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The case of intramolecular hydrogen bonding, hyperconjugation and classical effects on the conformational isomerism of substituted carbonyl and thiocarbonyl compounds

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Abstract

The conformational isomerism of substituted (substituents = OR and SR, R=H and Me) acetaldehydes and thioacetaldehydes is described in terms of intramolecular interactions, namely hydrogen bonding (when R=H), hyperconjugation involving the carbonyl or the thiocarbonyl system, and classical effects (steric and electrostatic interactions). 3D potential energy surfaces were obtained by scanning both X—C—C=Y (α) and R—X—C—C (ϕ) dihedral angles (X/Y=O and S) and used to identify local and global minima. Geometry optimization and NBO calculations, including determination of NLMO steric energies and deletion of hyperconjugative interactions, were then performed in order to find the governing factors for these conformational equilibria. Hyperconjugative contribution for hydrogen bonding showed to be more important for thioaldehydes, while O—H showed to be a better proton donor than S—H; however, hydrogen bonding also appeared to be as of electrostatic nature. Overall, orbital interactions, particularly those involving the π^* system, and classical factors (steric and electrostatic effects) drive the conformational isomerism of the title compounds.

Keywords: Conformational analysis; Hyperconjugation; Hydrogen bonding; Classical effects; (Thio)carbonyl compounds

1. Introduction

Conformational analysis has been subject of investigation to more than a century, since Sachse recognized the existence of two kinds of C—H bonds for the cyclohexane [1]. Knowledge about the conformational preferences of organic compounds may provide benefits to various fields of research, for example the relationship between conformation and reactivity/stereochemistry of several reactions [2], and the influence of ligands conformation on their bioactivity [3]. However, even for the simplest molecules, such as ethane, the governing factors of conformational equilibria are not well established [4,5]. Regarding carbonyl compounds, some studies have invoked intramolecular interactions, namely hyperconjugation involving the $\pi^*_{C=O}$ system, to understand the spectroscopic behavior of model compounds [6–11]. ICS (Intramolecular Interaction Chemical Shifts) and SCS (Substituent induced Chemical Shifts) values did not correlate well with usual substituent electronic and/or steric parameters in mono-substituted acetic acids, and this has been supposed to be due to orbital interaction involving the carboxyl group [6]. NMR coupling constants and infrared intensities have also demonstrated to be dependent on conformation of ketones and esters, and their conformational balance is assumed to be much due to orbital interactions [7–13].

Nevertheless, data about hydrogen bonding involving the carbonyl group as proton acceptor are scarce, though this seems to be a fascinating topic in conformational analysis, as pointed out by Roberts [14] in a spectroscopic study on succinic acid. This is still more critical when S—H and C=S bonds, such as in mercapto and

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very reactive thiocarbonyl compounds, are involved [15]. Conformational studies on mercapto-acetaldehyde has been previously performed using microwave spectroscopy [16], and the intramolecular hydrogen bond between S—H and C=O in this compound was supposed to contribute weakly for the rotational isomerism, but this does not seem to be completely understood and compared to the hydroxyl group. Thus, the goal of this work was to evaluate the hydrogen bonding involving O—H and S—H groups as proton donors, as well as C=O and C=S bonds as proton acceptors. In addition, other hyperconjugative interactions were also evaluated in describing the conformational equilibria. Hydroxy- and mercapto-substituted aldehydes and thioaldehydes, and their corresponding ethers and thioethers (Fig. 1), were used as model compounds for such purpose.

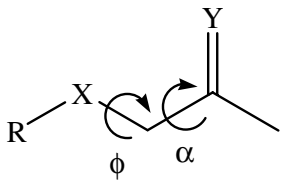

Fig. 1. Carbonyl and thiocarbonyl compounds: X/Y=O or S; R=H and CH_3. α and ϕ refer to the torsional angles.

2. Computational methods

The conformational search for the titled compounds was initially performed by scanning both X—C—C=Y (α) and R—X—C—C (ϕ) dihedral angles (X/Y=O and S; R=H and CH_3), from 0° to 360° in steps of 10°, at the HF/6-31g(d, p) level. Firstly, α was varied at constant ϕ, and the opposite was carried out afterwards. Each local and global minima were then optimized at the B3LYP/aug-cc-pVTZ level. NBO calculations [17], including deletion of all antibonding and Rydberg interactions, as well as calculation of the NLMO steric contribution, were also performed at the same level of theory. All calculations were performed using the Gaussian 03 program [18].

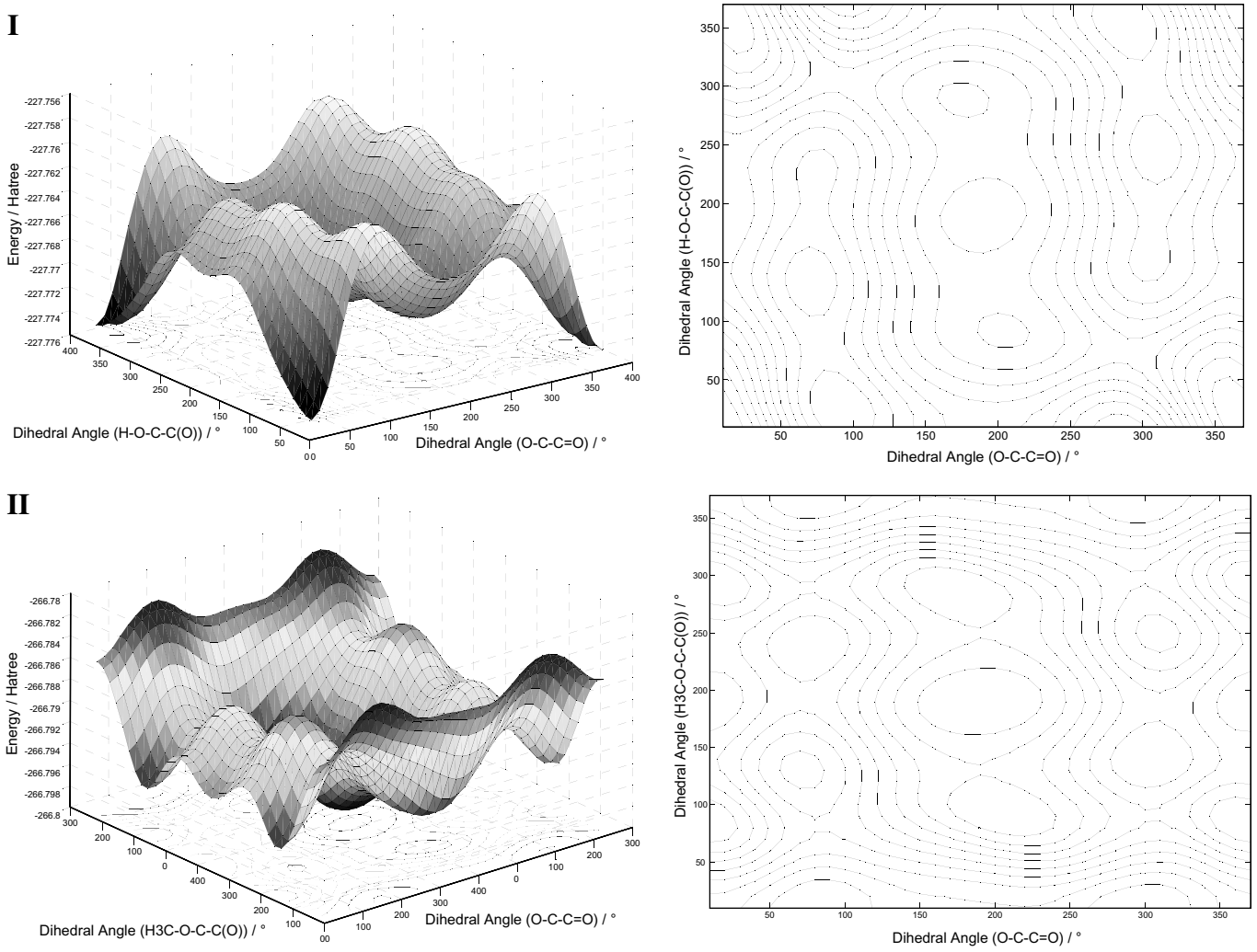

Fig. 2. 3D-PES and their 2D projections on the α *vs.* ϕ plot for hydroxy-acetaldehyde (**I**) and methoxy-acetaldehyde (**II**).

Table 1
Conformers of **I** and **II**, α and ϕ dihedral angles, dipole moments and energies[a] calculated at the B3LYP/aug-cc-pVTZ level

Parameter	**I**			**II**		
	sp-sp	*ac-sc*	*ap-ap*	*sp-sc*	*ac-sc*	*ap-ap*
$\alpha_{O-CH_2-C=O}$/°	0.0	165.6	179.9	3.2	166.0	179.9
$\phi_{R-O-CH_2-C(=O)}$/°	0.1	77.9	179.5	74.2	71.4	179.9
μ (Debye)	2.48	1.95	3.00	2.69	1.95	3.06
E_{full} (a.u.)	−229.142280	−229.136692	−229.136923	−268.451513	−268.447937	−268.453091
$E_{rel\ (full)}$	0.00	3.51	3.36	0.99	3.23	0.00
$E_{rel\ (hyperconjugation)}$	22.85	5.19	0.00	31.17	0.00	11.34
$E_{rel\ (steric)}$	5.03	0.00	0.47	7.09	0.00	6.06

[a] In kcal mol^{-1}.

3. Results and discussion

The studied compounds present two rotating dihedral angles, which may be varied to give the stable rotamers. Both α and ϕ dihedral angles (X—C—C=Y and R—X—C—C, respectively) were scanned in order to find the local and global energy minima, which were re-optimized at a sophisticated level of theory. Detailed discussions on the conformational equilibrium of each compound in the gas state, which provides important insights about intramolecular interactions, are separately and properly evaluated in the following sub-sections, and a general comparison of the results is then given at the end.

3.1. Hydroxy-acetaldehyde (*I*) and its methyl ether (*II*)

The most stable conformers of **I** and **II** were identified by analyzing the 3D potential surfaces (3D-PES) of

Table 2
Some important orbital interactions (kcal mol^{-1})[a] calculated through NBO for compounds **I** and **II**

Interaction	**I**			**II**		
	sp-sp	*ac-sc*	*ap-ap*	*sp-sc*	*ac-sc*	*ap-ap*
$\sigma_{C1H3} \rightarrow \sigma^*_{C4H6}$		0.90			0.91	
$\sigma_{C1H3} \rightarrow \sigma^*_{C4O7}$	2.53	0.86	0.96	3.71	0.75	0.96
$\pi_{C1O2} \rightarrow \sigma^*_{C4H5}$	1.46	1.41	1.02	1.33	1.37	1.08
$\pi_{C1O2} \rightarrow \sigma^*_{C\ 4H6}$	1.46		1.03	1.40		1.07
$\sigma_{C4H5} \rightarrow \sigma^*_{C1O2}$	1.28			1.71		
$\sigma_{C4H6} \rightarrow \sigma^*_{C1O2}$	1.29			1.46		
$\sigma_{C4O7} \rightarrow \sigma^*_{C1O2}$		1.19	1.54		1.08	1.38
$\sigma_{C4H5} \rightarrow \sigma^*_{C1H3}$			0.93			0.92
$\sigma_{C4H6} \rightarrow \sigma^*_{C1H3}$		1.66	0.93		1.67	0.93
$\sigma_{C4O7} \rightarrow \sigma^*_{C1H3}$	1.18			0.83		
$\sigma_{C4H5} \rightarrow \pi^*_{C1O2}$	5.94	6.03	4.56	5.56	5.95	4.51
$\sigma_{C4H6} \rightarrow \pi^*_{C1O2}$	5.93	2.21	4.59	5.46	1.87	4.48
$LP_{O2} \rightarrow \sigma^*_{C4O7}$		0.68	0.80		0.67	0.82
$LP_{O2} \rightarrow \sigma^*_{O7H8}$	1.77					
$LP_{O7} \rightarrow \sigma^*_{C1O2}$		0.58				

[a] Computed interactions above 0.5 kcal mol^{-1}.

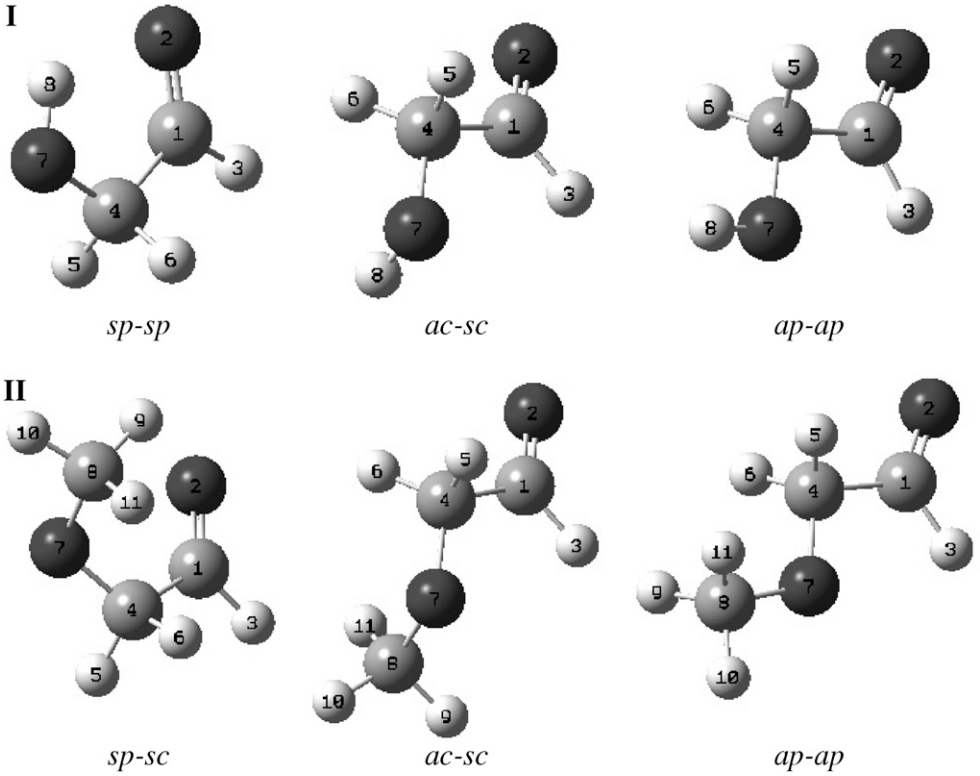

Fig. 3. Stable conformers for hydroxy-acetaldehyde (**I**) and methoxy-acetaldehyde (**II**).

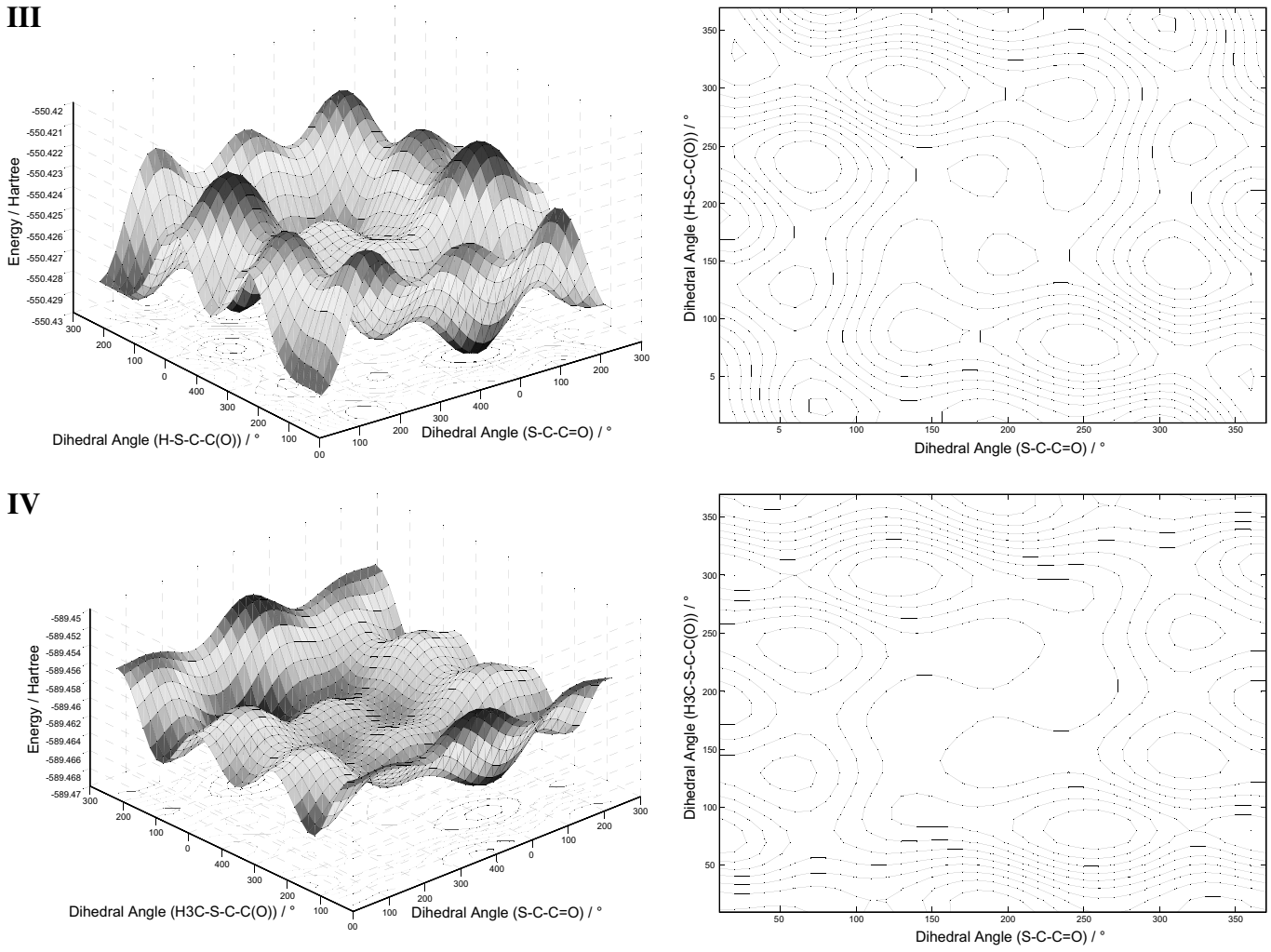

Fig. 4. 3D-PES and their 2D projections on the α *vs.* ϕ plot for mercapto-acetaldehyde (**III**) and methylthio-acetaldehyde (**IV**).

Fig. 2, whose 2D projections also indicate the corresponding stable structures. Conformers *synperiplanar–synperiplanar* (*sp-sp*), *anticlinal–synclinal* (*ac-sc*) and *antiperiplanar–antiperiplanar* (*ap-ap*) were found to be energy minima for **I**, while *sp-sc* replaces *sp-sp* for **II**. Table 1 shows that *sp-sp* is the most stable rotamer for **I** (3.51 and 3.36 kcal mol^{-1} more stable than *ac-sc* and *ap-ap*, respectively), in agreement with previous theoretical findings by Fan et al. [19] This picture changes for **II**, where *ap-ap* is the most stable rotamer (0.99 and 3.23 kcal mol^{-1} more stable than *sp-sc* and *ac-sc*, respectively).

The structures for the minima found in Fig. 2 are shown in Fig. 3. On the basis of steric and electrostatic factors, the *sp-sp* rotamer (compound **I**) is expected to be significantly more unstable than the remaining forms as well as the *sp-sc* rotamer (compound **II**). However, the high stability

Table 3
Conformers of **III** and **IV**, α and ϕ dihedral angles, dipole moments and energies[a] calculated at the B3LYP/aug-cc-pVTZ level

Parameter	**III**			**IV**		
	sp-sp	*ac-sc*	*ac-sc′*	*sp-sc*	*ac-sc*	*ac-sc′*
$\alpha_{S-CH_2-C=O}$/°	0.1	115.7	241.0	5.0	105.0	233.7
$\phi_{R-S-CH_2-C(=O)}$/°	0.0	295.8	282.4	293.7	289.2	271.0
μ (Debye)	2.72	1.79	2.82	2.59	1.58	3.57
E_{full} (a.u.)	−552.115159	−552.116697	−552.114821	−591.441091	−591.445136	−591.442005
$E_{rel\ (full)}$	0.96	0.00	1.18	2.54	0.00	1.96
$E_{rel\ (hyperconjugation)}$	13.69	1.52	0.00	9.53	2.31	0.00
$E_{rel\ (steric)}$	3.22	0.57	0.00	0.00	3.81	0.66

[a] In kcal mol^{-1}.

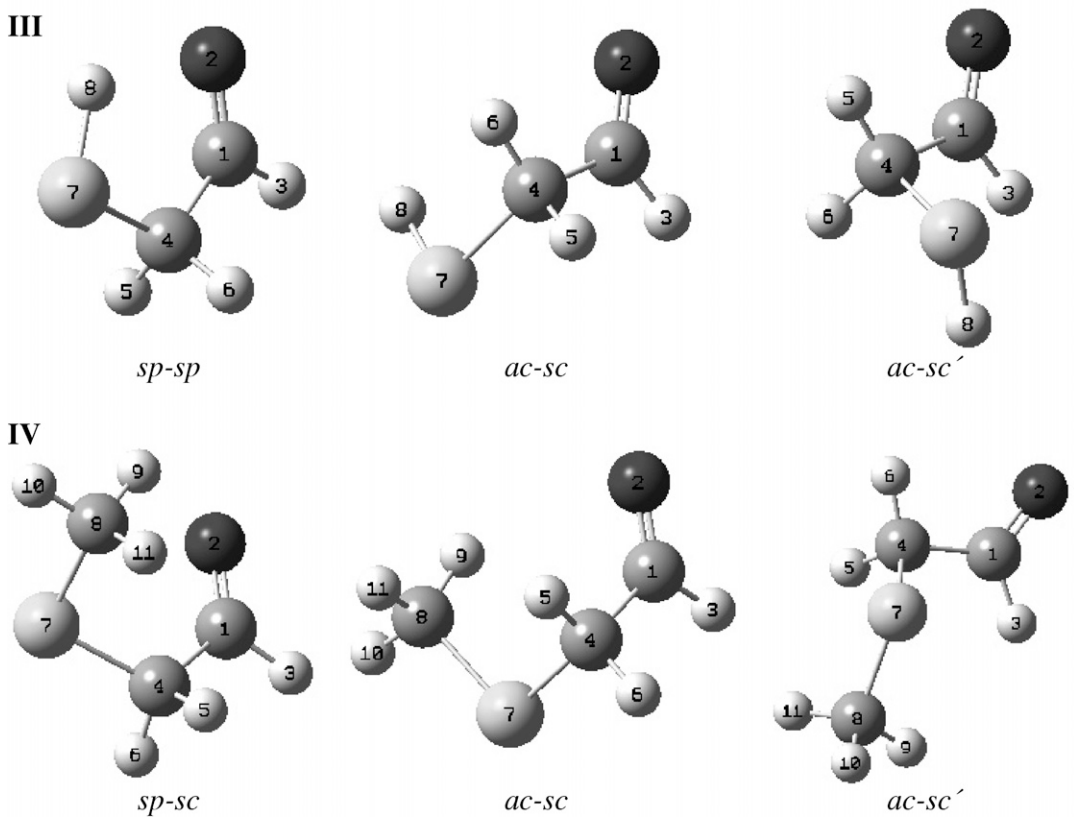

Fig. 5. Stable conformers for mercapto-acetaldehyde (**III**) and methylthio-acetaldehyde (**IV**).

observed for *sp-sp* (compound **I**) suggests that intramolecular hydrogen bonding must play an important role for its conformational isomerism, since *sp-sp* should present a high steric/electrostatic repulsion and, according to this sense, an opposite behavior for energetic should be observed, and also because its corresponding ether **II**, where an intramolecular hydrogen bonding is not possible, does not show *sp-sp* as a stable conformation.

An estimate for the energy of intramolecular hydrogen bonding in **I** (*sp-sp*) may be nearly calculated through Eq. (1), disregarding the difference between the steric effect of methoxy and hydroxy groups.

$$E_{\text{H-bonding (I)}} \approx \Delta E_{\mathbf{I}\ (ap\text{-}ap-sp\text{-}sp)} - \Delta E_{\mathbf{II}\ (ap\text{-}ap-sp\text{-}sc)} \quad (1)$$

where $E_{\text{H-bonding (I)}}$ corresponds to the hydrogen bonding energy operating in **I**, and $\Delta E_{\mathbf{I}\ (ap\text{-}ap\ -\ sp\text{-}sp)}$ and $\Delta E_{\mathbf{II}\ (ap\text{-}ap\ -\ sp\text{-}sc)}$ correspond to conformational energies of **I** and **II**, respectively.

This approximation gives an energy of 4.35 kcal mol^{-1} for the stabilization of **I** *sp-sp* due to intramolecular hydrogen bonding, which is larger than the values found for *trans*-2-halocyclohexanols (from 1.0 to 1.4 kcal mol^{-1} for Br, Cl and F derivatives) [20], where a similar approach was utilized. Delocalization contribution for this intramolecular hydrogen bonding may be obtained from NBO calculations; $LP_O \rightarrow \sigma^*_{O-H}$ interaction stabilizes *sp-sp* conformer by 1.77 kcal mol^{-1} (Table 2). In addition to the non-Lewis contributions, intramolecular hydrogen bonding in **I** *sp-sp* is also of electrostatic nature (C=O$^{\delta-}$...$^{\delta+}$H— O), giving the observed difference between the values of $E_{\text{H-bonding}}$ found from Eq. (1) and hyperconjugation (NBO data).

Clearly, intramolecular hydrogen bonding plays an important, if not the major, role for the conformational equilibrium of **I**, but other effects operate both in **I** and

Table 4
Some important orbital interactions[a] (kcal mol^{-1}) calculated through NBO for compounds **III** and **IV**

Interaction	**III**			**IV**		
	sp-sp	*ac-sc*	*ac-sc′*	*sp-sc*	*ac-sc*	*ac-sc′*
$\sigma_{C1H3} \rightarrow \sigma^*_{C4H5}$			1.95		2.05	
$\sigma_{C1H3} \rightarrow \sigma^*_{C4H6}$		1.96				1.90
$\sigma_{C1H3} \rightarrow \sigma^*_{C4S7}$	4.30			4.49		
$\pi_{C1O2} \rightarrow \sigma^*_{C4H5}$	1.47	1.31		1.52		1.72
$\pi_{C1O2} \rightarrow \sigma^*_{C4H6}$	1.47		1.53	1.45	0.96	
$\pi_{C1O2} \rightarrow \sigma^*_{C4S7}$		2.39	2.26		2.40	1.95
$\sigma_{C4H5} \rightarrow \sigma^*_{C1O2}$	1.82	2.20	0.74	1.68	0.54	1.39
$\sigma_{C4H6} \rightarrow \sigma^*_{C1O2}$	1.83	0.67	1.77	1.97	2.76	0.77
$\sigma_{C4S7} \rightarrow \sigma^*_{C1O2}$		0.73	1.02			1.32
$\sigma_{C4H5} \rightarrow \sigma^*_{C1H3}$			2.75		2.53	
$\sigma_{C4H6} \rightarrow \sigma^*_{C1H3}$		2.61				2.79
$\sigma_{C4S7} \rightarrow \sigma^*_{C1H3}$	2.07			1.93		
$\sigma_{C4H5} \rightarrow \pi^*_{C1O2}$	5.50	3.10		5.38		4.14
$\sigma_{C4H6} \rightarrow \pi^*_{C1O2}$	5.48		3.54	4.97	2.04	
$\sigma_{C4S7} \rightarrow \pi^*_{C1O2}$		5.54	4.85		6.92	4.41
$LP_{O2} \rightarrow \sigma^*_{S7H8}$	1.46					
$LP_{S7} \rightarrow \pi^*_{C1O2}$		2.81	2.36		3.81	2.67

[a] Computed interactions above 0.5 kcal mol^{-1}.

Table 5
Conformers of **V** and **VI**, α and ϕ dihedral angles, dipole moments and energies[a] calculated at the B3LYP/aug-cc-pVTZ level

Parameter	**V**			**VI**			
	sp-sp	*ac-sc*	*ap-ap*	*sp-sc*	*sp-ap*	*ap-sc*	*ap-ap*
$\alpha_{O-CH_2-C=S}$/°	0.1	142.4	179.8	0.4	0.0	153.7	180.0
$\phi_{R-O-CH_2-C(=S)}$/°	0.2	289.3	179.9	277.5	180.1	284.2	179.9
μ (Debye)	2.13	1.01	2.64	2.54	3.14	1.56	2.66
E_{full} (a.u.)	−552.102388	−552.096592	−552.095705	−591.410007	−591.410134	−591.411164	−591.411967
$E_{rel\ (full)}$	0.00	3.64	4.19	1.23	1.15	0.50	0.00
$E_{rel\ (hyperconjugation)}$	35.77	7.28	0.00	19.36	21.71	4.20	0.00
$E_{rel\ (steric)}$	8.93	0.00	0.81	0.86	1.00	0.55	0.00

[a] In kcal mol^{-1}.

II (for instance, see the high hyperconjugative contribution for the *sp-sp* and *sp-sc* stabilization in **I** and **II**, respectively, in Table 1). Such effects may be assumed as from Lewis-type and delocalization nature. The total energy of each conformer may be partitioned into Lewis-type and non-Lewis contributions by deletion of Rydberg and antibonding interactions using the NBO formalism. Thus, the classical effects may be achieved by $E_{(full)} - E_{(hyperconjugation)}$. However, important hyperconjugative effects, particularly *antiperiplanar* interactions (Table 2), strongly contribute for the conformer stabilities of **I** and **II**. The most evident hyperconjugative interactions of Table 2 favoring *sp-sp* (**I**) and *sp-sc* (**II**) in comparison to the remaining forms are those from σ_{CH} towards σ^*_{CO} and π^*_{CO}. Donating C—H bonds in *sp-sp* (**I**) and *sp-sc* (**II**) are reasonably well aligned to π^*_{CO}, resulting in great stabilization. Further-

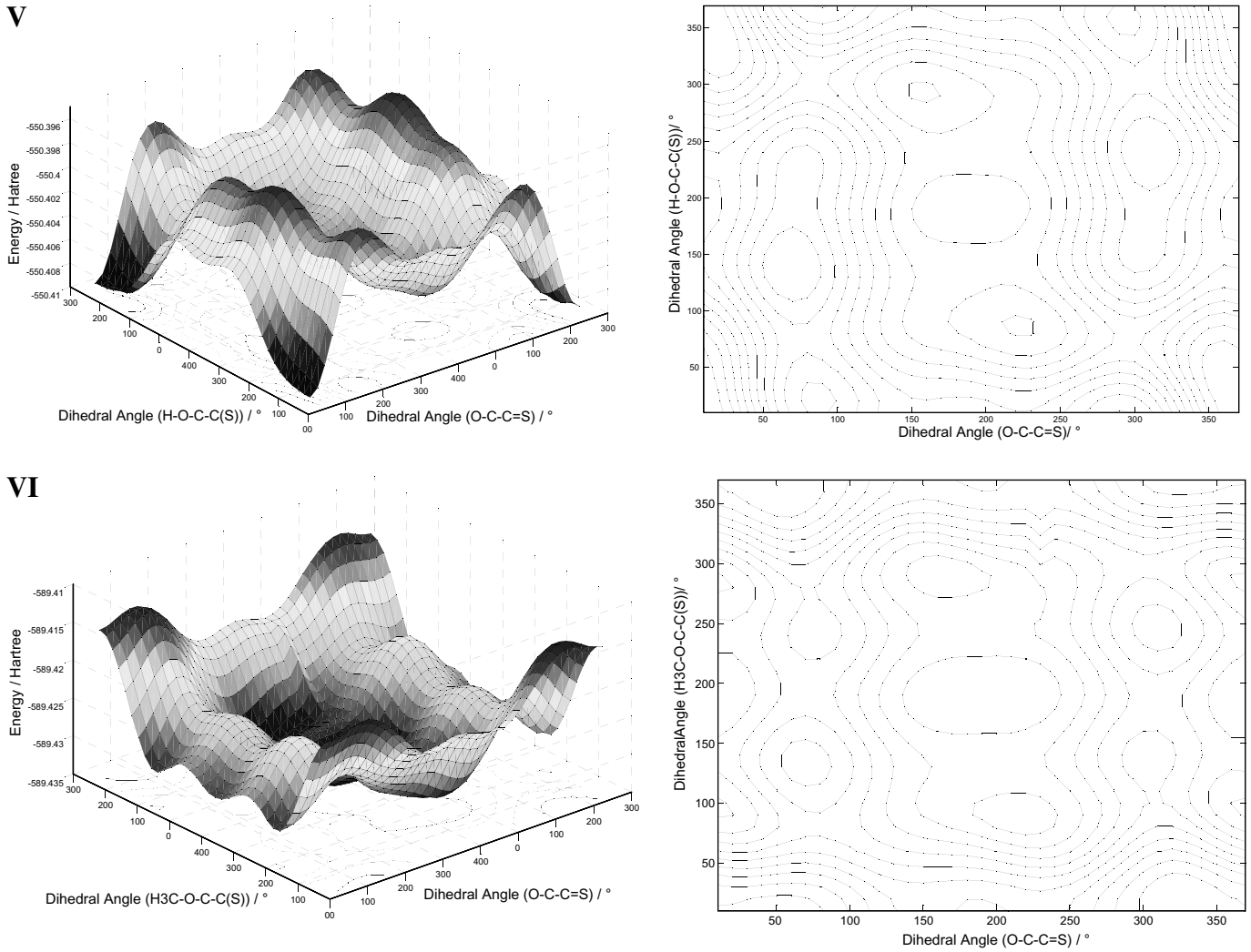

Fig. 6. 3D-PES and their 2D projections on the α *vs.* ϕ plot for hydroxy-thioacetaldehyde (**V**) and methoxy-thioacetaldehyde (**VI**).

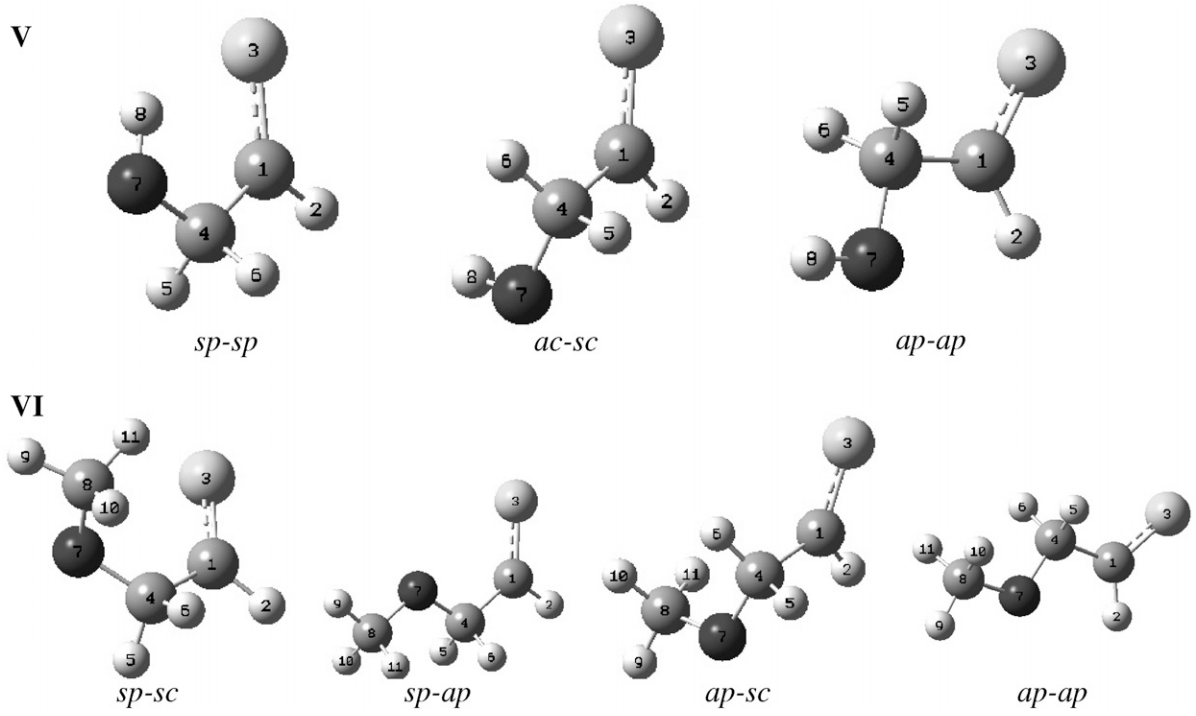

Fig. 7. Stable conformers for hydroxy-thioacetaldehyde (**V**) and methoxy-thioacetaldehyde (**VI**).

more, C—H bonds are not *antiperiplanar* to σ^*_{CO}, but the expected residual overlap component between such orbitals (which are not orthogonal) seems to contribute importantly for the lower energy of *sp-sp* (**I**) and *sp-sc* (**II**) conformers (from 1.3 to 1.7 kcal mol^{-1} of stabilization). Although the *ac-sc* conformer of both **I** and **II** experiences the minimum steric effect ($E_{rel\ (steric)}$) among all the structures, *sp-sp* (**I**), *sp-sc* (**II**) and *ap-ap* (**I** and **II**) are largely stabilized by delocalization interactions.

3.2. Mercapto-acetaldehyde (*III*) and its methylthio ether (*IV*)

The occurrence of an intramolecular hydrogen bonding in compound **I** was already expected due to the electronegative nature of the oxygen atom and to the polar character of the C=O bond. However, the same is not obvious for the corresponding thiol derivative, since few or no reports were dedicated to investigate interactions for such compounds. It has been shown that intramolecular F...H—S appears in fluoromethanethiol [21], but quantification for the similar interaction involving a carbonyl system has not yet been investigated. In addition, sulfur-containing compounds are also of interest for evaluation the donor ability of the S lone pairs and C—S bond towards the π^* system.

A 3D scanning of dihedral angles α and ϕ for **III** and **IV** (Fig. 4) reveals which energy minima correspond to conformers *sp-sp*, *ac-sc* and *ac-sc′* for **III**, and *sp-sc*, *ac-sc* and *ac-sc′* for **IV** (Fig. 5). For **III**, conformer *ac-sc* was found to be the most stable form by roughly 1 kcal mol^{-1} when compared to *sp-sp* and *ac-sc′*, Table 3. This behavior is different from that observed for **I**, which presents the *sp-sp* conformer as the most stable form. However, the energetic found for **III** does not exclude the possibility of an intramolecular hydrogen bonding in the *sp-sp* rotamer.

Table 6
Some important orbital interactions[a] (kcal mol^{-1}) calculated through NBO for compounds **V** and **VI**

Interaction	**V**			**VI**			
	sp-sp	*ac-sc*	*ap-ap*	*sp-sc*	*sp-ap*	*ap-sc*	*ap-ap*
$\sigma_{C1H2} \rightarrow \sigma^*_{C4H5}$			0.58				0.70
$\sigma_{C1H2} \rightarrow \sigma^*_{C4H6}$		2.00	0.59			1.90	0.65
$\sigma_{C1H2} \rightarrow \sigma^*_{C4O7}$	3.66	0.83	1.52	4.62	4.29	1.03	1.51
$\sigma_{C1S3} \rightarrow \sigma^*_{C4H5}$		2.35				2.24	1.49
$\sigma_{C1S3} \rightarrow \sigma^*_{C4O7}$		0.62	1.39			0.88	
$\pi_{C1S3} \rightarrow \sigma^*_{C4H5}$	2.11		1.55	1.95	2.19		1.60
$\pi_{C1S3} \rightarrow \sigma^*_{C4H6}$	2.12		1.53	2.08	2.19		1.66
$\pi_{C1S3} \rightarrow \sigma^*_{C4O7}$		2.59				1.82	
$\sigma_{C4H5} \rightarrow \sigma^*_{C1S3}$	2.29	1.83		2.53	2.51	1.44	
$\sigma_{C4H6} \rightarrow \sigma^*_{C1S3}$	2.28			2.49	2.51		
$\sigma_{C4O7} \rightarrow \sigma^*_{C1S3}$		1.53	2.44			1.62	2.27
$\sigma_{C4H5} \rightarrow \sigma^*_{C1H2}$			1.11				1.11
$\sigma_{C4H6} \rightarrow \sigma^*_{C1H2}$		2.96	1.13			2.65	1.04
$\sigma_{C4O7} \rightarrow \sigma^*_{C1H2}$	1.32			0.97	1.09		
$\sigma_{C4H5} \rightarrow \pi^*_{C1S3}$	6.35	5.45	4.86	5.96	5.70	5.85	4.65
$\sigma_{C4H6} \rightarrow \pi^*_{C1S3}$	6.37	0.63	4.82	5.45	5.70	1.08	4.78
$\sigma_{C4O7} \rightarrow \pi^*_{C1S3}$		1.35				0.81	
$LP_{S3} \rightarrow \sigma^*_{C4O7}$			0.80			0.53	0.81
$LP_{S3} \rightarrow \sigma^*_{O7H8}$	4.37						
$LP_{O7} \rightarrow \sigma^*_{C1S3}$	0.55		0.85				0.73
$LP_{O7} \rightarrow \sigma^*_{C1H2}$				0.50			
$LP_{O7} \rightarrow \pi^*_{C1S3}$		1.48				0.78	

[a] Computed interactions above 0.5 kcal mol^{-1}.

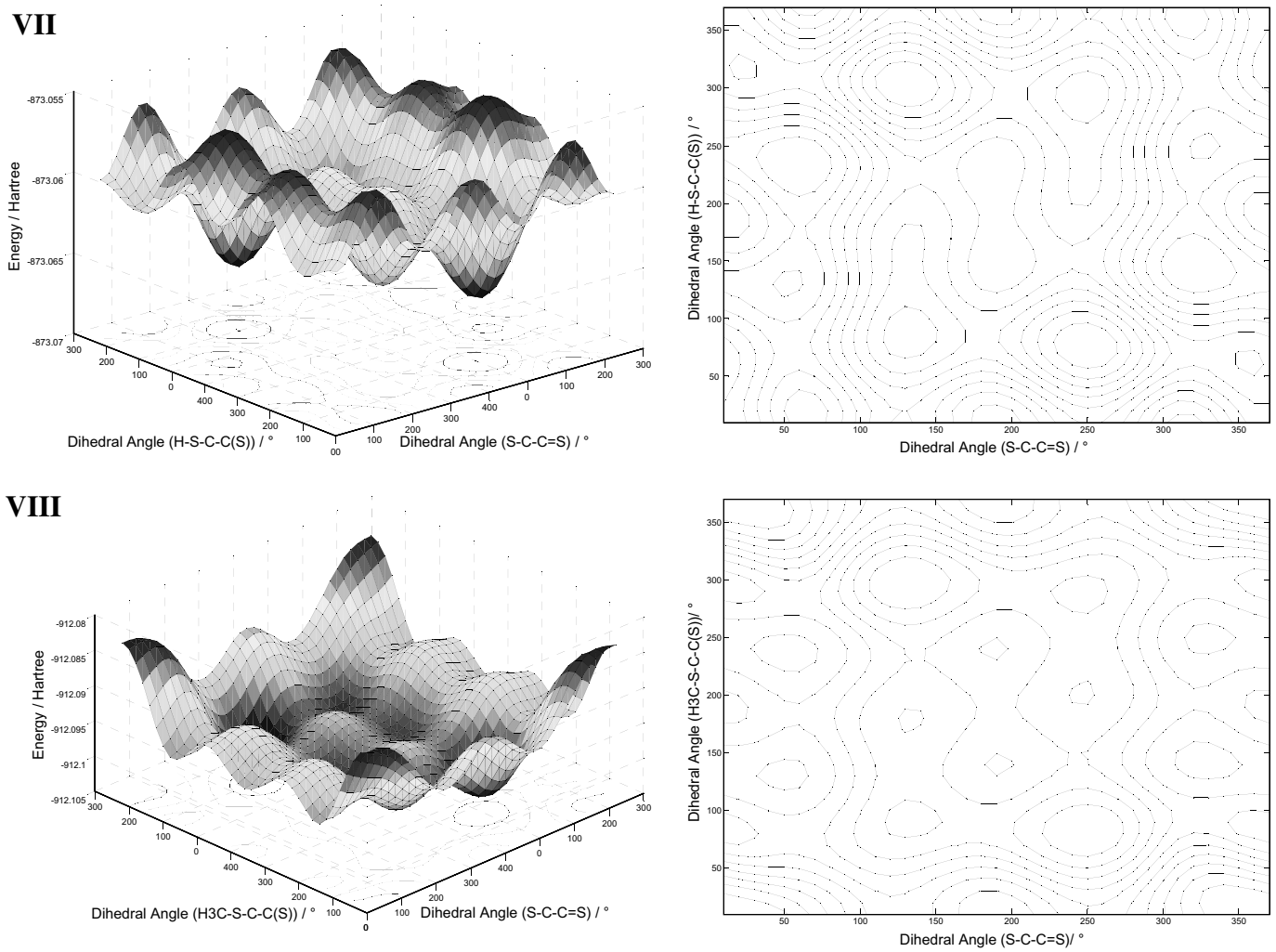

Fig. 8. 3D-PES and their 2D projections on the α *vs.* ϕ plot for mercapto-thioacetaldehyde (**VII**) and methylthio-thioacetaldehyde (**VIII**).

This may be due to two factors: steric hindrance involving the methylthio group of **IV** and an intramolecular hydrogen bonding in **III**. The steric effect of a methyl group has shown to be irrelevant for the conformational isomerism of methylcyclohexane and for a series of methylheterocyclohexanes [22]. The latter factor may be evaluated using an NBO analysis. This shows that the contribution from orbital interaction to the intramolecular hydrogen bonding in *sp-sp* in **III** ($LP_O \rightarrow \sigma^*_{S-H}$ is 1.46 kcal mol^{-1}, slightly smaller than the corresponding interaction in *sp-sp* of **I** (1.77 kcal mol^{-1}), and thus it must be considered.

Overall contribution from hydrogen bonding to the conformational energy of **III** may be approximately achieved by using Eq. (2), giving an energy for the hydrogen bonding in *sp-sp* (compound **III**) of about 1.58 kcal mol^{-1}:

$$E_{\text{H-bonding (III)}} \approx \Delta E_{\mathbf{III}\ (ac\text{-}sc-sp\text{-}sp)} - \Delta E_{\mathbf{IV}\ (ac\text{-}sc-sp\text{-}sc)} \quad (2)$$

where $E_{\text{H-bonding (III)}}$ corresponds to the hydrogen bonding energy operating in **III**, and $\Delta E_{\mathbf{III}\ (ac\text{-}sc\ -\ sp\text{-}sp)}$ and $\Delta E_{\mathbf{IV}\ (ac\text{-}sc\ -\ sp\text{-}sc)}$ correspond to conformational energies of **III** and **IV**, respectively.

Careful analysis of orbital interactions of Table 4 indicates that differences in the conformational preferences between **I** and **III**, as well as between **II** and **IV**, are essentially due to important $\sigma_{C-S} \rightarrow \pi^*_{C=O}$ and $LP_S \rightarrow \pi^*_{C=O}$ interactions in **III** and **IV** (conformers *ac-sc* and *ac-sc′*), which is correspondently unimportant (<0.5 kcal mol^{-1}) for **I** and **II**. Although conformer *ac-sc* experiences higher steric hindrance and roughly equal hyperconjugative energy when compared to *ac-sc′*, this conformation was found to be the most stable form for both **III** and **IV** compounds due to electrostatic factors, as presumed from the Lewis $E_{(\text{full})} - E_{(\text{hyperconjugation})}$ and $E_{(\text{steric})}$ energies, given in Table 3.

3.3. Hydroxy-thioacetaldehyde (*V*) and its methyl ether (*VI*)

It is well known that the carbonyl π^* system is poorly occupied, essentially due to the electronegativity difference between its components, C and O, and this strongly influences intramolecular interactions involving α-substituted

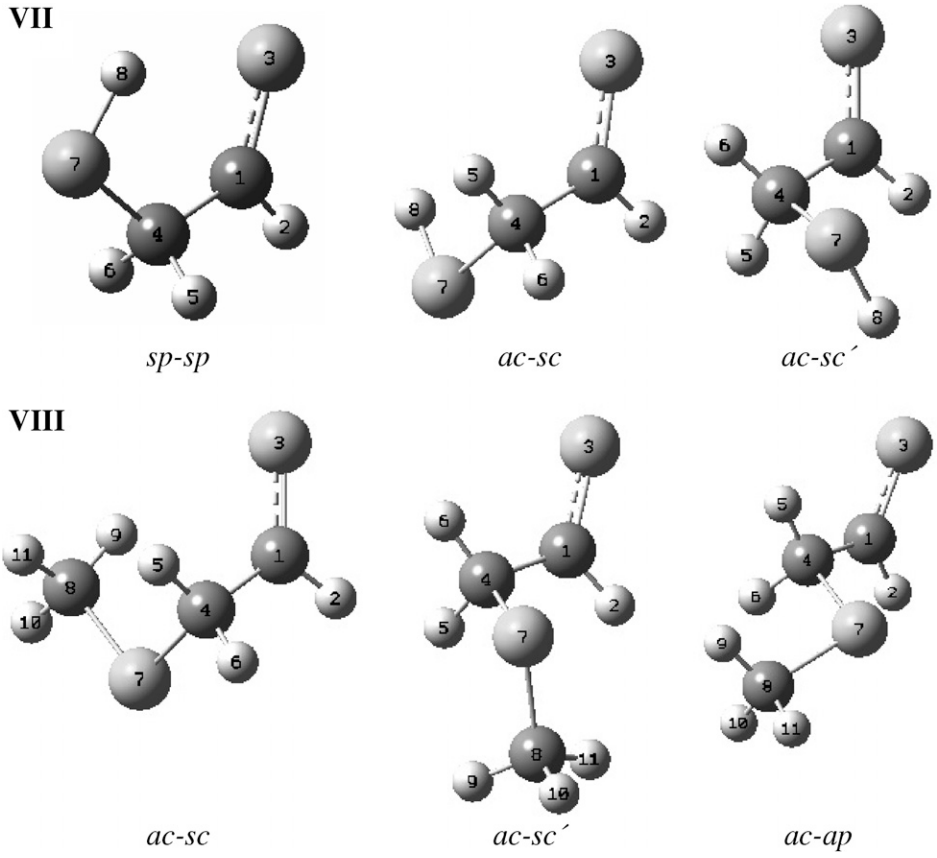

Fig. 9. Stable conformers for mercapto-thioacetaldehyde (**VII**) and methylthio-thioacetaldehyde (**VIII**).

carbonyl compounds and their conformational isomerism [11]. Nevertheless, investigation of the C=S donor/acceptor ability in thiocarbonyl compounds has not received the same attention yet. According to the small electronegativity difference between C and S, the electrophilic character of the C=S bond is supposed to be poor. However, the weak π_{CS} overlap, which is due to incompatibility of orbital sizes, should result in efficient delocalization processes from C—O and LP_O to the C=S antibonding orbital in **V** and **VI**, as well as for the hydrogen bonding C=S...H—O.

Compounds **V** and **VI** are useful models to investigate such suppositions. Theoretical calculations (Table 5 and Fig. 6) showed that there are three stable rotamers for **V** (*sp-sp*, *ac-sc* and *ap-ap*) and four stable rotamers for **VI** (*sp-sc*, *sp-ap*, *ap-sc* and *ap-ap*), which are illustrated in Fig. 7. The high stability of *sp-sp* rotamer for **V** evidences that this conformer experiences hydrogen bonding and its low energy compared to the remaining forms suggests that this interaction is highly stabilizing. This may be demonstrated by the NBO results, which show that contribution from orbital interaction to the intramolecular hydrogen bonding ($LP_S \rightarrow \sigma^*_{O-H}$) is 4.37 kcal mol^{-1}. Such interaction may also be of electrostatic nature (C=S$^{\delta-}$...$^{\delta+}$H—O) and this is an important factor driving the rotational isomerism of **V**. The total hydrogen bonding energy in *sp-sp* **V** may be approximately obtained through Eq. (3), analogous to Eqs. (1) and (2), giving an expressive value of 5.42 kcal mol^{-1}.

$$E_{\text{H-bonding (V)}} \approx \Delta E_{\text{V (ap-ap−sp-sp)}} - \Delta E_{\text{VI (ap-sp−sp-sc)}} \quad (3)$$

where $E_{\text{H-bonding (V)}}$ corresponds to the hydrogen bonding energy operating in **V**, and $\Delta E_{\text{V}(ap\text{-}ap\ -\ sp\text{-}sp)}$ and $\Delta E_{\text{VI}\ (ap\text{-}sp\ -\ sp\text{-}sc)}$ correspond to conformational energies of **V** and **VI**, respectively.

When the hydroxyl hydrogen of **V** is replaced by a methyl group, giving compound **VI**, the conformational preferences change and *sp-sp* is not a stable rotamer anymore, since an intramolecular hydrogen bonding is not possible. Instead, rotamer *ap-ap* appears to be 0.5 to 1.2 kcal mol^{-1} more stable than the remaining forms. This conformer showed to be the less stabilized form by hyperconjugative interactions, listed in Table 6, but slightly favored by steric effects (see $E_{(\text{steric})}$; Table 5) and mostly by electrostatic factors, as obtained from the Lewis $E_{(\text{full})} - E_{(\text{hyperconjugation})}$ and $E_{(\text{steric})}$ energies.

3.4. Mercapto-thioacetaldehyde (*VII*) and its methylthio ether (*VIII*)

In the previous sub-section, the C=S* orbital was tested as a C—O and LP_O acceptor, and the negatively charged thiocarbonyl sulfur as an O—H acceptor. Here, the bonding and antibonding π_{CS} system is evaluated taking S—R (R=H and CH_3) as an α-substituent, in order to complement this study, and the consequences of the resulting

Table 7
Conformers of **VII** and **VIII**, α and ϕ dihedral angles, dipole moments and energies[a] calculated at the B3LYP/aug-cc-pVTZ level

Parameter	**VII**			**VIII**		
	sp-sp	*ac-sc*	*ac-sc′*	*ac-sc*	*ac-sc′*	*ac-ap*
$\alpha_{S-CH_2-C=S}$/°	0.0	115.9	243.7	109.0	238.0	243.1
$\phi_{R-S-CH_2-C(=S)}$/°	0.1	297.0	282.9	287.0	273.6	207.0
μ (Debye)	2.28	1.37	2.40	1.42	3.23	3.39
E_{full} (a.u.)	−875.07296	−875.076438	−875.074266	−914.404634	−914.401601	−914.400718
$E_{rel\ (full)}$	2.18	0.00	1.36	0.00	1.90	2.51
$E_{rel\ (hyperconjugation)}$	21.94	3.02	0.00	7.78	3.41	0.00
$E_{rel\ (steric)}$	4.79	1.10	0.00	3.90	0.63	0.00

[a] In kcal mol^{-1}.

Table 8
Some important orbital interactions[a] (kcal mol^{-1}) calculated through NBO for compounds **VII** and **VIII**

Interaction	**VII**			**VIII**		
	sp-sp	*ac-sc*	*ac-sc′*	*ac-sc*	*ac-sc′*	*ac-ap*
$\sigma_{C1H2} \rightarrow \sigma^*_{C4H5}$		2.71		2.85		2.73
$\sigma_{C1H2} \rightarrow \sigma^*_{C4H6}$			2.70		2.71	
$\sigma_{C1H2} \rightarrow \sigma^*_{C4S7}$	5.18					
$\sigma_{C1S3} \rightarrow \sigma^*_{C4H5}$			0.94		0.88	
$\sigma_{C1S3} \rightarrow \sigma^*_{C4H6}$		1.02		1.13		0.90
$\sigma_{C1S3} \rightarrow \sigma^*_{C4S7}$		0.54	0.52		0.62	0.52
$\pi_{C1S3} \rightarrow \sigma^*_{C4H5}$	2.09		1.98		2.27	
$\pi_{C1S3} \rightarrow \sigma^*_{C4H6}$	2.09	1.80		1.45		1.97
$\pi_{C1S3} \rightarrow \sigma^*_{C4S7}$		4.07	4.10	3.99	3.57	3.74
$\sigma_{C4H5} \rightarrow \sigma^*_{C1S3}$	2.91		3.20		2.76	
$\sigma_{C4H6} \rightarrow \sigma^*_{C1S3}$	2.90	3.40		3.79		3.38
$\sigma_{C4S7} \rightarrow \sigma^*_{C1S3}$		1.25	1.36	1.04	1.67	1.43
$\sigma_{C4H5} \rightarrow \sigma^*_{C1H2}$		3.51		3.28	3.74	3.47
$\sigma_{C4H6} \rightarrow \sigma^*_{C1H2}$			3.66			
$\sigma_{C4S7} \rightarrow \sigma^*_{C1H2}$	2.40					
$\sigma_{C4H5} \rightarrow \pi^*_{C1S3}$	5.83		2.80		3.33	
$\sigma_{C4H6} \rightarrow \pi^*_{C1S3}$	5.85	2.72		2.05		3.32
$\sigma_{C4S7} \rightarrow \pi^*_{C1S3}$		6.58	6.10	7.75	5.88	6.50
$LP_{(1)S3} \rightarrow \sigma^*_{S7H8}$	0.56					
$LP_{(2)S3} \rightarrow \sigma^*_{S7H8}$	4.79					
$LP_{S7} \rightarrow \pi^*_{C1S3}$	0.78	2.89	2.37	4.13	3.20	1.33
$\pi^*_{C1S3} \rightarrow \sigma^*_{C4S7}$				0.89		

[a] Computed interactions above 0.5 kcal mol^{-1}.

interactions on the conformational isomerism of **VII** and **VIII** are then rationalized.

The most stable forms found for **VII** and **VIII** were *sp-sp*, *ac-sc* and *ac-sc′*, and *ac-sc*, *ac-sc′* and *ac-ap*, respectively, as illustrated by the minima in the 3D-PES of Fig. 8 and explicitly shown in Fig. 9. Compound **VII** exhibits its *ac-sc* structure as the most stable conformer (2.2 and 1.4 kcal mol^{-1} more stable than *sp-sp* and *ac-sc′*, respectively; Table 7). Existence of *sp-sp* as a stable conformer for **VII**, not for **VIII**, strongly indicates that it experiences hydrogen bonding, as demonstrated by the orbital interaction contribution for this phenomenon (Table 8), in which the $LP_S \rightarrow \sigma^*_{S-H}$ equals to 4.8 kcal mol^{-1}. However, despite the high stabilization of this conformation due to hyperconjugative interactions (Table 8), steric and, mainly, electrostatic repulsion disfavor *sp-sp* by a large amount, as concluded from $E_{(full)} - E_{(hyperconjugation)}$. Electron delocalization involving the S—H bond seems to be very relevant for the conformational isomerism of **VII**, since after exchanging the hydrogen by a methyl group to give the methyl thioether **VIII**, *sp-sp* does not appear as a stable rotamer. Nevertheless, hyperconjugation has also been found as a driving force governing the rotational isomerism of **VIII**. Although the higher steric hindrance for the *ac-sc* conformation in **VIII**, it is greatly favored by delocalization effects, and this could be particularly assigned to strong donations from σ_{C-S} and LP_S orbitals to the π^*_{C-S} system. Special attention should be given for an unusual antibonding–antibonding interaction ($\pi^*_{C1S3} \rightarrow \sigma^*_{C4S7}$), which occurs due to the high occupancy of the π^*_{C-S} orbital.

4. Conclusions

The effects governing the conformational equilibration of the titled compounds were evaluated through theoretical calculations, by using NBO analysis to compute steric, total Lewis-type and hyperconjugative energies, as well as which of the latter interactions were acting on the stable rotamers. General comparison between carbonyl and thiocarbonyl compounds reveals that C=S bond exhibits better proton acceptor capability due to hyperconjugation ($LP_S \rightarrow \sigma^*_{X-H}$) than the C=O bond. Since this is a space-dependent interaction, the observed behavior may be assumed as due to the large size of the sulfur non-bonding orbital. On the other hand, the negative charge on the carbonyl oxygen is supposed to be larger than in thiocarbonyl compounds due to the oxygen electronegativity, though the overlap of the $\pi_{C=S}$ bond is poor. Polarization of the C=O bond is responsible for the Coulombic attraction $C{=}O^{\delta-}\ldots{}^{\delta+}H{-}X$, the electrostatic nature of the hydrogen bonding. Also due to the electronegativity difference between O and S, energy results showed that hydroxyl groups are much better proton donors than thiols, as demonstrated by the *sp-sp* conformer stability in hydroxyl compounds, but not in mercapto compounds. However, C—S bond and sulfur lone pairs (in S—R) showed to be especially important, when compared with the corresponding oxygenated groups, as donors towards the $\pi^*_{C=Y}$ orbital.

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