Stereochemical and electronic interaction studies of some N-methoxy-N-methyl-2-[(4'-substituted)phenylsulfinyl]propanamides

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1. Introduction

Our recent IR, X-ray diffraction and theoretical studies performed on N,N-diethyl-2-[(4'-substituted)phenylsulfinyl]acetamides [1], indicated the existence of two pairs of cis (anti, syn) and gauche (anti, syn) conformers in the gas phase, the cis conformer pair being more stable than the gauche pair. The larger stability of the cis conformer pair is in line with both its geometry and the higher electronic density at the carbonyl oxygen atom due to a significant contribution of the [\(-\text{O} \cdots \text{C} = \text{N}\)] resonance structure, which allows a strong \(\text{O}^{\text{\text{I}}\text{\text{C}}\text{\text{O}}} \cdots \text{S}^{\text{\text{I}}\text{\text{D}}}\) charge transfer and Coulombic interactions along with the \(\text{O}^{\text{\text{I}}\text{\text{C}}\text{\text{O}}} \cdots \text{ortho-H}^{\text{\text{I}}\text{\text{P}}}\) intramolecular hydrogen bond. The gauche conformer pair is weakly stabilized through the \(\text{O}^{\text{\text{I}}\text{\text{S}}} \cdots \text{C}^{\text{\text{I}}\text{\text{C}}}\) Coulombic interaction. Thus, the single carbonyl band found in solution has been ascribed to the more stable and more polar cis conformer pair.

N-Methoxy-N-methylamides (Weinreb amides) are important acylating agents which have been widely used for preparation of ketones [2–4]. The efficiency of this reaction allowed us to synthesise some acyl derivatives of \(\beta\)-lactams in good yields, which was not possible through traditional methods employing other carboxylic acid derivatives [5–7]. A comparison between the energies of some relevant orbitals (computed by HF/6-31G**) of the N,N-diethylacetamide (a) [1] with those of the N-methoxy-N-methyl-acetamide (b) (present work) (data in Fig. 1) justifies the higher acylating ability of this amide relative to the former. In fact, in the amide b, containing the electron-withdrawing methoxy group (\(\text{\sigma}_{s} = 0.27\)) [8] bonded to the nitrogen atom, the ionization energy of the nitrogen lone pair \(n_{a}\) is increased by ca. 0.6 eV with respect to amide a, and simultaneously the electron-affinity of the \(\pi_{o}\) orbital increases in the same direction by ca. 0.5 eV. The increased ionization energy of the \(n_{a}\) lone pair of b in relation to a is responsible for both the slightly smaller \(n_{a}\) / \(\pi_{o}\) orbital interaction and the slightly poorer \(0 = \text{C} \cdots \text{N} \cdots \text{O} = \text{C} \cdots \text{N}^\prime\) conjugation, which in turn originates some pyramidalization of the nitrogen atom in the MeO-N(Me)-C(O) moiety for b. Conse-

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quently, the higher electron-affinity of the π* orbital in the N-methoxy-N-methylamide is responsible for the higher electrophilicity of its carbonyl carbon atom.

Moreover, the increased ionization energy of the carbonyl oxygen lone pair π(πCO) by ca. 0.4 eV in b relative to a must also occur in the cis conformer of N-methoxy-N-methyl-α-phenylsulfinylamides relative to N,N-diethyl α-phenylsulfinylamides [1], leading to a decrease of the O(CO)···SiR3 charge transfer interaction.

Therefore, it became of interest to study the IR spectra of the N-methoxy-N-methyl-2-[(4'-substituted)phenylsulfinyl]propanamides, bearing as substituents OMe 1, Me 2, H 3, Cl 4, NO2 5 (Scheme 1), along with ab initio and density functional theory calculations for compound 3 and X-ray diffraction analysis of compound 5, reported in the present paper. These compounds were chosen taking into account that the orbital and Coulombic interactions, which could operate in their cis and gauche conformers, should be affected by changes in the conjugation involving the 4'-substituent and consequently should influence the stabilization of the referred conformers.

2. Experimental

2.1. Materials

All solvents for IR measurements were spectrograde and were used without further purification. The N-methoxy-N-methyl-2-[(4'-substituted)phenylsulfinyl]propanamides, Y-Ph-S(O)CH[Me]C(O)N[OMe][Me] (Y = OMe 1, Me 2, H 3, Cl 4, NO2 5), were prepared as previously described [9,10]. As the title compounds present two stereogenic centers, i.e. the α-methylene carbon (C4 and C5) and the sulfinyl sulfur (S5 and S6) atoms (Scheme 1) a racemic mixture of two pairs of diastereomers ([C5S5,C6S6] and [C5S6,C6S5]) are obtained as they have been synthesised without asymmetrical induction. The pure sulfinylamides (1–4) are viscous liquids (a pair of diastereomers) which could not be resolved from chromatography on silica gel. The fractional crystallization of the amorphous yellow solid 4'-nitro-derivative (5) from chloroform/n-hexane affords initially the racemic mixture of C5S5,C6S6 diastereomer (mp 94–95°C), followed by the racemic mixture of C5S6,C6S5 diastereomer (mp 117–119°C) [10] in ca. 8:2 ratio. This proportion was estimated from the methyne (H-3) and methyl (H-6) hydrogen signals (Scheme 1) in the 1H NMR spectrum of 5, in CDCl3. These data are shown in Table 1 and illustrated in Fig. 2. Suitable crystals for X-ray analysis of the C5S5/C6S6 and C5S6/C6S5 diastereomer pairs were obtained by vapour diffusion from chloroform/n-hexane at 5°C. As the crystal structure of the C5S6/C6S5 diastereomer pair was already described [10], this paper reports the single crystal analysis

![Scheme 1](image-url)

**Table 1.** Methyl and methyne 1H NMR signals for the diastereomeric mixture (diast1, and diast2) for the N-methoxy-N-methyl-2-[(4'-substituted)phenylsulfinyl]propanamides, X-Ph-S(O)CH[Me]C(O)N[OMe][Me] (1–5) and for the resolved diastereomers of the 4'-nitro-derivative (5), in CDCl3.

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<thead>
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<th>Comp.</th>
<th>X</th>
<th>Diast.</th>
<th>δ&lt;sub&gt;αCH&lt;sup&gt;3&lt;/sup&gt;&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>δ&lt;sub&gt;CH&lt;sup&gt;3&lt;/sup&gt;&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>δ&lt;sub&gt;H&lt;sup&gt;α&lt;/sup&gt;CH&lt;sub&gt;3&lt;/sub&gt;&lt;/sub&gt;</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>4.39</td>
<td>6.9</td>
<td>97.0</td>
</tr>
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</table>

<sup>a</sup> Refers to the specification of each diastereoisomer.
<sup>b</sup> Refers to C5S5/C6S5 racemic mixture.
<sup>c</sup> Refers to C5S6/C6S5 racemic mixture.
<sup>d</sup> Chemical shifts in ppm relative to TMS.
<sup>e</sup> Coupling constants in Hz.
<sup>f</sup> Average percentage of each diastereomer estimated through the 1H methyl and methyne signals.
<sup>g</sup> Refers to the almost pure racemic mixture of C5S5,C6S6 and C5S6,C6S5 diastereomers, respectively.
<sup>h</sup> Refers to the almost pure racemic mixture of C5S6,C6S5 and C5S5,C6S6 diastereomers, respectively.
of the CRSS/CSSR diastereomer pair only. Fig. 3 shows the X-ray CRSS (a) and the CRSS (b) diastereomeric structures of 5.

2.2. IR measurements

The IR spectra were obtained on a FTIR Nicolet Magna 550 spectrometer, with 1.0 cm⁻¹ resolution. The carbonyl region (1800-1600 cm⁻¹) was recorded for carbon tetrachloride, chloroform, dichloromethane and acetonitrile solutions, at a concentration of 1.0 × 10⁻² mol dm⁻³, using a 0.519 mm sodium chloride cell. The carbonyl first overtone region (3600–3100 cm⁻¹) was recorded for a carbon tetrachloride solution (1.0 × 10⁻² mol dm⁻³) using a 1.00 cm quartz cell. The overlapped carbonyl bands (fundamental and first overtone) were deconvoluted by means of the Grams/32
2.5. Theoretical calculations

The geometries and electron charge distribution at the various atoms for the stable conformers of N-methoxy-N-methyl-2-phenylsulfanyl-propanamides (3) were computed at HF/6-31G* and at B3LYP/6-31G* level of theory using the Gaussian 98 package of programs [16]. The parent N-methoxy-N-methylpropanamidine (6) was computed at the HF/6-31G* level and the geometry of its anti conformer was used as the starting point to determine the preferred conformations for 3. For the C2S2/C3S2 diastereomers of 3, all the possible cis and gauche orientations of the C–S bond with respect to the carbonyl group were fully optimized, allowing complete relaxation of all internal parameters. Analytical frequency calculations confirm that all the conformations detected are stationary points on the Potential Energy Surfaces.

3. Results and discussion

Table 1 and Fig. 2 show the 1H NMR duplicated α-methyl [CH2CH] doublet (a)–(c) and the methine [CHS(O)] quartet (d)–(f) signals for the almost pure diastereomers (diast1 and diast2) [(a), (b) and (d), (e)] and for the diastereomeric mixture [(c) and (f)], respectively, of the 4-nitro-derivative 5, being their relative concentrations, in CDCl3, estimated from the averaged integrated intensities of both methyl and methylene signals, which gives the proportion of 83.6% for diast1 and 16.4% for diast2. The [CH3CH] doublet signals at 1.65 ppm and 1.23 ppm correspond to the diast1 and diast2, respectively, while the [CHS(O)] quartet occurs at 4.08 ppm and 4.39 ppm for diast1 and diast2, respectively. However, diast1 is obtained in ca. 97% and corresponds to the almost exclusive downfield [CH2CH] doublet and to the [CH] upfield quartet signals, after a diastereomeric separation. Similarly diast2 is obtained in ca. 97% and corresponds to the almost exclusive upfield [CH2CH] doublet and the [CH] downfield quartet signals.

X-ray analysis of each compound 5 pure stereoisomer indicates that 1H NMR signals of diast1 correspond to the C2S2/C3S2 diastereomeric racemic pair and the signals of diast2 are related to the C2S0/C3S0 diastereomeric racemic pair. Fig. 3 shows the ZORTEP views of C2S0 (a) and C3S0 (b) structures of 5. Table 1 shows that the same assignments of α-methyl doublet and methine quartet 1H chemical shifts along with JHCHD = 6.9 Hz coupling constant for diast1 and diast2 of the mixture of 5, also hold for the remaining diastereomeric mixtures of the 1–4 derivatives. Moreover the estimated averaged diastereomeric ratio of diast, relative to diast2 for the whole series is of ca. 70% and 30%, respectively.

1H NMR spectra of 5 were recorded in CCl4, CDC13 and CD2CN solutions, to verify if the diastereomers (diast1 and diast2) relative population varies on increasing the solvent polarity, through an enol intermediate, as it has been previously reported in α-methyl-3-sulfanyl-α-diethoxyphosphorylacetonones [17]. However, in opposition to the observed result for these mentioned acetophenones, both α-methyl doublet and methine quartet relative intensities did not change on increasing solvent polarity. This behaviour can be explained by the smaller acidity of methine hydrogen atom in comparison to the acetophenone derivatives.

Table 2 lists the stretching frequencies and the absorbance percentage of the analytically resolved carbonyl band doublets of

Table 2

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Y</th>
<th>CHCl3</th>
<th>CH2Cl2</th>
<th>CH3CN</th>
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<td>v</td>
<td>P</td>
<td>v</td>
<td>v</td>
</tr>
<tr>
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<td>OMe</td>
<td>1677</td>
<td>20.3</td>
<td>3329</td>
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<tr>
<td>2</td>
<td>Me</td>
<td>1600</td>
<td>78.7</td>
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</tr>
<tr>
<td>3</td>
<td>H</td>
<td>1678</td>
<td>21.4</td>
<td>3328</td>
</tr>
<tr>
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<td>1661</td>
<td>78.6</td>
<td>3302</td>
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<tr>
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<td>3331</td>
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<tr>
<td></td>
<td>1661</td>
<td>77.6</td>
<td>3302</td>
<td>76.3</td>
</tr>
<tr>
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<td>NO2</td>
<td>1679</td>
<td>17.1</td>
<td>3322</td>
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<td></td>
<td>1661</td>
<td>82.9</td>
<td>3302</td>
<td>75.7</td>
</tr>
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</table>

*a Intensity of each component of the carbonyl doublet expressed in percentage (P) of absorbance.
*b First overtone.
N-methoxy-N-methyl-2-[(4'-substituted)phenylsulfinyl]propanamides (1-5) in solvents of increasing relative permittivity [18], i.e. carbon tetrachloride ($\varepsilon = 2.2$) (fundamental and first overtone), chloroform ($\varepsilon = 4.8$) dichloromethane ($\varepsilon = 9.1$) and acetonitrile ($\varepsilon = 38$). The intensity of the higher frequency doublet component remains almost constant on going from carbon tetrachloride to

\[1710 \quad 1700 \quad 1690 \quad 1680 \quad 1670 \quad 1660 \quad 1650 \quad 1640 \quad 1630 \quad 1620 \]

\[\text{Absorbance} \quad 0 \quad 0.02 \quad 0.04 \quad 0.06 \quad 0.08 \quad 0.1 \quad 0.12 \quad 0.14 \quad 0.16 \quad 0.18 \]

\[\text{Wavenumber (cm}^{-1}) \]

Fig. 4. IR spectra of N-methoxy-N-methyl-2-[(4'-nitrophenyl)sulfinyl]propanamide (5) showing the carbonyl stretching band, in carbon tetrachloride [fundamental (a) and first overtone (b)], chloroform (c), dichloromethane (d) and acetonitrile (e).
chloroform, but increases progressively on going from these solvents to dichloromethane and acetonitrile, in the same way as the solvent polarity increases. These solvent effects and the occurrence of two carbonyl bands in the first overtone region at frequencies ca. twice those of the fundamental, and with about the same intensity ratios, strongly suggest that compounds 1–5 present, in solution, two stable conformers [19,20]. The solvent effect on the carbonyl band components for 5, taken as prototype of the whole series, is illustrated in Fig. 4. Table 2 also shows that the intensity of the higher frequency doublet component remains almost constant through the series 1–5, for each solvent.

Considering that the title compounds (1–5) are composed by a diastereomeric mixture (ca. 70% of diast-1 and ca. 30% of diast-2) (see Table 1), the resolved IR carbonyl bands of each diastereomer (diast-1) and (diast-2) for the nitro-derivative of 5, in the solvents above referred, are presented in Table 3 and in Fig. 5 and Fig. 6, respectively, while the spectrum of the mixture is shown in Fig. 4. Both diastereomers display doublets in all solvents, except for diast-2 in acetonitrile where a single carbonyl band is observed. As expected, the predominant diastereomer (diast-1) presents similar solvent effect on the carbonyl doublet as the polarity of the solvent increases. In fact, the intensity of the higher frequency doublet component increases on going from low polar solvents (carbon tetrachloride, chloroform) to high polar ones (dichloromethane and acetonitrile). However, a reverse solvent effect is observed for diastereomer (diast-2), i.e. there is a progressive decrease of the intensity of the higher frequency doublet component as the polarity of the solvent increases and it vanishes in acetonitrile solution. These solvent effects along with the occurrence of two carbonyl bands in the first overtone region at frequencies ca. twice as those in the fundamental and with about the same intensity ratios, strongly suggests that both diastereomers (diast-1 and diast-2) of 5 present in solution two conformers.

Aiming to determine the geometries for the stable conformations of each diastereomer for the series 1–5, computations at HF and B3LYP/6-31G** level of theory for the C8S8 (diast-1) and C6S6 (diast-2) diastereomers of the N-methoxy-N-methyl-2-phenylsulfinylpropanamide (3), taken as a representative compound, were performed. The same parameters were found for the calculations performed for each enantiomer (C8S8 and C6S6). In order to obtain the corresponding parameters for the fragment MeO-N(Me)=C=O, HF/6-31G** calculations for N-methoxy-N-methyl-lactamide (6) were performed.

Table 4 presents the results from the ab initio calculations for compound 6, showing that this compound exists in the gas phase almost exclusively in the less polar anti conformation, being the |O=C—N—OMe| dihedral angle ca. 160°, while for the less stable syn conformation the | angle is ca. 17° (Structures I and II, Scheme 2). The anti conformation is stabilized due to the shorter interatomic contact between one of the positively charged methyl hydrogen atom H(8) of the N-methyl group and the negatively charged carbonyl oxygen atom O(1), relative to the sum of the van der Waals radii (ΣvdW radii) (| = −0.27 Å), which leads to a significant attractive electrostatic interaction between them (hydrogen bond) (Table 5). The syn conformer is weakly stabilized through the contact between one of the positively charged hydrogen atom H(10) of the N-methoxy group and the negatively charged carbonyl oxygen atom O(1), whose interatomic distance is slightly shorter than the sum ΣvdW radii (| = −0.07 Å). On the other hand the syn conformer is significantly destabilized by the shorter interatomic contact between the negatively charged carbonyl oxygen atom O(1) and the methoxy oxygen atom O(9) relative to the ΣvdW radii (| = −0.44 Å), which leads to a significant electrostatic repulsion between them. Moreover the sum of the internal angles of the [MeO—N—Me—C=O] fragment of 6 is 344.8° which indicates some pyramidalization at the nitrogen atom as expected for a Weinreb amide. Table 6 shows the relevant data obtained at the HF level of theory for diast-1 and diast-2 of compound 3. This Table includes carbonyl frequencies computed at the B3LYP level for diast-1 and diast-2 of compound 3 along with the X-ray dihedral angles for diast-1, and diast-2 of compound 5. It should be pointed out that both calculations indicate the existence of three and two conformers for diast-1 and diast-2, respectively. Moreover the dihedral angles obtained in both calculations are very close to each other. However, the computed carbonyl frequencies are significantly different in both calculations. In fact, the frequencies of the three conformers for diast-1 are almost the same from the HF method. On the other hand, the carbonyl frequency of quasi-cis-2 (q-c2) conformer is higher than that of quasi-gauche (q-g) conformer for diast-2. These results do not match the experimental frequencies found for both diastereomers for 5 (Table 3). Moreover, B3LYP data presents two νCO degenerated frequencies (1668 cm−1) for the quasi-cis-1 and quasi-cis-2 conformers and a higher νCO frequency (1675 cm−1) for the gauche conformer of diast-1. For diast-2 the carbonyl frequency of the quasi-cis-3 conformer is only slightly lower than that of the quasi-gauche (q-g) conformer. The HF computed relative populations, of the quasi-cis-1 and quasi-cis-2 conformers sum up to 95% relative to the gauche conformer (5%) for diast-1, and the relative concentrations of the quasi-cis-3 (25%) and quasi-gauche (75%) conformers for diast-2, fit better with the corresponding experimental values than those obtained by the B3LYP method (Tables 3 and 6). Thus, the HF data along with the B3LYP νCO frequencies only, will be considered in the present paper.

Table 6 shows that the five conformations of 3 displays for the MeO—N—Me=C=O moiety the same geometry (|, | and | dihedral angles) of the most stable anti conformation of 6. However, in the q-c2 conformer of diast-1 an inversion of the configuration at the nitrogen atom occurs with an inversion in the signals of |, | and | dihedral angles only, but not their absolute values.
3.1. Enantiomeric pair (CrS/CrS) (diast1)

The most stable $q_{c1}$ conformer of diast1 displays the [PhS(O)] group ($\alpha = 36^\circ$) in a quasi-syn-periplanar (quasi-cis$_1$) geometry relative to the carbonyl group. The second more stable $q_{c2}$ conformer of diast1 presents the [PhS(O)] group ($\alpha = 46^\circ$) in a quasi-syn-clinal (quasi-cis$_2$) geometry relative to the carbonyl group. Additionally both conformers present almost the same $\alpha$, $\beta$, $\gamma$, and $\phi$ dihedral angles. Therefore both closely related conformers are shown as quasi-cis$_1$ in Structure III (Scheme 3). The least stable $g$ conformer of diast1 displays the [PhS(O)] group ($\alpha = 86^\circ$) in an anti-clinal (gauche) geometry relative to the carbonyl group (Structure IV.

Fig. 5. IR spectra of diastereomer1 of N-methoxy-N-methyl-2-[(4-nitrophenyl) sulfinyl] propanamide (5) showing the carbonyl stretching band, in carbon tetrachloride [fundamental(a) and first overtone (b)], chloroform (c), dichloromethane (d) and acetonitrile (e).
Scheme 3). Both q-c conformers are significantly more polar than the g conformer, and present degenerated carbonyl frequencies, which are lower than that of the g conformer (Table 6).

The geometry of q-c1 conformation allows a significant short intramolecular contact, relative to the ΣvdW radii (Δl = 0.33 Å), between oppositely charged carbonyl oxygen (−0.602e) and the sulfinyl sulfur (+1.074e) atoms (Tables 5 and 7), which is responsible for a strong C==O...S=O electrostatic and charge transfer (CT) (supported by eigenvector analysis) interactions. On the other hand, the larger α-dihedral angle (by ca. 11°) for the q-c2 con-
Table 4
Optimized relative energies (E, kJ mol⁻¹), dipole moments (µ, D), carbonyl frequencies (cm⁻¹), selected dihedral angles (deg) and selected interatomic distances (Å) for the minimum energy conformations of N-methoxy-N-methylacetamide (6), at HF/6-31G* level of theory.

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<th>Comp.</th>
<th>Config.</th>
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<th>ν (cm⁻¹)</th>
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* Conformer designation: syn and anti refers to the methoxy oxygen atom at the same side and at the opposite side relative to the carbonyl oxygen atom, respectively.

b Molar fraction of each rotamer in percentage.
c Scaling factor of 0.856.
d See Scheme 1.
e Sum of the van der Waals radii = 3.04 Å.
f Difference between non-bonded atoms distance and the sum of their van der Waals radii.
g Difference between non-bonded atoms distance and the sum of their van der Waals radii.
h Sum of the van der Waals radii = 3.04 Å.

The geometry of the gauche (g) conformer allows a short intramolecular contact relative to the vbD radii (r = 0.20 Å) between oppositely charged sulfanyl oxygen and the carbonyl carbon atoms (Tables 6 and 7), which is responsible for O(1)−0.51 Å participation of the carbonyl oxygen atom, O(1)−0.51 Å. intra-

Formed originates a slightly smaller contact relative to the vbD radii (r = 0.28 Å) between the carbonyl oxygen and the sulfanyl sulfur atoms, whose charges are almost the same for the CO...H(5)O(1) conformer (−0.601e) and smaller for the sulfur (1.066e) atom in comparison to those of the g-C1 conformer. This behaviour leads to a less strong O(1)−H(5)O(1) electrostatic and CT interactions, which in turn is in line with the larger stability of the g-C1 conformer (89.6%) with respect to that of the a-C1 conformer (10.4%), in spite of the same carbonyl frequencies found for both conformers. It should be mentioned that in general the O(1)−S(2) interatomic distances and CT interactions are of paramount importance for the stabilization of the cis and quasi-cis conformers in the α-carbonyl-sulfoxides (see Section 1).

Additionally, both quasi-cis (g-C1 and a-C1) conformers are stabilized almost into the same extent by the following electrostatic (hydrogen bond) interactions (Tables 5–7), whose contact between the interacting atoms is shorter than the vbD radii, as shown: (a) between one of the positively charged hydrogen H(5)H(5)O(1) and the negatively charged oxygen O(1) atoms (O(1)−H(5)O(1), r = 0.29 Å); (b) between one of the positively charged hydrogen H(5)O(1) and the negatively charged oxygen O(1) atoms (O(1)−H(5)O(1), r = 0.08 Å); (c) between the positively charged hydrogen H(5)O(1) and the negatively charged oxygen O(1) atoms (O(1)−H(5)O(1), r = 0.35 Å); (d) between the positively charged hydrogen H(5)O(1) and the negatively charged oxygen O(1) atoms, [O(1)−H(5)O(1), r = 0.27 Å]. Lastly the q-C1 conformer only is slightly stabilized by the contact between the positively charged hydrogen H(5)O(1) and the negatively charged oxygen O(1) atoms (O(1)−H(5)O(1), r = 0.07 Å).

From the above analysis, it seems reasonable to admit that the intramolecular electrostatic (hydrogen bonds) interactions, which stabilize the quasi-cis (g-C1 and a-C1) conformers, are practically counterbalanced by the electrostatic (hydrogen bonds) interactions which stabilize the gauche conformation. Therefore, the larger stability of the g-conformers over the gauche conformer is due to a larger contribution of the O(1)−S(2) electrostatic and CT interactions for the former conformers with respect to the weaker electrostatic stabilization for the latter conformer.

Table 5
Charge (e) at selected atoms, obtained at HF/6-31G* level of theory, for PhSO(CH(CH₃)NOMe)Me (3) and for N-methoxy, N-methylacetamide (6).

<table>
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<tbody>
<tr>
<td>3</td>
<td>C₅₋₇₅</td>
<td>q-c₁</td>
<td>-0.602</td>
<td>0.770</td>
<td>1.074</td>
<td>-0.811</td>
<td>-0.342</td>
<td>-0.492</td>
<td>0.207</td>
<td>0.189</td>
<td>0.127</td>
<td>0.176</td>
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<tr>
<td></td>
<td>C₅₋₇₅</td>
<td>q-c₂</td>
<td>-0.601</td>
<td>0.770</td>
<td>1.066</td>
<td>-0.808</td>
<td>-0.351</td>
<td>-0.483</td>
<td>0.205</td>
<td>0.206</td>
<td>0.126</td>
<td>0.173</td>
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<tr>
<td></td>
<td>C₅₋₇₅</td>
<td>g</td>
<td>-0.604</td>
<td>0.809</td>
<td>1.015</td>
<td>-0.813</td>
<td>-0.338</td>
<td>-0.501</td>
<td>0.202</td>
<td>0.213</td>
<td>0.126</td>
<td>0.172</td>
</tr>
<tr>
<td></td>
<td>C₅₋₇₅</td>
<td>q'-g</td>
<td>-0.605</td>
<td>0.779</td>
<td>1.047</td>
<td>-0.817</td>
<td>-0.344</td>
<td>-0.492</td>
<td>0.209</td>
<td>0.197</td>
<td>0.128</td>
<td>0.161</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>anti</td>
<td>-0.586</td>
<td>0.720</td>
<td>–</td>
<td>-0.337</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.115</td>
<td>0.121</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>syn</td>
<td>-0.571</td>
<td>0.733</td>
<td>–</td>
<td>-0.353</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.144</td>
<td>0.128</td>
<td>–</td>
</tr>
</tbody>
</table>

* Refers to the charge on the methyl or phenyl hydrogen atom which makes the nearest contact with the carbonyl or sulfynil oxygen atom.
atom of the phenylsulfinyl group is close to the carbonyl oxygen and is more hindered for the approaching of the solvent than that for the conformers (Structure VI). In fact, it shows the occurrence of a progressive decrease in the extent than that for the more polar and most stable conformer (1.71D), in gas phase, as the polarity of the compound increases. Nevertheless, a close inspection of the q-c conformers (Structure V, Scheme 3) shows that the C=O dipole is more hindered for the approaching of the solvent than that for the g conformer (Structure VI, Scheme 3) as the ortho hydrogen atom of the phenylsulfinyl group is close to the carbonyl oxygen atom in the q-c conformers only. Furthermore the S=O dipole, which is not hindered in both the q-c and g conformations seems to be solvated to approximately into same extent for both conformers. It is worth of mentioning that this abnormal solvent effect has already been observed in the α-alkylsulfinylacetophenones [21,22].

3.2. Enantiomeric pair (C5S5/C5S6) (diast2)

Table 6 shows that the geometry of the quasi-cis (q-c3) conformer for compound 5 is very similar to that found for the quasi-cis (q-c1) conformer for compound 3. In fact, their dihedral angles are close to those of the q-c1 conformer for diast1, except for the δ dihedral angle of q-c3 conformer (13.6°), whose absolute value is slightly larger than that of the g conformer (1.71D), in gas phase for 3 (Table 6), the solvent effect on the relative intensities of the carbonyl doublet found for diast1 of 5 (Table 3) is anomalous. In fact, it shows the occurrence of a progressive decrease in the concentration of the more polar and most stable q-c conformers relative to the less polar and less stable g conformer as the polarity of the solvent increases. In spite of the higher polarity of the q-c conformers (6.11 and 5.87D) in comparison to the g conformer (1.71D), in gas phase for 3 (Table 6), the solvent effect on the relative intensities of the carbonyl doublet found for diast1 of 5 (Table 3) is anomalous. In fact, it shows the occurrence of a progressive decrease in the concentration of the more polar and most stable q-c conformers relative to the less polar and less stable g conformer as the polarity of the solvent increases. Nevertheless, a close inspection of the q-c conformers (Structure V, Scheme 3) shows that the C=O dipole is more hindered for the approaching of the solvent than that for the g conformer (Structure VI, Scheme 3) as the ortho hydrogen atom of the phenylsulfinyl group is close to the carbonyl oxygen atom in the q-c conformers only. Furthermore the S=O dipole, which is not hindered in both the q-c and g conformations seems to be solvated to approximately into same extent for both conformers. It is worth of mentioning that this abnormal solvent effect has already been observed in the α-alkylsulfinylacetophenones [21,22].

Table 6

Optimized relative energies (E, kJ mol⁻¹), dipole moments (µ, D), frequencies (ν, cm⁻¹) and selected dihedral angles (deg) for the minimum energy conformation of stereoisomers (diast1 and diast2) for compound 3, at HF/6-31G* level, and X-ray geometrical data for compound 5

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Config.</th>
<th>Conf.</th>
<th>β</th>
<th>γ</th>
<th>φ</th>
<th>δ</th>
<th>δ'</th>
<th>δ''</th>
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<tr>
<td>3</td>
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<td>q-c1</td>
<td>0.00</td>
<td>69.2</td>
<td>6.11</td>
<td>1669</td>
<td>1668</td>
<td>35.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>q-c2</td>
<td>5.39</td>
<td>7.8</td>
<td>5.87</td>
<td>1669</td>
<td>1668</td>
<td>46.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>g</td>
<td>7.34</td>
<td>3.6</td>
<td>1.71</td>
<td>1668</td>
<td>1675</td>
<td>82.8</td>
</tr>
<tr>
<td></td>
<td>diast2</td>
<td>q-c1</td>
<td>6.55</td>
<td>4.9</td>
<td>4.42</td>
<td>1673</td>
<td>1675</td>
<td>35.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>q-c2</td>
<td>3.88</td>
<td>14.5</td>
<td>4.63</td>
<td>1663</td>
<td>1677</td>
<td>68.7</td>
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<tr>
<td>5</td>
<td>X-ray</td>
<td>diast1</td>
<td>g</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diast2</td>
<td>g</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
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<th>f</th>
<th>g</th>
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<td>X</td>
<td>Y</td>
<td>Z</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

* a diast1 and diast2 refers to the diastereomers C5S5 and C5S6, respectively (see text).
* b C5S5 and C5S6 refers to configuration of the α-carbon and sulfur stereogenic centers.
* c Conformer assignments; q-c, q-g and g refer to the quasi-cis, quasi-gauche and gauche conformers, respectively.
* d Relative energy.
* e Molar fraction in percentage.
* f Scaling factor of 0.860.
* g Scaling factor obtained at B3LYP/6-31G** level; scaling factor 0.960 (see text).
* hSee Scheme 1.
* i From Ref [10].
larger than that of the q-c1 conformer (66°) and its signal is reversed, as expected due to the inversion of the configuration of the sulfur stereogenic center (from S3S to S(R)). In fact, the comparison of Structure VII (Scheme 4) for the q-c1 conformer with Structure III (Scheme 3) for q-c2 conformer shows the inversion of the position of the phenylsulfinyl group relative to the O=–C=S–O pseudo-plane.

The geometry of q-c2 conformation also allows a significant short intramolecular contact relative to the ΣvdW radii (Δl = 0.32 Å), for the carbonyl oxygen and sulfurulfur atoms (Tables 5 and 7), which is responsible for strong O=–S...C=C electrostatic and charge transfer (CT) (supported by eigenvector analysis) interactions. Additionally, the q-c2 conformer is stabilized by the following electrostatic (hydrogen bond) interactions (Tables 5–7), whose contact between the interacting atoms is shorter than the ΣvdW radii, as shown: (a) between hydrogen H(C6NMe3) and the oxygen O(1) atom [O(1)...H(C6NMe3) Δl = 0.27 Å]; (b) between the hydrogen H(C6Ph) and the oxygen O(1) atom [O(1)...H(C6Ph) Δl = 0.36 Å]; (c) between the positively charged hydrogen H(C6+) and the negatively charged oxygen O(1) atom [O(1)...H(C6+) Δl = 0.33 Å].

The most stable q-g conformer of diast2 displays the [PhSO(O)] group (x = 69°) in a syn-clinal (quasi-gauche) geometry relative to the carbonyl group (Structure VIII, Scheme 4). This spatial arrangement allows the occurrence of two short contacts between the carbonyl oxygen and the sulfinyl sulfur atoms whose O=–S...C=C contact is shorter than the ΣvdW radii by 0.20 Å and between the sulfinyl oxygen and the carbonyl carbon atoms whose O=–C=C contact is shorter than the ΣvdW radii by 0.21 Å. These crossed short contacts allow the synergism of the moderate O=–C=C...O electrostatic and charge transfer interaction with the O=–S...C=C electrostatic interaction. Furthermore the q-g conformer is stabilized by the following electrostatic (hydrogen bond) interactions (Tables 5–7), whose contact between the interacting atoms is shorter than the ΣvdW radii, as shown: a) between the hydrogen H(C6NMe3) and the oxygen O(1) atom [O(1)...H(C6NMe3) Δl = 0.27 Å]; (b) between the hydrogen H(C6Ph) and the oxygen O(1) atom [O(1)...H(C6Ph) Δl = 0.36 Å]; (c) between the positively charged hydrogen H(C6+) and the negatively charged oxygen O(1) atom [O(1)...H(C6+) Δl = 0.33 Å].

Table 7
Selected interatomic distances (Å) involving the carbonyl oxygen [O(1)] atom for the minimum energy conformations of PhSO(CH)2N(O)Me (3) at HF/6-31G(d) level of theory and X-ray geometrical data for 4-NO2PhSO(O)CH(CH3)N(O)Me (5)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Config.</th>
<th>Config.</th>
<th>O(1)...S(4)</th>
<th>O(1)...H(6)</th>
<th>O1...H16</th>
<th>O1...H8</th>
<th>Δl</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>C3S3</td>
<td>q-c1</td>
<td>2.990</td>
<td>0.33</td>
<td>2.964</td>
<td>0.19</td>
<td>2.650</td>
</tr>
<tr>
<td></td>
<td>C3S3</td>
<td>q-c2</td>
<td>3.043</td>
<td>0.28</td>
<td>2.827</td>
<td>0.11</td>
<td>2.744</td>
</tr>
<tr>
<td></td>
<td>C3S3</td>
<td>g</td>
<td>3.388</td>
<td>0.07</td>
<td>2.591</td>
<td>0.13</td>
<td>3.157</td>
</tr>
<tr>
<td></td>
<td>C3S3</td>
<td>l</td>
<td>3.000</td>
<td>0.32</td>
<td>3.125</td>
<td>0.41</td>
<td>2.395</td>
</tr>
<tr>
<td></td>
<td>C3S3</td>
<td>q-c3</td>
<td>3.114</td>
<td>0.21</td>
<td>2.639</td>
<td>0.08</td>
<td>2.400</td>
</tr>
<tr>
<td>5</td>
<td>C3S3</td>
<td>g</td>
<td>3.525 (4)</td>
<td>0.20</td>
<td>2.66</td>
<td>0.06</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>C3S3</td>
<td>l</td>
<td>3.602(2)</td>
<td>0.28</td>
<td>2.50</td>
<td>0.22</td>
<td>3.36</td>
</tr>
</tbody>
</table>

The contacts are labeled with the letter D to indicate a direct contact between the interacting atoms, and with the letter l to indicate a longer contact. The distance between the interacting atoms (Δl) is given in Å, and the contact is labeled with the letter D to indicate a direct contact between the interacting atoms, and with the letter l to indicate a longer contact. The distance between the interacting atoms (Δl) is given in Å.

References:
2. From Ref. [10].
3. Refers to the contact between the carbonyl or methoxy oxygen atoms and the nearest methyl or ortho-phenyl hydrogen atom.
atoms \(\text{[O}_{\text{CO}}-\text{H}^+\text{NMe}_{3+}]\), \(\Delta l = 0.32 \text{ Å}\) (the same short contact found in the MeO–N(OMe)=C=O fragment of the reference compound 6 and in the q-c (q-c1, and q-c2), g (diast1) and q-c3 conformers (diast2) of 3); (b) between the hydrogen Hʻ(C'11) and the oxygen Oʻ(OMe) atoms \(\text{[O}_{\text{OMe}}=\text{H}^+\text{C(11)]}\), \(\Delta l = 0.43 \text{ Å}\); (c) between the hydrogen Hʻ(O=P) and the oxygen Oʻ(O=S) atoms \(\text{[O}_{\text{O=S}}=\text{H}^+\text{P(11)]}\), \(\Delta l = 0.15 \text{ Å}\); and (d) between the hydrogen Hʻ(OMe) and the oxygen Oʻ(OMe) \(\text{[O}_{\text{OMe}}-\text{H}^+\text{OMe}]\), \(\Delta l = 0.08 \text{ Å}\).

It should be pointed out that the charges at the relevant atoms are almost the same for both q-cj3 and q-g conformers (Table 5) and the sum of the relevant Oʻ...Hʻ\(^+\) short contacts relative to the \(\Sigma\)vdW radii for both conformers are approximately the same. Therefore, the cooperative \(\text{[O}_{\text{CO}}\text{Si}_{\text{SiO}}\text{electrostatic and charge transfer and the O}_{\text{SiO}}\text{Si}_{\text{CO}}\text{electrostatic interactions seems to be the main factors which stabilizes the q-g conformer into a larger extent with respect to the q-c conformer.}

The inspection of molecular models for the q-g conformer (Structure X, Scheme 4) shows that the closeness between the sulfanyl oxygen and the carbonyl carbon atoms along with the simultaneous approach of the carbonyl oxygen and the sulfanyl sulfur atoms precludes into some extent the solvation of these dipoles with respect to the same dipoles in the q-cj3 conformer (Structure IX, Scheme 4). Therefore, in spite of almost the same polarity of both conformers for diast2, the progressive increase of the \(v_{\text{CO}}\) intensity (concentration) of the q-cj3 conformer relative to that of the q-g conformer for 5, with the progressive increase of the relative permittivity of the solvent (see Table 3) is in perfect agreement with the more difficult solvation of the q-g conformer with respect to the q-cj3 conformer. Moreover, the lowering of the experimental carbonyl frequency of the q-cj3 conformer (1663 cm\(^{-1}\), in CCL\(_4\)) relative to that of the q-g conformer (1671 cm\(^{-1}\), in CCL\(_4\)) for diast1 is \(\Delta v = 8 \text{ cm}^{-1}\) only, while the lowering of the carbonyl frequency of the q-c (q-c1 and q-c2) conformers (1661 cm\(^{-1}\), in CCL\(_4\)) relative to that of the g conformer (1680 cm\(^{-1}\), in CCL\(_4\)) for diast2 is \(\Delta v = 19 \text{ cm}^{-1}\). These trends are in line with the B3LYP calculations (Table 6) for which the carbonyl frequency shift of q-c (q-c1 and q-c2) conformers relative to the g conformer for diast1 is \(\Delta v_{\text{CO}} = 7 \text{ cm}^{-1}\), while the carbonyl frequency shift of the q-c conformer relative to the q-g conformer for diast2 is \(\Delta v_{\text{CO}} = 2 \text{ cm}^{-1}\).

In spite of the larger stability of the q-g conformer with respect to the q-c conformer for diast2, the carbonyl frequency of the q-c conformer is lower than that of the q-g conformer by \(\Delta v = 8 \text{ cm}^{-1}\). This behaviour may be explained taking into account that the stronger \(\text{[O}_{\text{CO}}\text{Si}_{\text{SiO}}\text{electrostatic or charge transfer and the O}_{\text{SiO}}\text{Si}_{\text{CO}}\text{electrostatic interactions seems to play only a secondary role in determining the carbonyl frequency of the q-g conformer.}

\section*{Fig. 7. Synthon of diastereomer \(\text{C}_{\text{SiC}}\)/\(\text{C}_{\text{SiC}}\) (diast1) of 5 that gives rise to the supramolecular arrangement.}
X-ray single crystal analysis, performed for diastereomer 1 (racemic mixture: C₈S₈ and C₈R₈) and for diastereomer 2 (racemic mixture: C₈S₈ and C₈R₈) [10] of 5, indicates that both stereoisomers assume in the solid the anti-clinal (gauche) conformation with respect to the [O=C−C−S(O)Ph] dihedral angle and the anti geometry relative to the [O=C−N(Me)−OMe] moiety (see Table 6 and Fig. 3). In fact, the χ (100° to 104°) and ψ (−166° to −178°) dihedral angles for both diastereomers approach the gauche and quasi-gauche conformations of diast 1 and diast 2 of 3 in gas phase. The gauche formers of diast 1 and diast 2 in the solid of 5 allow several intramolecular C−H...O hydrogen bonds: O(1)…H(5a)...O(1) = 3.262(6) Å, H(8a)...O(5b) = 2.50 Å, C(8)...O(5b) = 3.262(6) Å, H(8a)...O(5b) = 2.47 Å, C(8)...H(9a)...O(11a) = 154°; C(15)...O(5c) = 3.311(7) Å, H(3)...O(11a) = 154°; C(3)...O(11a) = 154°; C(3)...H(3)...O(11a) = 154°; C(8)...O(5b) = 3.262(6) Å, H(8a)...O(5b) = 2.50 Å, C(8)...H(8a)...O(5b) = 136° (symmetry operations: a = −1, x, ...). In this, this synthon forms infinite chains parallel to the b direction through two hydrogen bonds: C(15)...O(5c) = 3.311(7) Å, H(15)...O(5c) = 2.34 Å, C(15)...H(15)...O(5c) = 151°; C(10)...O(1c) = 3.205(5) Å, H(10b)...O(1c) = 2.48 Å, C(10)...H(10b)...O(1c) = 133° (symmetry operation: c = x, y − 1, z). It has to be pointed out that the crystal packing of diast 2 has already been reported [10].

4. Conclusions

1H NMR spectra of N-methoxy-N-methyl-2-[(4-substituted)-phenylsulfinyl]-propanamides 1–5 in deuterochloroform solution, along with the X-ray diffraction analysis of the 4-nitro-derivative 5 have shown the existence of two pairs of diastereomers (racemic mixture) [C₈S₈/C₈S₈ (diast 1) and C₈S₈/C₈S₈ (diast 2)] in the ratio of ca. 7:3, respectively.

The vCO IR analysis of the title compounds supported by HF and B3LYP/6-31G* calculations of 3 and of the parent N-methoxy-N-methylpropanamide 6 (HF), has shown that diast 1 exists in an equilibrium between the two more polar quasi-cis (q-c) and q-c) and one gauche(g) conformers, the quasi-cis conformers being the more stable ones (lower vCO frequency component), due to a O(5c)/C(10) charge transfer interaction, which in turn is stronger than the O(5d)/C(10) electrostatic interaction which takes place in the g conformer (higher vCO frequency component). In opposition to what should be expected, the population of the low polar g conformer increases relatively to that of the quasi-cis conformers, as the solvent polarity increases. This behaviour is in agreement with the larger solvation of carbonyl group of the gauche conformer, while almost the same solvation takes place in the sulfinyl group.

The diast 2 occurs in the gas phase as an equilibrium of quasi-gauche (g-g) (higher vCO frequency component) and quasi-cis (q-c) (lower vCO frequency component) conformers of almost the same polarity, the former conformer being the most stable due to the synergism of the O(5c)/C(10) and O(5d)/C(10) electrostatic and charge transfer interactions. The crossed interactions bring closer the relevant atoms, which in turn makes difficult the solvation of carbonyl and sulfinyl groups of the quasi-gauche conformer with respect to the same groups in the quasi-cis conformer.

Moreover both q-c and g conformers of diast 1 and both q-c and q-g conformers of diast 2 are stabilised almost to the same extent through several intramolecular O[CO, SO]…H[CH, CH₃, o-Ph] hydrogen bonds.

X-ray single crystal analysis performed for diastereomer 1 (racemic mixture: C₈S₈ and C₈R₈) and for diastereomer 2 (racemic mixture: C₈S₈ and C₈R₈) [10] of 5 indicates that both stereoisomers assume in the solid the anti-clinal (gauche) conformation with respect to the [O=C−C−S(O)Ph] dihedral angle and the anti geometry relative to the [O=C−N(Me)−OMe] moiety. In addition the conformation of diast 2 is stabilized by several intramolecular O[CO, SO]…H[CH, CH₃, o-Ph] hydrogen bonds. For the crystal packing, the molecular synthon of diast 5 is made up of three molecules which are joined through two centro-symmetric H...O hydrogen bonds. In turn this synthon forms infinite chains parallel through two H...O hydrogen bonds.

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