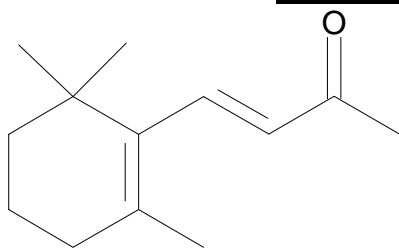


Calculating NMR Chemical Shifts for beta-ionone



Molecular orbital calculations can be used to get good estimates for chemical shifts. In this exercise we will calculate the chemical shifts for beta-ionone. You can then compare the calculated shifts with the experimental shifts, and in so doing verify that you made the correct assignments. This calculation will be done using the GIAO method. GIAO is an acronym for Gauge Invariant Atomic Orbitals. This approach insures that the magnetic properties of the atoms are handled properly.¹ The GIAO approach is a time consuming calculation, and we will take some short cuts. Because of this, we will need to apply a scaling factor to our results. In other words, the shifts will be in the right order, but they will be off by a small factor (e.g. the theoretical values will be too small by a factor of 1.23). We will use EXCEL to check this scaling factor.

You will do two types of quantum mechanical calculations. The first is a semi-empirical calculation. In semi-empirical calculations the values for important integrals are taken from experimental measurements. The second is an *ab initio* calculation. In *ab initio* calculations the important integrals are done directly from first principles. First principles means that the integrals are done either by looking up the integrals in integral tables or by doing the integrals numerically. The semi-empirical process is faster than *ab initio* calculations.

In semi-empirical calculations it is important to keep track of the experimental data that was used in finding the parameter for the integrals. For AM1 calculations, the molecules that were used were primarily hydrocarbons and simple oxygen containing compounds like alcohols, aldehydes, ketones, and carboxylic acids. AM1 calculations work very well for molecules that are in these classes. If you have nitrogen or heavy elements like sulfur or chlorine, PM3 calculations are better. The AM1 or PM3 simply signifies the sets of parameters that are used. The particular *ab initio* method that works best for calculating NMR properties is a variant of density functional theory, DFT, called B3LYP. We will talk about *ab initio* methods later in the course.

The step-by-step instructions will take you through three stages, which are summarized below:

Summary Outline;

Stage 1: You will draw the molecule and minimize the structure using MM2 molecular mechanics.

Stage 2: You will use Gaussian at the AM1 semi-empirical level to minimize the structure to find a good geometry. Finding a good geometry is called geometry optimization, so "OPT" is used as the keyword.

Stage 3: You will do the NMR shift calculation using the GIAO method at the B3LYP level at the geometry found in Stage 2. A calculation where you hold the geometry fixed and just calculate the energy and associated properties of the molecule is called a "single point" calculation, so "SP" is used as the keyword.

Instructions

Stage 1:

1. This calculation will be easiest using Gaussian on the Windows NT systems in the Schupf lab. On an NT system, log into the Gaussian account using the password "Awhfy?". You can remember this acronym as "Are we having fun yet?"
2. Start up Netscape, navigate to the PChem Home page and click on "Distance Geometry and MM2." The page will load and Java will be started. In the molecule window draw beta-ionone. Note that help is available by clicking on help. You don't need to draw in the hydrogens.
3. Distance geometry is useful if you have distance constraints to help determine the conformation of your molecule. For our purpose, however, we have no distance constraints, yet, so scroll down to the bottom of the constraints edit fields. Make sure "Add hydrogens" and "Set-up Gaussian98 Input" are checked. Then click on Submit. The MM2 minimized energy and structure will then be displayed. Scroll down to the Gaussian Input File Generator and choose the following options:
 - Method: Geometry Optimization
 - Model Hamiltonian: AM1
 - Basis Set: (skip this section, AM1 implies a specific basis set)
 - Charge: 0
 - Multiplicity: SINGLET
 - Output Options: choose none
 - Comment: type in whatever you like

4. Click on Submit. The Gaussian input file is then displayed in the scroll box at the bottom of the page. Using the mouse, select all the text in the scroll box and copy it to the clipboard.
5. From the Start menu, start-up Word with a new document. Paste in the contents of the clipboard. Then pull down the file menu and set the Save as type to "text only with line breaks." When you save the file, make sure to navigate to the D: drive and the Gaussian folder. Type in a file name, use letters and numbers only (no spaces or punctuation). Close down Word.

Stage 2:

6. From the Start menu, start-up Gaussian 98W. In Gaussian 98, pull down the File menu and choose Open. Set the Files of type to "All files". Navigate to the D: drive and the gaussian folder and open your beta-ionone file. Gaussian will load your input file into a special editor window. You don't need to change anything, you should just click on the "Run" icon. The file manager will appear. Type in a new file name, use letters and numbers only (no spaces or punctuation).
7. The MO calculation will then start, and the progress will be displayed in the main Gaussian window. This calculation will take about 5 minutes to complete. When the calculation is complete, you can view the molecule using RasMol. Pull down the Utilities menu and choose "External PDB viewer." RasMol will be started and your molecule will be displayed. When you are finished with RasMol, pull down the RasMol file menu and choose Exit.

Stage 3:

8. Upon completion, back in Gaussian pull down the File menu and choose Modify. The input file editor will be displayed once again. This time we need to make some changes. Change the Route Section to read:

```
#T TEST B3LYP/6-31G(d) SP Geom=CheckPoint SCF=Direct NMR
```

Believe it or not, by the end of the course you will really understand what all this means. For now let's just break each keyword out for a short description:

TEST: don't archive all the intermediate files (this saves a lot of file space)

B3LYP/6-31G(d): do the B3LYP calculation with a fairly modest atomic basis set

SP: do a single point calculation

Geom=CheckPoint: use the structure from the previous calculation

SCF=Direct: save the intermediate integrals in a disk file instead of keeping them in memory

NMR: do the GIAO chemical shift calculation

9. Select all the text in the Molecule Specification scroll box, and delete it. We do this because the molecule geometry will be specified from the CheckPoint file from the previous AM1 calculation.

10. Click on the Run button. The file manager will appear. Type in a new file name, use letters and numbers only (no spaces or punctuation). Once again the progress of the computation will be displayed in the main Gaussian window. This calculation will take about six hours, so leave a note on the computer that a long calculation is in progress and come back later. (Don't log out, if you log out the calculation will be killed.)

11. To view the numerical results, you can click on the yellow icon that has a magnifying glass on it in the upper right-hand corner of the Gaussian window. We first need to find out which hydrogens go together in each of the methyl groups and methylenes. Unfortunately, there is no good way to easily display the atoms with the proper atom numbers on them.² However, a Web based application has been developed that makes this process easier, as long as the molecule is not too large. Start up Netscape, navigate to the PChem Home page and click on "Gaussian98W Structure File Display." Click on browse, navigate to the D: drive and the Gaussian folder. Select your output file and click "Open." The file name should be displayed in the text box. You can tell if you got the correct file if it has a ".out" extension. Click on convert. The Gaussian output file will be displayed, and below that the 3D structure in a Chime window. The 2D stick structure has the proper atom numbers.

12. Now we can read off the chemical shifts. Scroll down to the section that looks like this:

Calculating GIAO nuclear magnetic shielding tensors.

GIAO Magnetic shielding tensor (ppm):

```
1 C   Isotropic = 158.9054   Anisotropy = 42.6840
   XX= 169.7778   YX= -16.5453   ZX= 12.9221
   XY= -21.3343   YY= 159.3514   ZY= -12.6809
   XZ= 4.7198    YZ= -1.1183   ZZ= 147.5870
Eigenvalues: 144.3985 144.9562 187.3614
2 C   Isotropic = -9.3932   Anisotropy = 181.9697
   XX= 15.0320   YX= 86.7475   ZX= -38.5124
   XY= 89.4731   YY= 18.7708   ZY= -13.1062
   XZ= -34.4217  YZ= -11.9061  ZZ= -61.9823
Eigenvalues: -87.0712 -53.0283 111.9200
```

Scroll down until you find the hydrogens. For example:

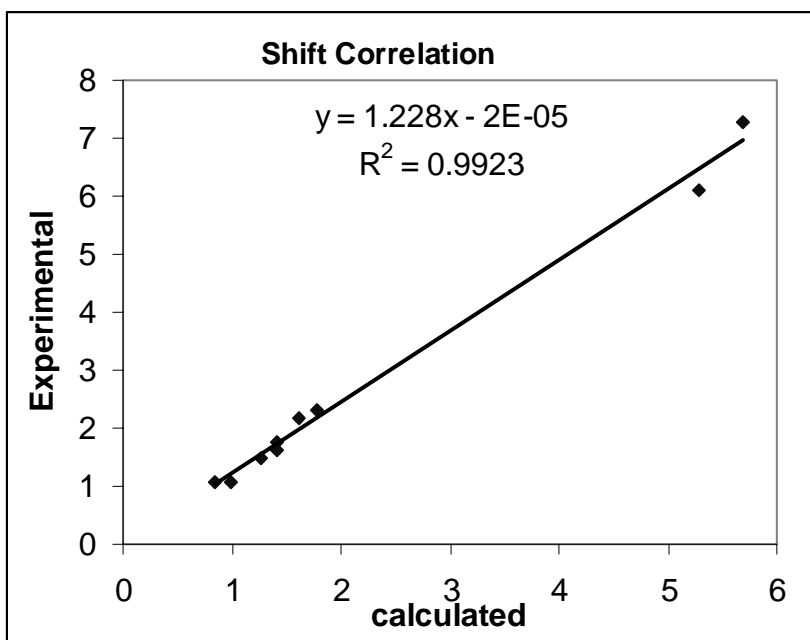
```
Eigenvalues: 160.4333 165.4304 168.3726
15 H   Isotropic = 29.5760   Anisotropy = 5.0298
   XX= 32.4314   YX= -0.0761   ZX= -2.3382
   XY= 0.1015   YY= 26.9679   ZY= -1.1402
   XZ= -0.2352  YZ= -1.3542   ZZ= 29.3286
Eigenvalues: 26.3873 29.4115 32.9292
16 H   Isotropic = 29.1019   Anisotropy = 5.4710
   XX= 30.7947   YX= 1.4534   ZX= 2.2040
   XY= 1.4384   YY= 30.2260   ZY= 1.0264
   XZ= 2.7856   YZ= -0.3504   ZZ= 26.2850
Eigenvalues: 25.1608 29.3957 32.7493
```

The chemical shift to record is the Isotropic value. For example, for hydrogen 15 the shift is 29.5760. Record the shift for each hydrogen in an EXCEL spreadsheet. To convert the shifts to ppm we need to subtract the chemical shift of the protons in TMS. A value of 31.2827 is an appropriate value for B3LYP/6-31G(d) level calculations.³ Multiply your shifts by 1.23.

13. Note that the chemical shifts for protons in the same methyl group aren't equivalent. This is because the shifts are calculated for a motionally frozen structure. The motion of the methyl group averages these different chemical environments. So average the chemical shifts of the protons in each methyl group and each methylene to make a fair comparison with your experimental values. Arrange the averaged results in a column of your spreadsheet in order of chemical shift. Match up these calculated chemical shifts with your measured chemical shifts. Match methyls with methyls, methylenes with methylenes, etc.

14. To see how well our calculation did, make a plot of the experimental chemical shift versus the calculated chemical shift (calculated on the horizontal axis). You should get a nice straight-line correlation.

Here's an example plot, without multiplying by 1.23 (you should use the factor of 1.23):



Questions:

1. Do the calculated and experimental peaks come in the correct order? That is, do the methylenes and methyl groups come in the same order for theory and experiment?
2. How good is the correlation between the experimental and calculated shifts?
3. Is the factor of 1.23 appropriate for this level of calculation?

Notes:

1. The GIAO procedure is designed so the choice of coordinate axis does not change the magnetic properties of the atom.
2. Instead of using the Web based “Gaussian98W Structure File Display” application we can get this information from the distance matrix. A portion of a typical distance matrix is shown below. You should scan through the output to find hydrogens that have distances to a carbon around 1.11 to 1.12 Å.

Distance matrix (angstroms):

		1	2	3	4	5
1	C	0.000000				
2	C	1.497550	0.000000			
3	O	2.393408	1.235201	0.000000		
4	C	2.501706	1.475506	2.389347	0.000000	
5	C	3.539697	2.511710	3.181458	1.335654	0.000000
6	C	4.097731	3.097316	3.436192	2.506931	1.463738
7	C	4.157117	3.574208	4.006335	3.287119	2.463316
8	C	3.690733	3.646346	4.406853	3.423530	2.943589
9	C	5.300221	4.759465	4.931664	4.685529	3.852512
10	C	5.258278	4.018452	3.945982	3.500684	2.501801
11	C	6.403751	5.182380	5.264466	4.309366	3.102626
12	C	5.171211	3.728780	3.327597	3.389962	2.854799
13	C	5.984670	4.879167	4.598392	4.711412	3.820948
14	C	6.338439	5.503708	5.452866	5.306224	4.310152
15	H	1.116506	2.152942	3.147159	2.720828	3.893366
16	H	1.118655	2.142878	3.081574	2.818041	3.516074
17	H	1.116695	2.162419	2.549643	3.458367	4.491925
18	H	2.866731	2.162394	3.090255	1.104165	2.119477
19	H	4.437794	3.496524	4.197019	2.111674	1.107390
20	H	3.083488	3.133891	4.127333	2.716637	2.483650
21	H	4.698594	4.722414	5.513431	4.335848	3.691866

For example, hydrogens 15, 16, and 17 are one methyl group, because they are all bonded to carbon 1. Hydrogen 18 is bonded to carbon 4 and hydrogen 19 is bonded to carbon 5. Hydrogens 18 and 19 are by themselves, so they are the hydrogens on the double bond.

3. You need to calculate the shift of TMS at the same level of calculation as you use for your molecule. This was done already for you to save time.

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