

^1H J_{FH} coupling in 2-fluorophenol revisited: Is intramolecular hydrogen bond responsible for this long-range coupling?

Rodrigo A. Cormanich,^a Marilua A. Moreira,^b Matheus P. Freitas,^b Teodorico C. Ramalho,^b Cléber P. A. Anconi,^b Roberto Rittner,^a Rubén H. Contreras^c and Cláudio F. Tormena^{a*}

The present study shows that a hydrogen bond between the OH group and the fluorine atom is not involved in the ^1H J_{FH} spin–spin coupling transmission either for 4-bromo-2-fluorophenol or 2-fluorophenol. In fact, according to a quantum theory of atoms in molecules analysis, no bond critical point is found between O–H and F moieties. The nature of the transmission mechanism of the Fermi contact term of the ^1H J_{FH} spin–spin coupling is studied by analyzing canonical molecular orbitals (see *J. Phys. Chem. A* 2010, 114, 1044), and it is observed that virtual orbitals play only a quite minor role in its transmission. This is typical of a Fermi contact term transmitted mainly through exchange interactions owing to the overlap of proximate electronic clouds; therefore, it is suggested to identify them as $^{n\text{TS}}J_{\text{FH}}$ coupling where n stands for the number of formal bonds separating the coupling nuclei. In the cases studied in this work is $n = 4$. Results presented in this work could provide an interesting rationalization for different experimental signs known in the current literature for proximate J_{FH} couplings. Copyright © 2011 John Wiley & Sons, Ltd.

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Introduction

The importance of NMR scalar spin–spin coupling constants (SSCCs) transmitted through hydrogen bonds emerged, fundamentally, from observing ^1H $J_{15\text{N}-1\text{H}}$ and ^2H $J_{15\text{N}-15\text{N}}$ SSCCs for DNA and RNA molecular systems.^[1,2] Recently, Alkorta *et al.*^[3] published a review reporting ^nH J_{XY} SSCCs including ^1H $J_{\text{FH}} = -4.42$ Hz in 4-bromo-2-fluorophenol.^[4] However, there is some evidence that, at least in some instances, O–H...F hydrogen bonds are not the mechanism to transmit through-space (TS) J_{FH} SSCCs, like, for example, 2,2,2-trifluoroethanol,^[5] where the prevalence of the *gauche* form is ascribed to a decrease of repulsion forces rather than to the formation of an attractive intramolecular hydrogen bond. The assertion about the lack of intramolecular hydrogen bonds in compounds **1** and **2** is also supported by several studies where it is concluded that covalently bonded fluorine atoms hardly ever act as hydrogen bond acceptors.^[6–11]

This disparate behaviour relating occurrence and the absence of hydrogen bond between 4-bromo-2-fluorophenol and 2,2,2-trifluoroethanol called our attention for performing a theoretical and experimental study on 4-bromo-2-fluorophenol (compound **1**) and 2-fluorophenol (compound **2**) (Fig. 1). For the former, it is known that ^1H $J_{\text{FH}} = -4.4$ Hz.^[4] For the latter, it was measured (in absolute value) as part of this work ^1H $J_{\text{FH}} = 4.8$ Hz in cyclohexane solution.

Calculations Section

Geometries of compounds **1** and **2** were optimized both as isolated molecules and taking into account the effect of the

relative permittivity of solvent (ϵ), which was modelled using the IPCM (Isodensity Polarizable Continuum Model) method, at the MP2/EPR-III level; for compound **1** using the aug-cc-pVDZ basis set for Br. ^1H J_{FH} couplings in compounds **1** and **2** were calculated using the CP-DFT/B3LYP methodology as implemented in the Gaussian03 package of programs,^[12] using the same basis set as used in the geometry optimization procedures. Second-Order Polarization-Propagator Approximation (Coupled-Cluster Singles-and-Doubles) SOPPA(CCSD)-SSCC,^[13–15] calculations were performed using the Dalton 2.0 program^[16] using the EPR-III basis set for hydroxyl hydrogen and fluorine atom. For oxygen, bromine, carbon, and remaining hydrogen atoms, the cc-pVDZ basis set was used. The NBO analysis was performed using NBO 5.0^[17] at the B3LYP/EPR-III level (for Br atom, aug-cc-pVDZ basis set was used). Quantum Theory of Atoms in Molecules (QTAIM) analysis was performed using the AIMALL^[18] program with the wave function obtained at MP2/EPR-III level (for bromine atom aug-cc-pVDZ basis set was used).

* Correspondence to: Cláudio F. Tormena, Chemistry Institute, University of Campinas C.P. 6154, 13083-970, Campinas, SP, Brazil. E-mail: tormena@iqm.unicamp.br

^a Chemistry Institute, University of Campinas, C.P. 6154 13083-970, Campinas, SP, Brazil

^b Department of Chemistry, Federal University of Lavras, C.P. 3037 37200-000, Lavras, MG, Brazil

^c Department of Physics, FCEyN, University of Buenos Aires and IFIBA-CONICET, Buenos Aires, Argentina

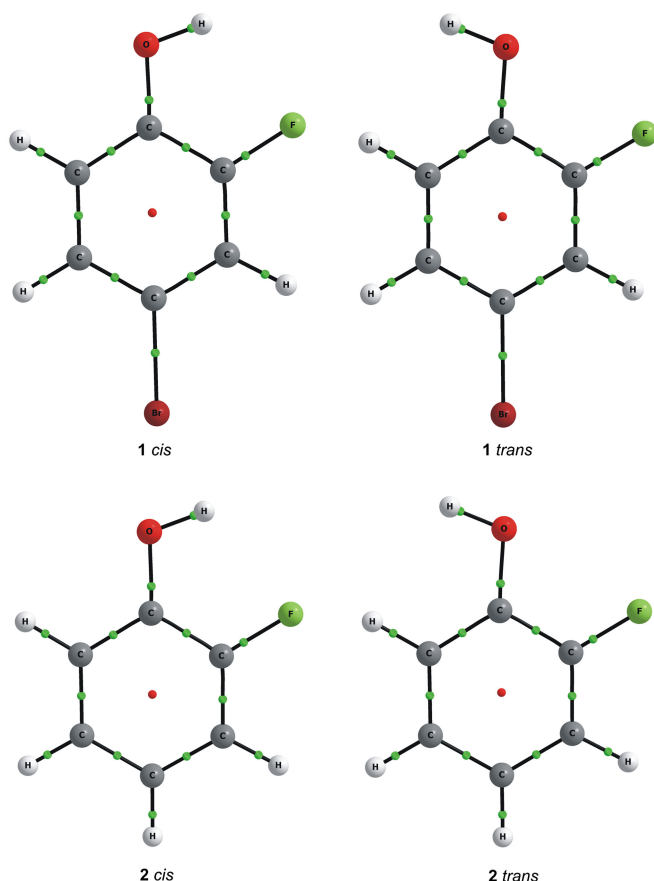


Figure 1. QAIM molecular graphics for compounds **1** and **2**. These analyses were performed at the MP2/EPR-III level (for bromine atom, the aug-cc-pVDZ basis set was used).

Results and Discussion

For compounds **1** and **2**, geometries of stable conformers were optimized as isolated molecules. Figure 1 shows the corresponding molecular graphics for QAIM^[19] analyses performed at the MP2/EPR-III level (for Br aug-cc-pVDZ basis set was used). It is observed that there is no BCP between hydroxyl hydrogen and fluorine atoms in the *cis* isomers of compounds **1** and **2**. This is taken as evidence that there is no hydrogen bond interaction between the hydroxyl group and the F atom.

Apparently, in compounds **1** and **2**, like in 2,2,2-trifluoroethanol,^[5] the *cis* conformation is preferential owing to a decrease of repulsion forces, when going from the *trans* to the *cis* conformers and not owing to the formation of an attractive intramolecular hydrogen bond. In fact, the larger stability for the *cis* conformers of compounds **1** and **2** for a low polarity solvent (the relative permittivity of cyclohexane is only 2.0) can be ascribed to larger dipole-dipole repulsion between the C₁—O₁ and the C₂—F₂ bonds for *trans* conformations, rendering the *cis* conformer as preferential both in isolated and low-polar media.

For compounds **1** and **2** as isolated molecules, NBO analyses yield LP₂(F)→σ*OH = 0.9 kcal mol^{−1} for both compounds in the *cis* conformation. This suggests that a hydrogen bond interaction takes place. Moreover, when the solvent dielectric permittivity effect is included in calculations, such interaction decreases for cyclohexane solution to LP₂(F)→σ*OH = 0.7 kcal mol^{−1}. However, no BCPs are found between the hydroxyl H and the F atoms

when performing QAIM analyses for both compounds, which is taken as evidence that there is no bond path^[20] between these two atoms. It is also noted that the calculated energies for the LP₂(F)→σ*OH interactions (close to 1 kcal mol^{−1}) are too small to characterize it as a hydrogen bond. In the current literature^[6,21,22], it is accepted that the QAIM method is more reliable than the NBO^[17] approach to characterize hydrogen bonds.

Ruling out the existence of a hydrogen bond for defining the preferential conformations for compounds **1** and **2**, it is interesting to analyze how the ⁴J_{FH} SSCC involving the hydroxyl proton is transmitted. Although conformational preferences can be accounted for resorting to the QAIM analysis, this does not hold for rationalizing the transmission pathways for the Fermi contact (FC) term of such ⁴J_{FH} SSCCs.

Energy data for preferential conformations in compounds **1** and **2** are shown in Table 1. They were obtained both as isolated molecules and using the IPCM method to model the solvent dielectric permittivity effect. ⁴J_{FH} SSCCs in isomers *cis* and *trans* of compounds **1** and **2** were calculated using both the CP-DFT/B3LYP methodology as implemented in the Gaussian03 package of programs and the SOPPA(CSSD) method as implemented in the Dalton program. All four terms of ⁴J_{FH} SSCCs (FC; spin dipolar, SD; paramagnetic spin orbit, PSO; and diamagnetic spin orbit, DSO) were taken into account (Table 2).

As can be observed in Table 2, ⁴J_{FH} is around −4.5 Hz for the *cis* isomers, whereas it is notably smaller, in absolute value, for *trans* isomers, suggesting that these couplings are mainly transmitted TS as it is already related in literature^[3,4] instead of being transmitted through bond.

As shown in Table 2, for *cis* conformations, the most significant contributions are the FC, PSO, and DSO terms. The latter follows a well-known trend [23a], that is, if the space is divided by a sphere whose diameter coincides with the distance between the coupling nuclei, then electrons inside that sphere yield a negative contribution to the DSO term whereas those outside that sphere yield a positive contribution. This trend was experimentally verified by studying the DSO term in several *geminal* SSCCs.^[23b] The TS transmission of the PSO term will be discussed in a forthcoming article. So far, it is enough to say that it strongly depends on the relative orientation between both proximate fragments, and its transmission does not depend on the existence of a hydrogen bond. We will concentrate here in the FC term, which is, in absolute value, the largest contribution.

Recently, a new approach to study coupling pathways for the FC term of SSCCs, was presented and it was dubbed FCCP-CMO^[24,25], which stands for FC coupling pathways studied using canonical molecular orbitals. The corresponding analysis is based on the polarization propagator (PP) expression for the FC term, Eqns (1–3)^[26–29]

Table 1. Calculated relative stabilities (kcal mol^{−1}) of *cis* and *trans* conformers in compounds **1** and **2** for an isolated molecule, in cyclohexane and in acetonitrile

Compound	1		2	
	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>
Isolated	0.0	2.6	0.0	2.7
Cyclohexane	0.0	1.5	0.0	1.5
Acetonitrile	0.6	0.0	0.5	0.0

Table 2. Theoretical contributions for ^1H J_{FH} coupling constants (Hz) for compounds **1** and **2**, for *cis* and *trans* conformers, which are compared with the respective experimental values

Compound	1				2			
Method	DFT		SOPPA(CCSD)		DFT		SOPPA(CCSD)	
Conformer	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>
FC	−5.4	0.6	−3.6	0.1	−5.6	0.6	−3.8	0.5
SD	−0.8	−0.4	−0.7	−0.3	−0.8	−0.4	−0.7	0.0
PSO	−3.1	1.3	−2.4	1.1	−3.1	1.3	−2.4	1.1
DSO	2.5	−2.3	2.4	−2.3	2.5	−2.3	2.4	−2.3
Total	−6.8	−0.7	−4.3	−1.4	−7.0	−0.8	−4.5	−1.5
Exp.	−4.4	n.o.	−4.4	n.o.	(−)4.8	n.o.	(−)4.8	n.o.

n.o., not observed.

$$^4J_{\text{FC}}^{\text{FH}} = \Omega^{\text{FC}} \sum_{ia,jb} ^4J_{ia,jb}^{\text{FC}}(\text{FH}) \quad (1)$$

where each term in this sum can be expressed as

$$^4J_{ia,jb}^{\text{FC}}(\text{FH}) = ^3W_{ia,jb} [U_{ia,H}^{\text{FC}} U_{jb,F}^{\text{FC}} + U_{ia,F}^{\text{FC}} U_{jb,H}^{\text{FC}}] \quad (2)$$

and $^3W_{ia,jb} = (^3A + ^3B)^{-1}_{ia,jb}$ are the elements of the inverse of the triplet PP matrix, and matrices 3A and 3B can be written in terms of bielectronic molecular integrals. For the present purpose, it is enough to recall that the 3W diagonal elements, $^3W_{ia,ia}$ are the largest, followed by quasi diagonal elements like, for instance, $^3W_{ia,ib}$. On the other hand, $U_{ia,H}^{\text{FC}}$ ($U_{ib,F}^{\text{FC}}$) are the FC 'perturbators', that is, the matrix elements of the FC operator, between the occupied i (j) and the virtual a (b) MOs evaluated at the H (F) site of the coupling nuclei, Eqn (3),

$$U_{ia,N}^{\text{FC}} = \langle i | \delta(\vec{r}_N) | a \rangle \text{ where } N = \text{F, H} \quad (3)$$

where $U_{ia,N}^{\text{FC}}$ corresponds to the overlap between occupied i and virtual a MOs at the site of the N (F or H) nucleus, which is proportional to the product of i and a MOs s % character at the N atom. $\delta(\vec{r}_N)$ is the Dirac's delta function.

Equations (1) to (3) can provide interesting insight into the nature of each FC coupling pathway. To know the spatial region spanned by each CMO, they are expanded in terms of Weinhold *et al.*^[30,31] NBOs, using the NBO 5.0 program.^[17] In the present case, the FCCP-CMO method indicates that the transmission of the FC term of ^1H J_{FH} SSCC for compounds **1** and **2** in their *cis* conformation is not mediated by any diagonal $^3W_{ia,ia}$ matrix element, but only by quasi diagonal $^3W_{ia,ib}$ elements where i stands for an occupied CMO containing in its NBO expansion the O-H and C-F bonding orbitals as well as the $\text{LP}_1(\text{F})$ lone pair, while a and b correspond to virtual CMOs containing in their NBO expansion either the (O-H)* or the (C-F)* antibonding orbitals, but none of them containing both antibonding orbitals are observed. Because we are dealing with ^1H J_{FH} , this is indicative that the role played by any covalent $\text{F}_2\text{--H}_{(\text{OH})}$ interaction in the transmission of its FC term is irrelevant. This suggests that the main transmission mechanism for that FC term originates in exchange interactions taking place in the region where the $\text{O}_1\text{--H}$ NBO bonding orbital overlaps with either the $\text{C}_2\text{--F}_2$ bonding orbital or the $\text{LP}_1(\text{F})$ lone pair orbital. This peculiar TS transmission of the FC term of SSCCs can easily be rationalized recalling that the FC term is transmitted like the 'Fermi hole'^[32]. Because the overlap between the latter two

orbitals is negative^[33], it can be expected that FC contributions originating in the overlap between the $\text{O}_1\text{--H}$ and the $\text{C}_2\text{--F}_2$ occupied orbitals are of the opposite sign to those originating in the overlap between the $\text{O}_1\text{--H}$ bonding and the $\text{LP}_1(\text{F})$ nonbonding electron pair orbitals. Apparently, the competition between these two types of contributions yields a small FC term for ^1H J_{FH} SSCC in compounds **1** and **2**, although the $\text{F}_2\text{--H}_{(\text{OH})}$ distance is only 2.21 Å whereas the sum of their respective van der Waals radii is $(1.47 + 1.20) = 2.67$ Å. This competition could be the rationalization why J_{FH} SSCCs originating in proximate molecular fragments were experimentally reported sometimes as positive and sometimes as negative.^[34]

Plots of such CMOs for *cis* rotamers of compounds **1** and **2** are displayed in Fig. 2, while the expansion terms of the occupied CMOs in compounds **1** and **2** in terms of NBO orbitals are given in Table 3.

Concluding remarks

Both the QTAIM and the FCCP-CMOs analyses are consistent with the idea that in *cis* conformers of compounds **1** and **2** the observed ^1H J_{FH} SSCCs actually are not transmitted through an $\text{F}_2\text{--H}_{(\text{OH})}$ hydrogen bond. Instead, the main transmission mechanism of its dominant FC term originates in exchange interactions between the overlapping of the electronic clouds surrounding both

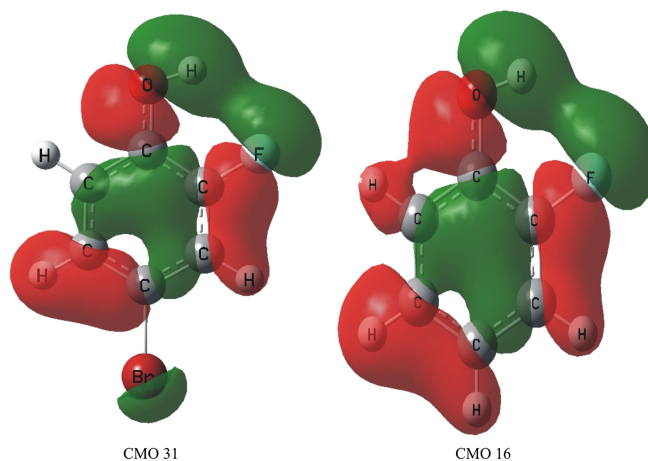


Figure 2. Plots of CMOs 31 in compound **1** and 16 in compound **2** calculated at the B3LYP/EPR-III level (for Br atom, the aug-cc-pVDZ basis set was used).

Table 3. Expansion of CMOs contributing to ^{17}F SSCC in terms of NBOs as given by the NBO 5.0 program for compounds **1** and **2**

Compound 1	Compound 2
MO 29 (occ): $\epsilon = -0.659245$ a.u. -0.438*[13]: BD (1) C1-C2 0.353*[10]: BD (1) C1-C6 0.311*[41]: LP (1) F2 -0.307*[5]: BD (1) C4-C5 0.300*[1]: BD (1) C3-C4 -0.300*[4]: BD (1) C3-H3 0.257*[12]: BD (1) C6-H6 0.246*[16]: BD (1) O1-H -0.243*[9]: BD (1) C5-H5 0.233*[15]: BD (1) C2-F2 MO 30 (occ): $\epsilon = -0.631353$ a.u. -0.354*[8]: BD (1) C5-C6 -0.348*[2]: BD (1) C2-C3 -0.299*[12]: BD (1) C6-H6 0.297*[5]: BD (1) C4-C5 0.283*[1]: BD (1) C3-C4 0.281*[16]: BD (1) O1-H -0.263*[44]: LP (1) Br 0.248*[14]: BD (1) C1-O1 0.242*[13]: BD (1) C1-C2 0.224*[41]: LP (1) F2 MO 31 (occ): $\epsilon = -0.593258$ a.u. 0.514*[16]: BD (1) O1-H 0.436*[14]: BD (1) C1-O1 -0.363*[15]: BD (1) C2-F2 -0.338*[41]: LP (1) F2 -0.265*[13]: BD (1) C1-C2 0.264*[9]: BD (1) C5-H5	MO 14 (occ): $\epsilon = -0.643935$ a.u. -0.428*[13]: BD (1) C1-C2 0.356*[10]: BD (1) C1-C6 0.307*[4]: BD (1) C3-H3 0.307*[27]: LP (1) F2 -0.284*[16]: BD (1) O1-H 0.279*[1]: BD (1) C3-C4 0.274*[5]: BD (1) C4-C5 -0.256*[9]: BD (1) C5-H5 -0.236*[12]: BD (1) C6-H6 0.234*[15]: BD (1) C2-F2 MO 16 (occ): $\epsilon = -0.582822$ a.u. -0.446*[16]: BD (1) O1-H -0.434*[15]: BD (1) C2-F2 -0.410*[27]: LP (1) F2 0.379*[14]: BD (1) C1-O1 0.277*[9]: BD (1) C5-H5 -0.263*[13]: BD (1) C1-C2 MO 17 (occ): $\epsilon = -0.539510$ a.u. -0.384*[12]: BD (1) C6-H6 -0.379*[2]: BD (1) C2-C3 0.355*[7]: BD (1) C4-H4 -0.333*[15]: BD (1) C2-F2 -0.317*[27]: LP (1) F2 0.267*[16]: BD (1) O1-H 0.248*[1]: BD (1) C3-C4 0.232*[5]: BD (1) C4-C5

NBOs contributing to important electronic densities at the sites of the coupling nuclei are highlighted. Because they belong to the same CMO, they transmit the FC term because the Fermi hole spans the whole region of each canonical molecular orbital.

coupling nuclei owing to their spatial proximity. These means that such SSCC can be better described as transmitted 'through space' than 'transmitted through a hydrogen bond'. Therefore, instead of representing it as $^{1h}J_{FH}$, it should be preferably represented as $^{nTS}J_{FH}$ SSCC, where n stands for the number of formal bonds separating the coupling nuclei. In the case under consideration is $n=4$, and therefore the SSCCs considered in this work should be characterized by $^{4TS}J_{FH}$.

In compounds **1** and **2**, the electronic clouds surrounding the coupling nuclei are represented by the O-H and C-F bonding orbitals and the LP₁(F) nonbonding electron pair orbital. Because the overlapping of the latter two at the site of the F nucleus yields a negative value^[33], it is expected that contributions originating in the O₁-H/C₂-F₂ overlap yields a positive contribution to the FC term of $^{4TS}J_{FH}$ SSCC while that originating in the O₁-H/LP₁(F) overlap a negative one. This observation might provide an interesting rationalization for the experimentally reported sometimes positive and sometimes negative values for proximate J_{FH} SSCCs regardless of the number of formal bonds separating the coupling nuclei.^[34] As a final remark, it is important to point out that proximate J_{FH} transmitted through hydrogen bonds were studied few years ago from both experimental and theoretical points of view.^[35-39]

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