

## On the Capriciousness of the FCCF Karplus Curve

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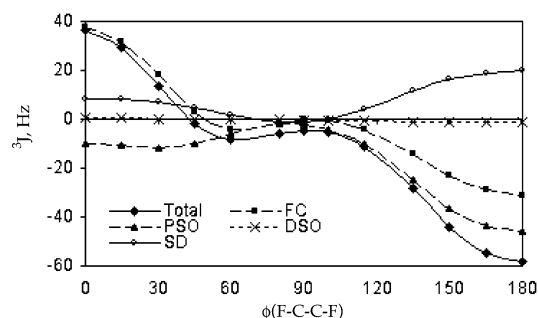
The Karplus equation, deduced in the 1960s,<sup>1</sup> is a convenient and powerful tool for determining individual torsion angles as well as overall molecular conformation. The familiar cosine curve correlating three-bond proton–proton NMR coupling constants,  $^3J$ , and  $\phi(\text{H}-\text{C}-\text{C}-\text{H})^2$  is found in university textbooks,<sup>3</sup> while empirical parametrizations<sup>4</sup> are employed in widely used molecular modeling packages.<sup>5</sup> Handy variations have been developed for  $\text{H}-\text{N}-\text{C}-\text{H}$ ,<sup>6</sup>  $\text{H}-\text{C}-\text{O}-\text{H}$ ,<sup>7</sup>  $\text{H}-\text{C}-\text{C}-\text{C}$ ,<sup>8</sup>  $\text{H}-\text{C}-\text{O}-\text{C}$ ,<sup>9,10</sup>  $\text{C}-\text{C}-\text{C}$ ,<sup>6a,10b</sup>  $\text{C}-\text{O}-\text{C}-\text{C}$ ,<sup>10</sup>  $\text{H}-\text{C}-\text{C}-\text{F}$ ,<sup>11</sup> and  $\text{H}-\text{C}-\text{O}-\text{P}$ <sup>12</sup> fragments.

Missing from the collection of  $^3J$ -to-torsion expressions is a well-behaved curve for  $\text{F}-\text{C}-\text{C}-\text{F}$ . Various authors have observed the lack of a  $^3J(\text{F},\text{F})/\phi(\text{F}-\text{C}-\text{C}-\text{F})$  dependence and noted an unpredictable substituent effect.<sup>13</sup> A typical set of observations concerns the fluorinated ethanes. For the *gauche* conformation of 1,2-difluoroethane (DFE) Abraham and Kemp have determined  $^3J_{\text{FF}}$  to be  $-11$  Hz and estimated the *trans* value at  $-30$  Hz.<sup>14</sup> By contrast fluoro substitution to give 1,1,2-trifluoroethane causes small fluctuations in  $^3J_{\text{FF-gauche}}$ , while drastically reducing the  $^3J_{\text{FF-trans}}$  to an estimated  $-19$  Hz. Addition of another fluorine (1,1,2,2-tetrafluoroethane) is reported to reduce  $^3J_{\text{FF-trans}}$  still further to  $-5$  Hz.<sup>15</sup>

In the present work we have examined the torsional profiles of butane and DFE as a function of  $^3J_{\text{HH}}$  and  $^3J_{\text{FF}}$ , respectively, using density functional theory (DFT) to predict the scalar coupling constants. The behavior of  $\text{F}-\text{CH}_2-\text{CH}_2-\text{F}$  by comparison with the classical Karplus behavior of  $\text{Me}-\text{CH}_2-\text{CH}_2-\text{Me}$  can be attributed to two effects: (1) the differential contribution of the various Ramsey terms contributing to  $^3J$ , and (2) the influence of the fluorine nonbonding electron pairs.

The  $^3J_{\text{HH}}$  and  $^3J_{\text{FF}}$  Karplus curves were derived by constraining  $\phi(\text{X}-\text{C}-\text{C}-\text{X})$  for each structure on the torsional paths to its indicated value followed by optimization at the B3LYP/6-311G(d,p) level of theory. Then,  $^3J(\text{total})$  was obtained by calculating all four Ramsey contributions to coupling (FC, SD, DSO, and PSO)<sup>16,17</sup> at the same level, using a protocol that provides semiquantitative predictions for  $^3J_{\text{FF}}$  in various fluorinated aromatic structures.<sup>18</sup> The fully positive  $^3J_{\text{HH}}$  trace<sup>17</sup> matches the expected  $^3J_{\text{HH}}/\phi$  relationship qualitatively and quantitatively, reinforcing the long-standing assumption that the FC term dominates scalar three-bond H–H coupling.<sup>1,19</sup>

The corresponding Karplus curve for DFE is depicted in Figure 1 with variation of the four Ramsey contributions. The  $^3J_{\text{FF}}(\text{total})$  for the fluorocarbon displays a sign change as the  $\text{F}-\text{C}-\text{C}-\text{F}$  dihedral angle moves from  $0$  ( $+37.5$  Hz) to  $180^\circ$  ( $-58.4$  Hz). The positive region of the curve from  $0$  to  $40^\circ$  is FC determined, while



**Figure 1.** The B3LYP/6-311G(d,p)  $^3J_{\text{FF}}$  Karplus curve for 1,2-difluoroethane illustrating  $^3J_{\text{total}}$  and the Ramsey term contributions. Only the SD contribution sustains a classic Karplus dependence.

the negative segment ( $40-180^\circ$ ) results from reinforcing FC and PSO terms. Both the sign of  $^3J_{\text{FF}}(\text{total})$  and the dominance of PSO have been anticipated by determinations of negative *trans*- $^3J_{\text{FF}}$ <sup>14,20,21</sup> and theoretical treatments.<sup>19,22</sup> Surprisingly, the range of variation from  $0$  to  $180^\circ$  is 7–8 times larger than that for the hydrocarbon ( $\Delta^3J_{\text{FF}} = 196$  Hz). The predicted  $^3J_{\text{FF-gauche}}$ , ( $71.7^\circ$ , exp  $71.0-71.3^\circ$ )<sup>23</sup> adequately represents the experimental value for liquid *gauche*-DFE ( $-11$  Hz, exp  $-7.2$  Hz), but the *trans* value ( $-58.4$  Hz) is twice as large as that estimated empirically ( $-30$  Hz).<sup>14</sup> To evaluate whether the calculated  $^3J_{\text{FF-trans}}$  is overestimated in absolute value, we reoptimized the *trans* conformer at the MP2-(FC)/6-311G(d,p) level and recomputed the coupling constant contributions with the B3LYP/6-311++G(3df,3pd) extended DFT basis set to give  $^3J_{\text{FF-trans}} = -65$  Hz. The earlier estimate<sup>14</sup> of this value for DFE may be too positive (cf. Supporting Information).

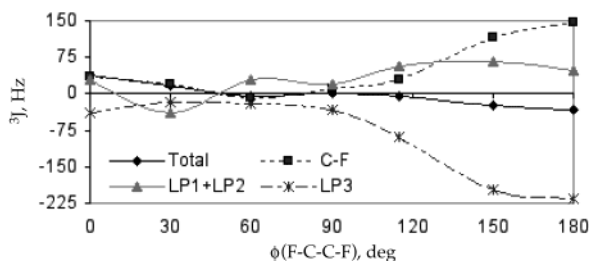
What is the origin of the qualitative  $^3J$  differences between DFE and butane? As a partial answer to this question we have applied natural J-coupling analysis (NJC)<sup>24</sup> to the substantial FC term along both torsional pathways. Dissection of  $^3J_{\text{HH}}(\text{FC})$  into localized bond contributions corresponds completely with prevailing views holding that the nuclear spin information is carried across the central C–C bond entirely by adjacent C–H bonds. The contribution is positive at all angles except at  $\phi(\text{H}-\text{C}-\text{C}-\text{H}) = 90^\circ$  where it vanishes.<sup>17</sup> It is noteworthy that the analysis reveals no contributions from either the C–C bonds or the methyl C–H bonds above 0.5 Hz.

A similar treatment for 1,2-difluoroethane illustrates a more complex pattern. The adjacent C–F bonds of DFE provide a  $^3J_{\text{FF}}(\text{FC})$  contribution qualitatively similar to the C–H bonds of butane (Figure 2). At  $0^\circ$  the  $\sigma(\text{C}-\text{F})$  value is positive ( $+35.5$  Hz), followed by a minimum at  $60^\circ$  ( $-9.3$  Hz) and a large positive contribution at  $180^\circ$  ( $+146.9$  Hz). The other semial influences on  $^3J_{\text{FF}}(\text{FC})$  arise from the three fluorine lone electron pairs. LP<sub>3</sub>, the in-plane p-orbital (Figure 3), runs negative at all torsional angles and qualitatively mirrors the positive C–F bond curve. Quantitatively however, the LP<sub>3</sub> component is considerably larger than the latter

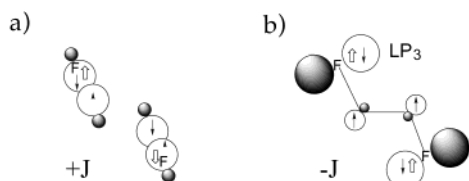
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**Figure 2.** NJC analysis of the Fermi contact term of  ${}^3J_{\text{FF}}$  for 1,2-difluoroethane rotation from 0 to 180°; the total FC value and the C–F bond and fluorine lone pair contributions are illustrated.



**Figure 3.** Spin–spin coupling in 1,2-difluoroethane. (a) Transmission by electrons in the C–F bonds leads to antiparallel nuclear spins and  $+J$ ; (b)  $\text{LP}_3$  transmission mediated by the C–H bonds causes parallel nuclear spins and  $-J$ .

for  $\phi(\text{F}-\text{C}-\text{C}-\text{F})$  from 90 to 180° leading to an overall negative  ${}^3J_{\text{FF}}(\text{FC})$  in this region. From 0 to 40° the sum of  $\sigma(\text{F}-\text{C})$  and LP components furnish the initial positive segment of  ${}^3J_{\text{FF}}(\text{FC})$ . In addition to these major coupling factors, the NJC analysis suggests that the C–H and C–C bonds and the fluorine core electrons also contribute  $-15$  to  $+10$  Hz to the overall F–F coupling. Thus, the F–CH<sub>2</sub>–CH<sub>2</sub>–F system employs a number of spin–spin transmission features absent in butane, the most prominent of which arises from  $\text{LP}_3$ . The negative character of  ${}^3J_{\text{FF}}(\text{FC})$  at large F–C–C–F dihedral angles likewise arises from this source. Figure 3 depicts a possible spin–spin coupling scheme. We hasten to add that this hypothesis is based on NJC analysis of the Fermi contact term alone. At the moment there is no comparable decomposition procedure to assess the PSO term which likewise makes a major contribution to  ${}^3J_{\text{FF}}(\text{total})$ .

Previous observations on the lack of a correlation of  ${}^3J_{\text{FF}}$  with the F–C–C–F dihedral angle have commented on the existence of substituent effects that tend to level both *gauche* and *trans* couplings to a  $-10$  to  $-20$  Hz window.<sup>13</sup> Our B3LYP/6-311G-(d,p) calculations reproduce the phenomenon. For example, while  ${}^3J_{\text{FF}}\text{-trans}$  in DFE is predicted to be  $-58$  Hz, the corresponding values in the *trans* conformers of 1,2,2-trifluoroethane and 1,1,2,2-tetrafluoroethane are calculated at  $-45$  and  $-9$  Hz, respectively. Ramsey term comparison reveals that SD and DSO are essentially constant along this series, while the FC term falls only slightly ( $-31$ ,  $-28$ ,  $-23$  Hz). The PSO quantity appears to be the decisive factor ( $-46$ ,  $-34$ , and  $-6$  Hz, respectively). This result underscores the notion that certain spin–spin couplings are not dominated by the FC term and that their prediction can only be achieved by computing all four Ramsey contributions.<sup>18,25</sup>

In summary, the variation of  ${}^3J_{\text{FF}}$  with dihedral angle for 1,2-difluoroethane is indeed characterized by a rich and variable Karplus-type curve with both positive and negative components. Unlike butane with a similar conformational energy profile,<sup>26</sup> the spin–spin coupling enjoys strong contributions from all four Ramsey terms, but the negative PSO term dominates from 80 to 180°. Not only does PSO determine the sign of  ${}^3J_{\text{FF}}$  on this section of the  ${}^3J$ -surface, it also appears to mediate the strong substituent effects.

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**Supporting Information Available:** Computational results (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>

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