Computational study of the anomeric effect in 2-[(4-substituted phenyl)seleno]-1,3-dithianes

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The conformational equilibrium of 1,3-dithiane-2-selenol and 2-[(4-substituted phenyl)seleno]-1,3-dithianes with NO_2, H, CH_3, OCH_3 and $N(CH_3)_2$ as substituents has been studied with PM3 and HF/6-31G*. Both methods confirm the preference for the axial conformers for these compounds with electron withdrawing groups enhancing this trend. The structural parameters have been used to assess the presence of the endo and exo anomeric effects in the axial conformers. NBO analysis for 1,3-dithiane-2-selenol has shown that delocalization involving the sulfur and selenium lone pairs and the C2−Se anti-bonding orbital plays a role in stabilizing the axial conformer for this compound. Single point energy calculations in solution with HF/6-31G*//HF/6-31G* mimic the experimental results to a great extent.

Introduction

One of the basic principles of conformational analysis, in six membered rings, is the equatorial preference of substituents over the axial position.[1] In 1955, J. T. Edward reported that the axial conformer of 2-methoxypyranose is more stable than the equatorial conformer (Scheme 1) contrary to general expectations.[2] This axial preference was termed the 'anomeric effect' and has been the subject of many investigations since then. Later, it was seen that the anomeric effect is not only observed in six membered rings or carbohydrates. A generalized anomeric effect was defined as 'the preference of the gauche position over the anti in segments R−X−A−Y where X is an atom that has lone pairs and Y is more electronegative than A.[3] This axial preference was interpreted in terms of stabilizing orbital interactions between n_x and σ^*_{A-Y}. A similar situation is present in the axial conformer of 2-methoxypyranose where the electrons are donated from the non-bonding orbital of O1 to the anti-bonding orbital of the C2−O3 bond. This interaction is optimum when the donor and acceptor fragments lie antiperiplanar to each other. The 'exo anomeric effect', defined by R. U. Lemieux and co-workers[4] describes the delocalization of electron density from the exocyclic oxygen to the anti-bonding orbital of C2−O1 (Scheme 1). On the other hand the endo
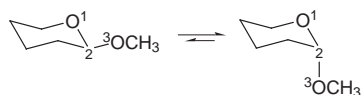
Scheme 1 The conformational equilibrium for 2-methoxypyranose

anomeric effect is defined as the delocalization of electrons from n_O to the σ^*_{C2-O3}.

Although several theoretical and experimental investigations on the anomeric effect are present in the literature for systems containing first and second row elements, similar work for selenium as well as for other third row elements is scarce.[5]

In 1985, NMR spectroscopic and X-ray crystallographic investigations on 2-[(4-methoxyphenyl)seleno]-1,3-dithiane and 2-[(4-trifluoromethylphenyl)seleno]-1,3-dithiane by Pinto *et al.* indicated that these compounds exist in the conformation in which the arylseleno moiety adopts an axial orientation.[6] On the other hand, the conformational analysis of 2-[(4-substituted phenyl)seleno]-1,3-dithianes with NO_2, CF_3, H, OCH_3 and

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$N(CH_3)_2$ substituents was carried out and the conformational free energies were evaluated by NMR analysis to produce systematic evidence for the role of stabilizing orbital interactions.[7] The observed anomeric behavior for these compounds was interpreted in terms of the interaction between n_S and σ^*_{C-Se} orbitals. It was reported that as the electron withdrawing ability of the substituent increases, the proportion of the axial conformer increases and lowers the energy of σ^*_{C-Se}, causing an important interaction between n_S and σ^*_{C-Se}. Pinto *et al.* reported the conformational equilibria of 2-[(4-substituted phenyl)seleno]-1,3-dithianes with NO_2, CF_3, Cl, F, H, CH_3, $O(CH_3)$ and $N(CH_3)_2$ substituents and provided additional evidence for n_S–σ^*_{C-Se} stabilizing orbital interactions and the existence of the anomeric effect in the S−C−Se fragments.[8] Evidence for the negative charge on Se is also given. The solvent dependence of some selected compounds showed no correlation with the relative permittivity and the behavior of the compounds in solution is interpreted in terms of dominance of stabilizing orbital interactions over the electrostatic interactions.[9] Plots of ln K *vs.* $1/T$ at low and high temperatures have been used to evaluate the enthalpic and entropic contributions to the S−C−Se anomeric effect for 2-[(4-methoxyphenyl)seleno]-1,3-dithiane in toluene, methylene chloride and acetone. The anomalous stability of the least polar axial conformer in solution is discussed in terms of specific solute–solvent interactions: it may be that due to the high internal pressure exerted by the solvent the axial conformer with the small molar volume is dominant in the more polar solvent or that the most polar double-bond/no-bond model is stabilized more in polar solvents. Additional evidence for the third row anomeric effect of selenium was given by examining 2-phenylthio- and 2-phenylseleno-1,3-diselenanes by ^{13}C and ^{77}Se NMR spectroscopy and a significant anomeric effect was detected.[10] Later, X-ray crystallographic analysis and the ^{77}Se NMR spectrum for selenium coronands provided evidence for a Se−C−Se anomeric effect.[11,12] The existence and origin of second row anomeric interactions have also been questioned experimentally based upon the absence of a conformational deuterium isotope effect in 2-deutero-5,5-dimethyl-1,3-dithiane. The authors proposed that π-donation by sulfur may not be the cause for the preferred axial orientation of electronegative substituents at the C2 atom of dithianes because of the absence of n_S–$\sigma^*_{C-H(D)}$ hyperconjugative interactions.[13]

The first theoretical studies on anomeric effects involving selenium were carried out by Salzner and Schleyer.[14] The MP4SDTQ/6-31G*(Se-Hu)//HF/6-31G*(Se-Hu) + ZPE level was used to model the different conformations of $CH_2(SeH)_2$.

The preferred C_2 conformation of $CH_2(SeH)_2$ and the 3p(Se)−σ*(C-Se) orbital interaction were in accord with weak hyperconjugation. Furthermore, selenium is positively charged even when S and Se are bound to the same C center. Salzner and Schleyer[15] investigated the origin of the anomeric effect in methanediol and its sulfur, selenium and tellurium derivatives by *ab initio* calculations through the MP2 level and by the natural bond orbital (NBO) analyses of Hartree–Fock wave functions: the gauche preference of SH, SeH and TeH substituents was found to decrease but not to disappear totally.

Additional theoretical evidence of selenium's anomeric effect was given by Pinto *et al.*[16] in their study of the torsional behavior in $HSCH_2SH$, $HSeCH_2SeH$, $HSCH_2SeH$, $HTeCH_2TeH$, $HSCH_2TeH$ and $HSeCH_2TeH$. At the 3-21G* level of computation anomeric interactions with tellurium have been found to be small but nonetheless present.

This work presents a theoretical semiempirical and *ab initio* study of 2-[(4-substituted phenyl)seleno]-1,3-dithianes which aims to shed light on the existence and origin of the anomeric effect in these compounds with NO_2, H, CH_3, OCH_3 and $N(CH_3)_2$ as substituents. The relative position of the substituents as well as the effect of the substituents on the relative position of the phenyl group is also discussed. Finally, the effect of the medium on the conformational equilibria is analyzed.

Computational methods

The conformational equilibrium of 1,3-dithiane-2-selenol and 2-[(4-substituted phenyl)seleno]-1,2-dithiane with NO_2, H, CH_3, OCH_3 and $N(CH_3)_2$ substituents was investigated computationally with the semiempirical PM3 method and at the Hartree–Fock level with the 6-31G* basis set.

The conformational search around all the single bonds was performed using the SPARTAN 4.0 program[17] with the MM2 option. The two low energy conformers located with MM2 were further fully optimized with the PM3 method and then at HF/6-31G* level using the GAUSSIAN 94[18] program. The optimized geometries (PM3) were taken to be the initial input geometries for the HF/6-31G* level. In cases where the stationary points located as global minima at the HF/6-31G* level were different from the global minima located with the PM3 method, optimizations at the HF/6-31G* level were carried out on the optimized structures (PM3) in order to test their energetics. The frequencies of all the compounds studied were evaluated with both methods in order to verify that the minimum energy conformers were stationary points. The bond lengths, bond angles and dihedral angles were checked to look for evidence for the anomeric effect. The thermodynamic properties ($\Delta H°$, $\Delta G°$, $\Delta S°$) for the conformational equilibrium reactions were used to determine a trend between the position of the substituent (axial *versus* equatorial) and its nature.

The natural bond orbital (NBO) method[19] was used to analyze and understand energy stabilizations which determine molecular conformations. Energy stabilizations were examined in terms of delocalizations of electron density from almost filled orbitals to almost empty neighboring orbitals. The energy associated with the anti-bonds was determined by deleting those orbitals from the basis set and recalculating the total energy to evaluate the associated variational energy lowering. The NBO method has been shown[14,15] to be a useful tool for the analysis of the type of interactions involved in the anomeric effect where the delocalization is a lone pair—σ* density shift. In the present work, delocalizations with sulfur and selenium lone pairs as donors were considered.

Structures optimized at the HF/6-31G* level of theory were analyzed in a polar medium (ε 2.4) with single point solvent calculations where the solvent was treated as a relative permittivity continuum and the shape of the cavity is Onsager's spherical cavity.[20] The keywords 'dipole' and 'volume' are used
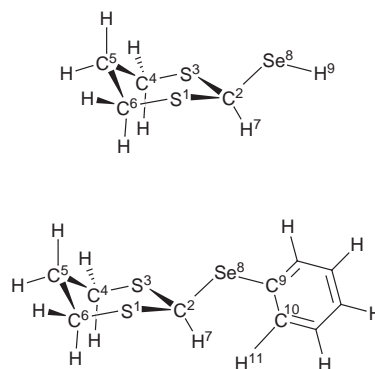
Fig. 1 The numbering system used for 1,3-dithiane-2-selenol and in 2-(phenylseleno)-1,3-dithiane

to specify the medium and the radius of the Onsager's spherical cavity respectively.

Results and discussion

The following numbering system is used for the axial and equatorial conformers of the compounds studied: **1** for 1,3-dithiane, **2-ax** and **2-eq** for 1,3-dithiane-2-selenol, **3-ax** and **3-eq** for 2-[(4-nitrophenyl)seleno]-1,3-dithiane, **4-ax** and **4-eq** for 2-(phenylseleno)-1,3-dithiane, **5-ax** and **5-eq** for 2-[(4-methylphenyl)seleno]-1,3-dithiane, **6-ax** and **6-eq** for 2-[(4-methoxyphenyl)seleno]-1,3-dithiane, **7-ax** and **7-eq** for 2-[(4-dimethylaminophenyl)seleno]-1,3-dithiane respectively. The numbering system used throughout the discussion is given in Fig. 1. The geometrical parameters and dipole moments for the optimized conformers are given in Table 1–Table 6. The Mulliken charges for the axial and equatorial conformers for compounds **1**–**7** are displayed in Fig. 2. The NBO energies for 1,3-dithiane-2-selenol are collected in Table 7. Table 8 shows the energetics of the conformational equilibrium for the compounds studied.

Structures
Experimental and theoretical studies have confirmed the preference for the chair conformation of 1,3-dithiane.[21] As seen from Table 1, due to the large size of sulfur, the S1−C2−S3 angle shows deviations from a pure tetrahedral arrangement. The conformational behavior of 1,3-dithiane with a small substituent, namely Se−H, has been analyzed before dealing with 2-[(4-substituted phenyl)seleno]-1,3-dithianes. With the PM3 method, in **2-eq** the C2−S1 and C2−S3 bond lengths are equal to each other whereas in **2-ax** the C2−S1 bond shortens and the C2−S3 bond lengthens (Table 1) in comparison to the same bonds in **2-eq**. The variation in length for the same bonds is not as significant at the HF/6-31G* level as at PM3 level of theory (Table 1). In compound **2-ax** the S1−C2−Se angle belonging to the short C2−S1 bond is larger than in **2-eq**. The S1−C2−Se bond angle varies from 96.2° in **2-eq** to 112.5° in **2-ax**; the same angle increases from 108.3° in **2-eq** to 114.1° in **2-ax**. In **2-ax**, the H7−C2−Se−H9 dihedral angle is 75.6° when the PM3 method is used and 73.5° at the HF/6-31G* level of theory. In **2-eq** the H7−Se−C2−H9 dihedral angle is 0.0° with the PM3 method and −31.5° at the HF/6-31G* level; in both cases the total dipole moment is smaller than in the other conformers generated by rotation of the Se−H bond around C2−Se.

The observed changes in bond lengths and bond angles in the axial conformer with respect to the equatorial conformer may be explained by the delocalization of the electrons from the lone pairs on Se and S. In **2-ax**, the axial lone pairs on S, Se and C2 are antiperiplanar to each other and the electrons on S move towards the other electronegative atom, Se. This delocalization is expected to increase the double bond character of the C2−S1 and C2−S3 bonds. On the other hand, in **2-ax**, due to the gauche arrangement of H7 and H9 one of the lone pairs of
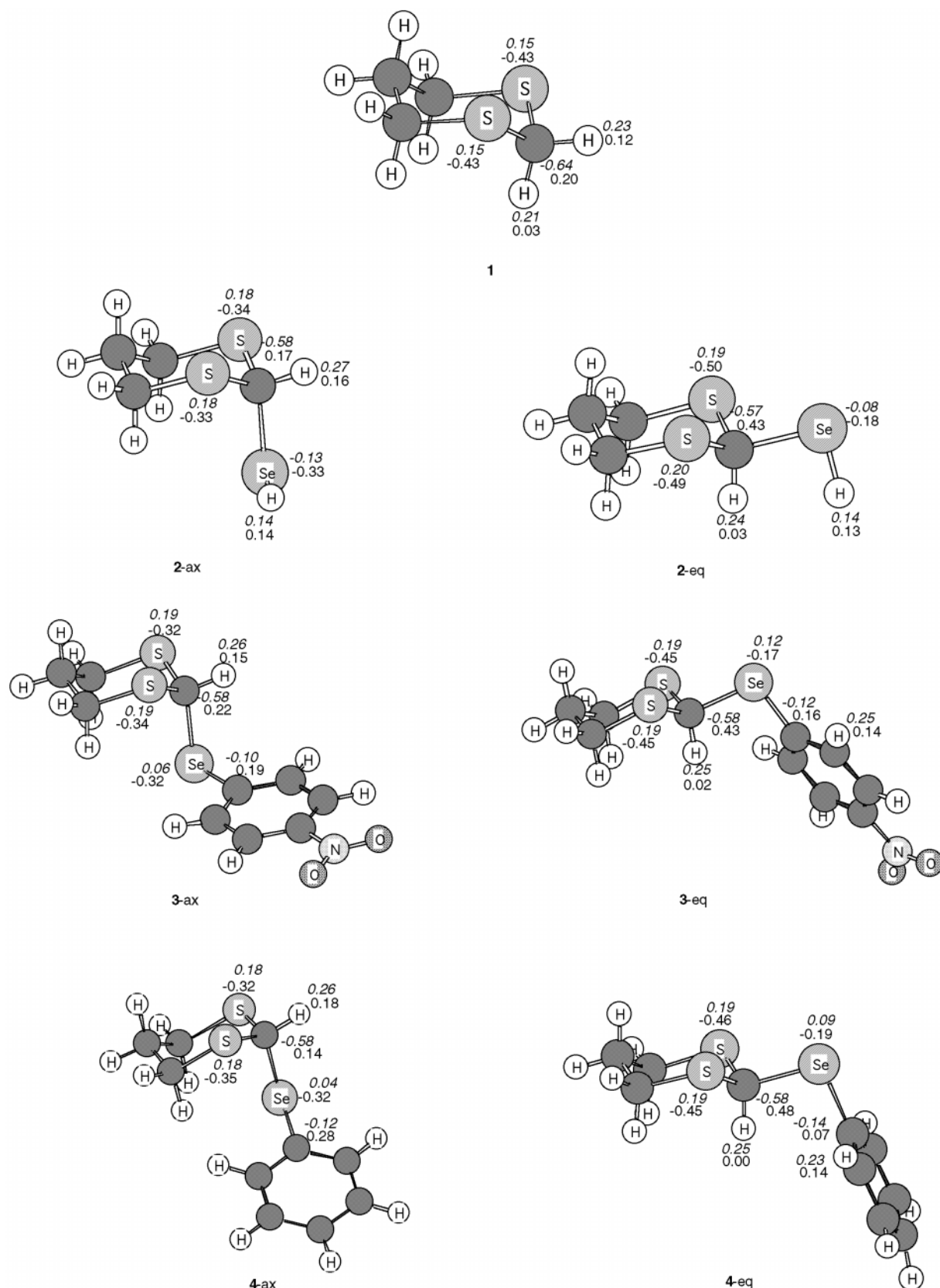
Fig. 2 Structures for the optimized axial and equatorial conformers (HF/6-31G*) for dithiane, 1,3-dithiane-2-selenol, and NO₂, H, CH₃, OCH₃-N(CH₃)₂ substituted 2-(phenylseleno)-1,3-dithianes. Mulliken charges on the atoms of interest are given in italics for HF/6-31G* and upright for PM3.

Se, the C2 and S3 atoms are also antiperiplanar to each other. A delocalization from the lone pairs on Se towards the C2–Se bond is expected to shorten the C2–Se bond and to elongate the C2–S3 bond. Actually, these two effects known as the endo anomeric effect (for the delocalization from the sulfur lone pairs towards Se) and the exo anomeric effect (for the delocal-

ization from the lone pairs on Se towards the S in the ring) oppose each other. The elongation of only one of the S–C bonds, rather than two, in **2-ax** is an indication of the presence of both effects in this compound. On the other hand, the C2–Se bond is longer in **2-ax** than in the **2-eq** confirming the dominance of the endo anomeric effect in this compound. The bond

Table 1 Selected bond lengths (Å), bond angles (°), dihedral angles (°) and dipole moments (D) of 1,3-dithiane and 1,3-dithiane-2-selenol

	1 PM3	1 HF/6-31G*	2-ax PM3	2-eq PM3	2-ax HF/6-31G*	2-eq HF/6-31G*
C2–S1	1.809	1.810	1.767	1.783	1.808	1.811
C2–S3	1.809	1.810	1.792	1.783	1.813	1.814
C2–Se	—	—	1.938	1.922	1.972	1.959
Se–H9	—	—	1.476	1.480	1.468	1.467
C2–H7	1.107	1.081	1.109	1.103	1.078	1.079
S1–C2–Se	—	—	112.5	96.2	114.1	108.3
S3–C2–Se	—	—	90.6	96.2	109.0	107.2
S1–C2–S3	116.9	115.2	121.4	118.4	114.5	115.1
C2–Se–H9	—	—	104.7	101.1	95.9	94.3
H7–C2–Se–H9	—	—	75.6	0.1	73.5	−31.5
Dipole	2.53	2.43	2.27	3.11	2.27	3.55
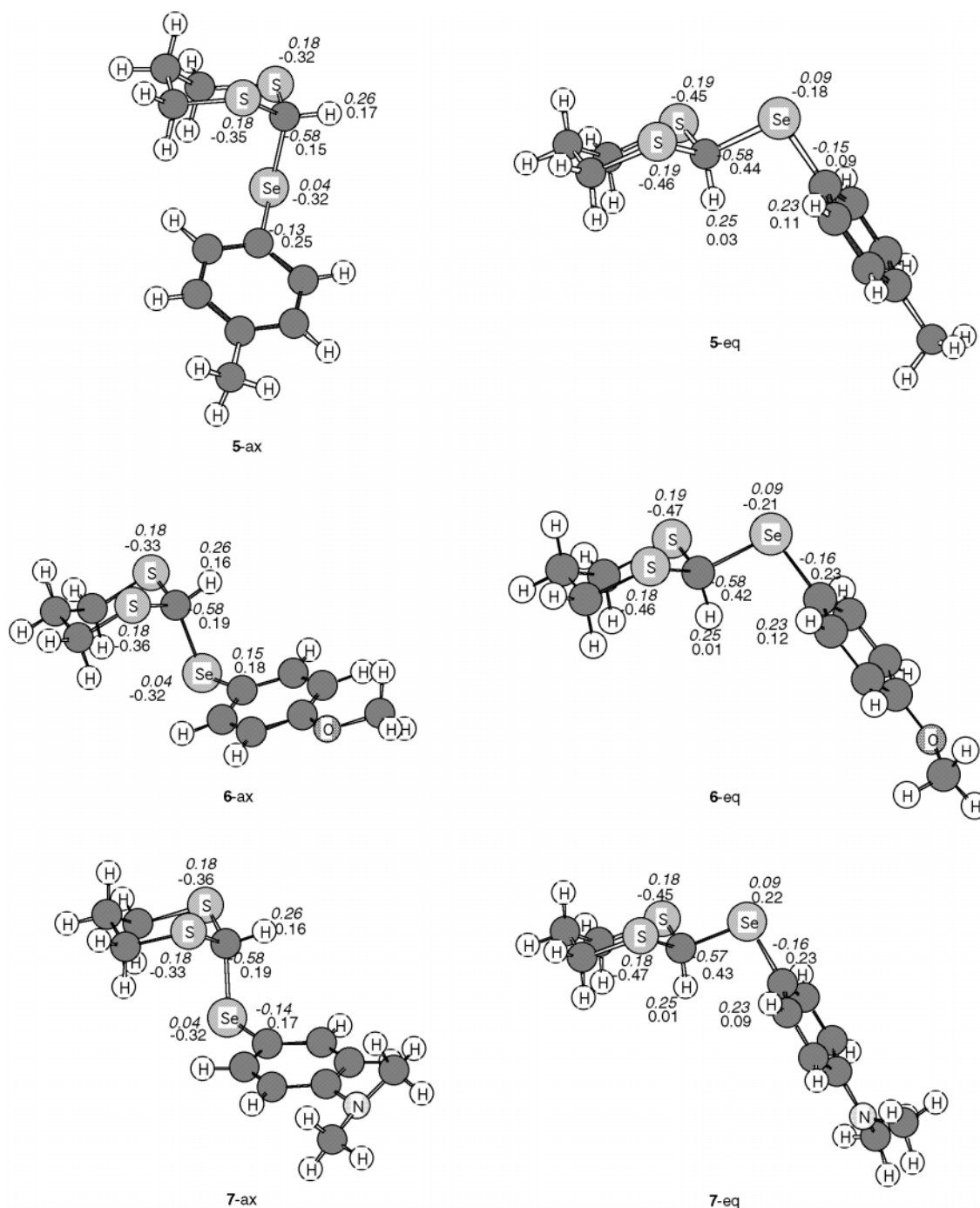
Fig. 2 (*Contd.*)

length and bond angle variations can be interpreted in terms of the partial sp² character gained by C2. The same stabilizing effect is explained in the literature by the double bond/no-bond

model.[22] This model explains the anomeric effect in terms of stabilizing orbital interactions taking place between the lone pair on the heteroatom and the anti-bonding acceptor bond. In

Table 2 Selected bond lengths (Å), bond angles (°), dihedral angles (°) and dipole moments (D) of 2-[(4-nitrophenyl)seleno]-1,3-dithiane

	3-ax PM3	3-eq PM3	3-ax HF/6-31G*	3-eq HF/6-31G*
C2–S1	1.763	1.781	1.808	1.812
C2–S3	1.795	1.781	1.812	1.812
C2–Se	1.957	1.930	1.976	1.961
Se–C9	1.885	1.886	1.914	1.914
C2–H7	1.109	1.111	1.079	1.079
S1–C2–Se	116.5	96.7	114.3	107.3
S3–C2–Se	87.6	96.7	109.0	107.3
S1–C2–S3	121.7	119.0	114.4	115.3
C2–Se–C9	112.8	104.4	99.2	97.7
H7–C2–Se–C9	72.5	−0.2	53.2	0.0
C2–Se–C9–C10	−163.4	0.3	−82.4	90.6
Dipole	7.20	7.00	5.49	4.85

Table 3 Selected bond lengths (Å), bond angles (°), dihedral angles (°) and dipole moments (D) of 2-(phenylseleno)-1,3-dithiane

	4-ax PM3	4-eq PM3	4-ax HF/6-31G*	4-eq HF/6-31G*
C2–S1	1.763	1.782	1.810	1.812
C2–S3	1.797	1.782	1.813	1.812
C2–Se	1.956	1.928	1.974	1.960
Se–C9	1.878	1.889	1.911	1.912
C2–H7	1.108	1.112	1.079	1.078
S1–C2–Se	116.3	97.2	114.3	107.6
S3–C2–Se	88.2	97.3	109.5	107.6
S1–C2–S3	120.7	118.8	114.0	115.1
C2–Se–C9	110.6	104.2	99.4	98.1
H7–C2–Se–C9	81.0	0.2	50.9	0.0
C2–Se–C9–C10	83.8	179.7	−84.0	90.7
Dipole	2.75	2.77	1.89	3.73

Table 4 Selected bond lengths (Å), bond angles (°), dihedral angles (°) and dipole moments (D) of 2-[(4-methylphenyl)seleno]-1,3-dithiane

	5-ax PM3	5-eq PM3	5-ax HF/6-31G*	5-eq HF/6-31G*
C2–S1	1.763	1.781	1.810	1.812
C2–S3	1.797	1.781	1.814	1.812
C2–Se	1.956	1.928	1.974	1.960
Se–C9	1.877	1.888	1.909	1.910
C2–H7	1.108	1.115	1.079	1.078
S1–C2–Se	116.2	97.3	114.3	107.6
S3–C2–Se	88.2	97.3	109.6	107.6
S1–C2–S3	120.7	118.8	113.9	115.1
C2–Se–C9	110.6	104.1	99.5	98.2
H7–C2–Se–C9	81.1	0.2	50.8	0.0
C2–Se–C9–C10	−99.9	179.6	−84.4	90.8
Dipole	2.89	2.75	2.05	3.97

Table 5 Selected bond lengths (Å), bond angles (°), dihedral angles (°) and dipole moments (D) of 2-[(4-methoxyphenyl)seleno]-1,3-dithiane

	6-ax PM3	6-eq PM3	6-ax HF/6-31G*	6-eq HF/6-31G*
C2–S1	1.763	1.782	1.810	1.812
C2–S3	1.797	1.782	1.814	1.812
C2–Se	1.956	1.930	1.974	1.960
Se–C9	1.873	1.877	1.905	1.906
C2–H7	1.108	1.103	1.079	1.078
S1–C2–Se	116.2	96.5	114.3	107.6
S3–C2–Se	88.2	96.0	109.6	107.6
S1–C2–S3	120.7	118.2	113.9	115.1
C2–Se–C9	110.5	104.4	99.8	98.5
H7–C2–Se–C9	81.0	−0.9	51.1	−2.3
C2–Se–C9–C10	−99.5	85.9	−85.8	−91.9
Dipole	2.89	3.01	1.28	4.22

Table 6 Selected bond lengths (Å), bond angles (°), dihedral angles (°) and dipole moments (D) of 2-[(4-dimethylaminophenyl)seleno]-1,3-dithiane

	7-ax PM3	7-eq PM3	7-ax HF/6-31G*	7-eq HF/6-31G*
C2–S1	1.764	1.782	1.811	1.812
C2–S3	1.797	1.782	1.814	1.812
C2–Se	1.955	1.930	1.974	1.961
Se–C9	1.872	1.876	1.905	1.906
C2–H7	1.108	1.103	1.079	1.078
S1–C2–Se	116.2	96.3	114.3	107.6
S3–C2–Se	88.4	96.3	109.7	107.6
S1–C2–S3	120.5	118.2	113.9	115.1
C2–Se–C9	110.5	104.3	99.6	98.5
H7–C2–Se–C9	80.8	0.0	50.7	0.9
C2–Se–C9–C10	−84.6	92.0	−84.8	91.0
Dipole	3.32	2.46	2.64	4.04

this work, we have used the NBO Fock matrix (HF/6-31G*) to provide an alternative explanation for the anomeric effect in compounds **2-ax** and **2-eq**. In compound **2-ax**, the main stabilization is due to the delocalization from the lone pairs on S1 and S3 towards C2–Se (Table 7). Donation of electrons into the σ* orbital should lengthen the C2–Se bond. Indeed, Table 1 shows an elongation of 0.013 Å for the C2–Se bond in **2-ax** in comparison with the same bond in **2-eq**. In both conformers the lone pairs on S1 and S3 are delocalized towards C2–S1 and C2–S3. Actually, minor differences in the C2–S1 and C2–S3 bond lengths for these compounds are detected. As expected, the sum of the HF/6-31G* delocalization energies, for all the n–σ* shifts, shows that the stabilization is greater for the lowest energy **2-ax** conformer (82.77 kcal mol^{-1}) in comparison to the **2-eq** conformer (76.33 kcal mol^{-1}).

The computational results for 2-[(4-substituted phenyl)-seleno]-1,3-dithianes have common features (Table 2–Table 6). In the equatorial conformers for compounds **2–7** the C2–S1 and C2–S3 bond lengths are equal. This symmetry is not present in the axial conformers; one of the C–S bonds shortens while the other one lengthens. The bond lengths calculated at the HF/6-31G* level are generally longer than the ones calculated when the PM3 method is used; but bond length variations are more significant when the latter method is used. In the equatorial conformers, the S3–C2–Se and S1–C2–Se bond angles are equal. In the axial conformers, the value of the S–C2–Se angle corresponding to the shortened C2–S bond increases. The widening of this angle is more pronounced when the PM3 method is used. It is worth noting that these interactions take place regardless of the orientation of the phenyl ring, they are caused by the antiperiplanarity of the C2–Se bond and the lone pairs of sulfur. The axial conformers possess an additional stabilizing effect due to the orientation of the group attached to Se. For all the compounds studied the Se–C10 bond is gauche to the C2–H7 bond.

The orientation of the phenyl group with respect to the

dithiane ring depends on whether the substituent occupies the axial or the equatorial position. When the PM3 method is used, the phenyl group is oriented perpendicular to the C2–Se bond in the axial conformers except for X = NO$_2$ where this group is coplanar with the C2–Se bond. The π electrons of the phenyl group are in resonance with the NO$_2$ group stabilizing this structure. In the equatorial conformers, the phenyl group is coplanar with C2–Se except for the N(CH$_3$)$_2$ and OCH$_3$ substituents (Fig. 1).

In compound **4-eq**, the coplanar arrangement of the phenyl group with the C2–H7 bond causes H7 and H11 to be 1.783 Å away from each other. However, the charges on H7 and H11 are so small (0.00e and 0.14e respectively) that the expected repulsive interactions are small. The preference of this coplanar conformation of the phenyl group with respect to the C2–H7 bond, in the equatorial conformers may be rationalized by a Se···H–C long range interaction. The distance between Se and H11 is approximately 2.81 Å, shorter than the distance

Table 7 NBO stabilization energies (kcal mol^{-1}) for 1,3-dithiane-2-selenol

	2-ax			2-eq	
	LP (1) S1 $\longrightarrow$ RY* C2	0.78		LP(1) S1 $\longrightarrow$ RY* C2	1.20
	LP(1) S1 $\longrightarrow$ BD* C2–S3	3.15		LP(1) S1 $\longrightarrow$ BD* C2–S3	2.09
	LP(1) S1 $\longrightarrow$ BD* C2–Se	2.28		LP(1) S1 $\longrightarrow$ BD* C2–H7	1.37
	LP(1) S1 $\longrightarrow$ BD* C5–C6	1.55		LP(1) S1 $\longrightarrow$ BD* C5–C6	1.05
	LP(1) S1 $\longrightarrow$ BD* C6–H$_{ax}$	0.89		LP(1) S1 $\longrightarrow$ BD* C6–H$_{ax}$	1.55
	LP(2) S1 $\longrightarrow$ RY* C2	0.74		LP(2) S1 $\longrightarrow$ RY* C2	0.67
	LP(2) S1 $\longrightarrow$ BD* C2–S3	6.30		LP(2) S1 $\longrightarrow$ BD* C2–S3	8.38
	LP(2) S1 $\longrightarrow$ BD* C2–Se	9.49		LP(2) S1 $\longrightarrow$ BD* C2–H7	5.35
	LP(2) S1 $\longrightarrow$ BD* C5–C6	5.05		LP(2) S1 $\longrightarrow$ BD* C5–C6	5.77
	LP(2) S1 $\longrightarrow$ BD* C5–H$_{eq}$	0.80		LP(2) S1 $\longrightarrow$ BD* C5–H$_{eq}$	0.80
	LP(2) S1 $\longrightarrow$ BD* C6–H$_{ax}$	5.30		LP(2) S1 $\longrightarrow$ BD* C6–H$_{ax}$	4.89
	SUM S1 LP $\longrightarrow$ BD*	36.33		SUM S1 LP $\longrightarrow$ BD*	33.12
	LP(1) S3 $\longrightarrow$ BD* C2–S1	2.82		LP(1) S3 $\longrightarrow$ RY* C2	0.67
	LP(1) S3 $\longrightarrow$ BD* C2–Se	2.17		LP(1) S3 $\longrightarrow$ BD* C2–S1	2.21
	LP(1) S3 $\longrightarrow$ BD* C4–C5	1.47		LP(1) S3 $\longrightarrow$ BD* C2–H7	1.15
	LP(1) S3 $\longrightarrow$ BD* C4–H$_{ax}$	1.02		LP(1) S3 $\longrightarrow$ BD* C4–C5	1.23
	LP(2) S3 $\longrightarrow$ RY* C2	0.88		LP(1) S3 $\longrightarrow$ BD* C4–H$_{ax}$	1.32
	LP(2) S3 $\longrightarrow$ BD* C2–S1	6.27		LP(2) S3 $\longrightarrow$ BD* C2–S1	7.66
	LP(2) S3 $\longrightarrow$ BD* C2–Se	7.21		LP(2) S3 $\longrightarrow$ BD* C2–H7	5.37
	LP(2) S3 $\longrightarrow$ BD* C4–C5	5.06		LP(2) S3 $\longrightarrow$ BD* C4–C5	5.68
	LP(2) S3 $\longrightarrow$ BD* C4–H$_{ax}$	5.47		LP(2) S3 $\longrightarrow$ BD* C4–H$_{ax}$	5.00
	LP(2) S3 $\longrightarrow$ BD* C5–H$_{eq}$	0.69		LP(2) S3 $\longrightarrow$ BD* C5–H$_{eq}$	0.69
	LP(2) S3 $\longrightarrow$ BD* Se–H9	1.92			
	SUM S3 LP BD*	34.98		SUM S3 LP $\longrightarrow$ BD*	30.98
	LP(1) Se $\longrightarrow$ BD* C2–S1	1.67		LP(1) Se $\longrightarrow$ BD* C2–H7	1.02
	LP(1) Se $\longrightarrow$ BD* C2–H7	0.65		LP(2) Se $\longrightarrow$ BD* C2–S1	5.40
	LP(2) Se $\longrightarrow$ RY* C2	0.55		LP(2) Se $\longrightarrow$ BD* C6–S1	2.37
	LP(2) Se $\longrightarrow$ BD* C2–S1	4.36		LP(2) Se $\longrightarrow$ BD* C2–H7	0.87
	LP(2) Se $\longrightarrow$ BD* C2–H7	3.39		LP(2) Se $\longrightarrow$ BD* C2–S3	0.94
	LP(2) Se $\longrightarrow$ BD* C6–H$_{ax}$	0.84		LP(2) Se $\longrightarrow$ BD* S3–C4	0.98
	SUM Se $\longrightarrow$ BD*	11.46		SUM Se LP $\longrightarrow$ BD*	12.23

stated by Iwaoka and Tomado[23] for a significant Se$\cdots$H–C electrostatic, long range interaction. On the other hand, the charges on Se and H11 are opposite in sign and a Se$\cdots$H–C long range interaction is likely to occur. The same explanations hold true for the compounds **3-eq** and **5-eq**.

The orientation of the phenyl group, with respect to the dithiane in the axial conformers, is the same with both methods: the least crowded perpendicular position is preferred. In the equatorial conformers, for all the substituents, the phenyl group is oriented perpendicular to the C2–Se bond contrary to the general trend observed with the PM3 method. The Se$\cdots$H–C long range interaction is unlikely to occur since at the HF/6-31G* level, Se and H11 have charges of similar sign.

According to PM3 results, the position of the phenyl group in the equatorial position is different for the two electron-donor groups, OCH$_3$ and N(CH$_3$)$_2$, in that the phenyl ring is perpendicular to the H7–C2 bond, contrary to the results for the other substituents with this method. Electron flow towards to C2–Se bond shortens this bond to 1.873 Å and 1.872 Å respectively. This distance is of 1.885 Å for X = NO$_2$ and 1.878 Å for X = H. Electron donation shortens the C2–Se bond, the H7 and H2 atoms approach each other, causing steric crowding and the phenyl group does not adopt the conformation where it would be coplanar with the C2–Se bond.

The position of the substituent with respect to the ring is another point of interest. The orientation of the NO$_2$, CH$_3$ and O(CH$_3$) groups in compounds **3**, **5** and **6** is described similarly with both methods. In **3-ax** and **3-eq**, the NO$_2$ substituent is in the same plane with the phenyl ring, allowing stabilizing interactions between the p orbitals of the phenyl ring and the lone pairs of NO$_2$. In compounds **5-ax** and **5-eq**, the hydrogens of the CH$_3$ group are staggered with the carbon atom of the phenyl group minimizing their repulsive interactions. For **6-ax** and **6-eq**, the carbon of the methoxy group is coplanar with the phenyl group allowing the lone pairs on oxygen to overlap with the p orbitals of the phenyl ring. In the case of the

N(CH$_3$)$_2$ substituent, the orientation of the substituent is described differently by the two methods. When the PM3 method is used, the carbon atoms of the methyl groups are staggered, the lone pair of nitrogen is in the same plane as the p orbitals of the phenyl group and the hydrogens of the methyl groups although staggered are very close to the ring hydrogens (1.78 Å). At the HF/6-31G* level, the lone pairs on N are not in the same plane as the phenyl group and the repulsion of the hydrogen atoms is minimized.

Charges

The Mulliken charge distribution shows similarities for the compounds studied (Fig. 2). With the PM3 method, the negative charge on Se is greater in the axial conformers ($\sim$−0.32e) than in the equatorial conformers ($\sim$−0.19e) due to the delocalization of electrons from the S atoms towards Se in the axial compounds. At the HF/6-31G* level, the charge on Se is very small: 0.04e for the axial and 0.09e for the equatorial conformers respectively. Although this difference is small it is consistent for all the substituents confirming the presence of the endo anomeric effect in these compounds.

Energetics

In a vacuum, with both methods, for all the substituents, the least polar axial conformers are more stable than the equatorial conformers. When the PM3 method is used, $\Delta(\Delta_f H)$ defined as $\Delta_f H_{ax} - \Delta_f H_{eq}$ and ΔG calculated as $\Delta(\Delta_f H) - T(S_{ax} - S_{eq})$ have been compared with the experimental data of Pinto *et al.*[7] Although the experimental trend has been reproduced qualitatively with $\Delta(\Delta_f H)$, a better quantitative agreement is observed when the changes in entropy are taken into account. The negative sign in the entropies is indicative of the fact that the equatorial conformer is more disordered than the axial conformer. Notice also that (Table 8) ΔS values follow the same trend as $\Delta(\Delta_f H)$s: the substituent in the equatorial position is more extended than in the axial position and is expected to

Table 8 Energetics (kcal mol^{-1}) for the conformational equilibrium for 2-[(4-X-substituted phenyl)seleno]-1,3-dithianes where X = NO$_2$, H, CH$_3$, OCH$_3$, N(CH$_3$)$_2$ and 1,3-dithiane-2-selenol

Substituent	PM3 $\Delta(\Delta_f H)^a$ ($\varepsilon = 1$)	PM3 $\Delta S/10^{-3}$ ($\varepsilon = 1$)	PM3 ΔG^b ($\varepsilon = 1$)	HF/6-31G* ΔH^c ($\varepsilon = 1$)	HF/6-31G* $\Delta S/10^{-3}$ ($\varepsilon = 1$)	HF/6-31G* ΔG^d ($\varepsilon = 1$)	HF/6-31G* ΔE^e ($\varepsilon = 2.4$)	$\Delta G_{exp}{}^f$ ($\varepsilon = 3.0$)
NO$_2$	−3.84	−0.87	−3.03	−0.96	−2.57	−0.19	−1.42	−0.90
H	−3.46	−4.82	−2.02	−0.68	−2.36	0.02	−0.52	−0.57
CH$_3$	−3.54	−4.93	−2.07	−0.69	−2.41	0.03	−0.48	−0.53
OCH$_3$	−3.66	−7.51	−1.43	−0.66	−2.31	0.03	−0.32	−0.59
N(CH$_3$)$_2$	−3.49	−7.56	−1.24	−0.68	−2.34	0.02	−0.46	−0.47
1,3-Dithiane-2-selenol	−3.68	−2.39	−2.80	−2.47	−2.56	−1.71	−2.69	—

^{a} $\Delta(\Delta_f H) = \Delta_f H_{ax} - \Delta_f H_{eq}$. ^{b} $\Delta G = \Delta(\Delta_f H) - T\Delta S$ at 298 K. ^{c} $\Delta H =$ (sum of electronic and thermal energy)$_{ax}$ − (sum of electronic and thermal energy)$_{eq}$. ^{d} $\Delta G = \Delta H - T\Delta S$ at 298 K. ^{e} $\Delta E = E_{ax} - E_{eq}$. ^{f} Reference 8.

have a larger volume. In the case of NO$_2$, both conformers are equally disordered maybe because of the sp^2 arrangement of the NO$_2$ group coplanar and in resonance with the phenyl ring. For the other sp^3 hybridized substituents, the equatorial conformers are more disordered. The ΔS values favor the equatorial conformers contrary to the trend in the free energies, thus, the equilibrium is not entropy driven.

At the HF/6-31G* level, changes in total enthalpies have been calculated by including the thermal corrections with the total energies. These results (Table 8, column 4) reproduce better the experimental findings than ΔG values. The rigid rotor and harmonic oscillator approximations used in G94 to evaluate the entropy may be the cause of this discrepancy.

We have addressed the question of how well the levels of theory presented here reproduce the effects of the higher level of theory [MP4SDTQ/6-31G*(Se-Hu)//HF6-31G*(Se-Hu)] used by Salzner and Schleyer[14] for CH$_2$(SeH)$_2$. For this purpose, we have optimized the C_2, C_s and C_1 conformations of CH$_2$(SeH)$_2$ with the PM3 method and at the HF/6-31G* levels of theory. The relative energies calculated by Salzner and Schleyer are 0.0 (C_2), 0.74 (C_1), 0.91 (C_s) whereas these values are 0.0 (C_2), 0.15 (C_1), 0.72 (C_s) at the HF/6-31G* level and 0.0 (C_2), 1.55 (C_1), 3.45 (C_s) with the PM3 method. These findings indicate that both methods can detect the order of stability for the stationary points corresponding to the local minima on the potential energy surface. On the other hand, relative energies are reproduced better at the HF/6-31G* level.

The energetics in solution mimic quite well the experimental findings.[9] The electron donor groups inhibit the anomeric effect and decrease the preference for the axial conformers. Single point calculations carried out in a polar medium at the HF/6-31G* level have stabilized the more polar equatorial conformer thus the preference for the axial conformer is expected to decrease as the relative permittivity of the solvent increases. Specific solute–solvent interactions are not taken into account with this method.

Conclusion

The computational analysis of the conformational behavior of 2-[(4-substituted phenyl)seleno]-1,3-dithianes has allowed us to come up with conclusions on the structures, the energetics and the applicability of the methods.

(1) For all the compounds studied, the axial conformer is more stable than the equatorial conformer. This fact is attributed mainly to the endo and exo anomeric effects present in the axial and absent in the equatorial conformers.

(2) The stability of the axial *versus* the equatorial conformer for 1,3-dithiane-2-selenol has also been explained with the NBO method: the lone pairs of S are delocalized towards the σ* orbital of C2−Se. The geometric features of **2-ax** and **2-eq** are also explained with this method.

(3) Both methods predict a greater preference for the axial conformer for 2-[(4-NO$_2$-phenyl)seleno]-1,3-dithiane rather than for 2-{[4-N(CH$_3$)$_2$-phenyl]seleno}-1,3-dithiane. Best quan-

titative agreement with experiment is obtained with HF/6-31G* in solution.

(4) For the axial conformation the phenyl group attached to Se prefers the gauche position, where the exo anomeric effect is present to maximize electron delocalization. The phenyl group is oriented in such a way as to minimize the steric effects within its vicinity.

(5) For the equatorial conformation no exo anomeric effect is detected, its presence would be very unfavorable because of steric hindrance between the phenyl group and the dithiane ring. For NO$_2$, H and CH$_3$ the position of the phenyl group with respect to the dithiane ring is different with the different methods.

(6) The long range interactions, assessed in the equatorial conformers when the PM3 method is used, may have been overestimated with this method as it was observed in our previous analysis for 5-substituted 1,3-dithianes.[19] The justification for the geometries located with PM3 and not with HF/6-31G* needs further investigation with DFT methods including electron correlation.

(7) Comparison of the order of stability for the different conformers of CH$_2$(SeH)$_2$ with previous results obtained at the MP4SDTQ/6-31G*(Se-Hu)//HF6-31G*(Se-Hu) level, has shown that although the methods used here mimic the qualitative trend, quantitative results are reproduced better at the HF/6-31G* level.

This study has enabled us to deduce new information about the orientation of the substituents, the geometrical parameters and dipole moments of the compounds studied as well as about the causes of the experimentally observed free energies.

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