Instructions for using the new Excel file to compute the DP4+ probability

- In order to simplify the new DP4+ calculations, an Excel file is provided from the authors which can be downloaded from:

http://www.sarotti-NMR.weebly.com

http://www.iquir-conicet.gov.ar/Sarotti-NMR

- The file contains 7 sheets (Figure S1).
  - *Main:* contains the selection of the level of theory, and enabled cells to introduce the experimental and calculated NMR data.
  - *Unscaled*: shows the unscaled chemical shifts, computed according to $\delta_{calc} = \sigma_{TMS}-\sigma_x$
  - *Scaled*: shows the scaled chemical shifts, computed according to $\delta_s = (\delta_{calc} - b)/m$
  - *Unscaled Errors*: shows the unscaled errors, computed according to $e_u = \delta_{calc} - \delta_{exp}$
  - *Scaled Errors*: shows the scaled errors, computed according to $e_s = \delta_s - \delta_{exp}$
  - *Detailed Results*: shows the scaled, unscaled, and full DP4+ results (*s*DP4+, *u*DP4+, and DP4+, respectively).
  - *Parameters Estimation*: contains the experimental data of the 8 selected molecules shown in Figure 5, and enabled cells to introduce the calculated NMR shifts required to estimate the [μ,σ] terms.

The "Main" sheet

- The "Main" sheet contains the enabled cells to introduce the experimental and calculated NMR data, and provides the results of the DP4+ calculations. It is divided in 4 different regions: A, B, C, and D.

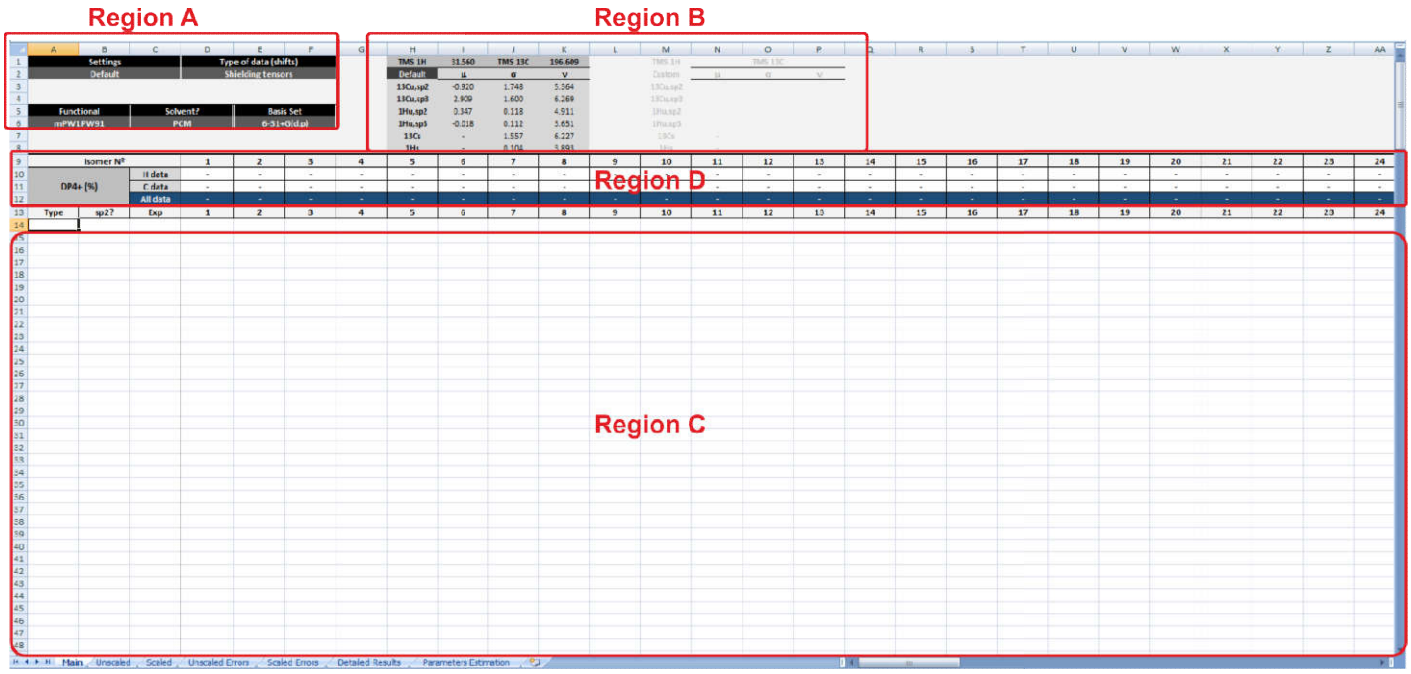


Figure S1

Region A: user selection (drop down lists):

- *Settings:* settings to be employed to compute the DP4+ probability (Default or Custom). The choice will be reflected in Region B.
  - "Default" option allows to use the [μ,σ,ν] terms calculated for a large set of 77 molecules at the 24 levels of theory evaluated in the original publication (JOC **2015**, *80*, 12526). If this option is selected, a new list is displayed with the following options:
    - *Functional:* functional used to perform the GIAO NMR calculations (B3LYP or mPW1PW91).
    - *Solvent?:* inclusion of solvent effect in the GIAO NMR calculations (PCM or Gas Phase).

- *Basis Set:* basis set used in the GIAO NMR calculations (6-31G*, 6-31G**, 6-31+G**, 6-311G*, 6-311G** or 6-311+G**).

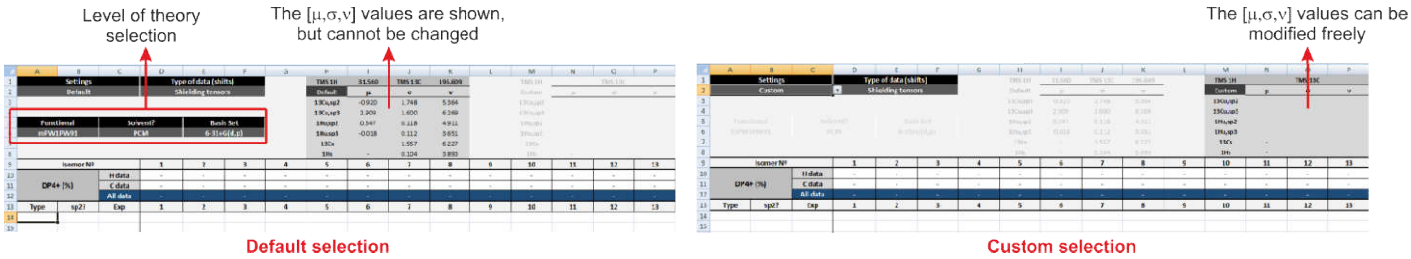
After the selection is done, the corresponding [μ,σ,ν] values and the isotropic shielding values for the reference standard (Tetramethylsilane, TMS) will be displayed in Region B.

- "Custom" option allows to set the values of the [μ,σ,ν] terms, which could be estimated in different ways. For example, using the full set of 77 molecules evaluated in the original publication at different levels of theory, using a large set of different molecules, or using the reduced set of 8 molecules shown in Figure 5 for preliminary calculations. If this option is selected, the 16 values of the [μ,σ,ν] set and the isotropic shielding values for the reference standard (TMS) should be provided in the enabled cells of Region B.

Region B: settings to compute the DP4+ probability

Contains the [μ,σ,ν] parameters required to perform DP4+ calculations. These values depend upon the level of theory employed during the calculations, and can be introduced in two different ways:

- If "Default" option is selected in Region A, the Default settings of the selected level of theory will be shown in Region B.
- If "Custom" option is selected in Region A, the Custom settings will be highlighted in Region B. These settings can be changed freely depending on the user preferences (for example, those obtained by using other levels of theory and/or a different set of test molecules). Warning: to obtain meaningful results, the modified parameters must be estimated at the desired level of theory using a large set of known compounds, or the recommended set of 8 molecules for preliminary calculations.



Region C: enabled cells to enter the data:

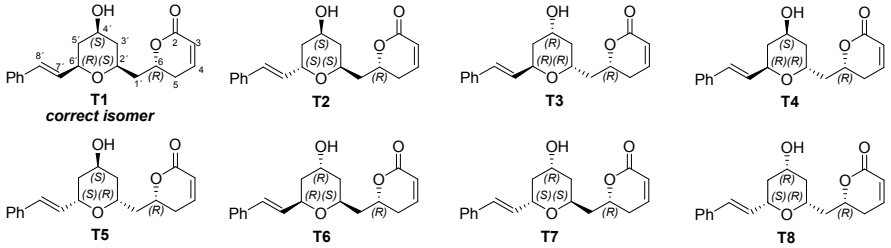
- *Nuclei:* enter the letter "C" (without quotes) for ^{13}C data or the letter "H" (without quotes) for ^{1}H data.
- *sp2?:* enter the letter "x" (without quotes) if the carbon is sp-sp^2 hybridized (or if the proton is attached to an sp-sp^2 hybridized carbon).
- *Experimental:* enter the experimental ^{13}C and/or ^{1}H chemical shifts.
- *Isomer 1, Isomer 2, etc:* enter the computed data for the candidate structures (either as isotropic shielding values, unscaled chemical shifts or scaled chemical shifts).

Region D: displays the DP4+ probabilities once the data are entered in Regions A, B and C.

Tutorial 1: DP4+ calculations using the "Default" option.

Calculated NMR data: compounds **T1-T8** at the PCM/mPW1PW91/6-31+G**//B3LYP/6-31G* level.

Experimental NMR data from compound **T1** (correct isomer). *Synthesis* **2019**, *51*, 1545.

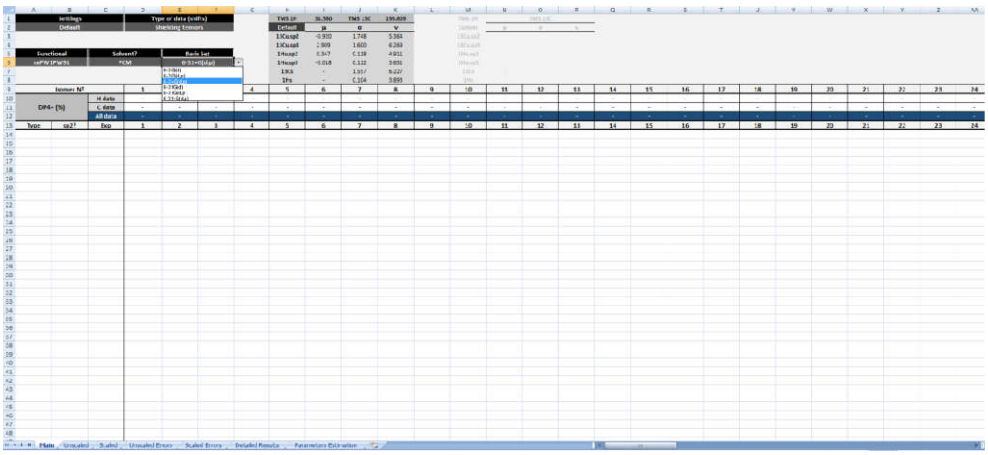


Step 1: perform a full conformational search using a suitable package (Hyperchem, Spartan, MacroModel, etc). It is recommended to keep all conformations within 5 kcal/mol (~21 kJ/mol) from the global minimum.

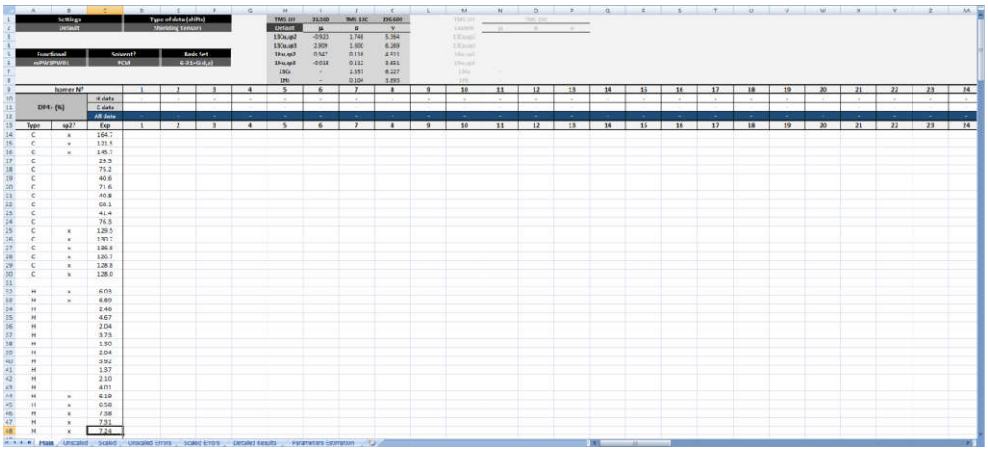
Step 2: optimize all conformations found at the B3LYP/6-31G* level (gas phase). Remove duplicates if necessary.

Step 3: perform the NMR GIAO calculations at the selected level of theory (in this case, at the PCM/mPW1PW91/6-31+G**) for all representative conformations. Compute the Boltzmann-averaged shielding values for each compound.

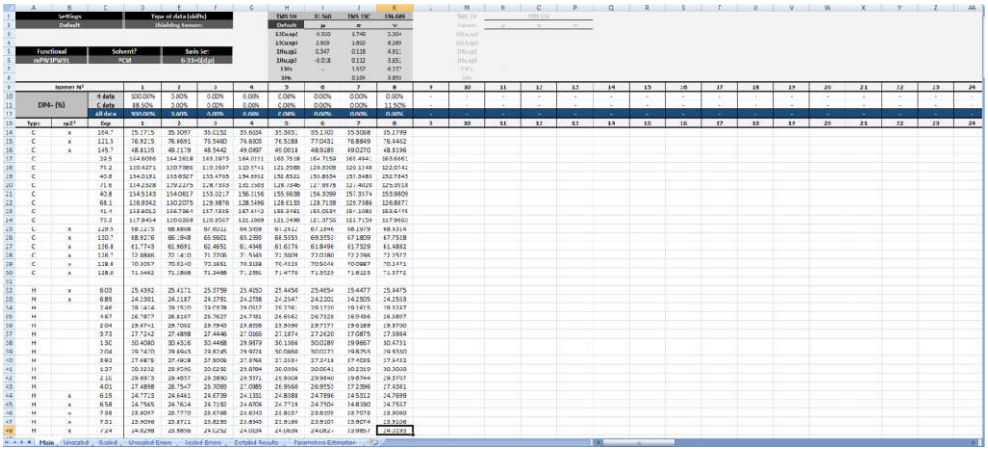
Step 4: open the Excel file, and select the "Default" and "Shielding tensors" options in Region A, and select the level of theory that was used to perform the NMR calculations. In this case, Functional > mPW1PW91; Solvent > PCM; Basis set > 6-31+G**.



Step 5: Introduce the experimental data. **Important: mark the sp^2 nuclei with "x". Otherwise, improper distributions will be used for those nuclei, with potentially negative effects in the DP4+ values.**

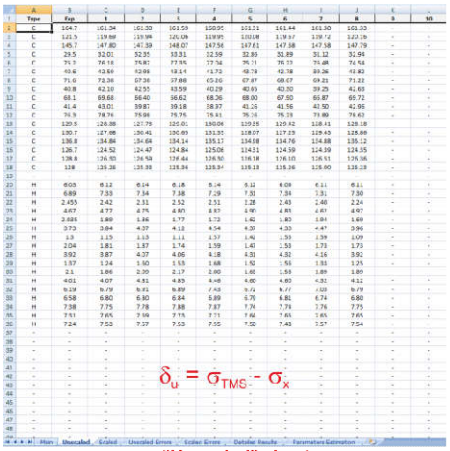


Step 6: Introduce the calculated averaged isotropic shielding values for each possible candidate structure (8 in this case). The data can be inserted manually or copy-pasted. The DP4+ values are automatically calculated and displayed for each isomer above the number of isomer. **Important: the NMR data must be assigned (know which shift corresponds to which nuclei). Using unassigned or misassigned NMR data might lead to erroneous results.**

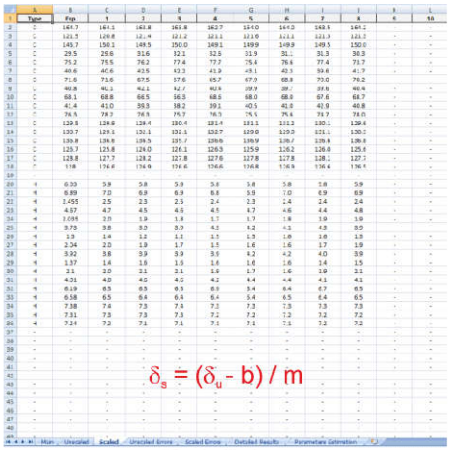


Warning: do not cut-paste information in this Excel file since it modifies the cell references for the hidden equations).

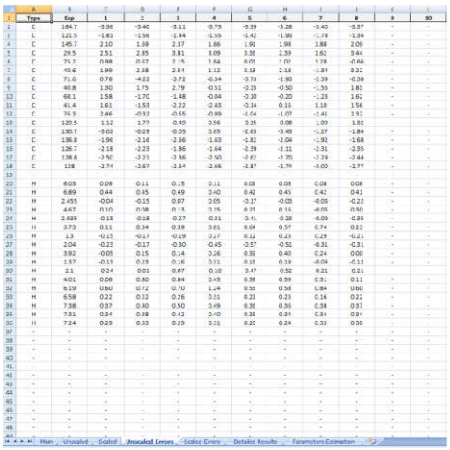
Once the Boltzmann-averaged isotropic shielding values are introduced, the calculated chemical shifts (both unscaled and scaled) are shown in the Unscaled and Scaled sheets, respectively. The corresponding errors can are shown as well in the Unscaled and Scaled errors sheets, respectively.



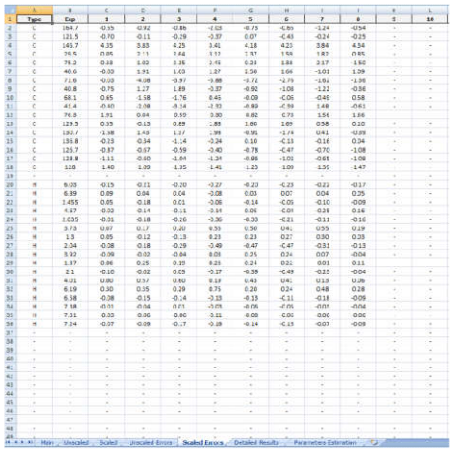
"Unscaled" sheet



"Scaled" sheet

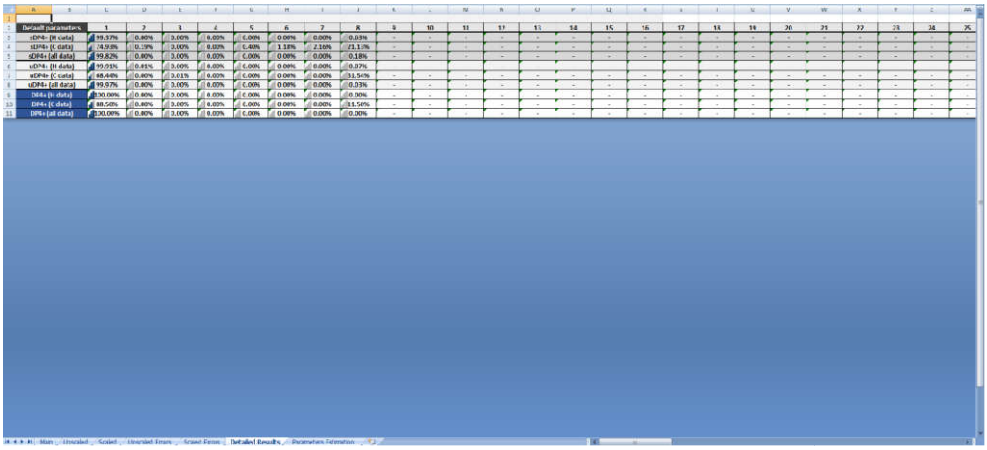


"Unscaled Errors" sheet



"Scaled Errors" sheet

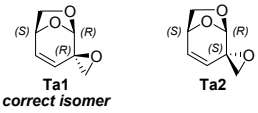
The probabilities computed using unscaled (*u*DP4+) and scaled (*s*DP4+), as well as using carbon and/or proton data, is shown in the sheet "Detailed Results"



Tutorial 2: DP4+ calculations using the "Custom" option.

Calculated NMR data: compounds **Ta1-Ta2** at the PCM/ωB97XD/6-311+G**//M06-2X/6-31+G** level.

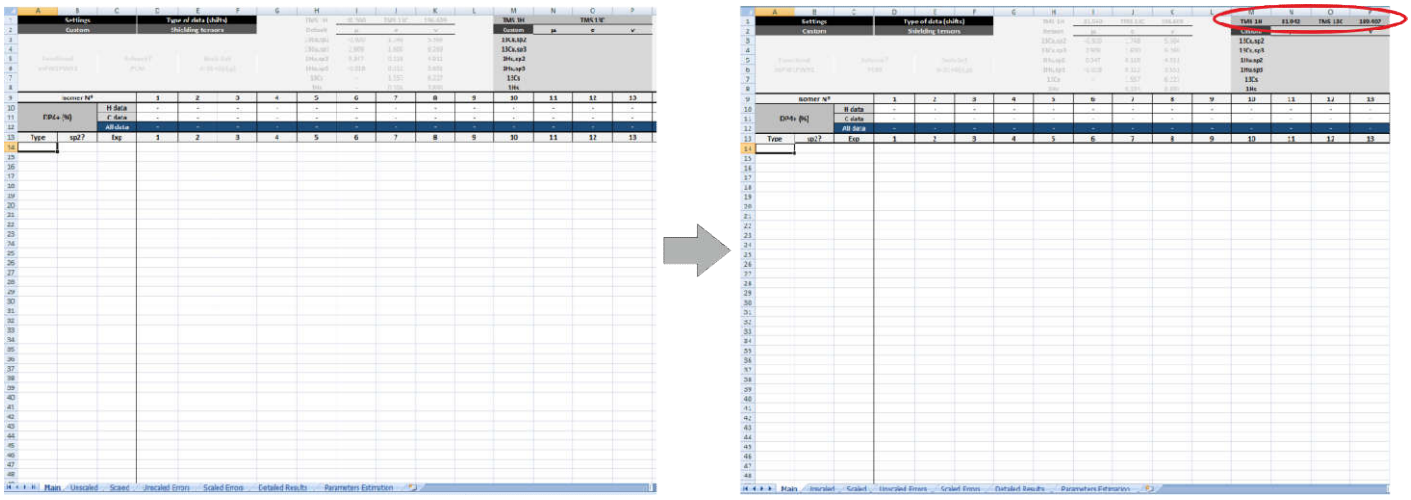
Experimental NMR data from compound **Ta1** (correct isomer). *JOC* **2015**, *80*, 12526



Step 1: The computational work should be done as described in the Tutorial 1, using the M06-2X/6-31+G** level for the geometry optimization step, and the PCM/ωB97XD/6-311+G** for the GIAO NMR calculation step.

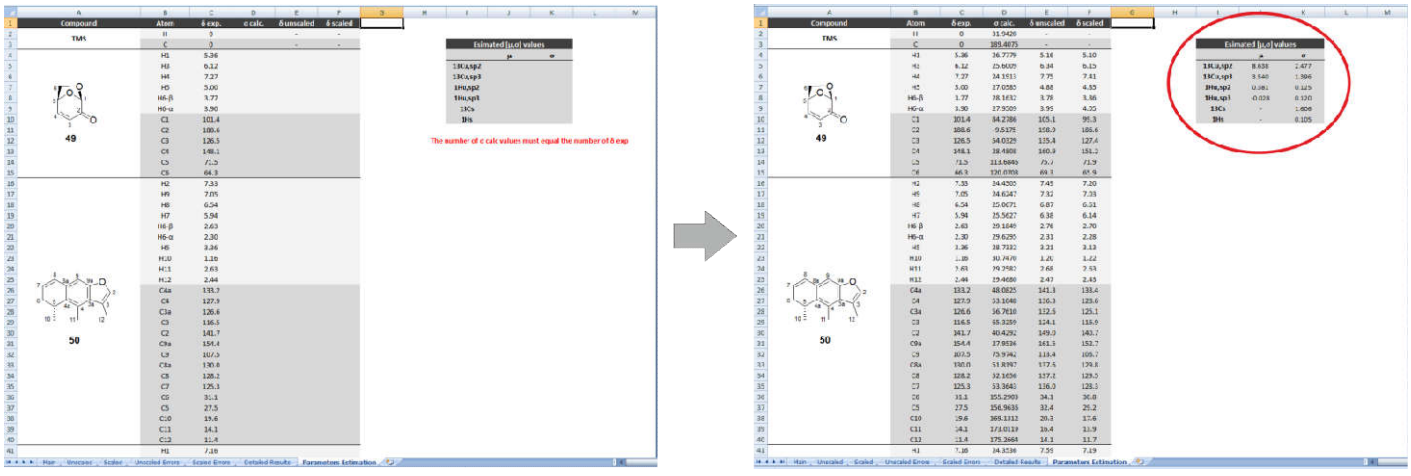
Step 2: open the Excel file, and select the "Custom" and "Shielding tensors" options in Region A. This will activate the edition of the [μ,σ,ν] values in Region B.

Step 3: compute the isotropic shielding values for the reference standard (TMS) at the same level of theory employed for the test compounds (PCM/ωB97XD/6-311+G**//M06-2X/6-31+G**), and introduce those values in the upper region of Region B.



Step 4: if the [μ,σ,ν] parameters have been previously estimated using a large set of molecules at the selected level of theory, fill the data in the lower part of Region B. If not, for preliminary calculations the values can be estimated with the 8 molecules shown in Figure 5. The NMR chemical shifts of compounds **49-56** must be computed at the PCM/ωB97XD/6-311+G**//M06-2X/6-31+G** level of theory, and the data must be filled in the "Parameters Estimation" sheet. Once all the σ_x values are introduced (along with the σ_0 values of TMS), the unscaled and scaled chemical shifts will be automatically computed, and the [μ,σ] values will be shown.

Important: the NMR data must be assigned (know which shift corresponds to which nuclei). It is essential to respect the assignment indicated in the Sheet. Using other assignments will lead to erroneous results.



Step 5: complete the Region B with these [μ,σ] values estimated in the previous step. Regarding the degrees of freedom (v), for preliminary estimations can be used the averaged values from the 24 levels of theory previously evaluated (see Table S14). Those values are: $v_{13Cu,sp2}$ = 8; $v_{13Cu,sp3}$ = 10; $v_{1Hu,sp2}$ = 8; $v_{1Hu,sp3}$ = 4; v_{13Cs} = 7; and v_{1Hs} = 4.

Step 6: complete the Region C with the experimental and calculated NMR data. The DP4+ values are shown in Region C.