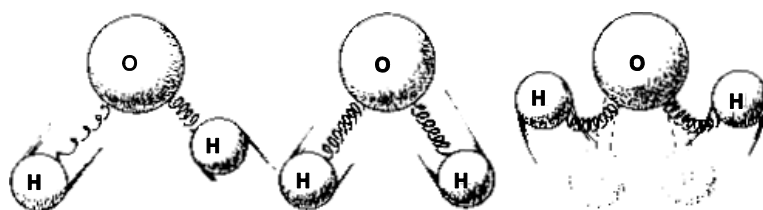


**Title: Conformational Analysis***New principles: Computational Chemistry, Molecular Mechanics, Relative Conformational Energies**Introduction:*

A conformation is a molecular geometry obtained by rotation about at least one single bond. This bond is typically a C-C single bond, but rotations about other bonds containing heteroatoms are also possible. Rotation about just one bond can generate a number of different geometries, yet it is usually possible to assign just one conformation as the lowest energy conformation. It is important that you be able to identify the lowest energy conformation in simple systems such as butane and cyclohexane. For complicated molecules, the “global” energy minimum may correspond to a structure resulting from a large number of bond rotations.

Molecular mechanics (MM) is a method for determining the “optimized” structure of simple molecules. The technique is an application of classical mechanics whereby the molecule is considered simply to be a collection of



hard spheres (the atoms) connected together by a set of stiff springs (the bonds). The calculation systematically changes the coordinates of the starting, or *input*, geometry and calculates the steric energy of each new generated structure. The components of the calculation include torsional strain, bond deformation (the difference between the actual bond length in the structure and “ideal” bond length), angle deformation (difference between the actual and “ideal” bond angle), Van der Waals interactions (steric hindrance), and dipole-dipole interactions.

Molecular mechanics is an energy minimization technique (there are other methods that are based on molecular orbital theory) that has become extremely useful to chemists. Drug companies routinely employ molecular mechanics to determine minimum energy geometries of potentially pharmaceutically efficacious compounds and then compare these geometries with the complementary geometry of an active site in human cells where such compounds would be expected to interact. It is possible, using energy minimization methods, to save time and money in developing new drugs by careful computer analysis of possible compounds before expensive synthetic efforts commence in the laboratory. Chemists have used molecular mechanics to predict which isomer will form preferentially in stereoselective reactions by investigating the geometries of structures similar to transition states that would be expected to lead to the different stereoisomers. Molecular mechanics results, combined with spectroscopic data, provide complimentary and supplementary information to X-ray methods for determining the geometry of peptides and small proteins.

In this exercise you will learn to use the CAChe (**C**omputer **A**ided **C**hemistry) software to input simple molecules, determine their minimum energy conformations, and generate a potential energy map for rotation around a single bond.

*Green aspects:*

Molecular modeling with the computer is a very green chemistry experiment! In addition, rather than printing pages and pages of pictures, you will be collecting your work in a Word document and sending it to your lab assistant. We calculate that this will save on the order of 1500 pages of paper.

## Using CAChe for Molecular Calculations and Modeling

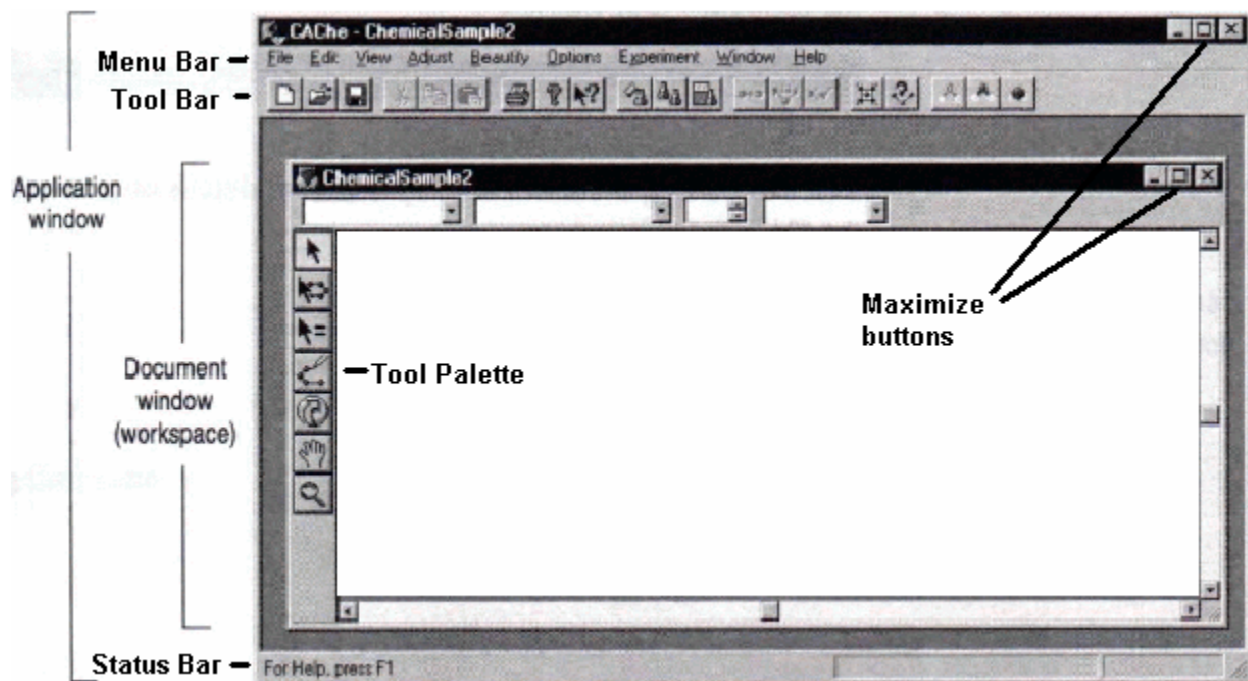
The CAChe program operates under the Windows or Macintosh operating system. In our computer laboratory, we use the Windows version, but we have a site license for both, and you can download either of these versions to your computer from the St. Olaf server. For more information about downloading, see the course toolkit at <http://www.stolaf.edu/depts/chemistry/facility/modeling>.

### Getting Started:

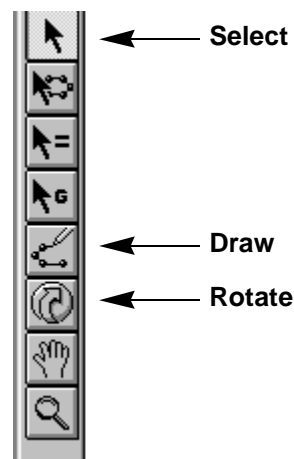
1. Check that the monitor and computer are both turned on.
2. Log in using your username and password.

### Basic Layout of the CAChe Program

Your instructor will demonstrate how to find the CAChe program. The screen should look something like the picture below. Maximize both the application window and the document window if they are not already maximized. Features of the application window include the **Menu Bar**, the **Tool Bar**, and the **Status Bar**.

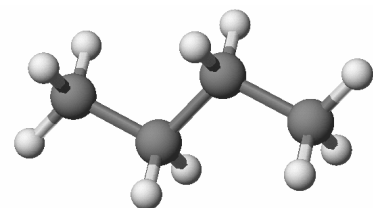


The front window is the workspace and has the **Tool Palette** on the left side. This palette has three types of “tools” for selection, drawing, and moving. Primarily you will find the **Select**, **Atom/Bond**, and **Rotate** tools to be most useful.

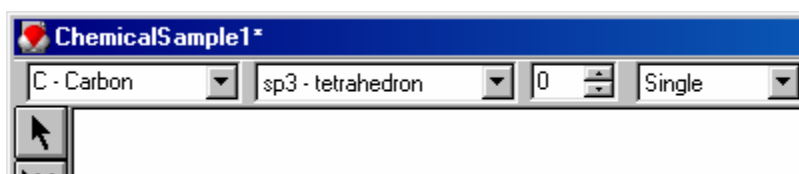


### Assignment 1a: Conformational Energies of Butane

The objective of this assignment is to become familiar with the CAChe program and to explore the relative energies of rotational conformations around the C2-C3 bond in *n*-butane.



Click on the tool **Atom/Bond** tool palette icon. At the top of the workspace window are four boxes allowing for element choice, type of hybridization of the atom, charge on the atom, and type of bond in which the atom is involved. The choices you need for drawing hydrocarbons are C-Carbon,  $sp^3$ -tetrahedron, 0, and single.

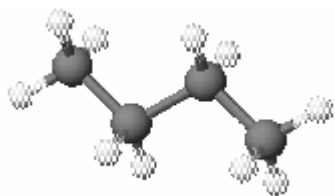


A cursor resembling a pencil appears in the workspace window. Position this cursor in the middle of the window and click the mouse. A darkly shaded sphere will appear. This is the first carbon atom in the four carbon atoms required for butane. Starting at the center of this atom, drag up a short distance and release the mouse. Two darkly shaded spheres connected by a vertical line should appear on the screen. Starting at the center of the second atom, drag over a short distance up and to the right and release the mouse again. Once more, and you have a rough butane model. Do not worry if the spheres are different shades or that the bond distances or bond angles are not perfect.

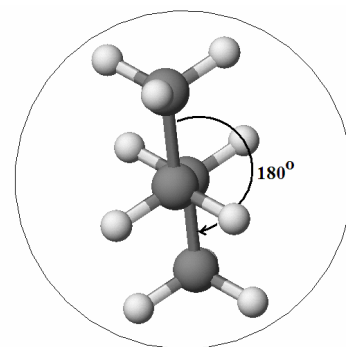
Click the **select** icon, then click anywhere off your structure. This selects all atoms. All of the atoms should now have the same shade of darkness. From the **Menu Bar** select **Beautify** and, under this, **Comprehensive**. This will add the correct number of hydrogens to each carbon, adjust the bond angles to be tetrahedral, and shorten or lengthen bond distances to correspond to the approximate bond lengths in butane. In other words, you now have realistic computer displayed model of the butane molecule.

Use the manipulation tools now to rotate the molecule, move it laterally or up and down, or scale it to a different size. If it does not look like what you would expect for butane, ask your instructor or lab assistant for help.

In order to calculate the energies of the various conformations relating to bond rotation, you will need to select the four atoms necessary to define a *dihedral angle*. This is done by first clicking on the **select** icon, then the first atom, then, while holding the **SHIFT** key down, clicking on the other three atoms involved in the dihedral, in order. The carbons should all be darkly shaded now (selected), and the hydrogens should be lightly shaded (unselected).

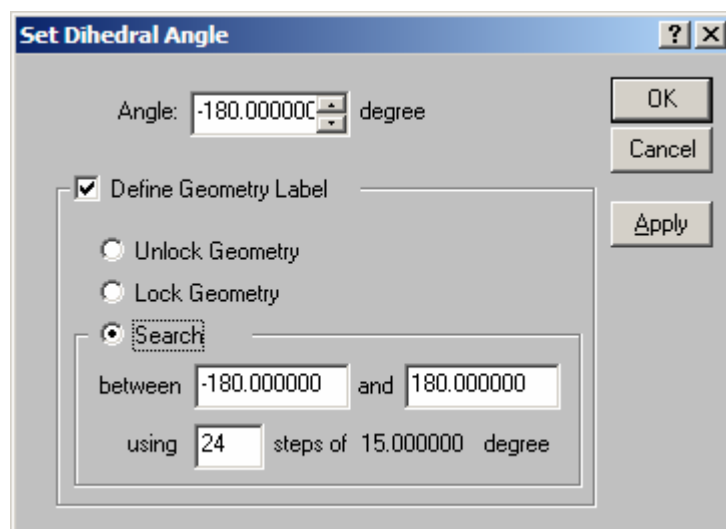


Note: a *dihedral angle* is measured in a plane perpendicular to a bond.



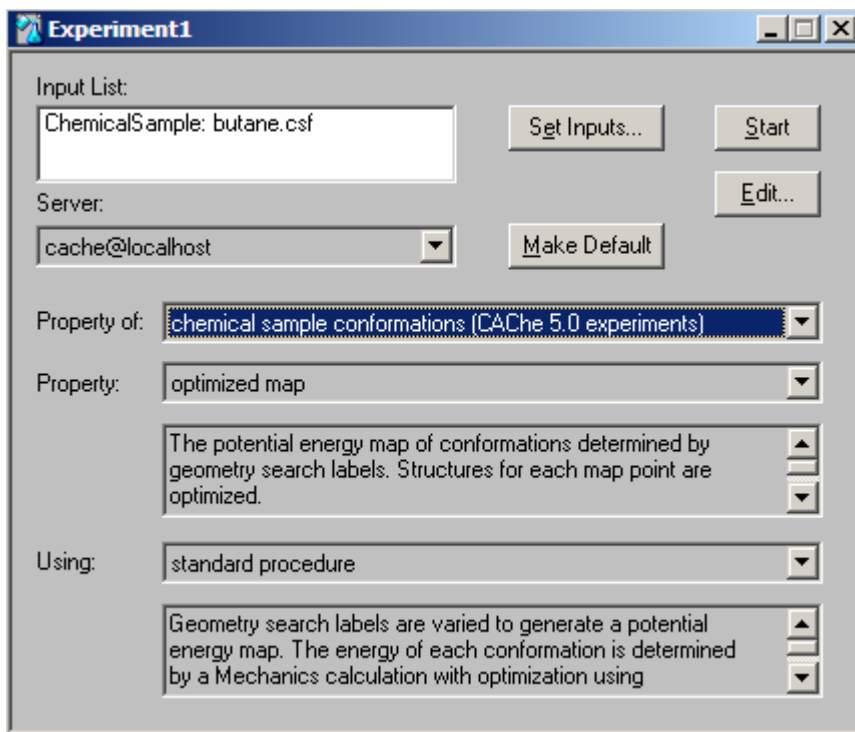
Click on **Adjust** from the **Menu Bar** and on **Dihedral Angle...** from the choices given. A new window (shown on the right) will appear. Check the box labeled **Define Geometry Label** and select the **Search** option. The information at the bottom of this window indicates the range of rotation about the selected bond and how many steps will be used. Click on **OK**.

Remove the shading by selecting the entire model. Save the structure. From the **Menu Bar** select **File**, then **Save As**. Save the structure under a name of your choice.

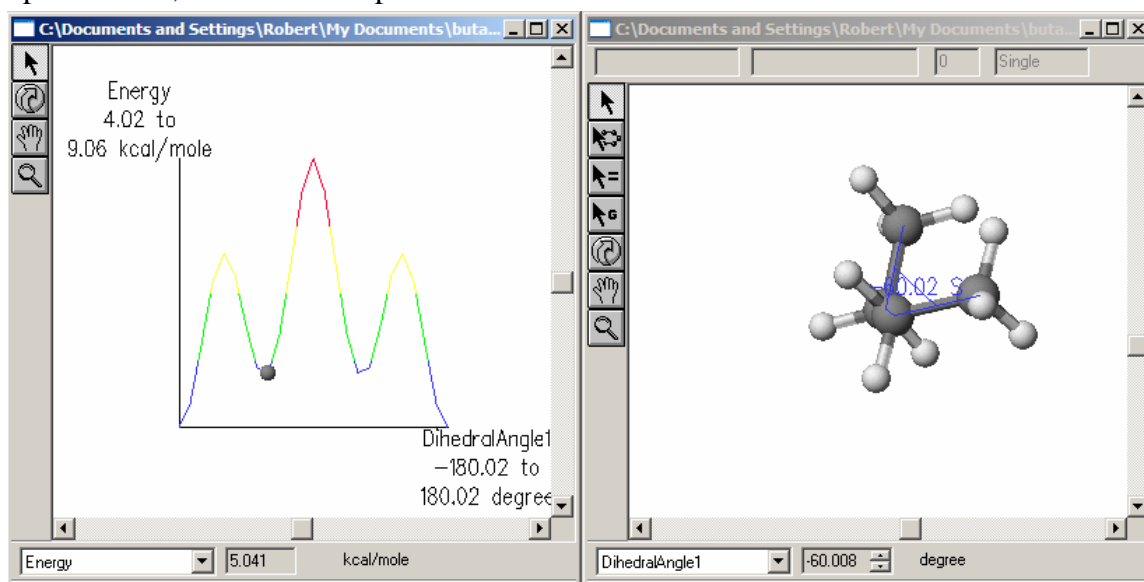


**Quick Tip:** You can easily select the entire model by first clicking on the **select** icon, then clicking anywhere on the background.

Select **Experiment** from the **Menu Bar** and, under this, **New**. Make the choices in the “Property of,” “Property,” and “Using” boxes as shown on the right. (They may look slightly different – These messages depend upon the version of CAChe you are using.) Click on **Start**. The calculation will begin, and results will be displayed in a new window.



When the calculation is complete, a new window with two parts will appear. The left half displays a graph (an “energy map”) of energy versus dihedral angle. Change the box in the lower left corner to read **Energy**. Somewhere on the graph will be a dot. The right half displays a model of the conformation corresponding to the energy and dihedral angle associated with that dot. Each half may be made active by clicking on it; the active window is highlighted. With the left window active, press a keypad arrow key. Notice the change in the model displayed in the right hand window. Identify which conformations correspond to energy maxima and minima in the energy diagram. When the right window is active, the manipulation tools can be used to rotate the molecule, move it sideways or up and down, or to shrink/expand the size of the molecule.



Note: Read the energy from the box on the left and the dihedral angle from the box on the right. Click on the graph on the left and use the keypad arrow keys. Also try **Edit** and **Animate along axis...**

Find the lowest-energy conformation. Start a Word document, and copy the graph and the model into it. You will deliver this document to your lab assistant at the end of the experiment.

### Questions to Answer in Your Word Document

1. From your data, what is the difference in energy ( $\Delta E$ ) calculated for CH<sub>3</sub>–CH<sub>3</sub>-eclipsed butane vs. *anti* staggered butane? Which is lower in energy? Why?
2. From your data, what is the difference in energy calculated for *gauche* vs. *anti* butane? Which is lower in energy? Why?

### Assignment 1b: Conformational Energy of a Designer Molecule

Draw an open-chain molecule of your choice having at least five carbon atoms and at least one branch. If you wish, you can add one or more oxygen or halogen atoms to the chain, but don't overdo it.

Select the four atoms necessary to define a dihedral angle, save the file, and calculate the energies of the various conformations. In your laboratory notebook record energy and structural information about the various maxima and minima of the map using Newman projections. Add the energy map and a picture of the model in its lowest energy conformation to your Word document.

### Questions to Answer in Your Word Document

3. Copy the picture of the lowest-energy conformation of your compound into your Word document. How many *gauche* interactions can you find? How many *anti*? How about eclipsed – any of those? What do you make of that?

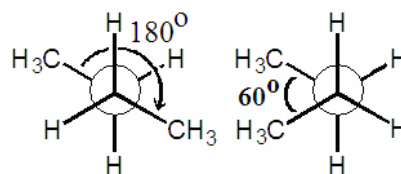
### Assignment 2a: Methylcyclohexane

See if you can use the same procedure you used above for butane to make a model of methylcyclohexane. Be sure to “beautify your structure. The two relatively low-energy conformations of methylcyclohexane (axial and equatorial) are shown on the next page. Which one did you get?



Quick Tip: You can copy the picture of the model from CAChe into Word just using the copy icon on the ToolBar, then pasting into Word. Before copying, adjust the size of the CAChe window to be just a bit larger than your model. A rectangle the size of this window will be clipped.

Note: a *Newman projection* is a view directly down a bond, allowing for easy depiction of dihedral angles.



**anti**

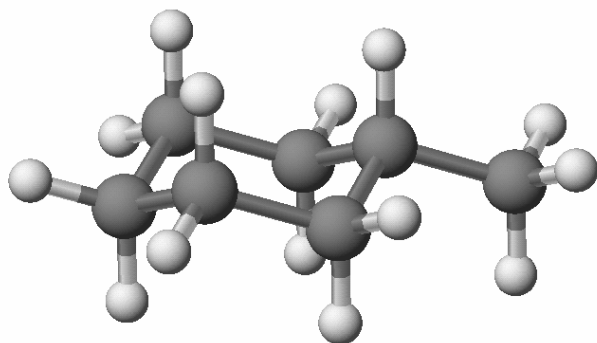
**gauche**

pronounced

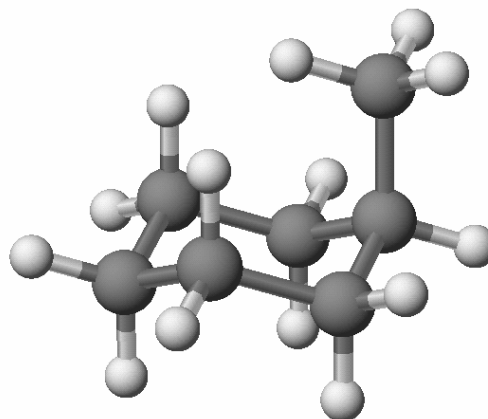
pronounced

“AN-tee”

“GOESH”



**equatorial methylcyclohexane**  
(C-CH<sub>3</sub> bond parallel to two ring bonds)



**axial methylcyclohexane**  
(C-CH<sub>3</sub> bond not parallel to a ring bond)

Calculate the energy of this conformation using a **New Experiment** and setting

Property of	chemical sample
Property	optimized geometry
Using	standard procedure

Record the energy of this model.

Generate the other low-energy conformation by inverting the configuration of the ring carbon atom bearing the methyl group. Calculate the record the energy of this second conformation.



Quick Tip: You can easily switch between axial and equatorial orientations by clicking on the **select** icon, selecting the ring carbon atom and pressing CTRL-I (for “invert”).

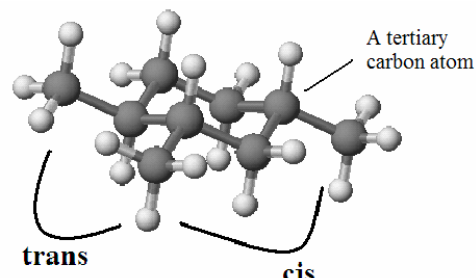
### Questions to Answer in Your Word Document

4. From your data, what is the difference in energy ( $\Delta E$ ) for axial vs. equatorial methylcyclohexane? Which is lower? Count the number of *gauche*-butane interactions specifically involving the CH<sub>3</sub> groups in each case. How does the number of *gauche*-butane interactions relate to the relative energies of the two conformations?

### Assignment 2b: 1,2-dimethylcyclohexanes

One at a time, make a model of each of the four (or are there three?) possible chair conformations of *cis*- and *trans*-1,2-dimethylcyclohexane. Optimize each structure and record in your laboratory notebook the energy in each case. Clip a picture of each into your Word document.

Note: *cis* means the two CH<sub>3</sub> groups are on the same face of the ring; *trans* means they are on opposite sides (as in *trans*-Atlantic).



### Questions to Answer in Your Word Document

5. Discuss the number and relative energies of the conformations of *cis* and *trans* 1,2-dimethylcyclohexane. Count up the *gauche* butane interactions for the three bonds connected to **tertiary carbon atoms**. Is there a correlation?

### Assignment 2c: 1,3-dimethylcyclohexanes

Make models of the four (or three?) conformations of *cis*- and *trans*-1, 3-dimethylcyclohexane. Calculate and record the energies of each, clipping them into your Word document.

### Questions to Answer in Your Word Document

6. Discuss the relative energies of the different conformations of *cis* and *trans* 1,3-dimethylcyclohexane in relation to *gauche* butane interactions involving the four ring bonds connected to tertiary carbon atoms.
7. What would you expect for the number and relative energies of the *cis* and *trans* 1,4-dimethylcyclohexane?

Summarize what you have learned today in your Word document and send it to your lab assistant by Email.