



Article Assessment of a Computational Protocol for Predicting Co-59 NMR Chemical Shift

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Abstract: In the present study, we benchmark computational protocols for predicting Co-59 NMR chemical shift. Quantum mechanical calculations based on density functional theory were used, in conjunction with our NMR-DKH basis sets for all atoms, including Co, which were developed in the present study. The best protocol included the geometry optimization at BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) and shielding constant calculation at GIAO-LC- ω PBE/NMR-DKH/IEF-PCM(UFF). This computational scheme was applied to a set of 34 Co(III) complexes, in which, Co-59 NMR chemical shift ranges from +1162 ppm to +15,100 ppm, and these were obtained in distinct solvents (water and organic solvents). The resulting mean absolute deviation (MAD), mean relative deviation (MRD), and coefficient of determination (R²) were 158 ppm, 3.0%, and 0.9966, respectively, suggesting an excellent alternative for studying Co-59 NMR.

Keywords: cobalt complexes; NMR; Co-59 chemical shift; basis set; DFT; NMR-DKH

1. Introduction

The use of cobalt (Co) coordination compounds in medicinal chemistry has increased in recent years. Studies in the literature have shown Co(III) complexes with antiviral [1–5], anti-inflammatory [5–7], antibacterial [5,8], and anticancer [9,10] activities. Regarding anticancer activities, Co(III) compounds act as cytotoxic ligand carriers to hypoxic regions, due to its redox properties [11]. Furthermore, cobalt is a less toxic metal than nonessential metals, such as platinum, and is present in biomolecules such as cobalamin, which represents an advantage its use in cancer treatments [5].

Nuclear Magnetic Resonance (NMR) spectroscopy provides fundamental information about the geometry and electronic structure of transition metal complexes [12]. As metals are important in different biological processes [13], NMR spectroscopy becomes a powerful technique for the speciation of transition metal complexes in solution and in biological systems [14]. The cobalt-59 (Co-59) nucleus is an NMR-active nucleus with a nuclear spin quantum number I = 7/2, and it has a natural isotopic abundance of 100% [15]. It is an important NMR probe because the signals are easily detectable in both solution and solid-states [16,17]. However, the high nuclear spin (I = 7/2) associated with a relatively large quadrupole moment can make the NMR peaks very broad [16,17], which implies low-resolution spectra. The Co-59 NMR chemical shift (δ^{59} Co) spreads over a very



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Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). broad range, about 18,000 ppm [16,17]. Moreover, the Co-59 NMR chemical shift is known for its sensitivity to the chemical environment in diamagnetic low-spin d⁶ Co(III) compounds [18], which highlights the value of Co-59 NMR in solving molecular structures, understanding isomerism, and assigning stereochemistry [19].

The computational study of NMR properties involving metallic nuclei is dependent on several factors, such as exchange-correlation in density functional theory (DFT), basis sets, solvent, and relativistic effects [12,20]. Some computational studies of Co-59 NMR are available in the literature [21–24]. Chan and Au-Yeung [22] proposed a computational scheme for predicting the δ^{59} Co. Among a set of 13 Co(III) complexes, with a Co-59 NMR chemical shift covering a range of 11,000 ppm, at the GIAO-B3LYP/TZVP(Co)/IGLO-II(Ligands) level, the mean relative deviation (MRD) was less than 30%. Godbout and Oldfield [23] studied a set of six Co(III) complexes at the B3LYP/Wachters'(Co)/6-31G(d)(Ligands) level. The authors found a coefficient of determination (\mathbb{R}^2) of 0.98 for the correlation between the calculated Co-59 NMR shielding constants (σ^{59} Co) and the experimental δ^{59} Co, with a slope of -0.83. However, their calculated δ^{59} Co from the experimental data had a mean absolute deviation (MAD) greater than 1000 ppm. Despite the high deviations among the experimental data, the model was able to quantitatively represent the trends. A set of four cobalt complexes were studied with the inclusion of implicit and explicit solvent effects by Bühl et al. [24]. Considering the CPMD (Carr-Parrinelo Molecular Dynamics) and QM/MM-BOMD (Quantum-Mechanical/Born-Oppenheimer Molecular Dynamics) approaches, the authors found a MAD of 400 ppm and 600 ppm, respectively. Furthermore, the authors showed that the solvent effects on both geometry and δ^{59} Co were welldescribed using the PCM (Polarizable Continuum Model) implicit model. Four-componentrelativistic (4c-Rel) calculations have been employed to calculate NMR chemical shifts in Co complexes [25–28]. Nonrelativistic (NRel) and relativistic (Rel) calculations of the NMR of light nuclei in the neighboring of metallic center were carried out by Semenov et al. [25]. The results showed that the shielding constant for ¹⁵N provides a relativistic deshielding correction of up to 9.3 ppm, showing that, even for a light nucleus, relativistic effects are important for an accurate description of the chemical shift and the solvent effect becomes more significant with larger dielectric constants. In their situation, there was a resulting increase of up to 13 ppm for the δ^{15} N. Furthermore, Samultsev et al. [26] studied the σ^{59} Co in $[Co(NH_3)_5(OH_2)]^{3+}$ complex and found a variation of 4.7% between the NRel and 4c-Rel values. When the Co metal center is replaced by iridium (Ir), the variation was 67.4%, demonstrating that the Rel corrections are more important for heavier nuclei. In another study, Samultsev et al. [27] calculated the δ^{59} Co for a set of 27 Co complexes employing NRel and 4c-Rel approaches. The authors quantified the average contributions of relativistic and solvent effects on the calculated shielding constants as 4% and 1.4%, respectively. However, a direct comparison between calculated and experimental values of δ^{59} Co was not performed. Recently, Samultsev et al. [28] studied the NMR shielding constants for Fe, Co, Ni, Pd, and Pt glycinates using the 4c-Rel calculation (4c-PBE0/dyall.ae3z level). They showed that the relativistic corrections resulted in an increase of 494 ppm and 483 ppm in the σ^{59} Co of the *fac*-[Co(gly)₃] and *mer*-[Co(gly)₃] complexes, respectively. However, the net effect on the δ^{59} Co was not reported.

Considering that there is still a gap in the literature regarding an accurate prediction of the Co-59 NMR chemical shift (δ^{59} Co) in cobalt complexes, the present study describes the results of a broad benchmarking of DFT protocols to predict δ^{59} Co for Co(III) complexes in solution. This is part of a continuous project aiming to calculate the NMR properties of transition metal complexes using our NMR-DKH basis sets, as described for Pt-195 [29–31] and Tc-99 [32] nuclei.

2. Theoretical Methodology

2.1. NMR-DKH Basis Set Development for Co

The NMR-DKH basis sets were proposed previously by Paschoal et al. for H-He, Li-Ne, Na-Ar, K-Ca, Ga-Kr, Rb-Sr, In-Xe, Pt [29], and Tc [32] atoms. These segmented allelectron relativistically contracted Douglas–Kroll–Hess (DKH) Gaussian basis sets were developed specifically for the NMR calculations, presenting excellent results in the study of Pt-195 [29–31], Xe-129 [33], and Tc-99 [32] NMR. In the present contribution, the same methodology was used in the development of a new NMR-DKH basis set for the Co atom [29,32].

Initially, for the construction of the new NMR-DKH basis set for Co, the maximum exponents per angular momentum (α_1 , l = s, p, d, f) were obtained with the Equation (1) [34–39]:

$$\alpha_{l} = k_{l} \frac{2f_{l}^{2}}{\pi \langle r_{l} \rangle^{2}} \tag{1}$$

where k_l values are 1, 4/3, and 8/5, and f_l is 33, 100, and 1000 for s, p, and d functions, respectively. In this equation, k_l is a scaling factor used in generating the exponent of each angular momentum to produce enough tight exponents to describe the core. The innermost radial expectation values ($\langle r_l \rangle$, in Bohr), obtained from the multiconfigurational Dirac–Fock (MCDF) numerical calculations of the Co atom in the ground state ((_4)F_(9/2)), were 0.056156329, 0.222395260, and 1.02444740 bohr for l = s, p, and d functions, respectively. The MCDF calculations were carried out with the GRASP90 program [40]. The following values were calculated for α_l (in Bohr⁻²): 201,875.076137984 (s), 2288.26618462583 (p), and 51.2453777725453 (d).

In the next step, a series of descending primitives was generated according to Equation (2) [34–39]:

ζ

$$= \alpha_l \chi^{-1} \tag{2}$$

where i is a positive integer, ζ corresponds to the Gaussian primitive exponent, and χ is a parameter used to determine the spacing and number of primitives. The χ values of $\chi_s = 2.50$, $\chi_p = 2.75$, and $\chi_d = 3.00$ were considered. A total of 81 primitive basis functions were generated (18s11p6d). The basis set was contracted as a triple- ζ basis set, in which only the first set of each angular momentum was contracted. The contraction coefficients were obtained from the coefficients of the atomic orbitals calculated at unrestricted Hartree–Fock (UHF) level with the inclusion of scalar relativistic corrections through the second-order Douglas–Kroll–Hess (DKH2) approximation [41–47]. This calculation was performed in GAUSSIAN 16 Rev. C.01 program [48].

Finally, the basis set was augmented with the addition of three sets of f-polarization functions, with the exponents being adjusted in order to minimize the atomic energy at the UHF-DKH2 level in the presence of an electric field (z = 0.01 a.u.) [49]. This calculation was also performed in GAUSSIAN 16 Rev. C.01 program [48]. Subsequently, the two sets of f-polarization functions with the highest exponent were also contracted.

As a result, the new triple- ζ -doubly polarized (TZ2P) NMR-DKH basis set for the Co has a set of 102 primitives (GTO) and 59 contracted (CGTO) basis functions, with the following contraction scheme: (18s11p6d3f) \rightarrow [12s6p3d2f]. The NMR-DKH basis set for Co is found in the Supplementary Material or downloaded from the Basis Set Exchange portal (https://www.basissetexchange.org/) [50].

2.2. Benchmarking the Computational Protocols

Computational protocols were benchmarking for prediction of the Co-59 NMR chemical shift in Co(III) complexes. Initially, a set of five cobalt complexes (Figure 1) were selected – $[Co(NH_3)_6]^{3+}$ (Cpx01) [51,52], $[CoCl(NH_3)_5]^{2+}$ (Cpx02) [52,53], $[Co(NO_2)(NH_3)_5]^{2+}$ (Cpx03) [52,54], $[Co(SCN)(NH_3)_5]^{2+}$ (Cpx04) [52,55], and $[Co(NCS)(NH_3)_5]^{2+}$ (Cpx05) [52,55] – which present experimental data for Co-59 NMR chemical shift and structure (X-ray). The $[Co(CN)_6]^{3-}$ complex (Ref) [56] was also selected because it is the internal reference in Co-59 NMR measurements [52].



Figure 1. Co(III) complexes considered in the initial set of the benchmarking. The geometries were optimized at BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) level: (a) Ref $-[Co(CN)_6]^{3-}$, (b) Cpx01 $-[Co(NH_3)_6]^{3+}$, (c) Cpx02 $-[Co(NH_3)_5Cl]^{2+}$, (d) Cpx03 $-[Co(NH_3)_5(NO_2)]^{2+}$, (e) Cpx04-[Co(NH₃)₅(SCN)]²⁺, and (f) Cpx05 $-[Co(NH_3)_5(NCS)]^{2+}$.

The geometries of the Co(III) complexes were optimized and characterized as minimum on the potential energy surface (PES) through harmonic frequency calculations (all frequencies real). For the geometry optimization and NMR calculation, the solvent effects (the same used in the experiments) were included, using the Integral Equation Formalism for the Polarizable Continuum Model (IEF-PCM), with the Radii set from the UFF force field [57]. The Co-59 shielding constant (σ^{59} Co) was calculated using the Gauge-Independent Atomic Orbital (GIAO) [58–62] approach and the Co-59 NMR chemical shift (δ^{59} Co) was calculated according to Equation (3) [20]:

$$\delta^{59} \text{Co} = \sigma_{\text{ref}} - \sigma_{\text{calc}} \tag{3}$$

where σ_{ref} is the calculated shielding constant for the $[Co(CN)_6]^{3-}$ (internal reference) in D₂O and σ_{calc} is the shielding constant calculated for the Co(III) complex under study.

The benchmarking scheme starts with the structures for the six Co(III) complexes (Figure 1) where the DFT-Functional/def2-SVP(Co)/def2-SVP(Ligands)/IEF-PCM(UFF) calculations were evaluated. A set of 21 DFT functionals were tested: BP86 [63,64], BLYP [63,65,66], PBE [67,68], PW91 [67,69,70], M06-L [71], TPSS [72], BB95 [63,73], B3PW91 [67,69,70,74], B3LYP [65,74,75], PBE0 [76], BHANDHLYP [77], M06 [78], M06-2X [78], TPSSh [72,79,80], B1B95 [73], BMK [81], LC-BLYP [63,65,66,82], LC- ω PBE [82–85], CAM-B3LYP [86], ω B97xD [87], and B97D3 [88]. In the next step, the Co-59 NMR chemical shift was calculated at GIAO-PBE/NMR-DKH/IEF-PCM(UFF) for each geometry obtained at distinct DFT levels. The DFT level that led to the best NMR agreement with experimental results, was selected for geometry optimization of all complexes. Once the protocol for geometry was defined, the DFT functional for predicting the Co-59 NMR chemical shift was assessed at GIAO-DFT-Functional/NMR-DKH/IEF-PCM(UFF), considering the same 21 DFT functionals previously tested for geometries. In total, 378 calculations were evaluated (Figure S1). The calculations were performed in GAUSSIAN 16 Rev. C.01 program [48].

2.3. Validation of the Best Computational Protocol

The best computational protocol (labeled as Model 1) was applied for prediction of the Co-59 NMR chemical shift (Equation (3)) of other 29 Co(III) complexes. Thus, included in the study was a total of 34 Co(III) complexes (29 used in the validation + 5 used in the benchmarking), with a Co-59 NMR chemical shift ranging from +1162 ppm to +15,100 ppm, and six distinct solvents (water—H₂O, dimethylsulfoxide—DMSO, acetonitrile—MeCN, methanol—MeOH, acetone, chloroform—CHCl₃, and benzene). Model 1 was also applied for predicting the Co-59 NMR chemical shift of four Co(III) complexes that provided experimental data in five distinct solvents (H₂O, formic acid—FA, DMSO, n,n-dimethylformamide—DMF, and MeOH). It is important to point out that almost all of the experimental data for the Co-59 NMR chemical shift of Co(III) complexes were obtained in water. Some data obtained in polar organic solvents are available, but data in non-polar organic solvents are very scarce.

3. Results and Discussion

3.1. Benchmarking the Computational Protocols

(a) The structures of Co(III) complexes

Considering that the NMR properties are very sensitive to the structure, an evaluation of the DFT functional in the geometry and in the δ^{59} Co was conducted. The def2-SVP basis sets, which showed good results for geometries of transition metal complexes [29–32], were considered for both cobalt and ligand atoms.

The performance of each computational protocol was assessed with the MRD and MAD calculated by Equations (4) and (5), respectively. These are:

$$MRD = \frac{1}{n_k} \sum_{k=1}^{n_k} \left| RD_{i,j/k} \right| \quad \therefore \quad RD_{i,j/k} = \frac{s_i^{expt} - s_{i,j/k}^{calc}}{s_i^{expt}} \times 100\%$$
(4)

and

$$MAD = \frac{1}{n_k} \sum_{k=1}^{n_k} AD_{i,j/k} \quad \therefore \quad AD_{i,j/k} = \left| s_i^{expt} - s_{i,j/k}^{calc} \right|$$
(5)

where RD and AD correspond to the relative and absolute deviation, respectively, i is the considered property (structural parameter or chemical shift), j is the protocol, and k is the Co complex under consideration. For example, $s_(Co - N, B3LYP/Cpx01)$ corresponds to the Co - N bond length calculated at B3LYP/def2-SVP(Co)/def2-SVP(Ligands)/IEF-PCM(UFF) protocol for complex 1 (Cpx 01-[Co(NH₃)₆]³⁺).

Tables S1–S6 show the calculated values for the bond lengths and bond angles with different DFT-Functionals for the six complexes in Figure 1. A total of 10 Co–L (L = ligand atom) bonds and 27 L–Co–L angles were evaluated. The MRD varied between 0.34% (PBE and BB95) and 1.28% (M06-2X) for the Ref– $[Co(CN)_6]^{3-}$, 1.18% (LC- ω PBE) and 2.02% (BLYP) for the Cpx01– $[Co(NH_3)_6]^{3+}$, 1.09% (M06) and 1.96% (BLYP) for the Cpx02– $[CoCl(NH_3)_5]^{2+}$, 0.82% (BB95 and TPSSh) and 1.72% (LC- ω PBE) for the Cpx03– $[Co(NO_2)(NH_3)_5]^{2+}$, 1.06% (B3PW91) and 2.57% (M06-2X) for the Cpx04– $[Co(SCN)(NH_3)_5]^{2+}$, and 0.97% (BHandHLYP) and 3.77% (B97D3) for the Cpx05– $[Co(NCS)(NH_3)_5]^{2+}$. From Tables S1–S6, it can be seen that all calculated bond lengths have an RD < 5%, with the highest RD = 4.84% for the Co–SCN bond ($[Co(NH_3)_5(SCN)]^{2+}$) with the BLYP and TPSS functionals. Regarding the bond angles, all calculated L–Co–L angles had an RD < 3%. The largest deviations were found for the Co–N2–C angle in the Cpx05, when a GGA or meta-GGA functional is considered, with an RD between 10% and 18%, approximately.

For all 10 bond lengths evaluated, the MRD varied between 1.15% (LC-BLYP) and 2.40% (BLYP), and for all 27 bond angles, the MRD varied between 1.04% (TPSSh) and 1.82% (B97D3) (Figure 2). Considering all 37 structural parameters, the MRD ranged between 1.08% (B3PW91) and 1.77% (M06-L) (Figure 2). Although a direct comparison be-

tween the experimental structural data, which are obtained in solid-state, and the calculated data, which are obtained in solution, is not the most appropriate, the analysis carried out is important, in that it demonstrates that the calculated structures are well-described and are not very sensitive to the used DFT functional. Thus, the best protocol chosen to describe the structure will be based on the property of interest, i.e., the δ^{59} Co.



Figure 2. Mean relative deviation (MRD, %) for the structural parameters of Co(III) complexes calculated at **DFT-Functional**/def2-SVP/def2-SVP/IEF-PCM(UFF) level.

For the δ^{59} Co (Table 1), we observed large variations with small changes in the geometries. From Figure 3, the sensitivity of the chemical shift and the geometry can be seen. Although the calculated absolute deviations (AD) for the δ^{59} Co are greater than 1000 ppm, the smallest MADs are found for geometries optimized with pure GGA or meta-GGA functionals. The BLYP geometries gave the smallest MAD, 1573 ppm (MRD = 19.0%). It is important to bear in mind that all DFT functionals presented an excellent description of the structural parameters, with an MRD for the BLYP functional of 1.72%.

Table 1. Calculated δ^{59} Co (ppm) at GIAO-PBE/NMR-DKH/IEF-PCM(UFF)//**DFT-Functional**/def2-SVP/def2-SVP/IEF-PCM(UFF) for Co(III) complexes.

DFT-Functional		Cpx01	Cpx02	Cpx03	Cpx04	Cpx05	MAD	MRD
GGA	BP86	6307	6689	5651	6352	6545	1973	23.8%
	BLYP	6673	7092	6041	6797	6941	1573	19.0%
	PBE	6368	6703	5695	6218	6566	1972	23.8%
	PW91	6299	6643	5622	6242	6493	2022	24.4%
meta-GGA	M06-L	6476	6824	5888	6505	6707	1801	21.7%
	TPSS	6248	6567	5541	6191	6409	2090	25.3%
	BB95	6506	6684	5783	6400	6701	1867	22.5%
Hybrid	B3PW91	6120	6501	5529	6127	6308	2164	26.1%
	B3LYP	6167	6605	5600	6288	6391	2071	25.0%
	PBE0	5946	6288	5368	5938	6139	2346	28.3%
	BHANDHLYP	5463	5865	4874	5537	5683	2797	33.8%

DFT-Functional		Cpx01	Cpx02	Cpx03	Cpx04	Cpx05	MAD	MRD
Hybrid meta-GGA	TPSSh	6085	6443	5440	6070	6207	2232	27.0%
	B1B95	5917	6280	5337	5870	6099	2381	28.8%
	BMK	5815	6305	5264	5874	6158	2398	29.0%
	M06	5833	6207	5324	5827	6039	2435	29.4%
	M06-2X	5421	5732	4798	5472	5680	2861	34.6%
	CAM-B3LYP	5731	6097	5140	5732	5929	2556	30.9%
	LC-BLYP	5362	5666	4765	5267	5521	2965	35.8%
LK	LC-wPBE	5791	6085	7189	5635	5949	2152	25.6%
corrected	B97D3	6318	6530	5811	6447	6423	1976	23.8%
	ωB97xD	6030	6381	5391	5972	6111	2305	27.8%
	Experimental	8152	8852	7643	8410	8350	-	-

Table 1. Cont.

Ref = $[Co(CN)_6]^{3-}$, $Cpx01 = [Co(NH_3)_6]^{3+}$, $Cpx02 = [Co(NH_3)_5Cl]^{2+}$, $Cpx03 = [Co(NH_3)_5(NO_2)]^{2+}$, $Cpx04 = [Co(NH_3)_5(SCN)]^{2+}$, $Cpx05 = [Co(NH_3)_5(NCS)]^{2+}$. Experimental δ^{59} Co values, measured in D₂O in relation to the internal reference complex ($[Co(CN)_6]^{3-}$ in D₂O), obtained from Chan et al. [52]. MAD = mean absolute deviation, Equation (5); MRD = mean relative deviation, Equation (4).



Figure 3. Mean relative deviation (MRD, %) for the structural parameters of Co(III) complexes calculated at **DFT-Functional**/def2-SVP/def2-SVP/IEF-PCM(UFF) level, and MRD for the δ^{59} Co calculated at GIAO-PBE/NMR-DKH/IEF-PCM(UFF) level. The DFT functionals in the X-axis refer to the level used for geometry optimization.

If the calculated δ^{59} Co for each Co(III) complex is evaluated separately, the geometries of BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) presented the lowest RD for all complexes: 18.1% for Cpx01–[Co(NH₃)₆]³⁺, 19.9% for Cpx02–[Co(NH₃)₅Cl]²⁺, 21.0% for Cpx03–[Co(NH₃)₅(NO₂)]²⁺, 19.2% for Cpx04–[Co(NH₃)₅(SCN)]²⁺, and 16.9% for Cpx05–[Co(NH₃)₅(NCS)]²⁺. Therefore, the protocol BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) was chosen as the most suitable for the geometry optimization of Co(III) complexes. It is worth clarifying that BLYP geometries agree with X-ray data within 1.72%, which is the second-worst performance among the 21 DFT functionals tested (Figure 2). Nonetheless, BLYP geometries gave the best NMR agreement with the experiment. This apparent paradox might be understood if we realized that the geometries were optimized in solution and compared to the solid-state data (X-ray), some differences are expected. On the other hand, the NMR was calculated in

solution and compared to the solution experimental data, therefore, the NMR calculation is more suitable to set the best geometry, as mentioned previously.

(b) Protocol for predicting the Co-59 NMR chemical shift (δ^{59} Co)

The role of the DFT functional to predict δ^{59} Co was assessed at GIAO-DFT-Functional/ NMR-DKH/IEF-PCM(UFF)//BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF), considering the same set of 21 DFT functionals used previously. The BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) optimized geometries were considered in this benchmarking. The calculated values of δ^{59} Co for the Co(III) complexes (Figure 1) are presented in Table 2. The results show that for Cpx01 ([Co(NH₃)₆]³⁺), the lowest AD (37 ppm) is obtained with the CAM-B3LYP functional. The LC-BLYP functional has the lowest AD for Cpx02 ([Co(NH₃)₅Cl]²⁺) and Cpx04 ([Co(NH₃)₅(SCN)]²⁺) (10 ppm and 27 ppm, respectively). The LC- ω PBE functional gave the lowest AD for Cpx03 ([Co(NH₃)₅(NO₂)]²⁺) and Cpx05 ([Co(NH₃)₅(NCS)]²⁺) (60 ppm and 13 ppm, respectively).

Table 2. Calculated δ⁵⁹Co (ppm) at GIAO-**DFT-Functional**/NMR-DKH/IEF-PCM(UFF)//BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) for Co(III) complexes.

DFT-Functional		Cpx01	Cpx02	Cpx03	Cpx04	Cpx05	MAD	SD	MRD
GGA	BP86	6467	6872	5871	6602	6736	1772	124	21.4%
	BLYP	6054	6387	5545	6149	6303	2194	154	26.5%
	PBE	6673	7092	6041	6797	6941	1573	121	19.0%
	PW91	6522	6923	5934	6646	6780	1720	124	20.8%
mata	M06-L	4745	4941	4496	4759	4971	3499	261	42.2%
meta-	TPSS	5439	5752	5066	5529	5663	2792	182	33.7%
GGA	BB95	6617	7021	5971	6729	6912	1631	135	19.7%
	B3PW91	8335	9138	7822	8788	8759	287	96	3.4%
Hybrid	B3LYP	7777	8337	7283	8058	8106	369	86	4.4%
	PBE0	9001	10,053	8978	10,013	9561	1240	244	15.0%
	BHANDHLYP	10,828	12,847	10,784	12,360	11,767	3436	499	41.4%
	TPSSh	6079	6546	5718	6317	6432	2063	141	24.9%
Hybrid	B1B95	9508	10,725	9634	10,483	10,179	1824	249	22.1%
meta-	BMK	13,132	15,018	12,739	14,850	14,068	5680	574	68.5%
GGA	M06	14,199	15,839	13,529	15,201	15,079	6488	437	78.3%
	M06-2X	25,260	29,621	23,322	29,962	28,460	19,044	2257	229.3%
LR corrected	CAM-B3LYP	8162	8732	7856	8377	8225	100	73	1.2%
	LC-BLYP	8382	8862	7749	8437	8283	88	78	1.1%
	LC-wPBE	8176	8826	7703	8505	8337	44	30	0.5%
	B97D3	6979	7426	6337	7141	7232	1258	107	15.2%
	wB97xD	8604	9255	8314	9001	8997	553	107	6.7%
	Experimental	8152	8852	7643	8410	8350	-	_	-

Ref = $[Co(CN)_6]^{3-}$, $Cpx01 = [Co(NH_3)_6]^{3+}$, $Cpx02 = [Co(NH_3)_5Cl]^{2+}$, $Cpx03 = [Co(NH_3)_5(NO_2)]^{2+}$, $Cpx04 = [Co(NH_3)_5(SCN)]^{2+}$, $Cpx05 = [Co(NH_3)_5(NCS)]^{2+}$. Experimental δ^{59} Co values, measured in D₂O in relation to the internal reference complex ($[Co(CN)_6]^{3-}$ in D₂O), obtained from Chan et al. [52]. MAD = mean absolute deviation, Equation (5); MRD = mean relative deviation, Equation (4). SD = standard deviation of absolute deviations (AD).

From the MAD analysis (Table 2), it is observed that δ^{59} Co is also very sensitive to the DFT functional, with MAD varying between 49 ppm (LC- ω PBE) and 19,049 ppm (M06-2X). The GGA and meta-GGA functionals showed MAD ranging from 1631 ppm (BB95) to 3499 ppm (M06-L). It is interesting to note that when the Minnesota functionals are considered, a significant increase in MAD is observed, with an increase in the % of HF exchange of 3499 ppm for the M06-L (0% of HF exchange), 6488 ppm for the M06 (27% of HF exchange), and reaching 19,049 ppm with the M06-2X (54% of HF exchange). The BMK (42% of HF exchange) and BHandHLYP (50% of HF exchange) also showed high MAD, 5680 ppm and 3436 ppm, respectively. Only six DFT functionals had an MAD below 1000 ppm: the hy-

brid functionals B3LYP (364 ppm) and B3PW91 (292 ppm), and the long-range (LR) corrected functionals ω B97xD (558 ppm), CAM-B3LYP (106 ppm), LC-BLYP (93 ppm), and LC- ω PBE (49 ppm). This indicates that LR correction plays an important role in predicting δ^{59} Co. Considering the MRD, the six best DFT functionals showed an MRD < 5%, with the LC- ω PBE functional presenting an MRD = 0.6%.

Finally, in order to check the performance of the protocols for all Co(III) complexes, the standard deviation (SD) of the AD was also evaluated (Table 2). The lowest SD (30 ppm) was obtained for the LC- ω PBE functional, indicating that the GIAO-LC- ω PBE/NMR-DKH/ IEF-PCM(UFF)//BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) protocol, named as Model 1, presents a similar accuracy for all complexes and is, therefore, the best choice for predicting δ^{59} Co in Co(III) complexes.

3.2. Validation of the Computational Protocol

The best computational protocol, namely, GIAO-LC- ω PBE/NMR-DKH/IEF-PCM(UFF)// BLYP/def2-SVP/IEF-PCM(UFF) — Model 1, was applied to a new set of 29 Co(III) complexes, not included in the initial set, aiming at validating the protocol. Then, a total of 34 Co(III) complexes were studied in the present paper, with a wide range of δ^{59} Co, from +1162 ppm to +15,100 ppm. It should also be noted that among the 34 complexes studied, 22 had their δ^{59} Co measured in water (H₂O), 10 in polar organic solvents (DMSO, MeOH, MeCN, or acetone), and two in non-polar organic solvents (CHCl₃ and benzene).

The calculated δ^{59} Co with Model 1 are presented in Table 3 where the MAD and MRD for all 34 Co(III) complexes were 158 ppm and 3.0%, respectively. Figure 4 shows the correlation between the experimental and calculated δ^{59} Co with Model 1 including all 34 Co(III) complexes studied. The coefficient of determination (R²) of 0.9966, the slope of 0.9837 ± 0.0102, and the y-intercept of 67.4421 ± 78.7321 illustrate the quality and the predictive capacity of the proposed computational protocol.

Table 3. Calculated δ^{59} Co (ppm) at GIAO-LC- ω PBE/NMR-DKH/IEF-PCM(UFF)//BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) for the set of 34 Co(III) complexes studied in the present paper. The values shown in square brackets are found in ref. [27] considering a Rel-4c approach.



Calc. Calc. Срх Structure Solvent Expt. Срх Structure Solvent Expt. 2-2+ CN NH3 NC// _{III}NH₃ H₃N_{1/1/1} "SCN 1162 ^b 8505 8410 a 1072 04 D_2O 21 D_2O NC 'CN H₃N NH₃ CN NH3 $[Co(NH_3)_5(SCN)]^{2+}$ [Co(NH₃)(CN)₅]²⁻ 2+ NH₃ NH₃ NC_{IIIII} _{NN}NH₃ H₃N₁₁₁₁ "^{III}NCS 05 D_2O 8337 8350 a 22 D_2O 3917 3947 ^b H₃N NH3 NC¹ **CN** ΝH₃ ΝH₃ mer-[Co(CN)₃(NH₃)₃] [Co(NH₃)₅(NCS)]²⁺ 2+ NH3 H_2 H₃N_{1/1/1} CN "¹¹N₃ 8695 8842 a 06 D_2O 23 D_2O 4545 4364 ^b [9000.3] н H₃N NH₃ H₂ H_2 $\dot{N}H_3$ $[Co(NH_3)_5(N_3)]^{2+}$ cis-[Co(CN)2(en)2]+ 3+ NO₂ NH₃ H $H_3N_{\prime\prime\prime}$ _{MNH3} H₃N_{///} 07 MeOH 8149 8208 a 24 D_2O 7893 $8180\ ^{\rm b}$ NH₃ H₃N NH3 H₃N ΝH3 ċι $[Co(NH_3)_5(HIm)]^{3+}$ trans-[Co(NH₃)₄(NO₂)Cl]⁺ 3+ NH₃ H_2 NC/// H₃N 08 MeOH 8182 8215^b 25 D_2O 1934 2006 bH₃N¹ NH3 NC \mathbf{H}_{2} ΝH3 ĊN [Co(NH₃)₅(MeIm)]³⁺ [Co(en)(CN)₄]⁻ 3+ 2+ NH₃ OH2 H₂O_{/////} H₃N₁₁₁₁₁ "\Br _MOH₂ 8939 15,100 ^b 09 D_2O 8919 ^b 26 D_2O 15,485 [9119.4] H₂O H₃N NH3 ΌΗ2 о́н₂ ΝH₃ [CoBr(NH₃)₆]²⁺ $[Co(OH_2)_6]^{3+}$ HO ОН CN 2+ NH₃ H₃N₁₁₁₁₁ ""I 8935 108849 a 27 DMSO $4150\ ^{\rm d}$ D_2O 4363 [8639.2] нό òн Hal H₃ ΝH₃ [Co(NH₃)₅I]²⁺ trans-[Co(DH)2(CN)(py)]

Table 3. Cont.



Table 3. Cont.



Table 3. Cont.





Figure 4. Correlation between the experimental and calculated (Model 1) δ^{59} Co (ppm) for all 34 Co(III) complexes studied in the present paper. The level of theory was GIAO-LC- ω PBE/NMR-DKH/IEF-PCM(UFF)//BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF).

It is interesting to note the quality of Model 1 for the structural characterization of Co(III) complexes. The $Cpx04 - [Co(NH_3)_5(SCN)]^{2+}$ and $Cpx05 - [Co(NH_3)_5(NCS)]^{2+}$ present link-

age isomerism, with the Co-59 nucleus providing more deshielding in Cpx04, a trend that was well described by Model 1. Conversely, $Cpx07 - [Co(NH_3)_5(HIm)]^{3+}$ and $Cpx08 - [Co(NH_3)_5(MeIm)]^{3+}$ present the only difference in the replacement of an -NH by a -NCH₃ group in imidazole ligand, resulting in a change of only 7 ppm in the experimental δ^{59} Co. The values calculated with Model 1 also adequately described this trend with a difference of only 33 ppm between the calculated values.

Among the 34 Co(III) complexes included in the present work, six were recently studied by Samultsev et al. [27] using the 4c-Rel approximation. Our calculated results show that the values predicted by Model 1 ($20 \le AD \le 147$ ppm) were better than those predicted in ref. [27] for all six complexes (see Table 4).

Table 4. Calculated δ^{59} Co (ppm) at GIAO-LC- ω PBE/NMR-DKH/IEF-PCM(UFF)//BLYP/def2-SVP/def2-SVP/IEF-PCM(UFF) for the five Co(III) complexes that present experimental data in distinct solvents.

			δ ⁵⁹ Co			
Срх	Co(III) Complexes	Solvent	Model 1	Expt.	AD (ppm)	RD (%)
07	$[C_{\alpha}(N H_{\lambda}), (H m_{\lambda})]^{3+}$	D ₂ O	8132	8170	38	0.5%
07	[Co(INH3)5(HIIII)] [*]	MeOH	8149	8208	59	0.7%
08	$(C_{\alpha}(N H_{\alpha}))^{3+}$	D ₂ O	8161	8178	17	0.2%
	$[CO(INH_3)5(IMHIII)]^{*}$	MeOH	8182	8215	33	0.4%
11		D ₂ O	8473	8359	114	1.4%
	there $[C_{2}(ap)]$ (N) 1 ⁺	FA	8471	8280	191	2.3%
	trans-[C0(en) ₂ (1v ₃) ₂]	DMSO	8470	8350	120	1.4%
		MeOH	8468	8299	169	2.0%
12		D ₂ O	9331	8960	371	4.1%
	<i>trans</i> - $[Co(en)_2Cl_2]^+$	DMSO	9313	8870	443	5.0%
		MeOH	9296	8850	446	5.0%
13		D ₂ O	6396	6324	72	1.1%
		DMSO	6396	6395	1	0.0%
	trans-[Co(en) ₂ (NO ₂) ₂] ⁺	DMF	6397	6400	3	0.0%
		MeOH	6397	6381	16	0.3%
		MeCN	6397	6366	31	0.5%

Experimental δ^{59} Co values, measured in relation to the internal reference complex ([Co(CN)₆]³⁻ in D₂O), obtained from Chan et al. [52]. AD = absolute deviation; RD = relative deviation. HIm = imidazole; MeIm = methylimidazole; en = ethylenediamine.

In a separate analysis to examine the impact of the solvent used, the 22 complexes in water presented a MAD of 156 ppm and a MRD of 3.2%, while the 10 complexes in polar organic solvents (DMSO, MeCN, MeOH, or acetone) showed MAD and MRD of only 139 ppm and 2.6%, respectively. For the two complexes studied in non-polar organic solvents, an MAD of 274 ppm with an MRD of only 2.2% were obtained. This result shows that although Model 1 was obtained from a benchmarking considering complexes (Cpx01 to 05) studied in water, its application is valid for other distinct solvents used within the PCM approach.

Furthermore, for five of the 34 complexes studied, Cpx07, Cpx08, Cpx11—*trans*-[Co(en)₂(N₃)₂]⁺, Cpx12—*trans*-[Co(en)₂Cl₂]⁺, and Cpx13—*trans*-[Co(en)₂(NO₂)₂]⁺, experimental data for δ^{59} Co are available in more than one solvent. Experimental data show that changing the solvent generates a small variation in δ^{59} Co, with the largest difference observed, 79 ppm (~1%), between the values in H₂O and DMSO for Cpx11. Model 1 was applied to these five complexes considering the different solvents (Table 4). For Cpx07 and Cpx08, with H₂O or MeOH, it is experimentally observed that there is a small increase in δ^{59} Co for both complexes when MeOH is considered, which is predicted with Model 1 for both complexes. For Cpx11 (data in H₂O, FA, DMSO, and MeOH), Cpx12 (data in H₂O, DMSO, and MeOH), and Cpx13 (data in H₂O, DMSO, DMF, MeOH, and MeCN), the absolute deviations found with Model 1 considering the different solvents varied between 114 ppm and

191 ppm for Cpx11, 371 ppm and 446 ppm for Cpx12, and 1 ppm and 72 ppm for Cpx13. Even for Cpx12, which had a higher AD, the trend of the calculated values followed the same trend observed with the solvent variation. Therefore, Model 1 was able to adequately describe δ^{59} Co, regardless of the considered solvent.

Model 1 was applied to cobaloximes (Cpx27 to Cpx32), which are important Co(III) compounds used as a model for vitamin B_{12} in studies of their properties and mechanisms of action. The six studied cobaloximes present δ^{59} Co between 3270 ppm and 5371 ppm, with experimental values obtained in DMSO (Cpx27 and Cpx28), H₂O (Cpx29 and Cpx30), and acetone (Cpx31 and Cpx32). The calculated δ^{59} Co values (Table 3) for the cobaloximes also showed good agreement with the experimental values, with an AD varying between 124 ppm and 333 ppm, corresponding to an MAD of 189 ppm and an MRD of 4.6%. In addition, Model 1 was able to adequately describe the trend of δ^{59} Co as the axial cobaloximes ligands are changed (Figure 5).



Figure 5. Calculated δ^{59} Co (ppm) with Model 1, GIAO-LC- ω PBE/NMR-DKH/IEF-PCM(UFF)//BLYP /def2-SVP/def2-SVP/IEF-PCM(UFF), for all six cobaloximes studied in the present paper.

4. Concluding Remarks

The present study aimed to propose a computational protocol based on the DFT level to calculate the Co-59 NMR chemical shift (δ^{59} Co). An initial set of five Co(III) complexes and the internal reference in Co-59 NMR were selected for the DFT benchmarking, which included 21 DFT functionals and the basis set def2-SVP for all atoms. The geometries were optimized at all DFT-Functionals/def2-SVP/IEF-PCM(UFF) levels and further used for the prediction of δ^{59} Co at GIAO-PBE/NMR-DKH/IEF-PCM(UFF). Note that these two first steps included 252 calculations, from which the best scheme was selected: GIAO-PBE/NMR-DKH/IEF-PCM(UFF). The MAD and MRD for this protocol were 1573 ppm and 19.0%, respectively. With the aim of improving the protocol, the 21 DFT functionals were used to calculate δ^{59} Co, instead of PBE (126 calculations). The results demonstrated an important role of the long-range correction to the δ^{59} Co values, with the LC- ω PBE leading to the best agreement with the experimental data, MAD = 30 ppm and MRD = 0.5%. The final protocol was labeled as Model 1: GIAO-LC- ω PBE/NMR-DKH/IEF-PCM(UFF)//BLYP/def2-SVP/IEF-PCM(UFF).

Model 1 was applied to a new set of 29 Co(III) complexes, not included in the original set. Considering all 34 complexes, that present experimental data in water and in organic

solvents (polar and non-polar), the δ^{59} Co varied between +1162 ppm and +15,110 ppm. The MAD, MRD, and R² were 158 ppm, 3.0%, and 0.9966, respectively. Lastly, for five of the 34 complexes studied, which present experimental data in different solvents (H₂O, FA, DMSO, DMF, MeOH, and MeCN), Model 1 was also able to adequately describe the δ^{59} Co.

The results obtained in the present study suggest Model 1 as an excellent alternative to calculate the δ^{59} Co in Co(III) complexes, with an absolute error that is low enough to assign Co(III) complex structures.

Supplementary Materials: The following supporting information can be downloaded at: https://www.action.com/actionals //www.mdpi.com/article/10.3390/magnetochemistry9070172/s1, Table S1. Calculated bond lengths (Å) and bond angles (°) for Ref – $[Co(CN)_6]^{3-}$ at DFT-Functional/def2-SVP/def2-SVP/IEF-PCM(UFF) level. The mean relative deviation (MRD) in relation to the experimental X-ray values considering all structural parameters evaluated is also presented. Table S2. Calculated bond lengths (Å) and bond angles (°) for $Cpx01 - [Co(NH_3)_6]^{3+}$ at DFT-Functional/def2-SVP/def2-SVP/IEF-PCM(UFF) level. The mean relative deviation (MRD) in relation to the experimental X-ray values considering all structural parameters evaluated is also presented. Table S3. Calculated bond lengths (Å) and bond angles (°) for Cpx02-[Co(NH₃)₅Cl]²⁺ at DFT-Functional/def2-SVP/def2-SVP/IEF-PCM(UFF) level. The mean relative deviation (MRD) in relation to the experimental X-ray values considering all structural parameters evaluated is also presented. Table S4. Calculated bond lengths (Å) and bond angles (°) for Cpx03-[Co(NH₃)₅(NO₂)]²⁺ at **DFT-Functional**/def2-SVP/def2-SVP/IEF-PCM(UFF) level. The mean relative deviation (MRD) in relation to the experimental X-ray values considering all structural parameters evaluated is also presented. Table S5. Calculated bond lengths (Å) and bond angles (°) for Cpx04-[Co(NH₃)₅(SCN)]²⁺ at DFT-Functional/def2-SVP/def2-SVP/IEF-PCM(UFF) level. The mean relative deviation (MRD) in relation to the experimental X-ray values considering all structural parameters evaluated is also presented. Table S6. Calculated bond lengths (Å) and bond angles (°) for Cpx05–[Co(NH₃)₅(NCS)]²⁺ at DFT-Functional/def2-SVP/def2-SVP/IEF-PCM(UFF) level. The mean relative deviation (MRD) in relation to the experimental X-ray values considering all structural parameters evaluated is also presented. Figure S1. Benchmarking flowchart applied to obtain Model 1. Figure S2. 3D structure (with labels) of Co(III) complexes considered in the initial set of the benchmarking. Ref- $[Co(CN)_6]^{3-}$, Cpx01- $[Co(NH_3)_6]^{3+}$, Cpx02- $[Co(NH_3)_5Cl]^{2+}$, Cpx03-[Co(NH₃)₅(NO₂)]²⁺, Cpx04-[Co(NH₃)₅(SCN)]²⁺, and Cpx05-[Co(NH₃)₅(NCS)]²⁺. NMR-DKH basis set for the Co atom. Optimized structures (.xyz format) at BLYP/def2-SVP/S SVP/IEF-PCM(UFF) level of the 34 Co(III) complexes and internal reference complex.

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