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

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Abstract

The conformational analysis of some 4'-substituted 2-(phenylselanyl)-2-(ethylsulfanyl)-acetophenones bearing the substituents NO₂ (**1**), Br (**2**), H (**3**), Me (**4**) and OMe (**5**) was performed by ν_{CO} IR analysis, B3LYP/6-31+G(d,p) and single point polarisable continuum model (PCM) calculations, along with NBO analysis for **1**, **3** and **5**. Calculations for **1** to **5** indicate the existence of three stable conformations, c_1 , c_2 and c_3 , whose stability depends on the balance between electrostatic and orbital interactions that are strictly related to the geometrical arrangement. The comparison between the experimental IR spectra in solution and the computed data in gas phase for **1** to **5** allows the c_1 conformer to be assigned to the less intense component at higher frequency of the carbonyl doublet and both the c_2 and c_3 ones to the more intense lower frequency component. The sum of the calculated molar fraction of c_2 and c_3 conformers decreases from 95% to 63% on going from **1** to **5** (in gas phase), and this trend compares well with the PCM calculations and the IR experimental data for the majority of the solvents for all

compounds **1** to **5**. The NBO analysis for **1**, **3** and **5** shows that the sum of the relevant orbital delocalization energies for the c_1 , c_2 and c_3 conformers is almost constant and does not match the computed stability order. The lowest stability of the c_1 conformer for **1** to **3** can be related to the small value of the α dihedral angle that enables a strong electrostatic destabilizing repulsion between the $O_{CO}^{\delta-} \dots S^{\delta-}$ atoms. The relative stability of the c_1 conformer increases for **4** and **5** as the α dihedral angle enlarges and the repulsion is minimized. Moreover, the strong repulsive field effect between the $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}-S^{\delta-}$ dipoles exerted to a greater extent on the c_1 conformers of **1** to **3** with respect to **4** and **5**, causes a major increase of the corresponding C=O bond orders and related carbonyl frequencies. For the c_2 conformer, the electrostatic destabilizing repulsion between the $O^{\delta-} \dots Se^{\delta-}$ atoms is weaker than that involving the $O^{\delta-} \dots S^{\delta-}$ atoms in the c_1 conformer and therefore has negligible effects on the conformer stability that is mainly determined by the sum of the orbital interactions. The c_3 conformer has the shortest $S^{\delta-} \dots Se^{\delta-}$ contact for all compounds and thus the related electrostatic repulsion seems to be the most important factor that affects its stability. In conclusion, the computed order of stability of the three conformers for **1** to **5** depends on the electrostatic repulsions between close charged atoms rather than on the sum of the orbital delocalization energies that are quite similar for all the conformers.

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

Introduction

Previous reports from this laboratory of IR, UV, NMR and electron spectroscopies studies, supported by theoretical calculations of some (α -alkylthio)- and (α -phenylthio)-acetones, acetophenones, *N,N*-diethylamides, esters, thioesters [1,2], *N*-methoxy-*N*-methyl amides [3], and *N*-methyl- δ -valerolactams [4], indicated that the simultaneous occurrence of the $n_S \rightarrow \pi^*_{CO}$, $\sigma_{C-S} \rightarrow \pi^*_{CO}$ and $\pi_{CO} \rightarrow \sigma^*_{C-S}$ orbital interactions is the main controlling factor that determines the preference of the *gauche* (*axial*) conformer(s) over the *cis* (*equatorial*) one(s).

Additionally, ν_{CO} IR, α -methylene C^{13} NMR and $n \rightarrow \pi^*$ UV analyses of α -phenylseleno-*p*-substituted propiophenones have shown that the *gauche* conformer is even more stable than the *cis* one in comparison with the corresponding thio-analogue compounds, the *gauche* conformer being strongly stabilized by the same orbital interactions outlined above, with the sulfur atom replaced by the selenium one [5].

Taking into account that the n_{Se} lone pair (8.40 eV) and the σ_{C-Se} orbital (12.0 eV) [6,8] ionization energies are lower than those of the n_S lone pair (8.71 eV) and σ_{C-S} (12.68 eV) orbital [6,8] and that the electron-affinity of the σ^*_{C-Se} orbital (2.4 eV) is greater than that of the σ^*_{C-S} (3.25 eV) orbital [7,8], stronger ($n_X \rightarrow \pi^*_{CO}$, $\sigma_{C-X} \rightarrow \pi^*_{CO}$, $\pi_{CO} \rightarrow \sigma^*_{C-X}$) orbital interactions occur in the *gauche* conformer of the α -phenylseleno-propiofenones ($X=Se$) in comparison with the same conformer of the α -phenylthio-acetophenones. ($X=S$), as outlined in our previous paper [5]. This behaviour inspired us to study by means of IR spectra, density functional theory and NBO calculations some mixed acetophenones bearing in the α position both the phenylseleno and ethylthio substituents. In particular our study pointed to the 4'-substituted 2-(phenylselanyl)-2-(ethylthio)-acetophenones **1** to **5** (Scheme 1), as both the α -substituents in these

compounds should compete for the *syn-clinal (gauche)* geometry with respect to the carbonyl group. In addition, they were chosen taking into account that the orbital and coulombic interactions might be affected by changes in the conjugation involving the 4'-substituent which could affect the stabilization of their conformers. It should be emphasized that the conversion of ketones to enones, which are compounds of great synthetic versatility, can be accomplished by routes that involve compounds with electron-attractive groups, derived from sulfur, containing the phenylselenyl group whose elimination as selenoxide promotes the formation of insaturation [9].

It is known that the aminoacid selenomethionine [10], as well as sulfur-containing compounds [11], inhibit the cyclooxygenase-2 (COX-2) enzyme and consequently show anti-inflammatory activity. Therefore, there is a great interest in the development of selective COX-2 inhibition drugs containing selenium or sulfur substituents [12]. In order to gain a better insight, at a molecular level, of the mechanism of inhibition of the COX-2 enzyme we performed molecular docking studies on some organocalchogen compounds containing groups such as 4'-substituted 2-(phenylselenyl)-2-(ethylsulfanyl)-acetophenones [13]. Therefore, the study of the stereoelectronic interactions that determine the conformational equilibrium of compounds containing selenium and sulfur could contribute to the development of more efficient and specific drugs.

Experimental

Materials

All solvents for IR measurements were spectrograde and were used without further purification. The 4'-substituted 2-(phenylselenyl)-2-(ethylsulfanyl)-acetophenones **1** to **5** are new compounds and were prepared by a literature procedure [9] as follows: a THF

solution of 2-(ethylsulfanyl)-(4'-substituted)-acetophenone was added slowly to a stirred solution of LDA in THF at 195 K. After 40 minutes, a solution of phenylselenyl bromide in THF was added dropwise with immediate discoloration of the reactant. When the reaction mixture reached room temperature (ca. three hours), water was added and the product extracted with ethyl ether. The organic layer was washed with diluted HCl, water and dried over anhydrous magnesium sulphate. The obtained crude product was purified by flash chromatography on silica gel and, after solvent evaporation, a solid was obtained. The ^1H and ^{13}C NMR data and an elemental analysis for compounds **1** to **5** are presented in Table 1. The starting 4'-substituted 2-(ethylsulfanyl)-acetophenones 4'-Y-PhC(O)CH₂SEt were prepared as previously described [14].

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 1.0×10^{-2} mol dm^{-3} in *n*-hexane, 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 (1.0×10^{-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 [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 the conformers.

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.

Theoretical calculations

A conformational search (HF/STO-3G theory level) was performed with Spartan '06 [16] software. The obtained conformer geometries were used as initial inputs in all calculations carried out at 298 K using the methods and basis sets implemented in the Gaussian package of programs (G03-E01) [17]. The hybrid Hartree-Fock density functional B3LYP method [18] with the 6-31+G(d,p) basis set was used. 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) [19]. The NBO 3.1 program [20] 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 [21].

Results and Discussion

Table 2 lists the stretching frequencies and the absorbance percentage of the analytically resolved carbonyl band for the 2-(phenylselanyl)-2-(ethylsulfanyl)-(4'-substituted)-acetophenones **1** to **5** in solvents of increasing relative permittivity [22], i.e. *n*-hexane ($\epsilon = 1.9$), carbon tetrachloride ($\epsilon = 2.2$) (fundamental and first overtone),

chloroform ($\epsilon = 4.8$), dichloromethane ($\epsilon = 9.1$) and acetonitrile ($\epsilon = 38$). A carbonyl doublet is shown for the studied compounds in all solvents, with the exception of **1** (CCl_4 and CHCl_3) and **3** (CHCl_3), for which only a singlet is detected. The occurrence of two carbonyl band components in the first overtone region (CCl_4) at frequencies twice those of the fundamental minus ca. 19 cm^{-1} (twice the mechanical anharmonicity [23]) and with almost the same intensity ratio, is indicative of the presence of at least two conformers for the studied compounds, ruling out the existence of any vibrational effect in the fundamental transition of the ν_{CO} mode [24a, 24b].

The lowest frequency component of the carbonyl doublet is the more intense one in all solvents for the whole series **1** to **5** (ca. 100%-65%). In addition, the intensity of the highest frequency component progressively increases on going from electron-attracting to electron-donating (**1** to **5**) substituents in all solvents (ca. 0%-33%), with the exception of the most polar acetonitrile where no trend is observed. The relative intensity of the carbonyl doublet components is slightly influenced by the increase of relative permittivity of solvent. However, the solvent effect on the intensity of each doublet component depends on the nature of the 4'-substituent. In particular, the intensity of the higher frequency component increases up to 20% with respect to the lower one in compounds **1** and **2**, having electron-withdrawing groups, whereas it decreases (ca. 35%-8%) in compounds **3** to **5** (with hydrogen or electron-donating groups), as the relative permittivity of the medium increases. The solvent effect on the carbonyl band components is illustrated in Figure 1 for compound **5**, assumed to be a prototype of derivatives **1** to **5**.

Table 3 lists the frequency shifts ($\Delta\nu_{\text{CO}}$) of each component of the carbonyl doublet of the title compounds **1** to **5** (Table 2) with respect to the corresponding carbonyl frequencies of the parent acetophenones **6** to **10**, in CCl_4 . The simultaneous presence of

-SEt and -SePh substituents bound to the same carbon atom causes a decrease of the frequencies of both components with respect to the corresponding values of the parent acetophenones by about $\Delta\nu_{\text{CO}}=-7\text{ cm}^{-1}$ for the component at higher frequencies and $\Delta\nu_{\text{CO}}=-17\text{ cm}^{-1}$ for the lower one.

Taking into account the inductive effect (-I) exerted by the SEt ($\sigma_{\text{I}} = 0.23$) and SePh [$\sigma_{\text{I}} = 0.13$] substituents [26], a positive carbonyl frequency shift can be expected. Therefore, the results suggest the existence of both electrostatic and orbital interactions operating in the different conformers of compounds **1** to **5**, which act by decreasing the carbonyl bond order and thus the experimental carbonyl stretching frequencies with respect to the values recorded for the corresponding parent compounds.

DFT calculations at the B3LYP/6-31+G(d,p) level were performed to determine the optimized geometries and vibrational frequencies of the minimum energy conformations of compounds **1** to **5**. The calculation results, summarized in Table 4, indicate the existence of three distinct conformations, c_1 , c_2 and c_3 . It can be seen that the α and α' dihedral angles of the conformers are quite similar in series **1** to **5**. The c_1 conformer is characterized by the proximity between C-S and the C=O groups ($\alpha \approx 37^\circ$) (*quasi-syn-periplanar* geometry), whereas the C-Se group is almost perpendicular to the C=O one (*syn-clinal* geometry) ($\alpha' \approx -85^\circ$). Compounds **4** and **5** present α dihedral angles that are ca. 15° larger than in compounds **1** to **3**. The c_2 conformer corresponds to the reverse situation, i.e. the C-S and the C=O groups are almost perpendicular to each other ($\alpha \approx 88^\circ$) and the C-Se group is closer to the C=O one ($\alpha' \approx -39^\circ$). Finally, the c_3 conformer presents both C-S and C-Se groups away from the C=O one, with α and α' dihedral angles of ca. -130° and ca. 100° , respectively (*anti-clinal* geometries). Figure 2 illustrates the computed molecular structures of the c_1 , c_2 and c_3 conformers of **3**, taken as a prototype for the series.

Table 4 shows that the c_2 conformers are the most stable for compounds **1** to **4**, whereas the relative stability of the c_1 ones increases on going from **1** ($E_{\text{rel}} = 1.44 \text{ kcal mol}^{-1}$; 4.7%) to **5** ($E_{\text{rel}} = 0.0 \text{ kcal mol}^{-1}$; 36.9%). It should be noted that in the latter case the two conformers have about the same energy. Finally, the c_3 conformer is the intermediate one for derivatives **1** to **3** and the least stable for derivatives **4** and **5**.

The analysis of the vibrational frequencies shows that the c_1 conformers have the highest carbonyl frequency in the series, and the c_2 and c_3 ones have almost similar values. Therefore, the less intense component of the carbonyl doublet at higher frequency in the IR spectrum in solution should correspond to the c_1 conformer, and the c_2 and c_3 conformers contribute to the more intense component at lower frequency (Table 2).

The sum of the molar fraction of the c_2 and c_3 conformers decreases from ca. 95% to 63% on going from compound **1** to **5** (Table 4), and is thus dependent on the nature of the 4'-substituent. Simultaneously, the molar fraction of the c_1 conformer increases in the same direction. This result is closely in line with the trend observed experimentally in the IR spectra in solvents of low and medium relative permittivity ($n\text{-C}_6\text{H}_{14}$, CCl_4 , CHCl_3 and CH_2Cl_2).

The slight influence of the solvent on the relative intensity of the components of the carbonyl doublet can be attributed to the similarity of the dipole moment of the three conformers (Table 4). Although they overestimate values, PCM *single-point* calculations performed for compounds **1** to **5** (Table 5) show a trend quite similar to that observed experimentally (IR) as the solvent polarity increases. In fact the c_1 conformer population increases when the 4' position of the title compounds bears electron-withdrawing substituents (**1** and **2**) and decreases in the opposite case (**4** and **5**). However, for 4'-hydrogen derivative no match was found between the experimental and

PCM trends. Additionally, the PCM results indicate that the c_2 conformer is always more stable than the c_3 one.

In Tables 6 and 7 are reported, respectively, the ChELPG charges and the interatomic distances of some selected atoms for compounds **1** to **5** at the B3LYP/6-31+G(d,p) level, and Table 8 shows selected NBO interactions for **1**, **3** and **5**, calculated at the same level to analyze the nature of the orbital interactions which stabilize the conformers [20].

In the phenacyl group there are three important orbital interactions: 1) the $\pi_{C25=C26(Ph)} \rightarrow \pi^*_{C2=O1}$ conjugation whose mean energy value for the c_1 , c_2 and c_3 conformers increases, going from 4'-electron-attracting (ca. 17 kcal mol⁻¹) (**1**) to 4'-hydrogen- (ca. 19 kcal mol⁻¹) (**3**) and to 4'-electron-donating (ca. 22 kcal mol⁻¹) (**5**) substituents; 2) the $LP_{O1} \rightarrow \sigma^*_{C2-C3}$ and $LP_{O1} \rightarrow \sigma^*_{C2-C25}$ through bond coupling interactions [27] at mean energy values almost constant in the series **1**, **3** and **5** for the three conformers, namely 21 kcal mol⁻¹ for c_1 , 20 kcal mol⁻¹ for c_2 and 20 kcal mol⁻¹ for c_3 .

Moreover, minor energy orbital interactions between $LP_{(S \text{ or } Se)} / \sigma^*_{(C-S, C-Se, C-C)}$ take place (see Table 8), as a consequence of the suitable values of δ , δ' , β , β' or γ dihedral angles (see Table 4). For instance, all the c_1 and c_3 conformers, whose δ dihedral angles range between 67° and 94°, show a significant $LP_{S5} \rightarrow \sigma^*_{C3-Se13}$ orbital interaction of about 10 kcal mol⁻¹. Conversely, the mean value 85° of the δ' dihedral angle for all the c_2 conformers is responsible for the weaker $LP_{Se13} \rightarrow \sigma^*_{C3-S5}$ orbital interaction of ca. 5 kcal mol⁻¹. Moreover, all the c_2 conformers, as well as the c_1 one for compound **5**, have favourable β dihedral angles (70°) that allow the additional weak $LP_{S5} \rightarrow \sigma^*_{C2-C3}$ stabilizing interaction (4 kcal mol⁻¹), whereas the values of the β' dihedral angles (64° to 103°) are responsible for the weaker $LP_{Se13} \rightarrow \sigma^*_{C2-C3}$ interactions (ca. 2.5 kcal mol⁻¹)

for the c_1 and c_3 conformers of **1** and **2** and for the c_3 one of **3**. Finally, the γ angle of 75° allows the $LP_{S5} \rightarrow \sigma^*_{C6-C9}$ interaction (4 kcal mol $^{-1}$) for the c_1 and c_3 conformers of **1** and **3** and for the c_3 one of **3**.

The Y-C-C=O fragments (Y= S or Se) show the orbital interactions $LP_Y \rightarrow \pi^*_{CO}$ (a), $\pi_{CO} \rightarrow \sigma^*_{C-Y}$ (b), $\sigma_{C-Y} \rightarrow \pi^*_{CO}$ (c) and $\pi^*_{CO} \rightarrow \sigma^*_{C-Y}$ (d), that are maximized as the α or α' torsional angles get closer to 90° . When the sulfur atom is involved, these interactions stabilize all the c_2 conformers to a greater extent, whereas in the case of the selenium atom the stabilization occurs exclusively for all the c_1 and c_3 ones. Both interactions (a) and (b) are weak, less than 3 kcal mol $^{-1}$ (Table 8). On the other hand, the hyperconjugative interaction (c) increases from about 5 kcal mol $^{-1}$ in the c_2 conformers for Y=S up to about 7 kcal mol $^{-1}$ in the c_1 and c_3 ones for Y=Se. A larger increase is observed for the unusual interaction (d) [28], from ca. 3.7 kcal mol $^{-1}$ (Y= S, c_2 conformers) to 8 kcal mol $^{-1}$ (Y=Se, c_1 and c_3 conformers).

Additionally, the NBO orbital mean energy data [29] for the c_1 , c_2 and c_3 conformers of derivatives **1**, **3** and **5** show that the $\sigma^*_{C3-Se13}$ orbital has a higher electron affinity of ca. 53 kcal mol $^{-1}$ with respect to the σ^*_{C3-S5} one, that the σ_{C3-S5} bond is more stable than the corresponding $\sigma_{C3-Se13}$ bond by ca. 51 kcal mol $^{-1}$ and that the LP_{S5} lone pair is slightly more stable relative to the LP_{Se13} lone pair by ca. 6.9 kcal mol $^{-1}$. These findings are in line with the stronger $\sigma_{C3-Se13} \rightarrow \pi^*_{CO}$ (≈ 8 kcal mol $^{-1}$) and $\pi^*_{CO} \rightarrow \sigma^*_{C3-Se13}$ (≈ 7 kcal mol $^{-1}$) orbital interactions for the c_1 and c_3 conformers for all derivatives, with respect to the corresponding $\sigma_{C3-S5} \rightarrow \pi^*_{CO}$ (≈ 5 kcal. mol $^{-1}$) and $\pi^*_{CO} \rightarrow \sigma^*_{C3-S5}$ (≈ 2.7 kcal mol $^{-1}$) calculated for the c_2 conformers. Furthermore, the delocalization energies between the lone pairs LP_Y and σ^*_{C-X} (X= S or Se; Y= Se or S) orbitals show that the $LP_{S5} \rightarrow \sigma^*_{C3-Se13}$ interaction (≈ 10 kcal mol $^{-1}$) for the c_1 and c_3 conformers of compounds **1**, **3** and **5** is about twice as high as the $LP_{Se13} \rightarrow \sigma^*_{C3-S5}$ one for the c_2 conformers.

Because of the small difference between the sulfur and selenium lone pair ionization energies, the $LP_{S5} \rightarrow \pi^*_{CO}$ (for the c_2 conformer) and the $LP_{Se13} \rightarrow \pi^*_{CO}$ interactions (for the c_1 and c_3 ones) have a comparable delocalization energy value of about 3 kcal mol⁻¹.

The carbonyl oxygen lone pair is also responsible for several weak orbital interactions in the energy range of 0.6 to 1.1 kcal mol⁻¹, i.e. with the ethylsulfanyl group [$LP_O \rightarrow \sigma^*_{S5-C6}$ for the c_1 conformers of **1** and **3**; $LP_O \rightarrow \sigma^*_{C3-S5}$ for the c_3 conformers of **1**, **3** and **5**; $LP_O \rightarrow \sigma^*_{C6-H7}$ (hydrogen bond) for the c_2 conformers of **1** and **5** and c_1 of **5**] and with the phenylselanyl group [$LP_O \rightarrow \sigma^*_{Se13-C14}$ for the c_2 conformers of **1**, **3** and **5**; $LP_O \rightarrow \sigma^*_{C28-H33}$ (hydrogen bond) for the c_3 conformers of **3** and **5**].

It should be pointed out that the sum of the orbital interaction energies (ΣE) of the c_1 , c_2 and c_3 conformers for **1**, **3** and **5** presented in Table 8 do not match the electronic energies reported in Table 4, which identify the c_2 conformers as the most stable for derivatives **1** to **4** and the second most stable for derivative **5**. Conversely, the (ΣE) values suggest that for compounds **1** and **3** the c_1 conformers are the most stable, followed by the c_3 and c_2 ones, whereas for compound **5** the c_3 becomes the most stable and c_1 and c_2 have almost the same stability.

The lesser stability of the c_1 conformer relative to the c_2 and c_3 ones may be interpreted through the O...S and O...Se short contact analysis. In fact, the small α dihedral angle in the c_1 conformers for **1** to **3** forces the negatively charged carbonyl oxygen [-0.38e] and sulfur [-0.30e] atoms to get closer, at a distance significantly shorter than the sum of the van der Waals (Σ_{vdW}) radii (Δl ca. -0.37Å). This yields a strong electrostatic repulsion that destabilizes mainly the c_1 conformers (5%-11%) with respect to the c_2 (53%-79%) and c_3 (13%-42%) ones. For derivatives **4** and **5**, the electron-donating effect of the 4'-substituents induces a more negative charge on the carbonyl oxygen atom [-0.40e]; thus, the pronounced coulombic repulsion between the $O^{\delta-} \dots S^{\delta-}$ atoms helps to enlarge the α

dihedral angle by ca. 15° , to increase the distance O...S and to reduce Δl to -0.13 \AA . This behaviour stabilizes the c_1 conformers (28%-37%) to a greater extent relative to the c_2 (35%-66%) and c_3 (6%-27%) ones. In fact, in agreement with the experimental data in CCl_4 (Table 2), a progressive increase of the population of the c_1 conformer can be observed on going from **1** to **5** (Table 4). Moreover, the larger repulsive field effect [24a] between the $\text{C}^{\delta+}=\text{O}^{\delta-}$ and $\text{C}^{\delta+}-\text{S}^{\delta-}$ dipoles exerted on the c_1 conformers of **1-3** with respect to **4** and **5** causes a major increase of the corresponding C=O bond orders and carbonyl frequencies. Additionally, the progressively more negative carbonyl frequency shift (-5 cm^{-1} to -9 cm^{-1}) on going from **2** to **5** in CCl_4 (Table 3) for the higher frequency doublet component, ascribed to the c_1 conformer, is in line with the progressive increase of the calculated dihedral angle α . It should be pointed out that the *quasi*-constant larger negative carbonyl frequency shift (ca. -17 cm^{-1}) found for the lower frequency carbonyl component in the whole series further supports its assignment to the c_2 and c_3 conformers, for which the calculated carbonyl frequencies are almost coincident.

For the most stable c_2 conformer for **1** to **4**, the O...Se interatomic distance is shorter than the $\sum \text{vdW}$ radii and the value of Δl (about -0.42 \AA) indicates that the two atoms are closer than the O...S ones in the c_1 conformer. Nevertheless, because of the significantly smaller negative charge at the selenium atom [ca. -0.11e] with respect to that at the sulfur one [ca. -0.33e], the electrostatic repulsion between the $\text{O}^{\delta-}\dots\text{Se}^{\delta-}$ atoms is weaker than that acting in the c_1 conformer between the $\text{O}^{\delta-}\dots\text{S}^{\delta-}$ atoms. Therefore the stability of this conformer is slightly affected by this electrostatic interaction and mainly determined by the sum of the orbital interactions. Additionally, the $\text{O}_1^{\delta-}\dots\text{H}_{7(\text{Et})}^{\delta+}$ short contact (Δl ca. -0.27) acts to stabilize electrostatically the c_2 conformer for all derivatives.

The geometry of the c_3 conformers for **1** to **5** (Table 4) indicates that both the sulfur and the selenium atoms are far away from the carbonyl oxygen atom. Therefore, the O...S

and O...Se interatomic distances are larger than the \sum vdW radii and do not affect the stability of this conformation. On the other hand, the S...Se interatomic distance is the smallest one with respect to the \sum vdW radii ($\Delta l = -0.49 \text{ \AA}$) in comparison with the same contact for the c_1 and c_2 conformers. Thus, the electrostatic repulsion between the negatively charged S [ca. $-0.34e$] and Se [ca. $-0.24e$] atoms seems to be responsible for the low stability of the c_3 conformer, being the second stablest for **1** to **3** and the least stable one for **4** and **5**. Furthermore, the c_3 conformers for **3** and **5** are electrostatically stabilized through the $O_1^{\delta-} \dots H_{16(o-Ph)}^{\delta+}$ short contact (Δl ca. -0.20 \AA).

The balance of the orbital and electrostatic interactions indicates that the c_1 conformer is the least stable for derivatives **1** to **3** because of a strong repulsion between the negatively charged carbonyl oxygen and the sulfur atoms. As this repulsion weakens, the c_1 conformer becomes more stable, as in **4** and **5** where it comes to be, respectively, the second and first stablest rotamer. The c_2 conformer, in spite of the less intense orbital interactions, is more stable for **1** to **4** and has almost the same stability as the c_1 one for **5** as a consequence of the very weak electrostatic repulsion between the carbonyl oxygen and the slightly negatively charged selenium atom.

Taking into account that the sum of all the relevant orbital interaction energies for the c_1 , c_2 and c_3 conformers for **1**, **3** and **5** (Table 8) is almost constant with an average value of $100 \text{ kcal mol}^{-1}$, it may be concluded that the computed trend of stability (Table 5) of the referred conformers for derivatives **1** to **5** is mainly determined by the presence of short contacts between the carbonyl oxygen, sulfur and selenium atoms and their atomic charges.

Conclusions

The preferred conformations of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfanyl)-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 (for **1** to **5**) along with the NBO analysis (for **1**, **3**, **5**).

The DFT calculations indicated the existence of three stable conformations, c_1 , c_2 and c_3 , for **1** to **5**. The c_1 conformer displays a *quasi-syn-periplanar* geometry between the C-S and C=O groups, whereas the C-Se and C=O groups display a *syn-clinal* geometry. The c_2 conformer shows the C-S and C=O groups in a *syn-clinal* geometry, whereas the C-Se and C=O groups assume a *quasi-syn-periplanar* geometry. Finally, the c_3 conformer presents both C-S and C-Se groups away from the C=O one in the *anti-clinal* geometry.

The comparison between the experimental IR spectra and the computed data (gas phase) for **1** to **5** allows us to assign the less intense component of the carbonyl doublet, at higher frequency in the IR spectrum in solution, to the c_1 conformer, and the more intense at lower frequency to both the c_2 and c_3 ones. The sum of the molar fraction of the c_2 and c_3 conformers decreases from 95% to 63% on going from **1** to **5** (in gas phase), depending on the nature of the 4'-substituent. This trend is in agreement with the PCM calculations and the IR data for the majority of the solvents, thus proving that the calculations reproduce the experimental results for **1** to **5**. The slight influence of the increasing polarity of the solvent on the relative intensity of the carbonyl doublet components can be ascribed to the similarity of the dipole moment of the three conformers for each compound. In fact, the PCM calculations show a quite similar trend to the IR data as the solvent polarity increases, i.e. an increase of the c_1 conformer population relative to the sum of the c_2 and c_3 ones for **1** and **2** and a decrease of the c_1 relative population for **4** and **5**.

The NBO analysis shows that the c_1 , c_2 , and c_3 conformers for **1**, **3** and **5** are mainly stabilized by the following relevant orbital interactions: $\pi_{C25=C26(Ph)} \rightarrow \pi^*_{C2=O1}$

(conjugation), $LP_{O1} \rightarrow \sigma^*_{C2-C3}$ and $LP_{O1} \rightarrow \sigma^*_{C2-C25}$ (through bond coupling). Likewise, a series of medium energy interactions that occurs for suitable values of some dihedral angles, for instance $LP_Y/\sigma^*_{(C-X, C-C)}$, $LP_Y \rightarrow \pi^*_{CO}$, $\pi_{CO} \rightarrow \sigma^*_{C-X}$, $\sigma_{C-X} \rightarrow \pi^*_{CO}$, $\pi^*_{CO} \rightarrow \sigma^*_{C-X}$ (Y= S or Se, X= Se or S), along with some weaker orbital interactions as $LP_O \rightarrow \sigma^*_{X-C}$, $LP_O \rightarrow \sigma^*_{C-H}$ (hydrogen bond) helps to a lesser extent to stabilize the three conformers.

It should be pointed out that the sum of the selected orbital delocalization energies for the c_1 , c_2 , and c_3 conformers of **1**, **3** and **5** does not match the computed stability order. As a matter of fact, the geometry of the c_1 conformers for **1** to **3**, particularly the small value of the α dihedral angle, enables a strong electrostatic repulsion between the negatively charged carbonyl oxygen and sulfur atoms that destabilize to a greater extent the c_1 rotamers with respect to the c_2 and c_3 ones. When this repulsion is minimized for the enlarged value of the α dihedral angle and the related increase of the O...S atomic distance, as in compounds **4** and **5**, the relative population of the c_1 conformer increases.

The higher carbonyl stretching frequency of the c_1 conformer in compounds **1** to **3** with respect to **4** and **5** is strictly related to the increase of the C=O bond order caused by the repulsive field effect between the $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}-S^{\delta-}$ dipoles, larger in **1** to **3** than in **4** and **5**. This trend is in line with the progressively more negative carbonyl frequency shifts ($\Delta\nu_{CO}$), in CCl_4 , for the higher frequency component of the carbonyl doublet going from **2** to **5**.

The geometry of the c_2 conformer allows an electrostatic repulsion between the $O^{\delta-}...Se^{\delta-}$ atoms. Nevertheless, this destabilizing factor has negligible effects on the conformer stability, being weaker than the analogous $O^{\delta-}...S^{\delta-}$ repulsion in the c_1 conformer. Conversely, the short contact between the $S^{\delta-}...Se^{\delta-}$ atoms in the c_3 conformer is probably responsible for its low stability in all compounds.

Finally, it may be stated that the computed order of stability of the three conformers for the series **1** to **5** depends mainly on relevant short contacts and repulsions between the negatively charged carbonyl oxygen, sulfur and selenium atoms.

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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: *n*-hexane (a), carbon tetrachloride [fundamental(b) and first overtone (c)], chloroform (d), dichloromethane (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.

Scheme 1. Atoms labelling of 4'-substituted 2-(phenylselanyl)-2-ethylsulfanyl-acetophenones.