



CONFORMATIONAL STUDIES OF CARBONYL AND THIOCARBONYL COMPOUNDS

This work emphasizes the excellent quality of results obtained with extensions of PF1/PF2 force fields for oxygen and sulphur containing molecules. The combined use of Molecular Mechanics with other techniques, namely with vibrational spectroscopy, is also stressed.

1. INTRODUCTION

Close correlations between chemical properties of substances and their molecular preferred conformations as well as the biological importance of oxygen and sulphur containing compounds justify the opportunity of the studies herein reported. This paper reviews the results of combined Molecular Mechanics (MM), Quantum Mechanics (QM) and Vibrational Spectroscopy (VS) on some oxygen and sulphur containing compounds [1-8]. A special attention is given to the studies performed on carbonyl and thiocarbonyl compounds and to the MM method.

2. MOLECULAR MECHANICS CALCULATIONS

Molecular Mechanics is designed to provide accurate *a priori* molecular structures and energies. The method is a natural outgrowth from old ideas of bonds between atoms in molecules and Van der Waals forces between non-bonded atoms. It is a non-quantum mechanics method that works under the separation between electronic and vibrational degrees of freedom. As its fundamental formulations are common to Vibrational Spectroscopy, the method is particularly suitable to spectroscopists.

The MM method

- allows the description of structural details which are difficult to determine by any of the available experimental techniques;
- provides good estimates for the conformational dependence of molecular structures;
- uses a force field parameterized to reproduce a large amount of experimental information (vibrational frequencies, thermodynamic properties, molecular structures and conformational energies);
- provides results as accurate as quantum mechanical methods, but is much less computer time consuming. While a 3-21G calculation on methyl dithioacetate, using the

MONSTERGAUSS program [9] and one molecular geometry, is estimated to spend 24 hours of CPU time on a Data General MV8000 computer and costs \$15,000, a molecular mechanics calculation with the CONSISTENT FORCE FIELD (CFF) program [10] takes only 5 minutes of CPU time and costs \$60!

Among the disadvantages of the MM method, one should mention

— the difficulty to deal with conjugated molecular systems, as it does not consider explicitly the electrons, and

— the incapacity to begin the study of really novel families of compounds, as it needs to know the properties of some members of a given family to parameterize the force field.

MM calculations use an empirically derived set of equations for the Born-Oppenheimer surface, whose mathematical form are familiar from classical mechanics. These potential functions depend on the nuclear coordinates and on a set of adjustable parameters that is called the Force Field. Let us consider

$$E = f(\mathbf{X}, \sigma)$$

where E represents the molecular energy, \mathbf{X} is a vector of nuclear coordinates and σ represents the Force Field, which is optimized to provide the best fit of calculated and experimental properties of some simple molecules of a given class. It is assumed that corresponding parameters may be transferred from one molecule to another.

Reliable MM force fields should be judged by their combined *simplicity*, ie, a reduced number of parameters, and *efficiency*, ie, good estimates for the calculated molecular properties. Simple MM force fields include bond stretching, angle bending, torsion and van der Waals interactions,

$$E = \sum V_{\text{stretch}} + \sum V_{\text{bend}} + \sum V_{\text{torsion}} + \sum V_{\text{vdW}}$$

where the sums extent over all bonds, bond angles, torsion angles and non-bonded interactions (1-4 interactions and higher). The V terms used in our force fields have the following forms:

harmonic terms

$$V_{\text{stretch}} = (1/2) K_{bi}(b_i - b_{0i})^2$$

$$V_{\text{bend}} = (1/2) K_{\theta j}(\theta_j - \theta_{0j})^2$$

cosine type terms

$$V_{\text{torsion}} = (1/2) K_{\tau k}(1 + \cos(n_k \tau_k))$$

Buckingham exp-6 terms

$$V_{\text{vdW}} = A_i \exp(-B_i r_i) - C_i/r_i^6$$

After the functional forms of the potential energy terms are chosen, the model compounds needed for the force field parameterization are selected. These compounds should be simple, have well-known experimental properties, and contain all the specific interactions occurring in the members of the family of compounds to be studied. If the fit of calculated and experimental properties for the model compounds is good, then it is assumed that the calculated properties for other molecules of the same class of compounds should agree with experiment. Usually, a few "model" compounds are kept out of the parameterization process, to provide additional tests for the force field. Once this is determined, the potential energy function depends only on the nuclear coordinates. Then, the geometry of a given molecule is varied until the energy reaches a minimum in the potential energy surface and a series of molecular properties can be calculated for this conformation, namely, vibrational frequencies, thermodynamic properties, rotational constants, moments of inertia. In the CFF program, the vibrational calculations are performed in the cartesian coordinates space and the thermodynamical calculations use the formulary of statistical mechanics.

3. CONFORMATIONAL RESULTS

Alkanes, Alcohols and Ethers

The calculated values were obtained with the force field hereafter referred to as PF1 [1]. This force field has been parameterized using 9 alkanes and 10 alcohol and ether molecules.

Structures, barriers of internal rotation and conformer energy differences of the model compounds have been calculated in good agreement with the experimental values [1]. In particular, we should mention the excellent agreement between calculated and experimental C-C-H angles for isobutane (111.0° and 108.2°, calculated; and 111.0° and 108.1°, experimental [11], in C-H and CH₃ groups, respectively), C-C-C angle for propane (112.5°, calculated; 112.4°, experimental [12]), and dihedral angles in general [1].

Relative conformational energies are also in good general agreement with experiment and improve on existing calculated literature values [1]. The exception is the *gauche-gauche* barrier in the n-butane molecule, which is somewhat smaller than the experimental value.

We should also note the *anti* preference around the C-O bonds found for alcohols and ethers, as their sulphur containing homologues show a *gauche* preference around the C-S bonds.

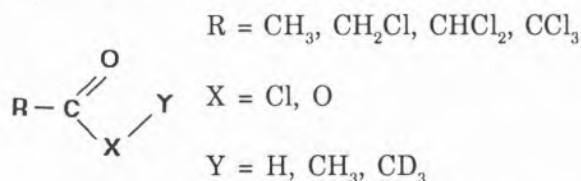
During parameterization, we emphasised chiefly a general agreement between calculated and observed vibrational frequencies. Generally, vibrational fitting in the molecular mechanics approach becomes poorer with increasing molecular symmetry, as symmetry is accompanied by reduction of force field parameters. The general quality of the results is only reasonable [1]. In alkanes, C-H stretching frequencies are quite acceptable (max. error 115 cm⁻¹, mean error 39 cm⁻¹; for references on experimental values see [10] or references therein).

Carbonyl compounds

The quality of the PF1 results for carbonyl compounds [1] is quite similar to the results obtained for alkanes, alcohols and ethers. We have used 11 molecules for the parameterization, 3 of them are α -chloro substituted compounds. The results for these latter compounds are particularly interesting.

For the α -chloro substituted carbonyl compounds, a combined MM/VS study has been performed. MM results provide structures, conformational energies, vibrational frequencies and thermodynamic properties. As these results refer to the isolated molecule, they should be correlated with the properties of the gas. On the other hand, VS results provide band assignments, differences in conformational energies in the liquid and conformational preferences in the solid. Comparison of MM and VS results elucidates on the principal interactions operating in the condensed phases.

The α -chloro substituted carbonyl compounds studied in this work are the following:



The internal rotations around R-C, C-X and X-Y, for Y = methyl, were considered. In particular, rotation around R-C yields the minima, maxima and conformational energy differences shown in Figure 1.

The following general trends can be concluded:

- 1) when R = CH₃, CCl₃, there is one stable conformation corresponding to the R-C bond eclipsing the carbonyl bond;
- 2) the staggered conformations correspond to maxima, in the potential energy surface;
- 3) the staggered conformations also correspond to maxima when R = CH₂Cl, CHCl₂. However, in these two cases two different

eclipsed conformations occur. Both are minima and the one with a Cl atom eclipsing the C=O bond is always the global minimum;

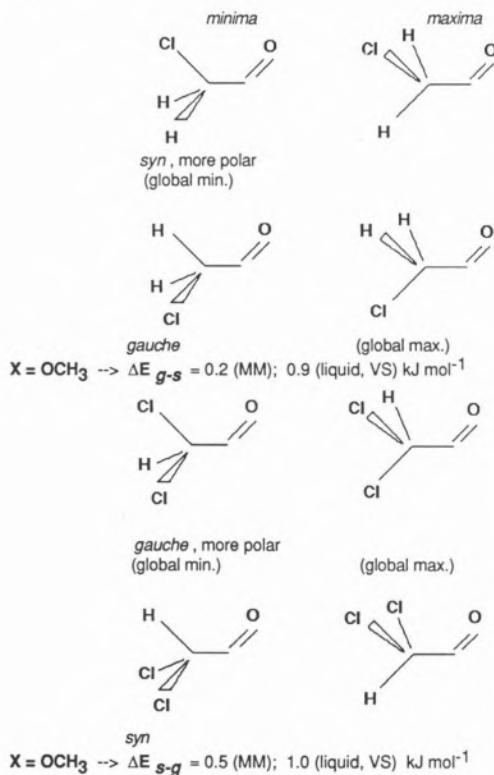


Figure 1

Relevant conformations resulting from rotation around the C_α -C bond in α -chloro substituted carbonyl compounds

4) the most polar forms are stabilized in the liquid;

5) VS shows that, in the solid phase at low temperatures, only the most polar form occurs. This observation suggests the importance of dipolar molecular interactions operating in the condensed phases.

As a general conclusion, we can say that conformations with an H or Cl atoms eclipsed with the C=O bond are stabilized relatively to the staggered conformations, which were found to be maxima. This conclusion can be also extended to propionaldehyde and some derivatives of propionic acid, which also show energy minima in the eclipsed conformations and maxima in the staggered ones [1, 13, 14].

Steric interactions in the *anti* form could justify, at least in part, this conformational preference as, for example, the *anti* form of $\text{CH}_2\text{F}-(\text{C}=\text{O})\text{F}$ is a minimum [15].

Figure 2 presents the vibrational spectra of $\text{CClH}_2\text{COOCH}_3$, in the pure liquid and in the solid. It is worthwhile to consider the $\nu(\text{C}=\text{O})$ frequency (cm^{-1}) in these molecules:

	$\text{CClH}_2\text{COOCH}_3$		$\text{CCl}_2\text{HOOCH}_3$	
	<i>syn</i>	<i>gauche</i>	<i>gauche</i>	<i>syn</i>
gas	1796	1794	1800	1795
liquid	1758	1749	1763	1755
solid	1739		(<)	

The following trends can be easily recognized: i) the carbonyl stretching frequencies of the acyl chloride molecules are larger than those of the corresponding ester compounds;

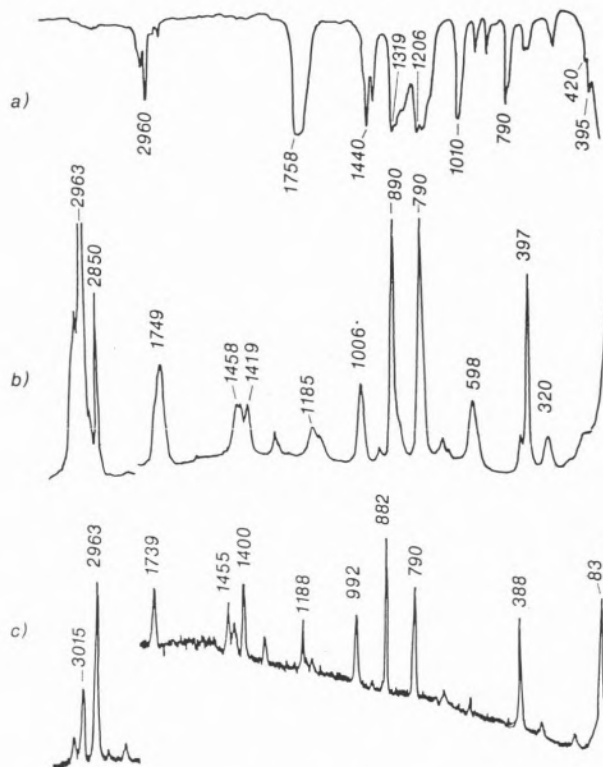


Figure 2

Vibrational spectra of $\text{CClH}_2\text{COOCH}_3$; a) infrared, pure liquid; b) Raman, pure liquid; c) Raman, pure solid

ii) the carbonyl stretching frequencies of the *gauche* forms of the α -disubstituted molecules are larger than those of the *syn* forms. Note that the *gauche* form is defined herein with respect to the dichloromethyl hydrogen atom, and so correlates with the *syn* form of the monosubstituted analogue defined with respect to the chloromethyl chlorine atom.

These spectral features are easily interpreted in terms of the degree of polarization of the C=O bond: a more polarized bond has a smaller double bond character and, therefore, a smaller C=O stretching frequency.

The chlorine atom is a net electron attractor whereas the methoxy group is a net electron donor. Thus, the polarization of the C=O group is greater in the ester molecules than in the acylchlorides, resulting in low carbonyl stretching frequencies for the methoxy derivatives.

When one of the chlorine atoms of the α -substituent group is eclipsed with the carbonyl oxygen atom, the C-Cl and C=O dipoles are aligned in the same direction. Then, electrostatic repulsion between these dipoles increases the C=O double bond character and, consequently, the C=O stretching frequency.

Comparison of carbonyl stretching frequencies shows also that the α -monochloro acylchlorides [1] have larger values than the corresponding conformers of the dichloro analogues, whereas the reverse situation is observed in the case of the esters. In order to explain these facts, one should take intramolecular group interactions into account. A second hydrogen-by-chlorine substitution makes the α -carbon more electronegative, reducing the carbonyl polarization, and increasing its stretching frequency. While this effect dominates in the ester molecules, it no longer prevails in acylchlorides because the additional repulsive through-space interaction between the carbonyl chlorine atom and the additional *gauche* chlorine atom of the dichloro molecules makes the carbonyl chlorine atom less electronegative. Therefore, the carbonyl bond becomes more polarized,

thus justifying the observed order of stretching frequencies. This polarization effect is not so important in the case of the ester molecules, due to the smaller charge on the methoxy oxygen atom.

Figures 3 and 4 correspond to the internal rotations around C-O and O-C respectively.

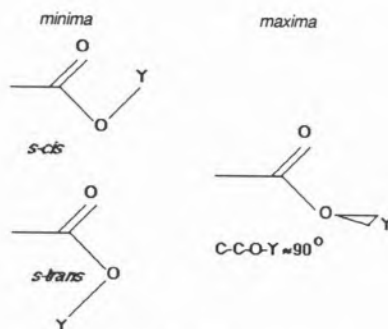


Figure 3

Relevant conformations resulting from internal rotation around the C-O bond in carboxylic acids and esters

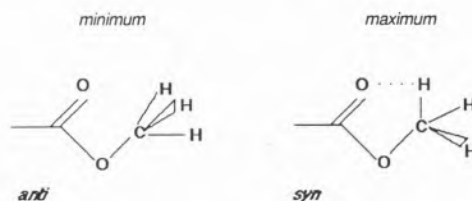


Figure 4

Relevant conformations resulting from internal rotation around the O-C bond in esters

The following general trends can be withdrawn from MM results:

- for all R groups, the internal rotation around the central bond in the acids and esters originates two stable conformations. In all the cases, the *s-cis* or the (*s-cis*, *anti*) forms are the most stable ones; the maxima always occurs for C-C-O-Y near 90°, when mesomeric delocalization cannot occur;
- finally, the methyl ester group always adopts an *anti* conformation. In fact, in the *syn* conformation, there is a strong steric

interaction between the carbonyl oxygen atom and the methoxy hydrogen atom (in the plane).

Thiols and Thioethers

In order to consider, in our MM studies, thiol and thioether molecules, we have extended the PF1 force field to deal with the sulphur atom [7]. The final set of force field parameters (PF2) have been obtained by fitting structures, conformational relative energies and vibrational frequencies of 4 thiol and 3 thioether molecules.

The calculated values and the experimental data for the model compounds are in good general agreement. We have also calculated new data for other thiol and thioether molecules.

The most interesting result we found for these classes of compounds relates with the preferred conformation around the C-S bonds.

It was believed at one time that the *anti* arrangement around the sulphur atom originated the most stable form. However, for ethyl-methyl-sulphide, our MM force field yields the most stable form for the conformation with a C-C-S-C *gauche* arrangement. Figure 5 shows a schematic representation of several stable conformations of methyl-propyl-sulphide and diethyl-sulphide and their energies relative to the most stable forms, as calculated by our MM force field. As a general and interesting conclusion, one should mention that the sulphur atom "prefers" a *gauche* arrangement in its immediate neighbourhood.

This conformational preference of sulphur atoms contrasts with that of oxygen. In fact, while for oxygen ethers the *anti* C-C-O-C arrangement is the most preferred (for instance, the most stable form in $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$ is the (*anti*, *anti*) con-

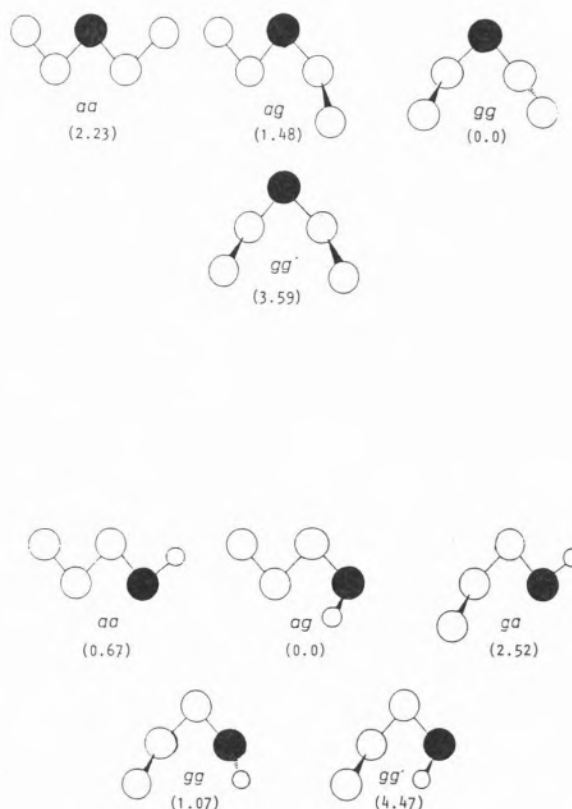


Figure 5

Schematic representation of diethyl sulphide and methyl propyl sulphide conformers and their relative energies (kJ mol^{-1})

formation), for sulphur thioethers the *gauche* C-C-S-C form is the most stable one. The distinct conformational behaviour of oxygen and sulphur atoms seems to suggest that the longer C-S bond lengths, leading to longer non-bonded H...H distances and to reduced steric hindrance in *gauche* conformations, might be the origin of the conformational preference of sulphur atoms.

Thiocarbonyl compounds

The absence of the necessary experimental data to parameterize the force field lead us to perform a series of extensive QM calculations

on these classes of compounds to obtain the necessary information.

A good choice of the basis sets for the QM calculations would, on one hand, provide reliable results and, on the other, be as simple as possible to reduce the computational time. Our previous calculations on $\text{FH}_2\text{C}-\text{C}(=\text{O})\text{F}$ and $\text{HC}(=\text{X})\text{XCH}_3$ [5,15], $\text{X}=\text{O}$ or S , showed us that a STO-3G basis set is not appropriate as the results are too poor; a 4-31G basis set is much time consuming for sulphur compounds. On the other hand, a 3-21G basis set provides results much similar to those obtained with a 4-31G basis set but is a much less time consuming calculation. Thus, we have chosen to perform the QM calculations with 3-21G basis sets. The best results were achieved with a 3-21G+d (S) basis set. The use of *d* orbitals (*polarization orbitals*) on sulphur atoms was found to be very important to obtain good values for C-S bond lengths. However, we decided to use the 3-21G basis and correct the C-S bond lengths with an empirical value obtained from the comparison between the 3-21G results and available experimental data for some sulphur containing molecules.

The 3-21G basis set gives very good structural results for thio and dithiocarbonyl compounds. As it is expected, the calculated C-H bond lengths are shorter than the microwave (MW) or electron diffraction (ED) values. In order to correct the $\text{C}=\text{S}$, $\text{C}(\text{sp}^2)\text{-S}$ and $\text{C}(\text{sp}^3)\text{-S}$ bond lengths one must subtract 3, 5 and 6 pm to the *ab initio* values. The angles and the remaining structural values are very close to experimental results.

Some interesting conclusions concerning the conformational dependence of the angles around the $\text{C}=\text{S}$ bond can be taken from our *ab initio* calculations (see Figure 6). In particular, the $\text{C}-\text{C}=\text{S}$ angle is approximately constant despite the conformational changes. By

contrast, the $\text{C}-\text{C}-\text{S}$ is very sensitive to the conformational state and appears to be always smaller than the $\text{C}-\text{C}=\text{S}$ angle. This structural feature should be correlated with stronger interactions between the α -groups and the S(thiol) atom.

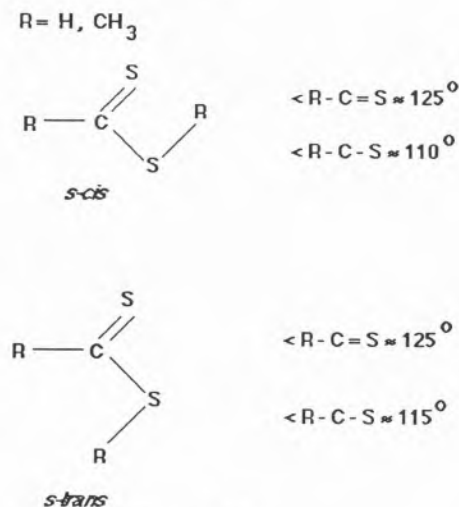


Figure 6

Relevant conformations resulting from internal rotation around the C-S bond in dithiocarboxylic acids and esters

It is also interesting to compare the results for conformational relative energies of thiopropionaldehyde with those of the propionaldehyde molecule [8]. Despite both molecules have energy minima in the same regions ($\text{X}=\text{C}-\text{C}-\text{C}$ dihedral angles equal to 0 and $\approx 120^\circ$, $\text{X}=\text{O},\text{S}$), the global minimum is the *syn* form ($\text{S}=\text{C}-\text{C}-\text{C} = 0^\circ$) in the case of the oxygen containing compound, while in thiopropionaldehyde it is the *gauche* ($\text{S}=\text{C}-\text{C}-\text{C} = 125.5^\circ$) conformation. This *gauche* conformational preference is particularly remarkable as this kind of conformation have been also found to be the most stable one for thiol and thioether molecules [7].

The MM force field which is being developed for $\text{C}=\text{S}$ containing molecules yields structural values in very good agreement with the 3-21G results. Table 1 summarizes the conformational energies obtained for several

Table 1

Relative conformational energies (kJ mol^{-1}) as given by ab initio 3-21G calculations and by Molecular Mechanics

Barriers of rotation		3-21G	PF2	Conformational energy differences	3-21G	PF2
$\text{CH}_3 - \text{C}(=\text{S})\text{H}$		6.02	5.98			
$\text{CH}_3 - \text{C}(=\text{S})\text{CH}_3$		4.56	4.60			
$\text{HC}(=\text{S}) - \text{SH}$		39.33	40.84	(<i>s-trans</i>)-(<i>s-cis</i>)	10.71	10.71
$\text{CH}_3 - \text{C}(=\text{S}) - \text{SH}$	$90^\circ - (\textit{s-cis})$	38.99	37.66	(<i>s-trans</i>)-(<i>s-cis</i>)	12.68	12.55
	$\text{CH}_3 -$	3.72	3.81			
$\text{CH}_3\text{CH}_2\text{C}(=\text{S})\text{H}$	$60^\circ - g$	4.06	6.82	<i>syn - gauche</i>	0.75	0.75
	$180^\circ - g$	3.64	6.11			
$(\text{CH}_3)_2\text{CHC}(=\text{S})\text{H}$	$60^\circ - \textit{syn}$	2.38		<i>gauche - syn</i>	1.00	
	$180^\circ - \textit{syn}$	2.13				

Table 2

Calculated and experimental frequencies (cm^{-1}) for thiocarbonyl compounds a)

	$\text{H}_2\text{C}=\text{S}$	$\text{CH}_3\text{C}(=\text{S})\text{CH}_3$	$\text{HC}(=\text{S})\text{SH}$	$\text{CH}_3\text{C}(=\text{S})\text{SH}$	$\text{CH}_3\text{C}(=\text{S})\text{SCH}_3$
$\nu\text{C}=\text{S}$	1056	1257	1012	1266	1273
	1059	1269	1163 or 1048	1225	1194
$\nu\text{C}-\text{C}$		1194 642		1141	1141
		1195 704		1110	1100
$\nu\text{C}(\text{sp}^2)-\text{S}$			715	565	558
			711	585	580
$\nu\text{S}-\text{C}(\text{sp}^3)$					746
					730
$\delta\text{C}=\text{S}(\text{ip})$	1004	393			
	991	388 b)			
$\delta\text{C}=\text{S}(\text{oop})$	992	438		451	440
	990	436		450	456
δCCC		379			
		380			
$\delta\text{S}=\text{C}-\text{S}$			312	308	269
			<500	310	200
$\delta\text{C}-\text{C}=\text{S}$				362	353
				390	339
$\delta\text{C}-\text{S}-\text{C}$					385
					387
$\tau\text{C}-\text{S}$				309	81
				343	157 b)
$\tau\text{C}-\text{C}$				106	104
				230	208

a) Upper values are experimental; lower values, calculated.

b) From normal coordinate analysis calculations.

thiocarbonyl compounds and compares these values with the corresponding QM (3-21G) results. As it is shown in Table 2, the calculated vibrational frequencies are also in good general agreement with the experimental values.

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RESUMO

Estudo conformacional de compostos carbonílicos e tiocarbonílicos.

Este trabalho salienta a excelente qualidade dos resultados obtidos a partir das extensões dos campos de forças PF1/PF2 a várias famílias de moléculas contendo átomos de oxigénio ou de enxofre e evidencia a utilização da Mecânica Molecular em simultâneo com outras técnicas, nomeadamente a Espectroscopia Vibracional.