Computing NMR parameters using ORCA

This practical comes with a short lecture on the basics of the computation of NMR parameters using standard electronic structure theory methods. By now you should have a rough idea what can be done and which computational techniques are common and useful. During the practical you should refine your skills by finding the appropriate exercises for you – don't work out all of them, but instead focus on the exercises that are at your level and pique your interest.

If you are a complete beginner, start from the beginning and you should be able to perform standard computations very quickly. If you have done these kind of computations before, start with the first exercises to learn how it is done in Orca and then turn to the more advanced exercises further down.

Note that there are several aspects which should be take home messages. One would be how simple and more complex computations can be carried out using Orca, another one would be the accuracy one can expect from these types of computations and the knowledge about the largest sources of error.

1 Getting started

This is a simple input file for the calculation of NMR chemical shieldings for a given molecule using the B3LYP functional and def2-TZVPP basis set:

```
!B3LYP RIJK def2-TZVPP def2/JK NMR

*xyzfile 0 1 inputcoords.xyz
```

We will mostly focus on DFT calculations and thus the TZ-basis is usually sufficient. The use of RIJK is highly recommended, but for larger systems RIJCOSX might be advantageous (see below). A D3 correction does not make sense in this case and, in contrast to vibrational frequency calculations, the NMR shieldings don't need to be calculated at the same level of theory as the geometry.

At the end of the output a table with all data on the NMR chemical shieldings can be found:

```
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CHEMICAL SHIELDING SUMMARY (ppm)
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  Nucleus  Element    Isotropic     Anisotropy
  -------  -------  ------------   ------------
       0      H         28.220          7.235
       1      C        129.100         80.677
       2      H         28.003          8.193
       3      H         28.005          8.196
       4      O        323.798         94.905
       5      H         32.195         18.027
```

(Note that I have chosen methanol as a first example)
The output is given in ppm and the values we get are *absolute chemical shieldings*. Note that this is not what is measured in experiment (we will come back to this later). The shieldings

are given to three decimals, however, small changes in the underlying algorithms (convergence thresholds, RI, numerical integration, ...) can already affect the first or second digit as we will see later.

2   The influence of basis sets, functionals and geometries

The absolute shieldings are a good quantity to estimate the influence of the basis set as there is no error compensation like in relative chemical shifts, which are formed as a difference from a standard.

Exercise 2.1: Let's stick to B3LYP for a moment. Compute the NMR chemical shieldings of methanol using some (or all) of the following basis sets: def2-SVP, def2-TZVPP, def2-QZVPP, cc-pVTZ, cc-pVTZ, pcSseg-1, pcSseg-2, pcSseg-3 and compare the number of basis functions and the results. Very large basis sets like the pcSseg-4 or cc-pCV5Z basis sets will give the shieldings 28.1, 124.1, 27.9, 320.6 and 31.9 ppm.

Exercise 2.2: In order to assess the functional dependence, compute the chemical shieldings of methanol using the def2-TZVPP basis set using (one or all of) the following methods: HF, BP86, BLYP, PBE, B3LYP, PBE0, TPSS, MO6L. CCSD(T) results using the TZ basis set yields values of 28.5, 147.2, 28.4, 345.2 and 32.5 ppm.

Exercise 2.3: The directory contains several geometries of methanol optimized using a variety of functionals. Note that these are not drastically different (you can estimate this by inspection of the nuclear repulsion energy). Calculate the NMR chemical shieldings for a few (or all) of these geometries using one of the functionals above along with the def2-TZVPP basis set.
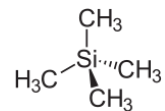
3   Computing experimental NMR spectra - chemical shifts

After having learned about how the level of theory influences the results in general, let us try to match some experimental values using DFT calculations. Note that in experiment only relative values – not the chemical *shielding* σ ($B_{local} = (1 - \sigma)B$) but the chemical *shift* δ is measured. This is due to the fact that the local field at the nucleus (B_{local}) cannot be measured and as a consequence, in experiment a reference compound must be used, which chemical shifts can be computed relative to:

$$\delta = \frac{\nu_{sample} - \nu_{standard}}{\nu_{standard}}$$

Note that above ν has been used and as a consequence the result is obtained in the somewhat exotic unit *parts per million*. This eliminates the field dependence and in practice it simply means to add an internal or externals standard compound, set its chemical shift to 0 and report all other shifts relative to it.

A typical standard for ^{13}C and ^{1}H is TMS and in order to match spectra relative to TMS, one must compute the NMR chemical shieldings for a molecule and for TMS and then subtract the values to arrive at relative shifts with respect to the standard.

Here is a table with experimental values from the AIST database (http://sdbs.db.aist.go.jp):

Molecule	Atom	Standard	Shift (ppm)
Methanol	^{13}C	TMS	50.1
Methanol	^{1}H	TMS	3.4 (CH_3) 4.0 (OH)
Benzene	^{13}C	TMS	128.4
Benzene	^{1}H	TMS	7.3
Glycine	^{13}C	TMS	175.1 (COOH) 43.2 (CH_2)
Glycine	^{1}H	TMS	3.6 (CH_2)
Pyrrole	^{13}C	TMS	117.9 (CNC) 107.0 (CC)
Pyrrole	^{1}H	TMS	8.0 (NH) 6.7 (HCN) 6.2 (HCC)
HF(gas)	^{19}F	CF_4	151
HF(gas)	^{1}H	TMS	-2.2
HF(gas)	^{19}F	SiF_4	46.9
HF(gas)	^{1}H	CH_4	-2.1
CF_4	^{19}F	$CFCl_3$	-62.5

Exercise 3.4: In relative chemical shifts of ^{13}C with respect to TMS, higher values are associated with nuclei which are de-shielded due to decrease of electron density at the nucleus. If the electron density at a nucleus is increased, the relative shift decreases as the nucleus is shielded more strongly. Compute the NMR chemical shifts for benzene and nitrobenzene and rationalize the results using what you know about the nucleophilic aromatic substitution.

Exercise 3.5: Let's try to match the experimental NMR spectrum of methanol. Compute the NMR chemical shieldings of TMS and evaluate the relative shifts. How good do these match and what is the influence of the method and basis set? Note that you should use the same level of theory for the standard as for the molecule (how large would the deviation be if you did not do this ?). One important thing to note is that the agreement is often especially good for nuclei like ^{13}C – these are usually shielded from the solvent by their substituents and heavy enough such that zero point vibration does not significantly affect the shieldings. Note that this is not the case for hydrogen, so be careful in the assignment of hydrogen NMR shifts (see below).
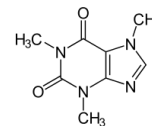
Exercise 3.6: Pick some examples from the table above and try to reproduce the chemical shifts from experiment. Note that some of the fluorine shifts can be especially difficult to compute, so be aware of your error bars when do actual applications!

4 Optimal benefit of error cancellation - using an internal standard

The internal standard is an "innocent" functional group like methyl for ^{1}H and ^{13}C. Referencing the NMR chemical shifts in the molecule to a functional group within the molecule
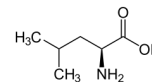
means overlaying the computed spectrum with the experimental one such that the internal standard shifts overlap. This way one does not need to compute a standard molecule and usually one can also benefit from error cancellation. Let's try this for a molecule that is a bit more complicated (spoiler alert! You can find the assignment of the structure to the chemical shifts on the last page).

Exercise 4.7: The alkaloid caffeine is a complex herterobicyclic molecule for which an assignment of the NMR shifts "by intuition" is not an easy task. Here are the experimental ^{13}C NMR chemical shifts in ppm : 155.3, 151.7, 148.7, 141.6, 107.5, 33.6, 29.7, 27.9. Try to assign the chemical shifts using TMS as a standard (overlay the data !) and using an internal standard. Think carefully about which atom to use as the internal standard and compare the results.

Exercise 4.8: Repeat the computation from the previous exercise using different functionals and basis sets in order to obtain the best agreement between experiment and theory.

Exercise 4.9: Caffeine is a rather complex molecule and the computational time can exceed the framework of the exercise. The amino acid Leucine is less complex. Complete the last two exercises on Leucine, here are the experimental ^{13}C NMR shifts relative to TMS in ppm: 173.8, 52.7, 40.0, 25.1, 22.7, 22.1.

5   Application - using nuclus independent chemical shifts (NICS) to investigate aromaticity

Aromaticity is a fundamental concept in chemistry and and much attention has been payed to its analysis in quantum chemistry. One possibility to gain insight into aromaticity is to sample the ring current effect in NMR close to the π-system. As this is not done by inspecting the chemical shielding of any of the atoms, this quantity is called Nucleus Independent Chemical Shielding (NICS). In Orca this is done by using a ghost atom (by adding ":" after the atom type), which, for technical reasons, needs to carry one basis function (by using "newgto"). A typical input for benzene looks like this:

```
! TightSCF NMR TPSS def2-tzvp def2/JK RI
! Grid7 GridX7

* gzmt 0 1
   H:                                newgto S 1 1 100000 1 end newauxJKgto S 1 1 200000 1 end
   H:  1   1                         newgto S 1 1 100000 1 end newauxJKgto S 1 1 200000 1 end
   C   1   1.39    2   90
   C   1   1.39    2   90  3   60
   C   1   1.39    2   90  4   60
   C   1   1.39    2   90  5   60
   C   1   1.39    2   90  3   -60
   C   1   1.39    2   90  6   60
   H   3   1.09    4   120 1   180
   H   4   1.09    3   120 1   180
   H   5   1.09    4   120 1   180
   H   6   1.09    5   120 1   180
   H   7   1.09    3   120 1   180
   H   8   1.09    7   120 1   180
*
```

Exercise 5.10: Compute the NICS for a series of benzyl systems with different substituents that increase or decrease the electron density in the π system and rationalize how the NICS change.

Exercise 5.11: Perform the same computations with thiophene, furan and cyclohexene and compare the results. If you don't know about it already, you might want to read up on the effect of ring currents in aromatic systems and their impact on NMR chemical shifts.

6 Solvent effects - using implicit solvent in the calculation of NMR chemical shifts

Orca offers the ability to compute NMR chemical shifts including implicit solvent models like CPCM. This means, that the wavefunction (or density) parameters are computed in the presence of a polarizable continuum that models the average influence of a given solvent with the molecule in question. While this works very well for weakly interacting solvents it has limitations for strongly interacting solvents that form compact solvation shells.
The input for a DFT calculations of the NMR shieldings including solvent looks like this:

```
! B3LYP RIJK def2-TZVPP def2/JK NMR CPCM(Toluene)

*xyzfile 0 1 acetone_b3lyp_toluene.xyz
```

Exercise 6.12: For acetone the gas-to liquid shifts have been measured. The experimental gas-to-aqueous solution shifts of the ^{17}O and ^{13}C NMR chemical shifts of the carbonyl chromophore in acetone are 75.5 and -18.9 ppm, respectively. (see Cossi, Crescenzi, O. J. Chem. Phys. 2003, 118, 8863 and Tiffon, Dubois, J. Org. Magn. Reson. 1978,11, 295.) Try to compute these values using DFT and implicit solvents using your functional of choice. Note that you should optimize the molecular structure including the implicit solvent first.

Exercise 6.13: Try to estimate which of the two effects is larger – the inclusion of the implicit solvent in the NMR calculation or the inclusion of the implicit solvent in the geometry

optimization. Hint: You will need six calculations for this.

7 Calculating NMR spin-spin coupling constants

In Orca, the different contributions to the spin-spin coupling constant can be computed using the eprnmr input block. While the constant has several contributions, let's focus on the Fermi contact term, as it is the dominating contribution for organic compounds. One of the most famous applications of spin-spin coupling constants is the Karplus curve, which relates the ^{3}J coupling constant in a HCCH arrangement to the dihedral angle of the atoms.

Exercise 7.14: The input files contain a relaxed scan of the dihedral angle in ethane. Compute the Fermi contact contribution to the ^{3}J coupling constant as a function of the dihedral angle. At 90 degrees it should be close to zero while it should go through a maximum of approximately 10 Hz around 0 (and 180) degrees. This has found extensive use in determining the conformation of the backbone of proteins.

8 Final notes

Spoiler alert! Here are the assignments of the NMR chemical shifts of caffeine and leucine in the order in which the shifts were given in the exercise :

Did you get them right ?