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Protocol for Calculating ^{13}C NMR Chemical Shifts of Flexible Organic Molecules

Authors: Fabio Luiz Paranhos Costa,*[a] Thais Forest Giacomello,[a] Rênica Alves de Morais Rocha,[a] Mariana Aparecida de Souza Martins,[a] Antonio Maia de Jesus Chaves Neto,[b] Gunar Vingre Da Silva Mota[b]

Address: [a]Departament of Chemistry, Federal University of Goiás, REJ Jataí 75801-615, Brasil.

[b]Natural Science Faculty, Federal University of Pará, ICEN UFPA Belém 66075-110, Brasil

Abstract: In this work, we present a new scale factor protocol for calculating ^{13}C NMR chemical shifts (GIAO-mPW1PW91/3-21G//mPW1PW91/3-21G) of flexible organic molecules. Considering a set of 22 molecules with different behaviors (27 different chemical shifts), we were able to generate a universal GIAO-HDFT with a basis set consistent with 3-21G basis set and linear scaling factors using a "chemical shift – chemical shift" correlation approach. NMR chemical shifts were computed at the mPW1PW91/3-21G level using the GIAO method and are given relative to that of TMS calculated at the same level of theory. Thus a scale factor equation was generated $\delta_{scalc} = 1.1\ \delta_{calc} - 3.8$, where δ_{calc} and δ_{scal} are the calculated and the linearly scaled values of the ^{13}C chemical shifts, respectively). The robustness of the new protocol and its applicability to practical problems were evaluated by the calculation of the chemical shifts for a natural compound with synthesis, biological and therapeutic interest: (-)-loliolide ((7aR)-6-hydroxy-4,4,7a-trimethyl-6,7-dihydro-5H-1-benzofuran-2-one) (a rigid molecule), figure **1a** [1]. For flexible molecules, a conformational analysis protocol was created. For evaluated the accuracy of this protocol was selected 2',6'-dihydroxy-4',4-dimethoxydihydrochalcone molecule (a very flexible molecule), figure **1b** [2]. Thus, in order to select the most stable conformer of flexible molecules, will be applied Monte Carlo (MC) simulations. So, a randomized conformational search of the 2',6'-dihydroxy-4',4-dimethoxydihydrochalcone molecule using the MC method with a search limit of 200 structures, and employing the Merck molecular force field (MMFF), by means of 10,000 simulations, as implemented in the Spartan'08 software package [3], considering an initial energy cutoff of 10 kcal.mol^{-1} was performed. In the first step the 43 more significant conformations of 2',6'-dihydroxy-4',4-dimethoxydihydrochalcone molecule, accounting for more than 99.99% of the total Boltzmann population in the first 10 kcal.mol^{-1}, were saved. This was, followed by single-point energy calculations at the PM6 and level of theory. The 31 more significant conformations within the range of 0.0–3.0 kcal.mol^{-1}, were selected to energy minimization calculations carried out at the mPW1PW91/3-21G level of theory. The 13 more significant conformations within the range of 0.0–2.5 kcal.mol^{-1}. Frequency calculations carried out at the mPW1PW91/3-21G level of theory confirmed the

optimized geometries to be local minima and delivered values of free energy at 298 K and 1 atm. In the last step the 7 more significant conformations within the range of 0.0–2.0 kcal.mol^{-1} were selected. Finally the lowest-energetic conformer was used to obtain the scaled chemical shifts. All HDFT calculations were carried out using Gaussian09 software [4]. In the calculations, no solvents effects were considered.

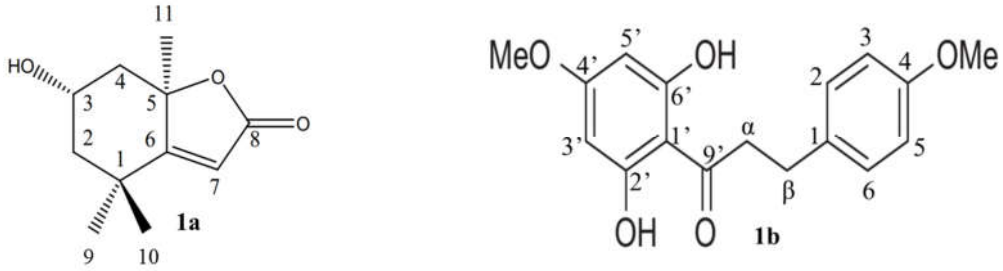

Figure 1. (-)-loliolide (**1a**) and 2',6'-dihydroxy-4',4-dimethoxydihydrochalcone (**1b**) structures.

In order to achieve widespread application of a scaling factor to GIAO-HDFT ^{13}C chemical shifts, it is desirable to combine excellent accuracy of MAD (mean absolute deviation) and RMS (root mean square). The data comparison demonstrated a great agreement between experimental and calculated NMR chemical shifts. For loliolide molecule MAD and RMS before (after), in ppm, application of the scale factor are: 5.71 (1.59) and 9.34 (1.81). For 2',6'-dihydroxy-4',4-dimethoxydihydrochalcone molecule MAD and RMS before (after) application of the scale factor are: 9.65 (1.30) and 11.02 (1.67). It means that using the equation 1 it was possible to cancel the systematic errors, even using modest basis set. In conclusion, GIAO-mPW1PW91/3-21G// mPW1PW91/3-21G linear regression obtained by using the experimental and the calculated data with the conformational analysis protocol, 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.

Key-words: GIAO-mPW1PW91/3-21G//mPW1PW91/3-21G, flexible molecules, NMR
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