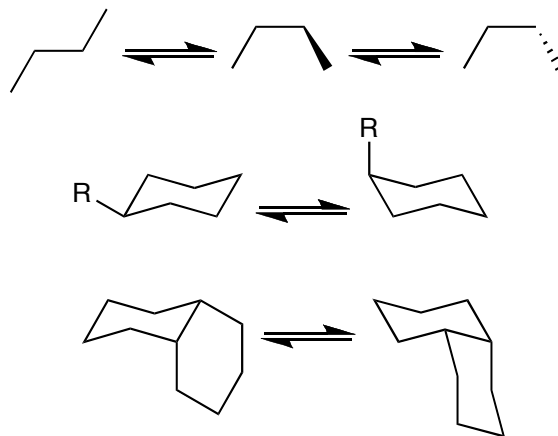


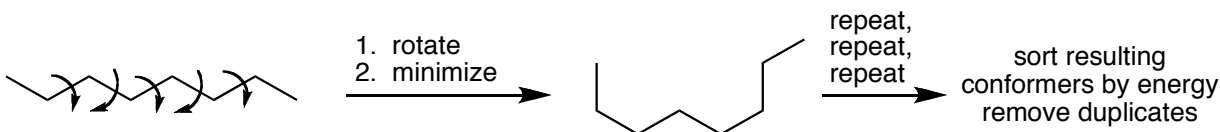
## Conformational Searching in Molecular Mechanics Calculations

Most molecules can adopt more than one low-energy conformation. Butane favors the anti conformation, but the gauche conformers are only 0.9 kcal/mol higher in energy. Substituted cyclohexanes can adopt two chair conformers in which substituents are either equatorial or axial. Cis-decalin adopts two different conformations as well.

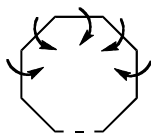


In thinking about molecular structure and reactivity, it is important to consider all low-energy conformations, and not just the lowest energy conformation of a molecule. The conformations are populated according to a Boltzmann distribution, such that their relative populations are proportional to  $e^{-G/RT}$ . Thus, butane comprises a 70:30 mixture of anti and gauche conformers at room temperature. In many cases, the lowest-energy conformation is not the conformation that reacts (i.e., the Curtin-Hammett principle). For these reasons, it is often important to know all the conformations that lie within a few kcal/mol of the global minimum.

For simple molecules, such as those shown above, it is often possible to figure out all of the different conformers by conformational analysis and to then calculate their relative energies (enthalpies) by molecular mechanics. For more complex molecules, it is better to carry out a *conformational search* to find all of the low-energy conformers. Many types of searches can be envisioned. One of the most efficient conformational searching methods is a *Monte Carlo search*. In this method the important bonds of the molecule are rotated by random amounts to generate a new structure, and the resulting structure is then "minimized". By repeating this process and sorting and comparing all the different conformers that are generated, it is possible to identify the different low-energy conformers of the molecule.



Many of the molecules that we want to look at are cyclic. For cyclic molecules, you cannot rotate about all the bonds, unless you break the ring open. To search the conformations of cyclic molecules, we break the ring open, rotate about all the key bonds, close the ring (if the ends are not near each other we reject the molecule at this point and try again), and minimize. For example, in cyclooctane, there are 5 key bonds that can rotate, excluding those involved in the ring closure and the adjacent bonds.



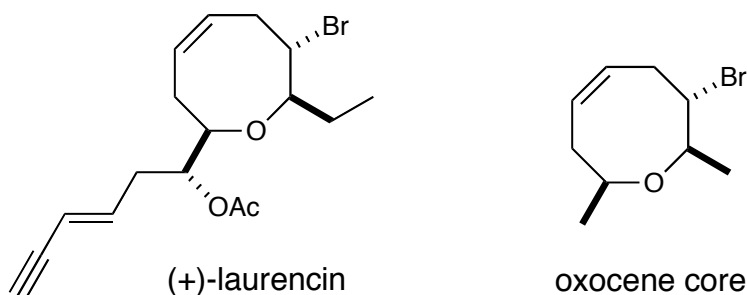
One problem with trying to locate all of the low energy conformers of a complex molecule by this method is that there are many conformers available! Butane has one key bond that can rotate, giving rise to 3 ( $3^1$ ) conformers. Pentane has two key bonds that can rotate. A simplistic analysis suggest that there are 9 ( $3^2$ ) conformers. Hexane has three; a similar analysis suggest there are 27 ( $3^3$ ) conformers. (There are actually only 6 and 17, respectively, because of symmetry and other considerations.). The same type of analysis applied to tridecane ( $C_{13}H_{28}$ ) gives 59049 ( $3^{10}$ ). When searching the conformations of complex molecules it may be difficult or impossible to find all of the low-energy conformations!

When using the Monte-Carlo conformational searching method you can never be completely sure you have found all of the low-energy conformers. If you keep finding the same ones over and over (many times) as the search progresses, and you don't find any new ones, then you have probably done a thorough search. If you do not find all of the low-energy conformers many (e.g., > 5-10 times), you need to do more Monte-Carlo searching steps. The default value in MacroModel of 1000 steps is good for small structures with a few rotatable bonds (e.g., half a dozen). For larger molecules with more bonds that can rotate, you will need more steps (e.g., 5000-10000 for ten bonds that can rotate.) For even larger molecules, a thorough search becomes prohibitive. Often measures to simplify the structure by truncating side-chains and other extraneous groups is useful.

Occasionally you will get two (or more) conformers with similar energy that look the same. Sometimes these are truly different conformers. Sometimes they are enantiomeric conformations (e.g., gauche<sup>+</sup> and gauche<sup>-</sup> butane). Sometimes these are the same conformer, differing only due to the nature of the minimization and comparison process. In the latter case, tightening the minimization criteria or loosening the comparison criteria of the program and repeating the conformational search will get rid of this problem. It is also possible that you did not allow enough iterations (e.g., by leaving It/S at 500 for a big molecule) and that your conformers are not true minima.

## Exercise

(+)-Laurencin is produced by red algae and was synthesized in the Overman group in 1995 (*J. Am. Chem. Soc.* **1995**, *117*, 5958). In this exercise, we are going to use conformational searching to generate models for the low energy conformers of the molecule. We will then compare them to available crystallographic and  $^1\text{H}$  NMR data. To keep the problem manageable and avoid confusion over differing conformations of the side chains, use the oxocene core structure shown above, in which the side-chains have been replaced with methyl groups.



**a.** Generate a model of the oxocene core. Build the model using the Maestro 3D builder. You may use the pencil tool to sketch an octagon and then use Add Hydrogens on the Edit menu to make the cyclooctane ring. Add the substituents and the oxygen and double bond. Clean up the structure using the Minimize command under the View menu.

Note: You will have an easier time seeing the stereochemistry if you change the representation to tubes using the Molecular Representation command under the Workspace menu.

**b.** Use MacroModel to generate a minimum energy structure for the oxocene core:

1. Select MacroModel/Minimization under the Applications menu.
2. Select MMFF under Force Field.
3. Select None under Solvent.
4. Under the Mini tab, enter a large number (for example 3000) for Maximum Iterations.
5. Select Start and give the Job the Name "oxocene".

**b.** Set up a Monte Carlo conformational search of the oxocene core. Make sure to choose an appropriate number of Monte Carlo steps and allow an appropriate number of minimization steps.

1. Select MacroModel/Conformational Search under the Applications menu.
2. Select MMFF under Force Field.
3. Select None under Solvent.
4. Under the Mini tab, enter a large number (for example 3000) for Maximum Iterations.
5. Under the CSearch tab, you may use the default (1000) for Maximum Number of Steps. **FOR A MOLECULE OF THIS SIZE, THIS DEFAULT IS OK. FOR A BIGGER MOLECULE WITH MORE DEGREES OF CONFORMATIONAL FREEDOM, YOU WILL NEED A MUCH BIGGER NUMBER AND MUCH MORE TIME.**
6. Select Start and give the Job the Name "oxocene-csearch".

c. Check the Project table and identify all conformers that lie within 5.0 kcal/mol (21 kJ/mol) of the global minimum.

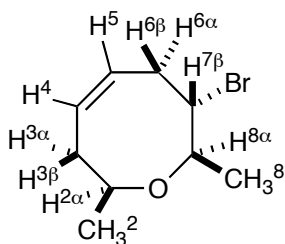
How many many low-energy conformers are there? \_\_\_\_\_

What are their relative energies? \_\_\_\_\_ kJ/mol

How many these conformers are appreciably (>5%) populated at room temperature? \_\_\_\_\_

d. Interproton distances of *roughly* 2.5 Å or less are typically associated with strong <sup>1</sup>H NMR NOEs, while interproton distances of *roughly* 3.5 Å or greater are typically associated with NOEs that are weaker or are not seen. Use the Measurements/Distances tool on the Tools menu to predict strong NOEs that you would expect to see within the oxocene core.

Don't worry about NOEs involving the methyl groups. Don't worry about the minor conformer(s) that make < 5% of the conformer population. Indicate the strong NOEs that you would predict to observe in laurencin.



H<sup>2α</sup> should give *strong* NOES with: \_\_\_\_\_

H<sup>7β</sup> should give *strong* NOES with: \_\_\_\_\_

H<sup>8α</sup> should give *strong* NOES with: \_\_\_\_\_

e. NOEs and coupling constants are important in stereochemical analysis. Use the Measurements/<sup>1</sup>H NMR Coupling tool on the Tools menu to predict the following coupling constants:

H<sup>7β</sup>-H<sup>8α</sup>: \_\_\_\_\_ Hz

H<sup>7β</sup>-H<sup>6α</sup>: \_\_\_\_\_ Hz

H<sup>7β</sup>-H<sup>6β</sup>: \_\_\_\_\_ Hz

f. If you wished to determine the whether the stereochemistry at C<sup>7</sup> was correctly assigned and you had experimental NOE and coupling constant data, what *other* molecular modeling experiment would you need to do? \_\_\_\_\_