

Proposed Exercise for the Organic Chemistry Section of the Teaching with Cache Workbook:

Assigning ^{13}C NMR Chemical Shifts for Substituted Benzenes

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Overview

The examination of chemical shifts allows students to measure both the dramatic and subtle electronic effects that occur when more than one substituent is added to a benzene ring. Some of these effects are not obvious and can not be predicted by simple empirical additivity models. The goal of this student exercise is to correctly assign the C-13 spectrum of 2-nitroaniline and related compounds using 2D-NMR techniques and to further support and interpret these assignments by quantum mechanical calculations.

Procedure Setup

Several new experimental procedures will need to be created in CAChe in order to calculate chemical shielding tensors. After this has been done, it will be easy to perform the necessary calculations without needing to edit procedures at the time of submission. First create a new category of experiments that can be done on a chemical sample:

1. In Procedure Editor select “Workspace” and navigate to the folder “Chemical Sample”
2. Select **File|New Property**. A folder called “New Property” will appear in the directory “Chemical Sample”.
3. Rename this folder “NMR”. This is the folder where all NMR experiments can be placed.
4. Now follow the instructions below to create each experiment:

Experiment 1: (Using Gaussian to calculate shielding tensors using GIAO Approach)

The Gauge-Including Atomic Orbital (GIAO) approach allows the computation of the absolute chemical shielding due to the electronic environment of individual nuclei. The results are not dependent on choosing an origin for the magnetic field. The calculation is very detailed and involves evaluating derivatives of the energy with respect to an applied magnetic field. In this sense, it is not an orbital-based approach. We will set up an experiment that will use the B88PW91 density functional and the DZVP basis set. Others methods and basis sets could be used, but this model is present in DGauss and so direct comparisons can be made to results obtained there.


1. Navigate to **Environment > Procedure Index > Spectra**
2. Click on one of the Gaussian procedures. Right-mouse click. Choose Copy.
3. Click on the “Spectra” folder and then paste (Ctrl-v).
4. A new procedure appears. Right mouse click on it and select rename. Give it the name: “NMR_Gaussian_GIAO-B88PW91-DZVP.”

5. Double-click on this newly created procedure. Now double-click the phrase “Run Gaussian Using Sample 1” to enter the new Parameters:
 - a. Check that the Calculation Type is “Single Point Energy.”
 - b. Select BPW91 from the list of density functionals.
 - c. In the basis set box, type “DGDZVP” (this is not available in the drop down list, but can be simply entered by typing in the box). The “DG” is Gaussian’s way of indicating this is a DGauss basis set.
 - d. Go to the File I/O and Extra Keywords tab. Type “NMR” in the field labeled “Extra Keywords.”
6. Click OK and then close the Experiment window. A prompt will appear asking if you wish to save the changes made, select “Yes.”
7. Navigate to the **Environment >Workspace > Chemical Sample > NMR**.
8. Right mouse click on the NMR folder and select new experiment.
9. Click Browse and find the new Gaussian procedure you just created.
10. Click OK. You now have a new experiment. Right mouse click on it to rename it to “Gaussian GIAO B88PW91 DZVP at current geometry”

OPTION1: If you will be interested in knowing the spin-spin coupling between nuclei, you can type “NMR=Spin” instead of just “NMR” in the extra keywords field. This calculation will be more time consuming.

OPTION2: You may want to create additional procedures and experiments at this point if you want to use any of the other functionals in Gaussian. For instance, the B3LYP and B3PW91 hybrid functionals with the larger basis sets (such as 6-311+G(2d,p)) should be used if high accuracy is desired.

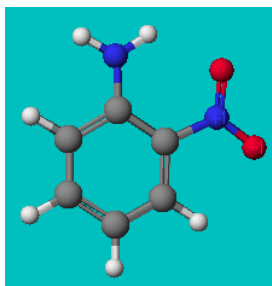
Experiment 2: (Using DGauss to calculate shielding tensors using LORG Approach)

1. Once again navigate to the **Spectra** folder of the Procedure Index. Click once on the **Spectra** folder icon to open it.
2. Create a new procedure by right-mouse clicking on the **Spectra** folder icon and selecting “new procedure.” Click on the new,  **New** , button and choose DGauss. Set the following parameters:
 - a. Check that the Calculation Type is “Energy” and Single Point.
 - b. Click the GGA radio box and select “B88-PW91” from the list below.
 - c. In the orbital basis set box, choose “DZVP.”
 - d. Go to the Properties tab. Check the NMR box.
3. Click OK and exit the “New Procedure” window. A prompt will appear asking if you wish to save the changes made, select Yes.
4. Right-mouse click on the new procedure and rename it:

“NMR_DGauss-B88PW91-DZVP”
5. Navigate to the **Environment >Workspace > Chemical Sample > NMR**.
6. Right mouse click on the NMR folder and select new experiment.
7. Click Browse and find the new DGauss procedure you just created.
8. Click OK. You now have a new experiment. Right mouse click on it to rename it to “DGauss LORG B88PW91 DZVP at current geometry”

Modeling NMR Spectra using both LORG and GIAO Theory

- Open the CAChe Workspace/Editor and construct a benzene ring by making a 6-membered ring of sp^2 hybridized carbons with alternating single and double bonds. Select **Beautify|Comprehensive** to add the hydrogens. Alternatively, you could retrieve the benzene molecule from the Fragment Library.
- Change one of the hydrogens on the ring to a nitrogen. Now change an adjacent hydrogen to a nitrogen as well. Add two oxygens to one of the nitrogens (alternatively, a properly built nitro group can be retrieved from the Function Groups in the Fragment Library).
- Select **Beautify|Comprehensive**. You should now have the 2-nitroaniline structure that looks like this:



- Select **Experiment|New**.
- Optimize the geometry of the molecule using AM1.
- Save this molecule after the job finishes.
- Setup the first experiment as:
 - Property of: Chemical Sample
 - Property: NMR
 - Using: DGauss LORG B88PW91 DZVP at current geometry
- After the job completes, go to the Workspace and select **Analyze|Chemical Properties Spreadsheet**.
- Select the Atom tab and scroll to the right of the spreadsheet.
- Record the data listed for each carbon atom under the heading LORG Chemical Shift.
- Now setup the second experiment as:
 - Property of: Chemical Sample
 - Property: NMR
 - Using: Gaussian GIAO B88PW91 DZVP at current geometry
- When the calculation finishes, navigate in windows to the folder where you saved the CAChe file. You will find a folder there with the name of your job and the “.io” extension. Go inside this folder and find the Gaussian output file (.out) stored there. Open this file with a windows text editor.
- Search for the string: “nuclear magnetic shielding tensor” (It is usually just over half way down the output file). This is what you are looking for in the file:

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Calculating GIAO nuclear magnetic shielding tensors.
SCF GIAO Magnetic shielding tensor (ppm):
 1 C Isotropic = 85.6931 Anisotropy = 170.5359
   XX= -12.8894 YX= 14.5636 ZX= 41.9268
   XY= 9.5200 YY= 79.2313 ZY= 4.2453
   XZ= 42.1854 YZ= 3.2314 ZZ= 190.7375
   Eigenvalues: -22.4438 80.1395 199.3837
 2 C Isotropic = 85.6929 Anisotropy = 170.5362
   XX= 82.6865 YX= -15.7321 ZX= 24.2662
   XY= -10.6886 YY= -19.4281 ZY= 13.3653
   XZ= 24.0076 YZ= 14.3792 ZZ= 193.8204
   Eigenvalues: -22.4443 80.1393 199.3837
 3 C Isotropic = 85.6930 Anisotropy = 170.5362
   XX= 68.0107 YX= 41.5891 ZX= 24.2781
   XY= 36.5457 YY= -5.2738 ZY= 3.1441
   XZ= 24.5366 YZ= 2.1303 ZZ= 194.3420
   Eigenvalues: -22.4442 80.1393 199.3838

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- Copy down the list of atoms and the value listed just to the right of “Isotropic” for each atom.
- To see how CAChe has assigned the numbers to each atom, Select **View|Atom Attributes** and under the “Label” tab select “Atom Number.” This will be necessary to tell which carbon shielding goes with which carbon in the molecule.

Laboratory Section

- Obtain a set of Spectra on this compound for analysis. Use TMS as your marker and CDCL₃ as a solvent. These spectra should include:
 - ¹³C Spectrum
 - ¹H Spectrum
 - 2D Spectra correlating the ¹H and ¹³C Spectra.

Analysis Section

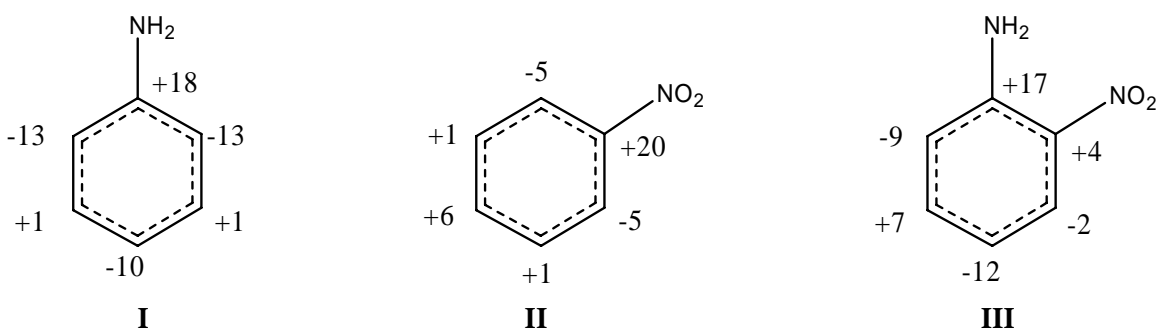
- Using the Spectra obtained, assign the peaks in the ¹³C NMR spectra to their respective carbons. First assign the ¹H spectrum based on the splitting patterns as well as the electronic environment of atom. Now use the 2D correlation spectrum to match hydrogens to their corresponding carbons.
- Make a table comparing the chemical shifts of each carbon from the computational methods to the shifts measured experimentally. Remember that the data recorded from DGauss and Gaussian is the absolute shielding at each nucleus. The chemical shift refers to how different this is from a reference shielding (such as the Carbon in tetramethylsilane - TMS). To calculate chemical shift, you need to subtract the absolute shielding of each carbon from the reference value for TMS. Here are some reference values so you do not need to do the calculation on TMS:

Method (using AM1 optimized geometries)	¹³ C Absolute Shielding for TMS
DGauss LORG B88PW91 DZVP	177.10
Gaussian GIAO B88PW91 DZVP	181.70
Gaussian GIAO B3LYP 6-311+G(2d,p)	180.51

- You should also compare your values to literature values. There is a convenient online source of NMR spectra here:
<http://www.aist.go.jp/RIODB/SDBS/menu-e.html>
- How well does each method compare to the experimental values? Which methods gave data closest to the experimental results?
- Discuss your findings in terms of the additivity (or non-additivity) of the two substituents on the ring. What assignment would have been made if you had used simple empirical rules commonly found in NMR reference books (1)?

Instructor's Notes

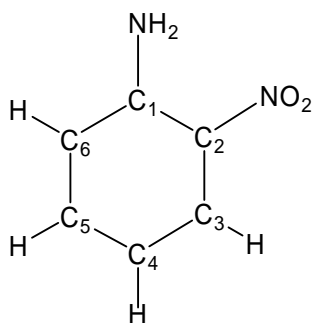
The ^{13}C spectrum of 2-nitroaniline was initially incorrectly assigned in the literature because the assignments were based on additivity parameters for amino and nitro groups. The actual assignment of peaks can be confirmed by 2D NMR experiments. Here is the central focus of this student investigation. Consider the carbon chemical shifts [ppm] relative to benzene for these three compounds:



Looking at the individual effects of adding a NH_2 group and NO_2 group, you would not expect to see the shifts in 2-nitroaniline (compound **III**) that are observed. For instance, the nitro group in compound **II** does not seem to effect the meta positions all that much. However, adding the nitro group to compound **I** changes the order of the peaks at the positions meta to it. This can only be explained by the presence of electronic factors caused by the interaction of the two substituents. These factors can be modeled using electronic structure theory, which gives the correct assignment.

The table below shows the actual data that would be obtained by students. Notice that both LORG and GIAO theory correctly predicts the relative positions of Carbons 4 and 6 in 2-nitroaniline. LORG theory does have some severe problems with carbon 1 (the carbon with the amino group attached). This is predicted by LORG to be at the opposite end of the spectrum (closest to TMS) instead of the far end of the spectrum. The Gaussian GIAO results simulate the spectrum with a 2 ppm mean absolute deviation from experiment.

This experiment could be modified to include the methyl derivatives of 2-nitroaniline. Some of these obey the rules of additivity for substituents and others do not. All assignments can be confirmed with 2D NMR experiments.



Shifts [ppm] rel. to TMS	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆
LORG B88PW91/DZVP	97.51	135.40	128.94	114.80	133.24	117.18
GIAO B88PW91/DZVP	143.34	135.40	131.68	118.49	136.48	119.06
Expt	145.05	132.10	126.01	116.85	135.76	118.99
Empirical Rules (1)	142.4	135.7	124.5	119.9	133.2	117.0

References

(1) Silverstein, R. M.; Bassler, G. C.; Morrill, T.C., "Spectrometric Identification of Organic Compounds," 5th ed., Wiley and Sons, New York, 1991, page 240.