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Conformational analysis of some *N*,*N*-diethyl-2-[(4'-substituted) phenylthio] acetamides



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HIGHLIGHTS

- Conformational analysis of *N*,*N*-diethyl-2[(4'-substituted)phenylthio]acetamides.
- Solvent effect on the conformational equilibrium through IR spectrocopy.
- Theoretical calculations in the gasphase and in solvents (PCM).
- Single crystal X-ray diffraction analysis.

G R A P H I C A L A B S T R A C T



Most stable conformers g(anti; syn) **Y** = OMe **1**, Me **2**, H **3**, Cl **4**, Br **5**, NO₂**6**

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Conformational analysis Infrared spectroscopy Theoretical calculations X-ray diffraction analysis N,N-diethyl-2[(4'-substituted)phenylthio]acetamides Solvent effect ABSTRACT

The conformational analysis of some *N*,*N*-diethyl-2[(4'-substituted)phenylthio]acetamides bearing the substituents OMe **1**, Me **2**, H **3**, Cl **4**, Br **5** and NO₂ **6**, was performed by v_{CO} IR analysis, along with B3LYP/6-311++G(d,p) and Polarisable Continuum Model (PCM) calculations, as well as NBO analysis for **1**, **3**, and **6** and X-ray diffraction for **4**. The results of the calculations indicated the existence of two stable conformation pairs, i.e. *gauche (anti; syn)* (most stable) and *cis (anti; syn)* in the gas phase. The *gauche* conformers were less polar with respect to the *cis* ones for **1** and **3**, but more polar for **6**.

The most intense IR carbonyl doublet component observed at the lower frequency can be ascribed to the *gauche* conformers *g(anti; syn)* for **3–6** in *n*-C₆H₁₄, which is in agreement with the *gauche* and *cis* relative stabilities and frequencies resulting from the PCM calculations. Similarly, the single IR band for **1** and **2** in *n*-hexane may be attributed to the *gauche* conformers. The PCM calculations compared well with the IR data for the compounds in solution, showing that there is a progressive increase of the *cis/gauche* population ratio as the solvent polarity increases. The NBO analysis indicated that the *gauche(anti; syn)* conformation in the gas phase was stabilized by the relevant LP_{S4} $\rightarrow \pi^*_{c2=01}, \pi^*_{c2=01} \rightarrow \sigma^*_{c3-54}$, and LP₀₁ $\rightarrow \sigma^*_{C11-H28}$ orbital interactions, which were absent in the *cis(anti; syn)* conformer. On the contrary, the *cis* conformer for derivatives **1**, **3**, and **6** were stabilized by the $\sigma^*_{c3-54} \rightarrow \sigma^*_{c2-01}, \pi^*_{c2=01} \rightarrow \sigma^*_{c3-54}$, and LP₀₁ $\rightarrow \sigma^*_{c11-H28}$ orbital interactions, which were absent in the *cis(anti; syn)* conformer. On the contrary, the *cis* conformer for derivatives **1**, **3**, and **6** were stabilized by the $\sigma^*_{c3-54} \rightarrow \sigma^*_{c2-15}$ orbital interaction (through bond coupling), along with the additional LP₀₁ $\rightarrow \sigma^*_{s4-c10}$ interaction for **6**. Moreover, the electrostatic repulsion between the C^{δ+}-S^{δ-} and C^{δ+}-S^{δ-} dipoles (Repulsive Field Effect) contributed to both the larger destabilization and increase of the v_{c0} frequency of the *cis* conformer with respect to the *gauche* conformer. X-ray single crystal analysis indicates that compound **4** assumes the $c_2(anti)$ conformation in the solid state, which is the

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conformation obtained by compound **6** in the gas phase. To obtain the largest energy gain, the molecules were arranged in the crystal in a six-molecules synthon mediated by C—H \cdots O and Cl \cdots Cl interactions, where the chlorine atoms were related by a crystallographic inversion center.

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Introduction

Over the years, intramolecular nonbonded interactions, such as S...O, have been detected in a large number of organic sulfur compounds [1]. Moreover, studies by Iwaoka et al. [2] have highlighted the importance of this interaction in the stabilization of protein folding. Our X-ray and ab initio (HF) studies [3] showed that the intramolecular S···O=C distance in the solid increased from 2-(4-nitrophenylthio)-cyclohexanone to 2-(4-nitrophenylsulfinyl)cyclohexanone and to 2-(4-nitrophenylsulfonyl)-cyclohexanone. Within the context of spectroscopic (IR, ¹³C NMR, UV, and UPS), X-ray diffraction, and theoretical studies of the compounds containing the $-C(O)CH_2S$ moiety, the results indicated that in the gas phase and in solution they prefer the gauche conformation [4]. In general, the stability of the *gauche* rotamers of β-carbonyl-sulfides has been attributed to π^*_{CO}/σ_{C-S} and π_{CO}/σ^*_{C-S} orbital interactions. The v_{CO} IR analysis along with *ab initio* computations and X-ray diffraction studies of *N*,*N*-diethyl-2-[(4'-substituted) phenylsulfinyl] acetamides [5], revealed that the *cis* conformer in the gas phase and in solution is more stable, but the quasi-gauche conformer is preferred in the solid state. Recent IR and DFT studies of some Nmethoxy-N-methyl-2-[(4'-substituted)phenylthio]-propanamides [6] indicated that the *gauche* conformation is the most stable for these compounds in the gas phase and in solution. As part of continuing research on conformational studies, we turned our attention to the *N*,*N*-diethyl-2-[(4'-substituted) phenylthio]acetamides: OMe 1, Me 2, H 3, Cl 4, Br 5, NO₂ 6 (Scheme 1). In this paper, we report the combined application of IR spectroscopy in solution (solvents of different polarities), for 1-6, theoretical calculations (B3LYP/6-311++G**) in the gas phase and Polarisable Continuum Model (PCM; solvents of different polarities) for 1, 3, and 6, and X-ray diffraction analysis for compound 4.

Experimental

Materials

All solvents for IR measurements were spectrograde and used without further purification. The *N*,*N*-diethyl-2-(phenylthio)-



$$\begin{split} & \beta = C(2) - C(3) - S(4) - C(10) \\ & \gamma = C(3) - S(4) - C(10) - C(11) \\ & \delta = O(1) - C(2) - N(5) - C(6) \\ & \delta' = O(1) - C(2) - N(5) - C(8) \\ & \epsilon = C(2) - N(5) - C(6) - C(7) \\ & \epsilon' = C(2) - N(5) - C(8) - C(9) \end{split}$$

Scheme 1. Atoms labeling of *N*,*N*-diethyl-2-[(4'-substituted)phenylthio]acetamides and definition of relevant dihedral angles. acetamide **3** is a known compound [7]. The *N*,*N*-diethyl-2-[(4'-substituted) phenylthio] acetamides (**1–2**, **4–6**) are new compounds and were prepared as described previously in the literature [8].

General Procedure for the preparation of **1–6**

Benzenethiol (10 mmol) was added to 10 mmol sodium in absolute ethanol. After 5 min, the resulting solution of sodium thiolate was added dropwise, with stirring to 2-bromo-*N*,*N*-diethylaceta-mide (10 mmol) in ethanol at 0 °C. The reaction was stirred at room temperature (r.t.). Water was then added to the reaction mixture followed by extraction with CH_2Cl_2 . The organic extract was dried over MgSO₄ and removal of the solvent yielded the product.

N,*N*-*diethyl*-2-*[*(4-*methoxyphenyl*)*thio*]*acetamide* 1: colorless oil; yield: 98%. Bp: 145 °C/0.05 mmHg. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.46–7.43 (m, 2H), 6.85–6.82 (m, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 3.35 (q, 2H, ³*J* = 7.2 Hz), 3.33 (q, 2H, ³*J* = 7.2 Hz), 1.16 (t, 3H, ³*J* = 7.2 Hz), 1.09 (t, 3H, ³*J* = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 167.8, 159.6, 134.5, 124.9, 114.5, 55.3, 42.4, 40.3, 38.6, 14.3, 12.9. Anal. calcd. for C₁₃H₁₉NO₂S: C, 61.63; H, 7.56; N, 5.53. Found: C, 61.59; H, 7.43; N, 5.75.

N,*N*-diethyl-2-[(4-methylphenyl)thio]acetamide 2: colorless oil; yield: 55%. Bp: 115 °C/0.03 mmHg. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.37–7.34 (m, 2H), 7.11–7.08 (m, 2H), 3.67 (s, 2H), 3.35 (q, 2H, ³*J* = 7.2 Hz), 3.30 (q, 2H, ³*J* = 7.2 Hz), 2.30 (s, 3H), 1.17 (t, 3H, ³*J* = 7.2 Hz), 1.09 (t, 3H, ³*J* = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 167.7, 137.2, 131.4, 131.3, 129.7, 42.5, 40.3, 37.7, 21.0, 14.3, 12.8. Anal. calcd for C₁₃H₁₉NOS: C, 65.78; H, 8.07; N, 5.90. Found: C, 65.56; H, 7.78; N, 5.99.

N,*N*-*diethyl*-2-(*phenylthio*)*acetamide* 3: white solid; yield: 81%. Mp: 43–45 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.47–7.43 (m, 2H), 7.32–7.18 (m, 3H), 3.73 (s, 2H), 3.37 (q, 2H, ³*J* = 7.2 Hz), 3.33 (q, 2H, ³*J* = 7.2 Hz), 1.19 (t, 3H, ³*J* = 7.2 Hz), 1.10 (t, 3H, ³*J* = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 167.5, 135.4, 130.4, 128.9, 126.8, 42.5, 40.4, 37.1, 14.4, 12.8. Anal. calcd, for C₁₂-H₁₇NOS: C, 64.53; H, 7.67; N, 6.27. Found: C, 64.27; H, 7.51; N, 6.33.

2-[(4-chlorophenyl)thio]-N,N-diethylacetamide 4: white solid; yield: 66%. Mp: 53–54 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.41–7.37 (m, 2H), 7.28–7.24 (m, 2H), 3.70 (s, 2H), 3.37 (q, 2H, ³J = 7.2 Hz), 3.33 (q, 2H, ³J = 7.2 Hz), 1.20 (t, 3H, ³J = 7.2 Hz), 1.10 (t, 3H, ³J = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 167.2, 133.8, 133.0, 131.7, 129.0, 42.5, 40.5, 14.4, 12.8. Anal. calcd. for C₁₂₋ H₁₆CINOS: C, 55.91; H, 6.26; N, 5.43. Found: C, 56.17; H, 6.38; N, 5.49.

2-[(4-bromophenyl)thio]-N,N-diethylacetamide 5: white solid; yield: 63%. Mp: 39–40 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.43–7.38 (m, 2H), 7.34–7.30 (m, 2H), 3.70 (s, 2H), 3.37 (q, 2H, ³J = 7.2 Hz), 3.33 (q, 2H, ³J = 7.2 Hz), 1.20 (t, 3H, ³J = 7.2 Hz), 1.10 (t, 3H, ³J = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 167.2, 134.5, 132.0, 131.8, 120.8, 42.5, 40.5, 36.9, 14.4, 12.8. Anal. calcd. for C₁₂H₁₆BrNOS: C, 47.69; H, 5.34; N, 4.63. Found: C, 47.65; H, 5.37; N, 4.55.

N,*N*-diethyl-2-[(4-nitrophenyl)thio]acetamide 6: yellow solid; yield: 61%. Mp: 63–65 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.15–8.10 (m, 2H), 7.52–7.47 (m, 2H), 3.87 (s, 2H), 3.41 (q, 4H, ³*J* = 7.2 Hz), 1.26 (t, 3H, ³*J* = 7.2 Hz), 1.13 (t, 3H, ³*J* = 7.2 Hz). ¹³C NMR (75.5 MHz, CDCl₃) δ (ppm) 166.2, 146.2, 145.4, 127.1, 123.9, 42.7, 40.7, 35.1, 14.4, 12.8. Anal. calcd. for C₁₂H₁₆N₂O₃S: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.66; H, 5.87; N, 10.19.

IR measurements

The IR spectra were recorded with a FT-IR Nicolet Magna 550 spectrometer with 1.0 cm^{-1} resolution. The carbonyl region (1800–1600 cm⁻¹) was recorded for *n*-hexane, carbon tetrachloride, chloroform, and acetonitrile solutions at a concentration of 2.0×10^{-2} mol/dm³ using a 0.519 mm sodium chloride cell. The carbonyl first overtone region (3600–3100 cm⁻¹) was recorded for a carbon tetrachloride solution (2.0×10^{-2} mol/dm³) using a 1.00 quartz cell. The overlapped carbonyl bands (fundamental and first overtone) were deconvoluted by means of the Grams/32 curve fitting program (version 4.04 Level II) [9]. The populations of the *cis* and *gauche* conformers were estimated from the maximum of each component of the resolved carbonyl doublet expressed as percentage of absorbance, assuming equal molar absorptivity coefficients for the studied compounds **1–6**.

NMR measurements

¹H NMR spectra were recorded on a Varian Inova 1 spectrometer operating at 299.947 MHz for 0.1 mol/dm³ solutions in chloroform-*d*. H chemical shifts are reported in ppm relative to TMS (internal standard).

X-ray measurements

X-ray crystallographic data were collected with a CAD4-Mach3 diffractometer using graphite-monochromated Mo K α radiation ($\lambda = 0.71073$ Å). Data were collected at 290 K and the structure was solved by direct methods with SIR92 [10] and refined by full-matrix least-squares on F^2 with SHELXL-97 [11]. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed (C—H = 0.93–0.98 Å) and refined riding with U_{iso} (H) = $1.2U_{eq}$ (C) and U_{iso} (H) = 1.5 U_{eq} (methyl-C). The key crystallographic data are given in Table 1. CCDC 936152 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge CB2 1EZ, UK; fax: +44 1223 336 33; e-mail: deposit@ccdc.cam.ac.uk.

| Tab | le | 1 | | | | |
|-----|----|---|--|--|--|--|
| - | | | | | | |

| Color/dimensions (mm) | Colorless/0.12 \times 0.08 \times 0.04 |
|--|--|
| Chemical formula | C ₁₂ H ₁₆ Cl N O S |
| Formula weight | 257.77 |
| Crystal system | Monoclinic |
| Space group | $P2_1/n$ |
| Unit cell dimensions | |
| a (Å) | 12.950(1) |
| b (Å) | 8.6036(9) |
| <i>c</i> (Å) | 13.069(1) |
| ~(ο) | 112.401(9) |
| Volume (Å ³) | 1346.2(2) |
| Ζ | 4 |
| Density (calculated) (g/cm ³) | 1.272 |
| Absorption coefficient (mm ⁻¹) | 0.419 |
| _ range for data collection (°) | 2.81-28.50 |
| Reflections measured | 3417 |
| Independent/observed reflections | $3417/1665 (R_{int} = 0.048)$ |
| Data/restraints/parameters | 3417/0/147 |
| Goodness of fit on F^2 | 1.003 |
| Final R indices $[I > 2_(I)]$ | $R_1 = 0.0465$ |
| | $wR_2 = 0.1160$ |
| R indices (all data) | $R_1 = 0.1369$ |
| | $wR_2 = 0.1481$ |
| $\Delta_ ho$ max, min, (e Å $^{-3}$) | 0.338/-0.277 |
| | |

Theoretical calculations

All calculations were carried out using methods and basis sets implemented in the Gaussian package of programs (G03.E01) [12]. Geometry optimizations were performed by the use of Becke's three-parameter hybrid functional combined with the Lee, Yang, and Parr (LYP) correlation functional, denoted as B3LYP [13]. The 6-311++G(d,p) basis set was employed for all involved atoms. Harmonic vibrational frequencies were computed and zero-point energy corrections were determined and included in all relative energy calculations. The polarizable continuum model (PCM) [14] approach was used for a full geometry optimization in *n*-heptane, carbon tetrachloride, chloroform, and acetonitrile, employing the same functional and basis set as in the gas-phase study. The NBO 3.1 program [15] was used as implemented in the GAUSSIAN 03 package, and the reported NBO delocalization energies (E2) were those given by second-order perturbation theory.

Results and discussion

Table 2 summarizes the stretching frequencies and absorbance percentage resulting from fitting the carbonyl IR band curve for the *N*,*N*-diethyl-2-[(4'-substituted)phenylthio] acetamides **1–6** in solvents with increasing relative permittivity [16], i.e. *n*-hexane ($\varepsilon = 1.9$), carbon tetrachloride ($\varepsilon = 2.2$), chloroform ($\varepsilon = 4.9$), and acetonitrile ($\varepsilon = 38$). Compounds **3–6** showed a carbonyl doublet in *n*-hexane, carbon tetrachloride, and chloroform, while compounds **1–2** displayed only a singlet in *n*-hexane, and behave similarly to **3–6** in the other solvents. In acetonitrile all compounds present a single, symmetrical band.

The lower carbonyl frequency component was approximately 2–5 times more intense than the higher frequency one in $n-C_6H_{14}$ for compounds **3–6** and in CCl₄ for **1–6**. The enhancement of the solvent relative permittivity increases the intensity of the higher carbonyl frequency component for compounds **3–6** going from $n-C_6H_{14}$ to CH₃CN and also for compounds **1–2** going from CCl₄ to CH₃CN. The solvent effect on the carbonyl band components for compound **3** is illustrated in Fig. 1. Moreover, Table 2 shows that, in the non-polar solvents, $n-C_6H_{14}$ and CCl₄, there is a discrete increase in the intensity ratio of the low frequency component with respect to the high frequency component, going from nitro **6** to methoxy **1** derivatives. For example, for $n-C_6H_{14}$, it increased from 76%/24% to 100%/0%, and for CCl₄ it increased from 69%/31% to 85%/15%.

The occurrence of two carbonyl band components in the first overtone region (CCl₄) for **1–6** at frequencies about twice of those in the fundamental region minus approximately 15 cm^{-1} (which corresponds to two times the mechanical anharmonicity) and with nearly the same intensity ratios, indicates that compounds **1–6** were present, in carbon tetrachloride, as two conformers [17a,17b]. The observed IR solvent effect suggests the existence of one conformer for **1–2** and two conformers for **3–6** in *n*-hexane, and two conformers in chloroform, and one conformer for **1–6** in acetonitrile.

In order to evaluate the geometry of the minimum energy conformations in the gas phase, B3LYP/6-311++G(d,p) calculations were performed for the *N*,*N*-diethyl-2-[(4'-substituted)phenylthio] acetamides **1**, **3**, and **6**. The calculated geometrical parameters, carbonyl frequencies (v_{CO}), relative energies (Boltzmann distribution), and dipole moments for the conformers, along with the X-ray dihedral angles of **4** are listed in Table 3.

Calculations indicated the existence of one pair of *syn-clinal* (*gauche*) conformers and one pair of *syn-periplanar* (*cis*) conformers, such as g and c_1 for **1** and **3** and g and c_2 for **6**. Additionally, each one of the g, c_1 , and c_2 conformers existed in an *anti-syn*

| Frequencies (v, | requencies (v, cm ⁻¹) and intensities of the carbonyl stretching bands in the IR spectra of N,N-diethyl-2-[(4'-substituted) phenylthio] acetamides, Et ₂ NC(O)CH ₂ S-C ₆ H ₄ -Y 1–6 . | | | | | | | | | | | | |
|-----------------|--|-----------------|----------------|------------------|----|------------------|----|-------------------|----|--------------------|-----|--|--|
| Compd. | Y | $n-C_{6}H_{14}$ | | CCl ₄ | | | | CHCl ₃ | | CH ₃ CN | | | |
| | | v | P ^a | ν | Р | $v^{\mathbf{b}}$ | Р | ν | Р | v | Р | | |
| 1 | OMe | - | - | 1657.7 | 15 | 3304.2 | 15 | 1638.5 | 38 | 1639.7 | 100 | | |
| | | 1657.4 | 100 | 1646.5 | 85 | 3278.5 | 85 | 1628.7 | 62 | - | - | | |
| 2 N | Me | - | - | 1657.4 | 16 | 3300.0 | 16 | 1638.0 | 40 | 1640.6 | 100 | | |
| | | 1657.9 | 100 | 1647.0 | 84 | 3278.1 | 84 | 1630.4 | 60 | - | - | | |
| 3 | Н | 1663.8 | 21 | 1657.4 | 17 | 3300.7 | 19 | 1639.4 | 40 | 1640.3 | 100 | | |
| | | 1655.7 | 79 | 1647.0 | 83 | 3279.4 | 81 | 1631.5 | 60 | - | - | | |
| 4 | Cl | 1664.0 | 28 | 1657.0 | 25 | 3302.1 | 21 | 1639.9 | 42 | 1641.6 | 100 | | |
| | | 1655.2 | 72 | 1646.9 | 75 | 3279.0 | 79 | 1632.5 | 58 | - | - | | |
| 5 | Br | 1664.9 | 29 | 1657.0 | 27 | 3301.9 | 23 | 1641.7 | 43 | 1641.5 | 100 | | |
| | | 1655.8 | 71 | 1646.6 | 73 | 3278.6 | 77 | 1632.0 | 57 | - | - | | |
| 6 | NO ₂ | 1666.3 | 24 | 1657.5 | 31 | 3304.1 | 28 | 1641.8 | 66 | 1643.3 | 100 | | |
| | - | 1655.2 | 76 | 1646.6 | 69 | 3279.8 | 72 | 1633.4 | 34 | - | - | | |

. ...

^a Intensity of each component of the carbonyl band expressed in percentage of absorbance.

^b First overtone.

Table 2



Fig. 1. IR spectra of N,N-diethyl-2-(phenylthio)-acetamide (3) showing the analytically resolved carbonyl stretching bands in n-hexane (a), carbon tetrachloride [fundamental (b) and first overtone (c)], chloroform (d), and acetonitrile (e).

equilibrium, as the $[-C(O)-NEt_2]$ group was almost planar (with δ and δ' dihedral angles of approximately 0.5° and 177°, respectively). The g(anti; syn) conformers of 1, 3, and 6 were the most stable and possessed a α dihedral angle (O1=C2-C3-S4) of about 95°. Rotation around this internal coordinate lead to the remaining minima on the ground state potential energy surface at α of approximately 6° of the $c_1(anti; syn)$ conformations for **1** and **3** and $c_2(anti; syn)$ conformations for **6**. For **1** and **3**, the g(anti; syn) conformers were less polar than the $c_1(anti; syn)$ conformers. However, we observed the opposite for 6, wherein the g(anti;

Table 3

Relative energies (*E*, kJ mol⁻¹), Boltzmann populations (*P*, %), dipole moments (μ , D), carbonyl harmonic frequencies (ν , cm⁻¹), and selected dihedral angles (°) optimized for different *cis*(*c*) and *gauche*(*g*) conformers of **1**, **3** and **6** at the B3LYP/6-311++G(d,p) level and the X-ray geometrical data for 4-Cl-C₆H₄-SCH₂C(O)NEt₂ (**4**).

| Compd. | Y | | Conf. ^a | E ^b | P ^c | μ | v _{C=0} | Dihedral angles ^d | | | | | | |
|--------|-----------------|-------|--|----------------------------|----------------------------|------------------------------|--------------------------------------|-------------------------------|------------------------------------|--------------------------------|-----------------------------|--------------------------------------|--------------------------------|------------------------------------|
| | | | | | | | | α | β | γ | δ | $\delta^{'}$ | з | ε |
| 1 | OMe | | g(anti) g(syn) | 0 3.14 | 69.5 19.6 | 2.23 2.17 | 1694.6 1692.0 | 95.6 97.6 | -94.3 -93.7 | 43.4 42.4 | -0.4 -0.8 | -177.0 -175.7 | -88.1 78.4 | -97.1 -105.8 |
| | | | c ₁ (anti) c ₁ (syn) | 5.16 8.46 | 8.6 2.3 | 4.45 4.29 | 1714.4 1713.8 | -7.6 -3.3 | -74.9 -76.1 | 85.5 87.1 | $0.1 \\ -0.4$ | -178.5 -178.9 | -88.4 78.5 | -96.6 -101.9 |
| 3 | Η | | g(anti) g(syn) c ₁ (anti) c ₁ (syn) | 0 3.35 7.78 11.44 | 76.3 19.7 3.3 0.8 | 3.08 3.00 4.74 4.66 | 1696.1 1693.5 1715.3 1714.8 | 97.8 99.6 -8.3 -5.2 | -90.3 -90.0 -75.7 -76.2 | 30.4 30.9 82.7 83.5 | -0.8 -0.6 0.5 0.1 | -177.8 -176.8 -178.2 -177.9 | -88.6 78.5 -88.2 78.3 | -96.1 -104.1 -96.4 -102.4 |
| 6 | NO ₂ | | g(anti) g(syn) c ₂ (anti) c ₂ (syn) | 0 3.19 7.59 10.78 | 74.9 20.6 3.5 1.0 | 9.18 9.15 7.87 7.82 | 1696.0 1694.2 1713.0 1710.7 | 99.9 100.6 -9.2 -8.2 | -81.5 -82.2 -176.7 -177.5 | 16.1 16.9 176.5 176.9 | -0.6 -0.5 0.2 -0.1 | -178.9 -177.9 -179.3 -177.9 | -87.6 78.1 -88.7 77.5 | -95.5 -102.6 -96.8 -105.0 |
| 4 | Cl | X-ray | c ₂ (anti) | - | | - | - | 2.5(5) | 175.1(2) | -155.0(3) | 5.4(6) | -174.8(4) | -89.6(6) | -97.8(5) |

^a Conformer designation; (g) and (c) refers to the *gauche* and *cis* conformers, respectively; *syn* refers to both *N*,*N*-diethyl methyl groups in the same half-space defined by the [–C(O)N] plane and *anti* refers to the methyl groups above and the other bellow the referred plane.

^b Relative energies.

^c Molar fraction in percentage..

^d See Scheme 1.



Fig. 2. Gauche and cis conformers obtained at B3LYP/6-311++G(d,p) level for 1 (a), 3 (b) and 6 (c).

syn) conformers were more polar than the $c_2(anti; syn)$ ones. The structures of the computed g(anti; syn), $c_1(anti; syn)$, and $c_2(anti; syn)$ conformers for **1**, **3** and **6** are illustrated in Fig. 2 [18].

The ε and ε' dihedral angles define the *anti* and *syn* conformers. That is, both methyls of the *N*,*N*-diethylcarboxamide group are at the same half-space defined by the [-C(O)-N] plane (for the *syn* conformer) or one methyl is in each half-space relative to the referred plane (for the *anti* conformer). The population ratio for each pair of conformers for **1**, **3**, and **6** g(anti)/g(syn), $c_1(anti)/c_1(syn)$, and $c_2(anti)/c_2(syn)$ of ca. 3.7 is very close to the previously computed (anti)/(syn) ratio for the *N*,*N*-diethylacetamide [5]. The larger population of the *anti* (g, c_1 and c_2) conformers of **1**, **3**, and **6** relative to the *syn* ones may be justified by the same factors which stabilize the *anti* conformer to a larger extent relative to the *syn* one for the parent *N*,*N*-diethylacetamide. Furthermore, each *anti-syn* pair for the (g, c_1 , and c_2) conformers of **1**, **3**, and **6**

exhibits almost the same dipole moment values along with very close computed carbonyl frequencies (Table 3).

The analysis of the gas phase-calculated g(anti; syn) populations for compounds **1** (89.1%), **2** (96%), and **6** (95.5%) do not indicate any substituent effect. However, the electron-withdrawing group (**EWG**) nitro leads to a *cis* [$c_2(anti; syn)$] conformer whose geometry differs from that of the *cis* (c_1) conformers for **1** and **3**. For instance, for the $c_2(anti; syn)$ conformers of **6**, the S(4)–C(10) bond becomes coplanar with the carbonyl group (with γ dihedral angles, of about 176°).

It should be noted that there is a reasonably good match between the theoretical (gas phase) *gauche/cis* population ratio and IR data in solution for non-polar solvents. In fact, the similarity of the carbonyl frequencies in the gas phase for the *anti* and *syn* pairs of the *cis* and *gauche* conformers originates a carbonyl doublet in solution for which the less intense, higher frequency component corresponds to the pair of the *cis* conformers and the lower frequency component corresponds to the more stable pair of the *gauche* conformers. In solutions of $n-C_6H_{14}$ and CCl₄, which are the least polar, *gauche* conformers (ca. 85%) are predominant with respect to the most polar *cis* ones. In the polar solvent, CHCl₃, we observed a decrease in the *gauche/cis* population ratio for **1–5** from 60%/40%, except for **6**, where the ratio remained at 34%/ 66%. Moreover, in the highly polar solvent, CH₃CN, the most polar *cis* conformer is the only one present.

To get further information on the conformational preferences in solution, the geometries found in the gas phase were optimized at B3LYP/6-311++G(d,p) using the PCM (Polarisable Continuum Model) method. The solvent effect was computed in n-heptane, carbon tetrachloride, chloroform, and acetonitrile, and selected parameters are summarized in Table 4.

The optimized geometries for **1**, **3**, and **6** taking into account the solvent effect are almost the same as in the gas phase. Only the $c_1(anti; syn)$ conformations for **1** presented a distortion in the α dihedral angle, which changed from -7.6° (gas phase) to 24.5° (acetonitrile).

Analysis of the population data presented in Table 4 indicates that the more polar *cis* conformers become more stable as the polarity of the solvent increases. While solvents of low polarity yield comparable results to those found in the gas phase, the strongly polar solvent (acetonitrile) is found to substantially lower the energy of the *cis* (c_1 ; c_2) conformers that possess larger permanent electric moments. This differential stabilization is sufficient to change the energy ordering of conformers in acetonitrile compared to that of the isolated molecule (gas phase) for compounds **1**, **3**, and **6**.

The comparison between experimental IR (Table 2) and PCM (Table 4) data provides further support of the fact that the most intense carbonyl doublet component for **3–6** (Table 2) in *n*-hexane may be attributed to the *gauche* conformers *g*(*anti*; *syn*), which are more stable and have a lower frequency than the *cis* ones. The single band for **1** and **2** in *n*-hexane (Table 2) may be attributed to the *gauche* conformers are smaller than those of the *g* conformers. However, the calculated frequencies and the solvent effect are in agreement with the experimental results.

The distribution of *gauche* rotamers for compounds **1–6**, which was estimated from experimental carbonyl band intensities in *n*-hexane, are not the same, but they are comparable to those obtained by B3LYP(PCM) calculations for **3** and **6**. In addition, the calculated frequencies trend compares well with the IR data.

To evaluate the energies of the donor–acceptor orbital interactions, we performed the natural bond orbital (NBO) analysis for the four conformers of **1**, **3**, and **6** (Table 5). The three strongest orbital interactions were LP_{N5} $\rightarrow \pi^*_{C2=O1}$ (ca. 65.5 kcal mol⁻¹; conjugative), LP₀₁ $\rightarrow \sigma^*_{C2-N5}$ (ca. 23.5 kcal mol⁻¹), and LP₀₁ $\rightarrow \sigma^*_{C2-C3}$ (ca. 18.6 kcal mol⁻¹; through bond coupling). They were observed for all the studied conformations, and were quite similar for **1**, **3**, and **6**. These results indicate that these orbital delocalizations are not responsible for the *gauche* preference since both *gauche* and *cis* conformers exhibit very similar NBO delocalization values.

The g(anti; syn) conformers preference in the gas phase may be ascribed to the occurrence of: $LP_{S4} \rightarrow \pi^*_{C2=01}, \pi_{C2=01} \rightarrow \sigma^*_{C3=S4}$, $\sigma_{\text{C3-S4}} \rightarrow \pi^*_{\text{C2=01}}, \pi^*_{\text{C2=01}} \rightarrow \sigma^*_{\text{C3-S4}}, \text{ and } LP_{01} \rightarrow \sigma^*_{\text{C1-H28}} \text{ orbital interaction was observed for some NV dimensional } \pi^*_{\text{C2=0}} \rightarrow \sigma^*_{\text{C-X}} \text{ interaction was observed for some NV dimensional } \pi^*_{\text{C2=0}} \rightarrow \sigma^*_{\text{C-X}} \text{ interaction was observed } \pi^*_{\text{C2=01}} \rightarrow \pi^*_{\text{$ for some N,N-dimethyl-2-haloacetamides by NBO analysis [19], and through electron spectroscopy for the N,N-diethyl-2-methylthioacetamide [20]. Moreover, the sum of the $LP_{S4} \to \pi^*_{C2=01}, \pi_{C2=01} \to \sigma^*_{C3=S4}, \sigma_{C3=S4} \to \pi^*_{C2=01}, \quad \text{and} \quad$ $\pi^*_{C2=01} \rightarrow$ σ^*_{C3-S4} interactions of approximately 13.7 kcal mol⁻¹ stabilizes the g(anti; syn) conformers for 1, 3, and 6 by almost the same amount.

In addition to the interactions mentioned above, the *g*(*anti*; *syn*) conformers are also stabilized by an intramolecular hydrogen bond between the carbonyl oxygen and the *ortho*-hydrogen atoms: $LP_{01} \rightarrow \sigma^*_{C11-H28}$. Its value increases progressively going from electron donating group (EDG) [OMe; 0.9 kcal mol⁻¹], to hydrogen [H; 1.4 kcal mol⁻¹], and then to EWG [NO₂; 1.7 kcal mol⁻¹].

Table 4

Relative energies (*E*, kJ mol⁻¹), Molar fraction in percentage (*P*, %), dipole moments (μ , D) and carbonyl harmonic frequencies ($\nu_{C=0}$, cm⁻¹) optimized for different *cis*(*c*) and *gauche*(*g*) conformers of **1**, **3** and **6** at the B3LYP/6-311++G(d,p) level including the solvent effect PCM method.

| Compd. | Conf. ^a | Heptan | e (ɛ = 1.9 | 9) | | $CCl_4 (\varepsilon = 2.2)$ | | | $CHCl_3 (\varepsilon = 4.9)$ | | | $CH_3CN \ (\varepsilon = 38)$ | | | | | |
|-----------------------------|-----------------------|----------------|----------------|------------------|-------|-----------------------------|------|------------------|------------------------------|------|------|-------------------------------|-------|------|------|------------------|-------|
| | | E ^b | P ^c | v _{c=0} | μ | Е | Р | v _{C=0} | μ | Е | Р | $v_{C=0}$ | μ | Е | Р | v _{C=0} | μ |
| 1 (OMe) | g(anti) | 0 | 65.2 | 1679.4 | 2.49 | 0 | 66.4 | 1676.2 | 2.50 | 0 | 54.5 | 1661.3 | 2.73 | 2.46 | 23.6 | 1645.9 | 3.03 |
| | g(syn) | 3.25 | 17.5 | 1677.8 | 2.43 | 3.65 | 15.2 | 1675.6 | 2.49 | 3.78 | 11.8 | 1660.3 | 2.79 | 6.32 | 5.0 | 1644.6 | 2.99 |
| | c ₁ (anti) | 3.84 | 13.8 | 1699.3 | 5.04 | 3.74 | 14.6 | 1696.6 | 5.20 | 1.81 | 26.2 | 1681.7 | 5.67 | 0 | 63.7 | 1660.3 | 6.45 |
| | $c_1(syn)$ | 7.20 | 3.5 | 1699.5 | 4.89 | 7.08 | 3.8 | 1694.5 | 4.99 | 4.90 | 7.5 | 1682.1 | 5.56 | 5.24 | 7.7 | 1661.2 | 6.27 |
| 3 (H) | g(anti) | 0 | 75.6 | 1679.3 | 3.41 | 0 | 75.7 | 1677.3 | 3.49 | 0 | 70.6 | 1662.6 | 3.84 | 0 | 49.3 | 1646.4 | 4.22 |
| | g(syn) | 3.50 | 18.3 | 1679.4 | 3.33 | 3.67 | 17.2 | 1676.0 | 3.39 | 4.01 | 13.9 | 1662.5 | 3.72 | 3.71 | 11.0 | 1646.4 | 4.12 |
| | $c_1(anti)$ | 6.84 | 4.8 | 1698.6 | 5.42 | 6.42 | 5.6 | 1695.2 | 5.55 | 4.28 | 12.5 | 1680.4 | 6.33 | 1.04 | 32.4 | 1663.0 | 7.10 |
| | $c_1(syn)$ | 10.04 | 1.3 | 1700.0 | 5.31 | 9.75 | 1.5 | 1695.2 | 5.48 | 7.80 | 3.0 | 1680.6 | 6.14 | 4.73 | 7.3 | 1663.5 | 7.10 |
| 6 (NO ₂) | g(anti) | 0 | 69.4 | 1681.7 | 10.25 | 0 | 70.9 | 1678.4 | 10.44 | 0 | 50.4 | 1665.1 | 11.42 | 2.30 | 22.8 | 1650.1 | 12.33 |
| | g(syn) | 3.35 | 18.0 | 1681.0 | 10.24 | 3.98 | 14.2 | 1677.5 | 10.41 | 3.74 | 11.1 | 1664.7 | 11.34 | 6.14 | 4.8 | 1649.4 | 12.34 |
| | c ₂ (anti) | 4.79 | 10.0 | 1694.8 | 8.69 | 4.42 | 11.8 | 1690.5 | 8.86 | 1.22 | 30.7 | 1671.8 | 9.53 | 0 | 58.0 | 1653.7 | 10.25 |
| | $c_2(syn)$ | 8.15 | 2.6 | 1692.8 | 8.67 | 7.77 | 3.1 | 1688.5 | 8.83 | 4.62 | 7.8 | 1671.6 | 9.33 | 3.44 | 14.4 | 1651.4 | 10.28 |

^a Conformer designation; (g) and (c) refers to the *gauche* and *cis* conformers, respectively; *syn* refers to both *N*,*N*-diethyl methyl groups in the same half-space defined by the [–C(O)N] plane and *anti* refers to the methyl groups above and the other bellow the referred plane.

^b Relative energies.

Molar fraction in percentage.

Table 5

Comparison of significant NBO energies (kcal mol⁻¹) of the interacting orbitals for the *anti* and *syn*, *gauche* (g) and *cis* (c_1 , c_2) conformers of **1**, **3** and **6** calculated at the B3LYP/6-311++G(d,p) level.

| Compd. | Y | Orbitals | Conform | nations | | |
|--------|-----------------|---|--|--|--|---|
| | | | g(anti) | g(syn) | $c_1(anti)$ | $c_1(syn)$ |
| 1 | OMe | $\begin{array}{l} LP_{N5} \rightarrow \pi^{*}_{C2=01} \\ LP_{01} \rightarrow \sigma^{*}_{C2-N5} \\ LP_{01} \rightarrow \sigma^{*}_{C2-C3} \\ LP_{01} \rightarrow \sigma^{*}_{C11-H28} \\ LP_{01} \rightarrow \sigma^{*}_{C4-C10} \\ LP_{030} \rightarrow \sigma^{*}_{C13-C12} \\ LP_{S4} \rightarrow \pi^{*}_{C10-C11} \\ LP_{S4} \rightarrow \pi^{*}_{C2=01} \\ \sigma^{*}_{C2=01} \rightarrow \sigma^{*}_{C2-S4} \\ \sigma^{*}_{C3-S4} \rightarrow \pi^{*}_{C2=01} \\ \pi^{*}_{C2=01} \rightarrow \sigma^{*}_{C3-S4} \end{array}$ | 65.3 23.6 18.5 0.9 - 29.4 9.0 1.6 2.4 - 4.6 5.5 | 61.0 23.5 18.4 0.9 - 29.3 9.1 1.6 2.4 - 4.6 6.0 | 65.6 24.3 20.8 - - 30.0 5.0 - - 3.2 - - | 65.2 24.2 20.8 - - 30.0 5.1 - - 3.2 - - |
| 3 | Η | $\begin{array}{l} LP_{N5} \rightarrow \pi^{*}_{C2=01} \\ LP_{01} \rightarrow \sigma^{*}_{C2-N5} \\ LP_{01} \rightarrow \sigma^{*}_{C2-C3} \\ LP_{01} \rightarrow \sigma^{*}_{C1-H28} \\ LP_{01} \rightarrow \sigma^{*}_{C4-C10} \\ LP_{S4} \rightarrow \pi^{*}_{C10-C11} \\ LP_{S4} \rightarrow \pi^{*}_{C2=01} \\ \pi^{*}_{C2=01} \rightarrow \sigma^{*}_{C3-S4} \\ \sigma^{*}_{C3-S4} \rightarrow \pi^{*}_{C2=01} \\ \pi^{*}_{C2=01} \rightarrow \sigma^{*}_{C3=S4} \end{array}$ | 65.6 23.6 18.6 1.4 - 13.1 1.5 2.4 - 4.3 5.5 | 61.9 23.5 18.6 1.3 - 13.0 1.5 2.5 - 4.3 5.8 | 65.9 24.3 20.3 - 4.65 - 3.0 - - c ₂ (anti) | 65.2 24.2 20.9 - - 4.7 - 3.1 - - c ₂ (syn) |
| 6 | NO ₂ | $\begin{array}{l} LP_{N5} \to \pi^*_{C2=01} \\ LP_{01} \to \sigma^*_{C2=N5} \\ LP_{01} \to \sigma^*_{C2=C3} \\ LP_{01} \to \sigma^*_{C1-H28} \\ LP_{01} \to \sigma^*_{S4=C10} \\ LP_{S4} \to \pi^*_{C10-C11} \\ LP_{S4} \to \pi^*_{C2=01} \\ \pi_{C2=01} \to \sigma^*_{C3-S4} \\ \sigma_{C3-S4} \to \pi^*_{C2=01} \\ \pi^*_{C2=01} \to \sigma^*_{C3-S4} \end{array}$ | 66.9 23.3 18.9 1.7 - 18.3 1.3 2.5 - 3.9 5.8 | 63.6 23.2 18.8 1.7 - 18.2 1.3 2.6 - 3.9 6.1 | 67.3 24.0 20.3 - 1.4 23.2 - 3.9 - | 68.1 23.9 20.5 - 1.5 23.2 - 3.9 - |

As expected, due to the strong electron-withdrawing effect of the 4'-nitro group, the largest contribution of LP₅₄ $\rightarrow \pi^*_{c10-C11}$ delocalization (conjugation) is observed for derivative **6** in both $c_2(anti; syn, ca. 23 \text{ kcal mol}^{-1})$ and $g(anti; syn, ca. 18 \text{ kcal mol}^{-1})$ conformers. In fact, due to its appropriate geometry the γ dihedral angle (177°), compound **6** assumes the $c_2(anti; syn)$ conformations. This differs from the $c_1(anti; syn)$ conformations for **1** and **3**, whose unfavorable γ dihedral angles of ca. 84° almost hinders the

Table 6CHELPG charges (e) at selected atoms in 1, 3 and 6 obtained at the B3LYP/6-311++G(d,p) level.

LP_{S4}/ $\pi^*_{C10-C11}$ interaction from occurring (ca. 4.9 kcal mol⁻¹). Similar for the *g*(*anti*; *syn*) conformers, the progressive increase in the γ dihedral angles going from approximately 16° for **6** to about 30° for **3** and to 42° for **1** leads to a decrease in the LP_{S4}/ $\pi^*_{C10-C11}$ interaction whose delocalization energies are approximately 18 kcal mol⁻¹, 13 kcal mol⁻¹ and 9 kcal mol⁻¹, respectively.

The *cis* [c_1 and $c_2(anti; syn)$] conformers are stabilized by the $\sigma_{C3-S4} \rightarrow \sigma^*_{C2-N5}$ interaction (through bond coupling) by ca. 3.1 kcal mol⁻¹. Moreover, the near-planarity of the [O=C–C–SPh] moiety (β dihedral angle ca. 177°) of the $c_2(anti; syn)$ conformers for **6** allows the occurrence of the LP₀₁ $\rightarrow \sigma^*_{S4-C10}$ interaction (ca. 1.4 kcal mol⁻¹) which is not possible for the $c_1(anti; syn)$ conformers of **1** and **3**, due to their unfavorable β dihedral angles of ca. 75°.

The CHELPG [21] charges for **1**, **3** and **6** are summarized in Table 6, while Table 7 displays the interatomic distances between some selected atoms and the difference between these contacts and the sum of the van der Waals (Σ vdW) radii (Δl) for **1**, **3** and **6**.

The **1**, **3**, **6** g(anti; syn) and the **1**, **3** $c_1(anti; syn)$ conformers are electrostatically stabilized by the close proximity of the positively charged *ortho* hydrogen atom (H28) and the negatively charged carbonyl oxygen atom (O1). In fact, the O···H mean value for the interatomic distance is shorter than the Σ vdW radii by about –0.41 Å for the **1**, **3**, and **6** g(anti; syn) conformers and –0.20 Å for the **1** and **3** $c_1(anti; syn)$ ones. The negatively charged O(1) and S(4) atoms of the *cis* conformers show interatomic distances shorter than the Σ vdW radii by ca. –0.27 Å for **1** and **3** and ca. –0.51 Å for **6**. The electron-withdrawing nitro-group is responsible for the smaller negative charges for both the sulfur (–0.224e) and oxygen (–0.506e) atoms for **6**, as compared to those for **1** and **3**, whose values are (–0.297e; –0.563e) and (–0.288e; –0.556e), respectively. This justifies the smaller S···O calculated short contact for **6**.

The shorter $0 \cdots S$ contacts of the *cis* conformers cause a strong Repulsive Field Effect [17a,22] between the $C^{\delta+}=O^{\delta-}$ and $C^{\delta+}=S^{\delta-}$ dipoles, which contributes to the larger destabilization of these conformers relative to the *gauche* ones, and to their higher v_{CO} frequencies observed in the gas phase (Table 3).

Additionally the short contacts $[O_1 \cdots H_{18(NCH2)} \text{ and } O_1 \cdots H_{20(CH3)}$ (Table 7)] are in agreement with the large electrostatic stabilization of the *anti* relative to the *syn* conformer [6]. The distance between the oppositely charged $O_1 \cdots H_{18(NCH2)}$ atoms is shorter than the ΣvdW radii by ca. -0.34 Å for the *anti* conformer and only by ca. -0.26 Å for the *syn* conformer. On the other hand, the $O_1 \cdots H_{20(CH3)}$ contacts for the *syn* and *anti* conformers do not contribute to the stabilization of either conformers.

The sum of the delocalization energies of the selected interactions has maximum mean values of ca. $159 \text{ kcal mol}^{-1}$ and $134 \text{ kcal mol}^{-1}$ for the *gauche* (*anti*; *syn*) conformers for **1** and **2**, respectively. The energies significantly decrease to ca. $149 \text{ kcal mol}^{-1}$ and ca. $118 \text{ kcal mol}^{-1}$ for the corresponding *cis*

| Compd. | Conf. | O(1)[CO] | C(2)[CO] | S(4) | N(5) | H(28) | H(18) | H(20) |
|--------|-----------------------|----------|----------|--------|--------|-------|--------|-------|
| 1 | g(anti) | -0.583 | 0.629 | -0.288 | -0.377 | 0.163 | 0.005 | 0.042 |
| | g(syn) | -0.569 | 0.693 | -0.291 | -0.421 | 0.147 | 0 | 0.044 |
| | $c_1(anti)$ | -0.563 | 0.705 | -0.297 | -0.556 | 0.136 | 0.013 | 0.059 |
| | $c_1(syn)$ | -0.558 | 0.694 | -0.301 | -0.584 | 0.132 | -0.013 | 0.066 |
| 3 | g(anti) | -0.566 | 0.671 | -0.288 | -0.375 | 0.127 | -0.001 | 0.018 |
| | g(syn) | -0.552 | 0.658 | -0.302 | -0.410 | 0.121 | -0.008 | 0.043 |
| | $c_1(anti)$ | -0.556 | 0.678 | -0.308 | -0.537 | 0.125 | 0.016 | 0.033 |
| | $c_1(syn)$ | -0.554 | 0.658 | -0.314 | -0.557 | 0.126 | -0.012 | 0.064 |
| 6 | g(anti) | -0.557 | 0.639 | -0.253 | -0.365 | 0.127 | 0.018 | 0.043 |
| | g(syn) | -0.546 | 0.635 | -0.257 | -0.403 | 0.122 | -0.006 | 0.050 |
| | c ₂ (anti) | -0.506 | 0.675 | -0.224 | -0.480 | 0.159 | 0.008 | 0.050 |
| | $c_2(syn)$ | -0.503 | 0.659 | -0.228 | -0.522 | 0.160 | -0.021 | 0.051 |

| | | | | 1 , | | | | 0 | |
|--------|-----------------------|----------------------|----------------|---------------------------|-------|---------------------------|-------|---------------------------|-------|
| Compd. | Conf. ^a | $O(1) \cdots S(4)^b$ | Δl^{c} | $O(1) \cdots H(18)^{d,e}$ | Δl | $O(1) \cdots H(20)^{d,e}$ | Δl | $O(1) \cdots H(28)^{d,e}$ | Δl |
| 1 | g(anti) | 3.552 | 0.23 | 2.371 | -0.34 | 2.937 | 0.22 | 2.354 | -0.36 |
| | g(syn) | 3.574 | 0.25 | 2.451 | -0.26 | 2.670 | -0.05 | 2.362 | -0.35 |
| | c ₁ (anti) | 3.045 | -0.27 | 2.369 | -0.35 | 2.938 | 0.22 | 2.526 | -0.19 |
| | $c_1(syn)$ | 3.041 | -0.27 | 2.448 | -0.27 | 2.681 | -0.04 | 2.545 | -0.17 |
| 3 | g(anti) | 3.583 | 0.26 | 2.366 | -0.35 | 2.955 | 0.24 | 2.296 | -0.42 |
| | g(syn) | 3.604 | 0.28 | 2.450 | -0.27 | 2.670 | -0.05 | 2.313 | -0.40 |
| | $c_1(anti)$ | 3.049 | -0.27 | 2.374 | -0.34 | 2.925 | 0.21 | 2.492 | -0.22 |
| | $c_1(syn)$ | 3.047 | -0.27 | 2.450 | -0.27 | 2.680 | -0.04 | 2.488 | -0.23 |
| 6 | g(anti) | 3.613 | 0.29 | 2.378 | -0.34 | 2.927 | 0.21 | 2.245 | -0.47 |
| | g(syn) | 3.621 | 0.30 | 2.456 | -0.26 | 2.670 | -0.05 | 2.255 | -0.46 |
| | $c_2(anti)$ | 2.808 | -0.51 | 2.380 | -0.34 | 2.957 | 0.24 | _f | _ |
| | $c_2(syn)$ | 2.802 | -0.51 | 2.471 | -0.24 | 2.667 | -0.05 | - | - |
| 4 | X-ray | 2.714(3) | -0.60 | 2.417(97°) | -0.31 | _f | - | - | - |
| | | | | | | | | | |

Selected interatomic distances (Å) for the conformations of compounds 1, 3 and 6 at the B3LYP/6-311++G(d,p) level, and the corresponding X-ray distances for 4.

^a Conformer designation.

^b Sum of the van der Waals (Σ vdW) radii = 3.32 Å.

 $^{\rm c}\,$ Difference between nonbonded atoms distance and the ΣvdW radii.

^d ΣvdW radii = 2.72 Å.

Table 7

^e Refers to the contact between the carbonyl oxygen and the nearest, phenyl, methylene or methyl hydrogen atom.

^f Interatomic distances significantly larger than the Σ vdW radii.



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

(*anti*; *syn*) conformers. However, due to the almost planar geometry of the [O=C-C-S-Ph] moiety for the *cis* (*anti*; *syn*) conformers of **6**, along with the smaller electrostatic repulsion between the C=O and C-S dipoles with respect to **1** and **3**, the sum of the delocalization energies for the *gauche* (*syn*, *anti*) conformers of **6** is only slightly higher (ca. 143 kcal mol⁻¹) than that of the *cis* conformers (ca. 141 kcal mol⁻¹).

The NBO analysis and the trend of the electrostatic interactions are in agreement with the higher relative abundance of the *gauche* (*anti*; *syn*) conformers found in the gas phase of ca. 93% with respect to that of the *cis* (*anti*; *syn*) conformers.

The molecular structure of **4**, determined by X-ray analysis, is shown in Fig. 3. The geometry observed in the solid state is very similar to the $c_2(anti)$ conformation obtained in the gas phase for compound **6** (Table 3). The orientation of the phenyl ring is away and coplanar with the carbonyl group resulting in an intramolecular S…O distance of 2.714 Å that is significantly shorter than Σ vdW radii by -0.60 Å. This short distance contributes to the stabilization of this conformation in the crystal.

The most prominent feature of the crystal packing is the formation of six-molecules synthon mediated by the C—H···O $(C1 \cdots O^i = 3.179(3) \text{ Å}$; C1—H1B···Oⁱ = 151°; symmetry operation: i = 3/2 - x, y - 1/2, $\frac{1}{2} - z$) and Cl···Cl interaction, as shown in Fig. 4. The Cl···Cl distance of 3.287(2) Å is less than the Σ vdW radii of 3.50 Å [23]. The geometry of this interaction is called Type I [24,25]: both C—Cl···Clⁱⁱ and Cⁱⁱ—Clⁱⁱ.··Cl angles (154.6(1)°; ii = 2 - x, -y, 2 - z) are equal, as the chlorine atoms are related by a crystallographic inversion centre. It is worth noting that calculations made by Awwadi et al. [26] determined that the strongest halogen···halogen interaction occurs when the halogens are attached to an sp²-hybridized carbon atom.



Fig. 4. A view in projection showing the supramolecular array sustained by C-H…O and Cl…Cl interactions.

Conclusions

The conformational analysis of N.N-diethyl-2-[(4'-substituted)phenvlthiol acetamides 1-6 (OMe 1, Me 2, H 3, Cl 4, Br 5, NO₂ **6**) was performed by v_{CO} IR analysis, B3LYP/6-311++G(d,p) gas phase and PCM calculations (for 1, 3 and 6), and X-ray diffraction (for 4).

Calculations for 1, 3, and 6 indicated the existence of two stable conformation pairs, gauche (anti; syn; most stable) and cis (anti; syn) in the gas phase. The comparison of experimental (IR) and theoretical (PCM) data allows the attribution of the most intense carbonyl doublet component to the more stable and lower calculated frequency gauche conformers g(anti; syn) for **3–6** in *n*-hexane and 1-6 in carbon tetrachloride. Analogously, the single band for 1 and **2** in *n*-hexane (IR) may be assigned to the gauche conformers. Additionally, the PCM data show that there is a progressive increase of cis/gauche population ratio as the solvent polarity increases (from $n-C_6H_{14}$ to CCl₄, to CHCl₃, and to CH₃CN), which is in agreement with the progressive increase of the intensity of the higher v_{CO} frequency component with respect to the lower v_{CO} frequency one.

In the gas phase, the gauche conformers are stabilized by relevant orbital interactions, namely $LP_{S4} \rightarrow \pi^*_{C_2=O_1}$, $\pi_{C2=O_1} \rightarrow \sigma^*_{C3-S4}$, $\sigma_{C3-S4} \rightarrow \pi^*_{C2=O_1}$, $\pi^*_{C2=O_1} \rightarrow \sigma^*_{C3-S4}$, and $LP_{O1} \rightarrow \sigma^*_{C11-H28}$, which are absent in the *cis* (*anti*; *syn*) conformers. In contrast, the *cis* rotamers are destabilized via enhanced electrostatic repulsion imposed by small torsional angles between the $C^{\delta+}$ - $S^{\delta-}$ and $C^{\delta+}$ = $O^{\delta-}$ dipoles. This Repulsive Field Effect is also responsible for their higher v_{CO} frequency in the whole series. In addition, the $\sigma_{\text{C3}-\text{S4}} \to \sigma_{\text{C2}-\text{N5}}^*$ orbital interaction (though bond coupling) contributes to the stabilization of the cis conformers for derivatives 1, 3, and 6. In 6, the near planarity of the O=C-C-S-Ph moiety allows for an additional stabilizing orbital interaction, $LP_{01} \rightarrow \sigma^*_{S4-C10}$. This interaction is absent in 1 and **3** derivatives as a consequence of the unfavorable geometry.

The sum of the energy contribution of the orbital interactions (NBO analysis) and the electrostatic interactions correlates well with the populations and the v_{CO} frequencies of both pairs of the cis and gauche conformers in the gas phase and in low-polarity solvents.

X-ray single crystal analysis indicates that compound 4 assumes the $c_2(anti)$ conformation in the solid state, which is the conformation obtained by compound 6 in the gas phase. The orientation of the phenyl ring is away and coplanar with the carbonyl group resulting in an intramolecular S...O distance that is significantly shorter than Σ vdW radii. This short contact contributes to the stabilization of this conformation in the solid. The most prominent feature in the crystal packing is the formation of a six-molecules synthon mediated by C-H···O and Cl···Cl interactions. The Cl \cdots Cl distance is less than the Σ vdW radii, and the chlorine atoms are related by a crystallographic inversion center.

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