Conformational behavior of 2-dimethylamino-1,3-dithiane in solution

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Ab initio **molecular orbital calculations in the gas phase and in chloroform have been carried out to study the conformational equilibrium of 2-dimethylamino-1,3-dithiane. Full optimizations at the HF/6-31G, HF/6-31G* levels and single point calculations at the MP2/6-31G* level have been performed. The influence of the solvent has been studied with a self-consistent reaction field (SCRF) continuum model. The effects of steric and electrostatic interactions on the axial–equatorial preference have been investigated. The present results have been compared with the available experimental data.**

Introduction

The structural characteristics of sulfur have led to numerous studies of sulfur bonding; the reactivity of organic sulfur compounds has resulted in the development of useful synthetic reagents.[1] The conformational behavior of six-membered, sulfur-containing saturated heterocycles is interesting and unusual since it involves conformational effects not explained by steric and dipolar interactions alone. In monosubstituted cyclohexanes, substituents prefer the equatorial position to avoid the repulsive steric interactions with the axial hydrogen atoms on C3 and C5: the bulkier the substituent the greater is the equatorial preference. The conformational behavior of substituted six-membered rings containing second- and third-row elements has been subjected to experimental and theoretical investigations during the past decade.[2–8] The substituents on heterocycles with oxygen and sulfur atoms behave differently to their cyclohexane analogues. The tendency of electronegative substituents to assume the axial rather than the equatorial orientation at C1 of a pyranoid ring (*i.e.* the anomeric effect) was discovered by Edward and Lemieux more than 25 years ago[3] and has been observed in many heterocyclic systems. It has been also determined that the magnitude of the anomeric effect is directly proportional to the electronegativity of the substituent, which has been measured by the difference in free energy between the axial and equatorial conformers. According to the interpretation of the anomeric effect, electrostatic dipole–dipole repulsion should disfavor the equatorial conformer while dipole–dipole attraction favors the axial conformer in the equilibrium shown in Scheme 1. The expected solvent effect is such that a stronger anomeric effect is predicted in less polar media. For 1,3-dithiane, the chair conformation is found to be the most stable experimentally[9,10] and computationally.[11] Juaristi and co-workers have described the conformational analysis of 2-substituted 1,3-dithianes [Y = CO_2H, CO_2CH_3, SCH_3, $N(CH_3)_2$ and COC_6H_5] experimentally and observed sizable anomeric effects for all these substituents except for Y = $N(CH_3)_2$.[8] 2-Dimethylamino-1,3-dithiane has been shown to exist in a predominantly (>95%) equatorial orientation. Our previous work on a computational investigation of the conformational behavior of 2-substituted 1,3-dithianes with PM3 has confirmed the experimental data for all the electronegative substituents besides $N(CH_3)_2$.[12] Semi-empirical calculations did not reproduce the 'abnormal' equatorial preference of the dimethylamino group.

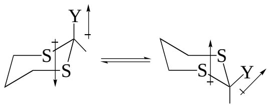
We have also undertaken the optimization of one of the above mentioned compounds (Y = CO_2H) with HF/6-31G* and have observed perfect agreement between PM3 and HF, $\Delta H_{rxn} = 4.20$ kcal mol^{-1} in both cases. It may be that the parametrization of N in PM3 is not adequate to reproduce the conformational energy of 2-dimethylamino-1,3-dithiane. It is thus the purpose of this research to elucidate the absence of an anomeric effect in the compound of interest despite the dipole of the dimethylamino group.

Table 1 Calculated relative energies and dipole moments for the optimized conformers of 2-dimethylamino-1,3-dithiane

		HF/6-31G		HF/6-31G*		MP2/6-31G*	
	ε^a	$E_{REL}{}^b$	μ^c	$E_{REL}{}^b$	μ^c	$E_{REL}{}^b$	μ^c
Ia	1	5.75	2.78	5.69	2.45	4.69	2.45
	4.7	1.94	3.44	2.58	3.01	1.83	3.01
IIa	1	6.07	2.71	4.72	2.16	2.94	2.16
	4.7	3.20	3.29	2.42	2.60	0.92	2.60
Ie	1	3.80	2.22	3.07	2.03	2.86	2.03
	4.7	0.00	2.93	0.00	2.63	0.00	2.63

[a] ε, relative permittivity of solvent. [b] E_{REL}/kcal mol^{-1} (relative energy). [c] μ/D (dipole moment).

Due to the influence of the solvent on the axial–equatorial equilibria of the 2-substituted 1,3-diheteroanes,[1] the role of the medium has been taken into account. A quantum mechanical continuum model developed by Rivail, Rinaldi and co-workers[13] based upon the Onsager reaction field[14] model has been used.



Scheme 1

Method of Calculation

Ab initio calculations were performed using the Gaussian 92 in the gas phase[15] and in solution[16] (Table 1). For both media, all geometries were fully optimized at the HF/6-31G and HF/6-31G* levels and were characterized by calculation of vibrational frequencies (Table 2). Additionally, single point MP2/6-31G* calculations have been performed in both media for all optimized conformers. The conformational energy of the axial–equatorial equilibrium has been calculated as the difference in total energies between the best axial and equatorial conformers. This difference is used as a measure of direction for the equilibrium and has been compared to the experimental free energy of the reaction, ΔG_{rxn} (Table 3).

The role of the solvent has been taken into account by means of a general SCRF model proposed for quantum chemical computations on solvated molecules.[17] In this model, the solvent is represented by an infinite dielectric continuum, characterized by its relative permittivity, ε, in which a cavity is created and the solute is placed in it. The charge distribution of the solute polarizes the continuum, which in turn creates an

Table 2 Calculated parameters for the conformers **Ia**, **IIa** and **Ie**. Bond lengths in Å, angles and torsional angles in degrees (values in parentheses are the results of calculations in chloroform)

	Ia		**IIa**		**Ie**	
	HF/6-31G	HF/6-31G*	HF/6-31G	HF/6-31G*	HF/6-31G	HF/6-31G*
S1–C2	1.882 (1.883)	1.827 (1.828)	1.882 (1.883)	1.826 (1.827)	1.916 (1.916)	1.845 (1.846)
C2–S3	1.922 (1.923)	1.849 (1.849)	1.882 (1.883)	1.826 (1.827)	1.884 (1.885)	1.827 (1.828)
H7–C2	1.076 (1.076)	1.080 (1.080)	1.085 (1.085)	1.090 (1.089)	1.076 (1.076)	1.080 (1.080)
N8–C2	1.419 (1.418)	1.436 (1.436)	1.451 (1.449)	1.456 (1.455)	1.416 (1.415)	1.432 (1.431)
C15–N8	1.450 (1.452)	1.445 (1.446)	1.467 (1.468)	1.457 (1.458)	1.457 (1.458)	1.452 (1.453)
C16–N8	1.457 (1.459)	1.450 (1.451)	1.467 (1.468)	1.457 (1.458)	1.456 (1.458)	1.450 (1.451)
S1–C2–S3	113.2 (112.6)	114.2 (113.7)	109.5 (109.1)	110.2 (109.9)	112.1 (111.6)	113.3 (112.8)
N8–C2–S1	114.3 (114.4)	113.7 (113.7)	112.7 (112.7)	113.1 (113.1)	112.1 (112.7)	113.1 (113.5)
N8–C2–S3	116.0 (116.2)	117.4 (117.6)	112.8 (112.7)	113.1 (113.1)	110.0 (110.3)	108.9 (109.1)
C15–N8–C2	119.3 (119.2)	117.1 (117.0)	115.1 (115.0)	113.1 (112.9)	119.3 (119.1)	117.0 (116.9)
C16–N8–C2	115.3 (115.2)	113.3 (113.1)	115.1 (115.0)	113.1 (112.9)	116.7 (116.4)	114.3 (114.1)
H7–C2–S1	102.4 (102.6)	101.8 (101.9)	104.1 (104.2)	104.0 (104.1)	106.0 (105.7)	106.7 (106.4)
H7–C2–S3	100.6 (100.8)	101.2 (101.3)	104.1 (104.3)	104.0 (104.1)	107.0 (106.9)	106.9 (106.7)
C15–N8–C2–H7	183.5 (181.7)	179.1 (177.6)	65.6 (65.2)	62.3 (62.2)	175.9 (175.3)	172.1 (171.7)
C16–N8–C2–H7	40.3 (39.4)	46.1 (45.1)	−65.4 (−65.7)	−62.3 (−62.2)	30.0 (30.7)	37.3 (37.5)

Table 3 Comparison of calculated free energy variation and experimental (Exp) ΔG values between conformers in the gas phase and in solution

	ΔG/kcal mol^{-1}			
ε	HF/6-31G	HF/6-31G*	MP2/6-31G*	Exp
1	−1.95	−1.65	−0.08	—
4.7	−1.94	−2.42	−0.92	*ca.* −2.00

electric field inside the cavity. Accordingly, the charge distribution and the geometry of the solute will change until the equilibrium is reached. The computer code utilized evaluates the energy and its first derivative up to sixth order so that solute–solvent interactions are evaluated at the multipole level. A general cavity shape[18] in which the cavity can take the shape of the molecular surface has been used in determining the solvent effect. The relative free energy in solution has been obtained by adding to the gas phase value the electrostatic free energy of solvation.

Results and discussion

Gas phase

When the dimethylamino group occupies the axial position two conformations generated by rotation around the C2–N8 bond have been located as minima: one with a methyl group on the dithiane ring (**Ia**) and another one with C_s symmetry having the lone pair above the ring (**IIa**). For the dimethylamino group in the equatorial orientation only one conformer has been located as a stationary point with one of the methyl groups anti to the axial H7 (**Ie**) (Fig. 1).

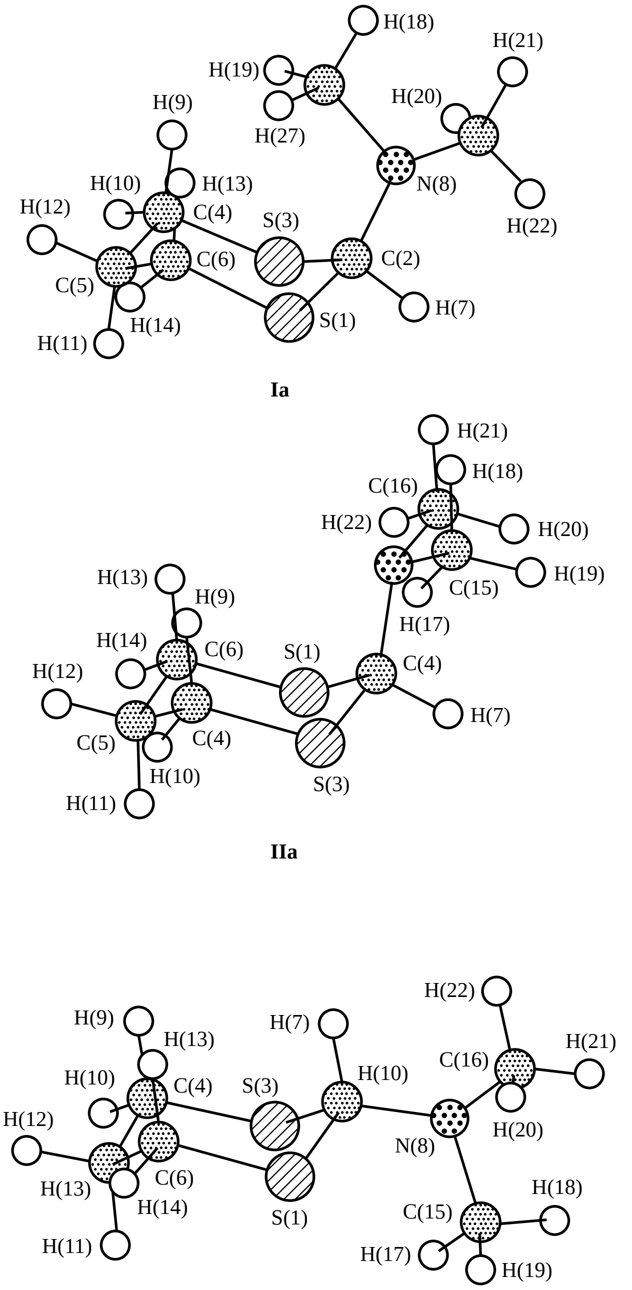
Analysis of geometrical parameters has shown that including polarization functions shortens the C–S bonds by 0.07 Å, whereas the increase in bond length for the C2–N bond is only 0.01 Å. As expected, polarization functions provide a larger volume to the free electrons of S and bond lengths change accordingly. The use of polarization functions on N has been determined to increase the accuracy of the calculations and the correspondence with the experimental data.[19] Thus, analysis of the conformational equilibrium will be based mainly on the results of the calculations carried out at the HF/6-31G* level.

The sulfur atoms in the dithiane ring are electron deficient centers: in the symmetric conformer **IIa**, the charge distribution on S is 0.14e. In the conformers **Ia** and **Ie** the S antiperiplanar to the lone pair on nitrogen is less positive (0.12e) than the other S (0.16e) as may be explained by partial neutralization of the former S by the flow of electrons from N.

As to the relative stability of the axial conformers, compound **IIa** is more stable than **Ia** by 0.97 kcal mol^{-1} with HF/6-31G* and by 1.75 kcal mol^{-1} with single point MP2 calculations; with HF/6-31G the two conformers are almost isoenergetic (Table 1). The energetic stability of **IIa** against **Ia** can be explained by a smaller steric interference of the dimethylamino group with H9 and H13: in compound **Ia** the closest distance between the axial hydrogens and the hydrogen atoms of the methyl group is 2.27 Å, whereas in compound **IIa** this distance is 2.86 Å. The steric hindrance between H9, H13 and the protons of the methyl groups in compound **Ia** is also confirmed by the deviation of C2 from a perfect tetrahedral geometry: the N8–C2–S1 and N8–C2–S3 angles measure 113.7 and 117.4° respectively. In compound **IIa** the same angles measure 113.1° each and in **Ie** they measure 113.1 and 108.9°. All the levels of calculation show a shift of equilibrium towards the 1,3-dithiane with the dimethylamino group at the equatorial position in agreement with the experimental results of Juaristi *et al.*[8] In single point energy calculations with MP2 the relative stability of **Ie** with respect to **IIa** decreases to 0.08 kcal mol^{-1} (Table 3); geometry optimizations at this level although expensive computationally may alter the relative energetics of the conformers.

The equatorial preference over the axial for the dimethylamino group can be rationalized in terms of the reverse *exo*-anomeric effect present when the substituent is at the equatorial position. In compound **Ie** the lone pair on N, the N atom itself, C2 and S are coplanar and the positive charge on S is thus stabilized. A similar arrangement is not present in the most stable axial conformer **IIa**, while on the other hand conformer **Ia** is destabilized by steric hindrance as mentioned already. Furthermore, the equatorial conformer **Ie** is the least polar compound at all levels of calculation. An *endo*-anomeric effect with electrons flowing from S to N would be expected for the dimethylamino group at the axial position. As explained already by Altona and co-workers[19] the nitrogen lone pair has a strong tendency to spread its electrons towards the carbon atom when an electron-withdrawing group is antiperiplanar to this lone pair. Following Praly and Lemieux[20] this effect may be counteracted by the sulfur displacing its electrons towards the same carbon atom. Calculations at the HF/6-31G* level show that the C2–N8 bond is less polar than the C2–S3 bond and is thus a poorer acceptor: in compound **IIa** the dimethylamino group has a total charge of −0.11e whereas each S has a charge of 0.14e and the C2–H7 group has a total charge of −0.09e. An electron flow from S towards N is thus unexpected, excluding the presence of *endo*-anomeric effect in the axial conformers.

In the gas phase conformation **Ia** is destabilized by nonbonded interactions involving the methyl group over the



Ia

IIa

Ie

Fig. 1 The optimized conformers for 2-dimethylamino-1,3-dithiane in the gas phase

six-membered ring; conformation **IIa** has no stabilizing *exo*-anomeric interactions available to it whereas **Ie** benefits from *exo*-anomeric stabilization.

Solution

Chloroform ($\varepsilon = 4.7$) has been chosen as the polar continuum to mimic the solvent used in the experimental analysis. Actually, the changes observed in the geometrical parameters by the presence of a polar environment are minor, as expected, due to the fact that the solute–solvent interactions are small:[13] bond lengths vary only by ±0.001 Å whereas bond angles change by ±0.5°. Dipole moments increase in solution as expected from the increase in the separation of charges in a polar medium.

The energetics discussed in solution are free energies: it has been shown that[21] the change from internal to free energy of a solute in solution does not play an important role in the case of the energetics. The more polar conformer **Ia** is more stabilized by a polar continuum than its analogue **IIa**. The solvation energy for **Ia** is greater than the corresponding solvation energy for **IIa** at all levels of calculation. Furthermore, **Ie** is the least polar conformer at all levels of calculation and it is expected to have the smallest solvation energy in contrast to the results in Table 1. The effect of higher multipole moments on the energy of solvation had to be taken into consideration. The contribution of the quadrupole and octapole moments to the energy of solvation are 1.767 96 and 0.638 93 for **Ie** and 1.146 12 and 0.563 21 for **IIa**. These findings show that higher multipole moments are more important in **Ie** than **IIa**. Multipole moments may be responsible for the stabilization of **Ie** more than the value anticipated, based upon the magnitude of the dipole moments only. The calculated conformational energy in solution (HF/6-31G*) shows a good agreement with the experimental value (Table 3). On the other hand, the 1 kcal mol^{-1} difference in conformational energy between experimental measurements and MP2/6-31G* may be due to the lack of geometry optimization at this level.

Steric effects and solvation seem to complement each other in predicting the equatorial conformer, **Ie**, to be the most stable in solution: the substituent occupies the least crowded position, where it is the most stabilized by a polar medium.

Conclusion

The calculated results for 2-dimethylamino-1,3-dithiane, investigated computationally in the gas phase and in chloroform ($\varepsilon = 4.7$), have shown that the *exo*-anomeric effect involving the nitrogen lone pair is the dominant effect in this molecule, explaining the experimental findings of Juaristi. The results obtained from the calculations in a solvated medium have shown that the general cavity shape is an effective model for investigating the solvent effect. It can be also concluded that use of polarization functions for elements like N, S, O are necessary to obtain reliable geometrical parameters.

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