

## “STUDY OF THERMODYNAMIC AND NMR PROPERTIES OF SOME CYCLOHEXANE DERIVATIVES”

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### ABSTRACT

The preferential conformations of a series of six-membered saturated heterocycles containing oxygen and sulfur atoms, 4-alkyl-6-methyl-1,3-dithiane, with alkyl=methyl, ethyl, propyl, isobutyl, tertbutyl have been studied by means of ab-initio theoretical methods. The chair conformation is the most stable structure found for all compounds studied here, likewise in its counterparts: cyclohexane, dithiane, and dioxane. The structures show anomalous effects of the chemical shifts, in C2 and C5, due to a  $\sigma$  C-S  $\rightarrow$   $\sigma^*$  C-Hec hyperconjugative interaction. They are also affected by normal Perlin effect in C2, where C2-Hec coupling constants are larger than C2-Hax.

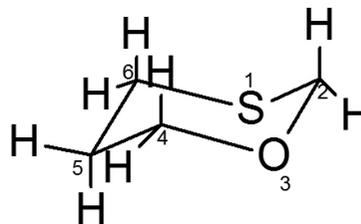
**Keywords:** 4-alkyl-6-methyl-1,3-dithiane; conformational analysis, NMR

### INTRODUCTION

The chemical properties of a compound depend on its geometry, i.e. on its atomic position in space. For many molecules this position does not remain constant but may change easily depending on various factors such as: steric, dipole-dipole, and van der Waals interactions, amongst others<sup>1,2</sup>. Long time ago it was suggested that molecules such as cyclohexane might change its geometry, but just in mid-last century this idea was experimentally proved<sup>3</sup>. These studies led to call such as structures *Conformations* which means any geometry that a molecule might take by simple rotation of single bonds. Another term deriving from above is *conformer* which describes conformations with a life time long enough to build up real chemical species. Moreover, this conformation corresponds to a minimum energy in the potential energy surface of the molecule<sup>4</sup>. According to Boltzmann distribution, conformers are in equilibrium with each other. The proportion in which each one is found in a system consisting of a large number of molecules of the same type, depends on its relative energy regarding the other conformers and on the system temperature. Every conformer has unique and slightly different properties. In a large group of molecules, where several conformers exists, each one of them will contribute to the system properties proportional to the number of molecules in such conformation. Accordingly, the most stable conformer will contribute to the system properties the most. When a conformational analysis is conducted, physical properties: density, dipole moment, solubility and energetic contents as well as chemical properties (relative reactivity) of conformers can be predicted, thus conformational analysis completes the structural analysis of a molecule, i.e. the description of connectivity, configuration and conformation of the atoms making the ring system. Understanding the factors that govern conformational preferences and interactions in six-membered heterocycles has been the subject of considerable scientific interest<sup>5,6</sup>. The chair conformation of cyclohexane has been compared to other heterocycles such as thioxanes<sup>7</sup>. *Cyclohexane* is a cyclic hydrocarbon with no angle or torsional strain. The lack of strain is easily explained since carbon-carbon bond angles are 109°. Nevertheless, if cyclohexane were flat, it would have a considerable torsional strain due to the eclipse of its 12 carbon-hydrogen bonds. Cyclohexane adopts a three-dimensional structure known as the *chair conformation*, in which no H-H eclipse exists, therefore, torsional strain does not exist since all C-H bonds are warped. During the past few years a number of conformational studies of cyclic molecules containing sulfur and oxygen, have been carried out, being heterocycles the most important compounds in chemistry for many years<sup>8</sup>. Understanding their conformations and structures along with their governing interactions is of considerable interest to different areas of chemistry<sup>9</sup>, since these structures are present in many molecules such as alkaloids, carbohydrates, insecticides and plant growth regulator. It is also that participates in natural drug production<sup>10</sup>. Numerous methods and techniques have been developed in order to observe the effect of many substituents and their equatorial or axial preference<sup>11</sup>. Many studies have provided conformational energy, differences calculated using proper potential functions. They contribute significantly to the qualitative understanding of forces and interactions determining not only conformations but also reactivity of substituted cyclohexane<sup>12</sup> for a range of substituent groups<sup>13-14</sup>.

Experimental and theoretical data of 1,3-dioxane derivatives are not very

conclusive with the factors involved in preferential conformations of this type of molecules. Therefore, the present work aims to study conformational equilibrium of heterocycles containing atoms such as sulfur and oxygen. Consequently, the notorious distortion in the zone corresponding to S1-O3-C4-C6 of 1,3-thioxane, unusual from a structural point of view, makes it suitable to study the effects of alkyl double substitution on carbons 4 and 6 of the ring (Fig.1)



**Figure 1:** 1,3-thioxane chair conformation.

In 4,6-dialkyl-1,3-thioxane, 1,3-dioxane and 1,3-dithiane synthesis, cis and trans isomers are produced<sup>14,15,16</sup>. In addition, in 1,3-thioxane, each isomeric form is made of position isomers due to the non-equivalence of the heteroatoms. Accordingly, Cis- 4,6-dialkyl-1,3-thioxane isomers (eq-eq or ax-ax) were studied by means of ab-initio theoretical methods. Geometry optimization has been carried out for all species with their corresponding substituent (methyl, ethyl, propyl, iso-butyl, tert-butyl). Bond distances, angles and corresponding energies were determined. The structures found, in all cases, correspond to minima in the hypersurface of the potential energy, since no imaginary frequencies were found after vibrational frequencies calculations. The Natural Bond Orbitals (NBO) analyses were performed to derive population analysis<sup>17</sup> in an attempt to explain the stereo-electronic effects in these of molecules. Since NMR is one of the most efficient tool used in experimental methods<sup>18-19</sup>, to determine the molecular and electronic structure, theoretically-simulated RMN spectra were calculated for all species aiming to obtain their chemical shifts and coupling constants, and see whether the calculated structures suffer any abnormal effect in their chemical shifts and/or either normal or reverse Perlin effect which might be affecting their chemical shifts and bond lengths. Accordingly, the analysis of NBO and NMR calculations will be focused on 2, 4, 5 and 6 either equatorial or axial carbon-hydrogen bonds.

### MATERIAL AND METHODS

Optimizations of the studied structures, were performed at HF<sup>20</sup>, B3LYP<sup>21</sup> and MP2<sup>22</sup> level by using 6-31G\*\* base and Gaussian 03<sup>23-24</sup> program. Once geometry optimizations occurred, (HF/6-31G\*\*) frequency calculations were done in order to ensure that the resulting structures correspond to a minimum energy conformation. Thermodynamic properties of the structures were obtained from frequency calculations.

Energies were derived from MP2 geometry calculations with a 6-311++G\*\* flexible base, that includes polarization and diffusion functions Method) calculations done at HF level and with a 6-311+G\*\* base.

Both NMR data of protons in gaseous phase and solution and calculations to obtain coupling constants were obtained with B3LYP geometry and by using 6-311+G\*\* base.

## RESULTS AND DISCUSSION

Torsion angles of atoms in the middle part of the chair in 1,3-dioxane, 1,3-dithiane and cyclohexane ( $C_6$ ,  $C_1$ ,  $C_3$  and  $C_4$ ) are studied. It is observed that it has a value of 0.0 degrees (table 1), while the torsion angle in the lower and upper part of the chair ( $C_2$ ,  $C_1$ ,  $C_6$  and  $C_3$ ) is 56°, 58° y 55° for these compounds, respectively.

**Table 1:** Geometry Optimization at HF/6-31G\*\* level for cyclohexane, dioxane, dithiane and thioxane.

	Cyclohexane	Dioxane	Dithiane	Thioxane
Bond length (Å)				
X1a-C2	1.532	1.385	1.810	1.817
C2-X3a	1.532	1.385	1.810	1.386
C4-C5	1.532	1.524	1.529	1.525
C5-C6	1.532	1.524	1.529	1.528
Bond angles (°)				
X1a-C2-X3a	111.5	112.4	115.2	113.1
C2-X3a-C4	111.5	112.8	99.4	114.5
C2-X1-C6	111.5	112.8	99.4	96.5
X3a-C4-C5	111.5	110.0	114.3	112.5
X1a-C6-C5	111.5	110.0	114.3	111.3
Torsional angles (°)				
C5-C4-X3a-C2	54.8	56.0	57.6	65.1
C5-C6-X1a-C2	54.7	56.0	57.6	50.1
C4-C6-X1a-X3a	0.0	0.0	0.0	0.9

a) X1 and X3= C, O o S for cyclohexane, dioxane, dithiane and thioxane. X3= O for thioxane.

Therefore the chair structure of 1,3-dithiane is slightly warped due to the larger sulfur atomic ratio when compared to oxygen and carbon<sup>25</sup>. On the other hand, the (S1-O3-C4-C6) central torsional angle in 1,3 thioxane is 2°, whereas cyclohexane has a torsion angle of 0°. Consequently, it is observed that the chair conformation is much more twisted, and the dihedral angles in the upper and lower part of the structure are different. In fact, when the heterocycle contains oxygen or sulfur, the dihedrals are 50° and 65°, respectively. Therefore, the regular chair structure found in dioxane, dithiane and cyclohexane show notorious deviations. In addition, differences in size, electronegativity and polarization associated with oxygen and sulfur are reflected in the structure, conformation and reactivity of thioxane. Moreover, estereoelectric<sup>26</sup> effects cause significant changes on chemical shifts and coupling constants in the <sup>1</sup>H and <sup>13</sup>C NMR spectra of these structures. Wolfe et al.<sup>27</sup>, proposed the term "Perling Effect" to indicate that C-H bonds affected by anomeric interactions are longer and weaker and their coupling constants smaller. However, Juaristi et al.<sup>28,29</sup>, reported the existence of "Inverse Perlin Effect" in 1,3 dithiane showing that the longest bond has the highest coupling constant. The same author reported abnormalities in chemical shifts of <sup>1</sup>H-NMR of 1,3-diheterocyclohexane<sup>30</sup> arguing that stereoelectronic interactions cause anomalous chemical shifts of  $C_2$  in 1,3-dithiane and in  $C_5$  in 1,3-dioxane. Specifically C-S  $\sigma \rightarrow \sigma^* C-H_{eq}$  hyperconjugative interaction which was proposed as a result of an increase of  $C_2-H_{eq}$  bond electronic density for high-field shifts of  $H(2_{ax})$  and a low-field shift for  $H(2_{ax})$ . Since stereoelectronic effects can arise in "2 orbitals-2 electrons" interactions between an electronic couple of a bonding or non-bonding orbital and an antibonding orbital, those compounds with strong anomeric effect are expected to be suitable example for searching significant departures of proportionality between the s-character of the bond and its corresponding coupling constant<sup>31</sup>. The influence of this type of interactions causes changes in energy, geometry, atomic charges, bond order, among other properties. An effective method to identify and explain stereoelectronic interactions is the analysis known as NBO "natural bond orbital analysis", developed by Weinhold et al.<sup>32</sup>. Kleinpeter et al.<sup>33</sup> carried out a similar study using trans-1,4-di-substituted cyclohexane by analyzing the -O-COCX<sub>3</sub> bond for CX<sub>3</sub>= Me, Et, iso-Pr, ter-Bu, CF<sub>3</sub>, CH<sub>2</sub>Cl, thus changing its polarization. It

was reported that the s C-C/ $\sigma$  C-H  $\rightarrow \sigma^*$  C-O hyperconjugative effect would destabilize the di-equatorial conformer favoring axial double substitution. Additionally, to the stereoelectronic effect the conformer destabilization takes place by increasing the electron density of substituents. Frequency calculations at HF geometry were performed in order to obtain thermodynamic properties. If DG values (table 2), are observed isomeric reactions 11 $\leftrightarrow$ 21; 12 $\leftrightarrow$ 22; 13 $\leftrightarrow$ 23; 14 $\leftrightarrow$ 24 y 15 $\leftrightarrow$ 25 where substituents corresponding to equatorial group R2, isomer I, are those energetically favored. This is attributed to a clear reduction of 1,3-diaxial steric factors and to a nuclear repulsion reduction because Isomer I substituent groups are equatorially located.

**Table 2:** Thermodynamic Data for cis A series. (kcal/mol).

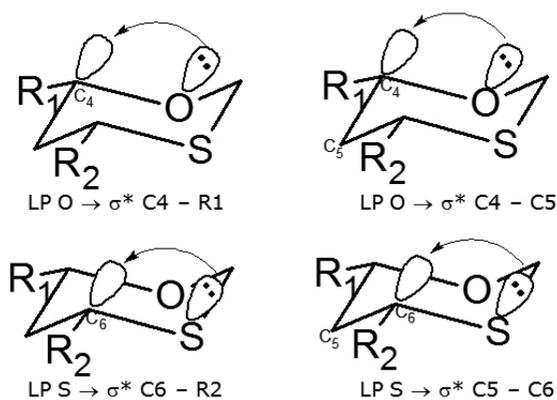
Interconversion Reaction <sup>a,b</sup>	$\Delta H$	$\Delta G$	%II
11A $\rightarrow$ 21A	19,13	19,25	0
12A $\rightarrow$ 22A	19,02	19,20	0
13A $\rightarrow$ 23A	19,39	19,25	0
14A $\rightarrow$ 24A	21,51	22,53	0
15A $\rightarrow$ 25A	22,50	23,52	0

a) DH and DG in Kcal/mol.

b) Calculated energies at MP2/6-311++G\*\* level.

The nuclear repulsion difference between isomers I and II (Structures) with size increases so the difference achieve a value of ca. 80 Kcal/mol, when the substituents is ter-butyl.

These structures are also affected by hyperconjugative interactions that contribute to their stabilization. The interactions that contribute the most are: LP O  $\rightarrow \sigma^*$  C4 - R1, followed by LP O  $\rightarrow \sigma^*$  C4 - C5, Interactions LP S  $\rightarrow \sigma^*$  C6 - R2 y LP S  $\rightarrow \sigma^*$  C5 - C6 also contributes to isomer I stabilization at a lesser extend (figure 2).



**Figure 2:** Relevant Hyperconjugative Interactions in isomer Cis of isomer II are conformationally limited due to an important 1,3-diaxial steric hindrance as both substituents are axially located making 1,3-diaxial repulsion of HaxC2-RaxC6, HaxC2-RaxC4 increase and become energetically unstable. The <sup>1</sup>H-NMR data for these species, chemical shifts (d) and coupling constants (J) are given in table 3. In figure 3 the chemical shifts of axial and equatorial protons of the structures under study are plotted. From table 3, it can be inferred that Hax and Hec chemical shifts are different depending on the extension of the shielding which can be higher than H shift of TMS the more vulnerable is the H in their midst.

Thus, it is observed that both axial and equatorial protons of carbon 2 are the most unshielded (Figure 3). Protons at carbon 5 are the more protected axial protons and thereby the most shielded. Chemical shifts for axial protons of carbon 4 and 6 decreased being proton of carbon 6 more shielded which indicates that sulfur atom would be protecting it. The higher electron density around a proton the higher is shielding and the smaller is the chemical shift.

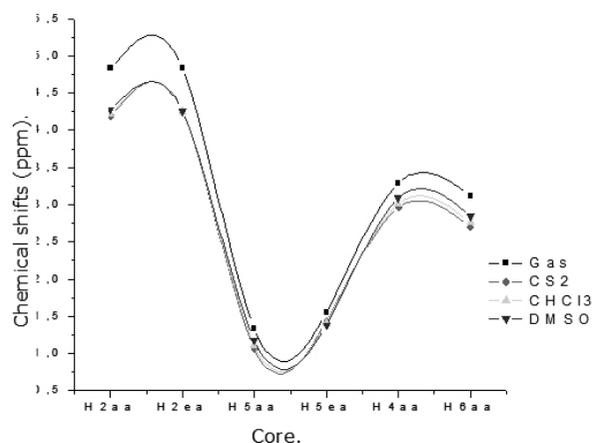


Fig.3. Calculated Chemical shifts of isomer 12 cis A (R1- methyl; R2- ethyl).

It can be concluded that, serie cis A shows small differences between axial and equatorial chemical shifts of protons bounded to a single carbon atom. The change from gaseous to solutions shows significant differences between chemical shifts of H2 protons and sulfur atom protection would affect carbon 6-proton more than oxygen atom affects proton at carbon 4. Chemical shifts also show stereoelectronic interactions which may be responsible for anomalous chemical shifts as found in C2 hydrogen of 1,3-dithiane<sup>34</sup>. These parameters can be compared with those found for cyclohexane where dHec > dHax and is reflected in longer C-Hax bonds than equatorial ones.

Chemical shifts of cis A serie were studied and no anomalous effect in C2 was found as they show dHec > dHax, where Hec are displaced to low fields and Hax to high fields (table 3).

Table 3: <sup>1</sup>H- NMR parameters of calculated and experimental protons for Cis 4,6-dimethyl-1,3-thioxane.(ppm).

Nucleous	<sup>1</sup> H-NMR parameters				
	Gas	CS <sub>2</sub> a	CHCl <sub>3</sub> a	DMSOa	Exp <sup>a</sup>
H2a	4,85	3,92	4,12	4,12	4,66
H2e	4,81	4,03	4,22	4,22	4,66
H5a	1,53	0,95	1,15	1,15	1,20
H5e	1,23	1,01	1,20	1,20	1,67
H4a	3,29	2,66	1,86	2,86	2,90
H6a	2,99	2,30	2,50	2,50	2,90
2J2a2e	-9,39				-
2J5e5a	-12,1				13,5
3J5a4a	8,92				11,0
3J5e4a	1,94				2,40
3J5a6a	9,49				11,0
3J5e6a	2,51				2,80

a) Data calculated at B3LYP/6-311++G\*\* level<sup>33</sup>.

Table 3 also shows important information on experimental values of <sup>1</sup>H-NMR where calculated values are observed to follow the same tendency as experimental values. These values are accurate enough to continue with proposed calculations of the following series for which no experimental values has been reported. Cuevas et al. reported for cyclohexane values of axial carbon hydrogen coupling constant lower than those of equatorial carbon hydrogen. This phenomenon is known as Normal Perlin effect.

This effect was observed in C2 (table 4) where C<sub>2</sub>-H<sub>ec</sub> coupling constants are higher than C<sub>2</sub>-H<sub>ax</sub> clearly showing an increase in C<sub>2</sub>-H<sub>ax</sub> bond length due to a hyperconjugative interaction of (σ C-S → σ\* C-H<sub>ec</sub>) bond that would weaken this type of bond. C<sub>5</sub> would show a reverse Perlin effect

Table 4: Bond Length in Å of C<sub>2</sub> and C<sub>5</sub> axial and equatorial hydrogen's and coupling constants in (Hz) of cis A series.

Isomer	Bond Length and Coupling constants H <sub>2ax</sub> v H <sub>2ec</sub>				Δa	Bond Length and Coupling constants H <sub>5ax</sub> v H <sub>5ec</sub>				Δa
	C2	C2	1JC2	1JC2		C5	C5	1JC5	1JC5	
	Hax	Hec	Hax	Hec		Hax	Hec	Hax	Hec	
11A	1,087	1,080	150,6	152,5	1,9	1,086	1,089	125,7	118,9	-6,9
12A	1,089	1,080	150,6	152,5	1,9	1,085	1,089	125,7	118,2	-7,6
13A	1,087	1,080	150,6	152,5	1,8	1,084	1,089	125,8	118,2	-7,6
14A	1,087	1,080	150,5	151,9	1,5	1,087	1,087	125,2	118,5	-6,7
15A	1,087	1,080	150,5	152,1	1,5	1,084	1,085	125,7	118,2	-7,5

$$\Delta a: \text{Perlin Effect} = {}^1J_{C,Hec} - {}^1J_{C,Hax}$$

## CONCLUSIONS

At least for the structures study here, ab-initio theoretical calculations allow derive reliable geometries and energetic conformations. Moreover, calculations such as NMR, NBO analysis, in the gas phase or solution and scanning the potential energy hypersurfaces, lead us to conclude that:

1) (HF, B3LYP y MP2) ab-initio methods provided results, good enough to reach the objectives of the present work; Reasonable structures of all 4,6-dialkyl - 1,3-tioxane species were obtained. "Normal" geometric parameters were derived in all cases and conformational energies, thermodynamic properties and NMR parameters of protons both in gaseous phase and solution by using PCM method were also obtained.

2) The structures of 1,3 tioxane derivatives show an upper zone, a flat middle one and a slightly flat lower zone compared to data for 1,3 dioxane. Accordingly, in the upper zones an increase in the (S1-C2-O3) bond angles takes place. A value of ca. 113° has been obtained. In (C6-C5-C4) bond angles takes values of 115° in the lower zones and C-C-C-O and S1-C2-O3-C4 strain angles of ca. τ ≅ 58° and 63° values were calculated, respectively.

3) Geometry optimization of structures under study shows similar bond and angle length, with differences less than or equal to 0,02 Å.

4) Cis serie has a purely steric control due to 1,3-diaxial repulsive decreases of HaxC2-HaxC6, HaxC2-HaxC4 favoring isomers I. 12A is the exception since it is being affected by LPS → σ\* C6-Rax, LPS → σ\* C5-C6, LPO → σ\* C4-R2 and LPO → σ\* C4-C5 hyperconjugative effects.

5) Chemical shifts for axial protons of all estructures show that C2 protons have longer chemical shifts than C4 and C5. Axial proton at Carbon 2 is the most unshielded and both axial and equatorial protons of carbon 5 are the most shielded.

6) The structures are affected by Normal Perlin Effect in C2 where all C2-Hec coupling constants are higher than C2-Hax as evidenced by an increase in C2-Hax bond length due to a C-H (σ C-Hax → σ\* C-Hax) hyperconjugative interaction which would weaken this type of bond.

7) C5 would show a reverse Perlin effect, where J C5-Hax > J C5-Hec as shown by an increase in C5-Hec bond length.

## ACKNOWLEDGEMENTS

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