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Unexpected Geometrical Effects on Paramagnetic Spin−Orbit and Spin−Dipolar $^2J_{FF}$ Couplings

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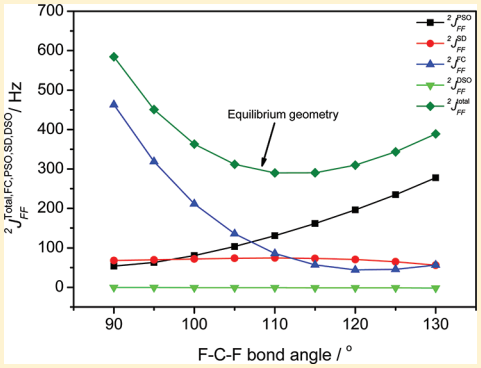
ABSTRACT: The second-rank tensor character of the paramagnetic spin−orbit and spin−dipolar contributions to nuclear spin−spin coupling constants is usually ignored when NMR measurements are carried out in the isotropic phase. However, in this study it is shown that isotropic $^2J_{FF}$ couplings strongly depend on the relative orientation of the C−F bonds containing the coupling nuclei and the eigenvectors of such tensors. Predictions about such effect are obtained using a qualitative approach based on the polarization propagator formalism at the RPA, and results are corroborated performing high-level ab initio spin−spin coupling calculations at the SOPPA(CCSD)/EPR-III//MP2/EPR-III level in a model system. It is highlighted that no calculations at the RPA level were carried out in this work. The quite promising results reported in this paper suggest that similar properties are expected to hold for the second-rank nuclear magnetic shielding tensor.



INTRODUCTION

Fluorinated organic compounds are of paramount importance as pharmaceuticals, such as Lipitor, Risperdal, Prozac, and Flurithromycin.[1] Apart from pharmaceutical fluorinated organic compounds there is another extremely important class of compounds where ^{19}F NMR spectroscopy is a key technique to study them, i.e., fluorine-modified oligonucleotides.[2] While organic fluorinated compounds emerge in chemical industry (materials, pharmaceuticals, agrochemicals, fine chemicals) due to the well-established behavior for fluorine substitution,[3] this does not hold for trends of ^{19}F NMR spectroscopic parameters, although their sensitivity to inter- and intramolecular interactions are well recognized. For instance, there are many studies involving J_{FF} spin−spin coupling constants (SSCC) transmitted through space[4−7] and/or through bond;[8−13] there are several aspects related to the influence of stereoelectronic interaction on the Fermi contact (FC), the paramagnetic spin−orbit (PSO) and spin−dipolar (SD) contributions, and the diamagnetic spin−orbit (DSO) contributions involved in transmission mechanisms of J_{FF} SSCC, which are not well understood yet.

In the particular case of $^2J_{FF}$ SSCCs in fragments of type F−C−F very important contributions originating in the PSO and SD terms are known, and they are surprisingly sensitive to electron-withdrawing groups bonded to the intermediate C atom.[14,15] To understand factors determining such unusual trends, in this study we applied a semiqualitative approach, reported previously,[16] specially suited to understand electronic factors originating trends of high-resolution NMR parameters. As shown below, when applying this model, it is predicted that the isotropic value of either the PSO or the SD terms may depend rather strongly on the angles formed by each C−F bond containing the coupling nuclei and the eigenvectors of the respective tensors.

To carry out a study to verify whether predictions made with our qualitative model are supported, high-level ab initio calculations for the four Ramsey terms are undertaken. To this end, difluoromethane is taken as the model compound. Why? Because this particular compound is suited for this type of verification owing to its symmetry properties which allow us to determine the eigenvectors for either the PSO or the SD second-rank tensors just on the basis of symmetry considerations.

It is highlighted that the main result reported in this work is the description of a geometrical effect detected in the isotropic averaged values of the **PSO** and **SD** second-rank tensors. In fact, the isotropic part of the **PSO** and **SD** tensors corresponding to $^nJ_{FF}$ SSCC depend strongly on the C−F bond orientations with respect to eigenvectors of those second-rank tensors. In the model compound studied in this work these isotropic averaged PSO and SD noncontact terms increase when increasing the angle between the C−F bonds and the eigenvectors of these second-rank tensor properties. To our knowledge, such effect has not been reported before in the literature.

RESULTS AND DISCUSSION

Brief Account of the Qualitative Approach Employed in This Work. In the isotropic phase the indirect J_{FF} SSCC is made up from four terms,[17] eq 1

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$$ {}^{n}J_{FF} = \frac{1}{3}Tr({}^{n}\mathbf{J}_{FF}) = {}^{n}J_{FF}^{FC} + {}^{n}J_{FF}^{SD} + {}^{n}J_{FF}^{PSO} + {}^{n}J_{FF}^{DSO} \quad (1) $$

As shown in previous papers,[18] the expressions of second-order contributions to eq 1, i.e., PSO, SD, and FC written in terms of the polarization propagator formalism, PP, within the random phase approximation, RPA, are particularly suited to analyze interactions and factors that define their trends along series of compounds. However, it is stressed that in this work no calculation was carried out at the RPA level. Particular emphasis is put here on studying PSO and SD terms in ${}^{2}J_{FF}$ SSCCs since they are by far less studied than the FC term. In a previous work[14] it was shown that in ${}^{2}J_{FF}$ SSCCs the sum of the PSO and SD terms can be substantially larger than the FC contribution.

Qualitative Analysis of Second-Order Terms. This analysis considers that each second-order terms of eq 1 are described as the emission and receptor of the spin information associated to the three second-order terms of eq 1. Any coupling nucleus can play the role of emission or reception since ${}^{n}J_{AB} = {}^{n}J_{BA}$ always. They are connected through the transmission mechanism, i.e., the PP matrix.

PSO Term. The PSO term shows nonsymmetric second-rank tensor character, and in the isotropic phase only one-third of its trace contributes to PSO in eq 1. The respective PP expressions are

$$ {}^{n}J_{F1F2}^{PSO} = \frac{1}{3}\sum_{\nu} J_{F1F2}^{PSO,\nu\nu} \text{ with } {}^{n}J_{F1F2}^{PSO,\nu\nu} = -\Omega^{PSO}\gamma_{F}^{2}\sum_{ia,jb} {}^{n}J_{ia,jb}^{PSO.\nu\nu}(F_1F_2) \quad (2) $$

where Ω^{PSO} is a positive constant and

$$ {}^{n}J_{ia,jb}^{PSO\nu\nu}(F_1F_2) = U_{ia,F_1}^{PSO,\nu 1}W_{ia,jb}U_{jb,F_2}^{PSO,\nu} \quad (3) $$

where $U_{ia,F1}^{PSO,\nu}$ and $U_{jb,F2}^{PSO,\nu}$ are the "perturbator" terms centered at the F coupling nuclei.

${}^{1}W_{ia,jb} = ({}^{1}A + {}^{1}B)_{ia,jb}^{-1}$ are the elements of the inverse of the singlet PP matrix. The corresponding perturbators are

$$ U_{ia,F_1}^{PSO,\nu} = \langle i|\frac{(\vec{r}_{F_1} \times \vec{\nabla})_{\nu}}{r_{F_1}^{3}}|a\rangle \quad (3F1) $$

and

$$ U_{jb,F_2}^{PSO,\nu} = \langle j|\frac{(\vec{r}_{F_2} \times \vec{\nabla})_{\nu}}{r_{F_2}^{3}}|b\rangle \quad (3F2) $$

They show vector character, and the **PSO** second-rank tensor is determined by the tensor product between the (3F1) and the (3F2) perturbators. Since in this paper only the isotropic part of the PSO term is studied, the same Cartesian components of those perturbators should be taken. However, from expressions 3F1 and 3F2 is evident that it is much easier to interpret them if local Cartesian coordinate systems are employed for each F atom. In fact, since within each bracket appears the 90° rotation operator along the ν axis and centered in the corresponding F atom, the local system shown in Figure 1b is quite easy to rationalize.

It must be recalled that Figure 1a corresponds to the PSO eigenvectors in CF_2H_2. The two C−H bonds are contained in the (Y,Z) plane, while the C−F bonds are contained in the (X,Y) plane. When increasing the F−C—F angle while keeping the (Y,Z) plane as a bisector of that angle, the (X,Y,Z) continuous to be the PAS system of the modified CF_2H_2 molecule. This is the main reason why CF_2H_2 is chosen as a model compound. In each local coordinate system $LP_1(F)$ is along the ψ axis, $LP_2(F)$ is along the ξ axis, the $LP_3(F)$ is along the ζ axis, and the (F−C) bonding and (F−C)* antibonding orbitals are along the negative ψ axis. This indicates that components of the numerator of each perturbator (eq 3) are as follows: rotating $LP_3(F)$ + 90° around the ξ axis, it overlaps with the (F−C)* antibonding orbital, yielding a negative ψ component. Similarly, rotating $LP_2(F)$ −90° around the ζ axis it overlaps with the (F−C)* antibonding orbital, yielding a negative ψ component; however, since the rotation angle is negative, this component is positive. Note that these signs were reversed when taking into account the negative sign in eq 2. This point indicates that when considering the PSO trace there is a competition between them and the actual **PSO** sign, which may be positive or negative. Obviously, the contribution of rotating either $LP_1(F)$ or the (F−C) bond 90° around the ψ axis is negligible when compared with the former two. However, it is now necessary to express such results in terms of only one Cartesian coordinate system in order to obtain the trace of the **PSO** tensor, eq 2. To this end, we chose the **PSO** PAS, as shown in Figure 1a. For this reason the rotated elements inside the brackets must be projected onto the PAS system (X,Y,Z) before performing the bracket integration. It is not trivial to obtain an expression of the projected rotation operator onto the PAS system. However, some important insight can be taken into account for this simple example considering that the ζ and Z components are equal to each other. The ξ and ψ components for $C-F_1$ and $C-F_2$ bonds projected onto the PAS X axis cancel each other. Then only the ψ component should be projected onto the Y axis. In the denominators of eqs 3F1 and 3F2 this projection is through the same α angle over the whole integration region and a factor $\cos^3\alpha$ can be taken out of the integration operator. Since $\cos^3\alpha \leq 1$ it is observed that when both C−F bonds are parallel to *PAS* axes the PSO term of the corresponding J_{FF} SSCC takes its smallest absolute value. It is a geometrical effect that increases notably the Y component when increasing the α angle, i.e., when the F−C bonds containing the F coupling nuclei depart from the PAS system.

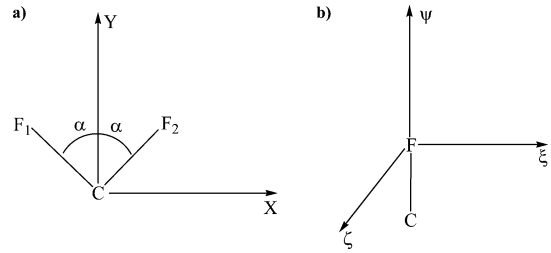

Figure 1. (a) Configuration for the C−F bonds expressed in the **PSO** principal axis system (X,Y,Z). (b) Local Cartesian coordinate system for each of the fluorine coupling nuclei are labeled with Greek letters, ξ, ψ, ζ.

Qualitative Analysis of the SD Term. The SD contribution to ${}^{n}J_{FF}$ SSCC is also an asymmetric second-rank tensor, and in the isotropic phase its contribution is ${}^{n}J_{F1F2}^{SD} = (1/3)\Sigma_{\nu}J_{F1F2}^{\nu\nu}$ and each component can be written as

$$ {}^{n}J_{F1F2}^{SD,\nu\nu} = -\Omega^{SD}\gamma_{F}^{2}\sum_{ia,jb} {}^{n}J_{ia,jb}^{SD.\nu\nu}(F_1F_2) \quad (4) $$

with

$$ {}^{n}J^{SD\nu\nu}_{ia,jb}(F_1F_2) = U^{SD,\nu\nu 3}_{ia,F1} W_{ia,jb} U^{SD,\nu\nu}_{jb,F2} \quad (5) $$

It is observed that also in the SD case the second-rank tensor character originates in both perturbators. However, these perturbators themselves show second-rank character. For values considered in isotropic media, only diagonal elements are relevant, eq 6

$$ U^{SD,\nu\nu}_{ia,F1} = \langle i|\frac{r_{F1\nu}r_{F1\nu} - r^2_{F1}}{r^5_{F1}}|a\rangle;\ U^{SD,\nu\nu}_{ia,F2} = \langle i|\frac{r_{F2\nu}r_{F2\nu} - r^2_{F2}}{r^5_{F2}}|a\rangle \quad (6) $$

Further, it is recalled that this is a qualitative analysis, and therefore, it is necessary to look for the main contributions that define a given trend. Equations 6 correspond, apart from the geometric term inside the bracket, to the overlap between the occupied LMO i and the vacant LMO a. In each case the two main perturbator terms are those with i = $LP_1(F)$ or (F−C) and a = (F−C)*, i.e., to overlaps of types $LP_1(F)/(F-C)^*$ and (F−C)/(F−C)*. As it is known[18c] these two overlaps must have opposite signs. Obviously, the largest component must be along the ψ axis, Figure 1b, and components along the ξ and ζ are neglected. It is noted that in front of eq 4 there is a negative sign, indicating that the main positive contribution comes from the $LP_1(F)/\sigma^*(F-C)$ overlap. Projecting now these contributions onto the PAS system, Figure 1, the main diagonal terms in the PAS system are given by

$$ U^{SD,YY}_{ia,F1} = \langle (F_1-C)|\frac{r_{F1\nu}r_{F1\nu} - r^2_{F1}\cos^2\alpha}{\cos^5\alpha r^5_{F1}}|(F_1-C)^*\rangle \quad (7a) $$

and

$$ U^{SD,YY}_{ia,F1\ LP/(F-C)^*} = \langle LP_1(F_{F1})|\frac{r_{F1\nu}r_{F1\nu} - r^2_{F1}\cos^2\alpha}{\cos^5\alpha r^5_{F1}}|(F_1-C)^*\rangle \quad (7b) $$

Analogous expressions for diagonal YY perturbators for F_2 hold. It is noted that the angular dependence is notably more complicated than that for the PSO term since in the integrands the cos α expression does not enter as a factor in brackets.

It must be highlighted that such expressions are approximate and valid only for the model compound chosen in this work. Besides, it is recalled that eqs 7a and 7b are of opposite sign; therefore, it is expected that the isotropic SD dependence on α would be smoother than that for the PSO term.

In order to verify whether trends predicted in the above rationalization about trends of the PSO and SD terms are supported, theoretical calculations were carried for $^2J_{FF}$ SSCCs in the model compound mentioned above, i.e., CF_2H_2. Theoretical $^2J_{FF}$ SSCC were obtained at the SOPPA-(CCSD)[19−21] level using the Dalton 2.0 program[22] employing the EPR-III basis set. All geometries were optimized at the MP2/EPR-III level. Although in this compound such coupling is not amenable to measurement due to its high symmetry and to the 100% natural abundance of the ^{19}F isotope, in the literature there are reliable calculations suggesting that this *geminal* J_{FF} coupling for the equilibrium geometry is dominated by noncontact PSO and SD terms.[14] In fact, for that geometry, calculated at the SOPPA(CCSD)/EPR-III//MP2/EPR-III level, these values are obtained, $^2J_{FF}$ = 293.9 Hz, with DSO = −1.0, PSO = 121.9, SD = 74.2, and FC = 98.8 Hz, confirming that PSO + SD is about twice the FC term. Calculations for different F−C−F angles around its equilibrium value were carried out at the same level, changing the F−C−F angle in 5° steps from 90° to 130° and allowing relaxing all other geometrical parameters. Results for the FC, PSO, SD, and DSO terms versus the F−C−F angles are displayed in Figure 2. It is observed that the PSO and SD terms follow the trends predicted by the qualitative analysis discussed above, with the dependence on the α angle being notably more important for the isotropic PSO than for the SD isotropic contribution. These conclusions resemble correctly the trends predicted from the qualitative model.

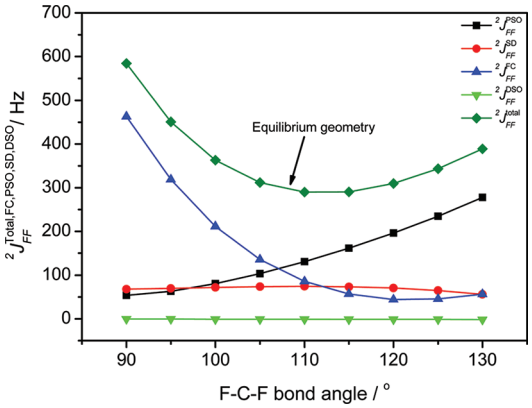

Figure 2. FC, PSO, SD, and DSO contributions to $^2J_{FF}$ SSCCs versus the F−C−F bond angle for difluoromethane calculated at the SOPPA(CCSD)/EPR-III level. Geometrical changes preserved the F−C−F plane as bisector for the H−C−H angle and H−C−H was kept as a symmetry plane; consequently, eigenvectors of both PSO and SD second-rank tensors are evident for each angle based on elemental symmetry considerations.

It is noted that the DSO term is close to 1 Hz in the whole region considered, i.e., in this region the DSO is negligible compared with the other three contributions. In fact, this trend is quite expected because, since it is well known, the DSO contribution to a given SSCC satisfies the following property: if the whole region occupied by a molecule is divided in two parts by means of a sphere whose diameter is equal to the distance between the coupling nuclei then electrons inside that sphere yield a negative contribution while those outside it yield a positive contribution. Of course, the coupling nuclei are assumed to be on the surface of that sphere.[23]

As we can observe from Figure 2 the FC term is also an important contribution for the total $^2J_{FF}$ coupling, but since this is an isotropic contribution and its behavior due to bond angle changes is known[6−15] any comments will be not introduced in this work.

■ CONCLUDING REMARKS

In the present study an interesting geometrical effect on the noncontact PSO and SD isotropic contributions to fluorine−fluorine SSCCs is reported. This effect can be easily described saying that in the isotropic phase their actual values depend strongly on the orientation of the C−F bonds containing the fluorine coupling nuclei with respect to the orientation of the principal axis system of the **PSO** and **SD** second-rank tensors. Apparently, these effects could rationalize some trends already known for calculated J_{FF} SSCCs where large variations were observed for these noncontact terms. Only three known cases

are quoted here, i.e., fluorinated pyridine and quinoline derivatives,[24] the different values reported by Shtarev et al.[25] and contributions to Karplus-like equations for $^3J_{FF}$ SSCCs.[26] In all cases theses can predict important contributions from the "geometric effect" discussed in this short communication.

As a final comment it is worth mentioning that our qualitative approach predicts an analogous geometrical effect on the isotropic nuclear magnetic shielding constant not only for fluorine but also for at least ^{13}C and ^{17}O nuclear magnetic shielding constants. Work along this line is in progress, and results will be reported in forthcoming papers.

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Notes

The authors declare no competing financial interest.

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