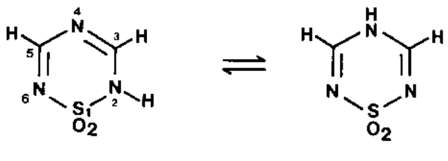
A THEORETICAL STUDY OF THE STRUCTURE AND TAUTOMERISM OF 1,2,4,6-THIATRIAZINE 1,1-DIOXIDE

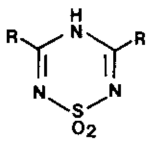
José Elguero[a]*, José Luis G. de Paz[b], Pilar Goya[a],
Juan Antonio Páez[a], and Isabel Rozas[a]
[a]Instituto de Química Médica, C.S.I.C.,
Juan de la Cierva, 3, 28006 Madrid, Spain
[b]Departamento de Química, Facultad de Ciencias,
Universidad Autónoma de Madrid, 28049 Madrid, Spain

Abstract - "Ab initio" theoretical calculations have been used to study the structure and annular tautomerism of 2(4)H-1,2,4,6-thiatriazine 1,1-dioxide. The 4H-tautomer has been found to be the most stable in agreement with ^{1}H-, ^{13}C- and ^{15}N-nmr data.

The 1,2,4,6-thiatriazine 1,1-dioxide skeleton is present in several structures of considerable biological interest.[1] In spite of this fact, no theoretical calculations have been reported[1] probably owing to the difficulty to correctly describe the hypervalent sulfur atom.[2] In this paper, we will discuss the structure of the parent 2(4)H-1,2,4,6-thiatriazine 1,1-dioxide 1, with special emphasis on annular tautomerism, i.e. tautomerism involving exclusively ring atoms.[3]



1a 1b



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In the case of compound 1, ^{1}H-, ^{13}C- and ^{15}N-nmr data provide conclusive evidence for the existence of the 4-NH tautomer 1b in DMSO solution.[4] The 3,5-ditrifluoromethyl derivative presents a unique signal in ^{19}F-nmr, which is consistent with a 4H structure **2** (R=CF_3).[5] With functional groups at positions 3 and/or 5 (R=OH, NH_2), more tautomers are possible, but still the 4-NH ones seem the most stable.[1]

Computational details

Polarized basis sets, STO-3G*[6] and 3-21G(*)[7] were selected. The calculations were performed using the Gaussian 80 series of programs[8] and Murtagh-Sargent optimization procedures.[9] Fully optimization of the geometries was carried out only at the STO-3G* level (noted, as usual, STO-3G*//STO-3G*). On this geometries punctual 3-21G(*) calculations were carried out (3-21G(*)//STO-3G*).

Results:

Geometries

STO-3G* fully optimized geometries of tautomers **1a** and **1b** are reported in Table 1. In the case of planar structures (less stable, see later), the planarity has been imposed, in order to explore local minima and to estimate ring inversion barriers.

Table 1
Calculated geometries of 1,2,4,6-thiatriazine 1,1-dioxide **1**

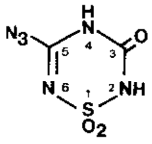
Bond lengths (Å)	S_1-O_7	S_1-O_8	S_1-N_2	S_1-N_6	N_2-C_3	N_6-C_5	C_3-N_4	C_5-N_4
1a planar	1.448	1.451	1.709	1.696	1.393	1.290	1.294	1.436
1a nonplanar	1.450	1.442	1.709	1.711	1.411	1.291	1.291	1.443
1b planar	1.446	1.446	1.723	1.723	1.281	1.281	1.404	1.404
1b nonplanar	1.450	1.442	1.726	1.726	1.283	1.283	1.413	1.413

Bond angles (°)	O_7-S_1-O_8	S_1-N_2-C_3	N_2-C_3-N_4	C_3-N_4-C_5	N_4-C_5-N_6	C_5-N_6-S_1	N_2-S_1-N_6
1a planar	122.3	124.8	126.8	114.9	131.5	122.2	99.8
1a nonplanar	122.6	118.4	125.2	114.7	130.9	118.4	97.7
1b planar	124.1	119.3	126.6	121.1	126.6	119.3	106.9
1b nonplanar	123.7	117.4	126.3	118.9	126.3	117.4	105.4

Torsion angles (°)	S_1-N_2-C_3-N_4	N_2-C_3-N_4-C_5	C_3-N_4-C_5-N_6	N_4-C_5-N_6-S_1
1a planar	0.0	0.0	0.0	0.0
1a nonplanar	-31.9	0.7	13.6	6.3
1b planar	0.0	0.0	0.0	0.0
1b nonplanar	-5.7	-18.5	18.5	5.7

The C-H and N-H bond lengths are 1.095±0.001 Å for all structures and 1.025±0.002 (**1a**) and 1.020±0.002 Å (**1b**) respectively. The results obtained indicate that in the case of nonplanar forms tautomer **1a** would have a twisted structure and tautomer **1b** a boat structure.

Since we have been unsuccessful in obtaining suitable crystals of **1**, the calculated geometries of Table 1 are to be compared with literature results on two related structures **3**[10] and **4**.[11]



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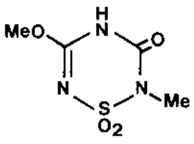

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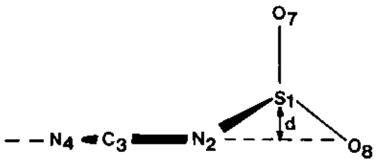
Both exist in the crystal in folded conformations, corresponding to our "nonplanar" structures, with the sulfur atom above the mean plane formed by the five other ring atoms:



$d(\mathbf{3}) = 0.441$ Å
$d(\mathbf{4}) = 0.259$ Å
$d(\mathbf{1a},np) = 0.615$ Å
$d(\mathbf{1b},np) = 0.482$ Å

Both are 2H,4H-tautomers (and not 2H,6H-ones). This and the presence of a carbonyl group at C_3 and a substituent on C_5, make comparisons delicate. Theoretical calculations reproduce the fact that S_1-O_7 is longer than S_1-O_8 and yields reasonable N-C distances. On the other hand, S-N distances are overestimated in the calculated geometries (+ 0.09 Å) and the experimental fact[10,11] that S_1-N_2H is longer than S_1-N_6= is not reproduced by the calculations. The bond angles are quite different; if we compare the sulfamide fragment of compounds **3** and **4** with that of **1a** (=N-SO_2-NH-) i.e. the experimental averaged values for O_1-S_1-O_8 (117.0°) and N_2-S_1-N_6 (105.0°) with the calculated ones (Table 1), 122.6 and 97.7°, it appears that the calculations enlarge the O-S-O angle at expense of the N-S-N one.

Energies

The values of energies for the four situations described in Table 1 are collected in Table 2.

Table 2
Calculated energies (hartrees) and relative energies (kcal.mol^{-1}) of 1,2,4,6-thiatriazine 1,1-dioxide **1**

Compound	STO-3G*//STO-3G*		3-21G(*)//STO-3G*	
1a planar	-778.6353	8.5	-783.9466	1.8
1a nonplanar	-778.6407	5.1	-783.9389	6.6
1b planar	-778.6480	0.6	-783.9494	0.0
1b nonplanar	-778.6489	0.0	-783.9434	3.8

STO-3G*//STO-3G* values clearly show that the 4H tautomer **1b** is the most stable and that nonplanar structures are slightly more stable than the planar ones (this is particularly true for the 2H tautomer which corresponds to molecules **3** and **4**). 3-21G(*)//STO-3G* energies favor the planar conformations with regard to the STO-3G*//STO-3G* values by kcal.mol^{-1} 8.2 (**1a**) [(6.6-1.8) - (5.1-8.5)] and 4.4 kcal.mol^{-1} (**1b**) [(3.8-0.0) - (0.0-0.6)]. We have already observed this behaviour of the 3-21G(*) basis set in the related case of 1,2,6-thiadiazine 1,1-dioxides.[2] Moreover, these calculations being punctual, it is reasonable to assume that they do not correspond to energetic minima.

Atomic charges and dipole moments

We have collected in Table 3 the data corresponding to STO-3G*//STO-3G* calculations of the most stable forms.

Table 3

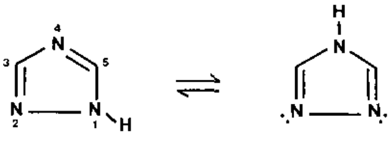
Gross atomic population and dipole moments of nonplanar forms of 1,2,4,6-thiatriazine 1,1-dioxide **1** (STO-3G*//STO-3G*)

Compound	S_1	N_2	N_6	C_3	C_5	N_4	O_7	O_8	μ(D)
1a nonplanar	15.504	7.339	7.235	5.808	5.833	7.270	8.232	8.222	3.48
1b nonplanar	15.531	7.246	7.246	5.809	5.809	7.339	8.235	8.227	6.98

No experimental data are available to test the values of Table 3 except for the ^{15}N-nmr chemical shifts (DMSO) of compound **1b**. In agreement, at least qualitative with the calculations, the signal of N_4 appears at 238.3 ppm whereas those of N_2 and N_6 appear at 142.4 ppm.[4] The fact that tautomer **1b** has the higher dipole moment would make it even more favoured in solution.

Discussion

Theoretical calculations provide an explanation to the fact that in 1,2,4-triazole **5**, tautomer **5a** is much more stable than tautomer **5b**[3,12] both in gas phase and solution whereas the reverse is true for 1,2,4,6-thiatriazine 1,1-dioxide.



5a **5b**

A qualitative explanation of the relative low stability of tautomer **5b** compared with tautomer **1b**, is that in the latter the SO_2 group prevents the lone pair/lone pair repulsion present in **5b** (between N_1 and N_2). We have estimated[13] that this repulsion amounts to 7.2 kcal.mol^{-1}, which roughly correspond to the shift of the equilibrium from 1,2,4,6-triazole ($\delta\Delta G=3,9$ kcal.mol^{-1}, *STO-3G//STO-3G*)[12] to 1,2,4,6-thiatriazine 1,1-dioxide ($\delta\Delta G=-5.1$ kcal.mol^{-1}, Table 2).

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