Computation of Through-Space $^{19}F-^{19}F$ Scalar Couplings via Density Functional Theory

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Abstract: By using density functional theory it is demonstrated that the long-range $^{19}F-^{19}F$ *J*-couplings ($^{>3}J$) seen in small organic molecules can be calculated with good accuracy using small molecule fragments and in some cases complete molecules. The results reproduce the exponential distance dependence of *J* seen experimentally, demonstrate the dominance of the Fermi contact interaction, and rule out any significant covalent or through-bond contributions to *J* in these systems. The calculations also verify an experimentally observed $^{19}F-^{19}F$ *J*-coupling seen between two [6-F]Trp residues in the protein dihydrofolate reductase (for $d = 2.98$ Å), where there is clearly no covalent bonding between the two ^{19}F sites. The results also clarify the abnormally small *J*-couplings seen previously in phenanthrenes and cyclohexenes, which are shown by *ab initio* and molecular mechanics geometry optimizations to be due to conversion of the supposedly planar structures to more distorted but less sterically hindered structures. These distortions increase the F−F distance and thereby reduce J_{FF}. The lack of any appreciable covalent bonding between the ^{19}F atoms in both the protein and the model systems, but the presence of significant *J*-couplings, emphasizes that all that is required is Fermi contact, and the close spatial proximity of atoms. This result is of considerable current interest in the context of (long range/through-space) hydrogen bond *J*-couplings in macromolecules.

Introduction

The origin of long-range through-space *J*-couplings has been of interest for many years,[1] and more recently there has been considerable interest in the nature of trans hydrogen bond *J*-couplings.[2] Both types of scalar couplings show an exponential decrease in *J* with internuclear separation, and are of interest from the perspectives of structure determination and refinement, as well as electronic structure determination. In early work, Buckingham and Cordle[3] addressed the origin of long-range *J*-coupling using a semiempirical approach, and more recently Mallory et al.[4] and Del Bene et al.,[5] among others, have begun to address the problem of through-space *J*-couplings using quantum chemical methods. Here, we describe the application of density functional theory (DFT) methods to compute long-range $^{19}F-^{19}F$ *J*-couplings, defined here as $^{>3}J_{FF}$ couplings. We use both complete molecules as well as a fragment-based approach, which deletes any through-bond contribution to J_{FF}, and we demonstrate excellent accord between theory and experiment in a variety of systems, with the Fermi contact term clearly dominating J_{FF}.

Experimental Section

All spin−spin coupling constants were computed with DFT by using the program deMon-NMR.[6−11] This approach considers the Fermi contact (FC), paramagnetic spin−orbit (PSO), and diamagnetic spin−orbit (DSO) contributions to *J*. The FC term is determined by using finite perturbation theory,[12−14] the PSO term is determined by using sum-over-states density functional perturbation theory,[8,9] and the DSO term is determined by numerical integration.[9,10] The spin-dipolar contribution to *J* is disregarded, since it is computationally expensive and its magnitude is negligible for long-range couplings.[10,11] The Perdew and Wang exchange functional[15] and the Perdew correlation functional were used,[16,17] along with the IGLO-III basis set[18] and a FINE RANDOM grid with 64 points of radial quadrature.[19]

The molecular geometries of all organic molecules containing $^{19}F-^{19}F$ couplings were obtained by *ab initio* Hartree−Fock geometry

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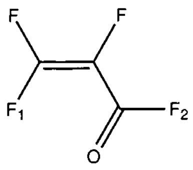
optimization (Gaussian 98[20]) of molecular mechanics derived[21] starting structures. A uniform 6-31G(d,p) basis set was used for the geometry optimizations.[20] The geometries of the non-hydrogen atoms in the smaller, model species were obtained from these fully optimized molecules, and terminated with hydrogen atoms at standard bond length.[21]

The structure of [6-F]Trp dihydrofolate reductase (DHFR) complexed with methotrexate (MTX) and dihydro-nicotinamide-adenine-dinucleotide phosphate (NADPH) was obtained by modifying an existing 1.7 Å X-ray structure of DHFR-MTX-NADPH.[22] Each of the four Trp residues in DHFR were mutated at the 6-position to form the [6-F] species. The geometry of the entire protein was then allowed to relax by performing 2000 steps of molecular mechanics optimization (CHARMm, CFF potential).[23]

Results and Discussion

We investigated a range of systems, beginning with the perfluoropropenones, **1** and **2**. While the magnitude of the experimental ${}^4J_{F_1F_2}$ coupling in **1** is less than 2 Hz,[24] a large through-space contribution in **2** arises from the close spatial proximity of F_1 and F_2,[3] resulting in a ${}^4J_{F_1F_2}$ of 84.5 Hz.[24] We found that the DFT calculations are able to reproduce this distinction between through-bond, **1**, and through-space, **2**, couplings: the calculated ${}^4J_{F_1F_2}$ couplings for **1** and **2** are −0.7 and 83.0 Hz, respectively, Table 1. To eliminate all possible through-bond contributions to the calculated ${}^4J_{F_1F_2}$ in **2**, we next considered a series of nonbonded models, **3**−**5**, having the same F−F separation as in **2**, and the same F−C(H) vector orientations. The result obtained using the nonbonded model **3** is in reasonably good accord with experiment, $J_{FF} = 71.5$ Hz, Table 1. For **4** the results are less good, $J_{FF} = 55.2$ Hz, and for the simplistic $(HF)_2$ model **5** the results are poor, $J_{FF} = 33.2$ Hz. It is likely, however, that models **4** and **5** are simply less adequate representations of the local F_1/F_2 chemical environment seen in **2**. The most complex nonbonded model, **3**, has a J_{FF} that is within 15% of the experimental ${}^4J_{F_1F_2}$ of **2**, and thus validates the idea that the coupling in **2** is primarily through-space.



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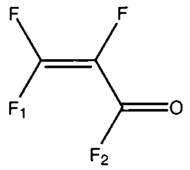

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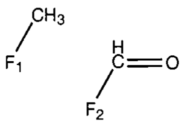

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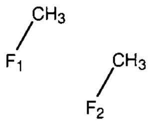

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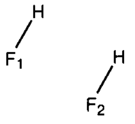

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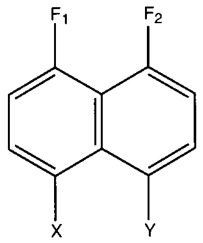
We then investigated the couplings in a series of larger molecules whose couplings have been attributed to the through-space mechanism.[4] Here, we used smaller model species, to reduce computational expense. To begin with, we considered several substituted 1,8-difluoronaphthalenes **6** and **7**, using 2,4-difluoro-1,3-pentadienes **8**, in which all non-hydrogen atoms were positioned based upon full *ab initio* geometry optimization of the difluoronaphthalenes, **6** and **7**. In the 10 systems considered (**6a**−**f**; **7a**−**d**, Table 1) the optimized F−F distances range from 2.474 to 2.761 Å, and the computed J_{FF} values range from 76.4 to 41.9 Hz, Table 1, with the Fermi contact term dominating J_{FF} in all cases.



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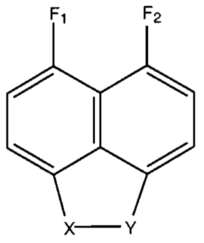

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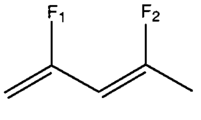

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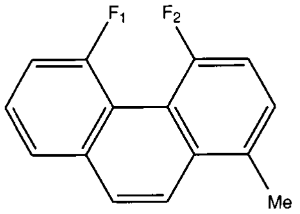
We next investigated the 4,5-difluoro-1-methylphenanthrene,[25] **9**, using the model 1,4-difluorobutadiene, **10**. Model **10** was obtained by extracting the appropriate geometry optimized C_4F_2 fragment from **9**, which contained torsion angle distortions. The optimized F−F distance in **9** is 2.389 Å and corresponds to a very large ${}^5J_{FF}$ of some 170 Hz—a value well reproduced in the DFT calculations on **10**, which yielded a ${}^5J_{FF}$ of 186.4 Hz, Table 1.



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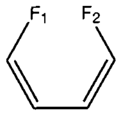

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We were also able to clarify a seeming contradiction to the through-space origin of J_{FF}. The *cis* F_1−F_2 coupling in bis-4,5-(difluoromethylene)cyclohexene,[26] **11**, is anomalously low, based upon a planar, standard-bond-length structure, which makes $d_{FF} = 1.5$ Å. We find that the geometry-optimized d_{FF}

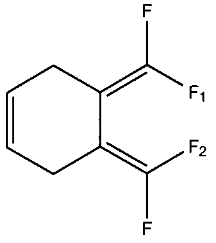

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Table 1. Through-Space DFT $^{19}F-^{19}F$ Couplings

molecule	model	FC^a (Hz)	PSO^b (Hz)	DSO^c (Hz)	J_{FF}^{Calc} (Hz)	J_{FF}^{Exp} (Hz)	d_{FF}^{Calc} (Å)
1	1	2.0	−1.4	−1.2	−0.7	2.0	4.16
2	2	48.2	33.6	1.0	83.0	84.5	2.60
2	3	81.9	−11.0	0.7	71.5	84.5	2.60
2	4	88.3	−33.7	0.6	55.2	84.5	2.60
2	5	79.7	−46.5	0.0	33.2	84.5	2.60
6a (CN,CN)	8	84.1	−19.9	1.0	65.2	83.5	2.49
6a (CN,CN)	4	144.9	−43.5	0.7	102.1	83.5	2.49
6a (CN,CN)	5	141.1	−56.8	0.0	84.4	83.5	2.49
6b (−CO−O−CO−)	8	50.7	13.3	0.9	64.8	61.9	2.58
6b (−CO−O−CO−)	4	92.2	−36.6	0.6	56.2	61.9	2.58
6b (−CO−O−CO−)	5	90.4	−48.3	0.0	42.1	61.9	2.58
6c (CH_3,CH_3)	8	95.3	−21.0	1.0	75.3	85.2	2.47
6c (CH_3,CH_3)	4	156.9	−46.1	0.7	111.5	85.2	2.47
6c (CH_3,CH_3)	5	153.0	−58.9	0.0	94.2	85.2	2.47
6d (H,H)	8	56.4	12.6	0.9	69.8	59.0	2.57
6d (H,H)	4	100.0	−38.2	0.6	62.4	59.0	2.57
6d(H,H)	5	97.5	−49.6	0.0	47.9	59.0	2.57
6e (H,CN)	8	62.9	12.3	0.9	76.2	66.1	2.55
6e (H,CN)	4	111.1	−39.2	0.7	72.6	66.1	2.55
6e (H,CN)	5	106.5	−51.4	0.0	55.1	66.1	2.55
6f (H,CH_3)	8	64.0	11.4	0.9	76.4	65.6	2.55
6f (H,CH_3)	4	110.9	−39.6	0.7	72.0	65.6	2.55
6f (H,CH_3)	5	106.3	−51.3	0.0	55.0	65.6	2.55
7a ($-CH_2-CH_2-$)	8	34.4	15.0	0.7	50.1	28.4	2.72
7a ($-CH_2-CH_2-$)	4	69.4	−28.8	0.5	41.2	28.4	2.72
7a ($-CH_2-CH_2-$)	5	61.2	−36.9	0.0	24.3	28.4	2.72
7b (−CH=CH−)	8	26.3	14.8	0.7	41.9	36.7	2.76
7b (−CH=CH−)	4	57.3	−26.4	0.5	31.5	36.7	2.76
7b (−CH=CH−)	5	50.8	−33.8	0.0	17.0	36.7	2.76
7c (−CPh=CPh−)	8	26.6	14.8	0.7	42.2	36.6	2.76
7c(−CPh=CPh−)	4	57.6	−26.5	0.5	31.7	36.6	2.76
7c (−CPh=CPh−)	5	51.1	−33.9	0.0	17.2	36.6	2.76
7d (−CHPh−CHPh−)	8	34.8	15.0	0.7	50.6	28.8	2.72
7d(−CHPh−CHPh−)	4	69.3	−28.7	0.5	41.1	28.8	2.72
7d (−CHPh−CHPh−)	5	61.1	−36.8	0.0	24.2	28.8	2.72
11	11	22.9	−5.1	1.1	18.9	∼30	2.85
11	4	39.8	−8.4	0.5	31.9	∼30	2.85
11	5	44.5	−25.9	0.0	18.7	∼30	2.85
9	10	217.3	−32.0	1.1	186.4	∼170	2.39
9	4	231.1	−30.0	0.9	202.1	∼170	2.39
9	5	251.5	−42.0	0.2	209.6	∼170	2.39
DHFR	4	38.5	−6.2	0.6	32.9	17 ± 2	2.98
DHFR	5	39.7	−9.4	0.1	30.4	17 ± 2	2.98

in **11** is actually 2.85 Å, due to the torsion produced by F−F repulsion, and that DFT predicts a J_{FF} of 18.9 Hz, in accord with the experimental estimate of ∼30 Hz.[26]

This success then led us to evaluate through-space *J*-couplings in a protein, specifically, the long-range coupling seen by Kimber and co-workers[27] between two [6-F]-Trp residues in a dihydrofolate reductase-NADPH-MTX complex from *Lactobacillus casei*. This coupling is either a $^{398}J_{FF}$ coupling through bonds, or a direct, through-space interaction between two neighboring Trp residues. As pointed out in the original paper,[27] there must be two Trps which are very close together in space (even though none are close in the primary sequence). This was indeed later shown to be the case,[22] and the J_{FF} coupling can be attributed to the interaction between the ^{19}F nuclei on Trp 5 and Trp 133, Figure 1. Since the structure of the F-Trp labeled protein is not known, we mutated all four Trp residues to the [6-F]Trp species in an existing 1.7 Å DHFR-NADPH-MTX crystal structure,[22] and used a $(CH_3F)_2$ model, **4**, in which the C−F vector orientations reproduced those seen in the protein model. The F−F distance was 2.98 Å, as deduced from a molecular mechanics minimization of the entire protein.[23] Although this yielded J_{FF} = 32.9 Hz, greater than the 17 ± 2 Hz seen experimentally, the result validates the idea that the two ^{19}F nuclei couple through-space as a result of their proximity in the folded protein.

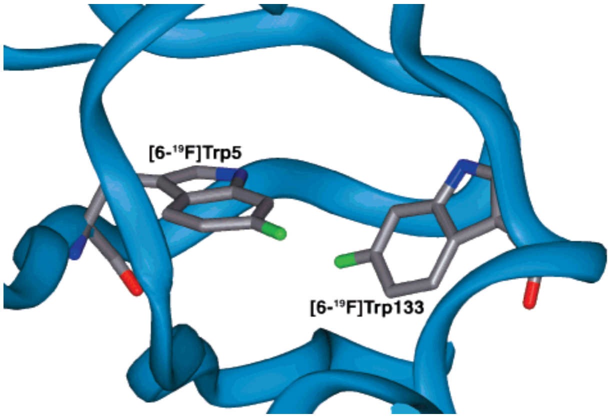

Figure 1. The proximity of the [6-F]Trp5 and [6-F]Trp133 side chains in the protein [6-F]Trp DHFR complexed with MTX and NADPH. The fluorine nuclei (green) are approximately 3 Å apart.

When all of the calculated results are compared with experiment, we obtain very good agreement; the correlation

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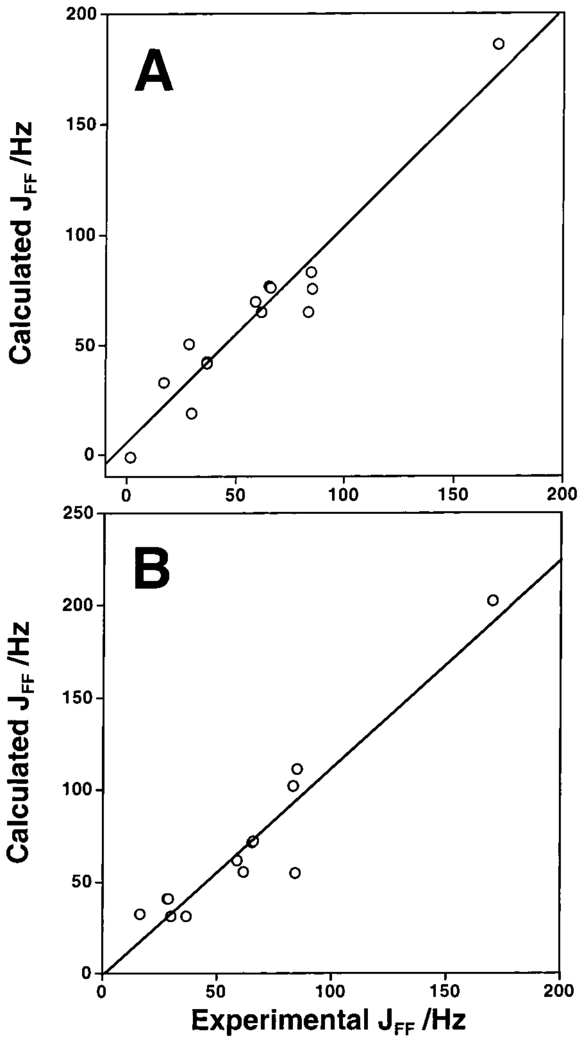

Figure 2. Calculated versus experimental J_{FF} in several organic molecules and in the protein DHFR: (A) calculated results using, as appropriate (Table 1), full molecular geometries (**1**, **2**, **11**), 2,4-difluoro-1,3-pentadienes (**8**), 1,4-difluorobutadiene (**10**), and the fluoromethane dimer (**4**) (DHFR) with slope = 0.98 and R^2 = 0.92; (B) calculated results using only fluoromethane dimer models (**4**) with slope = 1.13 and R^2 = 0.90.

has a slope of 0.98 and an R^2 value of 0.92, Figure 2A. To determine whether there is a major through-bond contribution to these couplings, mediated by either a σ or π-aromatic system, we next considered the effect of using **4** as a nonbonded model for all of the through-space coupled nuclei. The results strongly support the through-space origin of these $^{>3}J_{FF}$ couplings, Table 1. The agreement between theory and experiment remains very good, with a slope of 1.13 and an R^2 value of 0.90, Figure 2B. Using the minimal $(HF)_2$ model, **5**, decreases the R^2 value to 0.87, and produces a slope of 1.21. Since there are no covalent (shared-electron pair) interactions involved between the *J*-coupled nuclei, the experimental observation of *J* clearly does not indicate covalent bonding between coupled nuclei *per se*, as has been assumed in some cases for ^{nh}J trans hydrogen bond couplings, and which we argue elsewhere are in almost all cases closed-shell (electrostatic or van der Waals) type interactions.[28]

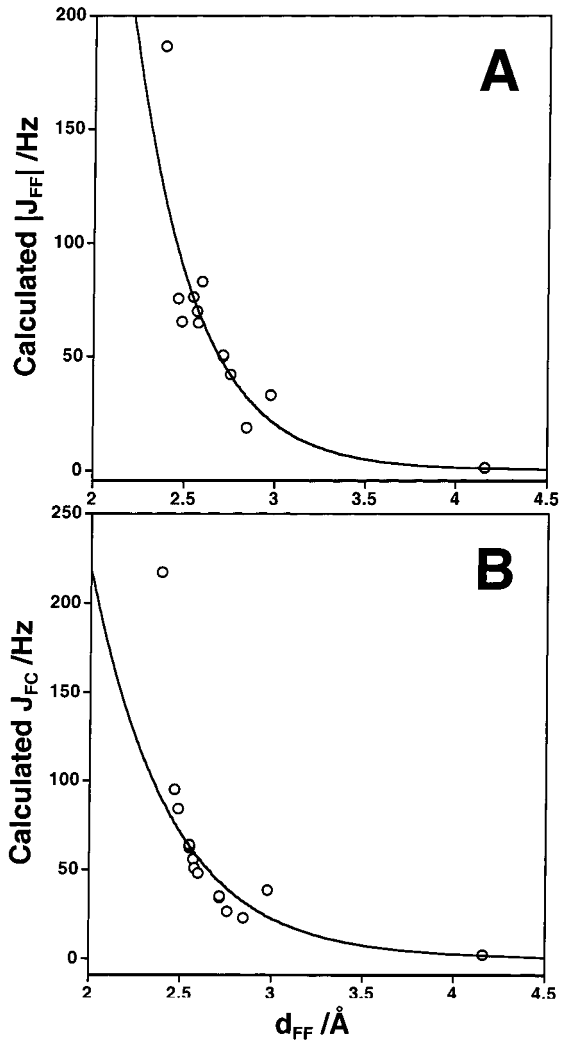

Figure 3. The exponential distance dependence of the calculated *J*-couplings. (A) $|J_{FF}|$ versus the fluorine−fluorine internuclear separation, d_{FF}; R^2 = 0.96. (B) The Fermi contact contribution to *J*, J_{FC}, versus d_{FF}; R^2 = 0.88.

For both through-space J_{FF} and trans hydrogen bond ^{nh}J-couplings, *J* has been shown to fall off exponentially with internuclear distance,[2,4] due to the rapid decrease in magnitude of the overlap integrals and the Fermi contact. Results for all of the systems described here (optimized at HF/6-31G(d,p)) are shown in Figure 3A, and we show in Figure 3B the change in the Fermi contact term, J_{FC}, with distance, in the same set of compounds. Both the *J* and J_{FC} terms fall off exponentially with d_{FF}, with R^2 values of 0.96 and 0.88, respectively. The Fermi contact interaction plays the major role in the through-space *J*-coupling in the fluorine compounds we have investigated, although in a few instances the paramagnetic spin−orbit term also appears significant, Table 1. Interestingly, Bryce and Wasylishen[29] have recently concluded that the influence of J_{PSO} can be greater than expected, although clearly additional theoretical approaches will be desirable to validate more precisely the various contributions to these through-space *J*-couplings.

Conclusions

In summary, the results we have presented represent the first detailed comparison between experimental long-range *J*-couplings and those computed by using density functional theory. There is very good agreement between theory and experiment (R^2 value of 0.92, N = 15, and a slope of 0.98), with the

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[28] Arnold, W. D.; Oldfield, E. *J. Am. Chem. Soc.* **2000**, In press.

[29] Bryce, D. L.; Wasylishen, R. E. *J. Am. Chem. Soc.* **2000**, *122*, 3197−3205.

exponential decrease in *J* with d_{FF} also being found in the calculations. The use of small dimer models, $(HF)_2$ and $(CH_3F)_2$, speeds up the computation of J_{FF}, and since the results found for both covalent and nonbonded models are very similar, supports the idea that through-bond contributions to *J* in the parent systems are all quite small. These results also support the idea that the observation of *J*-couplings in hydrogen-bonded systems provides evidence neither for nor against the existence of covalent, shared-electron pair type interactions, since *J*-couplings can be both seen experimentally and computed theoretically in systems which have no such bonds.

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