

Conformational Analysis with *Spartan Model* (aka "*SpModel*")¹

The activities described on the following pages show you how to perform a complete conformational analysis of three different molecules. They are interesting in their own right, but, taken collectively, they demonstrate all of the operations needed to analyze the conformational preferences of *cis* and *trans*-3,3,5-trimethylcyclohexanol, the two alcohols that you have prepared and characterized in lab. Please refer to these instructions when you undertake the conformational analysis of these alcohols and prepare your lab report.

Conformational analysis by computer? Our usual method for performing a conformational analysis is to imagine or draw all of the important conformers of a molecule and identify the most stable one(s). How can a computer help? Why might a computer even prove necessary at times?


The first answer to these questions is a computer can juggle more interactions than our minds can. The more complexity we see in a molecular structure, the more likely we are to throw up our hands and say, "ask the computer." Second, a computer can give quantitative estimates of conformer energy, and these can be used to calculate equilibrium constants and concentrations.

Caution. *SpModel* (and especially *Sp08*) contain a large number of useful tools for making models. Choosing the wrong tool is not really a "mistake", but it might lead to an incredibly time-consuming (and possibly useless) calculation. Read each instruction carefully before you perform each step.

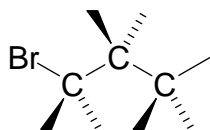
Overview. The activities covered here include:

1. Building *anti* 1-bromopropane. Optimizing its geometry and measuring bond angles and distances.
2. Building *gauche* 1-bromopropane using *internal rotation*. Optimizing its geometry and using the *anti* and *gauche* energies to calculate K_{eq} for the *anti-gauche* conformer equilibrium.
3. Building and optimizing *trans*-1-ethyl-3-methylcyclohexane conformers. Calculating K_{eq} for the conformational equilibrium. Repeating the same steps for *trans*-2-ethyl-6-methylcyclohexanone.



Spartan Model activity #1

- ✓ Click with the *left* mouse button (unless told otherwise).
- ✓ Start *SpModel* by *double*-clicking on its desktop icon (or select from **Start: All Programs** menu).
- ✓ Maximize the program window by clicking on the **Maximize** button  in the upper right corner.







Build a model of 1-bromopropane, CH₃CH₂CH₂Br



1-bromopropane
anti conformer
H are not shown


- ✓ Click on the **New** icon . This replaces the "view" window with the "build" window (the build window contains an atom "palette" on the right side) and it selects the **Add** icon .


¹ All of these activities can also be carried out using *Spartan'08* (aka *Sp08*). We prefer that you use *SpModel* because it has a simpler interface.

- ✓ If necessary, click on the sp^3 hybridized C atom in the palette , then click somewhere in the green window. This places one carbon atom plus four yellow “free valences” in the window. The free valences are used to add more atoms to the model. If they are not used, they will automatically change into hydrogens, so this structure can also be regarded as a model of methane, CH_4 .
- ✓ Add a second carbon by clicking on the *tip* of a free valence. Repeat this to add a third carbon. You should have a three-carbon model at this point.
- ✓ Add bromine by clicking on the Br atom in the palette , then click on the *tip* of the *anti* free valence of an *end* carbon so that your model has an *anti* conformation (see drawing on pg. 1).
- ✓ When you finish building, click on the **View** icon  to return to the “view” window.
- ✓ **Correcting mistakes.**
 - Select **Undo** from the **Edit** menu. This will usually undo the most recent operation.
 - Click on the **Delete** icon , then click on the atom(s) that offend you. When you are finished making corrections, click on  to return to the “build” window, or click on  to return to the “view” window.
 - Select **Clear** from the **Edit** menu. This makes the entire model vanish.
- ✓ **Moving your model.** Try these operations:
 - **Rotate.** Press *left* mouse button and move mouse.
 - **Translate.** Press *right* mouse button and move mouse.
 - **Grow/Shrink.** Press **Shift** key and *right* mouse button simultaneously, and move the cursor up and down on the screen

Measure some bond distances and bond angles

Whenever you build a model, *SpModel* uses a table of standard bond distances and bond angles to position the atoms. This “initial” geometry is a *reasonable guess* as to what your molecule looks like, but it is probably not too reliable because complicated molecules are usually affected by factors (steric repulsion, electrostatic interactions, electron delocalization, and so on) not found in “standard” molecules. You can easily demonstrate the “complicated” nature of 1-bromopropane for yourself:

- ✓ Click on the **Distance** icon . Notice the **Distance(,)** label that appears in the lower right corner.
- ✓ Click on a *pair* of neighboring C atoms. The atoms turn gold as you click on them (they are “selected”) and the distance between them (in Å) appears in the lower right corner.
 - Short-cut: You can also get a bond distance by clicking on a bond. The bond will turn gold when it is selected.
 - Hint: You can *unselect* any item by clicking on it a second time.


- ✓ Record the C1-C2² and C2-C3 bond distances in the following table under “Initial geometry”.
- ✓ Click on the **Angle** icon . Notice the **Angle(,,)** label that appears in the lower right corner.
- ✓ Click on C3, then C2, and then C1 (in this order). The atoms turn gold and the CCC bond angle (in °) appears in the lower right corner. Record the CCC bond angle under “Initial geometry”.
- ✓ Click on Br, C1, and C2 (in this order) and record the BrCC bond angle under “Initial geometry”.
- ✓ How do the geometrical parameters listed under “initial geometry” indicate that the model is based on “standard” distances and angles?


	Initial geometry	Optimized <i>anti</i> geometry	Optimized <i>gauche</i> geometry
C1-C2 bond distance			
C2-C3 bond distance			
CCC bond angle			
BrCC bond angle			
strain energy			

Optimize your model's geometry using the Minimize icon , (molecular mechanics)

“Optimization” (aka “geometry optimization”, “minimization”, and “energy minimization”) is a procedure that uses energy calculations to obtain more accurate molecular geometries. The idea behind optimization is simple: the model's geometry is changed incrementally by adjusting the position of each atom, then the model's energy is calculated at the new geometry. The “adjust/calculate” cycle is repeated until a minimum-energy, or optimized, geometry is discovered. The result, an “optimized” model, has a lower energy than any model with a similar geometry.

As you might expect, optimization works only if the computer has a reliable method for calculating the energy. At the very least, an energy calculation should take into account interactions that a “standard” molecule might lack: steric repulsion, electrostatic interactions, long-range resonance, and so on. Unfortunately, no method for calculating energy is ever completely satisfactory. One method might estimate steric repulsions incorrectly, while another might have difficulties with electrostatic interactions. These are just models, after all, but they are usually more accurate than the “standard” geometry that we start with.

One way to optimize a model's geometry is to click on the **Minimize** icon . This option is useful for our purposes because 1) it is *simple* and *fast*, and 2) it relies on an energy calculation called “molecular mechanics” that is able to simulate steric interactions and modest electrostatic interactions, such as dipole-dipole interactions. Molecular mechanics calculations yield a sort of *strain energy* for the model so the minimum-energy geometry is the one that is least strained.

- ✓ Click on the minimize icon . The model's bond distances and angles are adjusted to give an optimized geometry. The *strain* energy of this model (in kJ/mol or kcal/mol) is shown in the lower right corner. Record this energy (and the units) in the table shown above in the “Optimized *anti* geometry” column. If you followed all of the directions correctly, your model's strain energy will be -8.96 kJ/mol (or -2.14 kcal/mol).

² Atom numbers are derived from the IUPAC name. C1 is the carbon bonded to bromine, C2 is the adjacent carbon, and so on.


Molecular mechanics optimizations are normally blazingly fast, especially for small molecules. However, you can monitor an optimization's progress by looking at the "stop sign" in the lower right corner. Red means "still working"; gray means "finished". You can stop an optimization in the middle by clicking on the red stop sign.

- ✓ Re-measure your model's bond distances and bond angles and enter your data in the "Optimized *anti* geometry" column of the table on the previous page. The distances and angles should have changed slightly. Notice that optimization makes the CC bond distances different from each other and it makes the bond angles different from each other. These differences occur because atoms always adjust their positions to reflect the unique combination of interactions found in a given molecule.
Optimization is an essential step in constructing molecular models.


Spartan Model activity #2

This activity shows you how to use internal rotation to convert *anti* into *gauche* 1-bromopropane. After that, you will optimize the *gauche* geometry and compare it to the *anti* geometry.

Use internal rotation to change conformation

- ✓ Click on the **Add** icon .
- ✓ Click on the C1-C2 bond to make it "active" (a small-red arrow encircles an "active" bond).
- ✓ *Rotate* the model (*left* mouse button) so that C1 is hidden behind C2 (you want the model to look like a Newman projection).
- ✓ Press the **Alt** key and the *left* mouse button simultaneously, and move the cursor up and down on the screen until Br and C3 are *gauche*.

Optimize your model's geometry using the "minimize" icon

- ✓ Click on the minimize icon . Record your model's strain energy in the "Optimized *gauche* geometry" column of the table in Activity #1. If you followed all of the directions correctly, your model's strain energy will be -7.35 kJ/mol (or -1.76 kcal/mol).

It might surprise you that "minimization" leads to a *gauche* structure and not the more stable *anti* structure. Recall that minimization relies on consecutive "adjust/calculate" cycles. Adjustments are restricted in magnitude so that each new model resembles the one that preceded it. This restriction also guarantees that minimization will yield the minimum-energy structure closest to the starting structure, the so-called "local" minimum. To find the very best structure for a molecule, the "global" minimum, one needs an "adjust" strategy that moves atoms larger distances.

Use *relative* strain energies to calculate a conformational equilibrium

Your calculations should show that the *anti* conformer is more stable (less strained) than the *gauche* conformer by 1.61 kJ/mol (0.38 kcal/mol). Now, we would like you to compute the equilibrium ratio of the *anti* and *gauche* conformers. This ratio depends on their relative *free energies*,

$$[anti]_{eq} / [gauche]_{eq} = K_{eq} = 10^{-\Delta G/2.3RT}$$

and free energy differences are not the same as strain energy differences. Free energy differences depend on enthalpy, entropy, and temperature:

$$\Delta G = \Delta H - T\Delta S$$

Combining formulas gives us:

$$\begin{aligned} K_{\text{eq}} &= 10^{- (\Delta H - T\Delta S)/2.3RT} \\ &= (10^{-\Delta H/2.3RT}) (10^{T\Delta S/2.3RT}) \\ &= (10^{-\Delta H/2.3RT}) (10^{\Delta S/2.3R}) \end{aligned}$$

Obviously, we need enthalpy, entropy, and temperature data if we want to calculate equilibrium concentrations.

The calculated difference in *strain energies* can be equated with the enthalpy change, ΔH . This value is 1.61 kJ/mol (0.38 kcal/mol) for *anti* \rightarrow *gauche* 1-bromopropane. The other values that are needed are $R = 8.31$ J/mol K (= 1.98 cal/mol K) and $T = 298$ K. Combining these values gives us:

$$K_{\text{eq}} = (10^{-\Delta H/2.3RT}) (10^{\Delta S/2.3R}) = 1.90 (10^{\Delta S/2.3R})$$

Rather than have you calculate ΔS , we will simply point out that the entire entropy term, $10^{\Delta S/2.3R}$, is roughly equal to the statistical ratio of conformers, $(\#anti)/(\#gauche)$, where $\#anti$ and $\#gauche$ are the number of independent, equivalent forms of each conformer. To determine these values, we ask "how many equivalent ways can we draw or build each conformer?" The *anti* form can only be built (or drawn) in only one way,³ but there are two mirror-image *gauche* conformers, so $(\#anti)/(\#gauche) = 1/2$. This leads to:


$$\begin{aligned} K_{\text{eq}} &= 1.90 (10^{\Delta S/2.3R}) = (1.90) (1/2) \\ [anti]_{\text{eq}} / [gauche]_{\text{eq}} &= 0.95 \end{aligned}$$

Even though the *anti* conformer is slightly more stable, we predict that there will be a tiny bit more *gauche* conformer at equilibrium at 298 K.

Measure some bond distances and bond angles

- ✓ Measure the appropriate bond distances and bond angles in *gauche* conformer, and record them in the "Optimized *gauche* geometry" column of the table on pg. 3.

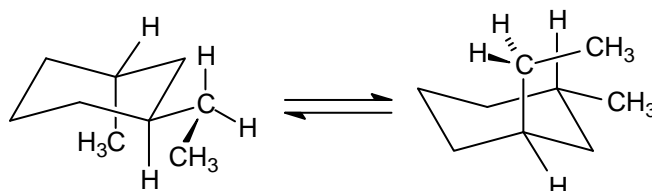
Compare the distances and angles for the *optimized* conformers. Based on these observations, can you suggest a hypothesis that would explain why the *gauche* conformer is more strained? (Hint: the *gauche* conformer contains larger bond angles. Which atoms, and what kind of interaction, are responsible for these larger bond angles?)



- ✓ When you are finished, close all of the open models by selecting **Close** from the **File** menu (or click on the **Close** icon )

³ If you also allow for internal rotation of the methyl group, there are three equivalent *anti* forms ($\#anti = 3$), and six equivalent *gauche* forms ($\#gauche = 6$), which still leads to $(\#anti)/(\#gauche) = 1/2$.

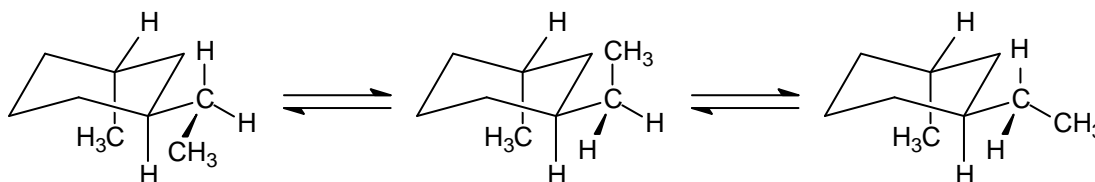
Spartan Model activity #3


Geometry and energy are always closely connected, but while we can easily “see” geometry, energy must be inferred or calculated. Consider the two chair conformers of *trans*-1-ethyl-3-methylcyclohexane shown below. Neither conformer manages to get both substituents into the preferred equatorial positions. This makes the preferred geometry an open question. The following activity shows you how to resolve this matter by comparing strain energies.

**Build and optimize “equatorial ethyl” *trans*-1-ethyl-3-methylcyclohexane**

- ✓ Click on the **New** icon .
- ✓ Select **Cyclohexane** from the **Rings** menu, and click somewhere in the green window.
- ✓ Add whatever atoms are necessary to make an *axial* methyl group and an *equatorial* ethyl group as shown above
- ✓ Click on the **Minimize** button  and record the strain energy here: _____

Internal rotation about the ring-ethyl bond generates three different conformers. To find the preferred conformation of the “equatorial ethyl” conformer, we rotate the ethyl group into each staggered position and calculate the strain energy.



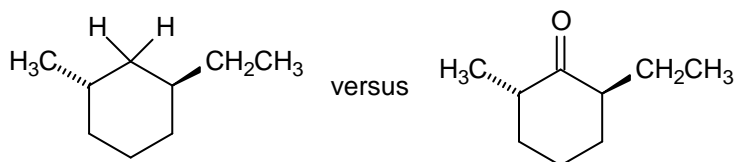
- ✓ Use internal rotation to move the ethyl group into another staggered “equatorial ethyl” conformer. Click on the **Minimize** button  and record the strain energy here: _____
- ✓ Repeat the above step to obtain the energy of the third “equatorial ethyl” conformer. Record the strain energy here: _____
- ✓ Compare the strain energies of the three “equatorial ethyl” conformers, and record the *lowest* strain energy in the table on pg. 7.

	strain energy (kcal/mol) <i>trans</i> -1-ethyl-3-methylcyclohexane	strain energy (kcal/mol) <i>trans</i> -2-ethyl-6-methylcyclohexanone
<i>equatorial</i> ethyl		
<i>axial</i> ethyl		
[<i>eq</i> Et]/[<i>ax</i> Et] @ 298K		

Build and optimize “axial ethyl” *trans*-1-ethyl-3-methylcyclohexane

- ✓ Use the same strategy to create and optimize three “axial ethyl” conformers. Record the *lowest* strain energy in the table.
- ✓ Based on the energies in the table, which conformer is more stable, *equatorial* ethyl or *axial* ethyl? Why do you suppose this is?
- ✓ Use the difference in conformer strain energies to calculate the equilibrium ratio of the *equatorial* ethyl and *axial* ethyl conformers.⁴ Record this ratio in the table.

Chemists like to believe that the behavior of a complicated molecule can be predicted by making extrapolating from the behavior of simple molecules. We have seen that this is roughly true when it comes to bond distances and bond angles, but what about conformational preferences? For example, is the preferred conformation of *trans*-2-ethyl-6-methylcyclohexanone (“complicated molecule”) identical to the preferred conformation of *trans*-2-ethyl-6-methylcyclohexane (“simple molecule”)?

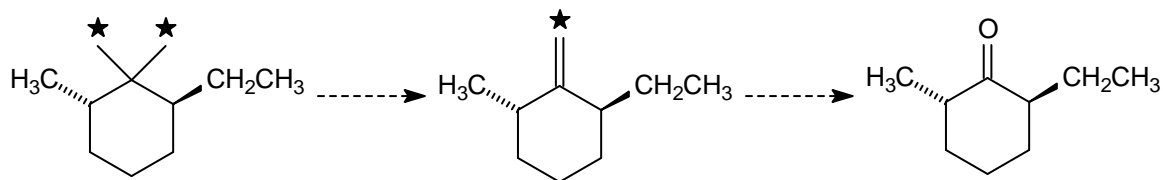



Notice that the structural formulas look quite similar. Look again at the cyclohexane models you have just built and try to imagine, if you can, C=O in place of CH₂. What would you predict about its conformational preferences? The same preferred conformation and a similar K_{eq}? The same preferred conformation, but a substantially larger K_{eq}? A change in the preferred conformation? Write down your prediction here:

Build and optimize “equatorial ethyl” *trans*-2-ethyl-6-methylcyclohexanone

- ✓ Rebuild “*equatorial* ethyl” 1-ethyl-3-methylcyclohexane model
- ✓ If necessary, click on the **Add** icon to open the “build” window
- ✓ Click on the sp² C hybridized atom in the palette , and then *double*-click on the C2 carbon atom. This replaces the two single bond free valences with one double bond free valence (see first step below):

⁴ You can ignore entropy changes for this calculation.



- ✓ Click on the double bond O atom in the palette  and single-click on the tip of the double-bond free valence. This creates a CO double bond and completes the desired model.
- ✓ Use the procedure described above to optimize the model geometry, record the strain energy, and perform internal rotations on the *equatorial* ethyl group. Record the strain energy of the lowest energy conformer in the table.

Build and optimize “axial ethyl” *trans*-2-ethyl-6-methylcyclohexanone

- ✓ Repeat all of the building steps starting with “axial ethyl” *trans*-1-ethyl-3-methylcyclohexane and build the corresponding cyclohexanone. Use the same procedure to find the lowest energy conformer of “axial ethyl” *trans*-2-ethyl-6-methylcyclohexanone model and record this energy in the table
- ✓ Based on the energies in the table, which conformer is more stable, *equatorial* ethyl or *axial* ethyl? Why do you suppose this is? (Look closely at your models for clues.)
- ✓ Use the difference in conformer strain energies to calculate the equilibrium ratio of the *equatorial* ethyl and *axial* ethyl conformers.⁵ Record this ratio in the table.

Questions for reflection

- ✓ Why is optimization always necessary?
- ✓ Are simple rules like “equatorial is preferred” always useful?
- ✓ Are simple molecules necessarily a good guide to the geometries and energies of complicated molecules?
- ✓ What aspects of a molecular formula ought to encourage you to make a model(s)?

HOLD ON TO THESE INSTRUCTIONS

(refer to them when modeling your alcohols and calculating K_{eq} for your lab report)

⁵ You can ignore entropy changes again.