A ^{13}C CHEMICAL SHIFT STATION FACTOR FOR POLYPHENOLS WITH REPLACED CHALCONES

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Key-words: GIAO-mPW1PW91/6-31G*/mPW1PW91/6-31G*, NMR, polyphenols, chalcones.

Several of the biologically active phytochemicals, such as phenolics, have been isolated and used against various health complications (Mahomoodally et al. 2018). One of the most powerful experimental techniques for obtaining three dimensional structures of complex molecules is Nuclear magnetic resonance (NMR) spectroscopy (Costa et al. 2010). In this work it was intended to create a ^{13}C NMR chemical shift (δ) protocol of polyphenols based on the application of scaling factor with chalcone molecules. This factor was obtained from a linear regression between experimental δ versus those calculated (Costa et al. 2010; Lodewyk, Siebert, and Tantillo 2012; Paranhos Costa et al. 2015) for a set of 20 selected chalcones. They were selected in order to guarantee a significant structural variety, covering several functional groups and complex structural frameworks. Thus, it was possible to guarantee that the protocol can be applied to any molecule of the polyphenol class. The δ calculations were computed at the mPW1PW91/6-21G(d) level of theory, using GIAO method and were obtained in relation to the δ of the calculated TMS at the same level of theory (Cimino et al. 2004). Due to their great conformational flexibility, the set of 20 chalcones, were submitted to randomized conformational searches using Monte Carlo method and MMFF force field. For complete conformational analysis and the conformers selection protocol see Giacomello *et al.* (Giacomello et al. 2017). All quantum mechanical calculations were performed in gas phase, using Gaussian 09 software package (Frisch MJ, Trucks GW, n.d.). Afterwards, in order to analyze the linear correlation between calculated and experimental δ , statistical analyzes of the results were performed. Thus, slope and intercept values obtained from this linear regression can be used to generate scaled δ (δ_{scal}), using the expression $\delta_{\text{scal}} = a \cdot \delta_{\text{calc}} \pm b$ (1). Thus, using a set of 20 chalcones the following equation was generated: $\delta_{\text{scal}} = 1.06 \cdot \delta_{\text{calc}} - 2.56$, $r^2 = 0.987$. For the chalcone set, the Mean Absolute Deviation (MAD) and the Root Mean Square Deviation (RMSD), in ppm, before and after (in parenthesis) the application of the equation (1) are: MAD = 4.31 (1.92) and RMS = 5.15 (2.54).

Figure 1. Structural representations of chalcones used for parametrization of the scaling factor obtained from calculated ^{13}C NMR δ .

Finally, the robustness of the new protocol and its applicability to others polyphenols class were evaluated by the calculation of the δ for 2 natural compounds with synthesis, biological and therapeutic interest: 2',6'-dihydroxy-4,4'-dimethoxy-dihydrochalcone (**I**) and 2-[3-(1,3-benzodioxol-5-yl) propyl]-5-methoxyphenol (**II**). For

these molecules the MAD and the RMSD, in ppm, before and after (in parenthesis) the application of the equation (1) are: **(I)** MAD = 4.66 (0.96); RMS = 5.21 (1.40) and **(II)** MAD = 4.94 (1.67); RMS = 5.44 (2.29). With the above, it can be concluded that GIAO-mPW1PW91/6-31G(d) level of theory, applied for gas-phase (any solvents effects were taken into account) calculations, together with the use of the scaling factor represented by the linear equation is an efficient and cost-effective tool for calculating ^{13}C NMR δ of polyphenols class, such as I and II.

Support: The authors are grateful to CNPq and FAPEG for scholarship and financial.

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