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Evaluation of some density functional methods for the estimation of hydrogen and carbon chemical shifts of phosphoramidates

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ABSTRACT

^{1}H and ^{13}C NMR chemical shifts were measured for three phosphoramidates and computed using the B3LYP, WP04, TPSSh, M06-2X and wB97X-D density functionals. The experimental and computed chemical shifts for hydrogen and carbon were compared using linear correlation (R^2), mean absolute error (MAE), root mean squared deviation (RMSD) and DP4 analysis. Applying a linear correction to the computed data improves the absolute accuracy and reduces random errors. For ^{13}C NMR shift data, results from the GIAO/wB97X-D/cc-pVTZ/SCRF combination show the lowest value of RMSD (2.073). For ^{1}H NMR shift data, CSGT/TPSSh/cc-pVTZ/SCRF shows RMSD of 0.070. The method that best applies to this class of compounds is CSGT/wB97X-D/cc-pVTZ/SCRF. DP4 analysis was used to correlate the chemical shifts (^{1}H and ^{13}C NMR) of the compounds and indicated that the method that best applies to this class of compounds is CSGT/wB97X-D/cc-pVTZ/SCRF, with DP4 analysis of 51.9%. In general, the best results were obtained when using implicit solvation model during calculations. The best method was applied on an external test set of 6 additional molecules and provided satisfactory results.

1. Introduction

The organophosphorus compounds form a class of compounds having at least one phosphorus atom connected to a carbon atom in their structure, which find wide application in several fields. Amongst these, one of the most common classes includes phosphoramidates, which incorporate one amide functional group derived from the phosphoric acid. It has been found that these compounds have particular importance due to their expressive biological activities. They are used in medicine due to their potential applications as anticancer [1–6], anti-HIV [7,8], inhibitors of hepatitis C virus [9–11] and antimalarial agents [12]. Within agriculture they are reported as urease inhibitors [13], herbicides [14] and insecticides [15,16]. In industry they find application both as antifire [17] and antirust additives in lubricating oils [18]. We recently published a review highlighting the main phosphoramidates with potential biological activity and applications within the medicinal area [19].

Continuing our work on the search for new compounds with insecticidal [15,16] and phytotoxic activities [20–24], a series of phosphoramidates were synthesized. In the last series of compounds, the urease inhibitory activity was evaluated [25].

It is widely believed that the biological activity of the phosphoramidates is correlated with their molecular properties [26,27]. Most studies focus on their crystal structures, DFT quantum chemical calculations and NMR measurements [28–30]. Whilst the application of NMR techniques to determine the relative spatial orientation of substituents has become a routine task, examples of structural and stereochemical misassignments still appear in the literature [31].

The accurate calculation of NMR chemical shifts with quantum chemical methods has provided an additional tool to supplement or in some cases even replace NMR assignments. In a recent work, we have characterized phosphoramidates using quantum chemical calculations coupled to both dynamic NMR studies and single crystal X-ray diffraction data [30].

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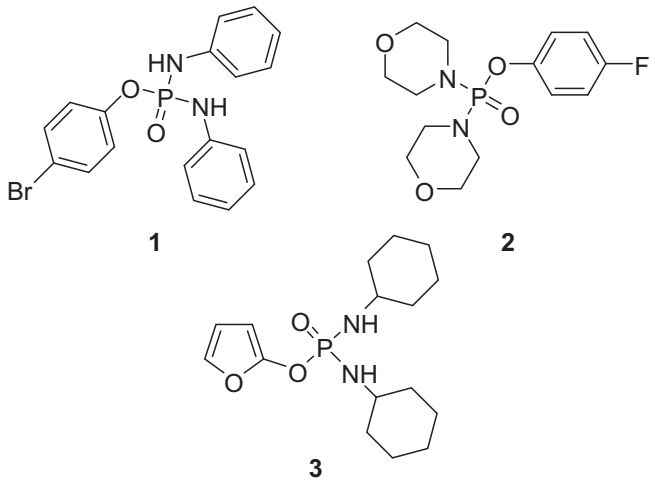

Fig. 1. Phosphoramidate **1–3** studied in the present work.

Advanced computational protocols have been developed for calculation of NMR chemical shifts, mainly ^{1}H and ^{13}C, as well as coupling constants of isolated molecules [32]. The theoretical task lies in calculating the molecular second-order magnetic response properties, in which the calculation of the nuclear magnetic shielding tensor plays a relevant role [32]. It is generally accepted that the calculation of these properties requires gauge-invariant procedures. Therefore, some theoretical methods have been proposed, in which the most commonly used approaches are: the GIAO (Gauge Including Atomic Orbital) and the CSGT (Continuous Set of Gauge Transformation) methods, which compute the current density induced by the magnetic fields by performing a gauge transformation at every point in space [33].

Geometry optimization is often the most time consuming step in determining the chemical shifts for the DFT and *ab initio* level calculations, particularly when several conformations are accessible in the conformational space. CPU time is particularly important in conformationally flexible molecules in which an extensive conformational search is necessary to determine the relative contribution of each conformer [33,35]. Therefore much effort has been paid to identify computational methods that afford good geometries for further high quality NMR predictions at minimal computational cost [34,36,37].

In the present contribution we evaluated the quality of a variety of functionals in an attempt to identify the best one for computation of NMR chemical shifts of the flexible phosphoramidates **1–3** (Fig. 1), taking into account the contributions of the most relevant conformers.

2. Experimental section

2.1. NMR studies

One dimensional ^{1}H and ^{13}C NMR spectra were acquired for phosphoramidates **1–3** (Fig. 1) with a MERCURY-300/Varian spectrometer at 300.069 MHz for ^{1}H (32 k data points, 30° excitation, pulse duration of 2.2 μs, spectral width of 6 kHz, acquisition time of 3.3 s and relaxation delay of 10 ms) and at 75.452 MHz for ^{13}C (32 k data points, 45° excitation, pulse duration of 6.5 μs, spectral width of 19 kHz, acquisition time of 0.8 s and relaxation delay of 2.0 s) in 5 mm probes with direct detection, using deuterated chloroform as solvent and tetramethylsilane (TMS) as internal standard (δ = 0.00). The data calculated and experimental chemical shifts are in Supporting Information.

2.2. DFT studies

The geometries of the phosphoramidates **1–3** were first designed in the SPARTAN'10 software [38]. Using the conformer distribution routine of SPARTAN'10 and the semi-empirical PM6 method [39] a conformational analysis was carried out to identify the most stable conformers for each derivative. Those conformers were then fully optimized in vacuum using the Becke three parameter hybrid functional combined with the Lee, Yang, and Parr correlation functional (B3LYP) [40] and the 6-31g(d,p) basis set [41]. Vibrational frequencies were computed for all of the optimized geometries to ascertain the nature of their stationary points on the potential energy surface. Only those geometries which were confirmed as a minimum on the potential energy surface were further employed to compute the NMR parameters.

NMR chemical shifts were computed with the B3LYP [40], WP04 [42], TPSSh [43], M06-2X [44] and wB97X-D [45] functionals and the 6-31g(d,p), 6-311++g(2d,p) and cc-pVTZ basis sets. The rationale behind the selection of these functionals was to include the most frequently used hybrid functional (B3LYP), two new hybrid meta-GGA functionals (TPSSh and M06-2X) and one long-range-corrected hybrid including dispersion corrections (wB97X-D). The empirically optimized hybrid GGA WP04 functional was also selected to evaluate its performance in the computation of the ^{1}H and ^{13}C of the phosphoramidates.

For comparison, the chemical shifts were calculated in the gas phase and including solvent effects by means of the continuum Solvent Model based on Density (SMD) approach [46], using chloroform as solvent. The Continuous Set of Gauge Transformations (CSGT) and Gauge-Including Atomic Orbitals (GIAO) methods were employed for computation of NMR shielding tensors. The signal of TMS calculated at the same level of theory was used as reference.

All the DFT calculations were performed using the Gaussian 09 program package [47].

Averaged chemical shifts for each isomer were obtained by means of Boltzmann weighted shifts averaged over the set of conformers, calculated by first averaging the chemical shifts of degenerate symmetry related carbon environments within each conformer (see Supporting Information). With this, each conformer contributes a percentage of its chemical shift value to the final total chemical shift, depending on its Boltzmann weighted population at 298 K:

$$\sigma^{x} = \frac{\sum_i \sigma_i^{x} \exp\left(-\frac{G_i}{RT}\right)}{\sum_i \exp\left(-\frac{G_i}{RT}\right)}$$

Here, σ^{x} is the weighted average shielding tensor of the atom(s), σ_i^{x} is the shielding constant for nucleus x in conformer i, R is the molar gas constant (8.3145 J K^{-1} mol^{-1}), T is the absolute temperature (298 K), and G_i is the Gibbs free energy of the associated conformer. Finally, TMS was optimized in a symmetry restricted (tetrahedral) geometry and the NMR shielding tensors for all atoms (carbons and hydrogens) were obtained at the same level. All final shifts were then calculated as $\sigma_{TMS} - \sigma_{calc}$. Data were scaled according to equation below:

$$\delta_{scaled} = \frac{\delta_{calc} - \text{intercept}}{\text{slope}}$$

Here, δ_{scaled} is the scaled chemical shift (ppm), δ_{calc} is the corresponding unscaled calculated chemical shift (ppm) and the intercept and slope are the parameters of a linear regression when plotting the experimental shifts against the calculated shifts for a given compound (see Supporting Information). The chemical shift of the carbon atom directly attached to the bromine atom in