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Stereoelectronic Interactions and the One-Bond C–F Coupling Constant in Sevoflurane

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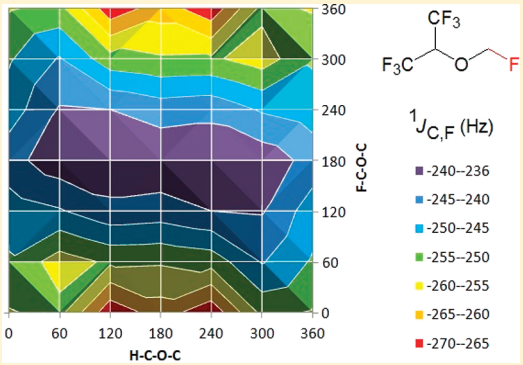
Supporting Information

ABSTRACT: The conformational preference of the widely utilized anesthetic fluoromethyl-1,1,1,3,3,3-hexafluoro-2-propyl ether (sevoflurane) has been investigated computationally and by NMR spectroscopy. Three conformational minima were located at the B3LYP/aug-cc-pVDZ level, but one is significantly more stable (by ca. 4 kcal/mol) than the other two. This is the case both for gas phase calculations and for solution NMR data. Although the main conformer is stabilized by electron delocalization ($n_O \rightarrow \sigma^*_{C-F}$), this type of hyperconjugation was not found to be the main driver for the conformer stabilization in the gas phase and, consequently, for the apparent anomeric effect in sevoflurane. Instead, more classical steric and electrostatic interactions appear to be responsible for the conformational energies. Also the $^1J_{CF}$ coupling constants do not appear to be dominated by hyperconjugation; again, dipolar interactions are invoked instead.



1. INTRODUCTION

The anomeric effect is a key concept in carbohydrate chemistry and the prototype for stereoelectronic control of molecular conformations. It can be defined as the preference of electronegative substituents (X) attached to the anomeric carbon (C-1) to occupy an *axial* orientation (α-anomer) instead of the less hindered *equatorial* orientation (β-anomer) that would be expected from steric considerations of a chair conformation.[1] The origin of this effect, which was observed for the first time by Edward in 1955,[2] has been attributed to antiperiplanar hyperconjugation ($n_O \rightarrow \sigma^*_{CX}$), which can operate simultaneously in both exo- and endo-directions in cyclic sugars.[3−5] However, interpretations based on repulsive dipole−dipole interactions have also been used to explain the anomeric effect for both isolated molecules and ones in solution (Figure 1), and a consensus on the relative contributions of these effects remains unresolved.[5−9] The anomeric concept has been extended to acyclic and other heterocyclic systems. Because fluorine is the most electronegative atom in organic chemistry with a low-lying σ^*_{CX} LUMO, a fluorine atom bonded to the anomeric carbon offers the best prospects of observing the ($n_O \rightarrow \sigma^*_{CX}$) hyperconjugative interaction. The anomeric effect has been investigated in a variety of acyclic compounds such as pnictogens[10] and isoflurane.[11] In these cases, hyperconjugation has been invoked as contributing to the minimum energy conformers.

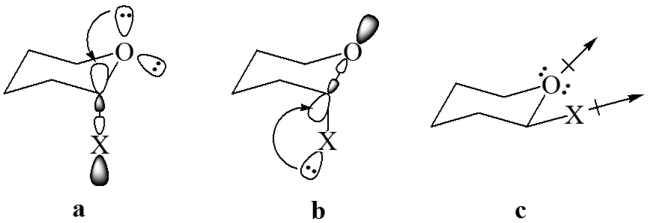


Figure 1. Possible explanations for the anomeric effect in substituted tetrahydropyrans: hyperconjugation (a) endo- and (b) exo-anomeric effect and (c) dipolar repulsion in the equatorial conformer.

Hyperconjugative interactions have been used to explain some NMR observations too; for example, in cyclohexane, the $^1J_{CH_{ax}}$ spin−spin coupling constant is generally smaller than the corresponding $^1J_{CH_{eq}}$. The assumption is that *axial* C−H bonds are longer and therefore weaker than *equatorial* bonds as a result of $\sigma_{CH} \rightarrow \sigma^*_{CH}$ hyperconjugative interactions from the more electron-rich antiperiplanar C−H bonds, relative to antiperiplanar C−C bonds. Thus, the Fermi contact (FC) term is reduced for axial C−H bonds and, therefore, the coupling decreases.[12] This phenomenon has been referred to as the "Perlin effect",[13,14] and it has also been described in sugars.[12,15] However, recently in tetrahydropyran, the Perlin effect has been attributed to dipolar interactions between the axial C−H bond with both the oxygen lone pairs and the polar C−O bond,

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not to the more classical $n_O \rightarrow \sigma^*_{C-H}$ hyperconjugation.[16] A similar interpretation has been proposed for the behavior of one-bond C−C coupling constants in ethers.[17] In 1,3-heterosubstituted cyclohexanes, a reverse Perlin effect ($^1J_{CH_{ax}} > {}^1J_{CH_{eq}}$) takes place, which has likewise been interpreted in terms of hyperconjugation;[18−31] for 1,3-dithianes, for instance, the reverse Perlin effect has been explained in terms of a dominant $\sigma_{C-S} \rightarrow \sigma^*_{C-H_{eq}}$ interaction rather than $n_S \rightarrow \sigma^*_{C-H_{ax}}$.[13,32] The $^1J_{CF}$ coupling constants in fluorocyclohexane have been measured ($^1J_{CF_{eq}} > {}^1J_{CF_{ax}}$);[33] this difference offers a useful conformational probe, although $^1J_{CF}$ are seldom used in this context. We have now used theory and NMR to study the conformation of sevoflurane (Figure 2), calling special attention to the relation between hyperconjugation and $^1J_{CF}$ coupling constants. There

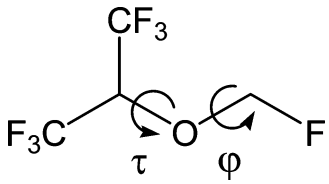

Figure 2. Sevoflurane and the τ and φ torsional angles.

are only a few theoretical and spectroscopic studies reported on this important clinical anesthetic.[34−36]

2. EXPERIMENTAL AND COMPUTATIONAL DETAILS

Sevoflurane was kindly provided by Cristalia Produtos Químicos Farmaceuticos Ltda. The ^{13}C NMR spectra were acquired on a Bruker Avance 500 spectrometer operating at 125.7 MHz, using variable temperatures (−90 °C, −50 °C, 0 °C, rt, and 50 °C) and solvents ($CDCl_3$, CD_2Cl_2, and CD_3CN solutions of ca. 50 mg mL^{-1} and also the neat liquid).

Geometries were fully optimized at the B3LYP/aug-cc-pVDZ level,[37] followed by evaluation of the harmonic frequencies, hyperconjugative interactions (from natural bond orbital analysis),[38] and single-point energy evaluations using the polarizable continuum model by Tomasi and co-workers (in its integral equation formalism[39]) and using a cavity built up using the UFF (radii with spheres around each solute atom) at the same level of theory. The $^1J_{C(H2),F}$ coupling constants were computed at the BHandHLYP/EPR-III level[40,41] (as sum of the Fermi contact, spin dipolar, and paramagnetic and diamagnetic spin orbit terms). Designed for the computation of hyperfine coupling constants, EPR-III basis is also well suited for the description of the Fermi contact part of the spin−spin coupling constants.[42] SOPPA-(CCSD)[43] coupling constant calculations were also performed with the Dalton 2.0 program[44] employing the EPR-III basis set for the coupled C and F in $^1J_{C(H2),F}$, and cc-pVDZ basis set for the remaining atoms. Hypersurfaces were built by varying the τ and φ torsional angles in steps of 30°, optimizing all other parameters at the B3LYP/aug-cc-pVDZ level. NBO analyses (at the same level) and NMR computations (at BHandHLYP/EPR-III level) were performed for a subset of these structures (angles varied in 60° steps). All calculations were performed using the Gaussian09 program.[45]

3. RESULTS AND DISCUSSION

Three stable conformers (minima) are identified in the hypersurface of sevoflurane (see the Ramachandran-type plot in Figure 3). Conformer **1** is calculated to be more stable than **2** and **3** both in the gas phase and in a polar solvent (acetonitrile), as depicted in Table 1. The X-ray crystal structure of its analog 1,1,1,3,3-pentafluoro-2-fluoromethoxy-3-methoxypropane[46] has a similar conformation to **1**, supporting this as the favored conformer. Additionally, the main infrared absorptions obtained experimentally from sevofluorane as a neat liquid correlate well with the calculated spectrum of that conformation (Supporting Information). There are no side bands or shoulders that might indicate significant contributions from competing conformers.

Conformers **1** and **2** have a conformation that could accommodate the $n_O \rightarrow \sigma^*_{CF}$ interaction, a feature confirmed by second-order perturbation analysis of donor−acceptor inter-

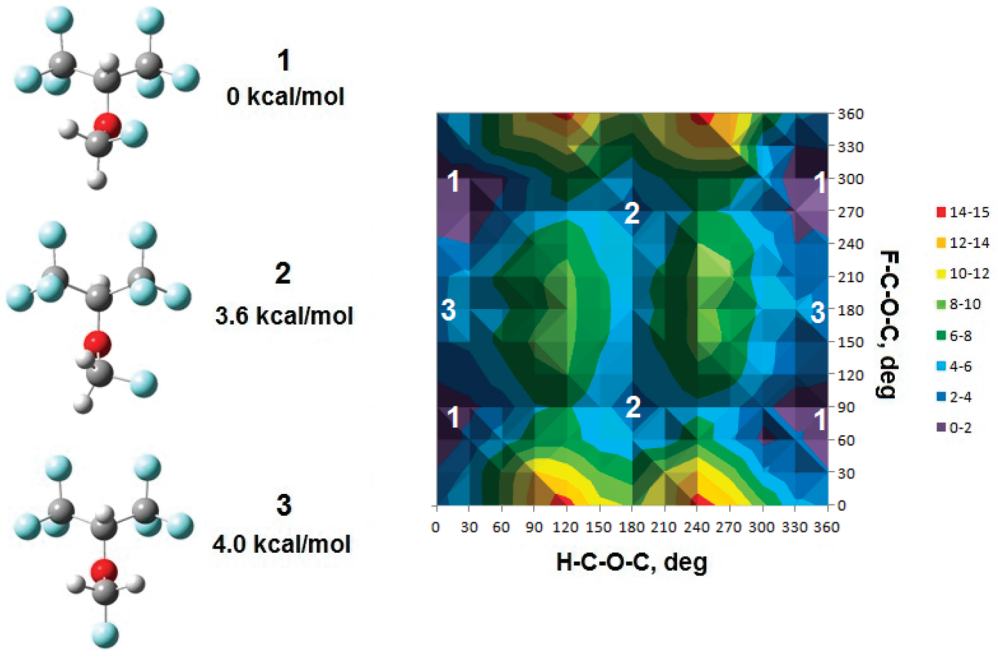

Figure 3. Two-dimensional surface (relative energies in kcal mol^{-1}) and stable conformers of sevoflurane for the isolated molecule.

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Table 1. Calculated Torsional Angles (deg), C−F Distance (Å), Dipole Moments (D), Energies (kcal mol^{-1}), and Contributions for the $^1J_{C(H2),F}$ Coupling Constants (Hz) for the Conformers 1−3 of Sevoflurane[a]

parameter	1	2	3
τ_{HCOC}	16.9 (−10.2)	173.9	0.0
φ_{FCOC}	69.2 (80.7)	90.0	180.0
d_{C-F}	1.395 (1.377)	1.390	1.367
μ	2.27	1.66	3.00
E_{rel,CH_3CN}	0.0	4.0	3.2
$E_{rel,C_6H_{12}}$	0.0	3.7	3.8
$E_{rel,gas}$	0.0	3.6	4.0
$E_{rel/total(hyperconjugation),CH_3CN}$	−8.9/1022.4	−5.1/1018.6	0.0/1013.5
$E_{rel/total(hyperconjugation),C_6H_{12}}$	−3.6/1026.9	−3.7/1027.0	0.0/1023.3
$E_{rel/total(hyperconjugation),gas}$	−0.4/1032.2	0.0/1031.8	−3.4/1035.2
$E_{rel(Lewis),CH_3CN}$	5.7	5.9	0.0
$E_{rel(Lewis),C_6H_{12}}$	0.0	3.8	0.2
$E_{rel(Lewis),gas}$	0.0	3.2	7.0
$n_O \rightarrow \sigma^*_{C(H2)-F}$ [b]	17.3/17.3/17.7	17.8/17.9/18.1	5.4/5.5/5.4
$n_O \rightarrow \sigma^*_{C-C(F3)}$ [b,c]	13.2/13.3/13.4	18.9/18.9/18.9	14.8/14.5/14.5
$n_F \rightarrow \sigma^*_{C-O}$ [b]	12.0/12.0/11.9	12.8/12.7/12.6	12.8/12.1/12.0
$^1J_{C(H2),F-CH_3CN}$	−242.2	−241.3	−232.2
$^1J_{C(H2),F-CH_2Cl_2}$	−242.7	−242.2	−233.5
$^1J_{C(H2),F-CHCl_3}$	−243.1	−243.2	−234.9
$^1J_{C(H2),F-C_6H_{12}}$	−244.7	−245.2	−238.0
$^1J_{C(H2),F-gas}$	−246.6	−248.0	−241.9
$^1J_{C(H2),F-gas}$ [SOPPA(CCSD)]	−228.7	−230.1	−221.6

[a]Values in parentheses are data from X-ray crystallography of the analog (+)-*S*-1,1,1,3,3-pentafluoro-2-fluoromethoxy-3-methoxypropane[46]. [b]Interactions in gas/C_6H_{12}/CH_3CN solutions. [c]Sum of both $n_O \rightarrow \sigma^*_{C-C(F3)}$ interactions.

actions in the natural bond orbitals (NBOs) (Table 1). However, this analysis reveals many more such donor−acceptor interactions throughout the molecule, which collectively sum to more than 1000 kcal mol^{-1}. The large difference in the $n_O \rightarrow \sigma^*_{CF}$ contributions between **1** or **2** and **3** is offset by these other interactions, to the extent that the least stable conformer **3** is more stabilized due to overall hyperconjugation than **1** and **2** in the gas phase (see $E_{rel/total(hyperconjugation)}$ values in Table 1). On the other hand, the energy for the natural Lewis structure, which can be estimated by subtracting the hyperconjugation energy from the total energy, indicates that **1** is the predominant conformer also in the absence of all hyperconjugative effects in the gas phase. This is most likely due to weaker steric/electrostatic repulsions. Therefore, the anomeric effect that is involved in **1** and also **2** but not **3** can be rationalized by classical interactions in the gas phase, as recently found for α-substituted tetrahydropyrans.[8] However, the situation changes in solution. In cyclohexane and acetonitrile, **1** remains the most stable conformer, but the contributions from hyperconjugation and steric/electrostatic interactions change. In cyclohexane, dipolar repulsion is little affected, except for the most polar conformer (**3**); in this solvent, hyperconjugation was calculated to govern the stability (and therefore the anomeric effect) of **1** and **2**. In highly polar CH_3CN, where intramolecular electrostatic repulsion is expected to be significantly reduced, **1** was found again to be the most stable conformer due now to the largest hyperconjugative contribution. Thus, reduced dipolar repulsion (in solution) favors anomeric hyperconjugation and particularly the $n_O \rightarrow \sigma^*_{C(H2)-F}$ in **1**.

NMR is an important tool for conformational analysis and most notably $^3J_{HF}$ and $^3J_{HH}$ coupling constants are used routinely in such analyses. However the $^1J_{C(H2),F}$ coupling constant is an interesting probe for this purpose and its utility is still emerging. Notably, the magnitude of one-bond C−H and C−C coupling constants have recently been attributed to dipolar interactions instead of hyperconjugation,[16,17] and because the highly polar C−F bond could impart even larger effects, the potential for $^1J_{C,F}$ in conformational analysis merits investigation. Unlike chemical shifts, intrinsic coupling constants tend to be rather insensitive to the experimental conditions (solvent, temperature), and therefore, changes in observed coupling constants can be largely attributed to changes in conformational equilibria.[47] We thus carried out a variable temperature NMR analysis of sevoflurane in different solvents (Supporting Information), focusing on the magnitude of $^1J_{C(H2),F}$. For the neat liquid, the magnitude of $^1J_{C(H2),F}$ was similar to that reported previously (223.7 Hz).[34]

From the computed relative energies in Table 1, conformer **1** is expected to be predominant in solution; however, the population of isomer **2** is anticipated to increase relative to **3** with temperature. Conformer **2** has the largest calculated $^1J_{C(H2)F}$ value and **3** the smallest one; therefore a net increase of $^1J_{C(H2),F}$ in the equilibrium mixture is anticipated with an increase in temperature. This trend was estimated using both BHandHLYP and SOPPA-(CCSD) methods; since trends, and not absolute values, are desired in this study, the BHandHLYP/EPR-III level was employed for further analysis. This is clearly observed in solvents of low polarity (e.g., from 225.4 Hz in $CDCl_3$ at −50 °C to 226.2 Hz in $CDCl_3$ at 50 °C, and from 224.8 Hz in CD_2Cl_2 at −90 °C to 225.3 Hz in CD_2Cl_2 at room temperature). In a more polar solvent, such as CD_3CN, **3** (the most polar conformer) should be stabilized more strongly by the solvent than **2**, and therefore, the $^1J_{C(H2),F}$ value should decrease. It is 2.2 Hz lower in CD_3CN (223.1 Hz) than in CD_2Cl_2 (225.3 Hz) at room temperature. In this case, a smaller change is computed for $^1J_{C(H2),F}$ of **1** in a polarizable continuum (decrease by 0.5 Hz on going from CH_2Cl_2 to MeCN, Table 1), but larger changes are predicted for the higher-lying isomers **2** and **3**. It may thus be difficult to distinguish unambiguously between direct solvent effects on the coupling constant (due to a change in response of the wave function) and indirect effects (due to a change in equilibrium composition). Overall, however, it appears that the $^1J_{C(H2),F}$ coupling constant is a sensitive probe for the electronic and geometric structure in sevoflurane.

In order to investigate the conformational dependence of the $^1J_{C(H2),F}$ coupling constant in sevoflurane, hypersurfaces were constructed to probe for possible correlations of $^1J_{C(H2),F}$ with the $n_O \rightarrow \sigma^*_{CF}$ interaction, a correlation that has been used to explain the origin of the Perlin effect in heterocycles.[12−15] However, no obvious relationship is apparent when the behavior of the $n_O \rightarrow \sigma^*_{CF}$ interaction is compared with that of the $^1J_{C(H2),F}$ coupling constant in sevoflurane. According to Figure 4, electron delocalization $n_O \rightarrow \sigma^*_{CF}$ appears to be weakest around φ (F−C−O−C) of 0° and 180°, while maximum and minimum $^1J_{C(H2),F}$ values can be found for these respective conformers.

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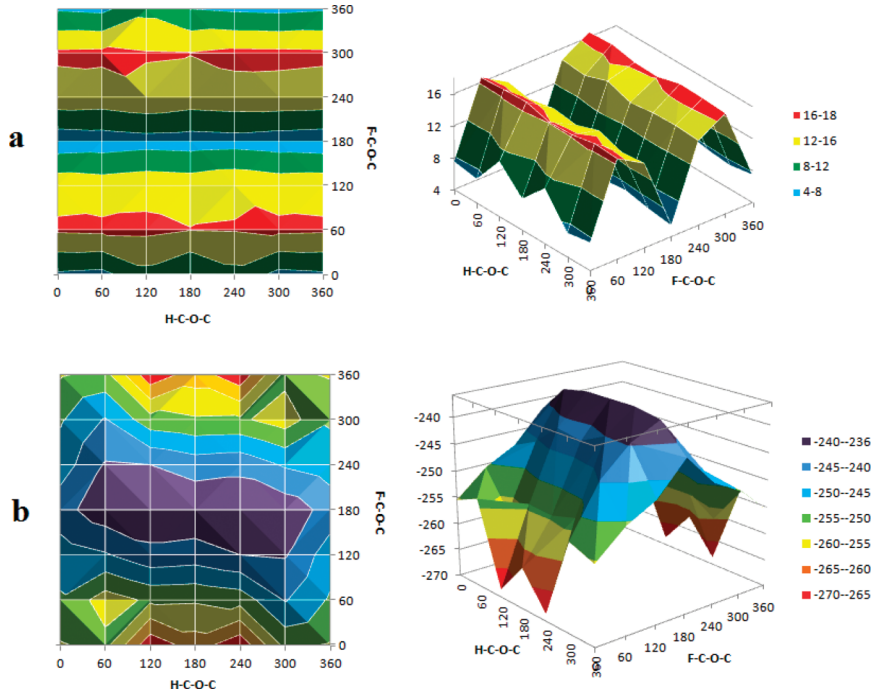

Figure 4. Energy (kcal mol^{-1}) of $n_O \rightarrow \sigma^*_{CF}$ interaction (a) and $^1J_{C(H2),F}$ coupling constant (b, Hz) as a function of the τ (H−C−O-C) and φ (F−C−O-C) torsional angles in sevoflurane.

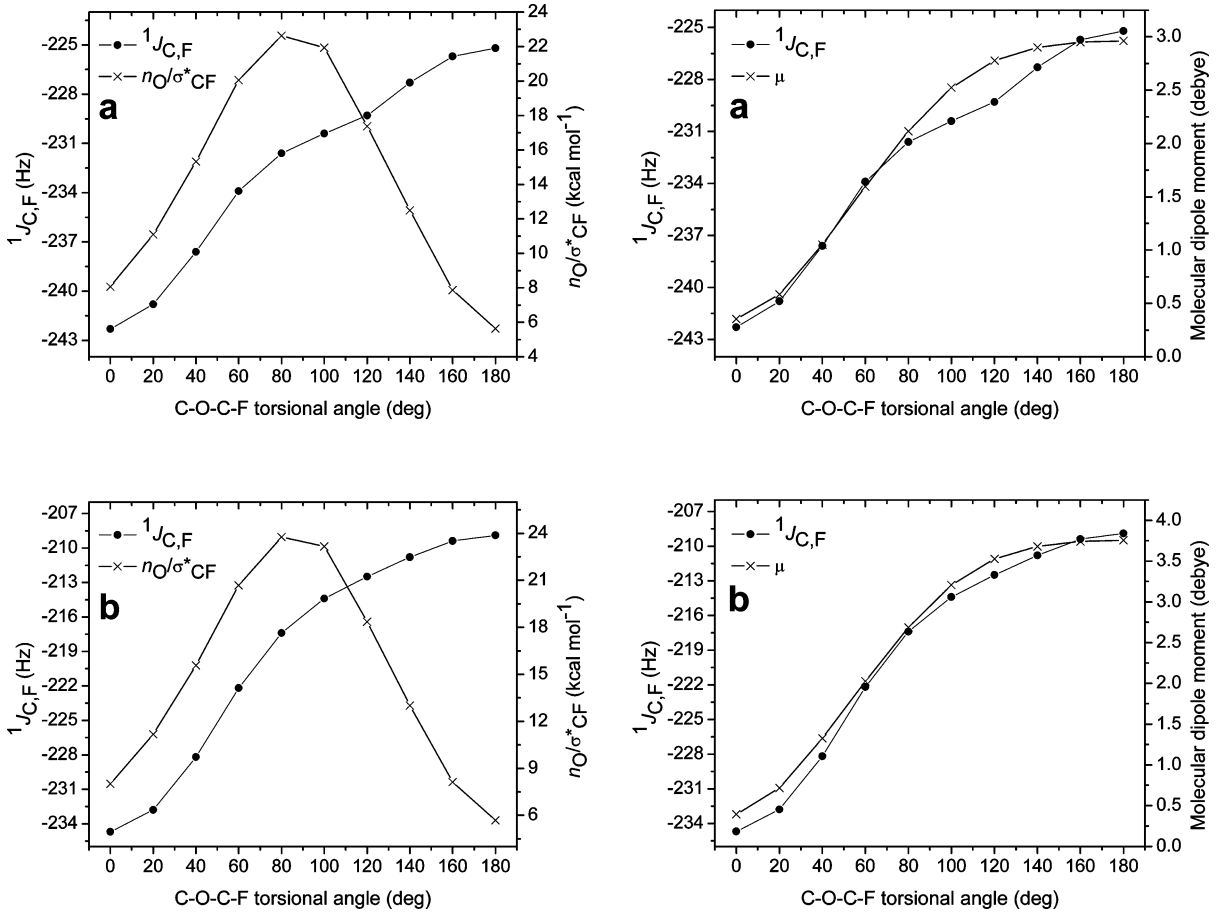

Figure 5. Dependence of calculated $^1J_{C,F}$ coupling constant with molecular dipole moment and with the $n_O \rightarrow \sigma^*_{CF}$ interaction in fluoro(methoxy)methane in (a) the gas phase and (b) acetonitrile solution.

To probe for a possible correlation of $^1J_{C(H2),F}$ with the O···F dipolar interaction, we performed calculations for the simpler model fluoro(methoxy)methane, where the mutual orientation between the C−F bond and the oxygen lone pairs dominates

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the overall molecular dipole moment. For this model, there is in fact a good correlation between $^1J_{C,F}$ and the dipole moment both in the gas phase and in CH_3CN solution (R^2 = 0.976 and 0.996, respectively), while there was no correlation found between $^1J_{C,F}$ and $n_O \rightarrow \sigma^*_{CF}$ (Figure 5). Since the total molecular dipole moment of sevoflurane itself is also dependent on the orientation of the two trifluoromethyl groups, a similar analysis is more complex in this case.

4. CONCLUSION

Hyperconjugation, widely invoked to explain the anomeric and Perlin effects, was not found to be the determining factor influencing the conformational preference for sevoflurane in the gas phase. Hyperconjugation is more significant in solution and particularly in polar solvents. Also it appears that the larger the molecular dipole, dominated by the interaction between the oxygen lone pairs and the polar C−F bond, the lower the $^1J_{C(H2),F}$ coupling constant. Similar findings have been found also for 1,2-difluoroethane;[48] variation of $^1J_{C(H2),F}$ is independent of hyperconjugation.

■ ASSOCIATED CONTENT

Supporting Information

Infrared, ^{13}C NMR, and theoretical data for sevoflurane. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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