“CONFORMATIONAL PREFERENCE OF 4-ETHYL- 6-METHYL-1,3-DITHIANES”

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ABSTRACT

Interconversion reaction of **I** $\leftrightarrow$ **II** conformers of 4-ethyl-6-methyl-1,3-dithiane (METDIT) has been studied by means of ab initio methods on the frame of MO theory. Optimized geometries at HF/6-31G** level correlate well with that found for the parent 1,3-dithiane from an x-ray diffraction study. Both conformers possess similar bond distances, but differ in up 12° in some dihedrals. Conformer **I** geometry presents the larger distortion from the regular 1,3-dithiane mainly due to difference between angles κ_1 and κ_2 (ca. 14°). In conformer **II** this difference is just ca. 3°. The energetics and thermodynamics were obtained with basis sets that include diffuse, polarization functions and electronic correlations at the second-order perturbation Møller Plesset theory. Gas phase thermodynamic predicts **II** to be in a 98% concentration. Low and medium high polarity solvents seem to exert no influence on the conformers concentrations. Thus the **I** $\leftrightarrow$ **II** interconversion reaction is largely displaced to **II** formation, both in the gas phase and solution. The calculated ¹H-NMR data, i.e., chemical shifts and one-bond C-H spin-spin coupling constants are predicted on the basis of the consistent results obtained for the parent 1,3-dithiane. For both conformers reverse Perlin effect takes place at C2 and C5. The C2 - H_{ax} and C2 - H_{eq} bond distances are similar (ca. 1.092 Å), whereas the C5 - H_{eq} are larger than the axial ones yielding smaller ¹J_{C-H} coupling constants.

Keywords: 4-ethyl-6-methyl-1,3-dithiane; conformational preference, NMR properties

INTRODUCTION

The study and understanding the factors ruling the preferred conformation in sulfur-containing six-membered heterocycles have become an important area of research. Cyclohexane has been the model molecule to learn more about structures and reactivities of other species like 1,3-dioxane, 1,3-dithiane and 1,3-thioxane. 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 dithiane, show that this part of the molecule is less planar as compared with dioxane, thought the former is more easily distorted upon hydrogen substitution by alkyl groups than the latter. 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 have also allowed the understanding of some anomalous structural and spectroscopic features¹⁻⁷. In fact, particular interest has been paid to chemical shift and one-bond ¹³C-¹H spin-spin coupling constants as they allow directly to study hyperconjugation. The two-electron/two-orbital hyperconjugative interactions between an occupied high-energy donor orbital and an empty low-energy acceptor orbital, may influence conformational equilibrium and reflect the departure of the actual structure from the ideal Lewis one⁶. These deviations show up themselves as geometric, electron density distribution, energies of the molecular orbitals, IR spectra and NMR properties³ changes. X-ray diffraction studies show that 2-phenyl-1,3-dithiane⁸ possesses a regular chair structure with angles and lengths in good agreement with the calculated values (HF/6-31G**). It is well known that hydrogen substitution distorts in a variable extent the “regular” heterocyclic ring. Energy calculations reveal that, in general, both alkyl equatorial and axial substitutions are possible and that their preferred conformation will depend on the nature, size, solvent and interaction of substituents and the sulfur lone pairs of electrons^{9,10}. In the present work, we have studied conformers **I** and **II** equilibrium in trans-4-ethyl-6-methyl-1,3-dithiane (METDIT) and see whether the calculated thermodynamic properties are consistent with the coexistence of both species as suggested by the ¹H-NMR spectra^{11,12} or some other factors govern the interconversion reaction. We have also explored the effect of the solvent, by using PCM model¹³⁻¹⁶, on such equilibrium. If the experimental and calculated data are in agreement, the type of hyperconjugative delocalization, that explain some structural and spectroscopic features could be proposed (derived from NBO analysis¹⁷). 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

Geometry optimization of conformers **I** and **II** of METDIT were carried out at HF/6-31G**, MP2/6-31G** and B3LYP/6-31G** levels using Gaussian 03 series of programs¹⁸. The initial geometries were those reported previously

for 1,3-dithiane^{4,8}. The energies derived at the MP2/6-31G**//HF/6-31G** and MP2/6-31G**//MP2/6-31G** were compared in order to determine whether or not geometries needed to be calculated at a correlated level to obtain accurate energies. The $\Delta E(\mathbf{I} - \mathbf{II})$ value of ca. 0.02 kcal/mol, derived suggests that optimization at correlated level is not needed. Similar calculations using DFT-B3LYP functional also show that the above difference is just ca. 0.11 kcal/mol. In fact, the largest differences in bond distances calculated at correlated and uncorrelated levels are ca. 0.009 Å whereas the bond angle largest variation is ca. 2.0° for both conformers. Frequency and IR intensities were predicted at the equilibrium geometries (HF/6-31G**) yielding all real frequencies so that all calculated structures are local minima. Energy calculations were carried out using a flexible basis set like 6-311+G** that includes both polarization and diffuse functions. Electron correlation at the second order Møller Plesset theory in the frozen core approximation was also included. Attempts to explore higher order Møller Plesset and QCISD using the same basis set failed due to our limited computational facilities. The calculated energies were corrected for zero point vibrational energies and enthalpies and free energy changes of interconversion were obtained from the corresponding sums of electronic and thermal enthalpies (H_{CORR}) and free energies (G_{CORR}), respectively. The solute-solvent interactions were calculated with the polarized continuum method (PCM)¹³⁻¹⁷ for which its capacity to reproduce solvation energies¹⁹ leads us to conclude that in general PCM behaves well, failing just in few cases. To apply PCM, the gas phase geometries were taken since very small changes in the geometrical parameters are observed for **I** and **II**, in going from the gas phase to the solution (see table I). In fact, optimization of all structures in several solvents show that bond distances largest variation is ca. 0.002 Å, whereas bond angles vary ca. 0.3 degrees. Relative free energies in solution conformers were obtained by adding the relative free energies in the gas phase (ΔG_{GAS}) and the relative free energies of solvation ($\Delta \Delta G_{\text{s}}$). The total free energy in solution includes both electrostatic and non-electrostatic contributions.

To obtain the theoretical ¹H shifts (δ) and the one-bond ¹³C-¹H coupling constants (¹J_{C-H}), the B3LYP/6-31G** geometries were obtained for all compounds studied here as well as the equilibrium geometry for TMS used as standard²⁰. The magnetic shielding tensors were calculated at B3LYP/6-311+G**//B3LYP/6-31G** level of theory using the GIAO (Gauge-Independent Atomic Orbital) method^{21,22}. 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). The effect of the solvents CS₂, CHCl₃ and DMSO (dimethylsulfoxide) on chemical shifts and one bond spin-spin coupling constants, though initially calculated, was no further considered as the changes in either δ and ¹J_{C-H} are less than 0.1 ppm and 1 Hz, respectively.

In order to study the electronic structures of conformers **I** and **II**, Natural Bond Orbital (NBO) 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 good linear correlation between the second-order perturbation hyperconjugative energies and the deletion procedure²³.

The transition state for the **I** $\leftrightarrow$ **II** interconversion reaction was characterized by a frequency calculation which yielded a single imaginary frequency (at ca. 92 cm⁻¹). This frequency corresponds to a ring deformation mode detected at ca. 80 cm⁻¹ in 1,3-dithiane⁷. The animation, using GaussView program²⁴, of such a mode confirm that 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) procedure²⁵. IRC calculations lead to the conclusion that the TS connects both the reactant and the product. According to the finding of one imaginary frequency and its animation and the IRC results, we can be sure that the TS is a true one.

RESULTS AND DISCUSSION

A) Molecular Structures

Selected structural parameters for conformers **I** and **II** are shown in table 1. To discuss the geometries of **I** and **II**, the dithiane chair has been divided into three parts (see figure 1, for atom numbering): a) the lower (in **I**) and upper (in **II**) parts of the chair involving S1, C2 and S3, b) the chair middle portion including both sulfur, C4 and C6 atoms and c) the upper (in **I**) and lower (in **II**) parts formed by C4, C5 and C6 atoms. In this way conformer **I** can be described as ⁵C₂ chair, whereas **II** is clearly a ²C₂ chair. The methyl group is bonded to C6 whereas the ethyl is on C4. The differences in the conformations come from the fact that in **I** the -CH₃ group is in an equatorial position and the ethyl group is axially bound to C4. In conformer **II**, the reverse situation is found, i.e., the methyl is axial and the ethyl is equatorial. For both conformers, the ethyl group was rotated to see whether another configuration came out. In fact, in each case the rotation of the ethyl group by ca 10° produced the same minima. The positions of the alkyl group in **I** produces the regular dithiane chair to be quite distorted, whereas in **II** this effect is smaller and thereby the ring is noticeably less distorted. In both cases, the methyl group seems to exert no effect on the close S1 atom. Defining the torsion angles made up by the atoms involved in each side of the heterocyclic ring: $\kappa_1 = \text{C2S1C6C5}$ and $\kappa_2 = \text{C2S3C4C5}$, we can see that the departures of these angles from the regular dithiane ($\kappa_1 = \kappa_2 = 57.8^\circ$) are ca. 2 and 11.7° for **I**, whereas in **II** the deviations are ca. 3 and 0.1°, respectively. These results indicate that in **I** the ring is distorted in the S3 side and that conformer **II** remains fairly unperturbed upon alkyl substitution. Accordingly, the distortion of **I** implies that the sulfur atom moves up by ca. 12°. The distortion of both conformers is not reflected in bond distances as the largest bond difference is just ca. 0.02 Å. The middle or central part of conformer **I** structure (measured by the dihedral S1S3C4C6) is also somewhat changed, as the S3 atom moves up ca 4.4°; S1 does not vary its position appreciably. This part of **II** stays fairly unaltered when compared with dithiane. This same situation is observed for the lower part of this chair. In conformer **I**, the lower part is twisted by ca. 10° towards the S3 side. The transition state (TS) resembles **I** to a small extend. The ring distortion is reflected in that S1 goes down and κ_1 increases by ca. 19° with respect to the corresponding angle in dithiane. S3 goes up and becomes close to the plane formed by the all atoms in the ring but S1. The animation of the imaginary normal mode shows that C5, S3 and S1 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 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. Other saddle points in the potential energy hypersurface were not “detected” most likely due to steric effects of sulfur atoms that would produce a larger repulsion with the bulky ethyl group leading to rather rigid structures.

Table 1. Optimized bond distances and angles for conformers **I** and **II** of 4-ethyl-6-methyl-1,3-dithiane and their transition state (TS) [HF/6-31G**]^a.

	I		TS		II	
	GAS	DMSO	GAS	DMSO	GAS	DMSO
r(S1-C2)	1.806	1.806	1.799	1.798	1.809	1.809
r(C2-S3)	1.810	1.810	1.824	1.824	1.809	1.809
r(S3-C4)	1.832	1.835	1.854	1.856	1.831	1.833
r(C4-C5)	1.541	1.541	1.552	1.553	1.533	1.533
r(C5-C6)	1.533	1.533	1.527	1.528	1.537	1.537
r(C6-S1)	1.827	1.827	1.822	1.823	1.829	1.831
r(C2-H7)	1.080	1.080	1.081	1.081	1.082	1.802
r(C2-H8)	1.082	1.082	1.081	1.081	1.082	1.081
r(C4-H11)	1.085	1.085	1.081	1.080	1.085	1.084
r(C4-C12)	1.541	1.541	1.540	1.540	1.538	1.538
r(C5-H9)	1.085	1.086	1.085	1.085	1.090	1.089
r(C5-H10)	1.089	1.088	1.086	1.086	1.083	1.083
r(C6-C20)	1.529	1.529	1.528	1.528	1.531	1.530
R(C6-H19)	1.083	1.082	1.086	1.085	1.085	1.085
<S1C2S3	115.4	115.0	116.9	116.3	115.3	114.8
<C2S1C6	99.4	99.7	97.6	97.3	101.0	101.2
<C2S3C4	103.7	103.9	109.6	109.5	99.7	99.7
<C4C5C6	119.5	119.6	119.5	119.9	116.3	116.4
<S3C4C5	113.8	113.7	119.9	119.9	112.4	112.3
<S1C6C5	112.4	112.4	110.4	110.8	112.6	112.5
<C2S1C6C5(τ_1)	59.7	59.8	76.4	76.4	54.8	54.8
<C2S3C4C5(τ_2)	4.1	46.2	13.4	13.6	57.9	58.2
<S1C2S3C4	54.8	55.1	14.6	16.9	59.1	59.6
<S3C2S1C6	60.1	60.4	52.4	54.8	58.9	58.5
<S1S3C4C6	4.5	4.5	25.2	25.2	1.0	1.2
<S3C4C5C6	55.7	55.4	8.3	5.5	66.4	66.4
<S1C6C5C4	64.1	63.8	57.5	54.7	64.4	64.1

a) Bond distances in Å and bond angles in degrees

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

B) Energetics and Thermodynamics

The conformers **I** $\leftrightarrow$ **II** interconversion reaction energetics and thermodynamics are given in table 2. The inclusion of electron correlation

at the second order Møller-Plesset theory and the 6-31G** basis set shows that the whole molecular system is stabilized by ca. 790 kcal/mol with respect to the corresponding Hartree-Fock level. The use of a larger basis set such as 6-311G** produces the system to gain of ca. 97 kcal/mol, whereas the inclusion of diffuse functions on the heavy atoms render a modest gain of ca. 6 kcal/mol. When diffuse functions are added to hydrogens the stabilization of the present molecular system is negligible, i.e., ca. 1.1 kcal/mol. According to these results the use of MP2/6-311+G** level in the calculations of the thermodynamics of the system under study is fully justified. The thermodynamics of $\mathbf{I} \rightleftharpoons \mathbf{II}$ interconversion reaction was calculated at the MP2/6-311+G** // HF/6-31G** level. An approximate relative % concentration of $\mathbf{II}$ ca. 98%, points towards a very low concentration of conformer $\mathbf{I}$ in the gas phase and solution, in apparent disagreement with the experimental $^1\text{H-NMR}$ data²⁵ obtained in CS_2 , CHCl_3 or CPC. In fact, a ΔG° of ca. -2.39 kcal/mol indicates that the interconversion reaction is displaced to the conformer $\mathbf{II}$ formation. However, it is worth noting that the $^1\text{H-NMR}$ spectra are well resolved just below the coalescence temperature (-95°C) showing the typical pattern of two AB-systems for the H-2 protons. Over T_c , the peaks due to the A-part (α_i and β_j) are not resolved. Since our calculations were carried out in the gas phase and room temperature, the results are not strictly comparable. The NMR data would indicate that the interconversion reaction slow down enough at low temperature to observe the spectra of both conformers. The activation energy $E^\ddagger$ for the forward reaction ($\mathbf{I} \Rightarrow \text{TS}$) is ca. 6.2 kcal/mol, a value expected for a TS reactant alike. The calculations of the $\mathbf{I} \Rightarrow \mathbf{II}$ interconversion indicate that this reaction would be an exothermic process ($\Delta H^\circ \approx -2.5$ kcal/mol) with a negligible entropy change ($\Delta S = -0.49$ cal K^{-1} mol $^{-1}$; $\Delta S_{\text{exp}} = -0.52$ e.u.). It is likely that the exothermic nature of this reaction could come from the breaking of some important hyperconjugation interactions that stabilized the axial position of the ethyl group in $\mathbf{I}$ and that are lacking in $\mathbf{II}$.

Table 2. Energetics for conformers $\mathbf{I}$ and $\mathbf{II}$ of 4-ethyl-6-methyl-1,3-dithiane and their TS in the gas phase

	I	TS	II
ENERGY	ABSOLUTE	VALUES ^a	
$E_o^{(1)}$ [HF/6-31G**]	-1068.26698	-1068.25780	-1068.27133
$E_o^{(2)}$ [MP2/6-31G**]	-1069.52906	-1069.51896	-1069.53325
$E_o^{(3)}$ [MP2/6-311G**]	-1069.68403	-1069.67375	-1069.68824
$E_o^{(4)}$ [MP2/6-311+G**]	-1069.69371	-1069.68358	-1069.69760
$E_o^{(5)}$ [MP2/6-311++G**]	-1069.69546	-1069.68533	-1069.69947
ZPE	0.21411	0.21378	0.21405
H_{CORR}	0.22504	0.22415	0.22495
G_{CORR}	0.17851	0.17876	0.17864
S	97.949	95.540	97.467
$E_o^{(4)} + \text{ZPE}$	-1069.47960	-1069.46980	-1069.48355
$E_o^{(4)} + H_{\text{CORR}}$	-1069.25456	-1069.24565	-1069.25860
$E_o^{(4)} + G_{\text{CORR}}$	-1069.30109	-1069.29104	-1069.30491
	RELATIVE	VALUES	
$\Delta E_o^{(4)}$	-2.48		
ΔH°	-2.53		
$T\Delta S^\circ$	-0.14		
ΔG°	-2.39		
$E^\ddagger$ c	6.15		

a) Absolute values in hartrees ; b) Relative values in kcal/mol ; c) Activation energy for the forward $\mathbf{I} \rightarrow \text{TS}$ reaction

C) Solvent Effect

The solvent-solute interactions were obtained using PCM method. Solvents of low dielectric constants such as carbon disulfide ($\epsilon = 2.60$) and CHCl_3 ($\epsilon = 4.90$) formerly employed to obtain the $^1\text{H-NMR}$ data^{11,12} were tried. High polarity solvent such as dimethylsulfoxide (DMSO, $\epsilon = 46.70$) was also included but similar results were obtained. The free energy changes in solution were obtained, as usual, from $\Delta G^\circ_{\text{SOLN}} = \Delta G^\circ_{\text{GAS}} + \Delta \Delta G^\circ_{\text{Solvation}}$. The relative

free energies in solution for both conformers as well as their free energies of solvation are given in table 3. Free energies indicate that both conformers are almost equally solvated in all solvents used in the present work, most likely due to their similar dipole moments (see table 3). Solvents polarities do not produce significant changes in the conformers concentration. When these results are compared with the gas phase concentrations, it can be realized that it is likely that thermodynamic and solvent polarities do not control the $\mathbf{I} \rightleftharpoons \mathbf{II}$ interconversion reaction and that kinetic effect might be very important in this process allowing for conformer $\mathbf{I}$ formation in agreements with the NMR data²⁵. Table 4, shows the solvent effect on the activation energy for the forward reaction. Excepting DMSO, the solvent studied here are those used to obtained el NMR data^{11,12}.

Figure 2. Energy Profile for the $\mathbf{I} \rightleftharpoons \mathbf{II}$ process

Table 3. Free energies of solvation (ΔG°_s) and in solution ($\Delta G^\circ_{\text{SOLN}}$) for conformers $\mathbf{I}$, $\mathbf{II}$ and their TS in different solvent (kcal/mol)

Solvent	ΔG°_s			$\Delta \Delta G^\circ_s$ (a)	$\Delta G^\circ_{\text{SOLN}}$ (b)	E_a (Soln.)
	I	TS	II			
Gas						6.15
CS_2 ($\epsilon = 2.60$)	-2.35	-1.68	-2.21	0.14	-2.22	5.48
CHCl_3 ($\epsilon = 4.90$)	-4.59	-4.05	-4.40	0.19	-2.17	5.61
DMSO ($\epsilon = 46.70$)	-6.59	-5.89	-6.48	0.11	-2.25	5.45

a) $\Delta G^\circ_{\text{Solvation}}$ contains all non-electrostatic terms

b) Values from $\Delta G^\circ_{\text{Solvation}} = \Delta G^\circ_{\text{Gas}} + \Delta \Delta G^\circ_{\text{Solvation}}$

Table 4. Bond lengths ($\text{\AA}$), chemical shifts (δ in ppm) and $^1J_{\text{C-H}}$ (in Hz) for 1,3-dithiane^a

Distance	this work	ref 5	δ	ref.4	Exp ^c	$^1J_{\text{C-H}}$	$^1J_{\text{C-H}}^d$	Exp. ^d
C2-H _{ax}	1.094	1.094	4.5	4.3	4.2	151.0	150.5	154.2
C2-H _{eq}	1.092	1.092	3.4	3.8	3.5	142.0	144.6	146.2
C4,6-H _{ax}	1.097	1.097	3.1	3.0	3.0	133.4	134.4	137.3
C4,6-H _{eq}	1.093	1.093	2.8	2.7	2.8	133.5	135.1	132.9
C5-H _{ax}	1.095	1.095	2.2	2.0	1.9	127.6	128.6	130.2
C5-H _{eq}	1.099	1.099	2.2	2.1	2.2	119.8	120.8	127.4

a) Bond distances and δ values calculated in the gas phase at B3LYP/6-31G**

b) Calculated chemical shifts from ref. 4 at the PP/IGLO-III//PP/DZVP** level

c) Experimental values from ref. 4, obtained in CH_2Cl_2

d) Experimental values from ref.5. Data collected in CD_2Cl_2

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

Bond	I			II		
	distance (Å)	δ	$^1J_{\text{C-H}}$	distance	δ	$^1J_{\text{C-H}}$
C2 – H _{ax}	1.092	4.6	152.6	1.093	4.7	151.5
C2 – H _{eq}	1.092	3.4	140.3	1.092	3.3	141.4
C4 – H _{ax}	1.096	3.3	130.8	1.096	3.5	134.3
C6 – H _{ax}	1.095	3.4	135.6	1.096	4.1	133.9
C5 – H _{ax}	1.096	2.2	125.4	1.094	2.6	127.1
C5 – H _{eq}	1.100	2.2	118.6	1.101	2.0	117.8

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

C) NMR Spectra

It has been found above (see section B) that conformer **II** concentration would be ca. 98% in the gas phase and in solution. Conformer **I** would achieve a very small concentration. The C2–protons NMR spectra of the almost 1:1 mixture of conformers **I** and **II** would show two typical AB systems patterns. Thus, experimental spectra¹² at low temperature (below T_c , i.e., ca. -95°C) reveals two quartets centered at ca. 3.70 ppm. The higher field first one, has been assigned to the coupled signals of $\text{H}\alpha_{\text{eq}}$ (**II**) and $\text{H}\beta_{\text{eq}}$ (**I**) whereas the downfield signals would correspond to $\text{H}\alpha_{\text{ax}}$ (**I**) and $\text{H}\beta_{\text{ax}}$ (**II**). At $T > T_c$, the collapsed signals (not given in reference 12) for both α and β protons are to be seen as a couple doublets. In fact, the δ values for the α_{eq} and β_{eq} have been calculated at ca. 3.3 and 3.4 ppm, respectively. Under this condition ($T > T_c$) the low filed signals were calculated at 4.6 and 4.7 ppm. The AB system showing higher intensity must corresponds to conformer **I**, i.e., the conformer with the equatorial methyl group. In the present work the NMR properties were calculated at the equilibrium geometries derived at B3LYP/6-31G(d,p) level, whereas the GIAO magnetic shielding tensors were obtained at B3LYP/6-311+G(d,p). To test the reliability of this level of theory, chemical shifts for 1,3-dithietane were calculated (see table 5) and compared with previously reported values⁴ and the experimental data³⁻⁵. In a similar way, the one-bond $^{13}\text{C} - ^1\text{H}$ coupling constants were derived for the parent compound. A close correspondence between the theoretical and experimental values were also found^{4,5}. The calculated δ and $^1J_{\text{C-H}}$ NMR data for 1,3-dithiane correctly indicate the reverse Perlin effects at C2 and C5, and allow us to feel confident in predicting the ^1H –NMR spectra of both conformers. Table 6 shows both the predicted chemical shifts and the spin-spin $^{13}\text{C} - ^1\text{H}$ coupling constants for the conformers **I** and **II** of METDIT. The δ values for **I** and **II** depart slightly from the corresponding values found for 1,3-dithiane, whereas variations of ca. 2-3 Hz were found for the calculated $^1J_{\text{C-H}}$ coupling constants at the C2 and C5 implying that spin-spin coupling constants are more sensitive to the changes occurring in the heterocyclic ring upon substitution. In both conformers the results indicate that $^1J_{\text{C-Hax}} > ^1J_{\text{C-Heq}}$ and thereby a “reverse Perlin” effect is operating on both C2 and C5, likewise in the parent 1,3-dithiane. Additionally, no linear correlation between coupling constants and bond distances has been found. In fact, differences of ca. 12.3 and 10.1 Hz between $^1J_{\text{C2-Hax}}$ and $^1J_{\text{C2-Heq}}$ for conformers **I** and **II** respectively, are not reflected in the axial and equatorial C2 – H bond distances where the corresponding differences is less than 0.004 Å. The C5 – H_{eq} is ca. 0.004 Å longer than the axial C – H bond in conformer **I** and ca 0.007 Å in **II**. The experimental data found in the parent 1,3-dithiane supports well our findings in both conformers. Alabugin⁶ suggests that the elongation of the equatorial bond could be explained in terms of dominant $\sigma\text{C}_5 - \text{H}_{\text{eq}} \rightarrow \sigma^*\text{C} - \text{S}$ two-electron/two-orbital hyperconjugation interactions. In fact, the second order perturbation energy ($E^{(2)}$) for such interactions are ca. 6.79 and 6.57 kcal/mol for **I** and **II**, respectively. The reverse interactions, i.e., $\sigma\text{C} - \text{S} \rightarrow \sigma^*\text{C}_5 - \text{H}_{\text{eq}}$ are less favored ($E^{(2)} = 2.62$ and 2.92 kcal/mol for **I** and **II**, respectively). Accordingly, the delocalization of electron density from the donor $\sigma\text{C}_5 - \text{H}_{\text{eq}}$ to the acceptor $\sigma^*\text{C} - \text{S}$ orbital is large enough to induce an elongation of the equatorial C-H bond, in both conformers, producing a weakening of such a bond and thereby a smaller spin-spin coupling constant (see table 6). On the other hand, it is interesting to see how conformer **I** is apparently stabilized by a pair of hyperconjugation interactions. Considering the main interactions derived from the NBO analysis, it can be realized that the magnitudes of $\sigma\text{C}_6 - \text{H}_{\text{ax}} \rightarrow \sigma^*\text{C}_5 - \text{H}_{\text{ax}}$ interactions in **I** and **II** are ca. 3.33 and 0.59 kcal/mol, implying that the C4 – C5 – C6 group forming the upper part

of the chair force the methyl group to lie equatorially. In conformer **II** the $\text{C}_i - \text{H}_{\text{ax}}$ ($i = 5$ or 6) bonds are not antiperiplanar and the interaction energy is not important (0.59 kcal/mol). However, the $\sigma\text{C}_4 - \text{H}_{\text{ax}} \rightarrow \sigma^*\text{C}_5 - \text{H}_{\text{ax}}$ interaction occurring in **II** only and completely equivalent to the interaction found in **I**, possesses an energy of ca. 3.67 and thereby would produce a counterbalance of the stabilizing factor found in **I**. The interaction of the axial ethyl group and the sulfur lone pairs of electrons^{9,10} in **I** can be inferred from the $n_{\text{S}(3)} \rightarrow \sigma^*\text{C}_4 - \text{C}_{12}$ hyperconjugation interaction with a magnitude of ca.5.78 kcal/mol. This interaction does not exist in **II**. On the other hand, the axial position of the methyl group in **II** is clearly the result of the $n_{\text{S}(1)} \rightarrow \sigma^*\text{C}_6 - \text{C}_{20}$ interaction with an energy of ca. 5.09 kcal/mol and that is absent in **I**.

CONCLUSIONS

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

- 1.- The gas phase ab initio calculations indicate that the conformers **I** and **II** posses a chair $^5\text{C}_2$ and $^3\text{C}_5$, respectively
- 2.- In conformer **I**, the position of the alkyl groups exert a strong influence in the regular structure of the 1,3-dithiane ring, whereas in **II** the heterocyclic ring remains fairly undistorted.
- 3.- Stereoelectronic effects are important in stabilizing the structure $^5\text{C}_2$ of **I**.
- 4.- Calculations of the energies of both conformers at second order perturbation Møller- Plesset electron correlation level and employing a basis set that includes diffusion and polarization functions such as 6-311+G** are necessary for the good description of the energetics of this molecular system.
- 5.- The ab initio calculations indicate that conformer **II** would be the predominant species, in the gas phase and in low and high polarity solvents like CS_2 , CHCl_3 and DMSO.
- 6.- It is suggested that conformer **I** would achieve similar concentration to conformer **II** at ca. -90°C due to the kinetic effect controlling the interconversion reaction.
- 7.- The Transition state (TS) looks like conformer **I** since the methyl and ethyl groups bonded to C6 and C4, respectively remain in these positions. In fact, animation of the imaginary vibrational mode indicates that S1 is the only ring atom presenting a large departure from its original position. This reasoning is complemented with the calculated value of the Brönsted coefficient (β) of ca. 0.45 and TS would resembles the reactant.
- 8.- The study of the solvent effect on the activation energy for the forward (Reactant $\rightarrow$ TS) reaction shows that the activation energy does not lower appreciably in the solvents tried here.
- 9.- The good correlation between the calculated ^1H chemical shifts and one-bond spin- spin coupling constants for 1,3-dithiane at B3LYP/6-311+G**// B3LYP/6-31G** level and the experimental data, convinced us to predict the NMR properties for conformers **I** and **II**.
- 10.- In both conformers a reverse Perlin effect seems to be operating at C2 and C5. C4 and C6 protons cannot be analyzed since H atoms have been replaced by either a methyl or ethyl group.

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