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Conformational and stereoelectronic investigation of chloromethyl methyl sulfide and its sulfinyl and sulfonyl analogs

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Abstract

The rotational equilibria of some sulfur-containing model compounds were theoretically determined, and a rationalization of the effects responsible for the results obtained is given. Experimental approaches, namely NMR and infrared, were also used to show the *gauche* (Cl—C—S—CH$_3$ fragment) prevalence for these compounds and allowed us to elucidate the orbital interactions involved in such systems. The *gauche* rotamer of the sulfide is about 3.2 kcal mol^{-1} more stable than *anti* in the gas phase. For the sulfinyl derivative the relative energies for the most stable rotamers are 0.0, 1.0 and 1.7 kcal mol^{-1}, corresponding to *gauche-1* (C—Cl antiperiplanar to S=O), *gauche-2* (C—Cl antiperiplanar to lone pair) and *anti*. The calculated energy difference (*anti-gauche*) between the sulfonyl rotamers is 2.6 kcal mol^{-1}. Natural bond orbital analysis indicated that the anomeric effect (n$_S$ → σ$^*_{C—Cl}$) plays the main role in stabilization of *gauche* in the sulfide compound, and that other important hyperconjugative interactions also occur for the remaining compounds.
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Keywords: Sulfur compounds; Hyperconjugation; NBO; NMR; Infrared

1. Introduction

Sulfur-containing compounds present remarkable participation in the metabolism of living systems. Their importance is indubitably from the biochemical point of view, since in this class of compounds are included the amino acids cysteine, homocysteine and methionine, as well as the glutathione, a tripeptide (Glu-Cys-Gly) encountered in most cells [1].

Regarding the rotational equilibria of sulfides, sulfoxides and sulfones, there are few or no reports available in the literature, especially concerning the quantification of rotamers and the rationalization of the governing effects in their equilibria. Thus, the use of model compounds is of interest in the course of evaluating stereoelectronic

effects, such as the anomeric effect, when oxygen atoms are included in a sulfide compound to give the sulfinyl and sulfonyl analogs. Such compounds, as illustrated in Scheme 1, are described here.

The anomeric effect is well known in the case of antiperiplanar interactions involving the oxygen lone pairs, such as in sugars, but it is supposed to be less effective in the case of C—S bonds, given the significantly larger C—S bond length when compared to a C—O bond [2]. However, several studies [2–6] have demonstrated that this effect has a crucial importance on the conformational equilibria of some six-membered rings, namely 1,3-dithianes and 1,3,5-trithianes.

Electrostatic attraction between the electronegative atom or group (X) and the positively charged methyl group in some substituted dimethyl ethers has been invoked to explain the higher stability of the *gauche* form in the X—C—O—Me fragment [7–9]. In addition, in a previous paper on chloromethyl methyl sulfide [10], the anomeric effect was not considered as responsible for the
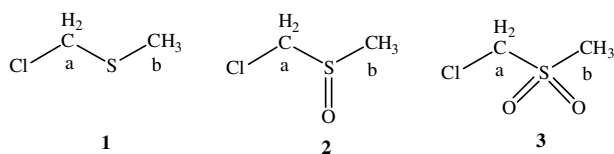
Scheme 1.

stabilization of the *gauche* rotamer in comparison to the *anti* form. Thus, the goal of this study was to determine the rotational preferences of chloromethyl methyl sulfide (**1**) and its sulfinyl (**2**) and sulfonyl (**3**) analogs, as well as to theoretically demonstrate the importance of hyperconjugative interactions in such systems.

2. Experimental

2.1. Computational details

Firstly, potential energy surfaces were obtained at the B3LYP/6-31g(d,p) level in order to identify the minima corresponding to each rotamer of compounds **1**–**3**. Subsequent optimization of the most stable rotamers was performed applying the B3LYP method [11] and the 6-311++g(3df,3pd) basis set, also including the Polarizable Continuum Model (PCM) [12] to take into account solvent effects on the rotational isomerism. All stable rotamers (geometries) were characterized as minima due to their positive values for vibrational frequencies. The zero-point energy was used to correct the electronic energies. Natural Bond Orbital (NBO) [13] calculations were carried out using the 6-311++g(3df,3pd) basis set, which adequately describes heavy and/or electronegative atoms, such as sulfur and chlorine. Calculations were performed using the Gaussian 98 package [14].

2.2. Compounds

Compound **1** was commercially available. ^{1}H NMR (300 MHz, CDCl$_3$/TMS): $\delta = 4.56$ (s, 2 H), 2,21 (s, 3 H).

Compound **2** was synthesized through chlorination of dimethyl sulfoxide with *N*-chlorosuccinimide, in methylene chloride and potassium carbonate. The product was distilled at 94 °C/4 torr (70%) [15]. ^{1}H NMR (300 MHz, CDCl$_3$/TMS): $\delta = 4.46$ (d, 1 H, $^2J = 11.0$ Hz) 4.34 (d, 1 H, $^2J = 11.0$ Hz), 2.71 (s, 3 H).

Compound **3** was obtained by oxidation of compound **1** with 30% hydrogen peroxide in acetic acid [16]. ^{1}H NMR (300 MHz, CDCl$_3$/TMS): $\delta = 4.50$ (s, 2 H), 3.07 (s, 3 H).

2.3. NMR experiments

^{13}C NMR spectra were obtained on spectrometers, operating at 75.45 and 125.70 MHz, respectively. The coupled ^{13}C spectra were obtained from *ca.* 20 mg cm^{-3} solutions with a probe temperature of 298 K. Spectra were all referenced to Me$_4$Si and the typical conditions were: spec-

tral width 18 or 28 kHz with 64 K data points and zero filled to 256 K to give a digital resolution of 0.1 Hz.

2.4. Infrared measurements

The infrared spectra were obtained by using a FT-IR spectrophotometer from solutions with concentrations of *ca.* 0.04 mol L^{-1}, using a NaCl cell with a spacer of 0.5 mm. Resolution of 1 cm^{-1} and 32 scans were utilized when collecting spectra and Lorentzian functions were used for deconvolution of the superimposed bands.

3. Results and discussion

3.1. Potential energy surfaces

The stable rotamers of compounds **1**–**3** were identified after building potential energy surfaces through rotating the Cl—C—S—CH$_3$ torsional angle, and optimizing structures from 0° to 360° in steps of 10°. Fig. 1 shows the minima of energy obtained at the B3LYP/6-31g(d,p) level. Minima with torsional angles 60° and 300° are designated as *gauche*, while the *anti* rotamer refers to the minimum at 180°. In the case of the sulfinyl compound (**2**), two different *synclinal* rotamers were identified, referred to as *gauche-1* (C—Cl antiperiplanar to S=O) and *gauche-2* (C—Cl antiperiplanar to the lone pair).

In the following paragraphs, the compounds are discussed separately, and a combined interpretation of the results is given later. Theoretical approaches were used to show the rotational behavior of **1**–**3**, both in the isolated and condensed state, as well as to help in rationalizing intramolecular interactions involved in these systems. Spectroscopic tools, namely infrared and NMR, were also applied to give support to some theoretical results.

3.2. Chloromethyl methyl sulfide (1)

The minima shown in Fig. 1a were optimized at the B3LYP/6-311++g(3df,3dp) level, in such a way that reliable values of energies and structural parameters are achieved. These are shown in Table 1, demonstrating that the *gauche* rotamer is the most stable form, in the isolated state, by 3.2 kcal mol^{-1}. The C—Cl bond is larger for the *gauche* rotamer, while the S—C(Cl) is larger for the *anti* form, indicating that a possible anomeric effect ($n_S \rightarrow \sigma^*_{C-Cl}$) is occurring in the *gauche* form, but not in the *anti*, leading to the resonance structure illustrated in Scheme 2. The calculated charge density on the chlorine atom also contributes to this statement, given that the charge over the *gauche* chlorine is −0.24 against −0.19 of the *anti* chlorine.

The population of the most polar rotamer (*anti*) increases with the increase in the polarity of the medium, as the result of the stabilization of intramolecular electrostatic interactions by the solvent dipole. This behavior may be confirmed through theoretical calculations, by using
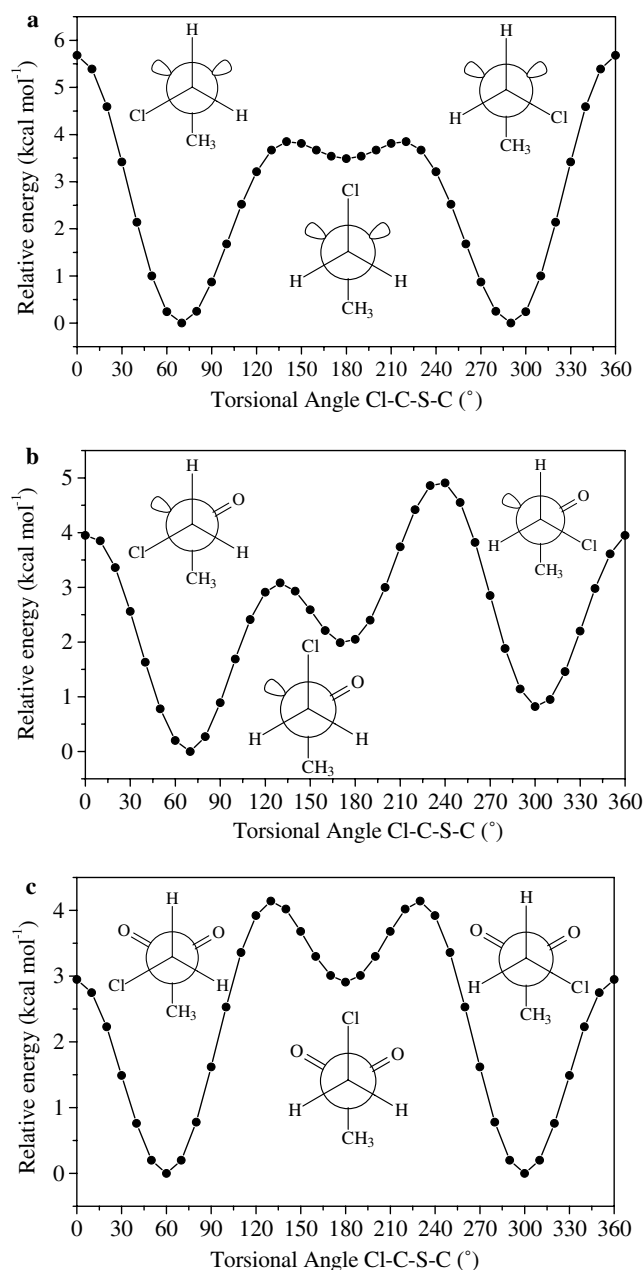
Fig. 1. Potential energy surfaces obtained at the B3LYP/6-31g(d,p) level for (a) chloromethyl methyl sulfide (**1**), (b) chloromethyl methyl sulfoxide (**2**), and (c) chloromethyl methyl sulfone (**3**).

Table 1
Calculated geometries[a] and relative electronic energies (ΔE in kcal mol^{-1}) for chloromethyl methyl sulfide (**1**) and chloromethyl methyl sulfone (**3**)

Parameter	(1)		(3)	
	gauche	anti	gauche	anti
r (ClC—H)	1.088	1.086	1.086	1.086
r (C—H)	1.085	1.089	1.087	1.087
r (ClC—S)	1.786	1.816	1.783	1.823
r (H₃C—S)	1.813	1.816	1.815	1.789
r (C—Cl)	1.821	1.788	1.776	1.768
r (S=O)	–	–	1.438	1.439
r (S=O)	–	–	1.443	1.439
∠(C—S—C)	100.7	98.2	104.6	101.2
∠(Cl—C—S)	115.5	109.5	114.2	110.6
∠(H—CCl—S)	109.5	111.0	106.5	109.2
∠(H—C—S)	109.4	109.7	108.0	108.1
∠(O=S=O)	–	–	120.7	120.9
∠(ClC—S=O)	–	–	108.9	108.2
∠(ClC—S=O)	–	–	104.2	108.2
∠(H₃C—S=O)	–	–	108.5	108.3
∠(H₃C—S=O)	–	–	108.9	108.3
ϕ (Cl—C—S=O)	–	–	−55.4	−66.3
ϕ (Cl—C—S=O)	–	–	174.6	66.3
ϕ (Cl—C—S—CH₃)	70.7	180.0	60.5	180.0
μ (debye)	1.89	2.93	3.41	5.30
ΔE_{rel}^{Vapor}	0	3.21	0	2.58
ΔE_{rel} ($\varepsilon = 2.2$)	0	3.19	0	2.21
ΔE_{rel} ($\varepsilon = 4.8$)	0	3.07	0	1.84
ΔE_{rel} ($\varepsilon = 9.1$)	0	3.03	0	1.66
ΔE_{rel} ($\varepsilon = 20.7$)	0	3.01	0	1.48
ΔE_{rel} ($\varepsilon = 37.5$)	0	3.00	0	1.46
ΔE_{rel} ($\varepsilon = 46.7$)	0	2.98	0	1.43

[a] Bond lengths in angstrom, bond and torsional angles in degrees.

Scheme 2.

models to represent molecules involved by a medium with a given dielectric constant (ε), recently described as relative permittivity. An appropriate model to perform these calculations is the PCM (Polarizable Continuum Model) [12], which was applied here to demonstrate that, even in solvents with high dielectric constants, the *gauche* rotamer is the prevalent form, according to the energies shown in Table 1.
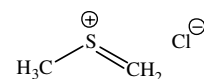
An experimental way of obtaining the data for rotational isomerism in compounds like **1** is to observe the behavior of coupling constants (J) when varying solvents, since J_{obs} is an average of intrinsic coupling constants (in this case, J_{gauche} and J_{anti}) and, thus, depends on the rotamer population. However, the observed coupling constants did not vary uniformly when changing solvents, as may be seen in Table 2, which can be due to two factors: the rotamer population does not vary with the solvent and/or J_{gauche} and J_{trans} are very similar. Since the energies of Table 1 indicate a percentage close to 100% for the *gauche* rotamer, both in the isolated and condensed phases, it is supposed that the rotamer population does not vary significantly and exists almost exclusively in the *gauche* form.

Infrared analysis gives support to the calculations, since just one band at the C—Cl stretching region (around 645 cm^{-1}) is observed from solutions in both CH$_2$Cl$_2$ ($\varepsilon = 9.1$) and acetone ($\varepsilon = 20.7$).

Natural bond orbital [13] analysis provides suitable information for the interpretation of the rotational behavior described above, since the energies of orbital interactions shown in Table 3 suggest that the *gauche* rotamer is highly stabilized by an anomeric effect involving the sulfur lone pair and the antibonding C—Cl orbital (n$_S \rightarrow \sigma^*_{C-Cl}$). The remaining interactions are roughly equivalent in

Table 2
Chemical shifts (ppm) and coupling constants (Hz) for **1**

Solvent	δ_{C_a}	δ_{C_b}	$^1J_{C_aH_a}$	$^3J_{C_aH_b}$	$^1J_{C_bH_b}$	$^3J_{C_bH_a}$
CCl$_4$	50.8	13.3	162.2	5.5	139.1	5.5
CDCl$_3$	52.5	15.5	163.6	5.5	139.7	5.5
C$_2$D$_2$Cl$_4$	50.8	13.4	166.8	5.5	139.9	5.5
Acetone-d$_6$	52.8	14.2	165.0	5.5	139.6	5.5
CD$_3$CN	53.4	15.0	164.7	5.5	139.4	5.5
Neat liquid	53.6	15.7	163.7	5.5	139.3	5.5

Table 3
Orbital interaction energies (kcal mol^{-1}) for **1** (computed interactions >0.5 kcal mol^{-1})[a]

Interaction	Energy (*gauche*)	Energy (*anti*)
$n_S \rightarrow \sigma^*_{CCl}$	13.4	2.9
$n_{Cl} \rightarrow \sigma^*_{C_aS}$	5.8	5.2
$n_{Cl} \rightarrow \sigma^*_{C_aH}$	6.1	7.2
$n_S \rightarrow \sigma^*_{C_aH}$	3.0	9.0
$n_S \rightarrow \sigma^*_{C_bH}$	7.8	8.9
Total	36.1	33.2

[a] Atom lettering refers to the different atoms of the compound structure.

energy and, clearly, the mentioned anomeric effect is the difference in this system. The difference between the sums of energies of orbital interactions is 2.9 kcal mol^{-1}, an indication that these are the important effects governing the rotational equilibrium of **1**, since the calculated difference of energy between the rotamers in the isolated state was in agreement with this value (3.2 kcal mol^{-1}).

3.3. Chloromethyl methyl sulfoxide (2)

A similar analysis was performed for compound **2**, although this is a more complex system, due to the existence of three different rotamers with very close energies. Calculations carried out at the B3LYP/6-311++g(3df,3pd) level showed that the *gauche-1* rotamer is the most stable form in the isolated state, whilst *gauche-2* and *anti* are 1.0 and 1.7 kcal mol^{-1} less stable, respectively. However, this figure changes when solvent effects are taken into account, according to PCM modeling [12], since in moderate to highly polar solvents, *anti* is predicted to be the most stable form, as shown in Table 4.

This is an expected behavior, considering that the *anti* rotamer is the most polar one, followed by *gauche-2* and *gauche-1*, respectively. Infrared spectra observed at the S=O stretching region, obtained in CH$_2$Cl$_2$ ($\varepsilon = 9.1$) and CH$_3$CN ($\varepsilon = 37.5$) solutions, corroborate the calculated results, showing a principal band at a lower wavenumber, referring to the *anti* rotamer, and secondary bands at intermediate (*gauche-1*) and higher (*gauche-2*) wavenumbers (Fig. 2). Its interesting to note that *gauche-2* changes from less to equally populated, when compared to *gauche-1*, on going from CH$_2$Cl$_2$ to CH$_3$CN, if infrared intensities are used to quantify rotamers, exactly as predicted by the theoretical calculations. NMR coupling constants (Table 5)

Table 4
Calculated geometries[a] and relative electronic energies (ΔE in kcal mol^{-1}) for chloromethyl methyl sulfoxide (**2**)

Parameters	*gauche-1*	*gauche-2*	*anti*
r (ClC—H)	1.086	1.089	1.087
r (C—H)	1.088	1.089	1.088
r (ClC—S)	1.842	1.838	1.842
r (H$_3$C—S)	1.815	1.813	1.823
r (C—Cl)	1.783	1.783	1.777
r (S=O)	1.488	1.482	1.482
$\angle$(C—S—C)	97.3	98.1	94.2
$\angle$(Cl—C—S)	112.6	116.1	110.3
$\angle$[H—C(Cl)—S]	107.3	106.6	108.5
$\angle$(H$_3$C—S=O)	107.0	107.3	106.8
$\angle$(Cl—C—S=O)	104.0	108.7	107.2
$\angle$(H—C—S)	108.3	108.2	108.6
ϕ (Cl—C—S—CH$_3$)	70.3	303.5	174.9
ϕ (Cl—C—S=O)	179.7	305.1	76.1
μ (debye)	2.35	3.88	4.51
ΔE_{rel}^{Vapor}	0	1.01	1.73
ΔE_{rel} ($\varepsilon = 2.2$)	0	0.59	0.66
ΔE_{rel} ($\varepsilon = 4.8$)	0.08	0.33	0
ΔE_{rel} ($\varepsilon = 9.1$)	0.40	0.60	0
ΔE_{rel} ($\varepsilon = 20.7$)	0.75	0.83	0
ΔE_{rel} ($\varepsilon = 37.5$)	0.85	0.91	0
ΔE_{rel} ($\varepsilon = 46.7$)	0.88	0.92	0

[a] Bond lengths in angstrom, bond and torsional angles in degrees.

can not be used to achieve experimental rotamer populations for this compound because the observed coupling constants did not vary significantly when changing solvent polarity.

Now, NBO [13] analysis may be used to interpret the rotational behavior of **2** in terms of orbital interactions present in this system. The $n_S \rightarrow \sigma^*_{C-Cl}$ interaction, which occurs in the *gauche-1* conformer of compound **1**, is also present only in the *gauche-2* conformer of compound **2**. However, other stronger interactions ($n_O \rightarrow \sigma^*_{C_aS}$ and $n_O \rightarrow \sigma^*_{C_bS}$), which occur in all three of its rotamers, are the main interactions responsible for their stabilization (Table 6).

Moreover, careful examination of the Newman structures of **2** rotamers (Fig. 1), in comparison with the sum of orbital interaction energies of Table 6, leads us to conclude that the electrostatic effects govern its rotational equilibrium in the isolated state. The *gauche-1* form is the most stable one (Table 4), although it is the less stabilized by orbital interactions in comparison to the remaining rotamers. This is due to the strong repulsion between C—Cl
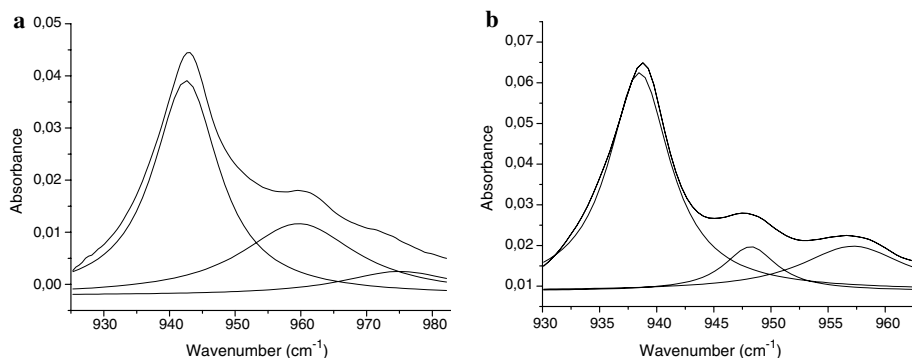
Fig. 2. Deconvoluted infrared spectra (S=O stretching region) of compound **2** in (a) CH_2Cl_2 and (b) CH_3CN.

Table 5
Chemical shifts (ppm) and coupling constants (Hz) for **2**

Solvent	δ_{C_a}	δ_{C_b}	$^1J_{C_aH_a}$	$^3J_{C_aH_b}$	$^1J_{C_bH_b}$	$^1J_{C_bH_a}$
CCl_4	58.4	37.4	161.0	5.5	138.1	5.5
$CDCl_3$	57.8	36.4	161.0	5.5	138.7	5.5
CD_2Cl_2	57.6	36.6	161.6	5.5	138.3	5.5
Acetone-d_6	60.0	36.7	161.6	5.5	138.6	5.5
CD_3CN	59.9	36.5	162.2	5.5	139.1	5.5
Neat liquid	56.8	35.8	162.4	5.5	139.4	5.5

Table 6
Orbital interactions energies (kcal mol^{-1}) of **2** (computed interactions >0.5 kcal mol^{-1})[a]

Interaction	Energy (*gauche-1*)	Energy (*gauche-2*)	Energy (*anti*)
$\sigma_{C_aH} \rightarrow \sigma^*_{SO}$	–	1.9	1.6
$\sigma_{C_bH} \rightarrow \sigma^*_{SO}$	2.1	1.9	1.9
$n_S \rightarrow \sigma^*_{C_aH}$	1.7	–	1.6
$n_S \rightarrow \sigma^*_{C_bH}$	1.8	1.9	2.0
$n_{Cl} \rightarrow \sigma^*_{C_aH}$	10.0	9.7	10.2
$n_{Cl} \rightarrow \sigma^*_{C_aS}$	7.1	7.8	6.5
$n_S \rightarrow \sigma^*_{CCl}$	–	5.5	–
$\sigma_{C_aS} \rightarrow \sigma^*_{SO}$	–	–	1.4
$\sigma_{C_bS} \rightarrow \sigma^*_{CCl}$	–	–	2.9
$n_O \rightarrow \sigma^*_{C_aS}$	23.3	26.6	25.8
$n_O \rightarrow \sigma^*_{C_bS}$	21.7	21.9	22.1
Total	67.7	77.2	76.0

[a] Atom lettering refers to the different atoms of the compound structure.

and S=O dipoles in the *gauche-2* and *anti* rotamers (the most polar rotamer), whose repulsion is not present in the *gauche-1* rotamer. However, on going from the gas phase to solution, the increase in medium polarity leads to a decrease in these intramolecular electrostatic interactions by the solvent dipole and, then, the orbital interactions also become important, making the *anti* rotamer more populated.

3.4. Chloromethyl methyl sulfone (3)

The two minima identified in the potential energy surface (PES) of Fig. 1c were optimized at the B3LYP/6-311++g(3df,3pd) level, in order to obtain more refined geometrical parameters and energies. In the isolated state,

the *gauche* rotamer demonstrated to be 2.6 kcal mol^{-1} more stable than the *anti* form, with the difference decreasing according to the increase of the solvent polarity (according to PCM modeling), as shown in Table 1. However, even in highly polar solvents, the calculated energies suggest that the *gauche* form is populated at more than 95%. As was observed for compounds **1** and **2** the NMR coupling constants (Table 7) for compound **3** cannot be used to achieve experimental rotamer populations for this compound because the observed coupling constants did not vary significantly when changing solvents, polarity.

The orbital interactions occurring in **3** were obtained through NBO [13] calculations, which showed that *gauche* is greatly stabilized by $n_O \rightarrow \sigma^*_{CS}$ and $n_O \rightarrow \sigma^*_{SO}$ hyperconjugation (Table 8). A simple interpretation may be given for this phenomenon, that is, such interactions are more favored in the *gauche* form than in the *anti*, due to the poorer push-pull effect between S=O and Cl in *gauche*, which allows sulfur and carbon atoms to be more positively charged than in *anti* and, consequently, favors electron donation from the oxygen to sulfur and carbon atoms. This seems to be relevant even in polar solvents, since *gauche* is highly populated in any medium.

Table 7
Chemical shifts (ppm), coupling constants (Hz) for **3**

Solvent	δ_{C_a}	δ_{C_b}	$^1J_{C_aH_a}$	$^1J_{C_bH_b}$
$CDCl_3$	56.8	38.7	160.1	139.1
CD_2Cl_2	57.8	38.2	160.4	139.1
Acetone-d_6	56.6	37.3	161.3	139.1
CD_3CN	56.5	37.3	161.3	139.1
DMSO-d_6	56.6	37.5	162.0	138.9

Table 8
Orbital interactions energies (kcal mol^{-1}) of **3** (computed interactions >0.5 kcal mol^{-1})[a]

Interaction	Energy (*gauche*)	Energy (*anti*)
$\sigma_{C_aH} \rightarrow \sigma^*_{SO_b}$	2.3	2.2
$\sigma_{C_bH} \rightarrow \sigma^*_{So_b}$	2.7	2.5
$\sigma_{C_aH} \rightarrow \sigma^*_{SO_a}$	–	2.3
$\sigma_{C_bH} \rightarrow \sigma^*_{SO_a}$	2.8	2.6
$n_{Cl} \rightarrow \sigma^*_{C_aS}$	7.9	5.3
$n_{O_2} \rightarrow \sigma^*_{C_aS}$	26.1	22.2
$n_{O_2} \rightarrow \sigma^*_{C_bS}$	22.6	18.2
$n_{O_1} \rightarrow \sigma^*_{C_aS}$	22.8	20.8
$n_{O_1} \rightarrow \sigma^*_{C_bS}$	22.4	20.1
$n_{O_2} \rightarrow \sigma^*_{SO_a}$	24.0	23.1
$n_{O_1} \rightarrow \sigma^*_{SO_b}$	22.2	21.3
Total	155.8	140.6

[a] Atom lettering refers to the different atoms of the compound structure.

4. Conclusion

The anomeric effect is the decisive interaction determining the *gauche* rotamer of the compound **1** as the most stable and almost exclusive form. This effect is also relevant for compound **2**, though its magnitude is smaller. For this compound, as well as for **3**, the main interactions are the $n_O \rightarrow \sigma^*_{CS}$ (also $n_O \rightarrow \sigma^*_{SO}$ for **3**) hyperconjugation, in addition to the classical electrostatic effect, which is due to the strong character of the S=O bond in presenting partial charges and to the chlorine electronegativity. Thus, an additional oxygen atom attached to the sulfur atom increases the electrostatic repulsion in the *gauche-2* and *anti* rotamers of **2**, and in the *anti* rotamer of **3**, the orbital interactions predominate over steric repulsion and govern the rotational isomerism of the title compounds. The agreement between calculated and experimental results is noteworthy, as well as are the NBO energies as supporting information for the observed behavior.

Acknowledgements

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