JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

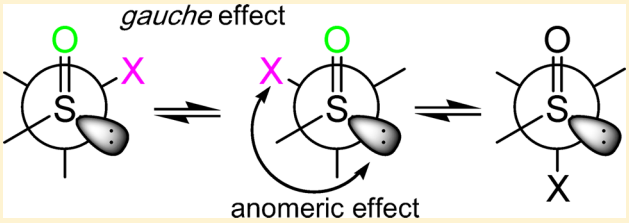
Simultaneous *gauche* and Anomeric Effects in α-Substituted Sulfoxides

Matheus P. Freitas*

Department of Chemistry, Federal University of Lavras, 37200-000 Lavras, MG, Brazil

Supporting Information

ABSTRACT: α-Substituted sulfoxides can experience both *gauche* and anomeric effects, since these compounds have the geometric requirements and strong electron donor and acceptor orbitals which are essential to make operative the hyperconjugative nature of these effects. Indeed, the title effects were calculated to take place for 1,3-oxathiane 3-oxide in polar solution, where dipolar effects are absent or at least minimized, while only the *gauche* effect is present in 2-fluorothiane 1-oxide. Since the fluorine atom is a suitable probe for structural analysis using NMR, the $^{1}J_{CF}$ dependence on the rotation around the F−C−S═O dihedral angle of (fluoromethyl)methyl sulfoxide was evaluated; differently from 1,2-difluoroethane and fluoro(methoxy)methane, this coupling constant is at least not exclusively dependent on dipolar interactions (or on hyperconjugation). Because of the nonmonotonic behavior of the $^{1}J_{CF}$ rotational profile, this coupling constant does not appear to be of significant diagnostic value for probing the conformations of α-fluoro sulfoxides.



INTRODUCTION

In order to investigate whether the *gauche* and anomeric effects can operate simultaneously, α-substituted sulfoxides (substituent OR, F) were computationally analyzed. The *gauche* effect is defined as the surprising tendency that electronegative groups have in preferring the *gauche* orientation instead of the *anti* orientation; the anomeric effect is the preference of electronegative substituents 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—this definition has been extended to acyclic compounds. The origins of both effects are assumed to be due to hyperconjugation,[1] but interpretations based on dipolar effects have also been invoked.[2−4] α-Substituted sulfoxides have the potential of experiencing both interactions simultaneously, although their importance to conformer stabilization has not been proved.

Sulfoxides play an important role in medicinal chemistry, e.g. as inhibitors of gastric acid secretion like the widely used omeprazole;[5] structural changes due to replacement of any atom by other substituents can affect bioactivity. α-Substitution by oxygen is expected to modify the physical and chemical properties of a sulfoxide molecule; likewise, replacing hydrogen by fluorine does not have a significant steric effect, but it influences the pK_a of functional groups and alters the solution conformation.[6,7] Both C−O and C−F bonds are polar and, therefore, subject to strong stereoelectronic effects. Particular attention is given to fluorinated derivatives, since ^{19}F is a suitable nucleus in NMR spectroscopy, which is a useful technique for structural analysis.

RESULTS AND DISCUSSION

1,3-Oxathiane 3-oxide (**1**, Figure 1) was computationally (B3LYP/aug-cc-pVDZ) found to be more stable in the SO_{ax} conformation than in the SO_{eq} form by 0.8 kcal mol^{-1} in the gas phase. The SO_{eq} conformation agrees with the X-ray crystal structure of 2-phenyl-1,3-oxathiane 3-oxide[8] but not with the more structurally similar compounds *trans*-5-methyl-3-oxo-1,3-oxathiane[9] and (2S_C,3R_S,4R_C)-2-methyl-4-propyl-1,3-oxathiane 3-oxide (Figure 1);[10] other examples of the preferred *gauche* orientation along the OCSO fragment can be found in the Cambridge Structural Database (43 hits from the $SOCH_2O$ substructure). Actually, a more general representation of 1,3-oxathio 3-oxide compounds is the model (methoxymethyl)-methyl sulfoxide ($CH_3SOCH_2OCH_3$); a conformational screening around the C−O−C−S and O−C−S−O dihedral angles gives the energy hypersurface of Figure 2, in which the global minimum **A** and a local minimum **G** correspond to *gauche* conformers relative to the O−C−S−O dihedral angle. The remaining forms are *anti* relative to this dihedral angle.

Indeed, both experiment[8−10] and theory suggest that conformers SO_{ax} and SO_{eq} must be populated very similarly in the equilibrium. In the gas phase, the SO_{ax} conformer of **1** is clearly disfavored because of higher steric/electrostatic repulsion, particularly due to *gauche* repulsion between the oxygen atoms. This can be confirmed by natural bond orbital (NBO) analysis,[11] using deletion of non-Lewis (starred) orbitals; the role of electronic delocalization can be quantitatively assessed by deleting all non-Lewis NBOs, giving

Received: July 18, 2012
Published: August 10, 2012

dx.doi.org/10.1021/jo3014885 | J. Org. Chem. 2012, 77, 7607−7611

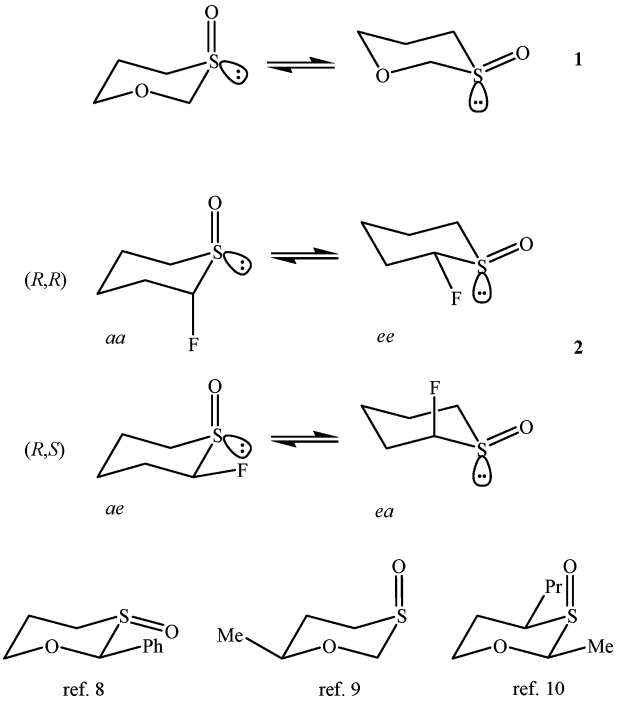


Figure 1. Conformational isomerism in 1,3-oxathiane 3-oxide (**1**) and 2-fluorothiane 1-oxide (**2**) and compounds obtained from the literature[8−10] using X-ray crystallography.

a "natural Lewis structure" wave function, which is perfectly localized, with all Lewis-type NBOs doubly occupied. Deletion of all hyperconjugative interactions involving antibonding and Rydberg orbitals indicates that the SO_{ax} conformer of **1** is ca. 15.5 kcal mol^{-1} more stabilized than the SO_{eq} conformer by electron transfers from filled to vacant orbitals (485.5 against 470.0 kcal mol^{-1} of stabilization) and, thus, the SO_{eq} conformer is less destabilized due to steric/dipolar effects by 16.3 kcal mol^{-1}. In **1**, the main vicinal hyperconjugative contributions in the SO_{ax} conformer relative to the SO_{eq} conformer is the $n_S \rightarrow \sigma^*_{CO}$ interaction (corresponding to the hyperconjugative nature of the anomeric effect), which is ca. 2 kcal mol^{-1} more stabilizing than the corresponding $n_S \rightarrow \sigma^*_{CH}$ interaction in the SO_{eq} conformer, and the $\sigma_{C2H,ax} \rightarrow \sigma^*_{SO}$ (corresponding to the hyperconjugative nature of the *gauche* effect), which is ca. 1 kcal mol^{-1} stronger than the corresponding $\sigma_{C5C6} \rightarrow \sigma^*_{SO}$ interaction in the SO_{eq} conformer (Table 1).

In solution, where dipolar interactions are minimized, the quantum effects in both conformers are more competitive: the total hyperconjugative energies in SO_{ax} and SO_{eq} conformers are quite similar in DMSO (448.8 and 448.6 kcal mol^{-1}, respectively). In fact, the calculated conformational energies in DMSO using the polarizable continuum model by Tomasi and co-workers (in its integral equation formalism[12]) and using a cavity built up using the UFF (radii with spheres around each solute atom) at the same level of theory indicate that SO_{ax} and SO_{eq} are very closely populated (indeed, a slight preference for the SO_{ax} conformer of **1** is calculated, by 0.3 kcal mol^{-1}). Consequently, SO_{ax} is calculated to be slightly less destabilized due to steric/dipolar effects than SO_{eq} (by ca. 0.1 kcal mol^{-1}), since the total energy is a contribution from quantum and Lewis-type interactions. Therefore, the endocyclic *gauche* and anomeric effects take place in polar solution, and the origins of these effects in **1** appear to be ruled by quantum and classical effects: while hyperconjugative interactions are prevalent in the

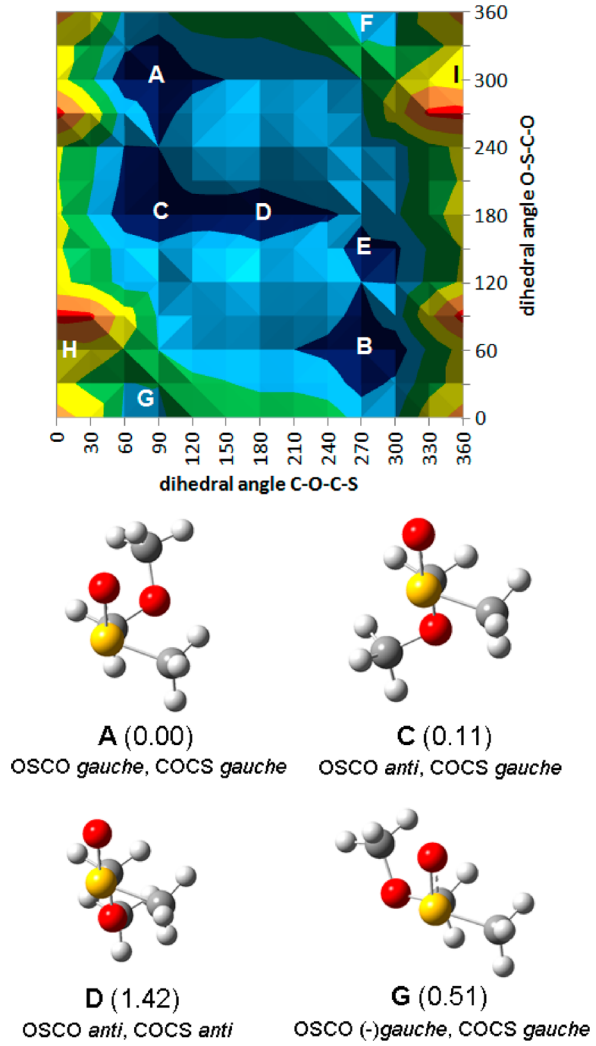


Figure 2. Conformational hypersurface for (methoxymethyl)methyl sulfoxide (B3LYP/6-31g(d,p)). After optimization (B3LYP/aug-cc-pVDZ level) of the minima **A**−**I** found in the hypersurface, conformers **A**, **B**, **F**, **H**, and **I** converged to be structurally equivalent to each other, as well as **C** and **E**. Relative energies (in kcal mol^{-1}) are given in parentheses.

SO_{ax} conformer (especially the $n_S \rightarrow \sigma^*_{CO}$ and $\sigma_{C2H,ax} \rightarrow \sigma^*_{SO}$ interactions), the reduced dipolar repulsion in polar solution also leads to the structure with a *gauche* O−C−S−O arrangement.

Because hyperconjugation and dipolar effects were found to operate in **1**, introduction of a vicinal fluorine atom in thiane oxide to give 2-fluorothiane 1-oxide (**2**) can be of interest, since the C−F bond is the most polar bond in organic chemistry and is thus subjected to strong dipolar and hyperconjugative (via the low-lying σ^*_{CF} orbital) interactions. The *gauche* effect in organofluorine compounds has been found to be due to antiperiplanar interactions between σ_{CH} as the electron-donor orbital and the σ^*_{CF} vacant orbital.[13−15] The anomeric effect has been attributed as due to both hyperconjugation and dipolar interactions.[1,4,16,17]

The *R*,*R* and *R*,*S* diastereoisomers of **2** are shown in Figure 1. In the gas phase (calculated at the B3LYP/aug-cc-pVDZ level), the *diaxial* conformer of the *R*,*R* diastereoisomer is significantly more populated than the remaining forms, which is clearly an effect of weaker electrostatic repulsion between the electro-

dx.doi.org/10.1021/jo3014885 | J. Org. Chem. 2012, 77, 7607−7611

Table 1. Relative Energies and Antiperiplanar Hyperconjugative Interactions in 1 (in kcal mol^{-1})[a]

param	1-SO$_{ax}$	1-SO$_{eq}$
E_{rel}(gas)	0.8	0.0
E_{rel}(DMSO)	0.0	0.3
$n_{O(1)}\rightarrow\sigma^*_{CS}$	0.9	0.6
$n_{O(2)}\rightarrow\sigma^*_{CS}$	15.2	14.6
$n_S\rightarrow\sigma^*_{CO}$	3.4	
$n_S\rightarrow\sigma^*_{CC}$	2.2	
$n_S\rightarrow\sigma^*_{CH2}$		1.3
$n_S\rightarrow\sigma^*_{CH6}$		1.6
$\sigma_{SO}\rightarrow\sigma^*_{CH2}$	0.6	
$\sigma_{SO}\rightarrow\sigma^*_{CH6}$		
$\sigma_{SO}\rightarrow\sigma^*_{CO}$		1.2
$\sigma_{SO}\rightarrow\sigma^*_{CC}$		0.7
$\sigma_{C2H}\rightarrow\sigma^*_{SO}$	1.8	
$\sigma_{CH6}\rightarrow\sigma^*_{SO}$	1.9	
$\sigma_{CO}\rightarrow\sigma^*_{SO}$		
$\sigma_{CC}\rightarrow\sigma^*_{SO}$		0.9
$\sigma_{CH2}\rightarrow\sigma^*_{CO}$	3.7	3.6
total hyperconjugation (gas)	485.5	470.0
total hyperconjugation (DMSO)	448.8	448.6

[a]Individual hyperconjugative interactions were similar in the gas and DMSO.

negative fluorine and oxygen atoms. It is worth mentioning that steric effects between oxygen and fluorine can also take place, but to a lesser extent, since replacement of hydrogen by fluorine does not have a significant steric effect.[6,7] The *anti* orientation of the SO and CF bonds is consistent with the X-ray crystal structure of (1*R*,4*R*,5*S*)-3-benzoyl-4-carbomethoxy-2,2-dimethyl-5-fluoro-1-oxothiazolidine.[18] However, the figure changes in polar (DMSO) solution, where the most polar forms (*R,R-ee* and *R,S-ae*) are the theoretically most stable ones (Table 2). In polar solution, where intramolecular dipolar interactions are reduced, steric effects and hyperconjugation are expected to be retained, thus dominating the conformational and configurational energies in **2**. The anomeric effect in its hyperconjugative nature ($n_S\rightarrow\sigma^*_{CF}$) does not appear to operate, since the form with an ability to exhibit such an interaction (*R,S-ea*) is not the main conformation in polar solution (relative energy of 0.6 kcal mol^{-1}). However, the three preferred forms in DMSO solution (*R,R-ee*, *R,S-ae*, and *R,S-ea*) have the *gauche* O−S−C−F arrangement; the *gauche* effect is clearly operating.

Table 2. Relative Energies and Antiperiplanar Hyperconjugative Interactions in 2 (in kcal mol^{-1})[a]

param	*R,R-aa*	*R,R-ee*	*R,S-ae*	*R,S-ea*
E_{rel}(gas)	0.0	2.0	1.1	2.5
E_{rel}(DMSO)	0.7	0.0	0.0	0.6
$\sigma_{C3H}\rightarrow\sigma^*_{CF}$	6.7	1.2	0.7	5.9
$\sigma_{SO}\rightarrow\sigma^*_{CF}$	1.5			
$n_S\rightarrow\sigma^*_{CF}$		0.7		3.7
$\sigma_{C3C4}\rightarrow\sigma^*_{CF}$		3.3	3.8	
$\sigma_{SC6}\rightarrow\sigma^*_{CF}$		3.0	3.1	
$\sigma_{CH6}\rightarrow\sigma^*_{SO}$	2.0		1.8	
$\sigma_{CH2}\rightarrow\sigma^*_{SO}$			1.6	
$\sigma_{CF}\rightarrow\sigma^*_{SO}$				
$\sigma_{C2C3}\rightarrow\sigma^*_{SO}$		0.8		0.8
$\sigma_{C5C6}\rightarrow\sigma^*_{SO}$		0.9		1.1
$n_F\rightarrow\sigma^*_{SO}$	1.0			
$n_O\rightarrow\sigma^*_{CF}$	2.0			
total hyperconjugation (gas)	511.4	512.7	521.4	521.4
total hyperconjugation (DMSO)	498.3	477.9	490.3	485.2

[a]Individual hyperconjugative interactions were similar in the gas and DMSO.

Hyperconjugative interactions have usually been analyzed on the basis of natural bond orbitals, and the deletion of all interactions involving electronic transfer from full to vacant orbitals can give insight into classical and nonclassical contributions for the structural stabilization of **2** (Table 2). Indeed, this model considers that the full energy of a system can be partitioned into Lewis-type and quantum-type contributions. In the gas phase, the *diaxial* form is the least stabilized by hyperconjugation, but it is the most stable one; this reinforces the hypothesis above that dipolar interaction is the dictating effect of the conformational/configurational stability and that *R,R-aa* should be the most stable form in the gas phase because of lower Lewis-type, repulsive interactions. However, in polar solution (DMSO), the *diaxial* form was calculated to be the most favored by hyperconjugation, despite its highest overall energy; thus, Lewis-type interactions between the *axial* heteroatoms seems to rule the lower stability of *R,R-aa* in DMSO solution. One of the most stable forms, *R,R-ee*, is not privileged by hyperconjugation, but it experiences the weaker steric effects; *R,S-ae*, the other lowest energy form, is predicted to have important hyperconjugative interactions, which govern the conformational isomerism toward the *R,S-ea* form. As a concluding remark for **2**, the *gauche* effect appears where dipolar interactions are absent (polar solution) in the conformational isomerism of the *R,R* (or *S,S*) diastereoisomeric form, but it is due to repulsion involving the fluorine and oxygen atoms.

NMR coupling constants have been shown to be an important probe for structural analysis and have been used to identify and interpret manifestations of stereoelectronic interactions, such as the *gauche* and anomeric effects, the main focus of this work.[19] $^1J_{CF}$ coupling constants are particularly useful for this purpose, since they are sensitive to conformational changes.[20] This coupling has shown to be dependent on dipolar interactions;[17,21] however, it increases (becomes more negative) with dipolar interactions involving the coupled fluorine in 1,2-difluoroethane[21] but decreases (becomes less negative) when the molecular dipole moment is dictated by the mutual orientation between the C−F bond and lone pairs, such as in sevoflurane.[17] α-Fluoromethyl sulfoxides are interesting models, since the fluorine atom can interact both with the S=O polar bond (which should have an effect similar to that of 1,2-difluoroethane) and with a sulfur lone pair (which should have an effect similar to that of sevoflurane). In order to investigate how the $^1J_{CF}$ coupling constants vary in such a system with the molecular dipole moment, (fluoromethyl)-methyl sulfoxide was utilized as a prototypical compound, while the coupling constant calculations were carried out at the BHandH/EPR-III level (the cc-pVDZ basis set was used for the sulfur atom).

The angular dependence of $^1J_{CF}$ in (fluoromethyl)methyl sulfoxide was found to be independent of the molecular dipole moment (Figure 3). This is probably because of the antagonistic dipolar effects of bonding (σ_{SO}) and nonbonding (n_S) orbitals on $^1J_{CF}$, which are both operating in this kind of compound, but it is also due to other interactions which possibly contribute for this coupling, such as hyperconjugation.

dx.doi.org/10.1021/jo3014885 | J. Org. Chem. 2012, 77, 7607−7611

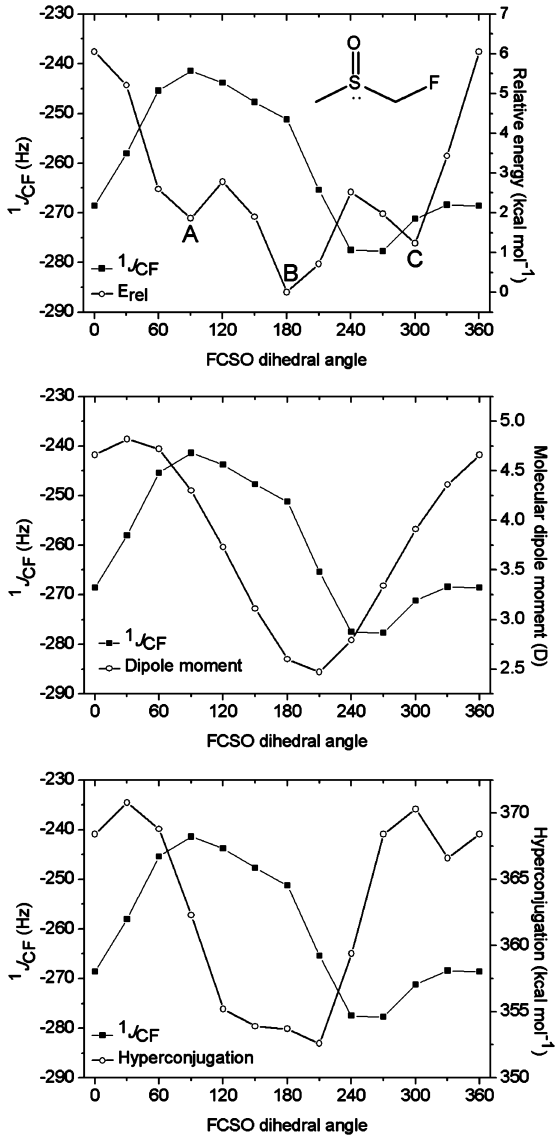


Figure 3. Angular dependence of $^1J_{CF}$ in (fluoromethyl)methyl sulfoxide and comparison with the relative energy of conformers A–C (top), molecular dipole moment (middle), and hyperconjugation (bottom).

For instance, the Perlin effect ($^1J_{CH,ax} < {}^1J_{CH,eq}$ in cyclohexane and tetrahydropyran rings) has been attributed to antiperiplanar interactions from σ_{CH} or n_O orbitals to σ^*_{CH}, resulting in longer and therefore weaker C–H_{ax} bonds in comparison to C–H_{eq} bonds.[22−25] This interpretation was refuted later,[26,27] but hyperconjugation has been found to be the dictating mechanism of coupling constants in many systems.[28] In **2**, the C–F bond length in *R,R-aa* was calculated to be only 0.01 Å longer than in the remaining forms. It is complex to establish any relationship between specific hyperconjugative interactions with $^1J_{CF}$ in (fluoromethyl)methyl sulfoxide, since many n_F-, σ_{CF}-, and σ^*_{CF}-based interactions (orbitals possibly involved in the coupling pathway) are importantly operating, but the sum of all hyperconjugative interactions on the basis of natural bond orbital analysis does not appear to correlate with $^1J_{CF}$ (Figure 3). Indeed, this behavior suggests that an interplay of classical and quantum interactions govern $^1J_{CF}$ in (fluoromethyl)methyl sulfoxide, such as in α-fluorosulfones.[29] Similarly to α-fluorosulfones,[29] this coupling constant does not appear to be of significant diagnostic value for probing the conformations of α-fluorosulfoxides, despite the calculated $^1J_{CF}$ for the global energy minimum of (fluoromethyl)methyl sulfoxide differing by ca. +10 to −20 Hz from the corresponding values of the local minima (Figure 3); this is due to the nonmonotonic behavior of $^1J_{C,F}$ in this prototypical compound.

In order to evaluate this, the $^1J_{CF}$ coupling constants for the stable conformers of (fluoromethyl)methyl sulfoxide were computationally estimated in a nonpolar solvent (cyclohexane) and in a polar solvent (DMSO), since conformer populations are expected to vary with solvent, while intrinsic couplings are supposed to be less sensitive to the medium than chemical shifts;[30] thus, changes in experimental coupling constants (average of individual J) when varying solvents are usually assumed to be only due to changes in conformations. The relative energies of conformers A–C of (fluoromethyl)methyl sulfoxide are depicted in Table 3; while the least polar conformer, B, is predominant in nonpolar solution (63%), A and C dominate in the polar solvent (42% and 40%, respectively). Thus, if the calculated, individual $^1J_{CF}$ coupling constants are averaged using the estimated populations in cyclohexane and DMSO, the overall $^1J_{CF}$ in C_6H_{12} for (fluoromethyl)methyl sulfoxide would be −249.0 Hz, while the corresponding value in DMSO would be −240.5 Hz. Experimentally, this finding would not be expected to give insight into the extent of conformational shift from nonpolar to polar media, since the dependence of $^1J_{CF}$ on solvent is at least comparable to that with conformational changes. In both solvents, the mean $^1J_{CF}$ value is similar to that of conformer B. Thus, the $^1J_{CF}$ coupling constant cannot be used to estimate the conformational population of α-fluorosulfoxides.

In summary, both *gauche* and anomeric effects can operate simultaneously in α-substituted sulfoxides. The nature of these effects, especially the anomeric effect, has been debated extensively in recent years[4,31] as being due to dipolar or hyperconjugative interactions. In this work, dipolar and hyperconjugative interactions were found to be competitive as driving forces of the above effects (when operating) in polar solution, where intramolecular dipolar interactions are minimized by the presence of a polar solvent; this information can be particularly useful for studies in living (aqueous) systems. Despite the fact that NMR coupling constants have been successfully applied to study conformations in solution, $^1J_{CF}$

Table 3. Calculated Data[a] for the Conformers of (Fluoromethyl)methyl Sulfoxide

	C_6H_{12}				DMSO			
conformer	E_{rel}	amt, %	μ	$^1J_{CF}$	E_{rel}	amt, %	μ	$^1J_{CF}$
A	0.80	16	5.5	−235.1	0.00	42	6.8	−226.0
B	0.00	63	3.1	−247.5	0.52	18	3.8	−243.1
C	0.65	21	4.8	−264.3	0.03	40	6.0	−254.6

[a] E_{rel} in kcal mol^{-1}, molecular dipole moment (μ) in D, and $^1J_{CF}$ in Hz.

dx.doi.org/10.1021/jo3014885 | J. Org. Chem. 2012, 77, 7607−7611

does not appear to be a significant tool in deciding the conformation of α-fluorosulfoxides, because of the non-monotonic behavior of the $^1J_{CF}$ rotational profile.

COMPUTATIONAL SECTION

Compounds were all optimized at the B3LYP/aug-cc-pVDZ theoretical level,[32] the same level used in the NBO calculations (version 5.0). Calculations using implicit solvent were carried out using the polarizable continuum model by Tomasi and co-workers (in its integral equation formalism[12]) and using a cavity built up using the UFF (radii with spheres around each solute atom) at the same level of theory. The 3D potential energy surface for (methoxymethyl)methyl sulfoxide was built from B3LYP/6-31 g(d,p) calculations. Coupling constant calculations were carried out at the BHandH/EPR-III level[33,34] (the cc-pVDZ basis set was used for the S atom). All calculations were performed using the Gaussian09 program.[35]

ASSOCIATED CONTENT

Supporting Information

Tables giving Cartesian coordinates and absolute energies for the optimized molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: matheus@dqi.ufla.br.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

I thank the FAPEMIG for financial support and the CNPq for a fellowship. Prof. Michael Bühl is also gratefully acknowledged for providing the CSD structures.

REFERENCES

(1) Alabugin, I. V.; Gilmore, K. M.; Peterson, P. W. *WIREs Comput. Mol. Sci.* **2011**, *1*, 109.
(2) Gooseman, N. E. J.; O'Hagan, D.; Peach, M. J. G.; Slawin, A. M. Z.; Tozer, D. J.; Young, R. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5904.
(3) Freitas, M. P.; Rittner, R. *J. Phys. Chem. A* **2007**, *111*, 7233.
(4) Mo, Y. *Nat. Chem.* **2010**, *2*, 666.
(5) Allenmark, S.; Bomgren, B.; Borén, H.; Lagerström, P. -O. *Anal. Biochem.* **1984**, *136*, 293.
(6) O'Hagan, D. *J. Org. Chem.* **2012**, *77*, 3689.
(7) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
(8) Hursthouse, M. B.; Hibbs, D. E. *Private communication*, 2003.
(9) Singer, G.; Heusinger, G.; Mosandl, A.; Burschka, C. *Liebigs Ann. Chem.* **1987**, 451.
(10) Pihlaja, K.; Sillanpaa, R.; Dahlqvist, M.; Stajer, G.; Ahlgren, M. *Struct. Chem.* **1993**, *4*, 203.
(11) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. *NBO 5.0*; Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, 2001.
(12) Cancès, E.; Mennucci, B. *J. Math. Chem.* **1998**, *23*, 309.
(13) Goodman, L.; Gu, H.; Pophristic, V. *J. Phys. Chem. A* **2005**, *109*, 1223.
(14) Souza, F. R.; Freitas, M. P.; Rittner, R. *J. Mol. Struct.* **2008**, *863*, 137.
(15) Buissonneaud, D. Y.; van Mourik, T.; O'Hagan, D. *Tetrahedron* **2010**, *66*, 2196.
(16) Martins, L. E.; Freitas, M. P. *J. Phys. Org. Chem.* **2008**, *21*, 881.
(17) Freitas, M. P.; Bühl, M.; O'Hagan, D.; Cormanich, R. A.; Tormena, C. F. *J. Phys. Chem. A* **2012**, *116*, 1677.
(18) Baba, D.; Ishii, H.; Higashiya, S.; Fujisawa, K.; Fuchigami, T. *J. Org. Chem.* **2001**, *66*, 7020.
(19) Juaristi, E.; Cuevas, G. *Acc. Chem. Res.* **2007**, *40*, 961.
(20) Fiorin, B. C.; Basso, E. A.; Tormena, C. F.; Rittner, R.; Abraham, R. J. *J. Phys. Chem. A* **2009**, *113*, 2906.
(21) Freitas, M. P.; Bühl, M.; O'Hagan, D. *Chem. Commun.* **2012**, *48*, 2433.
(22) Perlin, A. S.; Casu, B. *Tetrahedron Lett.* **1969**, *10*, 2921.
(23) Wolfe, S.; Pinto, B. M.; Varma, V.; Leung, R. Y. N. *Can. J. Chem.* **1990**, *68*, 1051.
(24) Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910.
(25) Anderson, J. E.; Bloodworth, A. J.; Cai, J.; Davies, A. G.; Tallant, N. A. *J. Chem. Soc., Chem. Commun.* **1992**, 1689.
(26) Cuevas, G.; Martínez-Mayorga, K.; Fernández-Alonso, M. C.; Jiménez-Barbero, J.; Perrin, C. L.; Juaristi, E.; López-Mora, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2360.
(27) Perrin, C. L.; Erdélyi, M. *J. Am. Chem. Soc.* **2005**, *127*, 6168.
(28) Contreras, R. H.; Peralta, J. E. *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *37*, 321.
(29) Freitas, M. P.; Bühl, M. *J. Fluorine Chem.* **2012**, *140*, 82.
(30) Abraham, R. J.; Bretschneider, E. In *Internal Rotation in Molecules*; Orville-Thomas, W. J., Ed.; Wiley: London, 1974; Chapter 13.
(31) Cocinero, E. J.; Çarçabal, P.; Vaden, T. D.; Simons, J. P.; Davis, B. G. *Nature* **2011**, *469*, 76.
(32) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.
(33) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(34) Barone, V. In *Recent Advances in Density Functional Methods*; Chong, D. P., Ed.; World Scientific: Singapore, 1996; Part I.
(35) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.02*; Gaussian, Inc., Wallingford, CT, 2009.