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**Conformational Analysis and Electronic Interactions of
Some 4'-substituted-2-ethylthio-phenylacetates**

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3 **Conformational analysis and electronic interactions of some 4'-**
4 **substituted-2-ethylthio-phenylacetates**
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Abstract

The conformational analysis of various 4'-substituted-2-ethylthio-phenylacetate compounds bearing the substituents NO₂ (**1**), Cl (**2**), H (**3**), Me (**4**) and OMe (**5**) was performed using infra-red (IR) spectroscopic analysis of the carbonyl stretching band (ν_{CO}) supported by B3LYP/6-31G(d,p), NBO, QTAIM and SM5.42R calculations for compounds **1**, **3** and **5**. The IR spectra in *n*-hexane indicate the presence of three components, whose intensities decrease upon increasing frequency. In solvents with high permittivity, while the low intensity component at higher frequency disappears, the relative intensity of the component at the intermediate frequency changes with respect to the lower frequency component with differing trends for the various derivatives. It can be observed that the intensity does not vary for compounds **1** and **2** that bear a electron withdrawing substituent at 4', while it increases in intensity for compounds **3-5**. The computational results predict the presence of three *gauche* conformers, defined by the orientation of the C-S bond with respect to the carbonyl group, whose intensities and ν_{CO} frequencies are in agreement with the experimental results. In solvents with increasing permittivity, the SM5.42R solvation model results reproduce the experimental trend observed for the two components in the low frequency region, while it overestimates the amount of the higher frequency conformer. NBO analysis suggests that all the conformers are stabilized to the same extent in the *gauche* conformation via $\sigma_{\text{C-S}} \rightarrow \pi^*_{\text{CO}}$ and $\pi_{\text{CO}} \rightarrow \sigma^*_{\text{C-S}}$ orbital interactions. The different stability can be attributed to the geometrical arrangement of the C(O)-CH₂-S-CH₂-CH₃ moiety, which assumes a six membered *chair*-like geometry in the g_1 conformer, a six membered *twisted-chair* like geometry in the g_2 conformer and a seven-membered *chair*-like ring in the g_3 conformer. Quantum theory of atoms in molecules (QTAIM) indicates that the ring geometries were formed and stabilized from short contacts between the oppositely

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3 charged carbonyl oxygen and the methylene/methyl hydrogen atoms, which interact
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5 through unusual intramolecular electrostatic hydrogen bonding that satisfies the
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7 Popelier criteria.
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1. Introduction

The conformational analysis of several acetate derivatives with various techniques have shown that the C=O and O-R groups in the O=C-O-R moiety preferentially assume a *cis* conformation in aliphatic acetates, both in solution¹ and in pure solvents.² The opposite *trans* conformation is found in aromatic acetates. For instance, the carbonyl stretching (ν_{CO}) of phenyl acetate shows three bands, one assigned to the *trans* conformer and the remaining to a Fermi resonance.^{3,4} A later infrared and Raman spectroscopy study on phenyl-*d*₅ and phenyl-*d*₃ acetates has shown that the carbonyl stretching vibration gives rise to a single symmetric ν_{CO} band.⁵ On the other hand, *ab initio* calculations⁶ suggest that the most stable conformer for phenyl acetate is the *cis* conformer in which the phenyl ring is orthogonal to the carbonyl group.

Previous spectroscopic (IR, UV, NMR and UPS) and theoretical studies on a variety of related compounds, for instance (α -alkylthio)-acetones, α -phosphorylaceto phenones, *p*-substituted-phenyl α -ethylsulfonylthioacetates and 2-sulfinyl-(4'-)-phenylthioacetates,⁷⁻¹³ indicate that the $n_{\text{S}} \rightarrow \pi^*_{\text{C=O}}$, $\sigma_{\text{C-S}} \rightarrow \pi^*_{\text{C=O}}$ and $\pi_{\text{C=O}} \rightarrow \sigma^*_{\text{C-S}}$ orbital interactions are the main factors that stabilize the *gauche* conformer over the *cis* conformer with respect to the α dihedral angle of O=C-C-S.

The present paper reports infra-red (IR) spectroscopic and theoretical studies of a variety of 4'-substituted-2-ethylthio-phenylacetates [EtSCH₂C(O)OPh-Y] bearing electron-withdrawing, hydrogen and electron-donating substituents [Y = NO₂ (**1**), Br (**2**), H (**3**), Me (**4**) and OMe (**5**)] in the *para* position of the phenyl ring. These compounds were chosen by taking into account that the inductive and mesomeric effects of the substituents may affect both the electrostatic and orbital interactions, and therefore the relative conformer populations for each compound, with the aim of recognizing the prevalent effects that determine the conformational equilibrium.

2. Experimental

2.1. Materials

All solvents used for IR measurements were of spectroscopic grade and used without further purification. The 4'-substituted-2-ethylthio-phenylacetates **1-5** are novel compounds and were prepared as follows: A solution of 2-ethylthioacetylchloride (1.7 mL, 16 mmol) in anhydrous ether (20 mL) at 0 °C was added dropwise to a stirred solution of 4'-substituted phenol (16 mmol) and pyridine (1.3 mL, 16 mmol) in anhydrous diethyl ether (14 mL). The reaction mixture was maintained at room temperature for 4 h and then washed with a solution of HCl (0.1 mol L⁻¹), water, a solution of NaOH (2%) and water. The organic layer was dried over anhydrous magnesium sulfate and the solvent removed in vacuo. Finally, the crude oil was purified by distillation under reduced pressure to obtain the corresponding product. 2-ethylthioacetylchloride was prepared using a literature procedure.¹⁴ The ¹H and ¹³C NMR spectra for compounds **1-5** and their elemental analyses have been reported in Table 1.

Table 1. Physical, ^1H and ^{13}C NMR spectra and elemental analysis for 4'-substituted-2-(ethylthio)-phenylacetates.

comp.	Y	^1H NMR ^a	^{13}C NMR	molecular formula	elemental analysis (%)		
					Calc.	C	H
1	NO ₂	8.26–8.24 (2H, m), 7.30–7.28 (2H, m), 3.45 (2H, s), 2.73 (2H, q, 7.5), 1.31 (3H, t, 7.5)	168.13, 155.32, 145.46, 125.26, 122.31, 33.25, 26.89, 14.21	C ₁₀ H ₁₁ NO ₄ S	Calc.	49.78	4.60
					Found	49.73	4.45
2	Br	8.52–8.49 (2H, m), 7.03–7.00 (2H, m), 3.44 (2H, s), 2.76 (2H, q, 7.5), 1.33 (3H, t, 7.5)	168.71, 149.64, 132.51, 123.16, 119.12, 33.22, 26.79, 14.22	C ₁₀ H ₁₁ BrO ₂ S	Calc.	43.65	4.03
					Found	43.88	4.01
3	H	7.41–7.37 (2H, m), 7.26–7.24 (2H, m), 7.13–7.11 (2H, m), 3.44 (2H, s), 2.77 (2H, q, 7.5), 1.34 (3H, t, 7.5)	169.04, 150.63, 129.45, 126.00, 121.34, 33.30, 23.74, 14.25	C ₁₀ H ₁₂ O ₂ S	Calc.	61.20	6.16
					Found	61.33	6.29
4	Me	7.21–7.17 (2H, m), 7.03–7.01 (2H, m), 3.46 (2H, s), 2.78 (2H, q, 7.5), 2.37 (3H, s), 1.36 (3H, t, 7.5)	169.29, 148.44, 135.70, 129.97, 121.01, 33.32, 26.76, 20.87, 14.26	C ₁₁ H ₁₄ O ₂ S	Calc.	62.83	6.71
					Found	62.62	6.66
5	OMe	7.05–7.02 (2H, m), 6.90–6.87 (2H, m), 3.79 (3H, s), 3.42 (2H, s), 2.75 (2H, q, 7.5), 1.34 (3H, t, 7.5)	169.47, 157.38, 144.15, 122.09, 114.15, 55.59, 33.28, 26.76, 14.26	C ₁₁ H ₁₄ O ₃ S	Calc.	58.48	6.24
					Found	58.68	6.24

^a ^1H and ^{13}C chemical shifts are reported in ppm relative to TMS using CDCl₃ as the NMR solvent. Coupling constants are reported in Hz.

2.2. IR spectroscopy

The IR spectra were recorded using a Michelson Bomem MB100 FTIR 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 using a 0.519 mm sodium chloride disc for the fundamental carbonyl region (1800–1600 cm⁻¹). The spectra of the carbonyl first overtone (3600–3100 cm⁻¹) were recorded in carbon tetrachloride (**2-5**) and dichloromethane (**1** and **6**) solution (1.0 × 10⁻² mol dm⁻³) using a 1.00 cm quartz cell. The overlapped carbonyl bands (fundamental and first overtone) were resolved using the Grams/32 curve fitting software, version 4.04, Level II.¹⁵ The population of the *gauche* conformers (*g*₁, *g*₂ and *g*₃) were estimated from the maximum of each component of the resolved carbonyl doublet or triplet and were expressed as a percentage of the absorbance, assuming equi-molar absorptivity co-efficients for the referred conformers.

2.3. NMR spectroscopy

¹H NMR and ¹³C NMR spectra were recorded on a Varian Inova 300 spectrometer operating at 300 and 75 MHz (**2** and **5**) and on a Bruker DRX 500 spectrometer operating at 500 and 125 MHz (**1**, **3** and **4**), respectively, for 0.1 mol dm⁻³ solutions using chloroform-*d* as the NMR solvent. ¹H and ¹³C chemical shifts were reported in ppm relative to the internal standard, TMS.

2.4. Theoretical calculations

The input guess geometries were obtained using the *Conformer Distribution* program with MMFF¹⁶ as implemented in the SPARTAN06 package¹⁷ and duplicates were discarded. It should be pointed out that these initial conformations are quite similar to those obtained by varying the γ dihedral angle (see results and discussion section) at the B3LYP/6-31G(d,p) level. Calculations for the gas phase geometry, harmonic vibrational modes and orbital interactions were carried out (at 298 K) for compound **1**, **3** and **5**, using the methods and basis sets implemented in the Gaussian 03 software. Condensed phase calculations were carried out using AMSOL 7.1¹⁸ software for Windows. The hybrid functional B3LYP¹⁹ with 6-31G(d,p) basis set²⁰ were used to fully optimize all *gauche* geometries and to calculate the harmonic frequencies and zero-point vibrational energies (ZPVE). The SM5.42R solvation model^{21, 22} at the PM3 level²³ simulates the solvent interactions and allows the determination of the Gibbs free energy of solvation,²⁴ while the NBO 3.1 program²⁵ implemented in the Gaussian 09²⁶ package was used to estimate the delocalization energy (E2) by means of the second-order perturbation theory. Quantum theory of atoms in molecules (QTAIM) was performed using the AIMALL software for a detailed interpretation of the results.²⁷ For

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3 comparison with the SM5.42R solvation model, PCM²⁸ and SMD²⁹ calculations were
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5 also performed as implemented in the Gaussian 09 package.
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9 10 **3. Results and Discussion**

11 The frequency and relative intensity of the resolved components of the carbonyl
12 stretching band for compounds **1-5** in solvents with increasing relative permittivity are
13 reported in Table 2. With the exception of compound **1**, which was not soluble in *n*-
14 hexane, the band shape for compounds **2-5** in *n*-hexane ($\epsilon = 1.9$) indicates the presence
15 of at least three main components, whose intensities decrease upon increasing
16 frequency. Upon increasing the permittivity of the solvent, two main effects can be
17 observed. In particular, the low intensity component at a higher frequency was no
18 longer detectable and the relative intensities of the two remaining components change at
19 different extents. For instance, in a solvent with medium permittivity, such as carbon
20 tetrachloride ($\epsilon = 2.2$), the intensity of the component in the lower frequency region
21 increases with respect to the second component for compounds **2** and **3**, while it
22 decreases for compounds **4** and **5**. In solvents with greater permittivity (chloroform,
23 dichloromethane and acetonitrile), the two components show an opposite trend. In
24 particular, the average intensity of the higher frequency component decreases for
25 compounds **1** and **2**, which are molecules bearing an electron-withdrawing substituent at
26 4'. For compounds **3-5**, the average intensity of the higher frequency component
27 increases with increasing permittivity and becomes relatively more intense to those
28 found in compounds **3** and **4** in all solvents. The solvent effect on the carbonyl band
29 components is illustrated in **Figure 1** for compound **3**, which was taken as a
30 representative of all the molecules investigated. The matching between the carbonyl
31 doublet profiles in the fundamental and the first overtone region (the latter was
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measured at the frequency twice that of the fundamental minus two times the mechanical anharmonicity⁴ of *ca.* 17 cm⁻¹) indicates the existence of at least two conformers in solution for compounds **1-5**,^{7,30} ruling out the existence of any vibrational effect on the fundamental transition of the ν_{CO} mode.

Table 2. The frequency (ν , cm⁻¹) and relative intensity of the carbonyl stretching band component in the IR spectra of 4'-substituted-2-ethylthio-phenylacetates [CH₃CH₂SCH₂C(O)OC₆H₄-Y (**1-5**)].

comp.	Y	<i>n</i> -C ₆ H ₁₄		CCl ₄				CHCl ₃		CH ₂ Cl ₂		CH ₃ CN	
		ν	<i>P</i> ^a	ν	<i>P</i>	ν ^b	<i>P</i>	ν	<i>P</i>	ν	<i>P</i>	ν	<i>P</i>
1	NO ₂	---	---	1778	29	3527	28	1776	24	1777	25	1776	32
		---	---	1760	71	3499	72	1756	76	1758	75	1758	68
2	Br	1778	22	---	---	---	---	---	---	---	---	---	---
		1769	31	1767	35	3523	36	1768	31	1769	32	1769	35
		1757	47	1753	65	3488	64	1748	69	1750	68	1752	65
3	H	1777	13	---	---	---	---	---	---	---	---	---	---
		1768	30	1766	31	3510	30	1754	71	1754	84	1757	84
		1757	57	1753	69	3483	70	1741	29	1742	16	1744	16
4	Me	1777	7	---	---	---	---	---	---	---	---	---	---
		1768	35	1762	47	3509	44	1754	57	1756	58	1759	60
		1757	58	1751	53	3482	56	1741	43	1745	42	1750	40
5	OMe	1775	11	---	---	---	---	---	---	---	---	---	---
		1766	23	1761	41	3516	37	1758	36	1757	46	1758	46
		1756	66	1750	59	3483	63	1745	64	1746	54	1749	54

^a The intensity of each component of the carbonyl stretching band is expressed as a percentage of the absorbance. ^b First overtone. ^c Compound not soluble in *n*-C₆H₁₄. ^d Undetected component.

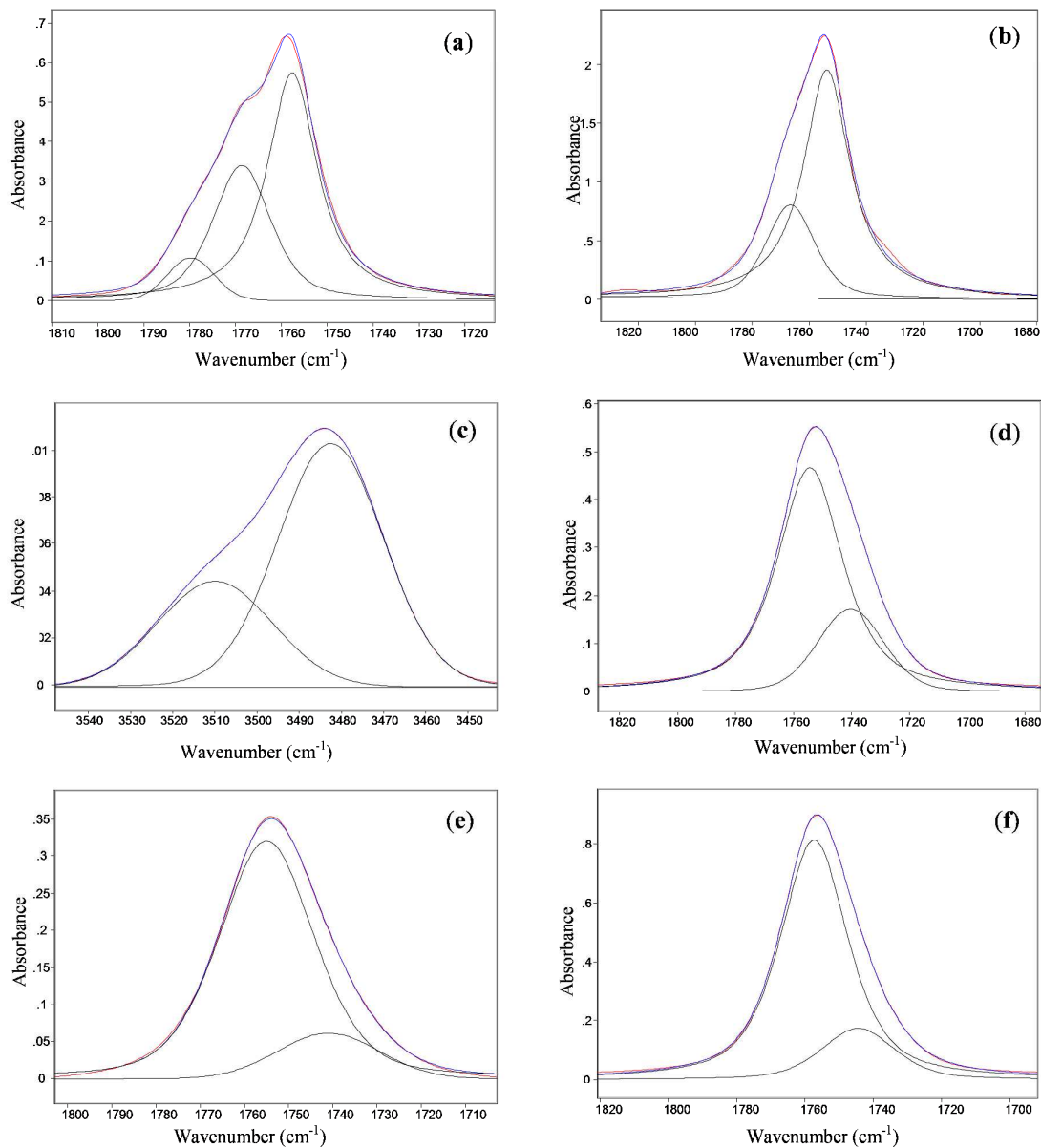


Figure 1. IR spectra of the carbonyl stretching band of 2-ethylthio-phenylacetate (**3**) in *n*-hexane (**a**), carbon tetrachloride [fundamental (**b**) and the first overtone (**c**)], chloroform (**d**), dichloromethane (**e**) and acetonitrile (**f**).

The relative Gibbs free energy, relative populations, dipole moments, carbonyl stretching frequencies and dihedral angles at the B3LYP/6-31g(d,p) level of theory for **1** (Y = NO₂), **3** (Y = H) and **5** (Y = OMe) are reported in **Table 3** and are taken as

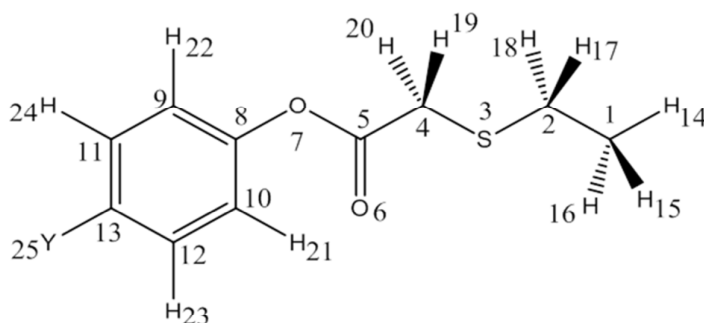
representatives for the whole series of compounds **1-5**. Moreover, the atom and dihedral angle labeling are summarized in **Scheme 1**.

Table 3. The relative free energies (kcal mol⁻¹), dipole moment (μ , D), carbonyl stretching band (ν , cm⁻¹) and selected dihedral angles ($^\circ$) for the minimum energy conformations of compounds **1**, **3** and **5** at the B3LYP/6-31G(d,p) level of theory.

comp.	Y	conf.	$\Delta G (E)^a$	$P (P)^b$	μ	ν	dihedral angles ^c				
							α	β	γ	δ	Φ
1	NO ₂	g_1	0.00 (0.00)	50 (47)	5.1	1827	-88	68	72	2	-42
		g_2	0.16 (0.11)	39 (39)	5.3	1830	-85	73	176	3	36
		g_3	0.89 (0.69)	11 (14)	5.4	1836	-101	88	-75	4	-45
3	H	g_1	0.00 (0.00)	45 (50)	2.6	1834	-84	67	65	-175	93
		g_2	0.02 (0.16)	43 (35)	2.7	1838	84	69	176	177	90
		g_3	0.78 (0.98)	12 (15)	2.9	1842	-93	85	-78	-174	91
5	OMe	g_1	0.00 (0.00)	46 (52)	3.5	1832	-84	62	66	-175	-90
		g_2	0.05 (0.18)	42 (37)	3.6	1835	85	-70	174	177	91
		g_3	1.08 (1.03)	12 (11)	3.9	1840	-93	84	-78	-174	93

^aThe relative free Gibbs energy (relative electronic energy plus ZPE correction). ^bThe relative population is reported as a percentage. ^cSee **Scheme 1**.

SCHEME 1



Y = NO₂ (1), Br (2), H (3), Me (4), OMe (5)

α = O(6)=C(5)-C(4)-S(3)

β = C(5)-C(4)-S(3)-C(2)

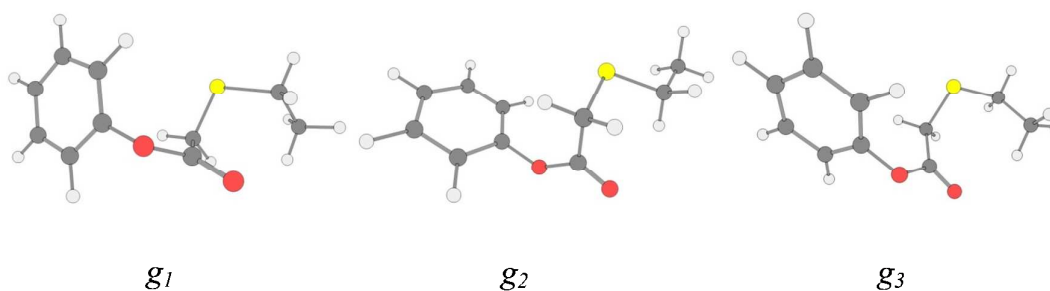
γ = C(4)-S(3)-C(2)-C(1)

δ = O(6)=C(5)-O(7)-C(8)

ϕ = C(5)-O(7)-C(8)-C(9)

Atoms labeling and definition of the relevant dihedral angles

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3 The calculation results for compounds **1**, **3** and **5** suggest the presence of three
4 stable *gauche* conformers in vacuo, labeled in order of decreasing stability and
5 increasing carbonyl stretching frequency as g_1 (ca. 50%, 1832 cm^{-1}), g_2 (ca. 37%, 1835
6 cm^{-1}) and g_3 (ca. 13%, 1838 cm^{-1}). The computed relative populations, as well as the
7 ν_{CO} frequencies of the three conformers are in good agreement with the experimental
8 findings of the IR spectra recorded in *n*-hexane for compounds **2-5**. All the
9 corresponding equilibrium geometries are shown in **Figure 2**. It should be noted that all
10 the conformers of a specific compound have almost equal dipole moments, *i.e.* ca. 5.3
11 D, 2.7 D and 3.6 D for compounds **1**, **3** and **5**, respectively (**Table 3**).
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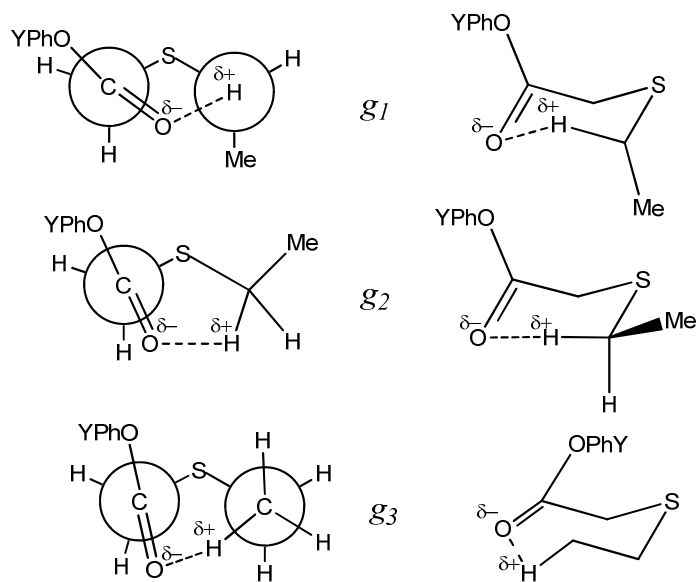


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36 **Figure 2.** The g_1 , g_2 and g_3 *gauche* conformers of compound **3** obtained at the
37 B3LYP/6-31G(d,p) level.
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42 The α dihedral angle (O=C-C-S) varies between 84–88° for the g_1 and g_2
43 conformers and between 93–101° for the g_3 conformer. These relatively small changes
44 suggest that the major contribution to the stability of the conformers should involve
45 other geometrical parameters (**Scheme 2**), for instance the equilibrium arrangement
46 with respect to the dihedral angles β (C-C-S-C) and γ (C-S-C-C). As a matter of fact, the
47 values of ca. 65° and ca. 68° for the β and γ dihedral angles, respectively, constrain the
48 g_1 conformers to adopt a six-membered *chair*-like geometry that was strongly stabilized
49 by the attractive electrostatic interactions between the oppositely charged carbonyl
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oxygen and methylene hydrogen (17) atoms separated by an interatomic distance that is significantly shorter than the sum of the van der Waals (Σ vdW) radii (Table 4 and 5). As far as the g_2 conformers are concerned, the values of the β dihedral angles are very close to those of the g_1 conformers (*ca.* 70°), while the γ angles increase up to *ca.* 175° . In this case, the attractive electrostatic interactions involving the positively charged methylene hydrogen (17) and the negatively charged carbonyl oxygen atoms, whose distance was shorter than the Σ vdW radii, leads to a six-membered ring configuration analogous to a *twisted chair* conformation. Finally, the β dihedral angle of *ca.* 86° and γ dihedral angle of *ca.* 77° for the g_3 conformer favors a seven-membered *chair*-like conformation that was stabilized by short contact interactions between the oppositely charged carbonyl oxygen and methyl hydrogen (14) atoms.

SCHEME 2



Y = NO₂ (1), H (3), OMe (5)

Table 4. Selected distances (Å) for the minimum energy conformations for compounds **1**, **3** and **5** at the B3LYP/6-31G(d,p) level of theory.

Comp.	Y	conf.	interatomic distances									
			O _{(6)...} H ₍₂₁₎ ^a	Δl^b	O _{(6)...} H ₍₁₇₎	Δl	O _{(6)...} H ₍₁₄₎	Δl	O _{(6)...} S ₍₃₎	Δl	S _{(3)...} C ₍₅₎	Δl
1	NO₂	<i>g</i> ₁	2.44	-0.28	2.57	-0.15	>4	---	3.45	0.13	2.75	-0.75
		<i>g</i> ₂	2.38	-0.34	2.58	-0.14	>4	---	3.42	0.10	2.76	-0.74
		<i>g</i> ₃	2.47	-0.25	>4	---	2.53	-0.19	3.61	0.29	2.80	-0.70
3	H	<i>g</i> ₁	>4	---	2.55	-0.17	>4	---	3.41	0.09	2.77	-0.73
		<i>g</i> ₂	>4	---	2.52	-0.20	>4	---	3.42	0.10	2.77	-0.73
		<i>g</i> ₃	>4	---	>4	---	2.42	-0.30	3.54	0.22	2.82	-0.68
5	OMe	<i>g</i> ₁	>4	---	2.53	-0.19	>4	---	3.41	0.09	2.77	-0.73
		<i>g</i> ₂	>4	---	2.51	-0.21	>4	---	3.42	0.10	2.77	-0.73
		<i>g</i> ₃	>4	---	>4	---	2.42	-0.30	3.55	0.23	2.82	-0.68
$\Sigma_{vdW}r$			2.72		2.72		2.72		3.32		3.50	

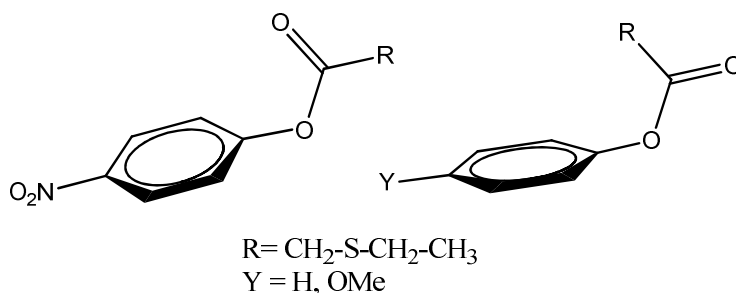
^a Interatomic distances. ^b The difference between the non-bonded atoms and the sum of the van der Waals radii.

Table 5. NPA charges (e) at selected atoms in compounds **1**, **3** and **5** obtained at the B3LYP/6-31G(d,p) level of theory.

comp.	Y	conf.	H(21)	H(17)	H(14)	O(6)	C(5)	S(3)
1	NO₂	<i>g</i> ₁	0.273	0.260	0.233	-0.581	0.817	0.233
		<i>g</i> ₂	0.275	0.257	0.243	-0.581	0.819	0.232
		<i>g</i> ₃	0.272	0.244	0.250	-0.576	0.823	0.231
3	H	<i>g</i> ₁	0.254	0.261	0.237	-0.574	0.817	0.221
		<i>g</i> ₂	0.254	0.263	0.239	-0.572	0.818	0.219
		<i>g</i> ₃	0.254	0.244	0.257	-0.570	0.823	0.220
5	OMe	<i>g</i> ₁	0.255	0.262	0.237	-0.576	0.817	0.219
		<i>g</i> ₂	0.255	0.263	0.238	-0.575	0.818	0.216
		<i>g</i> ₃	0.254	0.243	0.257	-0.573	0.823	0.220

The phenyl ring orientation with respect to the carbonyl group can be defined by the δ (O=C-O-C) and φ (C-O-C=C) dihedral angles. These angles have similar values for all the conformers of a specific derivative but differ to a large extent for the various compounds depending on the nature of the Y substituent. In particular, δ and φ are about 3° and 41°, respectively, for compound **1**, while both increase to about 176° and 91°, respectively, for compounds **3** and **5** (Table 3). For compound **1**, the small values for δ

and φ allow the short contact stabilizing interaction, $\delta^- \text{O}_{\text{CO}} \dots \text{H}(21)^{\delta+}$, which favors the *s-cis* conformation of the O=C-O-Ph moiety in this derivative (**Scheme 3**).

SCHEME 3

The conformers g_1 , g_2 , and g_3 have geometrical characteristics to form an intramolecular hydrogen bond (IHB) and their molecular graphs shown in **Figure 3** indicate that there is the formation of a bond path (BP) and bond critical point (BCP), referring to the non-usual $\text{O} \cdots \text{HC}$ IHB that satisfies the Popelier criteria, even if a relatively high ellipticity value of 0.2 for g_1 and g_2 and a small value of 0.04 for g_3 occurs. Other topological criteria were also evaluated (**Table 6**), since the same must be satisfied for the IHB exhibited by BPs to be stable and stabilize the conformer. The electron density (ρ_{BCP}) and electronic density Laplacian ($\nabla^2 \rho_{\text{BCP}}$) values at the BCP indicate that the interaction between the two moieties was a closed-shell one, such as an ionic and usual hydrogen bond interaction. Moreover, the ρ_{BCP} and $\nabla^2 \rho_{\text{BCP}}$ values are slightly higher for the g_3 conformer, in line with the stronger hydrogen bond interactions. Positive electron density energy (H) and positive values for the relationship $|V|/G$ between its kinetic (G) and potential energies (V) also corroborate with the assumption of an electrostatic hydrogen bond as suggested by Cremer and Kraka.³¹

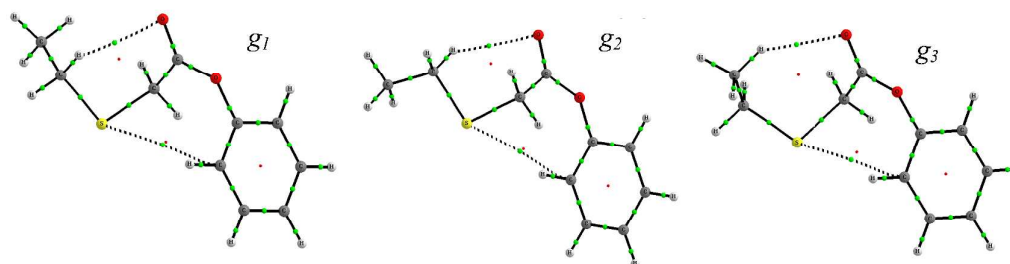


Figure 3. Molecular graphs for the g_1 , g_2 and g_3 conformers of compound **3**. The green points represent the bond critical points (BCP) and red points the ring critical points (RCP).

Table 6. The electronic densities (ρ), electronic density Laplacian ($\nabla^2\rho$) and bond ellipticity (ϵ), kinetic energy (G), potential energy (V) and Hamiltonian (H) of the H-bond BCP.

	BCP	ρ	$\nabla^2\rho$	E	G	V	H ^a	V /G
g_1	O ₆ H ₁₇	0.0091	0.0335	0.2739	0.0072	-0.0059	0.0012	0.8301
g_2	O ₆ H ₁₇	0.0094	0.0327	0.2081	0.0072	-0.0062	0.0010	0.8612
g_3	O ₆ H ₁₄	0.0107	0.0346	0.0467	0.0080	-0.0074	0.0006	0.9214

^a H = G + V

The presence of these IHB and their contribution to the conformers stability are further supported from the relaxed Potential Energy Surface (PES) scan calculated for compound **1** at the B3LYP/6-31G(d,p) level of theory as a function of the γ dihedral angle (**Figure 4**). The optimized geometry of the g_1 conformer was assumed as starting point and all the geometrical parameters were optimized at each step of 5° . The geometrical arrangements of the three minima allow short contact interactions between the oppositely charged carbonyl oxygen and the methylene/methyl hydrogen atoms, and correspond to the g_1 , g_2 and g_3 conformations. In particular, in the minimum at $\gamma = ca.$ 60° (g_1 conformer), the IHB occurs between O_{CO} and the methylene hydrogen H₁₇. On the contrary, in the second stable g_2 conformer ($\gamma = ca.$ 180°) the interaction involves the methylene hydrogen H₁₈. Finally, in the highest minimum at $\gamma = ca.$ -80° (the g_3 conformer), the short contact was established with one of the methyl group hydrogen atoms.

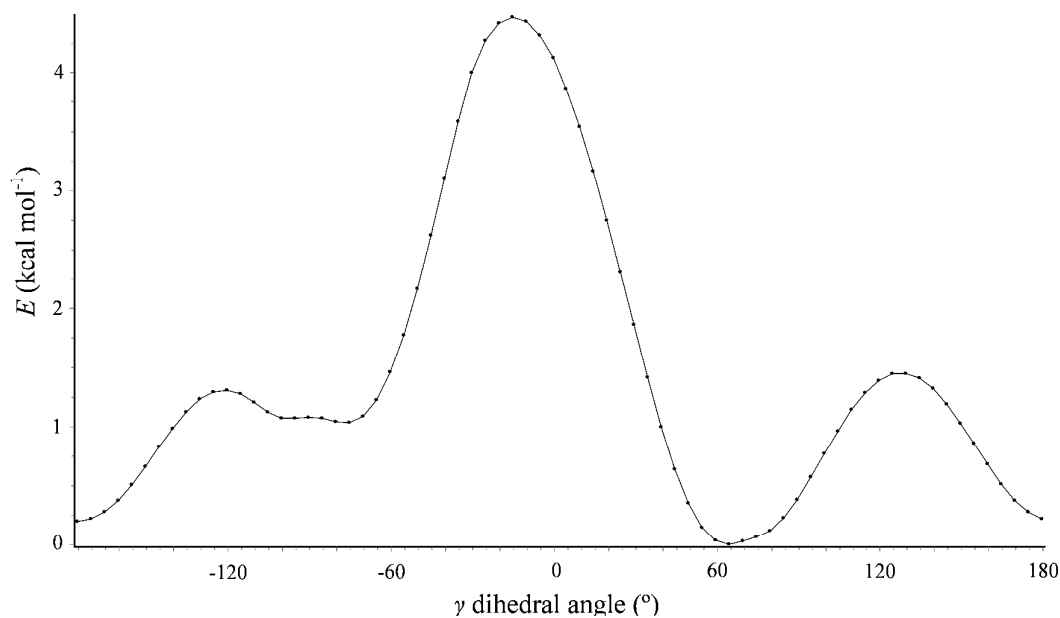


Figure 4. The relaxed potential energy surface (PES) of the γ dihedral angle ($C_4-S_3-C_2-C_1$) for compound **3** at the B3LYP/6-31G(d,p) level of theory.

The conformational equilibrium in the condensed phase of the three *gauche* conformers was studied by means of the SM5.42R solvation model at the PM3 level single point calculations for compounds **1**, **3** and **5**. The main results are reported in **Table 7** and indicate they are in accordance with the experimental findings obtained for compound **2-5** in *n*-hexane. In particular, the free energy of solvation was found to be similar for the three conformers ($\Delta_{\text{sol}}G = -9.9 \text{ kcal mol}^{-1}$), which indicates that they are stabilized to the same extent and their relative abundance was affected by negligible changes with respect to that calculated in the gas phase. Moreover, in line with the experimental IR assignments, the carbonyl stretching frequency increases as the conformer stability decreases.

In solvents with increasing permittivity, in contrast with the experimental IR spectra, the computational results predict the existence of the g_3 conformer, whose relative abundance was similar for all the derivatives and slightly affected by the nature of the

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3 solvent. On the contrary, the population of the g_1 and g_2 conformers undergo variations
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5 in line with the experimental data. In fact, the intermediate frequency g_2 conformer was
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7 stabilized to a larger extent with respect to the lower frequency g_1 conformer to become
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9 the relatively more abundant conformer for all the derivatives in solvents with a high
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11 dielectric constant such as chloroform, dichloromethane and acetonitrile. In summary,
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13 the variations in the relative abundance calculated for the g_1 and g_2 conformers were in
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15 agreement with the observed trend of the ν_{CO} doublets for compounds **3-5**, while the
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17 SM5.42R solvation model always overestimated the stabilization of the higher
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19 frequency g_3 conformer.
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23 In order to gain a better match with the experimental results, the three conformers of
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25 compounds **1**, **3** and **5** were fully optimized using a different approach with the PCM
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27 and SMD solvation models at the B3LYP/6-31G(d,p) level of theory. Unfortunately, no
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29 noticeable improvement was obtained with respect to the previous solvation model
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31 results. Once more, the calculations were not in line with the experimental IR data since
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33 they continue to predict the presence of the three conformers whose relative stabilities
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35 did not vary significantly in all the solvents studied. Therefore, these results will not be
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37 discussed further and are included in the supplementary information (**Table S1**, **Figure**
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39 **S1-S5**).
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Table 7 – Molar fraction in vacuo (%) obtained at the B3LYP/6-31G(d,p) level of theory, molar fraction (%) and free energy of solvation (kcal mol⁻¹) in the condensed phase obtained at the PM3 level of theory using the SM5.42R solvation model for compounds **1**, **3** and **5**.

comp.	Y	conf.	vacuum	<i>n</i> -C ₆ H ₁₄		CCl ₄		CHCl ₃		CH ₂ Cl ₂		CH ₃ CN	
			P ^a	P	Δ _{sol} G ^b	P	Δ _{sol} G	P	Δ _{sol} G	P	Δ _{sol} G	P	Δ _{sol} G
1	NO ₂	<i>g</i> ₁	47	47 ^c	-9.8 ^c	43	-12.5	37	-14.7	33	-15.9	30	-14.8
		<i>g</i> ₂	39	43 ^c	-9.9 ^c	43	-12.6	48	-14.9	52	-16.3	57	-15.4
		<i>g</i> ₃	14	10 ^c	-9.8 ^c	14	-12.6	15	-14.8	15	-16.2	13	-15.1
3	H	<i>g</i> ₁	50	48	-9.8	46	-11.1	43	-12.7	43	-13.6	37	-12.8
		<i>g</i> ₂	35	42	-9.9	44	-11.2	46	-12.9	43	-13.9	51	-13.7
		<i>g</i> ₃	15	10	-9.8	10	-11.2	11	-12.9	14	-14.0	12	-13.3
5	OMe	<i>g</i> ₁	52	48	-9.8	47	-11.2	43	-13.9	40	-13.8	37	-12.8
		<i>g</i> ₂	37	42	-9.9	43	-11.3	45	-13.1	46	-14.1	49	-13.1
		<i>g</i> ₃	11	10	-9.9	10	-11.3	12	-13.2	14	-14.2	14	-13.2

^a Molar fraction. ^b Free energy of solvation. ^c Experimental data was not obtained for comparison.

Natural bond orbital (NBO) analysis was performed for compounds **1**, **3** and **5** to recognize the relevant orbital interactions that contribute to conformer stabilization. In a previous discussion it was pointed out that the α dihedral angle assumes a similar value for the *g*₁ and *g*₂ conformers and was slightly greater for the *g*₃ conformers for all the derivatives studied. Therefore, it was reasonable to infer that the sum of the energies of the two main orbital interactions responsible for this geometrical arrangement ($\sigma_{C4-S3} \rightarrow \pi^*_{C5=O6}$ and $\pi_{C5=O6} \rightarrow \sigma^*_{C4-S3}$) should be comparable for the *g*₁ and *g*₂ conformers and slightly smaller for the *g*₃ conformers, regardless of the derivatives. This conclusion was confirmed by the NBO values reported in Table 8. In fact, although the former interaction mainly stabilizes the *g*₁ and *g*₂ conformers and the latter was slightly greater for the *g*₃ conformer, their sum was almost coincident with an average value of about 8.0 kcal mol⁻¹ for the *g*₁ and *g*₂ conformers and about 7.7 kcal mol⁻¹ for the *g*₃

conformer. In conclusion, these orbital interactions are likely to play a minor role in determining the observed difference in stability of the three *gauche* conformers.

Table 8. A comparison of the significant NBO interactions (kcal mol⁻¹) for the g_1 , g_2 and g_3 conformers of compounds **1**, **3** and **5** at the B3LYP/6-31G(d,p) level of theory.

orbitals	NO ₂ (1)			H (3)			OMe (5)		
	g_1	g_2	g_3	g_1	g_2	g_3	g_1	g_2	g_3
	E^a			E			E		
LP _{O7} (p)→π* _{C5=O6}	41.62	41.96	40.99	41.96	41.51	42.82	42.46	41.87	42.20
LP _{O7} (sp ₂)→π* _{C8=C9}	15.86	18.81	14.98	17.06	17.06	16.96	17.04	17.03	16.94
σ _{C4-S3} →π* _{C5=O6}	6.20	6.20	5.60	5.61	5.54	5.12	5.55	5.51	5.06
π _{C5=O6} →σ* _{C4-S3}	2.10	2.02	2.22	2.32	2.29	2.46	2.32	2.31	2.48
σ _{C4-S3} →σ* _{C2-H18}	1.02	---	0.91	0.99	---	0.88	1.00	---	0.88
σ _{C2-H18} →σ* _{C4-S3}	1.91	---	1.90	2.07	---	1.87	2.04	---	1.86
σ _{C4-S3} →σ* _{C2-C1}	---	1.26	---	---	1.25	---	---	1.25	---
σ _{C2-C1} →σ* _{C4-S3}	---	0.88	---	---	0.90	---	---	0.89	---
σ _{C5-C4} →σ* _{C5=O6}	0.95	0.93	0.95	0.74	0.74	0.76	0.72	0.72	0.74
σ _{C5=O6} →σ* _{C5-C4}	1.30	1.29	1.33	0.93	0.93	0.95	0.91	0.92	0.94
σ _{C2-S3} →σ* _{C4-H20}	---	1.17	---	---	1.14	---	---	1.13	---
σ _{C2-S3} →σ* _{C4-H19}	1.21	---	0.97	1.15	---	0.94	1.15	---	0.94
σ _{C4-H19} →σ* _{C2-S3}	---	1.27	---	---	1.28	---	---	1.28	---
σ _{C4-H20} →σ* _{C2-S3}	1.48	---	1.17	1.54	---	1.17	1.53	---	1.19
LP _{S3} (p)→π* _{C5=O6}	2.43	2.40	2.20	1.91	2.07	1.92	1.92	2.06	1.88
LP _{S3} (p)→σ* _{C4-H19}	---	1.82	0.63	---	1.99	0.55	---	1.98	0.53
LP _{S3} (p)→σ* _{C4-H20}	2.34	---	0.93	2.65	---	0.98	2.57	---	1.01
LP _{S3} (sp)→σ* _{C2-H17}	2.86	3.33	---	3.27	3.24	---	3.14	3.14	---

^a Interaction energy. ^b Interaction energy smaller than 0.5 kcal mol⁻¹.

The two oxygen (O7) lone pairs, LP_{O7(p)} and LP_{O7(sp₂)}, exhibit the appropriate symmetry to interact with the π*_{CO} (π*_{C5=O6}) and the π*_{ring} (π*_{C8=C9}) orbitals, respectively. These orbital interactions contribute to different extents towards the stabilization of the various conformers of compounds **1**, **3** and **5**. The stronger LP_{O7(p)}→π*_{C5=O6} interaction stabilizes all the conformers of all the derivatives to the same extent, namely by an average value of 41.9 kcal mol⁻¹. On the contrary, the interaction energy of the relatively weaker LP_{O7(sp₂)}→π*_{C8=C9} depends on the phenyl configuration with respect to the O(7)-C_{CO} bond, which was obtained from the values assumed by the φ dihedral angle. For instance, for compounds **3** and **5** that exhibit a

larger φ dihedral angle for all the conformers (*ca.* 91°), the stabilization was *ca.* 17.0 kcal mol⁻¹. On the other hand, for compound **1** this delocalization energy increases as φ decreases, varying from 14.94 kcal mol⁻¹ for the g_3 conformer ($\varphi = 45^\circ$) up to 18.81 kcal mol⁻¹ for the g_2 conformer ($\varphi = 36^\circ$).

The values of the γ dihedral angle account for the weak orbital interactions related to the position of the C(4)-S(3) bond with respect to the C(2)-H(18) or C(2)-C(1) bonds. In the g_1 and g_3 conformers, the six-membered (g_1) and the seven-membered (g_3) *chair-like* geometries of the aliphatic moiety previously described were favored by the orbital interactions $\sigma_{C4-S3} \rightarrow \sigma^*_{C2-H18}$ and $\sigma_{C2-H18} \rightarrow \sigma^*_{C4-S3}$, while in the g_2 conformer, the *twisted chair* conformation was maintained by the $\sigma_{C4-S3} \rightarrow \sigma^*_{C2-C1}$ and $\sigma_{C2-C1} \rightarrow \sigma^*_{C4-S3}$ interactions. Additionally, the three conformers were stabilized to a similar extent by the relatively larger $LP_{S3(sp)} \rightarrow \sigma^*_{C2-H17}$ and $LP_{S3(sp)} \rightarrow \pi^*_{C5=O6}$ orbital interactions that involve the sulfur atom (S3) lone pair.

5. Conclusions

The conformational preferences of the α -ethylthio *p*-substituted phenylacetates [EtSCH₂C(O)OPh-Y, Y = NO₂ (**1**), Br (**2**), H (**3**), Me (**4**) and OMe (**5**)] have been determined by ν_{CO} IR analysis (for compounds **1-5**) and theoretical calculations at the B3LYP/6-31G(d,p) level of theory (for compounds **1**, **3**, **5**). The theoretical results are in very good agreement with the IR spectra recorded in *n*-hexane, revealing the presence of three stable *gauche* conformers whose intensities decrease as the carbonyl stretching frequency increases. Moreover, the SM5.42R data shows that the stability of the lower frequency conformer (g_1) decreases relative to the intermediate frequency conformer (g_2) in solvents with a high dielectric constant, which is in agreement with the IR trend observed for compounds **3**, **4**, and **5**. However, this solvation model fails to reproduce

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3 the experimental findings in these solvents entirely. To be specific, the higher frequency
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5 component disappears and the IR spectra show only a doublet. On the contrary, the
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7 theoretical data continue to predict the existence of three conformers and overestimate
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9 the relative abundance of the higher frequency conformer (g_3).
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12 B3LYP/6-31G(d,p) calculations indicate that the three *gauche* conformers were
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14 stabilized by the $\sigma_{C4-S3} \rightarrow \pi^*_{C5=O6}$ and $\pi_{C5=O6} \rightarrow \sigma^*_{C4-S3}$ orbital interactions, which are
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16 responsible for their *gauche* geometry with respect to the α dihedral angle. The main
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18 difference between the conformers arises from the geometrical arrangement of the
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20 C(O)-CH₂-S-CH₂-CH₃ moiety, which can be described by the values of the β and γ
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22 dihedral angles. The most stable g_1 conformer displays a *chair-like* geometry, while the
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24 g_2 conformer, as a consequence of the wider γ dihedral angle, assumes a *twisted chair*
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26 conformation. In both cases, the six-membered ring closure occurs through an unusual
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28 O ^{δ^-} ₁₆...H ^{δ^+} ₁₇ electrostatic interaction. As for the g_3 conformer, the C(O)-CH₂-S-CH₂-
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30 CH₃ moiety was present as a seven-membered ring due to the short intramolecular
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32 contact, O ^{δ^-} ₁₆...H ^{δ^+} ₁₄. These interpretations are supported by QTAIM calculations,
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34 whose values at the BCP meet the Popelier criteria for electrostatic hydrogen bonding.
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36 Moreover, the three conformers were stabilized at about the same extent by the strong
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38 LP_{O7(p)}} \rightarrow π^*_{CO} and LP_{O7(sp2)}} \rightarrow π^*_{ring} interactions as a consequence of the suitable
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40 symmetry exhibited by the oxygen (O7) lone pairs. A series of relatively weak orbital
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42 interactions, *i.e.* $\sigma_{C-H} \rightarrow \sigma^*_{C-C}$, $\sigma_{C-C} \rightarrow \sigma^*_{C-H}$, LP_S \rightarrow σ^*_{C-C} , LP_S \rightarrow σ^*_{C-H} , $\sigma_{C-C} \rightarrow \sigma^*_{C-S}$ and
43
44 $\sigma_{C-H} \rightarrow \sigma^*_{C-S}$ contribute to mainly stabilize the g_1 conformer, followed by the g_2
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46 conformer and to a minor extent, the g_3 conformer. Finally, the O=C-O-C fragment
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48 assumes a *cis* geometry for all the conformers of compound **1** (Y = NO₂) and the
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50 opposite *trans* geometry for all the conformers of compounds **3** and **5**.
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