

“CONFORMATIONAL PREFERENCE IN 4,6-DIMETHYL-1,3-THIOXANE”

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ABSTRACT

Trans-4,6-dimethyl-1,3-thioxane shows two conformations as a result of the heterocyclic ring inversion. The **I** and **II** conformers interconversion process has been studied by means of ab initio methods. The thermodynamics of this reaction calculated at the MP2/6-311+G**//HF/6-31G** and B3LYP/6-311+G**//B3LYP/6-31G** levels yield ΔG° values of ca. -1.5 kcal/mol in the gas phase, implying that **II** is the most important species in the gas phase and that its relative concentration is ca. 93%. In solution of low and medium polarity solvents, PCM method predicts an 85% concentration for this species, consistent with an 83% estimated from $^1\text{H-NMR}$ spectra. The experimental NMR properties (δ and $^1J_{\text{C-H}}$) have not been reported since **I** and **II** separation could not be achieved. The results obtained for two long range $^4J_{\text{ax,eq}}$ and $^6J_{\text{eq,eq}}$ coupling constants of ca. 0.5 Hz are in good agreement with 0.41 Hz, calculated in the present work. The calculated chemical shifts for the C2 and C5 protons show that $\delta_{\text{Heq}} < \delta_{\text{Hax}}$ implying that some anomalous effects are operating, though the δ seems to be moderately insensitive C-H bond distances changes. The spin-spin coupling constants are much more sensitive to changes occurring in the ring. Thus, normal and reverse Perlin effects for $^1J_{\text{C-H}}$ are predicted for C2-H and C5-H are operating, respectively. The $\sigma_{\text{C5}} - \text{Heq} \rightarrow \sigma^*_{\text{C}} - \text{S}$ interaction would be the responsible for the very small elongation of the C5-Heq over the C5-Hax bond distances.

Keywords: 4,6 - dimethyl - 1,3 - Thioxane; conformational preference, NMR properties, NBO analysis.

INTRODUCTION

The study of the factors ruling the preferred conformation in sulfur-containing six-membered heterocycles has been an active area of research for a time already. Normally, cyclohexane has been taken as the model undistorted chair like structure to be compared with other substituted species such as 1,3-dioxane, 1,3-dithiane and 1,3-thioxane. Structure deviations and reactivity can be predicted for dialkyl derivatives of these heterocycles. In fact, the introduction of two heteroatoms produce important distortions in the “ideal” chair structure of cyclohexane. Thus, changes occurring in the aliphatic region of thioxane, show that this part of the molecule is less planar than dioxane, though the former is more easily distorted upon hydrogen substitution by alkyl groups than the later. Conformational analyses on substituted derivatives of these heterocycles have provided additional information on the different factors governing the preferred conformation adopted by the ring and also allowed to understanding some anomalous structural and spectroscopic features¹⁻⁵. In fact, particular interest have been paid to chemical shift and one-bond $^{13}\text{C-H}$ spin-spin coupling constants as they allow directly to study hyperconjugation. In the present work, we have studied the two conformers (**I** and **II**) equilibrium in trans-4,6-dimethyl-1,3-thioxane (DMT) and see whether the calculated model chemistry is consistent with the coexistence of both species as suggested by the $^1\text{H-NMR}$ spectra⁶⁻⁷. We have also explored the effect of the solvent, by using PCM model⁸⁻¹¹, on such equilibrium and approximately estimated the conformers relative concentrations. The transition state for the two conformers interconversion reaction have been found and the effect of the solvent on the activation energy also studied.

COMPUTATIONAL METHODS

Conformers **I** and **II** initial structures were fully optimized at HF/6-31G**, MP2/6-31G** and B3LYP/6-31G** levels using Gaussian 98 and 03 series of programs¹². Frequency and IR intensities were predicted at the equilibrium geometries (B3LYP/6-31G**) yielding all real frequencies so that all calculated structures are local minima. The calculated energies were corrected for zero point vibrational energies. Thermodynamic data (298 K, 1 atm) were derived from the vibrational modes within the harmonic oscillator, rigid rotor and ideal gas approximations. Energy calculations were carried out using a flexible basis set like 6-311+G** that includes both polarization and diffuse functions. Diffuse functions are important for molecules having lone pair of electrons (LP)¹³, and to into account the relative diffuseness of LP. On the other hand, polarization functions are useful in conformational studies where stereoelectronic effects play an important role¹⁴. Enthalpies and free energy changes of interconversion were obtained from the corresponding sums of electronic and thermal enthalpies and free energies, respectively. The solute-solvent interactions were calculated with the polarized continuum method (PCM)-SCRF method for which its capacity to reproduce solvation energies¹⁵ has been proved. In general PCM behaves well, failing just in few cases. In applying PCM the gas phase geometries were taken, since optimization in CS₂ produce almost no change in the gas phase structural parameters of **I** and **II** (largest bond length deviation

ca. 0.009 Å, whereas bond angles vary ca. 0.3 degrees). Free energies in solution (G°_{SOLN})^{16a} were calculated from $G^\circ_{\text{SOLN}} = \Delta G^\circ_{\text{GAS}} + \Delta \Delta G^\circ_{\text{S}}$, where the later term is the PCM solvation energy that includes both electrostatic and non-electrostatic contributions. The concentration of each species was estimated from the corresponding $\Delta G^\circ_{\text{SOLN}}$ value.

In order to study the electronic structures of conformers **I** and **II**, Natural Bond Orbital (NBO)^{16b} analyses were carried out on the B3LYP/6-31G** geometries and the energies of hyperconjugation interactions, the Fock (F_{ij}) matrix element corresponding to the orbital interactions and the energies of the donor and acceptor orbitals, derived. The hyperconjugation interaction energies were obtained from the second-order perturbation approach: $E_{(2)} = -2 \langle \sigma | F | \sigma^* \rangle^2 / \epsilon_{\sigma^*} - \epsilon_{\sigma}$, where the integral corresponds to the F_{ij} matrix element between interacting orbitals i and j whose energies are ϵ_{σ} and ϵ_{σ^*} . 2 stands for the population of the donor orbital. There is a very good linear correlation between the second-order perturbation hyperconjugative energies and the deletion procedure²³.

Theoretical ^1H shifts (δ) and the one-bond $^{13}\text{C-H}$ coupling constants ($^1J_{\text{C-H}}$), were obtained at the B3LYP/6-31G** geometries. The TMS, used as standard, geometry was also calculated at this level. Magnetic shielding tensors were calculated at B3LYP/6-311+G**//B3LYP/6-31G** level of theory using the GIAO (Gauge-Independent Atomic Orbital) method. Chemical shifts were derived with respect to the NMR isotropic magnetic shielding tensors (in ppm) from the corresponding standard tensor (TMS = 32.1 ppm for ^1H)¹⁶. The transition state for the **I** \rightleftharpoons **II** interconversion reaction was located using the synchronous transit-guided quasi-Newton (STQN) method^{17,18} characterized by a frequency calculation which yielded a single imaginary frequency. The animation of such a vibrational mode using GaussView¹⁹ program, confirm that the imaginary frequency corresponds to a ring deformation mode that conducts either to the reactant (conformer **I**) or the product (conformer **II**). The TS \rightarrow **I** and TS \rightarrow **II** paths were followed by an intrinsic reaction coordinate (IRC) procedure²⁰. IRC calculations lead to the conclusion that the TS connects both reactant and product. These three independent methods to analyze this vibrational mode point towards a true TS

RESULTS AND DISCUSSION

A) Molecular Structures

For conformers **I** and **II**, selected bond distances and angles describing mainly the ring geometries are given in table 1, whereas figure 1 shows the atom numbering used in table 1 and in setting the Z-matrix. The chair structure of conformers **I** and **II** has been divided into two parts: the one formed by S1-C2-O3 set of atoms (set 1) and the hydrocarbon part formed by C4-C5 and C6 atoms (set 2). Thus in **I**, set 1 is down and set 2 is up; the opposite situation is found in **II** (see figure 1). Thioxane is not planar in the zone connecting sets 1 and 2. In fact, in dioxane, dithiane and thioxane, the dihedral S1C6C4O3 varies from 0.00°, 0.08° and 1.39° for dioxane, dithiane and thioxane, respectively. The larger value found in thioxane can be attributed to the C-S and C-O bond distances difference and to the dissimilar spatial requirements of the heteroatoms (S and O).

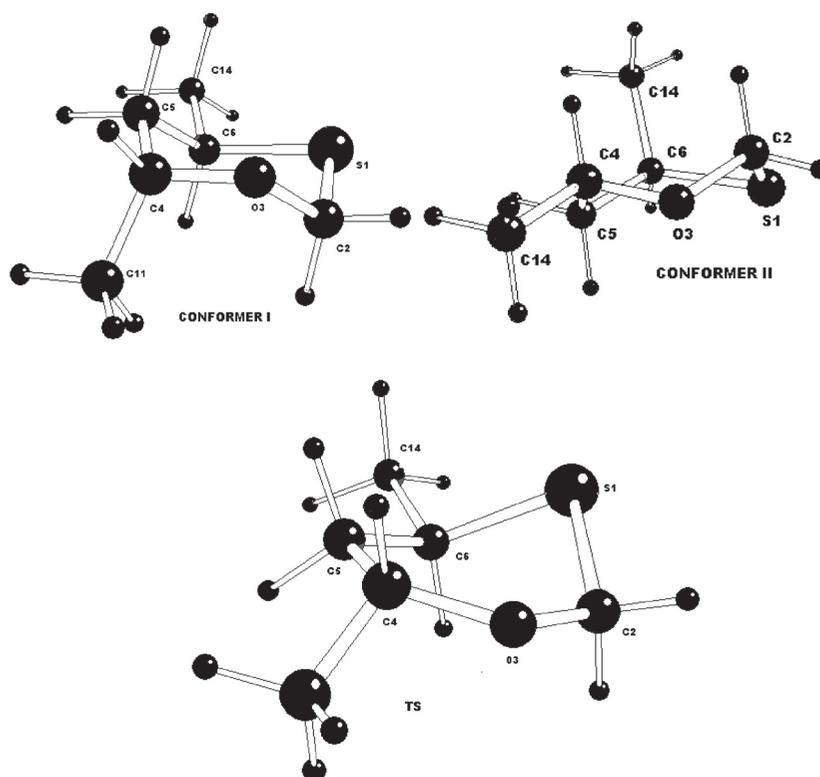


Figure 1. Optimized structures and atom numbering for conformers **I** and **II** of 4--6-dimethyl-1,3-dithiane and their TS.

Table 1. Optimized bond distances and angles (B3LYP/6-31G**) for conformers **I** and **II** and their transition state (TS)^a.

	I	TS	II
Bond distances (Å)			
S1-C2	1.846 (1.847)	1.832(1.834)	1.844(1.845)
C2-O3	1.402 (1.402)	1.400(1.400)	1.402(1.401)
O3-C4	1.438 (1.440)	1.443(1.445)	1.434(1.436)
C4-C5	1.541(1.541)	1.566(1.566)	1.536(1.536)
C5-C6	1.534 (1.534)	1.539(1.540)	1.541(1.541)
C6-S1	1.851 (1.842)	1.842(1.844)	1.856(1.856)
C2-H7	1.097 (1.097)	1.101(1.101)	1.092(1.092)
C2-H8	1.092 (1.092)	1.093(1.093)	1.100(1.099)
C4-H12	1.095 (1.097)	1.097(1.097)	1.104(1.103)
C4-Me	1.533 (1.527)	1.527(1.527)	1.522(1.522)
C5-H9	1.096(1.096)	1.096(1.096)	1.098(1.098)
C5-H10	1.099(1.099)	1.098(1.098)	1.096(1.096)
C6-Me	1.528 (1.528)	1.528(1.528)	1.533(1.533)
C6-H13	1.097(1.096)	1.098(1.097)	1.095(1.095)
Bond angles (deg)			
S1-C2-O3	114.0(113.8)	115.0(114.6)	113.7(113.5)
C2-S1-C6	96.1(96.1)	91.6(96.1)	97.0(97.0)
C2-O3-C4	115.5(115.4)	122.1(121.5)	113.4(113.3)
C4-C5-C6	115.3(115.4)	119.8(120.2)	115.2(115.2)
O3-C4-C5	111.7(111.6)	119.2(119.3)	111.2(111.1)
S1-C6-C5	109.6(109.6)	110.4(110.8)	109.9(109.9)
C2-S1-C6-C5 (κ_1)	50.9(50.8)	60.8(59.1)	47.4(47.4)
C2-O3-C4-C5 (κ_2)	60.3(60.6)	3.7(1.8)	65.4(65.6)
S1-C2-O3-C4	64.9(65.2)	38.4(41.6)	67.6(67.9)
O3-C2-S1-C6	55.7(55.8)	66.1(67.6)	54.7(54.7)
S1-C6-C4-O3	1.2 (1.2)	36.5(35.0)	3.4(3.5)
O3-C4-C5-C6	58.0(58.1)	4.7(6.1)	60.7(60.8)
S1-C6-C5-C4	58.3(58.2)	34.7(31.9)	55.9(55.9)

a) Structural values in CS₂ solution, are given in parentheses.

The non-regularity of thioxane is also reflected in the values of the torsion angles τ_1 and τ_2 with values of 50.7 and 64.8°, respectively. In 4,6-dimethyl derivatives, τ_1 (C2S1C6C5) are ca. 50.9 and 60.3° in **I** and **II**, respectively, whereas for τ_2 (C2O3C4C5) values of 47.4° and 65.4° were found for these conformers. Comparing these values with those of the parent compound it can be inferred that **I** is more distorted in the oxygen side, whereas **II** is distorted in S side. Conformer **II** would stabilize due to hyperconjugative interactions of the type LPS → σ^* C5-C6, LPS → σ^* C6-Me and LPS → σ^* C2-O3 (see NBO analysis).

The transition state for the **I** ⇌ **II** interconversion reaction looks like a large distorted species. In fact, as S1 moves up by ca 12°, O3 remains in its position. The most drastic changes are experienced by C2 and C5 that move up and down, respectively. These combined movements leads to an almost planar ring geometry (C2O3C4C5C6 ≈ 1°) with the exception of S1. The TS methyl groups on C4 and C6 are in axial and equatorial, respectively.

B) Energetics and Thermodynamics

Energetic and thermodynamics of conformers **I** ⇌ **II** interconversion reaction are given in table 2. The MP2 and DFT methods include electron correlation that is important in conformational analysis^{13,21}. In fact, at MP2/6-31G** and B3LYP/6-31G** levels the whole molecular system is stabilized by ca. 730 and 1701 kcal/mol (relative to de HF level), respectively. Basis sets with diffuse functions, such as 6-311+G** and 6-311++G**, are also important to account the diffuse nature of lone pairs of electrons¹³, whereas the inclusion of polarization functions are useful when hyperconjugative stereoelectronic interactions and third row elements are present²²⁻²⁵. The thermodynamics of the **I** ⇌ **II** interconversion reaction were calculated at the MP2/6-311+G** // HF/6-31G** and B3LYP/6-311+G**//B3LYP/6-31G** levels. Both levels of theory indicate that the use of a larger basis set than 6-31G** produces the system to gain ca. 99 (MP2) and 64 (DFT) kcal/mol. The addition of diffuse functions to the hydrogens leads to no further stabilization of the molecular system. An approximate relative concentration % of **II** ca. 93% points towards a very low concentration of conformer **I** in the gas phase. In fact, a ΔG° of ca.-1.566 kcal/mol indicates that the interconversion reaction is extensively displaced to the conformer **II** formation.

Table 2. Energetics for conformers I and II and their TS

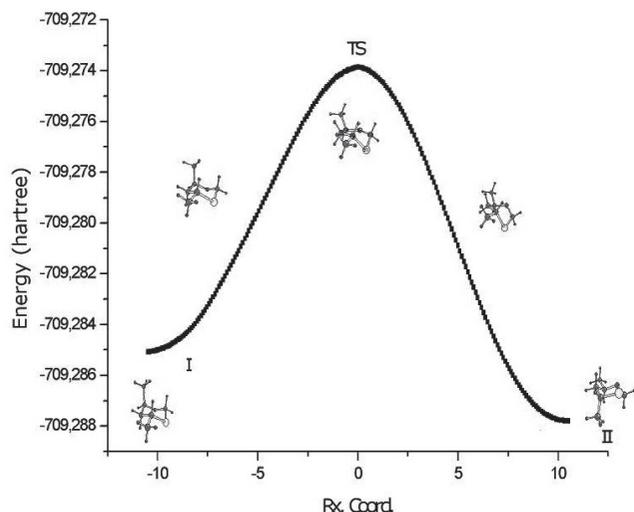
Energy ^a	Conformer I	TS	Conformer II
E ₀ ⁽¹⁾ [HF/6-31G**]	-706.576873	-706.562324	-706.579261
E ₀ ⁽²⁾ [B3LYP/6-31G** [MP2/6-31G**]	-709.287794 -707.741141	-709.273993 -707.725015	-709.289853 -707.743464
E ₀ ⁽³⁾ [B3LYP/6-311G** [MP**/6-311G**]	-709.382763 -707.886583	-709.369211 -707.870067	-709.385051 -707.889119
E ₀ ⁽⁴⁾ [B3LYP/6-311+G** [MP2/6-311+G**]	-709.388286 -707.899158	-709.374759 -707.883194	-709.390368 -707.901447
E ₀ ⁽⁵⁾ [B3LYP/6-311++G** [MP2/6-311++G**]	-709.388515 -707.900397	-709.374987 -707.884301	-709.390624 -707.902593
ZPE (B3LYP)	0.175333	0.174685	0.175141
ZPE (MP2)	0.187510	0.186752	0.187395
H _{CORR} (B3LYP)	0.184901	0.183777	0.184731
H _{CORR} (MP2)	0.196545	0.195417	0.196406
G _{CORR} (B3LYP)	0.142376	0.141875	0.142154
G _{CORR} (MP2)	0.154965	0.153973	0.154924
S ^b (B3LYP)	89.500	88.191	89.621
μ (D)	2.533	2.101	2.422
E ₀ ⁽⁴⁾ + ZPE	-709.212953	-709.200074	-709.215227
E ₀ ⁽⁴⁾ + ZPE + H _{CORR}	-709.028052	-709.016297	-709.030496
E ₀ ⁽⁴⁾ + ZPE + G _{CORR}	-709.070577	-709.058199	-709.073073
ΔH ^{o c}	-1.534 (-1.596)		
ΔG ^o	-1.566 (-1.534)		
E ^f	8.082(9.542)		

a) Energies, ZPE, thermal contributions to H^o and G^o in hartrees.

b) S in cal k⁻¹ mol⁻¹. Activation energy for the forward reaction.

c) ΔH^o, ΔG^o and E^f in kcal/mol. Values in parentheses are at MP2/6-31G** level.

This conclusion is in good agreement with the experimental finding that estimates ca 85% of **II** concentration²⁶. As usual in conformers interconversion reactions^{27,28}, entropy remains constant (ΔS = 0.121 cal K⁻¹ mol⁻¹), whereas enthalpy change appears controlling the interconversion. On account of the almost complete planarity of the ring, TS does not resemble the reactant or the product. The animation of the imaginary normal mode shows that C5 and O3 move up and down with rather large amplitudes, The C2H2 group simultaneously performs the same movement in such a way that conformer **I** is clearly “recovered”. Intrinsic reaction coordinate calculations (IRC) both in the forward and reverse directions (both at HF and DFT/6-31G**) lead to the reactant and product and thereby the TS is fully characterized. Figure 2 shows the energy profile which is consistent with a single saddle point at the TS. No other saddle points were “detected” most likely due to steric effects of sulfur atoms that would produce a larger repulsion with the bulky methyl group leading to rather rigid structures.

**Fig. 2-** Forward and reverse intrinsic reaction coordinates**C) Solvent Effect**

The solvent-solute interactions were calculated using PCM method. Solvents of low and medium high polarity (dielectric constants: 2.60, 4.90) and 46.70) were employed. The free energy changes in solution were obtained, as usual, from $\Delta G_{\text{SOLUTION}}^{\text{O}} = \Delta G_{\text{GAS}}^{\text{O}} + \Delta \Delta G_{\text{SOLVATION}}^{\text{O}}$ relationship. Their values are given in table 3.

Table 3. Free Energies of Solvation and in Solution for Conformers **I** and **II**.

Solvent	ΔG ^o _s				ΔG ^{ob} _{soln}	% II	E _a
	I	II	TS	G ^o _s			
Gas							8.08
CS ₂ (ε = 2.60)	-4.06	-3.77	-3.70	0.29	-1.276	89	7.72
CHCl ₃ (ε = 4.90)	-5.16	-4.79	-4.62	0.37	-1.196	88	7.54
DMSO (ε = 46.70)	-7.25	-6.87	-6.57	0.38	-1.186	88	7.78

a) $\Delta \Delta G_{\text{s}}^{\text{o}} = \Delta G_{\text{s}}^{\text{o}} \text{ II} - \Delta G_{\text{s}}^{\text{o}} \text{ I}$

b) $\Delta G_{\text{soln}}^{\text{o}} = \Delta G_{\text{gas}}^{\text{o}} + \Delta \Delta G_{\text{s}}^{\text{o}}$

c) The effect of solvent on the activation energies

From table 3 it can be inferred that the solvent polarities do not influence the interconversion reaction since conformer **II** relative concentration remains constant throughout the solvent dielectric constant. It likely that the small effect one can derive by applying PCM method is due to the very small dipole moment difference (Δμ = 0.111 D). Conformer **II** is the main species in the gas phase (ca. 93%) due to its intrinsic stability, but decreases to ca. 86% in solution in agreement with the experimental finding that in CS₂ solution, this species is in ca. 85% concentration²⁶.

D) NMR Spectra

The NMR properties were calculated at the B3LYP/6-31G(d,p) geometries and the GIAO magnetic shielding tensor obtained at the B3LYP/6-311+G(d,p) level of theory. To control the reliability of this level, the 1,3-thioxane chemical shifts and one-bond

¹³C-¹H coupling constants were also derived and compared with the theoretical and experimental data^{3,4} (table 4). The good agreement between the calculated and experimental NMR data allows to predict confidently the spectral properties for DMT conformers **I** and **II**. The ¹H-NMR spectra of a mixture of both conformers would show a typical two AB system pattern for the axial and equatorial protons attached to C2, i.e., two well separated four signal multiplets.

Table 4. C-H bond lengths (Å), chemical shifts (δ, ppm) and ¹J_{C-H} (Hz) for 1,3-thioxane.

Distance	ref. 4	this work	δ (4)	δ (this work)	δ (exp.) ^a	¹ J (4)	¹ J (this work)	¹ J (exp.) ^b
C2-H _{ax}	1.101	1.101	5.1	5.2	4.9	150.3	150.3	157.5
C2-H _{eq}	1.091	1.091	4.8	4.9	4.8	152.9	153.0	157.5
C4-H _{ax}	1.097	1.104	3.1	3.7	3.1	132.5	130.0	142.7
C4-H _{eq}	1.093	1.093	2.6	2.8	2.8	132.5	140.6	142.7
C5-H _{ax}	1.095	1.095	2.0	2.3	2.0	127.1	127.0	126.9
C5-H _{eq}	1.098	1.098	1.6	1.6	1.8	120.1	120.0	129.0
C6-H _{ax}	1.104	1.097	3.5	3.2	3.6	130.3	133.6	139.0
C6-H _{eq}	1.093	1.093	4.0	4.2	4.1	142.2	135.7	142.2

a) Data from reference 3

b) Data from reference 4

The two A parts of the **I** ↔ **II** system (H_{ax} (II) and H_β (I)) would show up at lower field than the two B parts of the systems (H_{ax} (I) and H_β (II)) will appear at higher field in a similar fashion than the 4-ethyl-6-methyl-1,3-dithiane behaves^{7,16}. As usual, the AB system with the methyl group equatorial (conformer **I**) and next to the sulfur will presents the highest intensity. At room temperature, both multiplets would collapse into two doublets calculated at 4.82 and 4.61 ppm (Δδ=0.21 ppm) and 5.48 and 5.39 ppm (Δδ=0.09 ppm), respectively. In the parent 1,3-thioxane (see table 4) and conformers of DMT (see table 5) the calculations indicate that ¹J_{C-Heq} > ¹J_{C-Hax} implying a normal Perlin effect is working at C2, whereas at C5 the opposite situation is observed and thereby the reverse Perlin effect must be operating.

Table 5. Predicted ¹H-NMR chemical shifts^a (δ in ppm) and one-bond coupling constants^a ¹J_{C-H} (in Hz) for conformers **I** and **II**.

Bond	I			II		
	distance (Å)	δ	¹ J _{C-H}	distance	δ	¹ J _{C-H}
C2 – H _{ax}	1.097	5.5	151.3	1.100	5.4	150.4
C2 – H _{eq}	1.092	4.6	152.4	1.092	4.8	152.3
C4 – H _{eq}	1.095	4.4	140.6	1.104	3.9	131.5
C6 – H _{ax}	1.087	3.5	134.7	1.095	3.2	135.9
C5 – H _{ax}	1.096	2.1	126.2	1.096	2.2	125.7
C5 – H _{eq}	1.099	1.7	118.9	1.098	1.6	119.5

a) Calculated values at B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p)

b) Experimental values for 1,3-thioxane, ref. 4.

The calculated spin-spin coupling constants for conformers **I** and **II** qualitatively reflect the effect that larger C-H bond distances lead to smaller ¹J_{C-H}. This observation agrees well with the data given in tables 4 and 5. The elongation of C5-Heq can be explained in terms of a dominant σC5-Heq → σ*C-S two-electron/two-orbitals interactions. In fact, the second order perturbation energies for the above interactions are ca. 5.56 and 5.85 kcal/mol for **I** and **II**, respectively. The reverse interactions (σC-S → σ*C5-Heq) are less favored with E₍₂₎ ca. 3.20 and 1.32 kcal/mol. The sensitivity of coupling constants to the changes occurring in the heterocyclic ring upon substitution is a well established observation^{3,5,16} now. No relationship between the chemical shifts (δ) and bond lengths have been found, most likely due to the rather insensitivity of δ to geometric changes in the ring. However, it is worth noting that equatorial and axial protons are displaced to higher and lower field, respectively, due to σC-S → σ*C-Heq hyperconjugative interactions.

CONCLUSIONS

The calculations carried out on the conformers **I** and **II** of 4,6-dimethyl-1,3-thioxane, allow to draw some interesting conclusions:

1.-The presence of two heteroatoms in the ring leads to important distortions that are reflected in the values of the torsional angles. The main deviations, with respect to dithiane, occur on the angles C2S1C4C5(τ₁) and C2O3C6C5(τ₂). τ₁ deviates by ca. 7° and 3°, whereas τ₂ departs by ca. 10° and 8°, in **I** and **II** respectively.

2.-Conformer **II** would be more stable than **I** due to hyperconjugative interactions of the type LPS → σ*C5-C6, LPS → σ*C6-Me and LPS → σ*C2-O3. The sulfur electron lone pairs are delocalising onto antiperiplanar C5-C6 and C2-O3 empty antibonding orbitals. These delocalisations are supported by high bond populations and orders.

3.-The gas phase calculations point to conformer **II** as the most stable species with a relative concentration of ca. 92%, whereas in solution conformer **I** increases its concentration to ca. 12%.

4.-The calculated chemical shifts for the C2 and C5 protons show that δ_{Heq} < δ_{Hax} implying that some anomalous effects are operating, though the δ seems to be somewhat insensitive to C-H bond distances.

5.-The spin-spin coupling constants are much more sensitive to changes occurring in the ring. Thus normal Perlin effect for ¹J_{C-H} are predicted for C2-H, whereas at C5 the reverse Perkin effect is operating. The σC5-Heq → σ*C-S interaction would be the responsible for the very small elongation of the C5-Heq over the C5-Hax bond distances.

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