Prediction of Coupling Constants using MacroModel and the Maestro User Interface

Vicinal coupling constants ($^3J_{HH}$) can help elucidate stereochemistry in cyclic and acyclic molecules. The H–C–C–H coupling constant depends on the dihedral angle between the associated C–H bonds, as well as the hybridization of the carbon atoms and the electonegativities of attached subsitituents. Dihedral angles of close to 180° (antiperiplanar) give rise to the largest couplings, and dihedral angles of close to 0° (synperiplanar) also give rise to large couplings. Dihedral angles of close to 30° (gauche) give rise to smaller couplings, and dihedral angles of close to 90° give coupling constants close to 0 Hz, which are often not observed.

MacroModel and the Maestro user interface allow the prediction of coupling constants and are a useful adjunct to determining stereochemistry. MacroModel is useful for calculating the geometries and energies of different conformers, and relationships between dihedral angle and $^3J_{HH}$ coupling constants (Karplus relationships) are available within the software for H–C–C–H groups with various hybridizations and substituents.

By conformational searching, it is possible to generate the energies of different conformers. If several conformers are close in energy (within a couple of Kcal/mol) and thus significantly populated, the set of low-energy conformers found can be used to calculate the coupling constant as a Boltzmann-weighted average. (For molecules with a singular low-energy conformer it is not necessary to do this.)

Name:_____

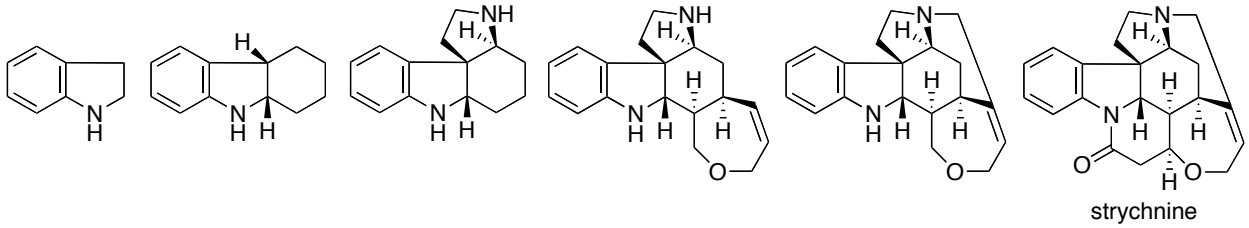
Exercise

Before begining this exercise, please review the following documents and exercises:

Calculation of Relative Energies of Conformers and Stereoisomers and Equilibrium Ratios of Products using Molecular Mechanics

Conformational Searching in Molecular Mechanics Calculations

1. Using the Maestro 3D Builder, construct strychnine in stages:



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

2. Clean up the structure as needed during the building process by typing "u" on the keyboard. You may also use the Clean Up tool on the Build Toolbar or the Minimize command under the View menu. If the nitrogen changes from blue to purple in the building process, this means that the atom type has changed from N to N+. To correct the atom type, use the Set Element tool (an A with 4 lines around it) on the Build Toolbar to change the element type back to N. (The Set Element tool has a pulldown menu that is activated by clicking and holding on the icon.) You may have to click twice on the nitrogen to correct the atom type. Similarly, if the oxygen atom changes from red to purple, this means that the atom type has changed from O to O+. Correct the atom type in the same way.

3. Save the project as Strychnine under the Project menu.

4. Use MacroModel to generate a minimum energy structure for strychnine:

a. Select MacroModel/Minimization under the Applications menu.
b. Select MMFF under Force Field.
c. Select None under Solvent.
d. Under the Mini tab, enter a large number (for example 3000) for Maximum Iterations.
e. Select Start and give the Job the Name "local-minimum".

6. Check the energy of your structure in the Project Table. It should be either 241.162 kJ/mol or 255.979 kJ/mol. If it is not check your structure and stereochemistry and correct any errors.

7. Set up a Monte Carlo conformational search of strychnine. Make sure to choose an appropriate number of Monte Carlo steps and allow an appropriate number of minimization steps.

a. Select MacroModel/Conformational Search under the Applications menu.

b. Select MMFF under Force Field.
c. Select None under Solvent.
d. Under the Mini tab, enter a large number (for example 3000) for Maximum Iterations.
e. 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.**
f. Select Start and give the Job the Name "strychnine-csearch".

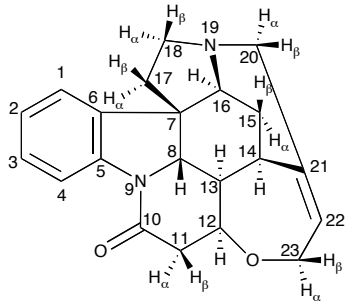
8. Check the Project table and identify all conformers that lie within 5.0 kcal/mol (21 kJ/mol) of the global minimum.

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? _____

9. On the Menu bar, choose: Tools --> Measurements --> Dihedrals then Click consecutively on each of the 4 atoms involved in the dihedral angle. Measure the H_{13}–C_{13}–C_8–H_8, H_{13}–C_{13}–C_{12}–H_{12}, and H_{13}–C_{13}–C_{14}–H_{14} dihedral angles.
Record your values below:



strychnine

H_{13}–C_{13}–C_8–H_8: _____

H_{13}–C_{13}–C_{12}–H_{12}: _____

H_{13}–C_{13}–C_{14}–H_{14}: _____

10. On the Menu bar, choose: Tools --> Measurements --> 1H NMR Coupling
then click on pairs of hydrogens to calculate the coupling constants predicted on the basis of their dihedral angle and the Karplus equation with parameters appropriate to the atoms involved.
Measure the H_{13}–H_8, H_{13}–H_{12}, H_{13}–H_{14} and coupling constants. Record your values below:

H_{13}–H_8: _____

H_{13}–H_{12}: _____

H_{13}–H_{14}: _____

11. What is the coupling pattern and coupling constants you would expect to observe for H_{13}:

12. H_{13} gives the most upfield peak in the ^{1}H NMR spectrum of strychnine. What is the coupling pattern and coupling constants you observe experimentally: _____

13. By how many Hz do each of the experimental and calculated values differ? _____

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