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***Corresponding authors:**

Paulo R. Olivato and Henrique J. Traesel

Conformational Analysis and Electronic Interactions Laboratory, Instituto de Química, Universidade de São Paulo, P. O. Box 26077, 05513-970, São Paulo, SP, Brazil.

E-mail: prolivat@iq.usp.br (P.R. Olivato)
hjtldq@gmail.com (H.J. Traesel)

Conformational analysis of some 4'-substituted 2-(phenylselanyl)-2-(methoxy)- acetophenones

Henrique J. Traesel^{a*}, Paulo R. Olivato^{a*}, J. Valença^a, Daniel N. S. Rodrigues^a, Julio Zukerman-Schpector^b, Maurizio Dal Colle^c

^a*Conformational Analysis and Electronic Interactions Laboratory, Instituto de Química, USP, CP 26077, 05513-970, São Paulo, SP, Brazil*

^b*Chemistry Department, Federal University of São Carlos, CP 676, 13565-905, São Carlos, SP, Brazil*

^c*Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Ferrara, 44121, Ferrara, Italy*

Abstract

A conformational study of some 4'-substituted 2-(phenylselanyl)-2-(methoxy)-acetophenones (OMe **1**, H **2**, and Cl **3**) was performed using IR carbonyl stretching band analysis supported by NBO and PCM calculations at the B3LYP/6-31+G (d,p) level for **1-3** and using X-ray diffraction for **1** and **2**. The computational results indicated the existence of three stable conformers for the series (c_2 , c_3 , and c_1 in order of decreasing stability), whose relative abundance changes with solvent permittivity. The experimental trend observed for the components of the triplet carbonyl band in all solvents matches well with computational results and thus allows for their assignment to distinct conformers. The relative population of the c_1 conformer increases in more polar solvents, becoming the most stable conformer in the highest permittivity solvent, acetonitrile, as indicated by IR spectra and PCM calculations. These findings are related to the *quasi* parallel geometry assumed by the $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}-O^{\delta-}$ dipoles, which favour stronger solvation. NBO analysis shows that the sum of the energies (ΣE) of the relevant orbital interactions stabilises the c_3 conformer of **1-3** slightly, likely due to the

minor contribution of the $LP_{O5} \rightarrow \sigma^*_{C3-Se10}$ interaction. However, only the c_1 conformer is significantly destabilized by the $O^{\delta-}(1)_{CO} \dots O^{\delta-}(5)_{OMe}$ short contact electrostatic repulsion, which is also responsible for its highest ν_{CO} frequency. In addition, the $LP_{O5} \rightarrow \sigma^*_{C2-C3}$ orbital interaction accounts for the lowest ν_{CO} frequency of c_3 conformer. X-ray single crystal analysis of compounds **1** and **2** indicates that in the solid state they assume the least stable c_1 conformation found in the gas phase. Molecules of these compounds are stabilised in the crystal through a series of C-H...O and C-H... π intermolecular interactions.

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

Introduction

Our previous studies of α -phenylseleno-*p*-substituted propiophenones using carbonyl stretching IR frequencies (ν_{CO}), α -methylene ^{13}C NMR, and $n \rightarrow \pi^*$ UV analysis, have shown that the simultaneous occurrence of the $n_{\text{Se}} \rightarrow \pi^*_{\text{CO}}$, $\sigma_{\text{C-Se}} \rightarrow \pi^*_{\text{CO}}$, and $\pi_{\text{CO}} \rightarrow \sigma^*_{\text{C-Se}}$ orbital interactions significantly improves the stability of the *gauche* conformer with respect to the *cis* one [1].

The ν_{CO} IR analysis of the α -(*p*-substituted-phenoxy)-*p'*-substituted-acetophenones X-PhC(O)-CH₂-OPh-Y (X and Y = NO₂, H, and OMe) [2] indicated the existence of *cis-gauche* rotational isomerism. Adding field (F), inductive ($-I_{\sigma}$), and mesomeric (M) effects in the *cis* rotamers of the derivatives with (X=H and OMe) for (Y= NO₂, H, and OMe) gives rise to a similar carbonyl bond order. This accounts for the observed almost constant positive carbonyl frequency shifts ($\Delta\nu$).

Additionally, for any Y substituent, the *gauche* conformers in the *p*-nitroacetophenones (X=NO₂) are more stable than the *cis* ones, while in the methoxyacetophenones (X=OMe) and acetophenones (X=H), the *cis* conformers are slightly more stable. This behaviour was ascribed to the π^*_{CO} (LUMO)/ $n_{\text{O(OPh-Y)}}$ orbital interaction, which stabilizes the *gauche* conformers of the (X= NO₂) derivative to a larger extent than the (X=OMe and H) ones.

The experimental photoelectron spectra of the Me₂X (X=Se and O) compounds indicate that both the n_{Se} lone pair (8.40 eV) and the $\sigma_{\text{C-Se}}$ orbital (11.0 eV) [3] ionization energies are lower than those of the n_{O} lone pair (10.04 eV) and the $\sigma_{\text{C-O}}$ orbital (11.91 eV) [3]. In addition, the $\sigma^*_{\text{C-Se}}$ (2.4 eV) [4] electron-affinity energy is higher than that of $\sigma^*_{\text{C-O}}$ (6.0 eV [5] or 4.2eV [4, 6]). Therefore, as shown in our previous papers [1, 2], the ($n_{\text{X}} \rightarrow \pi^*_{\text{CO}}$, $\sigma_{\text{C-X}} \rightarrow \pi^*_{\text{CO}}$, $\pi_{\text{CO}} \rightarrow \sigma^*_{\text{C-X}}$) interactions are stronger in the *gauche* conformer of the α -phenylseleno- propiophenones (X=Se) than for the analogous conformer in the α -phenoxy-acetophenones (X=O).

The above discussion prompted us to study mixed acetophenones bearing both the phenylseleno- and the methoxy- substituents in the α position using IR spectroscopy, density functional theory, and NBO calculations. This study analyses

4'-substituted-2-[phenylselanyl]-2-[methoxy]-acetophenones **1-3** (Scheme 1), as in these compounds the α substituents are expected to compete for the *syn-clinal* or *anti-clinal* (*gauche*) and *syn-periplanar* (*cis*) geometries with respect to the carbonyl group. In particular, these compounds were chosen taking into account that the orbital and electrostatic interactions that stabilize the conformers might be affected by changes in conjugation involving the 4'-substituents. This work is an extension of our recent conformational studies on the 2-(phenylseleno)-2-(ethylsulfanyl) acetophenones and their mono- and di-oxygenated derivatives [7, 8, 9].

Additionally, continuing with our interests in searching selective COX-2 inhibitors containing selenium-sulfur [7, 8, 9], and in molecular docking studies [10, 11] to understand the mechanism of inhibition, the crystal and molecular structures of the selenium-oxygen analogues 2-methoxy-1-phenyl-2-(phenylselanyl)ethanone (**2**) and 2-methoxy-1-(4-methoxyphenyl)-2-(phenylselanyl)ethanone (**1**) were determined.

Experimental

Materials

All solvents for IR measurements were spectrograde and were used without further purification. The 4'-substituted 2-(phenylselanyl)-2-(methoxy)-acetophenones **1-3** were synthesised by a literature procedure [12]: a THF solution of 2-(methoxy)-(4'-substituted)-acetophenone was added slowly to a stirred solution of LDA in THF at 195 K. After 30 min, a solution of phenylselenyl bromide with HMPA [13, 14] in THF was added dropwise with immediate discoloration of the reactant. Water was added and the crude product was extracted with ethyl ether or dichloromethane after the reaction mixture reached room temperature (*ca.* 3 h). The organic layer was washed with saturated NH_4Cl solution until neutralised and was then 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. Reagents were commercially available [2-methoxy-acetophenone **5**, Sigma-Aldrich; 2-methoxy-(4'-methoxy)- **4** and 2-methoxy-(4'-chloro)- **6** acetophenones, Novel Chemical Solutions].

Suitable crystals for X-ray analysis for **1** and **2** were obtained by vapour diffusion from chloroform/*n*-hexane at 283 K. ¹H and ¹³C NMR data and elemental analyses for compounds **1** to **3** are presented in Table 1.

IR measurements

IR spectra for the fundamental carbonyl region (1800-1600 cm⁻¹) were recorded with a FTIR Michelson Bomem MB100 spectrometer, with 1.0 cm⁻¹ resolution, at a concentration of 1.0 x 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 x 10⁻² mol dm⁻³) using a 1.00 cm quartz cell. The overlapping carbonyl bands (fundamental and first overtone) were deconvoluted using 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 triplet, expressed as a percentage of absorbance, assuming approximately equal molar absorptivity coefficients for all the conformers [16].

NMR measurements

¹H NMR and ¹³C 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 CDCl₃. ¹H and ¹³C chemical shifts are reported in ppm relative to the internal standard TMS.

X-ray measurements

Intensity data for **1** and **2** were measured at 290 K on a Bruker APEXII CCD diffractometer using MoK α radiation. Data processing and absorption corrections were accomplished with APEX2 and SAINT [17] for **1** and SADABS [18] for **2**. Unit cell data, X-ray data collection parameters, and details of structure refinement are given in Table 2. The structure was solved by direct methods [19] and full matrix least-squares

refinement on F^2 with anisotropic displacement parameters for all non-hydrogen atoms followed [20]. The C-bound H atoms were placed on stereochemical grounds and refined with fixed geometry (C–H=0.93–0.98 Å) and with Uiso=1.2–1.5 Ueq (carrier atom). The programs WinGX [21], PLATON [22], and ORTEP-3 for Windows [21] were also used in the study. Crystallographic data for the crystal structures were deposited in the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-1577490 and 1577491 for **1** and **2**, respectively.

Theoretical calculations

A Monte Carlo conformational search (HF/STO-3G theory level) was performed with Spartan '06 [23] software. The conformer geometries obtained were used as initial inputs in all calculations carried out at 298 K with the Gaussian package programs (G09-D01) [24] with a hybrid Hartree-Fock density functional B3LYP method [25, 26, 27] and the 6-31+G(d,p) basis set. Full geometrical optimizations and analytical harmonic vibrational frequency calculations were performed on the most stable conformers. Frequency analysis was carried out to verify the nature of the minimum state of the obtained stationary points, and to calculate the zero-point vibrational energy (ZPVE) corrections. To estimate solvation effects on the relative stability of the most relevant conformers, calculations were conducted on the optimized structures using the polarizable continuum model (PCM) [28, 29]. Due to the lack of symmetry presented by the three conformers (C_1 point group), the thermodynamic probability factor was the same ($\omega=2$) for all of them. The NBO 3.1 program [30] was used as implemented in the Gaussian 09 package, and the reported NBO delocalization energies (E2) were those given by second-order perturbation theory. Partial atomic charges were calculated using the grid-based ChELPG method [31].

Results and Discussion

The frequencies and relative intensities of the analytically resolved components of the carbonyl stretching triplet for compounds **1-3** in solvents of increasing relative

permittivity [32] [i.e., *n*-hexane, carbon tetrachloride (fundamental and first overtone), chloroform, dichloromethane, and acetonitrile] are reported in Table 3.

The ν_{CO} IR spectra indicate that the lowest frequency triplet component is the least intense for all compounds in all solvent, except for compound **3** in *n*-hexane. In addition, its relative intensity decreases in the more polar solvents dichloromethane and acetonitrile. At the same time, the most intense component corresponds to the middle frequency peak in low polarity solvents (*n*-hexane, carbon tetrachloride, and chloroform), and to the higher frequency peak in the more polar solvents dichloromethane and acetonitrile. This trend is different only for compound **2** in chloroform, which has a higher frequency component that is slightly more intense than the middle frequency one. The trend of the relative intensities of the triplet components seems to be unrelated to the electron-withdrawing or donating properties of the 4'-substituents in the low polarity solvents (*n*-hexane, carbon tetrachloride, and chloroform). However, an increase in the highest frequency component and a decrease in the middle frequency component is observed in the more polar solvents (dichloromethane and acetonitrile) going from the chlorine to the methoxy derivative. The solvent effect on the carbonyl band components for compounds **1-3** is illustrated in Figures 1-3, respectively.

The occurrence of three carbonyl band components in the first overtone region (carbon tetrachloride) at frequencies twice those of the fundamental minus *ca.* 17 cm^{-1} (twice the mechanical anharmonicity [33]), and intensity ratios comparable to those of the fundamentals, is indicative of the presence of at least three conformers for the studied compounds. This rules out the existence of any vibrational effect in the fundamental transition of the ν_{CO} mode [34, 35].

Some relevant dihedral angles and the vibrational frequencies of the minimum energy conformations in the gas phase calculated at the B3LYP/6-31G+(d,p) level for compounds **1-3** are reported in Table 4, along with X-ray dihedral angles for **1** and **2**. Calculations indicate the existence of three distinct conformers, c_1 , c_2 , and c_3 , which assume in the whole series a *quasi-syn-periplanar* geometry (c_1 , $\alpha \approx 31^\circ$) and *anti-clinal*

one (c_2 and c_3 , $\alpha \approx 130^\circ$) between the C-O and C=O groups. Moreover, all the conformers display an *anti-clinal* orientation between the C-Se and C=O groups, with $\alpha' \approx 94^\circ$ for c_1 and $\alpha' \approx 104^\circ$ for c_2 and c_3 . The computed molecular structures of the three conformers of compound **2**, taken as representative of the series, are reported in Figure 4.

As shown in Table 4, the c_2 conformers are significantly more stable ($P \approx 95\%$) than the c_3 ($P \approx 3\%$) and c_1 conformers ($P \approx 2\%$) for all compounds. The c_1 conformer exhibits the highest ν_{CO} frequency, followed by the c_2 and the c_3 conformers. Therefore, the middle carbonyl frequency, which is the most intense of the triplet components in the IR spectra, can reasonably be assigned to the c_2 conformers and, consequently, the highest and lowest frequency IR components can be assigned to the less intense c_1 and c_3 conformers, respectively. These assignments are further supported by analysis of the PCM results reported in Table 5. These calculations indicate an increase of the relative c_1 conformer population and a concomitant decrease of the c_2 population as solvent polarity increases. This is in line with experimental results in solution. In addition, the greater stability observed in the IR spectra of the c_1 conformer with respect to the c_2 conformer in the most polar solvent acetonitrile can be explained by stronger solvation of the *quasi* parallel $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}-O^{\delta-}$ dipoles.

ChELPG charges, interatomic distances of selected atoms, and NBO energies of selected donor-acceptor orbital interactions [30] for the three conformers of compounds **1-3** are presented in Tables 6, 7, and 8 respectively.

The strongest orbital interactions for the three conformers are the conjugative $\pi_{C22=C30} \rightarrow \pi^*_{C2=O1}$ at mean energy values of *ca.* 21 kcal mol⁻¹ (c_2 and c_3) and *ca.* 19 kcal mol⁻¹ (c_1), and the $Lp_{O5} \rightarrow \sigma^*_{C2-C3}$ and $Lp_{O5} \rightarrow \sigma^*_{C2-C22}$ through bond coupling interactions [36], which are approximately constant for the three conformers with a mean energy values of *ca.* 22 kcal mol⁻¹ and 19 kcal mol⁻¹, respectively. The c_1 and c_2 conformers are also largely stabilized (*ca.* 18 kcal mol⁻¹ vs. *ca.* 1 kcal mol⁻¹ for the c_3 one) by the $Lp_{O5} \rightarrow \sigma^*_{C3-Se10}$ interaction, which occurs at a β dihedral angle (*ca.* 163°) that forces the O₍₅₎ lone pair to lie almost parallel to the antibonding $\sigma^*_{C3-Se10}$ orbital.

This interaction is replaced by the $LP_{O5} \rightarrow \sigma^*_{C2-C3}$ interaction in the c_3 conformer (*ca.* 9.5 kcal mol⁻¹ vs. *ca.* 1.4 kcal mol⁻¹ for c_1 and c_2) as a consequence of the decrease of the β angle to *ca.* 75°. In addition, the *quasi-anti-periplanar* arrangement of the C₃-Se₁₀ and O₅-C₆ bonds, exhibited exclusively by the c_3 conformers, leads to the weak stabilizing interactions of $\sigma_{C3-Se10} \rightarrow \sigma^*_{O5-C6}$ and $\sigma_{O5-C6} \rightarrow \sigma^*_{C3-Se10}$ (*ca.* 2.7 kcal mol⁻¹ each).

The short contact electrostatic repulsion $O^{\delta-}(1)_{CO} \dots O^{\delta-}(5)_{OMe}$ that occurs solely in the c_1 conformer (see Table 7) is responsible for the repulsive field effect (RFE) [34] between the $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}-O^{\delta-}$ dipoles. This RFE leads to a decrease of the carbonyl oxygen charge (Table 6) of this conformer and, consequently, to an increase of its carbonyl bond order and ν_{CO} frequency. A concomitant effect is the weakening of the c_1 conformer conjugation energy $\pi_{C22=C30} \rightarrow \pi^*_{C2=O1}$ by *ca.* 2.4 kcal mol⁻¹ with respect to the c_2 and c_3 conformers. The $LP_{O5} \rightarrow \sigma^*_{C2-C3}$ orbital interaction, which is almost absent (*ca.* 1 kcal mol⁻¹) in the c_1 and c_2 conformers, stabilizes the c_3 conformer to a large extent (*ca.* 9.5 kcal mol⁻¹) and contributes to lower its ν_{CO} frequency by increasing the carbonyl group polarization.

The proper β' dihedral angles of *ca.* 50° for the c_1 conformer and *ca.* 120° for the c_2 conformer allow $LP_{Se10} \rightarrow \sigma^*_{C2-C3}$ and $LP_{Se10} \rightarrow \pi^*_{O1=C2}$ superjacent orbital interactions [37], which stabilize each conformer by a mean overall value of *ca.* 3.5 kcal mol⁻¹. On the other hand, the β' dihedral angle of the c_3 conformers (*ca.* 153°) inhibits the first interaction and reduces the second one to less than 0.6 kcal mol⁻¹. Conversely, the $LP_{O5} \rightarrow \pi^*_{O1=C2}$ interaction, which can take place for the appropriate β dihedral angle values (Table 4), is hindered for the c_1 and c_2 conformers and slightly favoured for the c_3 conformers (*ca.* 0.8 kcal mol⁻¹).

A series of orbital interactions, that is the $LP_Y \rightarrow \pi^*_{CO}$ (a), $\pi_{CO} \rightarrow \sigma^*_{C-Y}$ (b), and $\sigma_{C-Y} \rightarrow \pi^*_{CO}$ (c) (Y= O or Se), are maximized as the α or α' torsional angles approach 90°. As mentioned above, all interactions for (Y=Se) should be stronger than those with (Y=O) for favourable overlap of involved orbitals.

The energy of the $\sigma_{C3-Se10} \rightarrow \pi^*_{O1=C2}$ hyperconjugative interaction decreases from *ca.* 6.7 kcal mol⁻¹ in the *c*₁ conformer to *ca.* 5.5 kcal mol⁻¹ in the *c*₃ conformer, in line with the parallel progressive enlargement of the α' dihedral angle from *ca.* 94° to *ca.* 153°. In contrast, the corresponding $\sigma_{C3-O5} \rightarrow \pi^*_{O1=C2}$ hyperconjugative interaction has a negligible effect (less than 0.7 kcal mol⁻¹) for all conformers, as their α dihedral angles of 130° (*c*₂ and *c*₃) and *ca.* 31° (*c*₁) diverge from the optimal value of 90°. As expected, the $\pi_{C2=O1} \rightarrow \sigma^*_{C3-Se10}$ and the $\pi_{C2=O1} \rightarrow \sigma^*_{C3-O5}$ interaction energies follow the same trend as the $\sigma_{C3-Se10} \rightarrow \pi^*_{O1=C2}$ and the $\sigma_{C3-O5} \rightarrow \pi^*_{O1=C2}$ ones, respectively. In fact, the former decreases from 2.4 kcal mol⁻¹ (*c*₁) to 1.8 kcal mol⁻¹ (*c*₃), while the latter decreases from *ca.* 2.0 kcal mol⁻¹ in *c*₂ and *c*₃ to *ca.* 0.6 kcal mol⁻¹ in *c*₁.

The three conformers are further stabilized by the anomeric effect LP_{O5}/σ*_{C3-H4} at a mean energy value of *ca.* 3.4 kcal mol⁻¹. Nevertheless, the [O^{δ-}₅... H^{δ+}₃₁] and [Se^{δ-}₁₀... H^{δ+}₇] contacts at interatomic distances shorter than ΣvdWr by *ca.* -0.34 Å and *ca.* -0.07 Å are responsible for the hydrogen bonds LP_{O5}/σ*_{C30-H31} and LP_{Se10}/σ*_{C6-H7}, respectively. The former stabilizes the *c*₂ and *c*₃ conformers by *ca.* 0.8 kcal mol⁻¹, while the latter stabilizes the *c*₁ and *c*₂ conformers by *ca.* 0.8 kcal mol⁻¹. In addition, the *c*₂ and *c*₃ conformers are electrostatically stabilized by the short contacts Se^{δ-}₁₀... H^{δ+}₇ and Se^{δ-}₁₀... H^{δ+}₃₁, respectively, and the *c*₃ conformer is stabilized through the weak LP_{Se10}/σ*_{C31-H31} hydrogen bond (*ca.* 0.6 kcal mol⁻¹).

The sum of the NBO orbital interactions (ΣE) for compounds **1-3** shows that the *c*₁ and *c*₂ conformers are stabilized almost to the same extent (*ca.* 108 kcal mol⁻¹), while the *c*₃ conformer is less stabilised (*ca.* 101 kcal mol⁻¹). This difference can be ascribed to the sum of the LP_{O5} → σ*_{C3-Se10} and LP_{O5} → σ*_{C2-C3} orbital interactions, which favour the *c*₁ and *c*₂ conformers over the *c*₃ conformer by just *ca.* 9 kcal mol⁻¹. As pointed out above, the strong repulsive field effect which operates between the C^{δ+}=O^{δ-} and C^{δ+}-O^{δ-} dipoles destabilize only the *c*₁ conformer.

Therefore, the high stability of the *c*₂ conformer compared to the *c*₁ and *c*₃ conformers calculated in the gas phase (Table 4) seems likely to be related to a balance between the

simultaneous occurrence of orbital delocalization energies and coulombic repulsive interactions.

Relevant crystallographic information and final refinement parameters for **1** and **2** are given in Table 2. The ORTEP views of the asymmetric unit of **1** and **2** with atom labelling are shown in Figures 5 and 6, respectively.

Some relevant geometrical data for the crystallographic compounds **1** and **2** presented in Table 4 show that in the solid phase these compounds assume the conformation least stable in the gas phase (c_1), as evidenced by the almost coincident values of the torsional α - ϕ' angles. It should be pointed out that the intramolecular short contact $\text{Se}_{10}\cdots\text{H}_7$ (hydrogen bond) which contributes to the stabilization of the c_1 conformer in the gas phase also takes place in the solid phase for compounds **1** and **2**, as the interatomic distance is shorter than the ΣvdW radii by Δl ca. -0.17 Å.

Compounds **1** and **2** are stabilised in the crystal through a series of C-H...O and C-H... π intermolecular interactions (hydrogen bonds) as outlined below.

In compound **1** molecules are arranged in trimmers through two C-H... π interactions (Figure S1), which in turn are joined through a C-H...O interaction (Table 9).

In compound **2** there are two independent enantiomeric molecules in the asymmetric unit (Figure 6). Dihedral angles between the phenyl rings are $18.2(3)^\circ$ for the molecule with Se10 and $15.6(4)^\circ$ for the other molecule. The two independent molecules are linked through a C-H...O interaction that is linked to another pair of molecules through another C-H...O interaction. In turn these are connected through C-H... π interactions (Figures S2 and S3, Table 9).

Conclusions

The conformational preferences of the 4'-substituted 2- (phenylselanyl)-2-(methoxy)-acetophenones **1-3** (OMe **1**, H **2**, Cl **3**) were determined by ν_{CO} IR analysis, along with B3LYP/6-31+G(d,p) and PCM calculations, NBO analysis, and X-ray diffraction (for **1** and **2**). Theoretical data indicated the existence of three stable conformations for the whole series, labelled c_1 , c_2 , and c_3 in order of decreasing ν_{CO} frequencies. The c_2

conformer was most stable in the gas phase ($P \approx 95\%$) and the c_3 conformer was slightly more abundant than c_1 . PCM demonstrated an increase of the relative population of the c_1 conformer and a concomitant decrease of the c_2 population as solvent polarity increases, leading to inversion of their relative abundances in the highest polar solvent, acetonitrile. In addition, the c_3 conformer population decreases slightly in the more polar solvents. The good agreement between this trend and the experimental one observed for the components of the triplet carbonyl band allowed the assignment of the most intense middle frequency component of the triplet in the IR spectrum in low polarity solvents (from *n*-hexane to chloroform) to the c_2 conformer, and the highest and lowest frequency ones to the less intense c_1 and c_3 conformers, respectively. These assignments were further supported by a decrease of the intensity of the intermediate frequency component with respect to the highest one in solvents of increasing polarity, as well as by the reversal of their abundances in the more polar solvents dichloromethane and acetonitrile. The increased stability of the c_1 conformer in the polar solvents dichloromethane and acetonitrile was related to stronger solvation of the *quasi* parallel $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}-O^{\delta-}$ dipoles. This local solvation was favoured by an increase in carbonyl group polarization going from electron withdrawing to electron donating 4'-substituents, as confirmed by the IR spectral shape.

In all conformers in the series the C-Se group assumes an *anti-clinal* geometry with respect to the C=O one. However, the C-O/C=O groups are *quasi-syn-periplanar* oriented in the c_1 conformer and *anti-clinal* in both the c_2 and c_3 conformers.

The sum of the energy contributions (ΣE) of selected orbital interactions (NBO analysis) for compounds **1-3** affected the c_1 and c_2 conformers' stabilities to the same extent (*ca.* 108 kcal mol⁻¹) and affected c_3 conformer by *ca.* 7 kcal mol⁻¹ less. This difference was attributed to the $LP_{O5} \rightarrow \sigma^*_{C3-Se10}$ and $LP_{O5} \rightarrow \sigma^*_{C2-C3}$ orbital interactions which stabilise the c_3 conformer by *ca.* 9 kcal mol⁻¹ less than the c_1 and c_2 ones.

It should be noted that the strong repulsive field effect that acts between the $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}-O^{\delta-}$ dipoles destabilizes only the c_1 conformer and contributes to the increase of its ν_{CO} frequency. On the contrary, the $LP_{O5} \rightarrow \sigma^*_{C2-C3}$ orbital interaction (*ca.* 9.5 kcal

mol⁻¹) which affects mainly the *c*₃ conformer leads to the lowering of its ν_{CO} frequency by increasing the polarization of the carbonyl group.

In conclusion, the high stability of the *c*₂ conformer compared to the *c*₁ and *c*₃ conformers in the gas phase and in low polarity solvents results from a balance of orbital delocalization energies and coulombic repulsive interactions.

X-ray single crystal analysis of compounds **1** and **2** indicates that in the solid state they assume the least stable *c*₁ conformation found in the gas phase. These molecules are stabilised through a series of C-H...O and C-H... π intermolecular interactions.

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References and notes

- [1] P. R. Olivato, R. Ruiz Filho, J. C. D. Lopes, Conformational and electronic interaction studies of 2-seleno-substituted carbonyl compounds and the comparison with the 2-thio-analogues. XIII. α -phenylseleno-*p*-substituted propiophenones, Phosphorus, Sulfur, Silicon Relat. Elem. 92 (1994) 109-128.
- [2] S. A. Guerrero, P. R. Olivato, R. Rittner, A conformational analysis of some α -aryloxy *p*-substituted- acetophenones: Solvent effects on the ν_{CO} infrared bands, Can. J. Anal. Sci. Spect. 48 (2003) 181-188.

- [3] S. Cradock, R. A. Whiteford, Photoelectron spectra of methyl, silyl and germlyl derivatives of the group VI elements, *J. Chem. Soc. Faraday Trans. 2* (1972) 281-288.
- [4] A. Modelli, D. Jones, G. Distefano, M. Tronc, Electron affinity and dissociative electron attachment in saturated dialkyl group-16 derivatives, *Chem. Phys. Lett.* 181 (1991) 361-366.
- [5] J. C. Giordan, J. H. Moore, J. A. Tossel, W. Kaim, Interaction of frontier orbitals of group 15 and group 16 methides with the frontier orbitals of benzene, *J. Am. Chem. Soc.* 107 (1985) 5600-5604.
- [6] Refers to the electron-affinity of the diethyl ether.
- [7] C. R. Cerqueira, P. R. Olivato, M. Dal Colle, Conformational study of some 4-substituted 2-(phenylselanyl)-2-(ethylsulfanyl)-acetophenones, *Spectrochim. Acta. Part A.* 139 (2015) 495-504.
- [8] C. R. Cerqueira, P. R. Olivato, D. N. S. Rodrigues, J. Zukerman-Schpector, E. R. T. Tiekink, M. Dal Colle., Stereochemical and electronic interaction studies of 4'-substituted 2-(phenylselanyl)-2-(ethylsulfinyl)-acetophenones, *J. Mol. Struct.* 1133 (2017) 49-65.
- [9] C. R. Cerqueira, P. R. Olivato, D. N. S. Rodrigues, J. Zukerman-Schpector, E. R. T. Tiekink, M. Dal Colle, Conformational study of some 4 -substituted 2-(phenylselanyl)-2-(ethylsulfonyl)-acetophenones, *J. Mol. Struct.* 1084 (2015) 190-199.
- [10] N. Baptistini, I. Caracelli, J. Zukerman-Schpector, P. R. Olivato, C. R. Cerqueira, Docking molecular de compostos organochalcogênios anti-inflamatórios na enzima COX-2, in: 52º Congresso Brasileiro de Química, Área: 11 Bioquímica e

Biotecnologia (2012), available online at
<http://www.abq.org.br/cbq/2012/trabalhos/11/473-13176.html>

- [11] N. Baptistini, Analysis *in silico*, *in vitro* and *in vivo* of organochalcogen compounds as possible anti-inflammatories, PhD. Thesis (2015) University Federal of São Carlos, São Carlos, Brazil, available online at
<https://repositorio.ufscar.br/handle/ufscar/7554>
- [12] H. Reich, J. Renga, I. Reich, Organoselenium chemistry. Conversion of ketones to enones by selenoxide syn elimination, *J. Am. Chem. Soc.* 97 (1975) 5434-5447.
- [13] F. E. Romesberg, M. P. Bernstein, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, D. B. Collum, Structure of lithium hexamethyldisilazide (LiHMDS) in the presence of hexamethylphosphoramide (HMPA). Spectroscopic and computational studies of monomers, dimers, and triple ions, *J. Am. Chem. Soc.* 115 (9) (1993) 3475-3483.
- [14] H. J. Reich, W. H. Sikorski, Regioselectivity of addition of organolithium reagents to enones: The role of HMPA, *J. Org. Chem.* 64 (1999) 14-15.
- [15] Galactic Industries Corporation, 1991-1998, Salem, USA
- [16] P. R. Olivato, R. Rittner, Conformational and electronic interaction studies of some α -mono-heterosubstituted carbonyl compounds, *Rev. Heteroatom Chem.* 15 (1996) 115-159.
- [17] Bruker. APEX2 and SAINT. Bruker AXS Inc., Madison, WI, 2009.
- [18] G. M. Sheldrick, SADABS. University of Göttingen, Germany, 1996.
- [19] M. C. Burla, R. Caliendo, B. Carrozzini, G. L. Cascarano, C. Cuocci, C. Giacovazzo, M. Mallamo, A. Mazzone, G. Polidori, Crystal structure determination and refinement via SIR2014, *J. Appl. Cryst.* 48 (2015) 306-309.
- [20] G. M. Sheldrick, Crystal structure refinement with SHELXL, *Acta. Crystallogr. C* 71 (2015) 3-8.

- [21] L. J. Farrugia, WinGX and ORTEP for windows: An update, *J. Appl. Crystallogr.* 45 (2012) 849-854.
- [22] A. L. Spek, Single-crystal structure validation with the program PLATON, *J. Appl. Crystallogr.* 36 (2003) 7-13.
- [23] Spartan'06 Wavefunction, Inc. Irvine, CA. Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko, S. V. Levchenko, D. P. O'Neill, R. A. Distasio Jr., R. C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M. Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen, P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, E. F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C-P. Hsu, G. Kedziora, R. Z. Khalliulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Z. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock III, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer, J. Kong, A. I. Krylov, P. M. W. Gill and M. Head-Gordon, *Phys. Chem. Chem. Phys.* 8 (2006) 3172.
- [24] Gaussian 09, Revision D.01 M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, M.J. Millam, M. Klene,

- J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian, Inc., Wallingford, CT, 2009.
- [25] A. D. Becke, Density-functional thermochemistry. III. The role of exact exchange, *J. Chem. Phys.* 98 (1993) 5648-5652.
- [26] A. D. Becke, A new mixing of Hartree-Fock and local density-functional theories, *J. Chem. Phys.* 98 (1993) 1372-1377.
- [27] C. Lee, W. Yang, R. G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B* 37 (1988) 785-789.
- [28] M. Cossi, G. Scalmani, N. Rega, V. Barone, New developments in the polarizable continuum model for quantum mechanical and classical calculations on molecules in solution, *J. Chem. Phys.* 117 (2002) 43-54.
- [29] J. Tomasi, B. Mennucci, R. Cammi, Quantum mechanical continuum solvation, *Models. Chem. Rev.* 105 (2005) 2999-3093.
- [30] E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold, NBO Version 3.1 (Implemented in the GAUSSIAN 09 package of programs).
- [31] C. M. Breneman, K. B. Wiberg, Determining atom-centered monopoles from molecular electrostatic potentials. The need for high sampling density in formamide conformational analysis, *J. Comp. Chem.* 11 (1990) 361-373.
- [32] D. R. Lide, Ed. *CRC Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL, 2005.
- [33] N. B. Colthup, *Introduction to Infrared and Raman Spectroscopy*, Academic Press, New York, 3rd Edition. 1990.

- [34] L. J. Bellamy, *Advances in Infrared Group Frequencies*, Chapman and Hall, London, 1975, pp. 141-142.
- [35] A. Gaset, L. Lafaille, A. Verdier, A. Lattes, Infrared spectra of α -aminoketones: conformational study and evidence of an enol form, *Bull. Soc. Chim. Fr.* 10 (1968) 4108-4112.
- [36] C. C. Levin, R. Hoffmann, W. J. Hehre, J. Hudec, Orbital interaction in amino-ketones, *J. Chem. Soc. Perkin 2* (1973) 210-220.
- [37] S. David, O. Eisenstein, W. J. Here, L. Salem, R. Hoffmann, Superjacent orbital control. Interpretation of the anomeric effect, *J. Am. Chem. Soc.* 95 (1973) 3806-3807.

Figure and Scheme Captions

Fig. 1. IR spectra of 2-(phenylselanyl)-2-(methoxy)-4'-methoxyacetophenone **1**, 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. IR spectra of 2-(phenylselanyl)-2-(methoxy)-acetophenone **2**, 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. 3. IR spectra of 2-(phenylselanyl)-2-(methoxy)-4'-chloroacetophenone **3**, 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. 4. Molecular structures of the conformers of **2** obtained at the B3LYP/6-31+G(d,p) level. Adopted colours: H = white, C = grey, O = red, Se = orange.

Fig. 5. ORTEP view of the asymmetric unit of **1** showing atom labelling and displacement ellipsoids at the 30% probability level.

Fig. 6. ORTEP view of the two independent molecules in the asymmetric unit of **2**, showing atom labelling and displacement ellipsoids at the 50% probability level.

Scheme 1. Atom labelling of 4'-substituted 2-(phenylselanyl)-2-(methoxy)-acetophenones and definition of the relevant dihedral angles.

Supplementary Figures

Fig. S1. Trimer of **1** joined through two C-H... π interactions.

Fig. S2. Trimer of **2** evidencing C-H...O interactions.

Fig. S3. Tetramer of **2** highlighting C-H... π and C-H...O interactions.