ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2023, 59, 14661

Received 2nd November 2023,
Accepted 13th November 2023

DOI: 10.1039/d3cc05389j

rsc.li/chemcomm

The pitfalls of using J_{HF} spin–spin coupling constants to infer hydrogen bond formation in organofluorine compounds†

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Theoretical decomposition of "through space" spin–spin coupling constants (SSCCs) in organofluorine compounds signal that intramolecular hydrogen bonds (H-bonds) are not the primary mechanism of transmission for SSCCs. Increasing solvent polarity may disrupt H-bonds, but not necessarily the J_{FH} SSCC. Substituent effects may drastically alter the SSCC transmission pathway. Accurate SSCC analysis requires benchmarking theoretical calculations to support experimental data interpretation.

Scalar spin–spin coupling constants (SSCCs) serve as an indispensable tool in the exploration of the structure and reactivity of organic compounds, especially in the interpretation of nuclear magnetic resonance (NMR) spectra. Though the experimental procurement and interpretation of SSCCs for structure determination can be straightforward (when the experimental sign of the coupling constant is not of interest), their theoretical calculation is intricate. Indeed, the calculation of SSCCs is a complex process that involves four contribution terms (Ramsey) to the total SSCC [^nJ(N,M)]: the Fermi contact (FC), spin-dipole (SD), paramagnetic spin–orbit (PSO), and diamagnetic spin–orbit (DSO) terms as in the following equation:[1,2]

$$^nJ(\mathrm{N,M}) = {}^nJ^{\mathrm{FC}}(\mathrm{N,M}) + {}^nJ^{\mathrm{SD}}(\mathrm{N,M}) + {}^nJ^{\mathrm{PSO}}(\mathrm{N,M}) + {}^nJ^{\mathrm{DSO}}(\mathrm{N,M}) \quad (1)$$

where n denotes the number of chemical bonds between coupled nuclei N and M.

These terms signify different interactions between the spins of nuclei and the electrons that surround them. While it is imperative to compute all four Ramsey terms for a comprehensive understanding of the transmission pathways of SSCCs, the Fermi Contact (FC) term often emerges as the dominant contributor to the observed value of the SSCC. The FC term originates from the interaction between the electron and nuclear spins when the electron is located at the same point as the nucleus, predominantly influenced by orbitals that possess s-character. At a qualitative level, the FC term encapsulates the spherically symmetric component of the electron distribution that permeates the nucleus. Given that the spin of the electron can align either in parallel or in antiparallel fashion to the nuclear spin, there exists a differential in energy between these configurations. This difference in energy culminates in a net magnetization of the electron and, subsequently, the magnetization of the nucleus it is in "contact" with.[3–5]

Calculations of SSCCs involving F atoms can be challenging for several reasons, including calculating the FC term. Nuclei with lone electron pairs, such as F, present distinct challenges due to the complex interactions of these electrons with nuclear spins.[6] Thus, accurately determining the molecular magnetic properties of organolfuorine compounds has historically been an intricate task for computational approaches.[7] Even high level *ab initio* methods such as SOPPA(MP2) and EOM-CCSD, when employed on a range of fluorobenzene compounds with quadruple zeta basis sets, fail to reproduce experimental results accurately.[8] While high-level *ab initio* methods, including SOPPA(CCSD), HRPA, EOM-CCSD, and HRPA(D), might generally yield accurate results for SSCCs involving F atoms, such as J_{FH}, J_{FC} and J_{FF} SSCCs, their intensive computational demands render them less feasible for extensive systems or routine use in simulating organofluorine NMR spectra.[9,10] Consequently, DFT calculations are a method of choice due to their favorable cost-to-performance ratio. However, an expansive benchmark study is imperative for the effective utilization of DFT functionals, especially for SSCCs with organofluorine compounds.[11,12]

Beyond the computational challenges, it is common to view the observed experimental J_{FH} SSCCs of nonbonded atoms as indicative of hydrogen bond (H-bond) formation, and its

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† Electronic supplementary information (ESI) available: All calculation details, including Cartesian coordinates, benchmark studies of energies and SSCCs are available in the ESI. See DOI: https://doi.org/10.1039/d3cc05389j

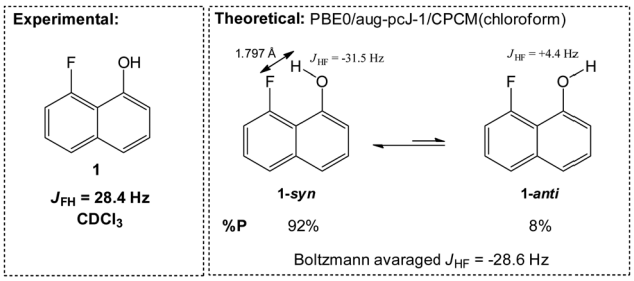


Fig. 1 8-fluoro-1-naphtol (**1**) and the experimental $J_{FH(O)}$ SSCC observed experimentally in $CDCl_3$. Structural representations of conformers **1-*syn*** and **1-*anti***, their calculated conformer populations (from ΔG energies) and Boltzmann averaged calculated J_{FH} SSCC at the PBE0/aug-pcJ-1/CPCM(chloroform) level.

absence as evidence of non-interacting atoms.[13] This study will demonstrate that SSCCs' transmission mechanisms in the FC term are more complex than experimental results typically imply and that benchmarking calculations are essential for the precise computation of SSCCs involving organofluorine compounds.

The first case study in the present work is 8-fluoro-1-naphtol **1** (Fig. 1). This molecule has an experimental value of 28.4 Hz for the $J_{FH(O)}$ SSCC in $CDCl_3$ as reported by Takemura *et. al.*[14] The molecule may have two conformers: **1-*syn*** and **1-*anti***, the former being the global minimum at all theoretical levels tested in this work. We applied all possible combinations among M06L, M06-2X, B3LYP, CAM-B3LYP, BHandHLYP and PBE0 functionals and the pcJ-0, pcJ-1, pcJ-2, pcJ-3, aug-pcJ-0 and aug-pcJ-1 basis sets. The CPCM implicit solvent model with parameters for chloroform was also included (see ESI†). By considering the calculated J_{FH} SSCCs for conformers **1-*syn*** and **1-*anti*** and their conformer populations, the PBE0/aug-pcJ-1 level showed the best match with experiment for **1**. All theoretical levels calculate a negative sign for J_{FH} SSCC, in contrast to experiment (Fig. 1). The J_{FH} SSCC is mainly transmited by **1-*syn*** (−31.5 Hz) against a value of +4.4 Hz for **1-*anti***. It seems reasonable to indicate that this SSCC is transmitted through a CF···HO H-bond, but a deeper investigation is necessary to analyse the J_{FH} mechanism of transmission in **1-*syn***.

The quantum theory of atoms in molecules (QTAIM) and noncovalent interactions (NCI) methods indicate the H-bond as topologically stable, with a relatively high electron density at the bond critical point (ρ). This H-bond possesses electrostatic character, as indicated by the positive values of the electron density Laplacian ($\nabla^2\rho$) and the total electron energy density (H_c) at the BCP (Fig. 2). The natural bond orbital (NBO) analysis[15] reveals that the H-bond is electrostatically stabilized (by considering H and F atomic charges and distances in the classical Coulomb equation, $E_{HF} = \frac{Q_H Q_F}{R_{HF}}$) by 10.15 kcal mol^{-1}, but stereoelectronically unstable since the steric effect between the 2p-type F lone pair n_F and the σ_{HO} orbital outweights the H-bond $n_F \rightarrow \sigma^*_{HO}$ hyperconjugative stabilization (Fig. 2). Overall, the intramolecular H-bond stabilization energy (E_{HB}) is 4.0 or 4.7 kcal mol^{-1}, as estimated by modified versions of Espinosa's original method[16] proposed by Afonin[17] and Jabłoński,[18] representing a weakly to moderately stabilized H-bond.[19]

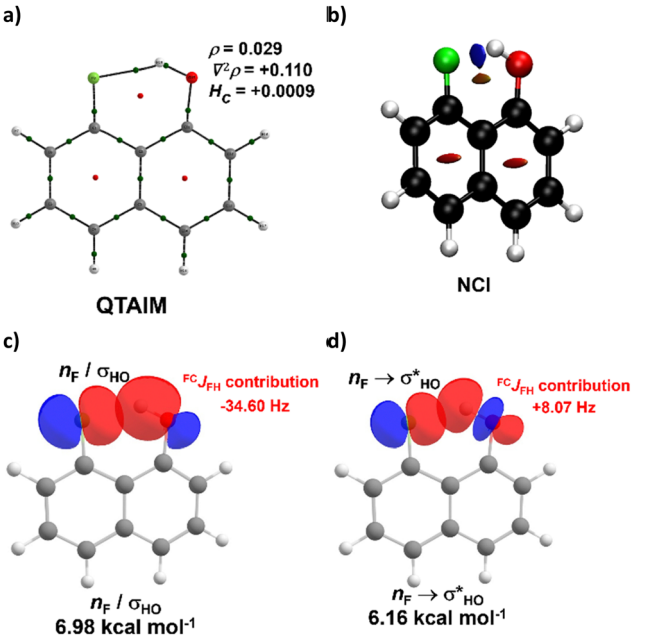


Fig. 2 (a) A QTAIM molecular graph for **1-*syn*** and the calculated values of electron density (ρ), Laplacian of the electron density ($\nabla^2\rho$) and total electron energy density (H_c) at the BCP in atomic units. (b) NCI isosurfaces for **1-*syn*** considering a value for the reduced density gradient of 0.5 a.u. and blue-green-red color scale in the range of $-0.02 < \text{sign}(\lambda_2)\rho < +0.02$ a.u. NBO interactions and the Fermi contact term ($^{FC}J_{FH}$) for the J_{FH} SSCC (red color) for (c) steric interaction between the 2-p type F lone pair n_F and the σ_{HO} orbital (d) H-bond $n_F \rightarrow \sigma^*_{HO}$ hyperconjugative stabilization.

There exists intramolecular H-bond with electrostatic character in **1-*syn***, but NBO analysis indicates that there is more repulsion than stabilization when only the orbital interactions are considered. Accordingly, the Natural J-Coupling analysis (NJC)[20] indicates that most of the FC term mechanism of transmission for the J_{FH} SSCC occurs due to the n_F/σ_{HO} steric interaction and not due to the stabilizing $n_F \rightarrow \sigma^*_{HO}$ hyperconjugation (Fig. 2). Steric effects (not H-bonding) are the mechanisms of transmission, even though a stabilizing electrostatic H-bond is formed in **1-*syn***. This observation agrees with 2-fluorophenol, which has a much smaller experimental SSCC in non-polar solvents (~4.4 Hz).[21]

More interestingly, the experimental value of J_{FH} in **1** decreases to 4.4 Hz in THF and 2.6 Hz in DMSO,[14] which may be interpreted as a higher ability of these solvents to act as H atom acceptors in an H-bond, thus disrupting the intramolecular CF···HO H-bond and the J_{FH} SSCC. Thus, we may anticipate that **1-*anti*** is the predominant conformer in THF, and particularly in DMSO. By considering a microsolvated (5 solvent molecules) complex of **1** in chloroform, THF and DMSO, only **1-*syn*** has an observed population in the GFN2-xTB[22] meta dynamics ensamble for chloroform, THF has its most stable conformer as **1-*anti*** with a calculated J_{FH} of +4.3 Hz for the global minimum (see ESI†) and only **1-*anti*** has a measurable population in DMSO. The calculated J_{FH} SSCC has a value of +3.6 Hz [QM/MM: PBE0/aug-pcJ-1:GFN2-xTB/

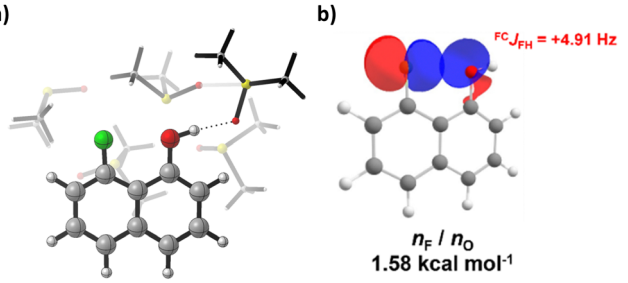


Fig. 3 (a) Global minimum in the ensemble of a 50 ps metadynamics GFN2-xTB simulation for **1** in DMSO (microsolvation with 5 explicit DMSO molecules embedded in a CPCM implicit solvent model with DMSO parameters). (b) Steric interaction between the 2-p type F lone pair n_F and the s-type O lone pair n_O orbital (PBE0/aug-pcJ-1/CPCM). The contribution of this interaction to the J_{FH} FC term is given in Hz (red color).

CPCM(DMSO)] for the most stable geometry in the ensemble (Fig. 3a). The smaller positive J_{FH} value for **1-*anti*** in DMSO than in THF can be anticipated by the higher β value[23] (solvent H-bond acceptor basicity) in DMSO (β = 0.74) in comparison to THF (β = 0.55) which elongates the O–H bond more in DMSO than in THF.

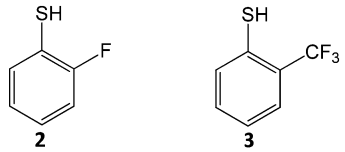
Even though only **1-*anti*** is predicted to be stable in DMSO by the microsolvation calculations, there is experimental and theoretical evidence that the J_{FH} SSCC is being transmitted. NJC analysis indicates that the most important mechanism for the J_{FH} transmission in **1-*anti*** is the steric interaction between a 2p-type F lone pair n_F and the s-type O lone pair n_O orbital (Fig. 3b). Such an interesting example for **1** is representative; even though an intramolecular H-bond is formed for the *syn* conformer, the transmission pathway of the SSCC exists not because of the H-bond itself, but the close contact between lone pairs and/or bonding orbitals either in the *syn* or *anti* conformer.

Another interesting example may be observed in the experimental J_{FH} SSCCs of 2-fluorothiophenol **2** and 2-(trifluoromethyl)thiophenol **3** (Table 1).[24,25] While there is a decrease in the SSCC for **2** with the increase of solvent polarity, there is an increase for **3**. One could interpret the decrease in **2** due to intramolecular H-bond disrupting, but what about **3**?

Experimentally, J_{FH} exhibits a negative sign for **2** and a positive sign for **3**, as demonstrated by E.COSY experiments.[24,25] Theoretical benchmarks identify B3LYP/aug-pcJ-1/CPCM as the optimal level of accuracy for both compounds. *Syn* conformers exhibit negative values and *anti* conformers positive ones for J_{FH} SSCCs for both molecules (see ESI†). Given that the *anti* conformer possesses a higher polarity, the *syn* conformer emerges as the most stable for **2** in non-polar solvents such as cyclohexane, chloroform, and dichloromethane. However, in solvents like acetone, its stability is almost surpassed by the *anti* conformer. Notably, since *syn* and *anti* conformers exhibit opposing signs for J_{FH}, the population-weighted J_{FH} value in **2** approaches zero in more polar solvents (see Table 1).

Conversely, the J_{FH} SSCC for **3** is experimentally positive, a finding that aligns with the superior stability of the *anti* conformer across all solvents, particularly in acetone. As solvent polarity increases, the population of the *anti* conformer for **3** rises, making it predominant in more polar solvents. In this way, **2** aligns with a more traditional understanding, with the SSCC being primarily transmitted by a *syn* conformer to form an intramolecular H-bond. In contrast, **3** deviates from this norm. It should be perceived non-classically, with its J_{FH} SSCC conveyed predominantly in the *anti* conformer through chalcogenic CF···SH interactions.

Table 1 Experimental and theoretical [B3LYP/aug-pcJ-1/CPCM(chloroform)] J_{FH} SSCCs (in Hz) for **2** and **3** with increasing solvent polarity. Calculated *syn*/*anti* conformer populations in percentage are given in between parenthesis. Calculated molecular dipoles (μ) in chloroform for *syn*/*anti* coformers are given in Debyes (italics)



2 **3**

μ (syn / anti) *1.78 / 3.22* *3.02 / 4.76*

Experimental/Theoretical

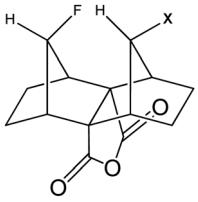
	2	**3**
Cyclohexane-d_{12}	−2.11/−3.18 (77 : 23)	+2.15/+1.38 (73 : 27)
$CDCl_3$	−1.18/−1.27 (67 : 33)	+3.00/+3.15 (37 : 63)
CD_2Cl_2	−0.78/−0.42 (62 : 38)	+3.50/+3.35 (34 : 66)
Acetone-d_6	0.00/+0.23 (59 : 41)	+4.70/+3.56 (30 : 70)

Other noteworthy examples include the "jousting" compounds (**4**) synthesized by Lectka *et al.*[26] These molecules manifest high experimental J_{FH} SSCCs that augment concomitantly with the enhanced electron-withdrawing ability of a given X substituent as indicated in Table 2. In these compounds, the CF···HC interactions are deemed stereoelectronically destabilizing, as the n_F/σ_{CH} steric interactions exert a greater destabilizing effect compared to the stabilizing $n_F \rightarrow \sigma^*_{CH}$ hyperconjugative interactions. However, by using classic Coulomb's equation with QTAIM charges, reveals a stabilizing electrostatic energy (U_e) arising from these H-bonds. This energy progressively increases in the sequence X = H, F, OH, Cl, CN. Multiple parameters – encompassing geometric, QTAIM, and NBO measures such as H-bond distances $r_{CF\cdots HO}$, electron density ρ, its Laplacian $\nabla^2\rho$, total energy density H_c at BCP, $n_F \rightarrow \sigma^*_{CH}$ hyperconjugation, and H-bond energy (E_{HB}) derived from Afonin's equation[17] - all escalate following this identical trend (see ESI†).

Interestingly, the decomposition of the FC term reveals that the mechanism of transmission of $^{FC}J_{FH}$ changes from being mainly due to Lewis/destabilizing interactions when X = H, F, OH or Cl to delocalization interactions when X = CN. Consequently, the J_{FH} SSCC transmission changes from being predominantly steric to hyperconjugative. This result exemplifies the intricate nuances inherent in SSCC mechanism transmission, while also highlighting the influence that substituents exert upon such mechanisms. The SSCC increases considerably for X = CN not just because the H-bond becomes stronger, but also because now the mechanism of transmission changes from steric to hyperconjugative.

Our present paper provides an in-depth analysis of the "through space" spin–spin coupling constant (SSCC) interpretation using

Table 2 Compound **4** experimental and PBE0/aug-pcJ-1/CPCM(chloroform) calculated J_{FH} SSCCs in Hz. NBO steric interaction between the 2-p type F lone pair n_F and the σ_{CH} orbital and $n_F \rightarrow \sigma^*_{CH}$ hyperconjugative interactions (in kcal mol^{-1}). Decomposition of the Fermi contact term ($^{FC}J_{FH}$) into its Lewis (Steric) and delocalization (hyperconjugative) contributions and repolarization are also given in Hz



4

	H	F	OH	Cl	CN
J_{FH} (Exp.)	12.2	17.5	18.7	24.5	30.7
J_{FH} (Theor.)	−12.5	−18.1	−19.0	−25.7	−33.6
n_F/σ_{CH}	10.12	8.46	9.36	10.59	11.67
$n_F \rightarrow \sigma^*_{CH}$	2.79	3.17	3.88	4.23	5.54
$r_{CF\cdots HO}$	1.897	1.870	1.853	1.829	1.810
q(H)	+0.05	+0.10	+0.08	+0.12	+0.13
Ue	−6.16	−12.03	−9.89	−14.94	−16.06
ρ	0.029	0.030	0.031	0.033	0.034
$\nabla^2\rho$	+0.029	+0.115	+0.119	+0.126	+0.131
H_c	+0.0008	+0.0012	+0.0013	+0.0015	+0.0017
E_{HB}	−3.90	−4.12	−4.27	−4.50	−4.66
$^{FC}J_{FH}$	−9.3	−14.3	−16.9	−23.2	−31.1
$^{Lewis}J_{FH}$	−9.8	−16.5	−29.9	−16.8	−5.3
$^{Deloc}J_{FH}$	−1.3	1.5	12.2	−8.6	−26.8
$^{Repol}J_{FH}$	1.8	0.7	0.8	2.2	1.0

organofluorine compounds as salient examples to understand $^{TS}J_{FH}$ SSCCs. Our findings challenge the prevalent notion that intramolecular H-bond formation predominantly drives the SSCC transmission mechanism. Furthermore, the assumed correlation between increased solvent polarity and H-bond/SSCC disruption is not universally applicable, as evidenced for compounds that have SSCCs transmitted by nonclassical long-range interactions. A noteworthy observation is the pronounced influence of substituent effects on SSCC mechanism, sometimes leading to inversion from steric to hyperconjugative in the SSCC transmission pathway. The integration of empirical and theoretical data highlights the crucial role of benchmark calculations to obtain accurate results for DFT calculations. Ultimately, this work emphasizes the need for meticulous interpretation of experimental SSCC data and the careful integration of theoretical calculations to ensure accurate and reliable conclusions.

RAC thanks FAPESP for a Young Researcher Award (#2018/03910-1) and for scholarships of GC (2022/16188-8) and BAP (#2023/14064-2). FAEPEX is acknowledged by a fellowship (#3472/23). CENAPAD-SP and CESUP are also acknowledged for the computational resources used in theory calculations.

Conflicts of interest

There are no conflicts to declare.

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