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Conformational study of some 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones

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Abstract

The analysis of IR carbonyl bands of some 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones **1-5** bearing substituents NO₂ **1**, Br **2**, H **3**, Me **4** and OMe **5**, supported by B3LYP/6-31+G(d,p) and single point PCM calculations, along with NBO analysis (for **1**, **3**, **5**) and X-ray diffraction (for **4**) was performed. Theoretical data indicated the existence of two stable conformations c_1 and c_2 . The former exhibits the highest ν_{CO} frequency and corresponds to the most stable (for **1-5**) and to the most polar one (for **2-4**). The sum of the energy contributions of selected orbital interactions (NBO analysis) of **1**, **3** and **5** is quite similar for both conformers. Nevertheless, adding the $\text{LP}_{\text{O}(\text{CO})} \rightarrow \sigma^*_{\text{C-H}[\text{CH}_2(\text{Et})]}$ and $\text{LP}_{\text{O}(\text{SO}_2)} \rightarrow \sigma^*_{\text{C-H}(o\text{-SePh})}$ orbital interaction energies, the c_1 conformer becomes significantly more stable than the c_2 one. The occurrence of these hydrogen bonds plays an important role in determining the geometry of the c_1

conformer. This geometry allows the oppositely charged $O^{\delta-}_{(CO)} \dots S^{\delta+}_{(SO_2)}$ and $O^{\delta-}_{(SO_2)} \dots C^{\delta+}_{(CO)}$ atoms of the carbonyl and sulfonyl groups to assume interatomic distances shorter than the sum of the van der Waals radii that stabilize the referred conformer. Likewise, this geometry favours the $O^{\delta-}_{(CO)} \dots O^{\delta-}_{(SO_2)}$ short contact and the consequent Repulsive Field Effect that increases to a greater extent the ν_{CO} frequency of the c_1 conformer with respect to that of the c_2 one. Therefore the more intense higher frequency carbonyl doublet component in the IR spectrum in solution can be ascribed to the c_1 conformer and the less intense component at lower frequency to the c_2 one. X-ray single crystal analysis of **4** indicates that this compound adopts the c_1 geometry. The molecules in the solid are linked in centrosymmetrical pairs through C9-H10...O36ⁱ hydrogen bond interaction along with the $LP_{Se} \dots \pi_{Ph}$ interaction.

Keywords: Conformational analysis; infrared spectroscopy; theoretical calculations; solvent effect; X-ray diffraction; 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones.

1. Introduction

Previous spectroscopic (IR, ^{13}C NMR, UV and UPS), dipole moment and X-ray diffraction studies, as well as theoretical calculations from our laboratory on some aliphatic β -carbonyl-sulfones $\text{Y}(\text{CO})\text{CH}_2\text{SO}_2\text{R}$ [$\text{Y} = -\text{Me}, -\text{Ar}, \text{NR}'_2, -\text{N}(\text{R}')(\text{OR}'), -\text{OR}'$ and $-\text{SR}'$; $\text{R} = \text{Me}, \text{Et}, \text{Ar}$] [1-9] indicated that in these compounds the *gauche* or *quasi-gauche* conformation(s) between the C=O and C-S bonds is preferred with respect to the *cis* one (s) in gas phase, in solution of low polarity solvents, and in the solid state. The stabilization of the *gauche* conformers of the β -carbonyl-sulfones has been ascribed to the $\pi_{\text{CO}}/\sigma^*_{\text{C-S}}$ and $\sigma_{\text{C-S}}/\pi^*_{\text{CO}}$ orbital interactions along with crossed electrostatic and charge transfer interactions between the oppositely charged atoms $\text{O}_{(\text{SO}_2)} \rightarrow \text{C}_{(\text{CO})}$ and $\text{O}_{(\text{CO})} \rightarrow \text{S}_{(\text{SO}_2)}$.

Moreover, *ab initio* and X-ray diffraction study of some bis-thio-acetophenones $\text{PhC}(\text{O})\text{CH}(\text{SR})(\text{SO}_2\text{R})$ ($\text{R} = \text{Me}$ and Ph) [10] indicated that in the gas phase and in the solid state the S-R and the C=O groups adopt the *gauche* geometry, while the SO_2R and the C=O ones assume the *quasi-cis* conformation. The stabilization of the *gauche* conformer was ascribed to the occurrence of the $\sigma_{\text{C-SR}}/\pi^*_{\text{CO}}$ hyperconjugative interaction that, by increasing the negative charge at the carbonyl oxygen atom, enhances the crossed $\text{O}^{\delta-}_{\text{CO}} \rightarrow \text{S}^{\delta+}_{(\text{SO}_2\text{R})}$ and $\text{O}^{\delta-}_{(\text{SO}_2\text{R})} \rightarrow \text{C}^{\delta+}_{(\text{CO})}$ electrostatic and charge transfer interactions.

Furthermore the ν_{CO} IR, α -methylene ^{13}C NMR and $n \rightarrow \pi^*_{\text{CO}}$ UV analyses of α -phenylseleno *p*-substituted propiophenones [11] have shown that the *gauche* conformer is strongly stabilized with respect to the *cis* one through the $n_{\text{Se}}/\pi^*_{\text{CO}}$, $\sigma_{\text{C-Se}}/\pi^*_{\text{CO}}$ and $\pi^*_{\text{CO}}/\sigma_{\text{C-Se}}$ orbital interactions. This behavior, along with the bis-thio-acetophenones study, prompted us to investigate by means of IR spectra, X-ray diffraction, density functional theory and NBO calculations, some mixed acetophenones bearing in the α

position both the phenylseleno and ethylsulfonyl groups, *i.e.* the 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones **1-5** (Scheme 1), as both substituents should compete for the *syn-clinal (gauche)* geometry with respect to the carbonyl group. Additionally, these compounds were chosen taking into account that the orbital and electrostatic interactions that are responsible for the relative stability of their conformers might be affected by changes in the conjugation involving the 4'-substituents.

Prostaglandins are inflammatory mediators generated by cyclooxygenases (COX's) [12]. Among these, COX-1 is constitutive and displays important physiological activities, while COX-2 is induced in inflammatory processes [12,13]. Therefore the inhibition of the latter would elicit anti-inflammatory activity. Unfortunately, most of the inhibitors act also on COX-1 causing undesirable side effects [14, 15]. Therefore there is a continuous search for selective COX-2 inhibitors, in particular for compounds containing selenium or sulfur [16-18]. As docking studies may be helpful to understand the mechanism of inhibition of COX's [19], a series of molecular docking studies were performed on compounds such as 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones [20]. As docking calculations rely on the knowledge of the molecular conformations, the study of the stereoelectronic interactions that modulate the conformational equilibrium will contribute to the development of new scaffolds for more COX-2 specific inhibitors.

2. Experimental

2.1 Materials

All solvents for IR measurements were spectrograde and were used without further purification. The 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones **1** to **5** are new compounds and were obtained following a literature procedure [21]. A THF

solution of 2-(ethylsulfonyl)-(4'-substituted)-acetophenone was added to a solution of LDA in THF at 195 K. After 40 minutes, a solution of phenylselenanyl bromide in THF was added dropwise to the enolate solution. After the reaction mixture reached room temperature (*ca.* three hours) water was added and extraction with ethyl ether was performed. The organic layer was washed with diluted HCl, water and dried over anhydrous magnesium sulphate. After evaporation of the solvent, the crude product was purified through flash chromatography on silica gel to obtain a pure solid. Suitable crystals for X-ray analysis for **4** were obtained by vapor diffusion from chloroform/n-hexane at 283 K. The ¹H and ¹³C NMR data and an elemental analysis for compounds **1** to **5** are presented in Table 1. The starting 4'-substituted 2-(ethylsulfonyl)-acetophenones 4'-Y-PhC(O)CH₂SO₂Et were prepared as previously described [22].

2.2 IR measurements

The IR spectra for the fundamental carbonyl region (1800-1600 cm⁻¹) were recorded with a FTIR Michelson Bomem – MB100 Model spectrometer, with 1.0 cm⁻¹ resolution, at a concentration of 1.0 x 10⁻² mol dm⁻³ in carbon tetrachloride, chloroform, dichloromethane and acetonitrile solutions, using a 0.519 mm sodium chloride cell. The spectra for the carbonyl first overtone region (3600-3100 cm⁻¹) were recorded in carbon tetrachloride solution and dichloromethane (1.0 x 10⁻² mol dm⁻³) using a 1.00 cm quartz cell. The overlapping carbonyl bands (fundamental and first overtone) were deconvoluted by means of the Grams/32 curve fitting program, version 4.04 [23]. 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 the conformers.

2.3. NMR measurements

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer operating at 500.130 and 125.758 MHz, respectively, for 0.1 mol/dm³ solutions in CDCl₃. ^1H and ^{13}C chemical shifts are reported in ppm relative to TMS, as internal standard.

2.4. X-ray measurements

X-ray crystallographic data were collected with an Agilent SuperNova (Dual, Cu at zero) diffractometer with an Atlas detector diffractometer using graphite-monochromated CuK α radiation ($\lambda = 1.54184 \text{ \AA}$). Data were collected at 100 K and the structure was solved by direct methods with SIR92 [24] and refined by full-matrix least-squares on F^2 with SHELXL-97 [25]. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed and refined riding with $U_{iso}(\text{H}) = 1.2U_{eq}(\text{C})$ and $U_{iso}(\text{H}) = 1.5 U_{eq}(\text{methyl-C})$. The key crystallographic data are given in Table 2. CCDC 1033705 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 33; e-mail: deposit@ccdc.cam.ac.uk.

2.5. Theoretical calculations

A conformational search (HF/STO-3G theory level) was performed with Spartan '06 [26] software. The obtained conformer geometries were used as initial inputs for all calculations performed at 298 K with the Gaussian package programs (G03-E01) [27], with a hybrid Hartree-Fock density functional B3LYP method [28] and 6-31+G(d,p) basis set. Full geometry optimizations and analytical vibrational frequency calculations were performed on the more stable conformers. Frequency analyses were carried out to

verify the nature of the minimum state of all the stationary points obtained and to calculate the zero-point vibrational energies (ZPVE) corrections. To estimate the solvation effects on the relative stability of the most relevant conformers, single-point calculations were conducted on the optimized structures using the polarizable continuum model (PCM) [29]. The NBO 3.1 program [30] was used as implemented in the Gaussian 03 package, and the reported NBO delocalization energies (E2) were those given by second-order perturbation theory. The partial atomic charges were calculated using the grid-based ChELPG method [31].

3. Results and Discussion

Table 3 collects the stretching frequencies and the absorbance percentage of the analytically resolved carbonyl band components for the 2-(phenylselanyl)-2-ethylsulfonyl)-(4'-substituted)-acetophenones **1** to **5**, in solvents of increasing relative permittivity [32], *i.e.* CCl₄ ($\epsilon = 2.2$) (fundamental and first overtone), CHCl₃ ($\epsilon = 4.8$), CH₂Cl₂ ($\epsilon = 9.1$) (fundamental and first overtone) and CH₃CN ($\epsilon = 38$).

The carbonyl stretching band shows two components in all solvents for compounds **3**, **4** and **5**, in CCl₄ and CHCl₃ for **1**, and in CCl₄ for **2**, with the higher frequency component significantly more intense than the lower frequency one. In addition, the singlet evidenced in the higher relative permittivity solvents CH₂Cl₂ and CH₃CN for **1** and **2** and CHCl₃ for **2** corresponds to the doublet higher frequency component.

The carbonyl band overtones show two components in CCl₄ and CH₂Cl₂ for **3-5** and in CCl₄ for **2**, while a single one in CH₂Cl₂ for **1** and **2**, at frequencies twice those of the fundamental minus twice the mechanical anharmonicity of $18 \pm 2 \text{ cm}^{-1}$ [33]. The fact that all the components have almost the same percentage of absorbance than the corresponding ones in the fundamental is indicative of the presence of two or one

conformers for the referred compounds, ruling out the existence of any vibrational effect in the fundamental transition of the ν_{CO} mode [34(a), 34(b)].

The intensity of the higher frequency component of the carbonyl doublet increases with respect to the lower one going from CCl_4 to CH_3CN , varying from *ca.* 84% to 100% for **1** and **2** and from *ca.* 60% to 88% for **3-5**. In addition, its intensity progressively increases going from the electron donating (OMe **5**, *ca.* 74%) to the electron withdrawing (NO_2 **1**, *ca.* 92%) 4'-substituents, in all solvents.

Table 4 lists the frequency shifts ($\Delta\nu_{\text{CO}}$) of each component of the carbonyl doublet of the title compounds **1-5** (Table 3) with respect to the carbonyl frequencies of the parent acetophenones **6-10**, in CCl_4 . The simultaneous presence of the $-\text{SO}_2\text{Et}$ and $-\text{SePh}$ substituents at the methyne carbon accounts for the shift to lower frequencies of both components with respect to the corresponding values of the parent acetophenones, namely *ca.* $\Delta\nu_{\text{CO}} = -12 \text{ cm}^{-1}$ for the higher frequency component and *ca.* $\Delta\nu_{\text{CO}} = -21 \text{ cm}^{-1}$ for the lower one. However, a positive shift value should be expected taking into account the inductive effect ($-I_{\sigma}$) exerted by the $-\text{SO}_2\text{Et}$ ($\sigma_{\text{I}} = 0.59$) and $-\text{SePh}$ ($\sigma_{\text{I}} = 0.13$) substituents [36]. Therefore, the experimental results suggest the existence of both electrostatic and orbital interactions operating in the different conformers of **1-5**, which act by decreasing the carbonyl bond order and thus the experimental carbonyl frequencies with respect to the values observed in the corresponding parent acetophenones.

In order to determine the geometries and vibrational frequencies of the minimum energy conformations in the gas phase, B3LYP/6-31G+(d,p) calculations were performed for compounds **1** to **5**. Some relevant data are reported in Table 5, along with the X-ray dihedral angles for **2**. The calculations indicate the existence of two distinct conformers c_1 and c_2 whose α and α' dihedral angles are quite similar in the series **1-5**, being the c_1

one the most stable for all the compounds. For the c_1 conformer, both the C-S/C=O ($\alpha \approx 55^\circ$) and C-Se/C=O ($\alpha' \approx 71^\circ$) groups are in the *syn-clinal* geometries, while in the c_2 one both groups adopt the *anti-clinal* conformation, that is $\alpha \approx 100^\circ$ and $\alpha' \approx 130^\circ$. The computed molecular structures of the c_1 and c_2 conformers of **2**, taken as a prototype for the series, are shown in Figure 2.

The vibrational frequencies analysis indicates that c_1 conformer has the higher carbonyl frequency. Therefore, the more intense higher frequency component of the carbonyl doublet in the IR spectrum in solution can be ascribed to the same conformer and the less intense component at lower frequency to the c_2 one.

The molar fraction of the most stable c_1 conformer increases progressively going from **5** (61.6%) to **1** ($\approx 92\%$), in line with the experimental trend observed in the IR spectra in all solvents, and thus it depends on the nature of the 4'-substituent.

The influence of the solvent on the relative intensity of the carbonyl doublet is in agreement with the higher dipole moment of the c_1 conformer with respect to the c_2 one for **2-5**, with the exception of the nitro-derivative **1** for which a reversal of the dipole moment order is observed. It should be pointed out that the *single-point* PCM (Polarisable Continuum Model) calculations, reported in Table 6 for all compounds, show a trend quite similar to that observed experimentally (IR), namely an increase of the c_1 conformer relative population as the solvent polarity increases. Additionally, the PCM results indicate that the c_1 conformer is always the more stable one.

The energies of donor-acceptor orbital interactions were evaluated through the natural bond orbital (NBO) analysis, calculated at the B3LYP/6-31G+(d,p) level for the two conformers of **1**, **3** and **5** (Table 7) [25]. The ChELPEG charges and the interatomic distances of some selected atoms for compounds **1-5** computed at the same level are reported in Tables 8 and 9, respectively.

The strongest orbital interactions are: a) the $\pi_{C25=C26(Ph)} \rightarrow \pi^*_{C2=O1}$ (conjugative), whose mean energy values for both conformers increase from about 19 kcal mol⁻¹ to about 24 kcal mol⁻¹, going from 4'-electron-attracting- (**1**) to 4'-electron-donating- (**5**) substituents; b) the $LP_{O1} \rightarrow \sigma^*_{C2-C3}$ (*ca.* 21 kcal mol⁻¹) and $LP_{O1} \rightarrow \sigma^*_{C2-C25}$ (*ca.* 19 kcal mol⁻¹) through bond coupling interactions [37], almost constant for both conformers in the series **1**, **3** and **5**. Furthermore, the *c*₂ conformer is slightly stabilized in the whole series by the additional $LP_{O1} \rightarrow \sigma^*_{C3-Se13}$ weak interaction (*ca.* 1 kcal mol⁻¹) related to the suitable α' angle value of *ca.* 131°.

In contrast, the favorable ϕ dihedral angle of *ca.* 103° on both conformers in the whole series allows the medium-weak $LP_{Se13} \rightarrow \sigma^*_{(C3-S5)}$ orbital stabilizing interaction of almost constant mean energy value of *ca.* 5 kcal mol⁻¹.

A series of orbital interactions, that is the $LP_Y \rightarrow \pi^*_{CO}$ (a), $\pi_{CO} \rightarrow \sigma^*_{C-Y}$ (b), $\sigma_{C-Y} \rightarrow \pi^*_{CO}$ (c) and $\pi^*_{CO} \rightarrow \sigma^*_{C-Y}$ (d) [38] (Y= S or Se), are maximized as the α or α' torsional angles get closer to 90°. The interactions involving the sulfur atom are stronger for the *c*₂ conformers, while those acting on the selenium one stabilize to a greater extent the *c*₁ rotamers, with the exception of the $\pi_{CO} \rightarrow \sigma^*_{C-Se}$ interactions whose energy values are almost equal for both conformers (*ca.* 1.3 kcal mol⁻¹). It should be pointed out that the sum of the referred hyperconjugative orbital interactions energies from (a) to (d) has a constant value of *ca.* 21 kcal mol⁻¹ for both conformers of **1**, **3**, and **5**, thus indicating that they stabilize to the same extent both the *c*₁ and the *c*₂ conformers.

The analysis of the atomic charges and distances evidences that the *c*₁ conformers are stabilized to a larger extent than the *c*₂ ones by two attractive electrostatic interactions between the oppositely charged atoms H^{δ+} and O^{δ-} separated by interatomic distances significantly shorter than the sum of the van der Waals ($\sum vdW$) radii, that is O_{CO(1)}...H(7)_[CH₂(Et)] (Δl *c*₁ *ca.* -0.38Å) and O_{SO₂(36)}...H(16)_[o-SePh] (Δl *c*₁ *ca.* -0.39 Å,

Δl_{c_2} *ca.* -0.27 Å). These short contacts are responsible also for the $LP_{O1(CO)} \rightarrow \sigma^*_{C6-H(7)}$ and for the $LP_{O(36)} \rightarrow \sigma^*_{C(15)-H(16)}$ orbital interactions (hydrogen bond). The former stabilizes only the c_1 conformer by *ca.* 2.6 kcal mol⁻¹, while the latter affects at larger extent the c_1 rotamer (*ca.* 2.8 kcal mol⁻¹) with respect to the c_2 one (*ca.* 1.3 kcal mol⁻¹). These hydrogen bonds are illustrated in Figure 2 for the c_1 and the c_2 conformers of **3**.

The two hydrogen bonds play an important role in determining the geometry of the c_1 conformers for **1**, **3** and **5**, and in particular they allow suitable δ and α torsional angles which are responsible of the following additional stabilizing interactions.

As a matter of fact, the δ torsional angle of *ca.* 46° forces the negatively charged sulfonyl oxygen and the positive carbonyl carbon to a distance shorter than the \sum vdW radii (Δl *ca.* -0.16 Å) and, analogously, the α torsional angle of *ca.* 55° constrains the oppositely charged carbonyl oxygen and the sulfonyl sulfur atoms to a short contact (Δl *ca.* -0.15 Å). Therefore, the c_1 conformers are strongly electrostatically stabilized through the referred short contacts, along with a weak $LP_{O(SO_2)} \rightarrow \pi^*_{CO}$ orbital interaction (0.5 kcal mol⁻¹) detected only for compound **3**.

The geometry of the c_1 conformer for **1-5** is responsible even for the electrostatic repulsion between the negatively charged $O^{\delta-}(1)_{CO} \dots O^{\delta-}(35)_{SO_2}$ separated by an interatomic distance slightly larger than the \sum vdW radii by (Δl *ca.* 0.33 Å). This contact originates the Repulsive Field Effect (RFE) [29a] between the $C^{\delta+}=O^{\delta-}$ and $(O)S^{\delta+}=O^{\delta-}$ dipoles which in turn increases the carbonyl bond order and consequently the frequency of the c_1 conformer with respect to the c_2 one, in line with the theoretical (Table 5) and experimental results (Table 3). Moreover, if the experimental carbonyl frequencies are compared to the corresponding values of the parent acetophenones (Table 4), the smaller medium negative carbonyl frequency shift of the c_1 conformer ($\Delta\nu = -12$ cm⁻¹) relative to that of the c_2 one ($\Delta\nu = -21$ cm⁻¹) is consistent with this behaviour.

Additionally, the progressive decrease of the c_1 conformer stability (population) with respect to the c_2 one can be related to the nature of the phenacyl 4'-substituent (Tables 3 and 5). In fact an electron donor 4'-substituent increases the polarization of the carbonyl group and yields to a stronger RFE between the $C^{\delta+}=O^{\delta-}$ and $(O)S^{\delta+}=O^{\delta-}$ dipoles which operate by decreasing the stability of the c_1 conformer. Conversely, an electron withdrawing 4'-substituent decreases the polarization of the carbonyl group and the consequent smaller RFE between the dipoles slightly lowers the stability of the c_1 conformer.

Accordingly, the carbonyl oxygen negative charge diminishes in the same direction, *i.e.* from -0.50e for the methoxy derivative (**5**) to -0.45e for the nitro substituted one (**1**).

The short contact between the negatively charged sulfonyl oxygen (*ca.*-0.57e) and selenium (*ca.*-0.19e) atoms in the c_2 conformer almost matches the \sum vdW radii, while the interatomic distance between O (*ca.*-0.57e) and Se (*ca.*-0.08e) in the c_1 one is larger than the \sum vdW radii by *ca.* 0.12Å. Therefore this electrostatic repulsion contributes into a larger extent to the destabilization of the former conformer with respect to the latter one.

The sum of the NBO orbital interactions (ΣE) for compounds **1**, **3** and **5** indicate that the c_1 conformer is more stable than the c_2 one by an average value of 3.6 kcal mol⁻¹. It should be pointed out that this value is close to the larger energy stabilization of the c_1 conformer with respect to the c_2 one due to the hydrogen bonds interactions (*ca.* 4.0 kcal mol⁻¹).

Therefore it seems reasonable to conclude that the calculated significantly larger stability of the c_1 conformer with respect to the c_2 one is due to the simultaneous occurrence of $O^{\delta-}_{(SO_2)}/C^{\delta+}_{(CO)}$ and $O^{\delta-}_{(CO)}/S^{\delta+}_{(SO_2)}$ electrostatic and orbital interactions

along with the relevant [$\text{H}^{\delta+}_{(o\text{-SePh})}\dots\text{O}^{\delta-}_{(\text{SO}_2)}$ and $\text{H}^{\delta+}_{(\text{CH}_2\text{Et})}\dots\text{O}^{\delta-}_{(\text{CO})}$] hydrogen bonds that determine the geometrical structure of this conformer.

X-ray single crystal analysis of **4** indicates that this compound, whose molecular structure is reported in Figure 3, assumes in the solid the most stable c_1 conformation found in the gas phase, as evidenced by the almost coincident values of the torsional α - γ' angles (Table 5). As expected, the single molecule in the solid is stabilized by the same intramolecular attractive electrostatic interactions that occur in the gas phase between the oppositely charged atoms of the sulfonyl and carbonyl groups, connected by distances shorter than the ΣvdW radii by (Δl mean value = -0.24\AA).

The molecule is further stabilized by the occurrence of the hydrogen bond through the $\text{O}^{\delta-}_{\text{CO}(1)}\dots\text{H}^{\delta+}(7)_{[\text{CH}_2(\text{Et})]}$ contact, shorter than the (ΣvdW) radii ($\Delta l = -0.20\text{\AA}$). On the contrary, the $\text{O}^{\delta-}_{\text{SO}_2(36)}\dots\text{H}^{\delta+}(16)_{[o\text{-SePh}]}$ hydrogen bond interaction observed in the gas phase disappears in the solid, as evidenced by the interatomic distance longer than the ΣvdW radii ($\Delta l = 0.24\text{\AA}$).

In order to obtain the larger energy gain from the crystal packing, the molecules in the crystal are linked in centrosymmetrical pairs through a C-H...O interaction ($\text{C9}\dots\text{O36}^i = 3.496(3)\text{\AA}$; $\text{H10}\dots\text{O36}^i = 2.59\text{\AA}$; $\text{C9-H10}\dots\text{O36}^i = 154^\circ$; symmetry operation: $1-x, y, 2-z$) which in turn are linked through a Se... π interaction, as shown in Fig. 4. The Se... π distance being 3.638\AA , a value normally found for this kind of interaction [39].

4. Conclusions

The most stable conformations of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones **1** to **5** (NO_2 **1**, Br **2**, H **3**, Me **4**, OMe **5**) were determined by ν_{CO} IR analysis, B3LYP/6-31+G(d,p) and single-point PCM calculations, NBO analysis (for **1**, **3**, **5**) and X-ray diffraction analysis (for **4**). Theoretical data indicated the existence of

two stable conformations (c_1 and c_2) for all compounds. Among these, the c_1 one is the most stable (for **1-5**), the most polar (for **2-4**) and has the highest ν_{CO} frequency. On these basis, the more intense higher frequency carbonyl doublet component in the IR spectrum in solution can be ascribed to the c_1 conformer and the less intense lower frequency one to the c_2 rotamer.

The conformer c_1 displays both the C-S/C=O and C-Se/C=O groups in the *syn-clinal* geometries, whereas the c_2 conformer presents the same groups in the *anti-clinal* geometries. The computed population of the more stable c_1 conformer depends on the nature of the 4'-substituent and increases progressively going from **5** to **1**. This trend is well reproduced in the experimental IR spectrum in solution where an increase of the absorbance of the higher frequency carbonyl doublet component (c_1 conformer) with respect to the lower one (c_2 conformer) can be observed in all solvents going from **5** to **1**.

Moreover, the relative intensity of the c_1 doublet component in solution increases as the solvent relative permittivity increases. This behaviour is in line with the PCM single-point calculations that predict a slightly augment of the relative abundance of the c_1 conformer with increasing solvent polarity.

The sum of the energy contributions of the selected orbital interactions (NBO analysis) is quite similar for both conformers of **1**, **3** and **5**. On the contrary, the additional $\text{H}^{\delta+}_{(o\text{-SePh})}\dots\text{O}^{\delta-}_{(\text{SO}_2)}$ and $\text{H}^{\delta+}_{(\text{CH}_2\text{Et})}\dots\text{O}^{\delta-}_{(\text{CO})}$ interactions (hydrogen bonds) stabilize to a greater extent the c_1 conformer with respect the c_2 one. Moreover, the occurrence of these interactions forces the $\text{O}^{\delta-}_{(\text{CO})}\dots\text{S}^{\delta+}_{(\text{SO}_2)}$ and $\text{O}^{\delta-}_{(\text{SO}_2)}\dots\text{C}^{\delta+}_{(\text{CO})}$ atoms to get closer than the $\sum\text{vdW}$ radii, thus contributing to a further stabilization of the c_1 conformer. Likewise, the geometry of the c_1 conformer allows the contact between the negatively charged $\text{O}^{\delta-}_{\text{CO}}\dots\text{O}^{\delta-}_{\text{SO}_2}$ which originates a Repulsive Field Effect between the $\text{C}^{\delta+}=\text{O}^{\delta-}$

and $(O)S^{\delta+}=O^{\delta-}$ dipoles that causes a major increase of the frequency of the carbonyl group of the c_1 conformer with respect to that of the c_2 one, as observed experimentally. Finally, the progressive increase of the population of the c_1 conformer going from **5** to **1**, that is from the 4'-methoxy- to the 4'-nitro- substituents, accounts for the decreased polarization of the C=O group from **5** to **1** and the consequent diminution in the same direction of the $O^{\delta-}_{CO}\dots O^{\delta-}_{SO_2}$ electrostatic repulsive destabilization.

X-ray single crystal analysis of **4** indicates that this compound assumes in the solid state the most polar and most stable c_1 conformation found in the gas phase. In order to obtain the larger energy gain from the crystal packing, the molecules in the crystal are linked in centrosymmetrical pairs through a $C-H_{[Me(Et)]}\dots O_{(SO_2)}^i$ hydrogen bond interaction which in turn are linked through by $LP_{Se}\dots\pi_{Ph}$ interaction.

To conclude, it should be pointed out that the most stable c_1 conformers of the title compounds adopt a *syn-clinal* geometry with respect to both Se-Ph/C=O and $SO_2Et/C=O$ groups, while the most stable conformers of the $PhC(O)CH(SR)(SO_2R)$ derivatives [10] assume a *syn-periplanar* and *anti-clinal* geometries with respect to S-R/C=O and $SO_2R/C=O$ groups, respectively (in gas phase and in the solid state).

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Figure and Scheme Captions

Fig.1. IR spectra of 2-(phenylselanyl)-2-(ethylsulfanyl)-4'-methoxy-acetophenone (**5**) showing the analytically resolved carbonyl stretching band in: carbon tetrachloride [fundamental(a) and first overtone (b)], chloroform (c), dichloromethane [fundamental(d) and first overtone (e)] and acetonitrile (f).

Fig.2. Molecular structures of **3** obtained at the B3LYP/6-31+G(d,p) level. Adopted colours: H= white, C= grey, O= red, S= yellow, Se=orange.

Fig.3 The molecular structure of compound **4**, showing the atom labeling and displacement ellipsoids at the 30% probability level for non-H atoms.

Fig.4 A view in projection of compound **4** showing the supramolecular array sustained by C—H \cdots O and Se \cdots π interactions.

Scheme1 Atoms labelling of 4'-substituted 2-(phenylselanyl)-2-ethylsulfonyl-acetophenones and definition of the relevant dihedral angles.