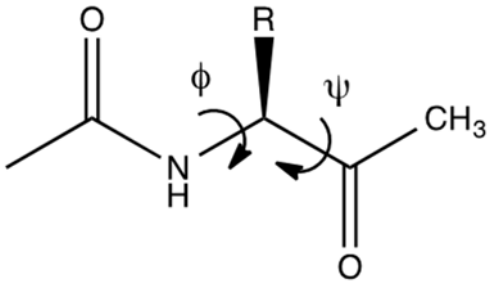
"Molecular forces that determine preferred torsional minima for peptides"

The energy of a protein can be calculated as the sum of several pairwise energy terms (i.e. bonded terms, including bond distance, bond angle, and dihedral angle terms; and non-bonded terms, including electrostatics and van der Waals interactions). Such an energy function is called a force field.

The backbone dihedral angle (torsional) terms are of particular importance when developing force fields to describe the energetics of peptides. An incorrect torsional potential may bias protein conformations toward physically unrealistic conformations—i.e. too much alpha-helix or too much beta-sheet structure.

To get it right, all-atom force fields such as AMBER[1] have been parameterized by adjusting the force constants to match quantum mechanical calculations of the total energy of a peptide molecule as a function of φ and ψ backbone dihedral angles. Our goal today is to perform a dihedral angle scan for the ψ angle of an amino acid residue (here we will work with alanine).

We will consider the following molecule (R=CH3 for alanine):



Procedure

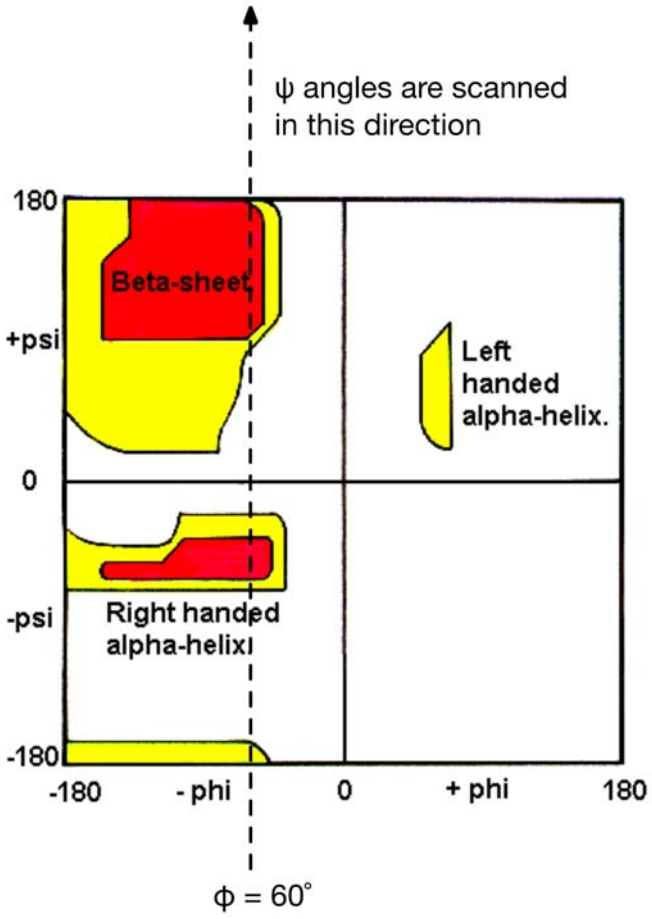
1. **Build the molecule**
   a. Start building a new molecule using *New Build*. In the right-hand panel, choose the *Peptide* menu, and click on "Ala". Before adding it to your workspace, notice that you are given a choice of setting the dihedral angles (α, β, or other). Click the "Other" button and set the custom dihedral angles to ψ = -180˚, φ= -60˚. Then click on the workspace to add the peptide.
   b. Next, add capping groups to the peptide. Use the *Organic* menu on the right-hand side to cap the N-terminus with an acetyl group $(C=O)CH_3$ and the C-terminus with an NH_2 group.
2. **Create copies of the molecule at different torsion angles**
   a. Go to Geometry > Set Torsions. Several yellow "cuffs" should show on each rotatable bond. For each dihedral angle except the ψ angle, click on the yellow cuff, and set *Conformations* to 0-fold = **Off**. Click on the ψ angle and set Conformations to 20-fold.

[1] Cornell, W. D., Cieplak, P., Bayly, C. I., Gould, I. R., Merz, K. M., Ferguson, D. M., et al. (1995). A second generation force field for the simulation of proteins, nucleic acids, and organic molecules. Journal of the American Chemical Society, 117(19), 5179–5197. doi:10.1021/ja00124a002

b. Then, click the right-most button (with a black triangle pointing down) and generate a list of these conformers. If it goes well, you should be able to play an animation (left bottom) to see how it scans through.

3. **Calculate the energy of each conformation**
   a. In Setup > Calculations… calculate "Energy" (not Equilibrium Geometry!) at the HF 6-31G* level in Vacuum (This is actually the basis set for the original AMBER parameterization (1994). Click Submit to submit the calculations. It should take a minute or two.
4. **Plot the results**
   a. After the calculation finishes, go to Display > Plots …
   b. Click the green "+" to add a plot, with the molecule as the x-axis and E kcal as the y-axis. Click the Merge button (little black triangle) to super impose the plot with the conformation. Cycle through to animation and see if you can identify the beta-sheet and alpha-helix minima.

NOTE: This is the direction your scan should proceed:



Name: **TUID:**

Section:

Question: What intramolecular forces do you think are important in determining these minima?