydrogen bonding, van der Waals and the hydrophobic effect. Cocaine has no ionizable groups, so it will not be charged and therefore electrostatic interactions are not important here.

5. What disease is the drug Trastuzumab used to treat? Briefly describe how it works to cure the patient (*please use the web and provide the appropriate citation*).

Trastuzumab is an antibody that is used to treat breast and stomach cancer. It binds to the HER2 receptor which is a growth factor receptor. This receptor is over-expressed in these cancers, leading to increased growth of the cancer cell in response to normal levels of the growth hormone. The antibody prevents the growth hormone from binding to the receptor, therefore preventing growth of the cancer cell.

Source: Wikipedia. **Note** that Wikipedia is always a good starting point for literature search, ***most*** of the pages are correct. However, you should also check the sources that are listed on the Wiki page and additional sources to verify critical information that would be important for your studies.

6. Write a short paragraph on Hers' disease. Your essay should discuss:

i) The normal function of the enzyme that is affected by this genetic disease.

ii) The consequence of loss of function to the individual.

(*please use the web and provide the appropriate citation*).

This is a glycogen storage disease where the individual is missing glycogen phosphorylase, the enzyme that releases glucose from glycogen. It is normally regulated by the hormone glucagon, which phosphorylates the enzyme.

Surprisingly, this deficiency is relative benign, with an enlarged liver and some growth retardation.