NMR ^{13}C CHEMICAL SHIFT FOR EFAVIRENZ

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The human immunodeficiency virus (HIV) infection, especially in low- and middle-income countries, is still considered a very important public health problem (Apostolova et al. 2017). The decrease in morbidity and mortality has been associated with an antiretroviral combination (Demir et al. 2018). Widely used in combination with other antiretrovirals for the treatment of HIV, efavirenz is a non-nucleoside reverse transcriptase inhibitor (Huang et al. 2017). The polymorphism, target of many studies, extensively observed in pharmaceutical applications, occurs when molecules adopt one packing arrangement and/or conformation in the crystal lattice (Riekes et al. 2012). 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). The synergism between experimental techniques and theoretical models is an important tool for structural determination. In this work our aim is to evaluate the ability of our protocol for calculations of ^{13}C NMR chemical shifts (δ) (Skachkov et al. 2010) to reproduce the experimental data obtained in solid state NMR (SSNMR) for form I of the efavirenz molecule, figure 1.

Figure 1. Structural representations of efavirenz.

Thus the calculated ^{13}C NMR δ of the efavirenz were obtained at the GIAO-mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory. The δ are obtained as $\delta_{\text{calc}} = \sigma_{\text{TMS}} - \sigma$, where σ_{TMS} is the isotropic shielding constant of the reference compound, tetramethylsilane (TMS), calculate at the same level of theory. The scaled δ (δ_{scal}) were obtained u the equation: $\delta_{\text{scal}} = 1.05 \cdot \delta_{\text{calc}} - 1.22$ (1) (Luiz Paranhos Costa et al. 2014). Afterwards, in order to analyze between the scaled and experimental chemical shift, statistical analyzes of the results were performed. This is translated into satisfactory MAD and RMSD values for the molecule used in the parameterization of the calculation protocol (Fukui 1997). For efavirenz molecule MAD and RMSD before (after), in ppm, application of the scale factor are: 6.00 (3.64) and 7.62 (4.82). Although GIAO method doesn't root in the plane wave pseudopotential formalism of the density functional theory (DFT) as GIPAW (gauge including projected augmented wave) (Pickard and Mauri 2001), it was possible to observe that the level of theory applied in this work led to a good

reproduction of SSNMR experimental chemical shift (Fandaruff et al. 2014). Thus, we can deduce that the use of a scaling factor, made from linear equation 1 (calculated x experimental) at the GIAO-mPW1PW91/6-31G(d) level for theory could be an efficient and low cost tool to minimize errors in the reproduction of ^{13}C SSNMR chemical shifts.

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