

An improved method of ^{13}C NMR chemical shift by GIAO-DFT calculations in the study of a synthetic prenylated 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 flavonoid and isoflavonoid and their derivatives.¹ Due to their bio-physico-chemical properties, the chalcones have been the focus of experimental and theoretical investigations.^{1,2} The large numbers of publications concerning the synthesis and biological evaluation of chalcone and their derivatives have shown the increase of the interest in these compounds, and in their potential for medicinal applications.³

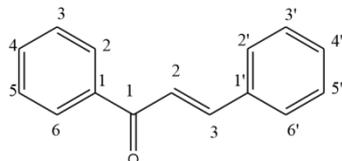


Figure 1. Structure of chalcone

In this work, we intend to investigate the ability of two different approaches in order to determine the ^{13}C NMR chemical shifts (δ) for the prenylated chalcone (PC) (2E)-1-(3,4-dimethoxyphenyl)-3-{3-methoxy-4-[(3-methylbut-2-en-1-yl)oxy]phenyl}prop-2-en-1-one, by use GIAO-DFT and GIAO-HF, to achieve a high cost-effectiveness ratio. In the first one, the calculated δ (δ_{cal}) will be scaled (δ_{scal} , where $\delta_{\text{scal}} = \delta_{\text{cal}} * 1.05 - 1.22$)⁴ at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory. In the second one, the δ_{cal} will not be scaled, the calculations will be performed using DFT methods (B3LYP, PBE1PBE, TPSS, M05-2X and M06-2X) and the HF method, all calculations will be performed using 6-311++G(d,p) basis set.⁵

METHODS

A randomized conformational search of the chalcone molecule **3** (fig. 1) 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 package⁶ considering an initial energy cutoff of 10 kcal.mol⁻¹ was performed. The lowest energetic conformer was selected to energy minimization calculations carried out at the mPW1PW91/6-31G(d) (fig. 2). Frequency calculations confirmed that the optimized geometries corresponds to a true minima on the potential-energy surfaces and delivered values of free energy at 298 K and 1 atm. ^{13}C atomic chemical shielding tensors (σ) and isotopic atomic δ were calculated from gauge including atomic orbitals (GIAO) theory with for same level theory and basis set used in the optimization molecular. Both in relation at the tetramethylsilane (TMS), these calculation were performed using the Gaussian 09 W software package.⁷

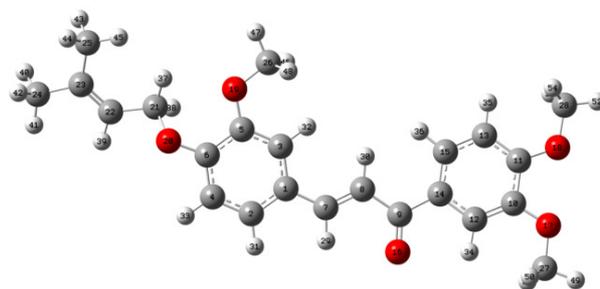


Figure 2 Optimized structure of PC at the mPW1PW91/6-31G(d) level of theory.

RESULTS AND DISCUSSION

The major differences between our geometry calculations results and those obtained by Espinoza-Hicks *et al.*,⁵ carried out at the M06-2X/6-311++G(d,p) level of theory, was noticed in the central zone, here described as a practically flat region with a maximal deviation from total planarity of 2.87°, while Espinoza-Hicks *et al.*⁵ point out 16°, approximately. Moreover, the methoxy groups at 18O and 17O are located in neighboring carbon atoms. Regarding the plane of the benzene A-ring, due to the steric hindrance, the methoxy groups are oriented at opposite sides, maintaining dihedral angle of 179.73° (176.46°, for Espinoza-Hicks *et al.* results)(10C–11C–18O–28C). For the other methoxy group, dihedral angle (11C–10C–17O–27C), we found -179.31° while Espinoza-Hicks *et al.* found -81.43°. In view of this difference in behavior, one would expect some discrepancy between the Espinoza-Hicks *et al.* calculated NMR ¹³C chemical shift for C12 and ours. Indeed, it was observed that our error was significantly smaller than the Espinoza-Hicks *et al.* error, 2.17 ppm and 10.32 ppm (for their the best result, see table 3), respectively.

The comparisons shown in Table 1 indicate that all DFT methods predict good results when these are compared to experimental values. It is important to point out that, after using the scaling factor our result at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory presents the smaller MAD (mean absolute deviation) and RMS (root mean square) errors, in despite of its less computational demanding. On the other hand, before using the scaling factor MAD and RMS errors were higher than those obtained at the GIAO-TPSS/6-11++G(d,p)//M06-2X/6-311++G(d,p) level of theory, which was the Espinoza-Hicks *et al.* best results. It shows how important is to apply scaling factors in order to improve the ¹³C NMR chemical shift calculations results, in spite of the use of small basis set as.

Table 1. Statistical data illustrating the performance of various methods for the GIAO calculation of ¹³C NMR chemical shifts (δ , in ppm) for the PC molecule.

Level	MAD	RMS
B3LYP/6-311++G(d,p)// M06-2X/6-311++G(d,p)	7.38	9.45
PBE1PBE/6-311++G(d,p)// M06-2X/6-311++G(d,p)	6.91	9.04
TPSS/6-311++G(d,p)// M06-2X/6-311++G(d,p)	4.44	5.92
M05-2X/6-311++G(d,p)// M06-2X/6-311++G(d,p)	19.35	22.35
M06-2X/6-311++G(d,p)// M06-2X/6-311++G(d,p)	17.28	20.23
HF/6-311++G(d,p)// M06-2X/6-311++G(d,p)	7.18	10.08
mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) (in this work)	3.97*	5.35*
	6.26**	7.47**

* from δ_{scal} , **from δ_{calc}

CONCLUSIONS

Despite the calculation approximations, such as a truncated basis set, as well as the non-considered effects, such as solvent and rovibrational effects, the chemical shifts calculated at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) using a simple relationship ($\delta_{\text{scal}} = 1.05 \delta_{\text{calc}} - 1.22$ where δ_{calc} and δ_{scal} are the calculated and the linearly scaled values of the ¹³C chemical shifts, respectively) were able to yield MAD and RMS errors as small as those obtained with all DFT methods using bigger basis sets, 6-311++G(d,p). A good agreement between the generated universal scaling factor and the simple linear regression (obtained by using the experimental and the calculated ¹³C NMR chemical shift) results was observed. Thus, its high cost-effectiveness ratio scaling factor, as well as its successful applicability to a real problem, was confirmed. In conclusion, mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) linear regression obtained by using the experimental and the calculated data, is a very attractive tool as an alternative to more



computationally demanding approaches, which are usually applied in order to achieve ^{13}C NMR chemical shift calculations.

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