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THEORETICAL AND EXPERIMENTAL ANALYSIS OF PROPERTIES IN HETEROCYCLES CONTAINING THE AMINOSULPHONYLLAMINO MOIETY

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A theoretical and experimental analysis of the geometric and electronic properties of compounds containing the aminosulphonylamino moiety was carried out. The theoretical properties were calculated using molecular orbital *ab initio* methods at the Hartree–Fock (HF) and second order Möller–Plesset (MP2) levels of theory, local density functional (LDF) *ab initio* methods and the semi-*ab initio* method, SAM1, on sulphamide and seven heterocyclic compounds containing the aminosulphonylamino group. The experimental analysis has been performed using x-ray structures of related compounds gathered in the Cambridge Structural Database together with experimental dipole moments and ^{13}CNMR shifts of some of the compounds studied. Comparison of the experimental analysis with the theoretical results indicates that none of the methods studied is the most adequate to describe the geometry and electronic distribution of these molecules. The use of the 6–31G* basis set to compute the geometry of these molecules and methods which include electronic correlation (MP2/61G*//RHF/6–31G*, MP2/6–31G* and LDF) to quantify their electronic distribution are proposed.

INTRODUCTION

In recent years, the aminosulphonylamino moiety (NSO_2N) has emerged as an important component of a large number of bioactive heterocyclic compounds. These biological activities range from antihistaminic,[1,2], for some 1,2,5-thiadiazole 1,1-dioxides, antiinflammatory, antipyretic and analgesic,[3] for some 1,2,6-thiadiazine 1,1-dioxides, to diuretic,[4] for some pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxides.

The presence of the sulphur atom and the large size of most of these molecules have limited the application of molecular orbital *ab initio* methods to this kind of compound in the past. Our earlier studies in model structures clearly showed the necessity of including polarization functions on the sulphur atom in order to properly describe the S—O bond.[5,6] In addition, a recent systematic study of a large series of small compounds containing sulphur[7] has indicated the limitation of some of the most frequently used molecular orbital methods.

For an adequate comparison of the theoretical results, experimental gas-phase data, when available, would be desirable. However, this is not the case with the compounds studied. Nevertheless, the structures of a number of compounds with this moiety have been described in the solid phase.[8] The average of this kind of data has been shown to be similar to gas phase results for other sets of compounds[9,10] and their statistical analysis has been used to confirm geometrical and energetic results provided by theoretical calculations.[11–13]

In this work, the theoretical results obtained with molecular orbital, local density *ab initio* methods and the recently described semi-*ab initio* method SAM1 were compared with experimental dipole moments and statistical results of x-ray geometries for heterocyclic compounds containing the aminosulphonylamino moiety. The comparison provides a basis to select the methods which describe better the overall experimental results and could be used to develop a molecular mechanics parametrization of this moiety.

EXPERIMENTAL

The compounds selected for this study involve a variety of molecules with the NSO_2N moiety, especially when this group is included in a ring (Figure 1). All the molecules were fully optimized using their symmetry when possible.

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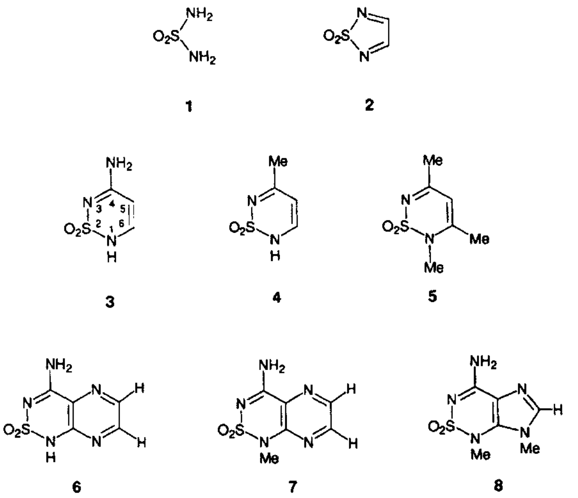

Figure 1. Compounds studied with the atom numbering used in this article

The selection of the methods used here was made according to a previous paper in which small molecules with sulphur were calculated.[7] The semi-empirical method PM3 was disregarded owing to its poor description of the geometry and dipole moments of this kind of compound. Similar reasons were used to exclude the minimal basis sets STO-3G* and MINI-1* from this study.

The remaining *ab initio* basis sets, 6–31G*[14] and MIDI-1*,[15,16] used previously, were chosen here, in addition to the local density functional *ab initio* method[17,18] included in the DMol program. The semi-*ab initio* method SAM1[19] was also used.

The *ab initio* molecular orbital methods were calculated with the Gaussian-92 program[20] at the RHF and MP2 (frozen core) levels of theory with the 6–31G* basis set and at the RHF level with the MIDI–1* basis set. The minimization was carried out using the Berny method. The default parameters were used for the integral cut-off and minimization convergence criteria.

The LDF *ab initio* calculations were carried out using the DMol program,[211] distributed by Biosym Technologies. A double zeta numerical basis set with polarization functions in all the atoms and the Janak–Moruzzi–Williams (JMW) exchange correlation potential were used. The geometry of the molecules was optimized until the gradient was smaller than 0·003 au.

The SAM1 calculations were carried out using the AMPAC package (Version 5.0).[22] The geometry optimizations were achieved using the EF minimization algorithm and the PRECISE keyword which increases the electronic and gradient requirement 100-fold.

RESULTS

The experimental and optimized calculated geometries of the molecules studied are gathered in Tables 1–3. Table 1 contains a selection of the bond distances, especially those in which the sulphur atom is involved, and Table 2 shows some of the bond angles of these molecules. The distances between the sulphur atom and the plane defined by the rest of the atoms in the five- and six-membered ring molecules studied (**2**–**8**) are given in Table 3.

Since the calculated geometries considered a hypothetical gas phase, a statistical average of the geometrical parameters of all the compounds with the aminosulphonylamino moiety in the Cambridge Structural Data Base[23] (CSD), October 1994 release, were calculated, to reduce the individual packing effects, and compared with a statistical analysis of the theoretical results for each method (Table 4). A similar analysis of the compounds with a six-membered ring was carried out (Tables 5 and 6).

The experimental and calculated dipole moments are given in Table 7 and a correlation analysis of this parameter for the different methods studied is presented in Table 8.

An additional analysis of the electronic description of the theoretical methods was carried out by checking their ability to correlate the calculated atomic charges with the experimental NMR shifts of the carbon atoms of the compounds studied for which these values were available (Table 9). The atomic charges were obtained using the Mulliken approximation[24] for all the methods. In addition, the Hirshfeld partitioned charges[25] were calculated with the DMol program.

DISCUSSION

Geometry

The geometric parameters calculated by the different methods used in this study show some differences with respect to the experimental values, the results obtained with the 6–31G* basis set at the HF level being the most similar to the experimental data. The results of this basis set in conjunction with the experimental values will be used to analyse the rest of the methods.

The semi-*ab initio* method SAM1 shows deep contrasts when compared with the experimental geometric parameters. Whereas it is the best method regarding the S—O bond distance and OSO angle (Tables 1, 2 and 4), it has serious problems in reproducing the environment of the nitrogens attached to the sulphur atoms, denoted by long N—S distances (Tables 1 and 5), very large S2—N3—C4 angles (Tables 2 and 6) and the calculated planarity of the thiadiazine ring (Table 3). Another indication of this problem is the

Table 1. Selected theoretical and experimental bond distances (Å)

Compound	Method	N1—S2	S2—N3	S2—O1	S2—O3
1	SAM1	1·655	1·655		1·448
	DMol[a]	1·650	1·681		1·453
	MIDI-1*[a]	1·651	1·676		1·441
	6–31G*[b]	1·629	1·652		1·420
	MP2/6–31G*	1·659	1·689		1·456
	Exp.[c]	1·620	1·620		1·430
2	SAM1	1·825			1·440
	DMol	1·717			1·448
	MIDI-1*	1·719			1·431
	6–31G*	1·696			1·415
	MP2/6–31G*	1·757			1·451
3	SAM1	1·791	1·586	1·443	1·443
	DMol	1·717	1·596	1·455	1·450
	MIDI-1*	1·706	1·618	1·440	1·436
	6–31G*	1·684	1·596	1·426	1·421
	MP2/6–31G*	1·719	1·632	1·459	1·454
	Exp.[d]	1·653	1·583	1·434	1·423
4	SAM1	1·775	1·623	1·443	1·443
	DMol	1·707	1·610	1·453	1·450
	MIDI-1*	1·692	1·640	1·437	1·436
	6–31G*	1·673	1·620	1·420	1·423
	MP2/6–31G*	1·707	1·653	1·456	1·453
5	SAM1	1·826	1·604	1·443	1·444
	DMol	1·722	1·606	1·455	1·452
	MIDI-1*	1·702	1·637	1·440	1·440
	6–31G*	1·686	1·615	1·426	1·422
	MP2/6–31G*	1·725	1·647	1·459	1·456
6	SAM1	1·765	1·596	1·444	1·444
	DMol	1·707	1·607	1·455	1·447
	MIDI–1*	1·701	1·629	1·441	1·434
	6–31G*	1·677	1·609	1·426	1·418
7	SAM1	1·804	1·590	1·444	1·444
	DMol	1·715	1·606	1·449	1·455
	MIDI–1*	1·702	1·628	1·437	1·441
	6–31G*	1·683	1·609	1·420	1·428
8	SAM1	1·845	1·574	1·444	1·444
	DMol	1·733	1·622	1·453	1·451
	MIDI–1*	1·723	1·637	1·439	1·439
	6–31G*	1·701	1·619	1·424	1·422
	Exp.[e]	1·670	1·607	1·427	1·421

[a] Taken from Ref. 7.
[b] Taken from Ref. 34.
[c] Taken from Ref. 35.
[d] Taken from Ref. 36.
[e] Taken from Ref. 33.

Table 2. Selected theoretical and experimental bond angles (°)

Compound	Method	N1—S2—N3	S2—N3—C4	O1—S2—O3
1	SAM1	103·2		121·2
	DMol[a]	107·0		125·0
	MIDI-1*[a]	105·2		123·4
	6–31G*[b]	106·6		123·4
	MP2/6-31G*	106·1		124·7
	Exp.[c]	111·4		119·2
2	SAM1	90·8		120·0
	DMol	97·5		122·7
	MIDI-1*	96·1		122·4
	6–31G*	96·5		122·0
	MP2/6–31G*	96·9		123·2
3	SAM1	99·0	133·6	117·7
	DMol	101·0	121·0	119·3
	MIDI–1*	101·1	120·6	119·2
	6–31G*	101·7	121·6	118·4
	MP2/6–31G*	100·3	118·7	119·9
	Exp.[d]	105·0	121·5	115·5
4	SAM1	99·2	132·5	118·3
	DMol	102·0	121·7	120·2
	MIDI-1*	101·7	121·0	119·8
	6–31G*	101·7	121·6	119·1
	MP2/6–31G*	100·7	119·0	120·5
5	SAM1	100·0	132·6	117·9
	DMol	103·1	119·6	119·3
	MIDI-1*	102·6	118·6	119·3
	6–31G*	103·1	119·9	118·6
	MP2/6–31G*	101·7	117·2	120·0
6	SAM1	100·1	135·1	117·8
	DMol	101·5	121·2	120·5
	MIDI-1*	101·3	120·5	119·9
	6–31G*	101·7	121·7	119·1
7	SAM1	100·5	135·4	118·0
	DMol	103·2	120·9	120·1
	MIDI-1*	102·4	119·8	119·6
	6–31G*	103·0	121·1	118·9
8	SAM1	102·1	135·5	117·5
	DMol	106·1	118·0	121·2
	MIDI-1*	105·8	118·5	120·7
	6–31G*	105·7	119·3	120·0
	Exp.[e]	106·8	118·3	117·8

[a] Taken from Ref. 7.
[b] Take from Ref. 34.
[c] Taken from Ref. 35.
[d] Taken from Ref. 36.
[e] Taken from Ref. 33.

Table 3. Distance between the sulphur atom and the plane defined by the rest of the atoms on the ring (Å)

Method	2	3	4	5	6	7	8
SAM1	0·00	0·00	0·00	0·03	0·00	0·00	0·06
DMol	0·00	0·56	0·48	0·56	0·62	0·58	0·68
MIDI-1*	0·00	0·55	0·48	0·59	0·58	0·64	0·65
6–31G*	0·00	0·50	0·50	0·56	0·63	0·60	0·64
MP2/6–31G*	0·00	0·64	0·61	0·67	—	—	—
Exp.	—	0·41[a]	—	—	—	—	0·66[b]

[a] Taken from Ref. 36.
[b] Taken from Ref. 33.

Table 4. Statistical analysis of the calculated and experimental S=O bond length (Å) and OSO bond angle (°) (Number of cases in parentheses)

Method	S=O	O=S=O
SAM1	1·443 ± 0·002 (14)	118·5 ± 1·3 (8)
DMol	1·452 ± 0·003 (14)	121·0 ± 1·9 (8)
MIDI-1*	1·438 ± 0·003 (14)	120·5 ± 1·6 (8)
6–31G*	1·422 ± 0·004 (14)	119·9 ± 1·8 (8)
MP2/6–31G*	1·455 ± 0·003 (8)	121·7 ± 2·2 (5)
Exp.[a]	1·426 ± 0·011 (180)	117·4 ± 2.5 (90)

[a] The refcodes of the compounds included in this analysis are givin in

Table 5. Statistical analysis of the bond distances (Å) in compounds with a thiadiazine ring

Method	No. of cases	N1S2	S2N3	N3C4	C4C5	C5C6	C6N1
SAM1	6[1]	1·801 ± 0·030	1·595 ± 0·017	1·310 ± 0·010	1·490 ± 0·022	1·433 + 0·042	1·377 ± 0·007
DMol	6[a]	1·717 ± 0·010	1·608 ± 0·009	1·315 ± 0·006	1·432 ± 0·018	1·384 ± 0·022	1·356 ± 0·009
MIDI-1*	6[a]	1·704 ± 0·010	1·632 ± 0·008	1·287 ± 0·007	1·458 ± 0·018	1·363 ± 0·029	1·366 ± 0·012
6–31G*	6[a]	1·684 ± 0·010	1·611 ± 0·009	1·289 ± 0·007	1·457 ± 0·017	1·364 ± 0·028	1·368 ± 0·012
MP2/6–31G*	3[b]	1·717 ± 0·009	1·644 ± 0·011	1·317 ± 0·003	1·435 ± 0·009	1·366 ± 0·007	1·366 ± 0·003
Exp.[c]	27[c]	1·661 ± 0·018	1·587 + 0·011	1·324 ± 0·020	1·432 ± 0·043	1·403 + 0·053	1·367 ± 0·017

[a] Data corresponding to compounds **3–8**.
[b] Data corresponding to compounds **3–5**.
[c] The refcodes of the compounds included in this analysis are given in Appendix B.

Table 6. Statistical analysis of the calculated and experimental bond angles (°) in compounds with a thiadiazine ring

Method	No. of cases	N1—S2—N3	S2—N3—C4	N3—C4—C5	C4—C5—C6	C5—C6—N1
SAM1	6[a]	100·2 ± 1·1	134·1 ± 1·4	119·6 ± 1·3	119·6 ± 1·0	124·1 ± 1·0
DMol	6[a]	102·8 ± 1·8	120·4 ± 1·4	123·5 ± 1·2	120·4 ± 0·9	120·9 ± 5·0
MIDI-1*	6[a]	102·5 ± 1·7	119·8 ± 1·1	124·5 ± 1·4	119·7 ± 0·8	122·1 ± 2·6
6–31G*	6[a]	102·8 ± 1·6	120·9 ± 1·0	123·7 ± 1·2	119·7 ± 0·8	122·0 ± 2·4
MP2/6–31G*	3[b]	100·9 ± 0·7	118·3 ± 1·0	125·3 ± 0·3	120·1 ± 1·1	120·8 ± 0·7
Exp.	27[c]	105·7 ± 1·8	121·7 ± 2·5	122·6 ± 3·2	121·0 ± 2·5	120·9 ± 3·7

[a] Data corresponding to compounds **3–8**.
[b] Data corresponding to compounds **3–5**.
[c] The refcodes of the compounds included in this analysis are given in Appendix B.

Table 7. Experimental and calculated dipole moments (D)

Compound	SAM1	DMol	MIDI-1*	6–31G*	MP2/6–31G*//RHF/6–31G*	MP2/6–31G*	Exp.
1	4·80	3·98[a]	4·32[a]	4·81[b]	4·39	4·35	3·9[c]
2	6·47	5·39	6·37	7·00	5·73	5·73	—
3	7·71	6·73	7·43	8·23	7·21	7·05	7·18[d]
4	6·86	6·06	6·85	7·58	6·22	6·45	6·42[d]
5	7·26	6·56	6·93	7·72	6·60	6·68	6·70[d]
6	8·08	6·35	7·62	8·48	7·13	—	—
7	7·58	5·88	7·36	8·09	6·72	—	—
8	7·46	7·00	7·74	8·54	7·50	—	7·09[e]

[a] Taken from Ref. 7.
[b] Taken from Ref. 34.
[c] Taken from Ref. 37.
[d] Taken from Ref. 32.
[e] Taken from Ref. 33.

Table 8. Root mean square deviation (D) of the dipole moments

	SAM1	DMol	MIDI-1*	6–31G*	MP2/6–31G*//RHF/6–31G*	MP2/6–31G*	Exp.
SAM1	0·00						
DMol	1·12	0·00					
MIDI-1*	0·31	0·91	0·00				
6–31G*	0·60	1·62	0·74	0·00			
MP2/6–31G*//RHF/6–31G*	0·66	0·51	0·46	1·16	0·00		
MP2/6–31G*	0·58	0·32	0·39	1·06	0·13	0·00	
Exp	0·62	0·23	0·47	1·17	0·29	0·26	0·00

Table 9. Correlation parameter of the atomic charges versus experimental ^{13}CNMR shifts[a] (ppm) using the equation: (^{13}CNMR shift)$_i$ = a(calculated charge)$_i$ + b; (r represents the correlation coefficient of the regresion)

Compounds	No. of cases	Parameter	SAM1	DMOL[b]	DMOL[c]	MIDI-1*	6–31G*	MP2/6–31G*//RHF/31G*	MP2/6–31G*
3–5	9	*r*	0·97	0·90	0·98	0·88	0·95	0·93	0·93
		St. dev.	8·78	14·81	6·36	16·56	10·91	12·82	12·28
		b	148·7	140·2	136·8	127·0	128·7	129·7	129·6
		a	143·4	108·4	378·4	108·9	79·47	108·7	112·0
6, 7	10	*r*	0·74	0·34	0·69	0·88	0·37	0·20	
		St. dev·	9·13	12·72	9·73	6·58	10·68	12·09	
		b	146·6	142·4	134·3	132·5	135·7	137·5	
		a	55·7	21·7	201·4	43·7	24·9	25·0	
8	4	*r*	0·84	0·41	0·99	0·91	0·90	0·86	
		St. dev·	11·52	19·59	3·04	8·92	29·22	11·03	
		b	142·7	134·1	125·8	120·9	115·6	114·5	
		a	59·8	42·0	336·7	54·7	55·0	77·8	
3–8	23	*r*	0·85	0·70	0·91	0·78	0·79	0·73	
		St. dev·	12·08	16·34	9·62	14·33	13·98	15·58	
		b	147·0	138·4	131·8	127·2	127·6	128·4	
		a	97·8	70·6	315·0	65·4	51·0	65·1	

[a] Experimental ^{13}CNMR shifts taken from Refs 30, 33 and 389.
[b] Mulliken charges.

predicted non-planarity of the amines in sulphamide in a way similar to that observed[7] in other non-*ab initio* methods such as the semi-empirical method PM3 but not experimentally. In principle, this could be due to its lack of d orbitals to describe the sulphur atom properly; however, previous studies have shown that the absence of d orbitals in *ab initio* methods usually produces very large S=O distances,[26] and this is not the case with this method.

The geometric results obtained at the HF level (MIDI-1* and 6–31G* basis sets) are very similar except for the bond distances involving the sulphur atom for which MIDI-1* provides longer distances than the 6–31G* basis set, *ca* 0·02 Å, and the experimental values (Tables 1, 4 and 5).

The two methods studied which include electron correlation (DMol and MP2/6–31G*) enlarge the bond distance by as much as 0·03 Å with respect to the RHF/6–31G* calculation (Tables 1, 4 and 5). A similar tendency of the MP2[26] and LDF[27,28] methods has been shown in previous studies. In addition, the MP2/6–31G* results present the worst calculated values for several angles (OSO in Table 4, N1—S2—N3 and N3—C4—C5 in Table 6).

The analysis of the experimental values (Tables 4–6) shows a small dispersion, which would simplify the molecular mechanics parametrization of this group and would ensure good reproducibility, in most cases, of the experimental geometric parameters using this methodology. As expected, the smallest variabilities are observed in the parameters in which the sulphur atom is involved that corresponds to the least variable part of the molecule. In general, the results obtained with the theoretical methods show a variability tendency similar to that observed for the experimental values.

In contrast to the small variation of the experimental bonds and angles in this kind of compound, a measure of the non-planarity of the thiadiazine ring, calculated as the distance of the sulphur atom to the plane defined by the rest of the atoms on the ring, shows a large dispersion of the experimental data. The average distance obtained from 27 compounds with this ring in the CSD is 0·383 Å, with a standard deviation of 0·19 Å. Even though most of the structures with small deviations from planarity contain an oxo group in position 4 or 6, there are other structures, such as 3,5-dimethyl-2-(2-phenylethyl)-1*H*,2*H*-1,2,6-thiadiazine-1,1-dioxide, in which this conformation of the ring could be adopted by π–π stacking with the aromatic moiety of another molecule in the crystal.[29] All these data could indicate a small energetic difference between the non-planar minima and the planar structures. The calculations support this idea since the difference in energy between the planar and non-planar structures is only 0·89 kcal mol for **3** and 0·72 kcal mol for **4** with the 6–31G* basis set (1 kcal = 4·184 kJ).

Electronic properties

The analysis of the calculated dipole moments indicates that only methods including electronic correlation, such as DMol, MP2/6-31G*//RHF//6–31G* and MP2/6–31G*//MP2/6–31G*, provide acceptable dipole moments (Tables 7 and 8). The worst calculated results of this property correspond to those obtained with the 6–31G* method with a root mean square (rms) deviation of the experimental results of 1·17 D. These results are in agreement with previous calculations that indicated the inadequacy of this basis set to evaluate this property in sulphur-containing compounds.[7]

Several workers have correlated calculated atomic charges with experimental 13CNMR shifts,[30,31] including compounds with the aminosulphonylamino moiety;[32,33] however, we found poor correlation coefficients and large standard deviations, in general over 10 ppm (Table 9). In addition, the coefficients obtained for each class of compounds studied, thiadiazines (**3–5**), pyrazinothiadiazines (**6** and **7**) and imidazothiadiazines (**8**), are very different. The smaller coefficients correspond to pyrazinothiadiazines and the larger to thiadiazines, which have values in the range of two to three times those obtained for pyrazinothiadiazines, depending on the method compared. Regarding the absolute value of the coefficients for each method, those corresponding to the Hirsfeld analysis are considerably larger than the rest, probably because the point charges derived from this method are smaller since they are complemented by dipole and quadrupole expansion of the electronic distribution.

CONCLUSION

The theoretical and experimental analysis of geometric and electronic properties of compounds bearing the aminosulphonylamino moiety has shown that none of the methods studied is suitable for a simultaneous geometric and electronic description of the molecules. The fastest method, SAM1, has some problems with the description of the geometrical parameters in which nitrogens attached to the sulphur atom are involved and overestimates the dipole moments by *ca*. The calculations performed at the HF level of theory (MIDI–1* and 6–31G*) provide the best geometric description, especially those of the 6–31G* basis set. Regarding the electronic description, the HF/6–31G* calculations give the worst dipole moments, overestimating the experimental values by 1·2 D on average. The HF/MIDI-1* calculations predict slightly larger dipole moments than the experimental values. Finally, the calculations which include electron correlation (DMol, MP2/6–31G*) provide longer bond distances but closer reproduce the experimental dipole moments more closely.

In conclusion, the best strategy for studying compounds containing the aminosulphonylamino moiety or for developing molecular mechanics parameters for it would be to carry out the geometry optimization of the structures with the 6–31G* basis set at the HF level of theory and perform single-point calculations with a method including electron correlation (LDF or MP2) to obtain a good electronic description.

Finally, the poor correlation of the calculated charges with the experimental ^{13}CNMR shifts indicate the low predictability of these kinds of correlations.

SUPPLEMENTARY MATERIAL

The coordinates of the optimized geometries of all the compounds studied here are available on request from the authors.

APPENDIX A

Refcode list of the 90 compounds included in the CSD used to evaluate the statistical average of the SO bond distance and OSO bond angle

AFUTDZ10, AMIMDZ, AMITDZ, ARPTZO10, ATDZDX, ATZCXB, ATZDZM10, ATZTHD10, BACPOK10, BACPUQ10, BEGBOE, BETBOR, BETBUX, BOTZUF, BOYNAE, CEJPAI, CHTDZO, CHTZOX10, CITSON10, CITSON10, CURKUV, CURKUV, DATTIB, DATTIB, DEJJIL, DEVLIZ, DIFLOT, DMAMSO, DOTVEN, DUGPAW, EMTAPC, EMTAPC, FAXVAB, FIHBIH, FIKHEM, FIKHIQ, FIRYUA, FIRZAH, FOGVIG01, FUWMOZ, GABGIZ, GABGUL, HAMPTZ, HTDZDX10, JAGWAP, JATLOF, JATMEW, JEWWEN, JINYAG, KAMWEA, KAMYEC, KAMYIG, KASMOG, KASMUM, KIBRAO, KIBRAO, KIKSEC, KODXUW, KTDZOX, KUPVEW, MCPZSI, MESLIM, MESLIM, MESLIM, MSITZX, MSITZX, RBFROX, SACROD, SACROD, SAJWOP, SEKNOL, SETHEE, SHNZXO10, SIKFUN, SIKFUN, SIKGAU, SIKGAU, SIZLUI, SOTGOX, STZPAX, TMSNSN, TMSNTZ10, TPNSOM10, VAFJUH, VAFTEB, VAFZEH, VEDTED, VEHLUP, VONSEW, VUNTON.

APPENDIX B

Refcode list of the 27 compounds included in the CSD used to evaluate the statistical geometrical average of the thiadiazine ring

AFUTDZ10, AMIMDZ, AMITDZ, ARPTZO10, ATDZDX, ATZDZM10, ATZTHD10, BACPOK10, BACPUQ10, BETBOR, BETBUX, BOYNAE, CEJPAI, CHTDZO, CHTZOX10, DOTVEN, FAXVAB, HTDZDX10, JAGWAP, KTDZOX, KUPVEW, RBFROX, SHNZXO10, VAFJUH, VAFTEB, VEDTED, VUNTON.

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