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Computational protocol for predicting the Nitrogen-15 NMR chemical shift in Pt(II) complexes using the NMR-DKH and NMR-ZORA basis sets

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Cancer presents a significant global health challenge, with approximately half of all chemotherapy treatments incorporating platinum complexes. However, Pt-based drugs can cause various side effects, including neurotoxicity and nephrotoxicity. Therefore, it is crucial to explore new compounds that offer improved effectiveness and fewer side effects[1]. Nuclear magnetic resonance (NMR) spectroscopy is essential for characterizing and investigating the reaction mechanisms of potential new Pt-based anticancer drugs[2,3]. In present study, a computational protocol for predicting the N-15 NMR chemical shift ($\delta^{15}N$) in Pt(II) complexes using the NMR-DKH and NMR-ZORA basis sets was proposed. Initially, a set of eight Pt(II) complexes were selected and their structures were optimized at the B3LYP/LANL2DZ/def2-SVP/IEF-PCM(UFF) level – Gaussian 16 Rev. C.01 program. The influence of the DFT functionals (23 functionals) and relativistic effects in predicting the $\delta^{15}N$ was assessed. Nonrelativistic (NR) and *quasi* relativistic (ZORA) Hamiltonians were employed in the prediction of the NMR shielding constant (σ) considering the protocols: NR: GIAO-DFT-Functional/NMR-DKH/IEF-PCM(UFF) – Gaussian 16 Rev. C.01, and ZORA: GIAO-DFT-Functional-SC-ZORA/NMR-ZORA/CPCM – ORCA 5.0.4. Regression linear models considering the $\sigma^{15}N_{calc}$ x $\delta^{15}N_{expt}$ were constructed for predicting the $\delta^{15}N$. The calculated results showed that the DFT functionals significantly influence the computational description of $\delta^{15}N$. However, the inclusion of the relativistic effects does not substantially contribute to the description of $\delta^{15}N$. In NR protocols, the mean relative deviation (MRD) varied from 1.0% (PBE) to 1.6% (MN15-L), while in ZORA calculations, the MRD varied from 0.7% (MN12-SX) to 30.9% (SSB-D). For calculating the $\delta^{15}N$, the best models can be described as: NR (GIAO-PBE/NMR-DKH/IEF-PCM(UFF) - $\delta^{15}N_{calc} = -2.0371\sigma_{calc} + 93.284$; ZORA (GIAO-MN12-SX/NMR-ZORA/CPCM) - $\delta^{15}N_{calc} = -2.9987\sigma_{calc} + 355.42$. Besides, the proposed empirical models describe the experimental behavior of the N-15 chemical shift and the various complexes formed in the cisplatin activation steps. In the next steps, new Pt(II) complexes will be included to construct and validate the computational protocol for calculating $\delta^{15}N$.

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