

Conformational analysis, MC simulation, experimental and GIAO-DFT ^{13}C NMR Calculation on 2'-hydroxy-3,4,5-trimethoxy-chalcone

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INTRODUCTION

Chalcones (1,3-diaryl-2-propen-1-ones) (Fig. 1) are important intermediates for the synthesis of biologically active compounds such as flavonoids, isoflavonoids and their derivatives.¹ Due to their bio-physico-chemical properties, among which we highlight the antioxidant activity, the chalcones have been the focus of experimental and theoretical investigations.^{1,2} Their properties are related, among other factors, to its great conformational freedom, as well as to the several patterns of substitution of A and B rings.⁴

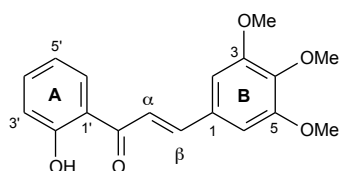


Figure 1. Structure of 2'-hydroxy-3,4,5-trimethoxy-chalcone molecule

The goal of this work is to investigate the ability of the scaling factor protocol at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory to predict the NMR ^{13}C chemical shifts (δ) of the 2'-hydroxy-3,4,5-trimethoxy-chalcone (chalcone) molecule. Moreover, it will be compared two different approaches for determining the chemical shift of the chalcone. In the first one (I), the absolute shieldings (σ) for all carbon atoms in each geometrically optimized conformers of the 2'-hydroxy-3,4,5-trimethoxy-chalcone molecule were calculated using the GIAO approximation at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) (NMR//optimization) level of theory, and further used to generate weighted average values for each atom considering the previously obtained conformational distribution, σ_{aver} . In

the second one (II), only the σ for the lowest energetic conformer was taken to account, σ_{lowe} .

METHODS

A randomized conformational search of the 2'-hydroxy-3,4,5-trimethoxy-chalcone molecule using the Monte Carlo (MC) method with a search limit of 200 structures, and employing the Merck molecular force field (MMFF) as implemented in the Spartan'08 software package⁵ considering an initial energy cutoff of 10 kcal.mol⁻¹ was performed. The conformation preferences of these molecules are ruled mainly by the formation of hydrogen bond interactions between the OH and C=O, see figure 2.

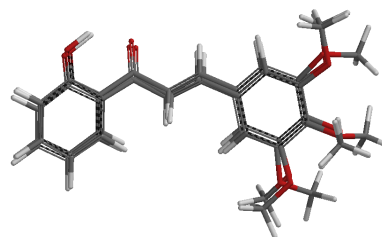


Figure 2. Superposition of the three lowest energy conformations of the chalcone molecule

In the approach (I), for each optimized conformer geometry, ^{13}C atomic chemical shielding tensors (σ) were computed at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory. Isotropic atomic chemical shifts (δ) in units of ppm were computed as differences between the atomic isotropic shielding of the solutes and corresponding reference atoms in tetramethylsilane (TMS). So, the Population-averaged chemical shifts for the selected conformers were computed assuming Boltzmann statistics, see equation 1, based on mPW1PW91/6-31G(d) free energies. Finally, the ^{13}C NMR chemical shifts were scaled according to Costa *et al*.⁷ Protocols.

$$\langle \delta \rangle = \frac{\sum_i \delta_i e^{-\Delta E_i / kT}}{\sum_i e^{-\Delta E_i / kT}} \quad (1)$$

In the approach (I), only the lowest-energetic conformer was used to obtain the scaled chemical shifts. The chalcone was obtained from Sigma Aldrich Chemical Co, ^{13}C NMR assignments are based on ^1H and ^1H - ^{13}C HSQC / HMBC spectra at 500 MHz and 125 MHz, using CDCl_3 .

RESULTS AND DISCUSSION

Our results are in very good agreement with empirical data. Indeed, ^{13}C chemical shifts calculated at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory reproduce the chalcone experimental data with small mean deviation (MD), see equation 2, and mean square deviation (MSD), see equation 3 error (see Table 1).

$$MD = \frac{\sum_{i=1}^n (\delta_{i\text{exp}} - \delta_{i\text{theor}})}{n} \quad (2)$$

where $\{\delta_{i\text{exp}}\}$ and $\{\delta_{i\text{theor}}\}$ are ^{13}C NMR experimental and theoretical (δ_{calc} and δ_{scal}) chemical shifts of the chalcone.

$$MSD = \sqrt{\frac{\sum_{i=1}^n (\delta_{i\text{exp}} - \delta_{i\text{theor}})^2}{n}} \quad (3)$$

Table I. Statistical data illustrating the performance of various methods for the GIAO calculation of ^{13}C NMR chemical shifts (δ , in ppm) for the chalcone

Level	MD MSD) ^a	MD (MSD) ^b
(I)	0.63 (1.80)	-1.43 (2.14)
(II)	-3.10 (3.45)	1.10 (1.81)

^aCalculated chemical shifts ($\delta_{\text{calc}} = \text{TMS} - \delta$) obtained by TMS subtraction; ^bScaled chemical shifts ($\delta_{\text{scal}} = 1.05\delta_{\text{calc}} - 1.22$) obtained by the generated universal scaling factors.

The main differences between experimental and scaled δ , level (I) and (II), were observed in carbons C4, OMe-3, OMe-4 and OMe-5. These differences are consistent with the 3 selected conformers (see fig. 2) to obtain the δ at the level (I). The reason is that they have different orientations of the OCH_3 group (atoms

C3, C4 and C5) with respect to the aromatic ring and the their δ are systematically dependent on the orientation of the methoxy group

Table II. Differences between scaled and experimental ^{13}C NMR chemical shifts (in ppm) in the chalcone relative to TMS.

Nuclei	Level (I)	Level (II)
C1	0.61	0.90
C2	1.00	0.50
C3	-0.77	-0.68
C4	-6.56	-1.12
C5	-1.45	-0.48
C6	1.00	0.50
α	-3.03	-3.57
β	3.72	3.75
C9	2.39	2.38
C1'	0.62	0.63
C2'	-2.52	-2.48
C3'	0.02	0.08
C4'	0.62	0.62
C5'	3.35	3.30
C6'	0.45	0.38
OMe-3	-2.86	1.89
OMe-4	6.71	1.96
OMe-5	-3.32	1.90

CONCLUSIONS

We investigated the ability of the scaling factor protocol at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory to predict the NMR ^{13}C δ of the 2'-hydroxy-3,4,5-trimethoxy-chalcone molecule. Although, the two approaches were able to reproduce the δ of the chalcone, significant differences in the calculated δ of the carbons C4, OMe3, OMe4 and OMe5 were observed. The best results were obtained at the level (II), where only the σ_{lowe} were taken to account to obtain in order to the

δ_{calc} . These findings suggest that, in this case, the level (II) is that best approach and that further analysis of the methoxychalcones is therefore justified.

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