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Stereochemical and electronic interaction studies of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl)-acetophenones

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Abstract

Infrared carbonyl band analysis, supported by B3LYP/6-31+G(d,p) and single-point PCM calculations, natural bond orbital (NBO) analysis and X-ray diffraction were carried out for the diastereoisomers of a selection of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl)-acetophenones bearing the substituents NO_2 **1a**, Br **2a**, H **3a**, Me **4a** and OMe **5a** for the C_RS_R/C_SS_S enantiomeric pair and Br **2b** and Me **4b** for the C_RS_S/C_SS_R pair. For the gas phase, the theoretical data indicated the existence of three stable conformations for the C_RS_R series and only two for the C_RS_S series. For the whole C_RS_R series **1a–5a**, the most stable c_1 and the intermediate c_2 conformers have similar ν_{CO} frequencies, lowered by about 20 cm^{-1} with respect to the less stable c_3. Likewise, the less stable c_2 conformers for the C_RS_S series **2b** and **4b** exhibit the higher ν_{CO} frequencies. The single-point PCM calculations show that the relative abundance of both the less stable c_3 C_RS_R and c_2 C_RS_S conformers, in the gas phase, progressively increases as the dielectric constant of the media increases. The balance between the electrostatic and orbital interactions controls the calculated stability for compounds **1a–5a** (C_RS_R/ C_SS_S), along with the ν_{CO} frequency order of the three conformers. Conversely, the larger stabilisation of the c_1 conformer with respect to the c_2 one in the **2b** and **4b** (C_RS_S/C_SS_R) compounds depends mainly on the orbital interactions $LP_{(S)} \rightarrow \sigma^*_{C-Se}$, $LP_{O(S-O)} \rightarrow \sigma^*_{C-H(CH2Me)}$ and $LP_{O(S-O)} \rightarrow \sigma^*_{C-H(o\text{-}PhSe)}$, which are present uniquely in the former conformer. The X-ray single crystal analysis indicates that the major component of **3a** (C_RS_R) adopts the same geometry as the c_2 conformer in the gas phase. Similarly, the solid-state structure of **2b** matches that of the c_2 conformer. The molecules in the solid are linked in centrosymmetrical pairs through $\pi\ldots\pi$ interactions between Se-bound phenyl rings, along with phenyl-C–H$\ldots$O(carbonyl) and phenyl-C–H$\ldots$O(sulphinyl) interactions.

1. Introduction

Previous conformational analysis performed on some β-carbonyl-sulfoxides $XC(O)CH_2S(O)R$ using (IR, ^{13}C NMR, UV and UPS) spectroscopic techniques, X-ray diffraction (XRD) and theoretical calculations have shown that the *gauche* conformer is the most stable for α-sulfinyl-ketones [1–3], α-sulfinyl-thioesters [4] and sulfinyl-esters [5], while the *cis* conformer is predominant for the α-sulfinylacetophenones and α-sulfinylamides [6–10]. The stabilisation of the *gauche* conformers for these compounds has been ascribed to the $\pi^*_{CO}/\sigma_{C\text{-}S}$ and, to a minor extent, the $\pi_{CO}/\sigma^*_{C\text{-}S}$ orbital interactions, while the larger stabilisation of the *cis* conformers has been attributed to the π_{Ph}/π^*_{CO} and n_N/π^*_{CO} conjugations, which originate the strong electrostatic $[S^{\delta+}=O^{\delta-}$ …. $C^{\delta+}=O^{\delta-}]$ and $n_{O(CO)}/\sigma^*_{SO}$ charge transfer interactions.

Additionally, an *ab initio* and XRD study of the bis-thio-acetophenone: α-methylthio-α-methylsulfinyl-acetophenone [6] indicated that in the gas and solid phases, the SMe group adopts the *gauche* geometry with respect to the C=O bond (dihedral angle *ca.* 90–93°), while the SOMe group assumes the *quasi-cis* geometry (dihedral angle 31–35°). The stabilisation of these conformations was ascribed to the occurrence of the hyperconjugative $\sigma_{C\text{-}SR}/\pi^*_{CO}$ interaction that, by increasing the negative charge at the carbonyl oxygen atom favours the $O^{\delta-}_{CO}{\to}S^{\delta+}_{(SO)}$ electrostatic and charge transfer interactions.

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

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the α position both the phenylseleno and ethylsulfinyl groups, as both should compete for the *syn-clinal* (*gauche*) and *syn-periplanar* geometries with respect to the carbonyl group. In particular, the 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl)-acetophenones **1**–**5** (Scheme 1) were chosen, taking into account the fact that the orbital and electrostatic interactions that stabilise the conformers might be affected by changes in the conjugation involving the 4'-substituents.

Finally, following our continuous search for compounds with anti-inflammatory activity [12] our previous studies of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones [13] prompted us to determine the crystal and molecular structure of the related compounds 2-(ethanesulfinyl)-1-phenyl-2-(phenylselanyl)ethan-1-ones to be used in molecular docking studies to ascertain the possibility of being a COX-2 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-(ethylsulfinyl)-acetophenones **1** to **5** are new compounds and were obtained following a literature procedure [14]. A THF solution of 2-(ethylsulfinyl)-(4'-substituted)-acetophenone, prepared as previously described [15], was added to a solution of LDA in THF at 195 K. After 20 min, a solution of phenylselanyl bromide in THF was added dropwise to the enolate solution. After the reaction mixture reached room temperature (*ca*. 3 h), water was added and extraction with chloroform was performed. The organic layer was washed with diluted HCl and water, and dried over anhydrous magnesium sulphate. After evaporation of the solvent, the crude solid was purified through flash chromatography with a 1:1 solution

of hexane and ethyl acetate. As the title compounds present two stereogenic centres, *i.e.* the α-methine carbon (C_R and C_S) and the sulfinyl sulfur atoms (S_R and S_S) (Scheme 1), and the synthesis was performed without asymmetric induction, a racemic mixture of two pairs of diastereomers, [C_RS_S/C_SS_R] and [C_RS_R/C_SS_S], was obtained. The ^{1}H NMR spectrum of the crude product indicated that the relative abundance of the C_RS_R/C_SS_S and C_RS_S/C_SS_R diastereomers changes for each 4'-substituent and that the diastereomer corresponding to the higher field double quartet pairs (hydrogens 7 and 8 from Scheme 1) always predominates, as shown in Fig. 1. This diastereomer was isolated by solubilisation in chloroform, followed by the addition of a small amount of n-hexane while maintaining the system at low temperature (around 280 K) until crystal formation occurred. These crystals were collected, washed and dried. For the 4'-bromo and 4'-methyl derivatives, it was also possible to recover the other pure diastereomer with a second selective crystallisation. The purity of the crystallised products (compounds **1a–4a**, **2b** and **4b**) was confirmed by ^{1}H NMR. Recrystallisation at low temperature in carbon tetrachloride gave pure crystals of compound **5a**.

XRD analysis of compound **2b** [16] indicated that the lower field ^{1}H NMR double quartet pairs (Fig. 1) should be unambiguously assigned to the C_SS_R/C_RS_S diastereoisomer. Consequently, the more intense signals at higher fields in the ^{1}H NMR spectra of compounds **1–5** correspond to the C_RS_R/C_SS_S diastereoisomer. In addition, the ^{1}H NMR analysis of the **4a** and **4b** methyl derivatives reveals that each C_RS_R/C_SS_S and C_SS_R/C_RS_S diastereomeric pair was purified at about 95% (Fig. 2). Suitable crystals for X-ray analysis for **3a** were obtained by vapour diffusion from chloroform/n-hexane at 283 K. The ^{1}H and ^{13}C NMR data and the elemental analysis for compounds **1–5** are presented in Tables 1 and 2.

2.2. IR measurements

The IR spectra for the fundamental carbonyl region (1800–1600 cm^{-1}) were recorded using a Michelson Bomem MB100 FTIR spectrometer with a 1.0 cm^{-1} resolution in carbon tetrachloride, chloroform, dichloromethane and acetonitrile solutions (1.0 x 10^{-2} mol dm^{-3}) using a 0.519 mm sodium chloride cell. The spectra of the carbonyl first overtone (3600–3100 cm^{-1}) were collected in carbon tetrachloride and dichloromethane solutions with a 1.00 cm quartz cell. The overlapping carbonyl bands (fundamental and first overtones) were deconvoluted by means of the Grams/32 curve fitting program, version 4.04 [17]. 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

^{1}H 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/dm^{3} solutions in CDCl$_3$. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS as the internal standard.

2.4. X-ray measurements

X-ray crystallographic data were collected at 100 K on an Agilent SuperNova diffractometer (Dual source, Cu at zero) fitted with an Atlas detector using graphite-monochromated Cu Kα radiation (λ = 1.54184 Å). The data were processed with CrysAlisPro [18]. The structure was solved by direct methods with SHEXLS97 [19] and

refined by full-matrix least-squares on F^2 with SHELXL-2014 [20]. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed and refined using the riding model approximation with U_{iso} (H) = 1.2–1.5 U_{eq} (C). Towards the end of the refinement, additional electron density peaks were apparent. These were modelled as an independent molecule. To be consistent with the ^{1}H NMR results (see section 2.1), the major component of the disorder was refined with a site occupancy equal to 0.95. Having a small occupancy, constraints and restraints were introduced for the minor component to ensure a stable refinement. Thus, the anisotropic displacement parameters (ADPs) of the atoms were set to those of the major component. The ADPs of the carbon atoms were restrained to be nearly isotropic. Further, the atoms of the Se–C(phenyl) and C–C(phenyl) groups were restrained to be nearly planar. The aliphatic C–C bond distances were restrained with 1.50±0.01 Å and the C=O double-bond distance was set to 1.25±0.01 Å. Finally, for the Se13/S5 and Se31/S5' atoms, pairs of bond distances were restrained to be within 0.01 Å of each other. The key crystallographic data are given in Table 3. The programs ORTEP-3 for Windows [21], PLATON [22], DIAMOND [23] and QMol [24] were also used in the analysis.

CCDC 1475836 contains the supplementary crystallographic data for this study. 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 [25] software for the $C_R S_R$ and $C_R S_S$ diastereomers for compounds **1a–5a** and **2b** and **4b,** respectively. The obtained conformer geometries were used as initial inputs for all

calculations performed at 298 K with the Gaussian package programs (G03-E01) [26] with a hybrid Hartree-Fock density functional B3LYP method [27(a),27(b),27(c)] and the 6-31+G(d,p) basis set [28]. Full geometry optimisations 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 energy corrections. To estimate the solvation effects on the relative stability of the most relevant conformers, single-point calculations were conducted on the optimised structures using the polarisable continuum model (PCM) [29(a),29(b)]. The NBO 3.1 program [30] was used as implemented in the Gaussian 03 package and the reported NBO delocalisation energies (E2) were those given by the second-order perturbation theory. The partial atomic charges were calculated using Natural Population Analysis (NPA) [30].

3. Results and discussion

3.1. Enantiomeric C_RS_R/C_SS_S diastereomer pair

The stretching frequencies of the fundamental and first overtone, as well as the absorbance percentage of the analytically resolved carbonyl band of (C_RS_R/C_SS_S) 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl) acetophenones (**1a–5a**) in solvents of increasing relative permittivity [31] are reported in Table 4. The low signal to noise ratio precludes the characterisation of the band profile in the first overtone regions of **1a** (in CCl_4) and **3a** (in CH_2Cl_2). The spectra in the carbonyl fundamental transition region show two components in acetonitrile for all compounds. The intensity of the low frequency doublet component progressively increases as the solvent polarity decreases until it becomes a singlet in compounds **1a** and **3a** in the low relative permittivity solvents chloroform and carbon tetrachloride, and the main doublet component (*ca.*

90%) for compounds **2a**, **4a** and **5a** in CCl$_4$. The observed trend is illustrated in Fig. 3 for compound **2a**, chosen as being representative of the series. This trend seems to be mainly determined by the solvent polarity rather than by a 4'-substituent effect related to the different nature of the groups involved, going from the electron-withdrawing nitro group (**1a**) to the electron-donating OMe one (**5a**).

The carbonyl first overtone bands, recorded in CCl$_4$ and CH$_2$Cl$_2$, match exactly the behaviour of the corresponding bands in the fundamental and, when a doublet is present, for **1a**, **2a**, **4a** and **5a**, the two components emerge with relative intensities almost equivalent to those previously found (Table 4). Moreover, all the resolved peaks along with the single peak of **3a** (in CCl$_4$) have frequencies twice that of the fundamental minus twice the mechanical anharmonicity of 20 ± 2 cm^{-1} [32]. The matching of the carbonyl band profiles in the two frequency regions suggests the presence of at least two conformers for the referred compounds, and at least one for **3a** (in CCl$_4$), ruling out the existence of any vibrational effects in the fundamental transition of the ν_{CO} mode [33(a),33(b)].

Aiming 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 the C$_R$S$_R$ diastereomer of compounds **1a**–**5a.** The calculation results, summarised in Table 5, indicate the existence of three distinct conformations, classified in order of decreasing stability for the whole series as c_1 (82–92%), c_2 (7–17%) and c_3 (< 1%). The dihedral angles α and α' formed by the carbonyl and the C-S and C-Se groups, respectively, are almost equivalent for all the 4'-derivatives and compel the c_1 conformer to assume *syn-clinal* ($\alpha \approx 90°$) and *syn-periplanar* geometries ($\alpha' \approx -30°$), respectively. Conversely, for both the c_2 and c_3 conformers, the C–S/C=O groups are nearly coplanar ($\alpha \approx 30°$), while the C–Se/C=O groups are almost perpendicular ($\alpha' \approx -$

90°). The major difference between the two conformers in each series consists of the different orientation of both the sulfinyl and the phenyl groups with respect to the carbonyl one, revealed, respectively, by the δ and γ' dihedral angles. In particular, the c_2 conformer displays a *quasi-anti* geometry (δ *ca.* 164° and γ' *ca.* 130°), while the c_3 conformer presents a *quasi-syn* orientation (δ *ca.* -94° and γ' *ca.* -119°). The computed molecular structures of the three conformers for compound **3a**, representative of the whole series, are shown in Fig. 4.

Additionally, it should be noted that the 4'-substituents hardly affect the geometry of each conformer in the series, with the exception of the rotation of the ethyl group indicated by the γ dihedral angle which varies from about 171° in compounds **1a**–**4a** to 61° (c_2) and -75° (c_3) in the **5a** derivative.

The least stable c_3 conformer exhibits the highest ν_{CO} frequency, while those of the c_1 and c_2 conformers differ by less than 3 cm^{-1}. As expected, the ν_{CO} frequency of all conformers increases progressively in the series **1a**–**5a**, going from the electron-donor methoxy derivative **5a** to the electron-attracting nitro derivative **1a**. Therefore, in line with the experimental findings, the more intense component at the lower frequency of the carbonyl doublet in solution may be ascribed to both the c_1 and c_2 conformers, and the less intense higher frequency one can be ascribed to the less stable c_3 conformer (Table 4). PCM single-point calculations performed for compounds **1a**–**5a** (Table 6) confirm these assignments. In fact, the sum of the relative abundances of the most stable c_1 and c_2 conformers decreases progressively as the solvent polarity increases and concomitantly the population of the c_3 conformer significantly increases. An important role in the observed larger solvation effect on the c_3 conformer with respect to the c_1 and c_2 ones seems to be played by the opposite geometry assumed by the two $C^{\delta+}=O^{\delta-}$ and $S^{\delta+}=O^{\delta-}$ dipoles, namely *syn* in the former conformer and *anti* in the latter ones. As a

matter of fact, the *syn* orientation forces the two dipoles to be closer, thus leading to a larger local dipole moment. Moreover, the larger Repulsive Field Effect (RFE) [33(a)] between the two dipoles in the c_3 conformer, with respect to the c_1 and c_2 ones, increases its carbonyl bond order and consequently its ν_{CO} frequency.

In order to determine the nature of the orbital interactions that affect the stability of the different conformers of compounds **1a**, **3a** and **5a**, some selected NBO interactions, NPA charges and interatomic distances, calculated at the B3LYP/6-31+G(d,p) level [31], are reported in Tables 7, 8 and 9, respectively.

The strongest interactions acting on the phenacyl group are the $\pi_{C25C26} \rightarrow \pi^*_{C2O1}$ conjugation and the $LP_{O1} \rightarrow \sigma^*_{C2C3}$ and $LP_{O1} \rightarrow \sigma^*_{C2C25}$ through bond coupling interactions [34]. For all the conformers in the whole series, the latter interactions are almost constant (*ca.* 20 kcal mol^{-1}), while the former increases progressively going from the 4'-electron-attracting nitro derivative **1a** (*ca.* 18 kcal mol^{-1}) to the 4'-electron-donating methoxy derivative (*ca.* 23 kcal mol^{-1}).

The suitable ϕ' torsion angles for the c_1 (*ca.* 78°) and c_3 conformers (*ca.* -88°) allow the occurrence of the $LP_{Se13} \rightarrow \sigma^*_{C3S5}$ interaction (*ca.* 6 kcal mol^{-1}), which is weakened to *ca.* 3.5 kcal mol^{-1} in the c_2 conformer. In addition, the favourable ϕ angle (*ca.* -77.5°) gives rise to the $LP_{S5} \rightarrow \sigma^*_{C3Se13}$ interaction (3.4 kcal mol^{-1}) uniquely in the c_3 conformer.

The Y-C-C=O fragments (Y = S or Se) exhibit four additional orbital interactions that are maximised as the α or α' torsional angles approach 90°, that is the $LP_Y \rightarrow \pi^*_{CO}$, $\pi_{CO} \rightarrow \sigma^*_{C-Y}$ and $\sigma_{C-Y} \rightarrow \pi^*_{CO}$ interactions, as well as the unusual $\pi^*_{CO} \rightarrow \sigma^*_{C-Y}$ interaction [35]. Therefore, as suggested by the conformer geometries in Table 5 and confirmed by the NBO energies in Table 7, these interactions almost exclusively stabilise the c_1 conformer when the sulfur atom is involved (α of around 90° for all

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derivatives), and solely the c_2 and c_3 conformers as concerns the selenium fragment (α'
of around -90° for the whole series **1a**–**5a**).

The suitable geometry of the c_1 conformers leads to contacts shorter than the sum of
the van der Waals (ΣvdW) radii between the oppositely charged $O^{\delta-}_{(35)SO}$ and $H^{\delta+}_{(27)o\text{-}Ph(CO)}$ atoms, as well as the $O^{\delta-}_{(1)CO}$ and $H^{\delta+}_{(7)CH2(Et)}$ atoms (Tables 8 and 9), which
contribute electrostatically to their stabilisation. Moreover, the short distance
$O_{(35)}\ldots H_{(27)}$ is also responsible for the considerable $LP_{O35}\rightarrow \sigma^*_{C26H27}$ stabilising orbital
interaction (hydrogen bond) (mean energy of *ca.* 3.0 kcal mol^{-1}). Analogously, the
proper values of the δ and γ' dihedral angles in the c_2 and c_3 conformers allow the
contacts, shorter than the ΣvdW radii, between the negative $O_{(35)SO}$ and positive $H_{(16)o\text{-}PhSe}$ atoms to give raise to the $LP_{O35}\rightarrow \sigma^*_{C15H16}$ stabilising orbital interactions (hydrogen
bonds). These hydrogen bonds in the molecular structure of the c_1, c_2 and c_3 conformers
of the representative compound **2a** are illustrated in Fig. 4. In addition, the c_1 and c_3
conformers are slightly stabilised by the weak electrostatic interactions originated by the
contacts $Se^{\delta-}_{(13)\ldots} H^{\delta+}_{(7)CH2(Et)}$ close to the ΣvdW radii, as well as by the related weak
$LP_{Se13}\rightarrow \sigma^*_{C6H7}$ orbital interaction.

Similarly to the 2-sulfinylacetophenones [8] in the geometries of the c_2 (δ *ca.* 164°)
and c_3 (δ *ca.* -94°) conformers, the negatively charged carbonyl oxygen and positive
sulfinyl sulfur atoms, separated by intramolecular contacts shorter than the ΣvdW radii,
are responsible for an electrostatic stabilising interaction that is stronger in the c_3
conformers. It is interesting to note that the *anti-periplanar* configuration of the sulfinyl
sulfur atom with respect to the carbonyl group evidenced in the c_2 conformer favours
the weak $LP_{O1}\rightarrow \sigma^*_{S5O35}$ charge transfer interaction, which is absent in the c_3 conformer.

Additional stabilising electrostatic and charge transfer interactions caused by short
contacts between oppositely charged atoms take place in the c_1 conformers, as a

consequence of the *quasi-syn-periplanar* orientation of the $C^{\delta+}=O^{\delta-}$ and $C^{\delta-}-Se^{\delta+}$ groups, along with the *quasi-anti-periplanar* geometry of the C=O and Se-C$_{Ph}$ groups (β' *ca.* -156°) and to a lesser extent by the $O^{\delta-}_{(35)SO}....C^{\delta+}_{(2)CO}$ contact with a distance slightly larger than the ΣvdW radii. Moreover, the *quasi-syn-periplanar* orientation is also responsible for the weak $LP_{O1} \rightarrow \sigma^*_{Se13C14}$ orbital interaction.

As previously discussed, the repulsion between the $C^{\delta+}=O^{\delta-}_{(1)}$ and $S^{\delta+}=O^{\delta-}_{(35)}$ dipoles is significantly larger in the c_3 conformers, favoured by their *syn* orientation, opposite to the *anti* geometry assumed by the c_1 and c_2 conformers. Therefore, the sizable RFE between the two dipoles should destabilise, to a greater extent, the c_3 conformers, thus increasing the carbonyl bond order and consequently the ν_{CO} frequencies. Both the computed and experimental findings fully support this assertion as the carbonyl frequencies of the c_3 conformers were found to be higher than those of the c_1 and c_2 conformers by *ca.* 20 cm^{-1} (theoretical values) and *ca.* 15 cm^{-1} (experimental values).

The sum of the NBO orbital interactions (ΣE) for compounds **1a**, **3a** and **5a** indicates that the c_3 conformer should be the most stable by *ca.* 93.7 kcal mol^{-1}, followed by the c_1 (*ca.* 90.4 kcal mol^{-1}) and c_2 (*ca.* 88.1 kcal mol^{-1}) conformers. Moreover, the sum of the NBO energies increases progressively for each conformer, going from electro-attracting (**1a**) to hydrogen (**3a**) to electron-donating (**5a**) substituents.

Conversely, as noted above, the coulombic repulsion between the $C^{\delta+}=O^{\delta-}$ and $S^{\delta+}=O^{\delta-}$ dipoles significantly destabilises the c_3 conformer with respect to the c_1 and c_2 ones. Therefore, it is reasonable to infer that this effect likely prevails over the sum of NBO orbital interactions to determine the lowest computed stability of the c_3 conformer. Alternatively, the c_1 conformer is more stable than the c_2 one by a mean value of *ca.* 2.3 kcal mol^{-1}. It should be stated that this value is in agreement with the computed larger stabilisation of the c_1 conformer with respect to the c_2 conformer (Table 5). This trend

may be attributed mainly to both the large coulombic stabilisation between $O^{\delta-}_{CO}\ldots Se^{\delta+}$ atoms and the $LP_{O1} \rightarrow \sigma^*_{Se13C14}$ orbital interaction. Therefore, the computed order of stability of the three conformers follows from a balance of electrostatic and orbital interactions.

Crystals of **3a** were resolved as a whole molecule disorder model. The molecule of the major component of the disorder, with a site occupancy = 0.95, is illustrated in Fig. 5(a), and that of the minor component is in the Supplementary Materials as Fig. S1. An overlay diagram of the two components of the disorder is shown in Fig. 5(b). From this, it is evident that the major difference between the molecules is related to the chirality of the sulfinyl-S5/S5' atoms. Minor conformational differences are apparent, as seen in the dihedral angle between the two aromatic rings of 3.14(15)° (major component) and 9.1(12)° (minor). The large standard uncertainty for the minor component notwithstanding, this difference is consistent with a greater deviation from a parallel disposition of the rings in the latter. The other difference relates to the relative orientation of the terminal ethyl groups, as seen in the C3–S5–C6–C9 torsion angles of 175.2(2) and -141(7)° for the major and minor components, respectively.

X-ray analysis of **3a** indicates that this compound assumes, in the solid state, a conformation where the geometry is close to that of the c_2 conformer found in the gas phase, as evidenced by the almost coincident values of the torsional α-ϕ, α' angles except for β'-γ' which differ significantly in the solid (Table 5). In fact, in the gas phase, the sulfinyl and phenyl groups display a *quasi-syn-periplanar* geometry, while in the crystal, they lie in the opposite direction. It should be noted that the single molecule in the solid is stabilised by the same intramolecular attractive electrostatic interactions that occur in the gas phase between the oppositely charged carbonyl oxygen and sulfinyl

sulfur atoms, connected by a distance shorter than the ΣvdW radii ($\Delta l = 0.43$ Å), but no longer than the $O^{\delta-}\ldots H^{\delta+}$ contacts (Table 9).

In order to obtain the larger energy gain, the molecular packing (Fig. 6), defined by the major component of the disorder, features readily identifiable C–H…O, C–H…S, $\pi\ldots\pi$ and Se…π interactions that cooperate to stabilise the three-dimensional structure. The most prominent interactions are the tight methine-C-H…O(sulfinyl) interactions that lead to centrosymmetric, eight-membered $\{\ldots OSCH\}_2$ synthons. Dimeric aggregates are connected by phenyl-C–H…O(carbonyl), phenyl-C–H…O(sulfinyl) and $\pi\ldots\pi$ interactions, with the latter being between centrosymmetric related Se-bound phenyl rings. Geometrical details are given in Table 10. In addition, a close Se(lp)…π(phenyl) contact is noted; such interactions and the supramolecular aggregates they sustain have been reviewed recently [36]. The Se…ring centroid separation is 3.72 Å, so the contact in **3** is most likely an example of a semi-localised Se(lp)…π(phenyl) contact as the Se atom is closer to the C19^i [3.399(3) Å] and C21^i [3.516(3) Å] atoms, rather than to the centroid (a delocalised interaction).

3.2. Enantiomeric C_RS_S/C_SS_R diastereomer pair

The relevant experimental IR data for the Br (**2b**) and Me derivatives (**4b**) are collected in Table 11, to compare with the analogous Table 4 for the C_RS_R/C_SS_S diastereomer.

The carbonyl stretching band shows two components in the non-polar solvent carbon tetrachloride for both compounds, with the low frequency one being the most prominent. Its relative intensity decreases at different extents for both derivatives as the solvent polarity increases, until it vanishes for compound **2b** in acetonitrile, as evidenced in Figs. 7 and 8 for **2b** and **4b,** respectively.

The carbonyl first overtone region shows two components for **4b** in CCl_4 and for **2b** in CH_2Cl_2, at frequencies twice those of the fundamental minus twice the mechanical anharmonicity of *ca*. 20 cm^{-1} [32], and relative intensities that match those of the corresponding fundamental ones. These findings, in agreement with the results previously described for the C_RS_R/C_SS_S diastereomer, indicate the existence of at least two conformers and exclude the occurrence of any vibrational effect [33(a),33(b)].

The B3LYP/ 6-31G+(d,p) calculation results, summarised in Table 12, indicate, at variance with those performed for the enantiomeric pair C_RS_R/C_SS_S, the existence in the gas phase of only two *cis* conformers. For both the **2b** and **4b** compounds, the c_1 conformer is the most stable and the less polar and, moreover, presents the lowest ν_{CO} frequency. All the dihedral angles of the c_1 conformers assume quite similar values for both derivatives. The same occurs for the c_2 conformers, with the significant exception of the γ torsion angle, related to the rotation of the ethyl group, that changes from about 163.7° in **2b** to -59.8° in **4b**.

Moreover, the α dihedral angles, as well as the α' ones, are almost coincident for all the conformers in all compounds. This implies that the carbonyl group in the c_1 and c_2 conformers of both derivatives adopts a *quasi-syn-periplanar* geometry with respect to the C-S group (α ≈ 39°) and a *syn-clinal* orientation with respect to the C-Se one (α' ≈ 90°). On the contrary, the carbonyl and sulfinyl groups have opposite geometries, that is *anti-periplanar* (δ ≈ 171°) in the c_1 conformers and *syn-clinal* (δ ≈ 69°) in the c_2 ones. The computed molecular structures of the two stable conformers are shown in Fig. 9 for **2b** and are representative of both compounds.

As evidenced by the PCM single-point calculations reported in Table 13, the relative abundances of the less stable c_2 conformers at higher frequencies decrease noticeably when moving from the gas phase towards solvents of increasing relative permittivity,

and to a major extent for the **2b** derivative. The trend shown by the c_2 conformers for both compounds agrees reasonably well with the experimental IR findings observed for the high frequency and less intense carbonyl doublet components in CCl_4. Therefore, these components should be assigned to the c_2 conformers and, analogously, the low frequency more intense ones can be assigned to c_1. The observed larger solvation effect on the c_2 conformer for both **2b** and **4b** is very similar to that previously described for the c_3 conformer of the C_RS_R/C_SS_S diastereomer and can be explained with the same arguments, that is the *syn* geometry (about 97°) adopted by the $C^{\delta+}=O^{\delta-}$ and $S^{\delta+}=O^{\delta-}$ dipoles with respect to the *anti*-relationship assumed in the c_1 conformer. Moreover, the $S^{\delta+}=O^{\delta-}$ dipole solvation is partially hindered in the **4b** compound by the closeness of the methyl group to the sulfinyl oxygen atom, as evidenced by the smaller value of the γ dihedral angle of -59.8° in comparison to -163.7° in the **2b** derivative. As a consequence, the solvation effect should be larger for **2b** with respect to **4b**, in agreement with the calculated and experimental IR results.

The comparison between the experimental IR intensities of the higher carbonyl frequency doublet component reveals a more pronounced solvent effect for the (RR/SS) c_3 conformer of **1a**–**5a** with respect to the (RS/SR) c_2 conformer of **2b** and **4b** (see Tables 11 and 4). This behaviour is likely a consequence of the presence of the short contact $O_{(35)SO}\ldots H_{(16)\ (o\text{-Ph})}$ (hydrogen bond) in the former and, on the contrary, of its absence in the latter. Furthermore, both the (RR/SS) c_2 and (RS/SR) c_1 conformers display the same $O_{(35)SO}\ldots H_{(16)\ (o\text{-Ph})}$ interaction, which partially inhibits to about the same extent as the solvent approach.

In order to analyse the main factors that determine the relative stabilities of the c_1 and c_2 conformers for compounds **2b** and **4b**, selected NBO interactions, NPA charges

and interatomic distances, calculated at the B3LYP/6-31+G(d,p) level [31], are reported in Tables 14, 15 and 16, respectively.

The phenacyl group of both the c_1 and c_2 conformers is affected by the same strong orbital interactions (about 20 kcal mol^{-1}) that take place in the enantiomeric pair C_RS_R/C_SS_S diastereomer, that is the $\pi_{C25C26}\rightarrow\pi^*_{C2O1}$ conjugation and the $LP_{O1}\rightarrow\sigma^*_{C2C3}$ and $LP_{O1}\rightarrow\sigma^*_{C2C25}$ through bond coupling interactions [34]. The former, like in the C_RS_R/C_SS_S compounds, was found to be slightly stronger for the 4'-electron-donating derivative **4b**.

The $LP_{Se13}\rightarrow\sigma^*_{C3S5}$ interaction, found in the C_RS_R/C_SS_S series also, stabilises to a similar extent both conformers by less than 6.0 kcal mol^{-1}, while the $LP_{S5}\rightarrow\sigma^*_{C3Se13}$ one, that is absent in the c_2 conformer due to the unfavourable δ (ca. 68.2 °) and ϕ (-59.0 °) dihedral angles, stabilises only the c_1 conformer by ca. 4.2 kcal mol^{-1}.

As in the (RR/SS) series, the extent of some interactions depends on the values assumed by specific dihedral angles. For instance, in the case of α and α', the unsuitable *synclinal* geometry of the c_1 and c_2 conformers (α of ca. 39.8º for both compounds) weakens the hyperconjugative interaction $\sigma_{C-S} \rightarrow \pi^*_{CO}$ (about 1 kcal mol^{-1}) and the unusual $\pi^*_{CO}\rightarrow\sigma^*_{C-S}$ orbital interaction (ca. 2.3 kcal mol^{-1}). On the contrary, the appropriate α' value of the O=C-C-Se moiety close to -90º for both conformers of **2b** and **4b** favours the $\sigma_{C-Se} \rightarrow \pi^*_{CO}$ hyperconjugation, as well as the $\pi^*_{CO} \rightarrow \sigma^*_{C-Se}$ orbital interaction. The former stabilises the c_1 conformer by ca. 7.2 kcal mol^{-1} and the c_2 conformer by ca. 5.8 kcal mol^{-1}, while the latter contributes to a further stabilisation of ca. 4.9 kcal mol^{-1} for the c_1 and 5.4 kcal mol^{-1} for the c_2. In addition, the α angles allow the contacts $O^{\delta-}_{(1)CO}\ldots S^{\delta+}_{(5)SO}$ to be shorter than the ΣvdW radii by -0.26 Å in c_1 and -0.36 Å in c_2.

Similarly, the proper values of the β, β' and γ' angles contribute to uniquely stabilising the c_1 conformers, as they constrain the $H^{\delta+}_{(16)o\text{-PhSe}}$ and $O^{\delta-}_{(35)SO}$ atoms, as well as the $O^{\delta-}_{(1)CO}$ and $H^{\delta+}_{(7)CH2(Et)}$ atoms, to contacts significantly shorter than the ΣvdW radii (Δl ca. -0.39 and -0.30 Å respectively). Moreover, the geometry of the c_1 conformers gives rise to the $LP_{O35} \rightarrow \sigma^*_{C15H16}$ and $LP_{O1} \rightarrow \sigma^*_{C6H7}$ orbital interactions (hydrogen bonds) of mean energies ca. 3.8 and 1.3 kcal mol^{-1}, respectively, absent in the c_2 conformers. This is evidenced in the molecular structures of the two conformers of **2b**, as reported in Fig. 9.

Overall, the computed and experimental order of stability of the two conformers for compounds **2b** and **4b** is in agreement with the sum of all the relevant NBO orbital interactions, which indicates that the c_1 conformer is the more stable by ca. 9 kcal mol^{-1}.

The X-ray single crystal analysis indicates that the geometry in the solid state of compound **2b** is strictly correlated to that of the c_2 conformer in the gas phase, as evidenced by the similar values of the torsional angles, except for the γ and γ' ones corresponding to the orientation of the ethyl and (Se)-phenyl groups (Table 12). The solid is stabilised by the same intramolecular attractive electrostatic interactions that occur in the gas phase for the c_2 conformer, as suggested by the relevant short contacts reported in Table 16. A more detailed view on the molecular packing and the stabilising intermolecular interaction that occur for **2b** in the solid state can be found in the literature [16]. It should be noted that the conformation of the minor component of the **3a** crystal structure with the $C_R S_S$ configuration (Table 5) is similar to that of the **2b** single crystal structure and, therefore, to that of the c_2 conformer of compounds **2b** and **4b** in the gas phase.

4. Conclusions

A conformational study of a selection of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl)-acetophenones bearing the substituents NO_2 **1a**, Br **2a**, H **3a**, Me **4a** and OMe **5a** for the C_RS_R/C_SS_S enantiomeric pair and Br **2b** and Me **4b** for the C_RS_S/C_SS_R pair was performed through the analysis of their IR carbonyl bands, supported by B3LYP/6-31+G(d,p) and single-point PCM calculations along with NBO analysis for **1a**, **3a**, **5a**, **2b** and **4b** and X-ray diffraction of **3**.

For the C_RS_R/C_SS_S compounds, the theoretical results indicated the existence, in the gas phase, of three conformers whose relative abundances are *ca.* 82–92% (c_1), *ca.* 7–17% (c_2) and *ca.* 1% (c_3). The computed ν_{CO} frequencies for the c_1 and c_2 conformers differ by less than 3 cm^{-1}, while the c_3 one is about 20 cm^{-1} higher. PCM single-point calculations indicate that the relative population of the c_3 conformer increases as the solvent relative permittivity increases, going from CCl_4 to CH_3CN. The larger solvation effect and the concomitant frequency increase of the c_3 conformers with respect to the c_1 and c_2 ones are likely related to the closeness of the $C^{\delta+}=O^{\delta-}$ and $S^{\delta+}=O^{\delta-}$ dipoles, which are *syn* oriented in the former and *anti* in the latter ones. This trend, compared to the experimental findings, allows to ascribe the c_1 and c_2 conformers to the low frequency more intense component of the ν_{CO} doublet and the c_3 conformer to the high frequency less intense one. All the conformers are electrostatically stabilised by short contacts (hydrogen bonds) between the sulfoxide oxygen $O^{\delta-}_{(35)SO}$ and one *o*-Ph-hydrogen $H^{\delta+}_{o\text{-}Ph}$ atoms. For the c_2 and c_3 conformers, these contacts involve the Se-Phenyl group *o*-hydrogen, while for the c_1 one, it is the phenacyl group *o*-hydrogen. The sum of the NBO energies suggests that the c_3 conformer should be the most stable one, in contrast with the computed stability order previously described. However, the effect of the strong Repulsive Field Effect between the *syn* oriented $C^{\delta+}=O^{\delta-}$ and $S^+=O^-$ dipoles

overcomes the sum of the NBO energies, thus destabilising at a larger extent this conformer with respect to the c_1 and c_2 ones. X-ray data of the major component of the disorder (compound **3a**) have shown that in the solid state, a single molecule assumes a conformation very similar to that of the c_2 conformer in gas phase. Furthermore, in the crystal, molecules are linked in centrosymmetrical pairs through $\pi\ldots\pi$ interactions between Se-bound phenyl rings, along with phenyl-C–H$\ldots$O(carbonyl) and phenyl-C–H$\ldots$O(sulphinyl) interactions.

Conversely, the computational results for the C_RS_S/C_SS_R compounds **2b** and **4b** indicate the existence of two conformers c_1 and c_2, with the former being the most abundant (*ca.* 99%), the less polar and with the lowest v_{CO} frequency. The good agreement between the PCM single-point calculations and the experimental solvent effect trend of the v_{CO} doublet components allows to assign the higher frequency c_2 conformer to the higher v_{CO} component in the IR spectra. The c_1 conformer is stabilised by the $LP_{(S)} \rightarrow \sigma^*_{C-Se}$ and $LP_{O(S-O)} \rightarrow \sigma^*_{C6-H7}$ orbital interactions, along with the intramolecular hydrogen bond between the sulfinyl oxygen $O^{\delta-}_{(35)SO}$ and Se-Phenyl *o*-hydrogen $H^{\delta+}_{o-Ph(16)}$ atoms. The absence of the latter interaction in the c_2 conformer leaves the sulfinyl oxygen atom accessible to the solvent molecules and thus accounts for its lower relative stability in the gas phase and its stronger solvation.

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Figure and scheme captions

Fig. 1. NMR signals of methylenic hydrogens of the crude mixture of diastereoisomers of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl)-acetophenones **1–5** with preferential formation of diastereomer C_SS_S/C_RS_R as a racemate.

Fig. 2. ^{1}H-NMR signals (double quartet pairs) of diastereotopic methylene hydrogen atoms [$CH_2S(O)$] of the purified (C_RS_R/C_SS_S) and (C_SS_R/C_RS_S) diastereoisomers of 2-(phenylselanyl)-2-(ethylsulfinyl)-4'-methylacetophenone (**4a** and **4b**).

Fig. 3. IR spectra of (C_RS_R/C_SS_S) 2-(phenylselanyl)-2-(ethylsulfinyl)-4'-bromoacetophenone (**2a**) showing the analytically resolved carbonyl stretching band, in: carbon tetrachloride [fundamental (a) and first overtone (b)], chloroform (c), dichloromethane (d) and acetonitrile (e).

Fig. 4. Molecular structures of the conformers of (C_RS_R) 4'-Br-PhC(O)CH[S(O)Et][SePh] (**2a**) obtained at the B3LYP/6-31+G(d,p) level. Adopted colours: H = white, C = grey, O = red, S = yellow and Se = orange.

Fig. 5. (a) Molecular structure of the major component comprising the crystal structure of **3a**, showing atom-labelling and displacement ellipsoids at the 70% probability level for non-H atoms, (b) overlay diagram of the two components of the structure of **3**. The major component is shown in the red image, and the molecules have been aligned so that the C=O and Se atoms are coincident.

Fig. 6. Molecular packing in **3a** (major component only) viewed in projection down the c-axis. The C–H…O, C–H…S and π…π interactions are shown as orange, blue and purple dashed lines, respectively.

Fig. 7. IR spectra of (C_SS_R/C_RS_S) 2-(phenylselanyl)-2-(ethylsulfinyl)-4'-methylacetophenone (**4b**) showing the analytically resolved carbonyl stretching band, in: carbon tetrachloride [fundamental (a) and first overtone (b)], chloroform (c), dichloromethane (d) and acetonitrile (e).

Fig. 8. IR spectra of (C_SS_R/C_RS_S) 2-(phenylselanyl)-2-(ethylsulfinyl)-4'-bromoacetophenone (**2b**) showing the analytically resolved carbonyl stretching band, in: carbon tetrachloride (a), chloroform (b), dichloromethane [fundamental (c) and first overtone (d)] and acetonitrile (e).

Fig. 9. Molecular structures of the conformers of (C_RS_S) 4'-Br-PhC(O)CH[S(O)Et][SePh] (**2b**) obtained at the B3LYP/6-31+G(d,p) level. Adopted colours: H = white, C = grey, O = red, S = yellow and Se = orange.

Figure S1. Molecular structure of the minor component comprising the crystal structure of **3b**, showing atom-labelling and displacements ellipsoids at the 70% probability level for non-H atoms.

Scheme 1. Atom labelling of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl)-acetophenones, 4'-Y-PhC(O)CH[S(O)Et][SePh] and definition of the relevant dihedral angles for the C_SS_S/C_RS_R (**a**) and C_RS_S/C_SS_R (**b**) series.