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# DFT Calculation of NMR $J_{FF}$ Spin−Spin Coupling Constants in Fluorinated Pyridines

**Verónica Barone,[†] Juan E. Peralta,[†] Rubén H. Contreras,*[,†] and James P. Snyder*[,‡]**

*Departamento de Física, FCEyN, Universidad de Buenos Aires, Buenos Aires, Argentina, and Department of Chemistry, Emory University, Atlanta, Georgia 30322*

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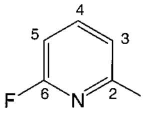
All four isotropic contributions to the NMR fluorine−fluorine coupling constants (Fermi contact, FC, spin-dipolar, SD, paramagnetic spin−orbit, PSO, and diamagnetic spin−orbit, DSO) have been calculated for 2,6-difluoropyridine, 2,4,6-trifluoropyridine, perfluoropyridine, and 2-Br-3,4,5,6,7,8-hexafluoroquinoline by means of density functional theory in combination with the rather modest 6-311G** basis set. Experimental values ranging from −20.3 to +45.8 Hz are semiquantitatively reproduced for three- to seven-bond couplings, suggesting that the different electronic effects responsible for the spin−spin interactions are adequately taken into account. In all cases, the relative importance of noncontact terms was examined. With few exceptions, the sum of the SD and PSO *noncontact* terms is larger than the FC *contact* contribution, even though in most cases the two noncontact values have opposite signs. The widespread assumption that the Fermi contact term dominates scalar spin−spin couplings in the case of light atoms would appear to be an oversimplification for $J_{FF}$ in polyfluorinated organic molecules. In addition, the CPU performance of the Fermi contact contribution calculated separately by the coupled-perturbed and the finite-perturbation methods was investigated showing the latter to be slightly more efficient.

## Introduction

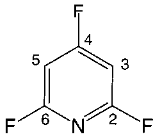
During the past few years, there has been a renewed interest in nuclear spin−spin coupling constants as probes to study a variety of molecular problems.[1] This interest stems mainly from important advances taking place during the past decade both experimentally and theoretically to determine and analyze such couplings. Nonrelativistic theoretical studies broadly followed two different methodological approaches: post-Hartree−Fock methods[2] and density functional theory, DFT.[3] Within the former, very accurate and reliable calculations were reported.[4] However, to obtain such reliable results, it has been necessary to employ extensive computational resources even for small-sized structures. Nonetheless, systematic calculation of spin−spin couplings in medium-sized compounds with reasonable accuracy has been envisioned as a useful and complementary tool for experimental determinations.[5]

Prediction of *J* couplings for lone-pair-containing nuclei is a challenging task for any computational method, and DFT-based methods are no exception to the rule.[6] However, recent preliminary $J_{FF}$ DFT calculations seem to be quite promising,[7] especially when all four contributions (Fermi contact, FC, spin-dipolar, SD, paramagnetic spin−orbit, PSO, and diamagnetic spin−orbit, DSO) are calculated with the coupled-perturbed Kohn and Sham approach (CP-KS) or, equivalently, with the finite perturbation theory scheme (FPT).[8] Very recently, a number of groups have reported calculation of the four terms for spin−spin coupling constants using both relativisitic and nonrelativistic DFT approaches.[5b,5c,9] In particular, the importance of noncontact terms in couplings of type $J_{XF}$[9] has been discussed, as has the prediction of these terms using the multiconfiguration self-consistent field (MCSCF)[10] and equation of motion−coupled cluster with single and double excitation (EOM−CCSD)[11] methodologies.

The aim of this work is to study the performance of DFT calculations for fluorine−fluorine coupling constants, $J_{FF}$, in fluorinated pyridines **1**−**4**. When all four Ramsey terms are taken into account, agreement between the total calculated couplings and the experimental values is very good. Therefore, it is expected that such values can shed light on the electronic transmission mechanisms of $J_{FF}$ couplings when applied more generally to aromatic compounds.



**1**



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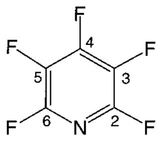

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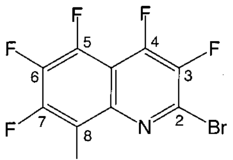

**4**

At present the sensitivity of calculated $J_{FF}$ to the basis set employed is not well-known in the DFT framework, especially for medium-sized compounds. For this reason, a comparison of individual $J_{FF}$ contributions for the model perfluoropyridine (**3**) calculated with five different basis sets has been undertaken. Because the relative efficiency of the CP-KS and the FPT techniques is unknown, compound **3** has also been employed to compare CPU times for calculating the FC term by the two approaches.

## Theoretical Basis

The interaction between nuclear magnetic moments and electrons can be described using Ramsey's nonrelativistic

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* To whom correspondence should be addressed. E-mail addresses: contrera@df.uba.ar and snyder@heisenbug.chem.emory.ed.

[†] Universidad de Buenos Aires.

[‡] Emory University.

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approach[12] as a sum of four perturbative operators as symbolized by eq 1.

$$H = \sum_{N<M} \hbar^2 \gamma_N \gamma_M \mathbf{I}_N^{t} \cdot \mathbf{h}_{NM}^{\mathrm{DSO}} \cdot \mathbf{I}_M + \sum_{N} \hbar \gamma_N \mathbf{I}_N^{t} \cdot (\mathbf{h}_N^{\mathrm{FC}} + \mathbf{h}_N^{\mathrm{SD}} + \mathbf{h}_N^{\mathrm{PSO}}) \tag{1}$$

The Fermi contact (FC) and the spin-dipolar (SD) terms represent the interaction between the magnetic moments associated with the nuclear spins and the electron spins, respectively. The paramagnetic and the diamagnetic spin−orbit terms (PSO and DSO) originate in the interaction between the nuclear magnetic moments and the electronic currents. The expression for each perturbative term in eq 1 follows.

$$\mathbf{h}_{NM}^{\mathrm{DSO}} = \frac{\alpha^4}{2} \sum_k \frac{(\mathbf{r}_{kN} \cdot \mathbf{r}_{kM})\mathbf{l} - \mathbf{r}_{kN} \mathbf{r}_{kM}^{t}}{{r_{kN}}^3 {r_{kM}}^3} \tag{2}$$

$$\mathbf{h}_N^{\mathrm{PSO}} = \alpha^2 \sum_k \frac{\mathbf{l}_{kN}}{{r_{kN}}^3} \tag{3}$$

$$\mathbf{h}_N^{\ \mathrm{SD}} = \alpha^2 \sum_k \mathbf{S}_k \cdot (\nabla_k \mathbf{F}_N) \tag{4}$$

$$\mathbf{h}_N^{\mathrm{FC}} = \frac{8\pi}{3} \alpha^2 \sum_k \mathbf{S}_k \delta(\mathbf{r}_{kN}) \tag{5}$$

The term $\mathbf{l}_{kN}$ is the angular momentum of the *k*th electron relative to nucleus *N*; $\mathbf{S}_k$ is the associated spin operator, and $(\nabla_k \mathbf{F}_N)$ is the electron *k* electric field gradient operator at the site of the nucleus *N*.

The spin−spin coupling tensor can be defined as

$$\mathbf{J}_{NM} = \frac{1}{h} \frac{\partial^2 E}{\partial \mathbf{I}_N \partial \mathbf{I}_M} \tag{6}$$

*E* being the electronic energy of the system. In an isotropic phase, where no preferred direction exists, molecular tumbling will average any anisotropy to zero, giving rise to the isotropic spin−spin coupling of expression 7.

$$J_{NM} = \frac{1}{3} \mathrm{Tr}(\mathbf{J}_{NM}) \tag{7}$$

Because the DSO operator, eq 2, is bilinear in the coupled nuclear moments, the DSO contribution to the coupling can be obtained readily as its expectation value, using the electronic ground state of the system. The remaining three operators, eqs 3−5, are linear in the nuclear moments. Therefore, to evaluate NMR spin−spin couplings, it is necessary to obtain the first-order correction to the electronic ground state. This correction can be derived from either wave function based or DFT approaches. In this work, calculation of all four terms within the DFT framework was implemented in the Gaussian 98 suite of programs.[13]

## Theoretical Calculations

All geometry optimizations for **1**−**4** were performed with Gaussian 98[13] at the DFT-B3LYP/6-311G** level. In all calculations involving compound **4**, both geometry and *J* coupling, Br inner-shell electrons were taken into account by means of the LANL2DZ pseudopotential (PP). Previous work has shown that for *J* couplings not involving the heavy atom, the use of LANL2DZ PP yields the correct substituent effect.[14] To derive insight into the influence of basis set on each term of $J_{\mathrm{FF}}$ couplings, those for compound **3** were calculated using five different basis sets as reported below. An account of $J_{\mathrm{FF}}$ calculations performed in this work is given as follows.

**FC Term.** The first-order density matrix, $\mathbf{P}^{(1)}$, was chosen to represent the first-order change in the electronic ground state due to the presence of a perturbation. To obtain the first-order correction, two different perturbation schemes were employed, the single FPT[15] and the CP methods. Both approaches can be used within either the Kohn−Sham (KS) or the Hartree−Fock (HF) schemes.

Implementation of the FPT method is carried out in three steps. (1) A finite perturbation of size $\lambda$ is added to the one-electron part of the electronic Hamiltonian.[15] To this end, the matrix elements of the one-electron KS operator, $h_{\mu\nu}^{\alpha,\beta}$, are replaced by $h_{\mu\nu}^{\alpha,\beta} \pm \lambda A_{\mu\nu}^{N}$, where $A_{\mu\nu}^{N}$ stands for the matrix elements of the Dirac delta function in the atomic basis set employed,

$$A_{\mu\nu}^{N} = \langle \phi_\mu | \delta(\mathbf{r}_N) | \phi_\nu \rangle = \phi_\mu(\mathbf{R}_N) \phi_\nu(\mathbf{R}_N) \tag{8}$$

(2) An unrestricted SCF calculation is performed in the presence of the perturbation. When implementing the single FPT calculation, two points must be carefully considered: (1) results must not depend on whether the perturbation is placed at the *M* or the *N* nucleus, and (2) results must be independent of the perturbation size, $\lambda$. Both conditions are satisfied automatically if calculations are performed within the linear response range of $\lambda$. However, it is important to realize that the values of $\lambda$ within a given range depend on the basis set employed as well as on the physical problem under study. (3) Once the SCF procedure has converged, the FC term can be obtained from the resulting $\alpha$ and $\beta$ density matrices:

$$J_{NM}^{\mathrm{FC}} = \frac{h}{\lambda} \left(\frac{\gamma_N}{2\pi}\right) \left(\frac{\gamma_M}{2\pi}\right) \left(\frac{8\pi}{3}\right)^2 \left(\frac{\alpha^4}{4}\right) \mathrm{Tr}((\mathbf{P}_N^{\alpha} - \mathbf{P}_N^{\beta}) \mathbf{A}^M) \tag{9}$$

The linear response in eq 9 is guaranteed as long as the density matrix ($\alpha$ and $\beta$) reflects only the first-order change, that is,

$$\begin{cases} \mathbf{P}_N^{\alpha} = \mathbf{P}_N^{(0)} + \lambda \mathbf{P}_N^{(1)} \\ \mathbf{P}_N^{\beta} = \mathbf{P}_N^{(0)} - \lambda \mathbf{P}_N^{(1)} \end{cases} \tag{10}$$

where a closed-shell ground state is implied. Replacing eq 10 with eq 9 gives

$$J_{NM}^{\mathrm{FC}} = h \left(\frac{\gamma_N}{2\pi}\right) \left(\frac{\gamma_M}{2\pi}\right) \left(\frac{8\pi}{3}\right)^2 \left(\frac{\alpha^4}{4}\right) \mathrm{Tr}(\mathbf{P}_N^{(1)} \mathbf{A}^M) \tag{11}$$

Equation 11 is particularly useful if the first-order change in the density matrix is evaluated using the CP-KS equations. The CP subroutines are already implemented in the standard version of the Gaussian 98 program. Therefore, the implementation of the *J*-coupling calculations within this approach consists of introducing the proper perturbative operators into the subroutines.

**SD Term.** The SD term is calculated using the FPT scheme. The SD perturbative operator, eq 4, can be partitioned into three operators in such a way that each contains one Cartesian component of the electronic spin. For each of these projections, six perturbations must be considered,

$$h_{N,pq}^{\mathrm{SD}} = \lambda \sum_k S_{k,p} (\nabla_k \mathbf{F}_N)_{pq}, \quad p, q = x, y, z \tag{12}$$

where $\lambda$ stands for the perturbation size. For this reason, the evaluation of the SD contribution is by far the most time-consuming. A detailed description of the SD calculation using FPT is available.[7]

**PSO Term.** The FPT approach is one of the simplest ways to introduce a perturbation to the basic molecular Hamiltonian in any electronic structure program (e.g., Gaussian 98). For purely imaginary perturbations such as the PSO perturbative operator, eq 3, however, implementation of the FPT approach requires the wave function (or the KS molecular orbitals in the DFT framework) to become complex, an option not available in many computer programs. For this reason, the PSO term was evaluated using the CP-KS method in the present work. Because the matrix representation of this operator was not available in the Gaussian 98 package, the matrix elements in the atomic basis set were obtained by using the Dalton 1.0 program.[16] The first step is to solve the CP equations for an imaginary perturbation, as given by eq 3. After convergence requirements are satisfied, the isotropic PSO contribution can be obtained as

$$J_{NM}^{\mathrm{PSO}} = \frac{\gamma_N}{2\pi}\frac{\gamma_M}{2\pi}h\frac{1}{3}\,\mathrm{Tr}\Big(\sum_{\mu\nu}(\mathbf{P}_N^{(1)})_{\mu\nu}(\mathbf{h}_M^{\mathrm{PSO}})_{\mu\nu}\Big) \qquad (13)$$

where the subscripts $\mu$ and $\nu$ are employed for the matrix representation in the atomic basis set.

**DSO Term.** The DSO term is obtained straightforwardly if the matrix representation of the DSO operator, eq 2, in the atomic basis set is available,

$$J_{NM}^{\mathrm{DSO}} = \sum_{\mu\nu}(\mathbf{P}^{(0)})_{\mu\nu}(\mathbf{h}_{NM}^{\mathrm{DSO}})_{\mu\nu} \qquad (14)$$

where $(\mathbf{h}_{NM}^{\mathrm{DSO}})_{\mu\nu}$ is the matrix element of the isotropic part of the DSO operator in the atomic basis set and $(\mathbf{P}^{(0)})_{\mu\nu}$ stands for the zero-order density matrix elements. Because the DSO integrals were not available in the Gaussian 98 package, the Dalton 1.0 program[16] was employed to calculate them.

## Results and Discussion

To study the sensitivity of aromatic $J_{\mathrm{FF}}$ couplings to basis set, perfluoropyridine **3** was examined as a test structure. Experimental values[17] are compared with results from five basis sets as illustrated in Table 1: (A) cc-pVDZ for C and N and aug-cc-pCVDZ[18] for F; (B) 6-311G** for C and N and aug-cc-pCVDZ for F; (C) cc-pVTZ for all atoms; (D) cc-pVTZ for C and N and aug-cc-pVTZ-J[19] for F; (E) cc-pVTZ for C and N and aug-cc-pCVTZ for F. Each has been used in combination with the B3LYP density functional[20] as implemented in Gaussian 98.[13] The general sensitivity to basis set of the FC term is similar to that of the SD and PSO contributions. As is well-known for Hartree−Fock calculations,[21] the DFT calculation of the DSO term shows a low sensitivity to basis set. Although the predictions from all five basis sets deliver reasonable agreement with the measured aromatic $J_{\mathrm{FF}}$ couplings, basis sets B and D (optimized to reproduce coupling constants using the SOPPA approach[22])[19] provide the closest match to experiment. Each furnishes an average deviation of 2.3 Hz for the six $J_{\mathrm{FF}}$ couplings. For this reason, all other $J_{\mathrm{FF}}$ couplings discussed in the present work were calculated with the less-demanding basis set B. For such calculations, it has been recommended that at least a triple-$\zeta$ basis set be employed.[1a] Basis set B would appear to use a double-$\zeta$ basis for fluorine. It should be noted, however, that this is not a standard double-$\zeta$ recipe because, following the recommendation made by Helgaker et al.,[1a] four tight s-functions have been added at the site of the coupled fluorine atoms.

**TABLE 1: Basis Set Dependence of $^nJ_{\mathrm{FF}}$ Couplings and Ramsey Contributions (in Hz) for Pentafluoropyridine 3**[a]

| basis set | term | $^3J(\mathrm{F_2F_3})$ | $^3J(\mathrm{F_3F_4})$ | $^4J(\mathrm{F_2F_4})$ | $^4J(\mathrm{F_2F_6})$ | $^4J(\mathrm{F_3F_5})$ | $^5J(\mathrm{F_2F_5})$ |
|---|---|---|---|---|---|---|---|
| A | FC | −14.6 | −4.9 | −2.3 | −6.7 | −5.0 | 4.4 |
| | SD | 12.8 | 10.8 | 2.8 | −4.9 | −0.9 | 17.5 |
| | PSO | −15.6 | −22.5 | 12.6 | −0.8 | 5.5 | 8.8 |
| | DSO | 0.1 | 0.2 | −1.1 | −1.0 | −1.1 | −1.1 |
| | total | −17.2 | −16.4 | 11.9 | −13.4 | −1.5 | 29.5 |
| B | FC | −14.4 | −5.1 | −2.4 | −6.4 | −4.9 | 4.3 |
| | SD | 13.0 | 10.9 | 2.8 | −5.0 | −1.0 | 17.6 |
| | PSO | −15.6 | −22.4 | 13.1 | −0.6 | 5.8 | 8.9 |
| | DSO | 0.1 | 0.2 | −1.1 | −1.0 | −1.1 | −1.1 |
| | total | −16.8 | −16.4 | 12.3 | −13.0 | −1.2 | 29.6 |
| C | FC | −12.4 | −5.0 | −2.4 | −4.5 | −4.3 | 4.5 |
| | SD | 15.5 | 12.9 | 3.2 | −5.8 | −1.6 | 20.2 |
| | PSO | −16.6 | −24.0 | 14.1 | −1.4 | 5.0 | 8.1 |
| | DSO | 0.1 | 0.2 | −1.1 | −1.1 | −1.0 | −1.1 |
| | total | −13.3 | −15.9 | 13.8 | −12.8 | −2.0 | 31.6 |
| D | FC | −16.2 | −4.3 | −2.0 | −9.1 | −5.4 | 6.7 |
| | SD | 13.7 | 11.5 | 3.1 | −5.3 | −1.2 | 19.3 |
| | PSO | −17.1 | −24.2 | 13.4 | −1.2 | 5.0 | 8.8 |
| | DSO | 0.1 | 0.1 | −1.1 | −1.1 | −1.1 | −1.1 |
| | total | −19.5 | −16.8 | 13.3 | −16.6 | −2.7 | 33.7 |
| E | FC | −14.4 | −3.7 | −1.9 | −7.9 | −5.0 | 5.7 |
| | SD | 14.3 | 12.0 | 3.2 | −5.6 | −1.3 | 20.2 |
| | PSO | −17.2 | −24.3 | 13.5 | −1.2 | 5.0 | 9.0 |
| | DSO | 0.1 | 0.1 | −1.1 | −1.1 | −1.1 | −1.1 |
| | total | −17.2 | −15.9 | 13.7 | −15.7 | −2.4 | 33.7 |
| | expt[b] | −20.3 | −18.1 | 13.7 | −15.0 | 0.0 | 26.3 |
| | expt − B | −3.5 | −1.7 | 1.4 | −2.0 | 1.2 | −3.3 |
| | expt − D | −0.8 | −1.3 | 0.4 | −1.6 | 2.7 | −7.4 |

[a] Basis set A uses cc-pVDZ for C and N and aug-cc-pCVDZ for F (235 total number of contracted AOs); basis set B uses 6-311G** for C and N and aug-cc-pCVDZ for F (259); basis set C uses cc-pVTZ for all atoms (385); basis set D uses cc-pVTZ for C and N and aug-cc-pVTZ-J for F (470); basis set E uses cc-pVTZ for C and N and aug-cc-pCVTZ for F (555). All calculations were performed with the B3LYP density functional. [b] Experimental values taken from ref 17.

**TABLE 2: Comparison of CPU Times (arbitrary units) for the Calculation of the FC Term in Pentafluoropyridine 3 Employing the CP-KS and the FPT Methods**[a]

| basis set | CP-KS | FPT |
|---|---|---|
| B (259)[b] | 94 | 81 |
| C (385)[b] | 370 | 341 |
| D (555)[b] | 1162 | 1061 |
| E (470)[b] | 713 | 715 |

[a] A description of the basis sets is given in the text. [b] The total number of basis functions in parentheses.

Another important consideration for calculating NMR spin−spin coupling in medium-sized compounds is the performance of the method employed. Thus, before turning to larger compounds, a comparison of CPU times necessary to calculate the FC term for pentafluoropyridine (**3**) was made for the CP-KS and FPT procedures for different basis sets. The results are exhibited in Table 2, indicating that the performance of both methods is approximately the same, although the FPT procedure in general shows somewhat shorter CPU times. Therefore, the FTP method was employed for the calculation of FC and SD terms reported in this work.

In Table 3, calculated $J_{\mathrm{FF}}$ coupling constants in **4** are compared with the corresponding experimental values taken from Matthews.[23] The agreement between experiment and calculations is excellent even though experimental values range

**TABLE 3: Fluorine−Fluorine Couplings and the Corresponding Ramsey Contributions for 2-Br-hexafluoroquinoline 4 Evaluated Using Basis Set B (Hz)**[a]

| coupling | FC | SD | PSO | DSO | total | expt[b] |
|---|---|---|---|---|---|---|
| $^3J(F_3F_4)$ | −4.4 | 18.8 | −28.8 | 0.3 | −14.1 | −15.4 |
| $^3J(F_5F_6)$ | −4.3 | 16.8 | −30.4 | 0.3 | −17.5 | −17.4 |
| $^3J(F_6F_7)$ | −3.9 | 8.5 | −23.3 | 0.3 | −18.4 | −19.0 |
| $^3J(F_7F_8)$ | −5.5 | 16.8 | −27.5 | 0.2 | −15.9 | −16.6 |
| $^4J(F_4F_5)$ | 42.1 | −0.7 | 3.8 | 1.1 | 46.3 | 45.8 |
| $^4J(F_5F_7)$ | −3.0 | −1.4 | 4.9 | −1.0 | −0.5 | 1.4 |
| $^4J(F_6F_8)$ | −3.3 | −1.0 | 7.5 | −1.0 | 2.2 | 3.0 |
| $^5J(F_3F_5)$ | 1.2 | 6.6 | 1.7 | −0.6 | 9.0 | 6.8 |
| $^5J(F_4F_6)$ | 0.6 | 6.0 | 0.7 | −0.6 | 6.7 | 5.0 |
| $^5J(F_4F_8)$ | 0.0 | 4.2 | −3.5 | −0.8 | 0.0 | 1.4 |
| $^5J(F_5F_8)$ | 2.7 | 18.5 | −1.0 | −1.0 | 19.2 | 15.4 |
| $^6J(F_3F_6)$ | −0.6 | −4.0 | 0.2 | −0.7 | −5.0 | −2.8 |
| $^6J(F_4F_7)$ | −0.6 | −4.4 | 0.4 | −0.7 | −5.3 | −3.5 |
| $^6J(F_3F_8)$ | −0.6 | −4.8 | −0.5 | −0.7 | −6.6 | −4.3 |
| $^7J(F_3F_7)$ | 0.9 | 8.7 | 0.9 | −0.7 | 9.9 | 7.6 |

[a] All calculations were performed with the B3LYP density functional. [b] Experimental values from ref 23.

from −19.0 to +45.8 Hz. With one exception, the signs of the couplings are faithfully reproduced, while the largest difference ($\Delta J = 3.8$ Hz) is observed for $^5J(F_5F_8)$. For all other couplings, the accuracy is sufficient to discuss trends followed by both the contact (FC) and noncontact contributions. One of the most significant features of the couplings displayed in Table 3 is that, with few exceptions, the sum of the SD and PSO terms is larger than the FC contribution, even though in most cases these two noncontact terms have opposite signs.

It is informative to compare the FC trends shown in Tables 1 and 3 with those observed for $^nJ_{HH}$ couplings in aromatic compounds, because the latter are assumed to be dominated by the FC contribution.[24] The FC term for all $^3J_{FF}$ couplings is negative, which contrasts with the positive $^3J_{HH}$ couplings found for unfluorinated aromatic compounds. It is remarkable that in **3** the absolute value of the FC term for $^3J(F_2F_3)$ is notably larger by 9−11 Hz (basis set B) than that for all other three-bond $J_{FF}$ couplings displayed in these two tables. By way of contrast, in pyridine, $^3J(H_2H_3) = 4.9$ Hz, while $^3J(H_3H_4) = 7.7$ Hz.[25] The difference has been ascribed mainly to the nitrogen lone-pair orientation effect on the former.[26] When taken in an algebraic sense, the trend seems to indicate that in a pyridine ring the nitrogen lone-pair orientation effect corresponds to a negative contribution for both $^3J(H_2H_3)$ and $^3J(F_2F_3)$ couplings. Thus, by comparison with $^3J(X_3X_4)$, $\Delta J = -3.0$ and $-11.9$ Hz, respectively. If we assume that the lone-pair effect does not extend significantly to substitutents at the C3 and C4 centers, it is considerably more important for the fluorinated system. This is comprehensible in terms of interactions between the lone pair at nitrogen and those at flanking fluorine implying a putative through-space factor for fluorinated pyridines absent in the parent species.

For couplings between fluorine nuclei separated by more than three formal bonds, $^nJ_{FF}$ ($n > 3$), the sign of the FC term alternates with the number of bonds between the coupled nuclei, that is, negative for an even number of bonds and positive for an odd number, $(-1)^{2n+1}$. This sign rule is the same as that observed for the $\pi$-transmitted component of aromatic $J_{HH}$ couplings.[27] Such a result suggests that in aromatic compounds the FC term of $^nJ_{FF}$ couplings ($n > 3$) is largely characterized by a $\pi$-transmission mechanism. It should be noted that $^4J(F_4F_5)$ in **4** is a conspicuous exception to this rule. This *peri coupling* is well-known to be dominated by a through-space mechanism (vide infra).[8,28] It is interesting to note that SD contributions show the $(-1)^{2n+1}$ alternating sign rule for all $^nJ_{FF}$ couplings displayed in Table 3, even for $n = 3$. However, in Table 1, this rule does not hold for the SD contribution to $^4J(F_2F_4)$. For this reason, the latter as well as $^4J(F_2F_6)$ are considered below in greater detail. Most PSO contributions displayed in Table 3 follow a $(-1)^n$ alternating sign rule. The exceptions are $^5J(F_3F_5)$ and $^5J(F_4F_6)$, although the absolute values of the deviations are small. There are two additional outliers to the rule as illustrated by Table 1, $^4J(F_2F_6)$ and $^5J(F_2F_5)$ in **3**. The absolute value of the former is very small and not worthy of further comment. On the other hand, the latter PSO term makes a significant contribution to the para-like coupling in **3** (8.9 Hz). This contrasts with the corresponding PSO term for the similar coupling in the benzene ring of compound **4** (−1.0 Hz).

It is known that conjugation effects are very important for transmitting long-range $J_{FF}$ couplings. One well-defined case is the $^9J_{FF}$ coupling in fluorinated derivatives of biphenyl.[29] Apparently, a delocalized $\pi$-electronic system constitutes an efficient pathway for transmitting the SD term.[7,30] Results displayed in Table 3 suggest that this does not hold for the PSO term because, in most cases of long range coupling ($n > 4$), the PSO contribution is considerably smaller than the SD one. However, for $n = 3$, the double bond character of bonds belonging to the coupling pathway seems to be important for PSO transmission. A case in point is the comparison between SD and PSO terms for $^3J(F_5F_6)$ and $^3J(F_6F_7)$ given in Table 3. It is known that in fused aromatic rings, such as naphthalene or quinoline, the double bond character of the $C_5{=}C_6$ bond is notably larger than that of the $C_6{=}C_7$ bond.[31] When going from the former to the latter coupling, an important reduction in the absolute values of the SD and PSO terms is observed. However, the absolute value of the experimental coupling is only slightly increased because these two effects are of opposite sign. The smaller double bond character of $C_6{=}C_7$ must also influence[32] the FC term of $^3J(F_6F_7)$, although the effect is less important than that for the noncontact terms. These observations contrast with the corresponding trend for $J$(H,H) couplings in naphthalene in which $^3J(H_1,H_2) = 8.3$ Hz and $^3J(H_2,H_3) = 6.9$ Hz.[33] For F atoms placed in a para orientation, the SD term also seems to be important for $^5J_{FF}$ couplings.[7] Results displayed in Tables 1 and 3 support such an assertion. Thus, the calculated SD contribution to $^5J(F_2F_5)$ in **3** (17.6 Hz, basis set B) is similar to that for $^5J(F_5F_8)$ in **4** (19.2 Hz), contrasting with the PSO behavior (8.9 and −1.0 Hz, respectively).

Signs of the DSO contribution are consistent with the known trend and easily rationalized with one of the possible partitions that are described in the literature.[5c,34] If the space spanned by the electrons is divided in half by a sphere the diameter of which is determined by the coupled nuclei, then electrons inside that sphere yield a negative contribution while those outside yield a positive contribution.[34a] The total DSO term is given by the sum of two such contributions.

There are several features of the calculated four-bond coupling constants displayed in Tables 1 and 3 that deserve further comment. The main features of $^4J(F_3F_5)$ in **3** (−1.2 Hz) and $^4J(F_5F_7)$ and $^4J(F_6F_8)$ in **4** (1.3 and 3.0 Hz, respectively) are similar. On the other hand, several aspects of $^4J(F_2F_4)$ and $^4J(F_2F_6)$ (12.3 and −13.0 Hz, respectively*)* are notably different, both from the former four-bond couplings, and from each other. The shortest coupling pathway for $^4J(F_2F_6)$ includes the nitrogen atom. However, the absolute value of its experimental coupling is close to that of $^4J(F_2F_4)$, but the signs are opposite. The situation resembles somewhat the trend observed for $^4J(H_2H_4)$ and $^4J(H_2H_6)$ couplings in pyridine, the latter[35] being the only

**TABLE 4: Calculated $^4J_{FF}$ Couplings and the Corresponding Ramsey Contributions for 2,5-Difluoropyridine 1 and 2,4,6-Trifluoropyridine 2 Using Basis Set B (Hz)[a]**

| compound | $^4J_{FF}$ | FC | SD | PSO | DSO | total | expt[b] |
|---|---|---|---|---|---|---|---|
| **1** | $^4J(F_2F_6)$ | −8.2 | −4.6 | 2.7 | −1.1 | −11.2 | −12.2 |
| **2** | $^4J(F_2F_6)$ | −9.0 | −4.5 | 1.8 | −1.1 | −12.8 | −13.0 |
| **2** | $^4J(F_2F_4)$ | 1.9 | 2.3 | 13.1 | −1.0 | 16.2 | 19.2 |

[a] All calculations were performed with the B3LYP density functional. [b] Experimental values from ref 38.

known negative aromatic $J_{HH}$ coupling in both pyridine and benzene derivatives.[36] In some 4-X-pyridine, the $^4J$ coupling was reported as positive.[37]

To examine more closely the behavior of $^4J(F_2F_4)$ and $^4J(F_2F_6)$, calculations were also performed for structures **1** and **2** for which the experimental $^4J_{FF}$ couplings are known.[38] The predictions are compared with the corresponding experimental values in Table 4, in which agreement between the two sets is very good. It is observed that the calculated $^4J(F_2F_6)$ couplings in **1** and **2** (−11.2 and −12.8, respectively) are similar to that in **3** (−13.0 Hz), in agreement with the experimental values. On the other hand, the calculated $^4J(F_2F_4)$ coupling in **2** (16.2 Hz) is somewhat larger than that in **3** (12.3 Hz). The results in Table 3 suggest this to arise from a substituent effect for the FC term. That is, while the SD and PSO $^4J(F_2F_4)$ values for **2** and **3** are nearly identical, FC for this coupling amounts to 1.9 and −2.4 Hz, respectively. Consequently, the fluorines at C3 and C5 in **3** clearly lower $J^{FC}$ for the spin−spin interactions between the flanking fluorines.

The very large positive $^4J(F_4F_5)$ coupling in **4** is dominated by a through-space mechanism, which has been discussed in many papers.[8,28] The main feature of such a coupling was rationalized by Mallory et al.[39] as originating in overlap of the fluorine lone pairs. A similar conclusion was recently reached by applying the NJC (natural *J* coupling) dissection analysis[40] to a selection of *peri*-difluoronaphthalene derivatives.[8]

## Conclusions

Modern DFT methodology permits the semiquantitative evaluation of NMR spin−spin couplings in medium-sized compounds with the expenditure of only modest computational resources. The fluorinated derivatives of several pyridines and a quinoline chosen for the present study show a variety of $J_{FF}$ couplings spanning a broad range of experimental values (from −20.3 to 45.8 Hz). For all couplings predicted, the experimental $^nJ_{FF}$ values ($3 \leq n \leq 7$) are reliably reproduced in magnitude and sign, although they are influenced by a wide diversity of factors. One of the notable features observed for the calculated couplings is that most of them are dominated by *noncontact* contributions, even though the oppositely signed SD and PSO terms tend to compensate in a number of cases. The widespread assumption that scalar coupling constants are adequately represented by the Fermi contact component clearly does not hold for coupled fluorine nuclei separated by three to seven bonds. A number of recent papers have hinted at this possibility.[7,8,41] Although it is tempting to conclude that the predominance of noncontact contributions to $J_{FF}$ couplings holds primarily for unsaturated or highly conjugated fluorine-containing compounds, the recent work of Shtarev, Michl, and co-workers,[11] as well as that of Bryce and Wasylishen,[9b] suggests that saturated fluorocarbons are subject to an element of capriciousness similar to that described above.

The ability of the DFT/B3LYP approach in combination with the modest 6-311G** basis set to accurately describe $J_{FF}$ couplings is quite promising. It can be envisioned that its systematic application will prove to be a complementary tool to experimental measurement of spin−spin coupling constants and thereby provide insight into aspects of molecular structures in compounds of chemical or biological interest or both.

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