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Conformational Analysis and Electronic Interactions of Some 2-ethylsulfinyl-(4′-Substituted)-phenylacetates

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Abstract

The analysis of the infrared carbonyl bands of some 2-ethylsulfinyl-(4'-substituted)-phenylacetates bearing the substituents NO_2(**1**), Cl (**2**), Br (**3**), H(**4**), Me (**5**) and OMe (**6**), along with B3LYP/6-31G(d,p), SM5.42R solvation model calculations and natural bond orbital (NBO) analysis was carried out. Theoretical data indicated the existence in the gas phase of three stable *gauche* conformers, whose relative abundances in condensed phase change at different extent in the series **1**-**6**, depending on the solvent permittivity. The comparison between the IR spectra in solvents of increasing permittivity (from CCl_4 to CH_3CN) and the calculated SM5.42R data in solution allows a precise assignment of the experimental band components to the distinct conformers. The sum of the main relevant NBO orbital interactions energies does not match the calculated B3LYP relative energies of the three stable conformers of **1**-**6** in the gas phase. On the contrary, the short contact analysis indicates that the electrostatic interactions largely control their relative stability and play a basic role to determine the calculated ν_{CO} frequencies order. Moreover, as these contacts dictate the specific

geometry assumed by each conformer, the electrostatic interactions determine their different solvation properties too, thus accounting for the experimental stability observed in solution.

Keywords: Conformational analysis; infrared spectroscopy; theoretical calculations; solvent effect; 2-ethylsulfinyl-(4'-substituted)-phenylacetates

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Introduction

Previous conformational analysis performed on some β-carbonyl-sulfoxides $XC(O)CH_2S(O)R$ through (IR, ^{13}C NMR, UV and UPS) spectroscopies and X-ray diffraction have shown, in line with theoretical calculations, that the *gauche* conformer is the most stable for the α-sulfinylketones[1–3] andα-sulfinylthioesters[4],while the *cis* one is predominant for the α-sulfinylacetophenones and α-sulfinylamides[5–9]. The stabilisation of the *gauche* conformers has been ascribed to the π^*_{CO}/σ_{C-S} and, to a minor extent, to the π_{CO}/σ^*_{C-S} orbital interactions, while the π_{Ph}/π^*_{CO} and n_N/π^*_{CO} conjugation, which originate strong electrostatic $[S^{\delta+}{=}O^{\delta-}\ldots C^{\delta+}{=}O^{\delta-}]$ and $n_{O(CO)}/\sigma^*_{SO}$ charge transfer interactions account for the larger stabilisation of the *cis* conformation.

In the MeC(O)X series [10], the experimental carbonyl oxygen lone pair (n_O) ionisation energy (E_i) shows a progressive increase ongoing from amide (X = NEt_2) to acetophenone(X = Ph), butanone (X = Et), thioester (X = SEt) and ester (X = OEt), while the electron affinity (E_{ea}) of the π^*_{CO} orbital increases in the order $E_{amide}<E_{ester}<E_{butanone}<E_{thioester}$. Accordingly, the 2-ethylsulfinyl-(4'-substituted)-phenylthioacetates display four *gauche* conformers [*q-q-g-sin*, g_3*-sin*, g_1*-anti* and *q-*g_2*-sin*], which are largely stabilised by the $\pi_{CO}/\sigma^*_{C-S}$and the σ_{C-S}/π^*_{CO} orbital interactions [4].In contrast, the $n_{O(CO)}/\sigma^*_{SO}$ charge transfer does not significantly act on the *cis* conformer stability as a consequence of the sizeable energy gap between the involved orbitals.

In the case of α-sulfinylesters, it should be noted that the π^*_{CO} and the $n_{O(CO)}$ energy levels in the reference ester are further apart. Therefore, both the orbital interactions (π^*_{CO}/σ_{CS}, $\pi^*_{(CO)}/n_s$ and $\pi^*_{(CO)}/n_{O(SO)}$) and the ($n_{O(CO)}/\sigma^*_{S-O}$) charge transfer that stabilise the *gauche* and the *cis* conformers, respectively, are weakened. As a

consequence, it is difficult to infer *a priori* which could be the most stable conformation. Thus, in order to elucidate the nature of the different electronic interactions that determine the conformational equilibrium of the α-sulfinylesters, as well as the changes in the conjugation involving the 4'-substituents, the present paper reports experimental infrared and theoretical analysis of some 2-ethylsulfinyl-(4'-substituted)-phenylacetates**1**–**6**[11] (Scheme 1).

Besides the structural studies, sulfinylesters are a class of compounds of relevant interest in the field of biological/medicinal chemistry. Recent application includes the facilitation of the encapsulation of dexamethasone in nanoparticles used in targeted drug delivery to treat some inflammatory diseases [12(a), 12(b)].

Experimental

Materials

All solvents for IR measurements were spectrograde and were used without further purification, except the dimethoxymethane, which was treated with sodium wires followed by fractional distillation before the measurement. The 4'-substituted-2-ethylsulfinyl-phenylacetates **1**–**6** are novel compounds and were prepared following procedures outlined in the literature [13]. To a stirred solution of sodium metaperiodate (2.14 g; 10 mmol) in 20 mL of water at 0ºC, a solution of 4'-substituted-2-ethylsulfanyl-phenylacetate (10 mmol) in acetone (25 mL) and water (10 mL) was slowly added. The reaction mixture was maintained at room temperature for 32–48 hours and was monitored by TLC until no sulfide-ester was detected. The product was extracted with CH_2Cl_2 and dried over anhydrous magnesium sulfate. The solvent was removed under low pressure without heating and the obtained solid was purified by flash column chromatography (*n*-hexane:ethyl acetate; 3:7). The starting 4'-substituted-2-ethylsulfanyl-phenylacetates were prepared as previously described [14]. The ^{1}H and ^{13}C NMR spectra for compounds **1**–**6** and their elemental analyses are reported in Table 1.

IR measurements

The IR spectra were recorded using a Michelson Bomem MB100 FTIR spectrometer, with 1.0 cm^{-1} resolution at a concentration of 1.0 x 10^{-2}mol L^{-1} in carbon tetrachloride, dimethoxymethane (**3**), chloroform, dichloromethane and acetonitrile using a 0.519 mm sodium chloride cell for the fundamental carbonyl region (1800–1600 cm^{-1}). The spectra of the carbonyl overtone (3600–3100 cm^{-1}) were recorded in a carbon tetrachloride (**2**, **3**, **4** and **5**) and dichloromethane (**1** and **6**) solution (1.0 x 10^{-2}mol L^{-1}), using a 1.00 cm quartz cell. The overlapped carbonyl bands (fundamental and first overtone) were resolved by means of the Grams/32 curve fitting software, version 4.04, Level II [15]. The populations of the conformers were estimated from the maximum of each component of the resolved carbonyl doublet, expressed as a percentage of absorbance, on the assumption of equal molar absorptivity coefficients for all conformers.

NMR measurements

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova300 spectrometer operating at 300 and 75 MHz (**2**, **5** and **6**) and on a Bruker DRX 500 spectrometer operating at 500 and 125 MHz (**1**, **3** and **4**), respectively, for 0.1 molL^{-1} solutions in chloroform-*d*. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS, as an internal standard.

Theoretical calculations

The starting geometries were obtained with the *Conformer Distribution*, a Monte Carlo approach [16] program using the MMFF [17], as implemented in the SPARTAN06 package [18]. Calculations for the gas phase geometries, harmonic vibrational modes and orbital interactions were carried out at 298 K, using methods and basis sets implemented in Gaussian 09 [19]. The hybrid functional B3LYP[20] with the 6–31G(d,p) basis set [21] was used for full optimisation of all the *gauche* geometries and to calculate the orbital interactions, the analytical harmonic frequency and the zero-point vibrational energies (ZPVE). The SM5.42R solvation model [22(a), 22(b)] at the PM3 level [23], carried out using the AMSOL 7.1 [24],allows for simulating the solvent interaction and obtaining the free Gibbs energies of solvation[25]. The NBO 3.1 program [26], as implemented in the Gaussian 09 package, was used to estimate delocalisation energies (E2) by means of the second-order perturbation theory.

B3LYP/6-31++G(d,p) calculations for **1** (Y = NO_2) and **4** (Y = H)[21] and MP2/6-31++G(d,p)[27] calculations for **4** were performed for comparison.

Results and Discussion

The stretching frequencies and the absorbance percentage of the analytically resolved carbonyl band for the 4'-substituted-2-ethylsulfinyl-phenylacetates **1**–**6** in solvents of increasing relative permittivity [28] are reported in Table 2.The IR spectrum of compound **1** shows three components in the low permittivity solvents carbon tetrachloride (ε = 2.2) and dimethoxymethane (ε = 2.7), and only a single component in the higher permittivity solvents chloroform (ε = 4.2), dichloromethane (ε = 9.1) and acetonitrile (ε = 38.8). In contrast, a doublet was recorded for compounds **2**–**6** in all solvents, with the exception of compounds **2** and **3** in acetonitrile for which a singlet was found.

The relative intensity of the carbonyl doublet higher frequency component for **4**–**6** increases progressively from about 30% in the non-polar solvent $CCl_4$to about 63% in the most polar CH_3CN. A different trend of the solvent effect was observed for the same component on compounds **2** and **3**. In fact, its relative intensity slightly increases from *ca.*20% in CCl_4 to 35% in $(CH_3O)_2CH_2$, then decreases in $CHCl_3$ and CH_2Cl_2(*ca.*14%), until becoming the unique component detected in CH_3CN (100%). For compound **1** in CCl_4, the middle frequency carbonyl triplet component is the most intense (72%), followed by the higher (23%) and the lower (5%) frequency ones. The same order is maintained in $(CH_3O)_2CH_2$, in spite of a relative intensity increase (39%) of the higher frequency triplet component. The latter corresponds to the singlet recorded in the solvents of higher permittivity $CHCl_3$, $CHCl_2$ and CH_3CN.

The solvent effect on the carbonyl band components of **1**, **3** and **4** is illustrated in Figs. 1–3. It should be pointed out that the carbonyl singlet bands found in acetonitrile for **2** and **3** correspond to the higher frequency doublet components of these derivatives in all other solvents, as confirmed by the close correlation between the Hammet's σ_P constants [29(a), 29(b)] (Table S1) and the higher frequency doublet components of **4**–**6** and the singlet ones of **1**–**3** measured in acetonitrile (Fig. S1).

In the first overtone region, a single band for **1** in CH_2Cl_2 and two carbonyl components for compounds **2**–**5** in CCl_4 and **6** in CH_2Cl_2 were recorded, at frequencies twice those of the fundamental minus two times the mechanical anharmonicity of *ca.* 23 cm^{-1} [30].

Therefore, although the observed solvent effect is not evidence of rotational isomerism, the matching between the carbonyl band profile in the fundamental and in the first overtone regions strongly suggest the occurrence of at least one or two conformers in the solution for compounds **1** and **2**–**6**, respectively, ruling out the existence of any vibrational effect on the fundamental transition of the ν_{CO} mode [29(b). 31]

Furthermore, the unexpected doublet relative intensities of derivatives **2**and **3**,shown in the halogenated solvents chloroform and dichloromethane, may be ascribed to intermolecular interactions between the halogenated solvents and the aromatic compound or to complexes between two halogenated compounds through intermolecular charge transfer [32(a), 32(b)].

The relevant data calculated at the B3LYP/6-31G(d,p) level for compounds **1**–**6**, reported in Table 3,indicate the existence in the gas phase of three distinct stable *gauche* conformations, labelled in order of decreasing stability for the whole series as g_1 (*ca.* 70%, intermediate ν_{CO} frequency 1824–1821cm^{-1}), g_2 (*ca.* 21%, lowest ν_{CO}1815–1809 cm^{-1})and g_3 (*ca.* 9%, highest ν_{CO}1862–1854 cm^{-1}). The g_1 and g_2 conformers are *syn–clinal* with respect to the α dihedral angle O=C-C-S (α ≈ 81°and 65°, respectively), while the g_3 conformer presents an *anti-clinal* geometry (α ≈ 105°), as shown in Fig. 4. It should be noted that, due to the favourable values of the β dihedral angles for all derivatives in the g_1 (β ≈ -35°) and g_3 (β ≈ -19°) conformers, the sulfinyl oxygen atom points towards to the *ortho*-phenyl hydrogen and the carbonyl carbon atoms. On the contrary, in the g_2 conformers (β ≈ 170°), it lies in the opposite direction with respect to both these atoms, while, as a result of the values assumed by the α dihedral angles (54°–73°), the carbonyl oxygen atom gets close to both the *ortho*-phenyl hydrogen and the sulfinyl sulfur ones.

In order to check if the inclusion of diffuse functions can modify the stability order and the geometries of the conformers found at the B3LYP/6-31G(d,p) level, B3LYP/6-31++G(d,p) calculations were performed for compounds **1** (Y = NO_2) and **4** (Y = H), taken as representative for the series (**1-6**). The results, summarized in Table S2 (see supplementary material), show that the geometries and the carbonyl frequencies of the g_1, g_2 and g_3 conformers, as well their order of stability, fairly match the corresponding values calculated at the B3LYP/6-31G(d,p) level. Thus, the conclusions drawn from the B3LYP/6-31G(d,p) analysis are confirmed and entirely supported. On the contrary, the MP2/6-31++G(d,p) results (Table S2) fail to reproduce the experimental data, yielding

relative energies, carbonyl frequencies and geometries for the g_1, g_2 and g_3 conformers of **4** that significantly differ from those obtained by both the B3LYP/6-31++G(d,p) and B3LYP/6-31G(d,p) calculations. On the other hand, it is well recognized in literature that the experimental vibrational frequencies are more accurately reproduced by B3LYP calculations than by the MP2 approach [33(a), 33(b), 33(c)].

The relative stability of the three conformers in the solution was investigated by solvation free energy calculations performed with the SM5.42R model at the PM3 level. The results presented in Table 4 indicate that, in the low dielectric constant solvent carbon tetrachloride, the population of the most stable g_1 conformer fairly matches that in the gas phase for all derivatives, while the relative abundance of the g_2 and g_3 ones is inverted. In particular, the g_2 conformer population drastically decreases to 1–7% in CCl_4 and to *quasi* zero in all other solvents. At the same time, the population of the g_3 conformer increases with respect to that of the g_1 one in the solvents of progressively higher permittivity, becoming the most stable in acetonitrile for all derivatives. This trend is reasonably in line with the experimental IR findings for **2**–**6** and enables the assignment of the higher frequency components of the ν_{CO} doublets to the $g_3$conformers, the lower frequency components to the g_1 ones and the vanishing band in the solution to the g_2 second stable conformer in the gas phase. Analogously, the experimental higher and intermediate triplet ν_{CO} frequency components found in CCl_4 and $(CH_3O)_2CH_2$ for compound **1** can be ascribed to the g_3 and g_1 conformers, respectively, whereas the least intense lowest triplet ν_{CO} frequency component, no longer detectable in the other more polar solvents, corresponds to the g_2 one.

The observed experimental and calculated solvent effect son the relative populations of the g_3 and g_1 conformers for the series **1**–**6** are in line with the higher dipole moment of the former conformers with respect to the latter ones (Table 3). In fact, the difference between the dipole moments ($\Delta\mu = \mu_{g3} - \mu_{g1}$)varies from 0.7 (for **1**) to 3.3 D (for **6**). In contrast, the g_2 conformer presents the smallest μ value for **1**–**3** and the intermediate one for **4**–**6** with respect to the g_3 and g_1 values.

Table 5 summarises the interatomic distances between some atoms and their difference (Δl) from the sum of the van der Waals radii (ΣvdWr), while Table 6 collects selected NPA atomic charges at the B3LYP/6–31G(d,p) level for compounds **1**–**6**.

As previously described (Fig. 4), the geometries of the g_1 and g_3 conformers are stabilised by attractive electrostatic interactions between the oppositely charged sulfinyl oxygen O(4) and both the carbonyl carbon C(6) and *ortho*-phenyl hydrogen H(22)

atoms, separated by interatomic distances close to ($O^{\delta-}_{(4)}\ldots H^{\delta+}_{(22)}$ for **2**–**6**) or shorter ($O^{\delta-}_{(4)}\ldots H^{\delta+}_{(22)}$ for **1** and $O^{\delta-}_{(4)}\ldots C^{\delta+}_{(6)}$ for **1**–**6**) than the ∑vdWr. Analogous stabilising interactions take place on the g_2 conformer, involving the negatively charged carbonyl oxygen O(7) and both the positively charged *ortho*-phenyl hydrogen H(22) and sulfinyl sulfur S(3) atoms. In this case too, the interatomic distances are close to ($O^{\delta-}_{(7)}\ldots S^{\delta+}_{(3)}$ for **1**–**3**) or shorter ($O^{\delta-}_{(7)}\ldots H^{\delta+}_{(22)}$ for **1**–**6** and $O^{\delta-}_{(7)}\ldots S^{\delta+}_{(3)}$ for **4**–**6**) than the ∑vdWr. Moreover, the g_1 and g_2 conformers allow for an additional contact, shorter than the ΣvdWr, between the negatively charged carbonyl oxygen O(7) and the positively charged *alpha*-methylene hydrogen $H_{(18,19)}$ atoms. Finally, the suitable values of the α and β dihedral angles enable, only in the g_3 conformer, the electrostatic interaction $O^{\delta-}_{(8)}\ldots H^{\delta+}_{(18,19)}$ between the phenoxyl oxygen O(8) and the *alpha*-methylene hydrogen $H_{(18,19)}$ atoms, connected by an interatomic distance shorter than the ΣvdWr by about -0.30 Å.

It should be pointed out that the negatively charged sulfinyl oxygen O(4) and phenoxyl O(8) atoms for both the g_1 and g_3 conformers are separated by identical distances, slightly longer than the ΣvdWr (Δl ≈ 0.15 Å). In contrast, the sulfinyl oxygen O(4) and the carbonyl O(7) atoms are closer in the$g_3$conformer (Δl ≈ 0.34 Å) relative to the g_1 one (Δl ≈ 0.54 Å). Thus, the $O^{\delta-}_{(4)}\ldots O^{\delta-}_{(7)}$ contacts originate a destabilising Repulsive Field Effect (RFE) [34] between the $C^{\delta+}{=}O^{\delta-}$ and $S^{\delta+}{=}O^{\delta-}$ dipoles, stronger in the g_3 conformer with respect to the g_1 one, which accounts for the increase of the carbonyl bond order and, consequently, for the higher ν_{CO} frequency observed for the g_3 conformer.

In order to investigate the effect of the orbital interactions on the g_1, g_2 and g_3 conformer stability**,** the energies of selected donor–acceptor orbital interactions, evaluated for **1**–**6** through NBO analysis [35] at the B3LYP/6-31G(d,p) level, are reported in Table 7.

In the carboxyphenyl [C-C(O)OPh] moiety, the relevant orbital interactions, in order of decreasing energy, are the $LP_{O8}\rightarrow\pi^*_{C6=O7}$conjugation (**1**), the $LP_{O7}\rightarrow\sigma^*_{C6-O8}$ (**2**) and the $LP_{O7}\rightarrow\sigma^*_{C6-C5}$ (**3**) through bond coupling interactions. For all conformers of derivatives **1**–**6**, the mean energies of the through bond coupling interactions (**2**) and (**3**) [36] keep almost constant values of *ca.* 37 and 19 kcal mol^{-1}, respectively. At variance, the $LP_{O8}\rightarrow\pi^*_{C6=O7}$ conjugation (**1**) progressively increases in the g_1 and g_2 conformers, going from the 4'-electron-attracting (*ca.* 44 kcal mol^{-1}) (**1**) substituent to the 4'-electron-donating (*ca.* 47 kcal mol^{-1}) (**6**) one. An analogous trend is observed for the g_3 conformer, at mean energy values smaller by about 4 kcal mol^{-1} for all derivatives. The

decrease of the interaction energy for g_3 is a consequence of the smaller [C=O ↔ C^+-O^-] conjugation due to the stronger RFE in this conformer. Moreover, in the same conformer, the $LP_{O8(P)}\rightarrow\sigma^*_{C2-H18}$ orbital interaction (hydrogen bond) increases the ionisation energy of the phenoxyl oxygen lone pair (O8) and, therefore, decreases the [O-C=O ↔ $^+$O=C-O^-] conjugation. Consequently, the ν_{CO} frequency of the g_3 conformer further increases, as confirmed by the smallest occupancy of the $\pi^*_{C6=O7}$ orbital (Table S3).

The S-C-C=O moiety shows the hyperconjugative interactions $\sigma_{C5-S3}\rightarrow\pi^*_{C6=O7}$ (a), $\pi_{C6=O7}\rightarrow\sigma^*_{C5-S3}$ (b) and the unusual $\pi^*_{C6=O7}\rightarrow\sigma^*_{C5-S3}$ [37] (c), which are maximised as the α dihedral angles get closer to 90°. This is confirmed, for all derivatives **1**–**6**, by the mean energy values of about 5 (for a), 1.5 (for b) and 6 kcal mol^{-1} (for c) for the g_2 conformers (α ≈ 60°), which are smaller than are those that correspond to the g_1 (α ≈ 80°) and g_3 (α ≈ 105°) ones by about 2 kcal mol^{-1}(for a and c) and 0.5 kcal mol^{-1} (for b).

In the same way, the $LP_{O8(P)}/\pi^*_{C9=C10}$ orbital overlap increases as the ϕ dihedral angle decreases while, concomitantly, the $LP_{O8(SP2)}/\pi^*_{C9=C10}$ decreases. Accordingly, the $LP_{O8(P)}\rightarrow\pi^*_{C9=C10}$ and $LP_{O8(SP2)}\rightarrow\pi^*_{C9=C10}$ conjugation energies are, respectively, *ca.* 11 and 3 kcal mol^{-1} for the g_2 conformer (ϕ ≈ 50°) and *ca.* 2 and 6 kcal mol^{-1} for the g_1 and g_3 ones (ϕ ≈ -74°). In conclusion, the sum of the energies involved leads to a globally higher interaction for the g_2 conformation (about 6 kcal mol^{-1}).

In agreement with the short contact analysis, the $O^{\delta-}_{(7)}\ldots H^{\delta+}_{(18,19)}$ and $O^{\delta-}_{(8)}\ldots H^{\delta+}_{(18,19)}$ attractive electrostatic interactions account for, respectively, the weak $LP_{O7(P)}\rightarrow\sigma^*_{C2-H18}$ orbital interaction (hydrogen bond) for the g_1 and g_2 conformers and the equivalent $LP_{O8(P)}\rightarrow\sigma^*_{C2-H18}$ one for g_3, with energies in the range 0.5–1.5 kcal mol^{-1} for **1**–**6**.

Additionally, the $O^{\delta-}_{(4)}\ldots H^{\delta+}_{(22)}$ contacts, close or shorter than the ΣvdWr only in the g_1 and g_3 conformers of **1**–**3** derivatives, are responsible for the $LP_{O4(P)}\rightarrow\sigma^*_{C10-H22}$ and the $LP_{O4(SP3)}\rightarrow\sigma^*_{C10-H22}$ weaker orbital interactions, of about 0.7 kcal mol^{-1}.

Moreover, the $O^{\delta-}_{(4)}\ldots C^{\delta+}_{(6)}$ short contacts cause, in addition to significant electrostatic interaction, the weak $LP_{O4(P)}\rightarrow\pi^*_{C6=O7}$ charge transfer (≤ 0.8 kcal mol^{-1}) exclusively in the g_1 and g_3 conformers in the series **1**–**6**.

The sum of the NBO orbital interactions energies (ΣE) for the g_1, g_2 and g_3 conformers along the series **1**–**6** shows that, for the compounds bearing electron-withdrawing substituents in the *para*-position **1**–**3**, the g_2 conformer is more stabilised (*ca.*132kcal mol^{-1}) than are both the g_1 and g_3 ones by *ca.*5 kcal mol^{-1}. However, for the hydrogen (**4**) and the electron-donating substituent (**5**), the g_1 and g_3 conformers become more

stable (*ca.* 127kcal mol^{-}1) with respect to the g_2 one by *ca.*2 kcal mol^{-1}, while in the methoxy derivative (**6**), all of the conformers are stabilised almost to the same extent (*ca.*126 kcal mol^{-1}).

These results do not match the calculated B3LYP relative energies of g_1, g_2 and g_3 conformers of compounds **1**–**6** in the gas phase, indicating that the g_1 conformer is the most stable (*ca.* 71%), followed by the g_2 (*ca.*20%) and the g_3 ones (*ca.* 9%).

The analysis of the role played by the coulombic interactions could be helpful to better understand the reasons for the relative stability calculated for the referred conformers.

The g_3 conformer is significantly destabilised via the coulombic repulsion between the $O^{\delta-}_{(4)[SO]}$...$O^{\delta-}_{(7)[CO]}$ atoms and is electrostatically stabilised by the short contact interactions $O^{\delta-}_{(8)[o\text{-}Ph]}$...$H^{\delta+}_{(18,19)[CH2]}$, $O^{\delta-}_{(4)[SO]}$...$C^{\delta+}_{(6)[CO]}$, $O^{\delta-}_{(4)[SO]}$...$H^{\delta+}_{(22)[o\text{-}Ph]}$. The lowest stability of this conformer, as well as its highest ν_{CO} frequency, may be partially rationalised by the RFE between the $S^{\delta+}$=$O^{\delta-}$ and$C^{\delta+}$=$O^{\delta-}$ dipoles, which in turn allows the formation of a solvent shell around them (Scheme 2, Fig. 4). This effect is also responsible for its larger solvation energy that progressively increases as the relative permittivity of the solvent increases (Table 4). Furthermore, the $O^{\delta-}_{(8)}$…$H^{\delta+}_{(18,19)}$ short contact, absent in the g_1 and g_2 conformers, is responsible for the $LP_{O8(P)}\rightarrow\sigma^*_{C2\text{-}H18}$ hydrogen bond interaction, which further increases the ν_{CO} frequency through the increase of the ionisation energy of the phenoxyl oxygen lone pair (O8) and the decrease of the [O-C=O ↔ $^{+}$O=C-O^{-}] conjugation, as previously outlined.

These results are consistent with the assignment of the g_3 conformer to the highest ν_{CO} frequency component, whose intensity rises progressively from the non-polar solvent CCl_4 to the more polar CH_3CN (single band for **1**–**3** and the more intense one for **4**–**6**) (Table 2).

Scheme 2 highlights the short contacts involving the negatively charged carbonyl oxygen atom $O_{(7)}$ and, respectively, the positively charged $H_{(22)[o\text{-}Ph]}$, $S_{(3)}$and $H_{(18,19)[CH2]}$ atoms, which significantly contribute to electrostatically stabilising the g_2 conformer and to lower its ν_{CO} frequency by increasing the polarisation of the $C^{\delta+}$=$O^{\delta-}$ dipole. The referred interactions significantly hinder the approach of the solvent molecules towards the carbonyl oxygen atom. Therefore, the decreased solvation of the g_2 conformer is in line with the SM5.42R calculations (Table 4) that indicate a significant decline of its relative abundance from about 20% in the gas phase to 1% in the non-polar solvent CCl_4, until completely vanishing in the more polar solvents. Obviously, this behaviour

is in good agreement with the absence of the corresponding ν_{CO} band component in the solution (Table 2).

The three electrostatic interactions involving the carbonyl oxygen $O_{(7)}$ atom that are responsible for the *g2* conformer stabilisation, as described above, have a minor effect on the *g1* one. In fact, although the charges on the $O_{(7)}$, $H_{(22)[o\text{-}Ph]}$, $S_{(3)}$ and $H_{(18,19)[CH2]}$ atoms are similar for both conformers (Table 6), the related contacts show some relevant differences (Table 5). In particular, the $O^{\delta-}_{(7)}...S^{\delta+}_{(3)}$average contact is shorter than is the ΣvdWr for the *g2* conformer ($\Delta l_{g1\ aver}$=0.06 Å, $\Delta l_{g2\ aver}$=-0.05 Å),while the $O^{\delta-}_{(7)}...H^{\delta+}_{(18,19)}$ one is slightly more favourable for the *g1* conformer ($\Delta l_{g1\ aver}$=-0.34 Å, $\Delta l_{g2\ aver}$=-0.28 Å). On the contrary, the $O^{\delta-}_{(7)}...H^{\delta+}_{(22)}$average distance is significantly longer than is the ΣvdWr (Δl_{aver}=0.54 Å) in the *g1* conformer and is shorter (Δl_{aver}=-0.15 Å) in the *g2* one. Therefore, all of these interactions stabilise, to a major extent, the *g2* conformer relative to the *g1* one. However, in the *g1* conformer, two additional short contacts occur that involve the negatively charged sulfinyl oxygen atom O(4), namely the $O^{\delta-}_{(4)[SO]}...H^{\delta+}_{(22)[o\text{-}Ph]}$ and the $O^{\delta-}_{(4)[SO]}...C^{\delta+}_{(6)[CO]}$ one. It should be noted that the O(4) negative charge is almost twice that of the carbonyl oxygen atom O(7) in the contacts described for the *g1* and *g2* conformers. Therefore, these additional electrostatic interactions largely contribute to the g_1 conformer stabilisation.

Finally, all three coulombic interactions that act in the *g2* conformer involve the carbonyl group and thus contribute to the decrease, as previously discussed, of the ν_{CO} frequency as a consequence of the improved C=O bond polarisation. On the other hand, only two of the main interactions that stabilise the *g1*conformer, that is the $O^{\delta-}_{(7)}...H^{\delta+}_{(18,19)}$ and the $O^{\delta-}_{(4)[SO]}...C^{\delta+}_{(6)[CO]}$ ones, involve the atoms of the carbonyl group and can affect its polarisation. Therefore, the carbonyl stretching frequency of the *g1* conformer decreases, but to a minor extent with respect that of the *g2* one, in agreement with both the theoretical and the experimental results.

Therefore, it is reasonable to state that the electrostatic interactions, rather than the sum of the orbital interactions, play a basic role in determining the observed stability of the three gauche conformers in the gas phase, as well as the ν_{CO} frequencies' order of derivatives **1**–**6**.

Conclusions

The conformational study of some 2-ethylsulfinyl-(4'-substituted)-phenylacetates bearing the substituents NO_2(**1**), Cl (**2**), Br (**3**), H (**4**), Me (**5**) and OMe (**6**) was performed by IR measurements, B3LYP/6-31G(d,p) and SM5.42R calculations, along with natural bond orbital (NBO) analysis for **1**-**6**. Theoretical data indicated the existence in the gas phase of three stable *gauche* conformers, whose relative abundances vary from *ca.*71% (g_1, intermediate carbonyl stretching frequency), to *ca.* 20% (g_2, lowest frequency) and *ca.* 9% (g_3, highest frequency). The SM5.42R solvation model shows that the relative stability of the three conformers in solution is affected by changes related to the solvent permittivity. In the non-polar solvent CCl_4, the relative abundance of the g_1 conformer remains almost constant with respect to that in the gas phase for all derivatives, while the g_2 one heavily decreases to 7% for **1** and less than 2% for **2**-**6** until to disappear in all the other solvents. Concomitantly, as the solvent permittivity increases, the g_3 conformer population increases over the g_1 one, until to become the most stable in acetonitrile for all derivatives. Experimentally, the carbonyl stretching IR band shows three components for derivative **1** in the low dielectric constant solvents CCl_4 and $CH_2(CH_3O)_2$ and a single component in the other solvents of higher permittivity. Differently, compounds **2**-**6** display a doublet in all solvents, except for **2** and **3** in acetonitrile for which a singlet was recorded. A detailed analysis of the experimental IR findings and the SM5.42R data allows a reliable assignment of the band components to the distinct *gauche* conformers. The sum of selected NBO orbital interactions energies for the g_1, g_2 and g_3 conformers in the series does not match the corresponding B3LYP relative energies calculated in the gas phase. On the contrary, the electrostatic interactions between charged atoms at distances shorter than the ∑vdWr properly account for the relative stability and the ν_{CO} frequencies of the conformers in gas and in solution.

The g_3 conformer is mainly stabilized by the $O^{\delta-}_{[o\text{-}Ph]}...H^{\delta+}_{[CH2]}$, $O^{\delta-}_{[SO]}...C^{\delta+}_{[CO]}$ and $O^{\delta-}_{[SO]}...H^{\delta+}_{[o\text{-}Ph]}$ short contacts and strongly destabilized by the coulombic repulsion between the negatively charged sulfinyl and carbonyl oxygen atoms. This effect is responsible too for its highest ν_{CO} frequency. Moreover, the RFE that takes place between the $S^{\delta+}=O^{\delta-}$ and $C^{\delta+}=O^{\delta-}$ dipoles accounts for its larger solvation energy that increases in solvents of higher permittivity.

The short contacts $O^{\delta-}_{[CO]}...H^{\delta+}_{[o\text{-}Ph]}$, $O^{\delta-}_{[CO]}...S^{\delta+}_{(3)}$ and $O^{\delta-}_{[CO]}...H^{\delta+}_{[CH2]}$ that stabilize the g_2 conformer contribute also to decrease its solvation energy, in agreement with the missing in solution of the corresponding band component. The same interactions occur

in the g_1 conformer too at interatomic distances similar or longer than in the g_2 one. However, the former is stabilized to a larger extent than the latter by the two additional short contacts $O^{\delta-}_{[SO]}...H^{\delta+}_{[o\text{-}Ph]}$ and $O^{\delta-}_{[SO]}...C^{\delta+}_{[CO]}$ that involve the sulfinyl oxygen atom charged almost twice than the carbonyl oxygen in the g_2 conformer. Finally, it should be noted that the atoms of the carbonyl group are involved in two coulombic interactions in the g_1 conformer and in three in the g_2 one. Consequently, as the $C^{\delta+}=O^{\delta-}$ bond polarization increases at larger extent in the g_2 conformer, its ν_{CO} frequency lowers with respect to that of the g_1 one, in line with the theoretical and experimental results.

In conclusion, the electrostatic interactions largely control the calculated stability as well as the ν_{CO} frequency order of the three *gauche* conformers of compounds **1**-**6** in the gas phase. Moreover, the peculiar geometry of each conformer is responsible for their distinctive solvation properties that significantly affect the conformer stability in solution.

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Figure and Scheme Captions

Fig. 1. IR spectra of 2-ethylsulfinyl phenyl acetate (**4**) showing the carbonyl stretching band in carbon tetrachloride [fundamental (a) and first overtone (b)], dimethoxymethane (c),chloroform (d), dichloromethane (e) and acetonitrile (f).

Fig. 2. IR spectra of 2-ethylsulfinyl-4'-nitrophenyl acetate (**1**) showing the carbonyl stretching band in carbon tetrachloride (a), dimethoxymethane (b),chloroform (c), dichloromethane [fundamental (d) and first overtone (e)] and acetonitrile (f).

Fig. 3. IR spectra of 2-ethylsulfinyl 4'-bromophenyl acetate (**3**) showing the carbonyl stretching band in carbon tetrachloride [fundamental (a) and first overtone (b)], dimethoxymethane (c),chloroform (d), dichloromethane (e) and acetonitrile (f).

Fig 4. Molecular structures of the *gauche* conformers (g_1, g_2 and g_3) of **4** obtained at B3LYP/6-31G(d,p) level. Adopted colours: H= white, C= grey, O= red, S= yellow.

Scheme 1. Atom labelling of 4'-substituted 2-ethylsulfinyl-phenylacetates and definition of the relevant dihedral angles.

Scheme 2. Differential solvent effect for the three *gauche* conformersg_1, g_2 and g_3 for **1**–**6**.

Supplementary material

Fig S1. Plot of the carbonyl stretching wavenumbers ($\bar{\nu}$) of the single component (for **1**–**3**) and the higher carbonyl doublet component (for **4**–**6**) of the ethylsulfinilesters (in acetonitrile) *versus* the σ_p Hammet constants of the 4'-substituents yielding the equation: $\bar{\nu} = 5.4\ \sigma_p + 1758.7$($n$ = 6; R = 0.901; SD = 2.3 cm^{-1}).

Table S1. σ_P Hammett constants for *para*-Y substituents of (**1**)–(**6**).

Table S2. Relative energies (kcal mol^{-1}), dipole moments (μ, D), selected angles (deg), carbonyl stretching frequencies (cm^{-1}) for the minimum energy conformations of 4'-substituted 2-ethylsulfinyl-phenylacetates at B3LYP [6-31G(d,p) and 6-31++G(d,p)] levels for (**1**) and (**4**) and MP2/6-31++G(d,p) level for (**4**).

Table S3. Occupancy of $\pi^*_{C=O}$ orbital obtained at B3LYP/6-31G(d,p) level for the4'-substituted-2-ethylsulfinyl-phenylacetates (**1**)–(**6**).