

DP4+ App

<https://github.com/Sarotti-Lab/DP4plus-App>

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Instructive and general recommendations for MM-DP4+

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Overview and usage recommendations

The DP4+ App is a comprehensive software designed to perform parameterized DP4+ and MM-DP4+ calculations seamlessly. Additionally, it offers the capability to conduct Custom-DP4+ calculations, allowing users to parameterize any required level of theory. With its friendly graphical interface, users can easily manage multiple Gaussian calculations and automate information processing for probabilistic calculations.

To get started with the application, simply create a folder and ensure that it contains the following files:

- Well-labeled Gaussian output files: These files should include NMR calculations for all conformers of each isomeric candidate. Make sure to label them appropriately for easy identification.
- Excel file with experimental information: This file should contain the necessary experimental data along with the correlation labels for each nucleus corresponding to the Gaussian calculations.

By providing these files, the DP4+ App can efficiently process the information and perform the desired calculations.

To ensure optimal use of the program, it is recommended to follow the guidelines below:

- Minimize the number of candidates: While the DP4+ App can handle any number of isomers, keeping the candidate count to a minimum offers several advantages. It reduces both the overall computational cost and the risk of calculated data for an incorrect isomer yielding a better fit with experimental values compared to the correct candidate.
- Conduct a thorough conformational search: It is essential to obtain an accurate depiction of the conformational landscape of the system under study. Care should be taken to avoid improper computational work that could potentially affect the overall results. Systematic sampling is always

recommended, but in the case of highly flexible molecules, stochastic searches with a reasonably large number of steps should be carried out. All conformations within a safe energy window from the corresponding global minimum should be retained to avoid missing potentially significant conformations. For this application, it is advised to use a 5 to 10 kcal/mol cutoff value, employing the MMFF force field.

- Adhere to the suggested theory levels: It is important to use the recommended theory levels since DP4+ and MM-DP4+ were optimized for these levels. If the desired theory level is not parameterized, there is the option to parametrize the desired level by following the instructions provided in the Custom-DP4+ method.
- Ensure correct assignment of NMR data: The use of unassigned or misassigned NMR data can lead to erroneous results. When dealing with equivalent nuclei that undergo fast interconversion (e.g., methyl or some equivalent methylene groups), it is necessary to average the chemical shifts. Treating each proton signal independently, such as computing different chemical shifts for the same methyl group, is incorrect. Additionally, diastereotopic methylene protons often pose challenges with arbitrary correlation. Unless additional NMR information, such as NOE or J coupling, is available to discriminate between the pro-R and pro-S signals, the most suitable approach is to treat them as interchangeable signals. Detailed instructions are provided to assist you in addressing these issues effectively.

Probability calculations: DP4+, MM-DP4+ and Custom-DP4+

Prepare your files

To perform correlation calculations using the DP4+ App, it is necessary to prepare the required files. The program offers a range of controls to ensure precise data entry. The following guidelines should be followed to set up the files correctly:

The Excel file (.xlsx) should include the information on the "**shifts**" sheet. This sheet will be the only one read by the program and must adhere to the structure defined in Figure 1 (refer to Warnings and Input Control). Ensure that the column headers match accordingly. For isomers with the same labels, only three columns are required. However, if isomers use different labels, each candidate should have three labeling columns (label 1 | label 2 | label 3). The name of this document does not have any specific requirements as it will be selected individually.

The following columns are intended to place the correlation labels

if

All candidates with the same labels
Only 3 columns for all candidates

Candidates with different labels
3 columns for each candidates

	A	B	C	D	E	F	G	H	I	J	K
	index	nuclei	sp2	exp_data	exchange	label 1	label 2	label 3	label 1	label 2	label 3
1	1	C		73.7		7					
2	2	C		46.5		8					
3	3	C	1	175.5		9					
4	4	C		11.0		13					
5	5	C	1	141.5		4					
6	6	C	1	125.9		1	5				
7	7	C	1	128.1		2	3				
8	8	C	1	127.3		6					
9	9	C		60.5		11					
10	10	C		13.9		15					
11	11	H		5.09		21					
12	12	H		2.77		22					
13	13	H		1.12		26	27	28			
14	14	H	1	7.29		16	19				
15	15	H	1	7.29		17	18				
16	16	H	1	7.29		20					
17	17a	H		4.12	a	23	24				
18	17b	H		1.21	a	29	30	31			

Experimental index

sp2 nuclei must be indicated with character "1"

Interchangeable signals must be paired with letters

Sheet name: **shifts**

Figure 1. Excel sheet (experimental information and correlation labels)

NMR files have to be generated from calculations using the Gaussian software (.log or .out files) with the command line containing "#... nmr". Label these files according to the following convention, "n_m*_nmr.log", where :

- "n" represents the isomer ID,
- "m" denotes the conformer number, and
- "*" indicates a user annotation.

Figure 2. NMR Gaussian outputs

To specify your input files, utilize the designated buttons situated beneath the theoretical level selection panel. Each button will instantiate a navigation dialogue, facilitating the selection of your desired directories and files.

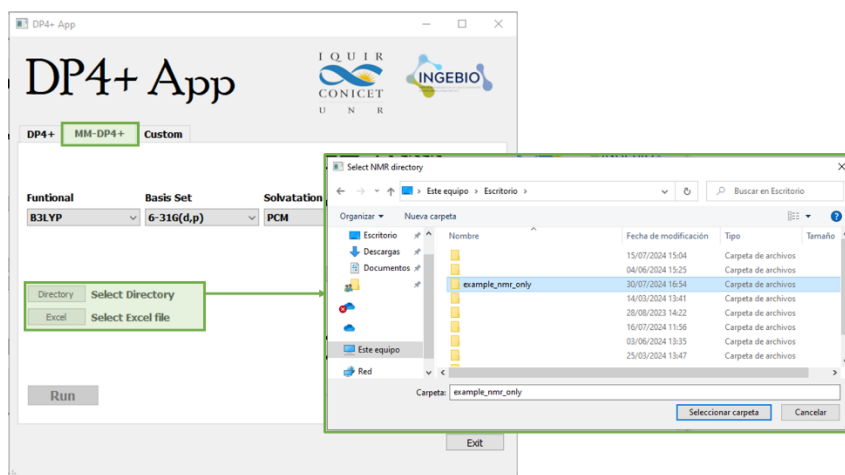


Figure 3. Folder and file selection in MM-DP4+ Tab

Perform MM-DP4+ calculation

With the DP4+ App, it is possible to determine the correlation probability using 60 pre-parameterized theory levels. These levels encompass a combination of different functionals, basis sets, and solvation modes. Out of the total, 36 levels were obtained through molecular mechanics using the MMFF force field.

MM mode theory levels combinations

Functional	Basis Set	Solvatation	Solvent (only for PCM)
B3L	6-31G(d,p)	GAS	CHCl ₃ , CH ₂ Cl ₂ , CCl ₄ , H ₂ O,
M06-2x	6-31+G(d,p)	PCM	MeOH, MeCN, DMSO, THF,
mPW1PW91	6-311+G(d,p)	SMD	Pyridine, Acetone, Benzene
wB97XD			

If a different solvent is needed, the 'Other' option can be used for entering H¹ and C¹³ TMS tensors (a popup window will allow you to enter the tensors).

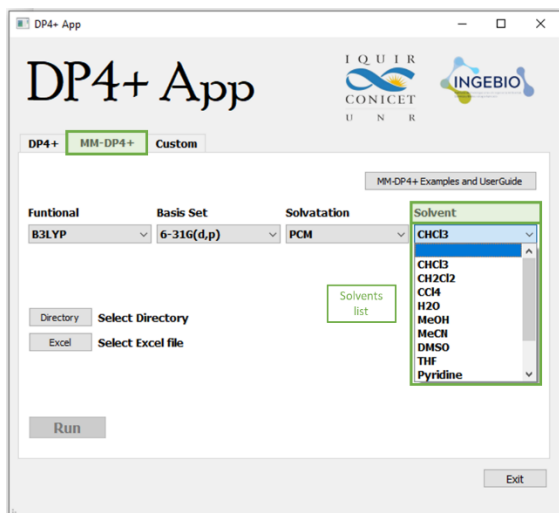


Figure 4. Solvent drop-down list

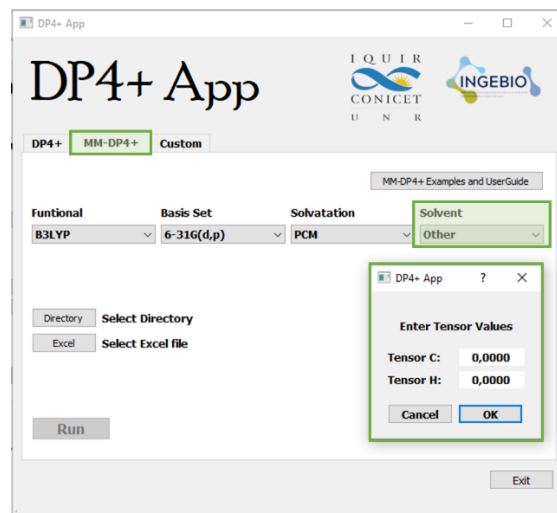


Figure 5. Pop-up window for "Other" option

Although calculations can be performed at any chosen level, the DP4+App optimizes usage by checking for consistency between the command lines in the Gaussian files and the selected theory level. When pressing the **Run** button if there is a discrepancy, a warning will be displayed, but the calculation can still proceed (see Figure 6).

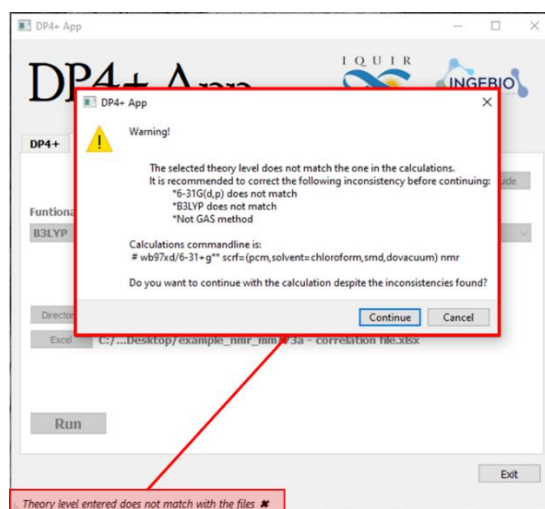


Figure 6. Example of miss matching theory level and command lines

For performing calculations at a theory level that is not mentioned, it is necessary to parameterize it first by following the instructions provided in the Custom mode (direct to the Custom tab and download the example).

Results output

After the completion of the calculation, a pop-up will confirm the successful execution, and the results will be presented in an Excel file located within the selected working folder, named *MM-DP4+plus_results*.

The Excel file will consist of:

- **Probability Results:** This sheet, labeled as "**results**," provides the probabilities of the candidates categorized by their nuclei, scaling, and the full version. It also displays the selected theory level, the command line used for the Gaussian calculations, and the automatic coincidence check.
- **Tensors:** Contains the Boltzmann-weighted tensors sorted according to the input labels.
- **Chemical Shifts:** Two sheets are dedicated to displaying the chemical shifts obtained from the calculations ("**d_sca**" and "**d_uns**").
- **Correlation Errors:** Similarly, two sheets are allocated for presenting the correlation errors ("**e_sca**" and "**e_uns**").

- **Parameters:** Reports distribution parameters and reference standard for correlation calculation.

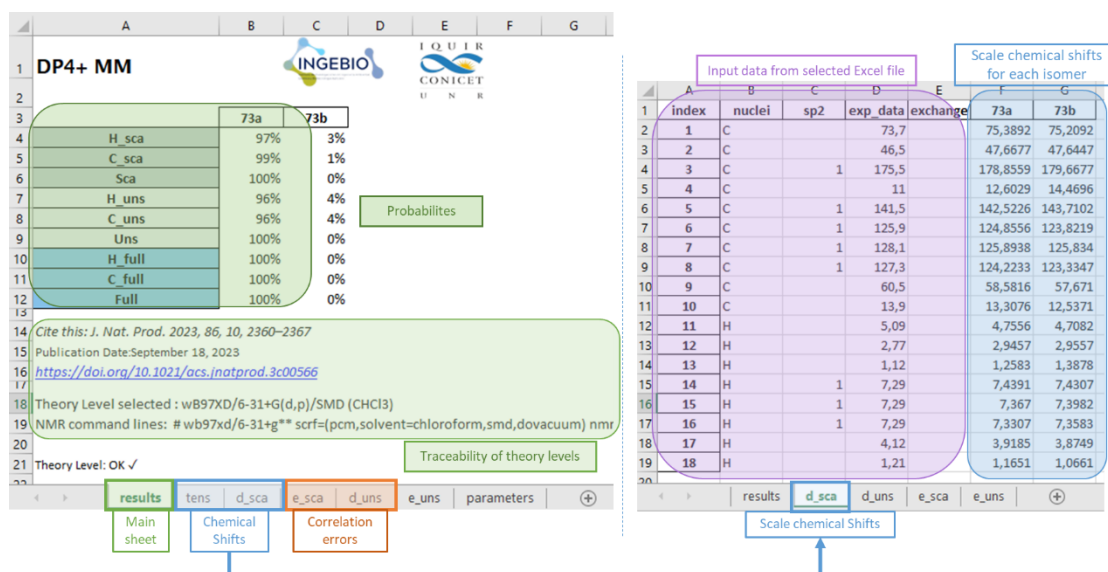


Figure 7. Output Excel file

In cases where the selected theory level does not align with the Gaussian calculation command line, a warning will be displayed, indicating any inconsistencies encountered (refer to Figure 8).

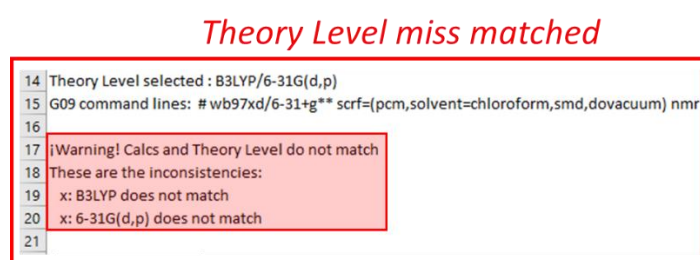


Figure 8. Examples of theory level miss selection

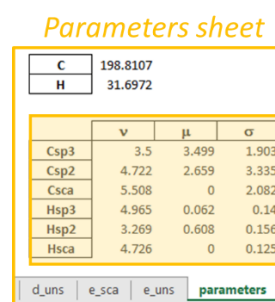


Figure 9. "Parameters" sheet view

HALO mode

HALO mode is an advanced feature of DP4+App designed to improve chemical shift predictions in halogenated molecules, particularly those containing chlorine (Cl) or bromine (Br). When such atoms are detected in the candidate structures, the program automatically prompts the user to choose between continuing with the standard DP4+ calculation or activating HALO mode. It is generally recommended to enable HALO under these conditions. Running both modes and comparing the outcomes can provide valuable insight into halogen-related effects.

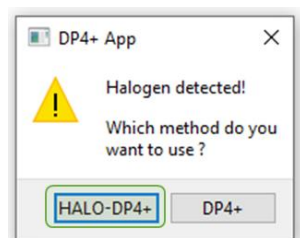


Figure 10. HALO decision pop-up

Once activated, HALO mode automatically identifies atoms directly bonded to halogens and adjusts their chemical shift referencing. Instead of using the conventional tetramethylsilane (TMS), these specific

nuclei are referenced against a set of calibrated multi-reference standards that better account for the local electronic influence of halogens.

The output reflects these adjustments. The “results” sheet includes an additional column labeled “halogen,” listing atoms affected by the correction. The “parameters” sheet provides both chemical shielding tensors and predicted shifts using TMS and the HALO reference, allowing for direct comparison.

	A	B	C	D	E	F	G	H
1	index	nuclei	sp2	exp_data	exchange	halogen	01	02
2	0	C		37.62		Cl	37.14111	37.24365
3	1	C	1	131.89			133.3838	132.2603
4	2	C	1	137.83			138.0245	137.3482
5	3	C		50.44		Cl	59.58443	50.26056
6	4	C		41.32			42.02208	41.66282
7	5	C		52.7		Br	50.86219	50.96821
8	6	C		41.36			43.99031	44.30445
9	7	C		69.98		Cl	60.88516	70.46705
10	8	C		20.47 a			19.5994	20.31483
11	9	C		28.53 a			26.64704	27.30997
12	10	H		4.04 b		Cl	4.084551	4.059182
13	11	H		4.18 b		Cl	4.167639	4.1776
14	12	H	1	5.95			6.043818	6.009501
15	13	H		4.97		Cl	4.672984	4.98616
16	14	H		2.53 c			2.43916	2.516492
17	15	H		2.68 c			2.51992	2.520318
18	16	H		4.83		Br	4.749598	4.784418
19	17	H		4.38		Cl	4.771834	4.393619
20	18	H		1.01 d			1.08724	1.096847
21	19	H		1.28 d			1.313255	1.305862

	A	B	C
1	mPW1PW	91.6-31+G	EXP
2	C Cl sp2	74.8367	117.42
3	C Cl sp3	142.6926	46.91
4	C Br sp2	77.4004	104.75
5	C Br sp3	152.2521	27.89
6	H Cl sp2	25.4042	5.59
7	H Cl sp3	28.10687	3.52
8	H Br sp2	25.213	6.16
9	H Br sp3	27.839	3.427
10	C	196.6095	
11	H	31.55999	

Figure 11. Examples results spreadsheet with “halogen” column and MSTD standards

Warnings and Input control

To enhance the user's understanding of anomalous results in DP4+ type calculations, DP4+App has implemented a comprehensive warning system. This system assists users in interpreting and identifying any unusual outcomes that may arise during the calculation process. Additionally, the application includes multiple checkpoints to validate the accuracy of data entry, ensuring reliable and consistent results.

Gaussian calculation files

DP4+App ensures the completeness of information from Gaussian calculation files by verifying the presence of the "Normal Termination" indicator in each file. If any file lacks this indicator, it will be automatically moved to a folder labeled "fail files" within the working folder.

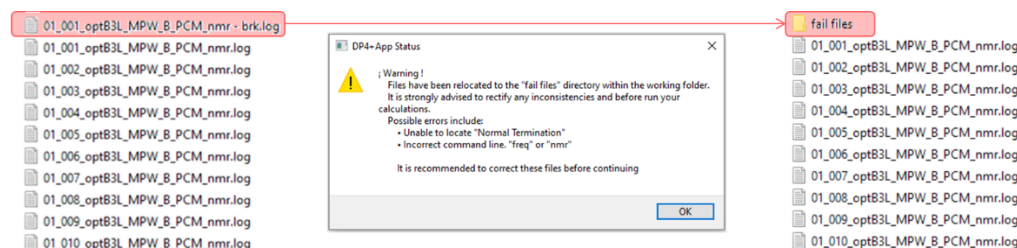


Figure 12. Example of a broken file (identified with brk) that is separated in fail folder

Data spreadsheet

The Excel spreadsheet provided for DP4+ App must follow a specific format, as illustrated in Figure 1. To ensure the accuracy of data entry, the program performs several checks on the spreadsheet:

- Column not found: Detects missing or incorrect column headers.
- Data not found: Identifies missing data in the 'nuclei', 'exp_data', or 'labels' columns.

- Incorrect data: Checks for valid data types in specific columns
 - For the 'nuclei' column, the data must be either 'C' or 'H'.
 - For the 'exp_data' column, the data must be a numerical value.
 - For the 'labels' column, the data must be an integer number.
 - For the 'sp2' column, the data must be 'X', 'x', or '1'.
- Mismatched diastereotopic labels: Notifies when diastereotopic labels are not paired correctly.
- Different number of candidate isomers and set of labels: Detects inconsistencies between the number of candidate isomers and the set of labels used.

If any of these situations occur, the program will be unable to proceed with the calculation. Therefore, the user needs to rectify any inconsistencies before proceeding further.

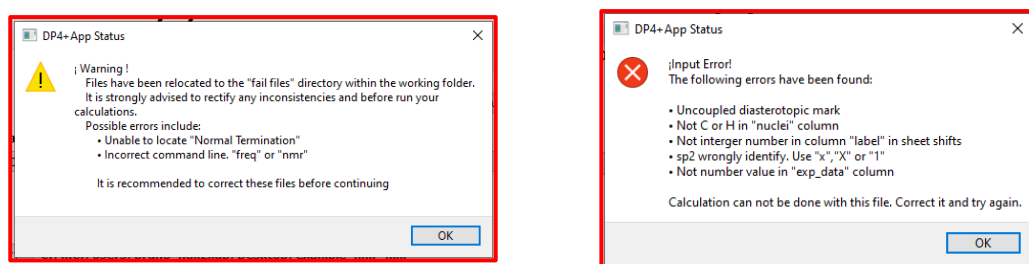


Figure 13. Examples of warning and input error

Calculation aborted

The software includes quality control checks that are initiated at the start of each calculation. Failure of these checks will result in the calculation being terminated and an error reported. Common causes for termination include:

- Inability to match a corresponding label (columns label 1 | label 2 | label 3).

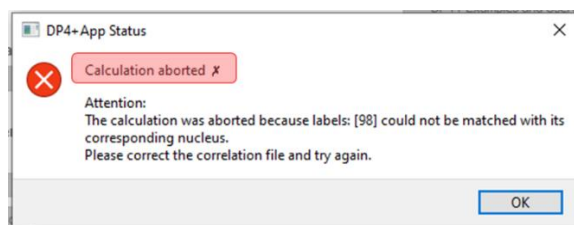


Figure 14. Example of aborted calculations

Questionable values

DP4+ App applies specific chemical criteria to validate the results of calculations. Any values that deviate from these criteria will trigger warnings to alert the user. The following conditions are considered questionable:

- $\sigma_H > 6\text{ppm}$ and $\sigma_C > 120\text{ppm}$, not marked as *sp2*
- $\sigma_H > 14\text{ppm}$, identified as ^{13}C
- $e_{\text{sca-H}} > 0.7$ and $e_{\text{sca-C}} > 10$, related to possible miscorrelation/missed assignment

While these warnings indicate potential issues, the calculations can still proceed. The highlighted cells will draw attention to the questionable values, allowing the user to evaluate their significance. If possible, it is recommended to experiment with different paths and interpret the results to make informed decisions.

For DP4+ type calculations, the warnings will be displayed on the **e_sca** sheet of the results.

	A	B	C	D	E	F	G	H
1	index	nuclei	sp2	exp_data	exchange	73a	73b	
2	1 C			73.7		-8.64583	-8.97892	
3	2 C			46.5		-14.5614	-14.7679	
4	3 C		1	175.5		13.15343	14.23648	
5	4 C			11		-20.9491	-18.9718	
6	5 C		1	141.5		3.750364	5.202798	
7	6 C			125.9		-1.75426	-2.99944	
8	7 C		1	128.1		-2.71407	-2.79137	
9	8 C		1	127.3		-3.90952	-4.98248	
10	9 C			60.5		-15.5238	-16.7685	
11	10 C			13.9		51.15417	50.82108	
12	11 H			5.09		-5.45829	-5.50291	
13	12 H			2.77		7.399502	7.581393	
14	13 H			1.12		-0.6099	-0.68703	
15	14 H		1	7.29		-8.33225	-8.39644	
16	15 H			7.29		-8.31415	-8.38816	
17	16 H		1	7.29		20.26961	20.40886	
18	17 H			4.12		-4.27804	-4.32062	
19	18 H			1.21		-0.67649	-0.69509	
20								

Figure 15. Example of deviant values for parametrization method

Malfunctions report

We strive to provide a reliable and efficient user experience with DP4+ App. However, if you encounter any malfunctions or issues while using the software, we appreciate your assistance in reporting them. By providing detailed information about the problem you encountered, you can contribute to the continuous improvement of DP4+ App.

Please report any faulty operations or unexpected behavior to the following email addresses:

- brunoafranco@uca.edu.ar
- zanardi@inv.rosario-conicet.gov.ar
- sarotti@iquir-conicet.gov.ar