Chemistry (4|6)0650 - Computational Chemistry Spring 2017
Professor J. Daniel Gezelter Due Mon. 2/27/2017

Computational Exercise 2

Today we'll be getting used to minimizing and building molecules using Avogadro. This is a great tool for exploring some of the methodologies using small molecules and short proteins. It is also a good tool for generating initial configurations for molecular dynamics simulations. We'll be revisiting this tool in the next lab as well, so this is mainly a warm-up to get you used to building, minimizing, and measuring chemical structures.

Drawing Structures:

1. You'll need to download and install "Avogadro" which is a neat tool for doing small molecule molecular mechanics.

   You can get it here: http://sourceforge.net/projects/avogadro/

   You'll want version 1.2.0 (earlier versions are somewhat buggy, and the rewritten version 2.0 doesn't have all of the features we need).

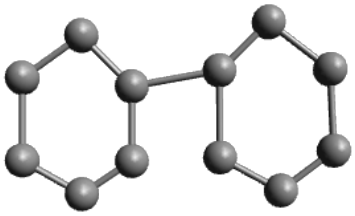
2. Navigate to your Applications and open `Avogadro`. (On a Mac, the first time you open the application, you will need to go into System Preferences → Security & Privacy, and then click the "Open Anyway" button where it tells you that "Avogadro" was blocked from opening.)

3. Use the draw tool  , and go to the `Tool Settings...` to *uncheck* the `Adjust Hydrogens` button.

4. Click in the main window to place a carbon atom.

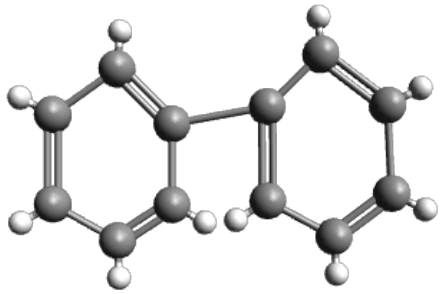
5. Drag from one atom to another location to make a carbon-carbon bond.

6. Sketch out the skeleton of the biphenyl structure:



7. Click the `Bond Order` drop-down and select "`Double`". Also, re-enable the "`Adjust Hydrogens`" check-box.

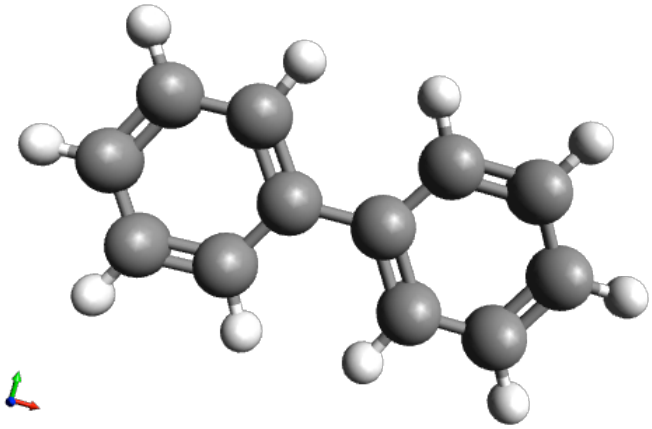
8. Click alternating bonds to convert the system to two conjugated rings:



This is a very uncomfortable geometry for biphenyl, so we want to allow the molecule to relax into a lower energy conformation.

9. Go to `Extensions → Molecular Mechanics → Setup Force Field...,` Pick the `MMFF94` Force Field, the `Steepest Descent` Algorithm, and a convergence criteria of `10e-2.` Click `OK.`

10. Go to `Extensions → Optimize Geometry.` You should get a structure that looks like this:



11. The measure tool  allows you to measure distance, angles, or dihedral angles.

    a. Click on two atoms to measure a distance.

b. Click on three atoms to measure the angle between them.

c. Click on four atoms to measure the dihedral angle between them. (Measure the dihedral or torsion angle between the two phenyl rings).

d. Right click (or Ctrl-click or ⌘-click) to clear the measurement and the list of selected atoms.

12. The bond-centric manipulation tool 

provides a "chemically-oriented" way to change bond lengths, angles, and dihedral angles.

    a. Click on the bond between the two phenyl rings. A rectangle will be drawn with the bond at the center. You can rotate this plane about the bond by clicking on the bond and dragging.

    b. Right click (or ⌘-click) on one of the atoms in the selected bond and drag to change the bond length. The current bond length is listed in the bottom left corner.

    c. Left click on one of the atoms in the selected bond and drag to change the bond angle. The atom you click on will move in the highlighted plane, with the other atom as the center of rotation. The appropriate angles will update interactively.

    d. Click on an atom *neighboring the bond* and drag to change the dihedral angle. Adjust the phenyl-phenyl ring dihedral until it is near 90°.

13. Re-optimize the geometry, this time using the `Conjugate Gradient` and a convergence criteria of `10e-7`. What is the optimum phenyl-phenyl dihedral angle now? What does your chemical intuition say about the *correct* phenyl-phenyl angle?

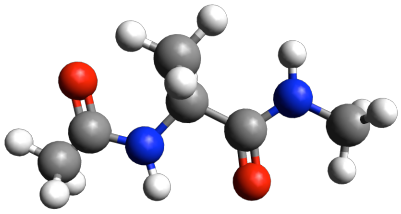
Building a Peptide

1. Start a new molecule (⌘N on a Mac - or just quit and restart Avogadro).

2. Go to `Build → Insert → Peptide`

3. We're going to create a peptide analogue which contains a single amino acid residue, alanine (Ala), flanked by two peptide bonds and capped at each end with methyl groups. To do this, insert the peptide sequence Gly-Ala-Gly. Close the "Insert Peptide" window.

4. The main window will contain the peptide, but it will have all of the atoms selected (surrounded by a blue halo). Use the selection tool to pick only a few atoms to delete with the "Delete" key. Then use the build tool, to modify the structure until you get the capped alanine structure:



Note that you may need to add hydrogens back to the structure with the drawing tool to make it look like the capped alanine in this picture.

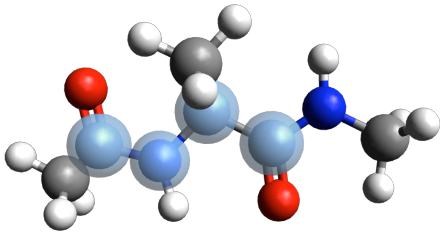
5. We will use the methyl group side chain of the Ala residue as our visual anchor point. Conformations will generally be oriented so that the Ala methyl group is at the top and slightly rotated forward. The Ala methyl group is attached to the Ala alpha-carbon (C_{a1}) at the center of the peptide.

   In this view, the Ala amide nitrogen (N_{H1}) is attached to the left of C_{a1}. The carbonyl carbon (C_{O-1}) to the left of N_{H1} represents the C-terminal end of the preceding residue.

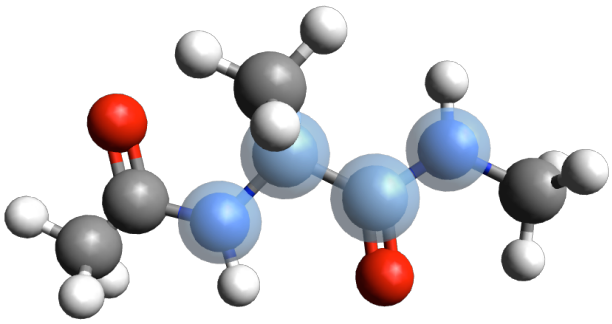
   Also in this view, the Ala alpha-carbonyl carbon (C_{O1}) is attached to the right of C_{a1}. The amide nitrogen (N_{H+1}) to the right of C_{O1} represents the N-terminal end of the succeeding residue. It may help to label the previous diagram.

   The methyl carbons at each end correspond to the alpha-carbons of the preceding and succeeding residues.

6. The ϕ angle is the torsion angle specified by the spatial positions of C_{O-1}, N_{H1}, C_{a1} and C_{O1}. These atoms are highlighted below. C_{O-1} is the left-most highlighted atom and C_{O1} is the right-most highlighted atom. In this conformation, $\phi = 180°$.



7. The ψ angle is the torsion angle specified by the spatial positions of N_{H1}, C_{a1}, C_{O1} and N_{H+1}. These atoms are highlighted below. N_{H1} is the left-most highlighted atom and N_{H+1} is the right-most highlighted atom. In this conformation ψ = 180°.



Energy related to torsional rotation

1. By using the measure tool and bond centered manipulation, change both the ϕ and ψ to 0°. Explain why this is a high-energy conformation.

2. Use the MMFF force fields, turn on the auto-optimization tool,  and drag around atoms until you find a low energy configuration (that is around -70 kcal / mol or so). What are the ϕ and ψ angles in this conformation?

Homework questions:

1. What is the optimum phenyl-phenyl dihedral angle in biphenyl? What is the *experimental* value? How was the experimental value derived? Why might yours differ? Why did you get different results when you started the calculation from the planar biphenyl vs. 90° biphenyl? Which optimized structure is correct?

2. When you find a low-energy structure for the capped alanine, what chemical interactions were stabilizing the structure? What is a Ramachandran plot? What do your values of ϕ and ψ correspond to on the Ramachandran plot?

3. In this problem, the goal is to compute the lowest energy structure for the pentapeptide met-enkephalin, whose sequence is `Tyr-Gly-Gly-Phe-Met`. Met-enkephalin is an opioid peptide neurotransmitter. Many local minima exist for this molecule, so it is a challenge to reach the global minimum. The student who finds the structure of the lowest energy will receive a *prize* from Dr. Gezelter.

The rules of this contest are:

- Use a molecule with charged COO^- and NH_3^+ ends.
- Use the MMFF forcefield.

You can use any technique mentioned in this course (energy minimization, molecular dynamics, conformational sampling), as well as any other resources (e.g., web and literature), to find the global minimum of the pentapeptide.

Be creative. Think about what you could do to reduce the configuration space explored by your protein.

You will submit a detailed report ***IN THE FORM OF A WEB PAGE*** describing how you reached the minimum for met-enkephalin and any particular difficulties, or interesting observations, you encountered along the way. Make sure that the Cartesian coordinate file and the energy value reached are available from your web page.

The winner (lowest energy conformation) will receive a prize, which will be topologically similar to a donut (although not necessarily edible).

Background Reading that may be helpful

Avogadro Documentation: http://avogadro.openmolecules.net/wiki/Documentation

M. Karplus and G. A. Petsko, "Molecular Dynamics Simulations in Biology," *Nature* **347**, 631-639 (1990).

K. A. Dill and H. S. Chan, "From Levinthal to Pathways to Funnels", *Nature Struc. Biol.* **4**, 10-19 (1997).

T. Lazaridis and M. Karplus, "'New View' of Protein Folding Reconciled with the Old Through Multiple Unfolding Simulations", *Science* **278**, 1928-1931 (1997).