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ORIGINAL PAPER

Theoretical studies on sulfanilamide and derivatives with antibacterial activity: conformational and electronic analysis

Esteban G. Vega-Hissi · Matías F. Andrada · Graciela N. Zamarbide · Mario R. Estrada · Francisco Tomás-Vert

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Abstract Quantum chemical methods have been used to study the conformational and electronic properties of sulfanilamide and derivatives with antibacterial activity. Calculations at B3LYP/6-311++G(3df,2p) level of theory predict the existence of four conformers for sulfanilamide depending on the orientation of p-amino and amide groups. Focusing on the sulfonamide moiety, amide NH_2 and SO_2 groups could exist either in an eclipsed or staggered arrangement. Gas-phase results predict the eclipsed conformer to be most stable but opposite to what has been rationalized previously, no stabilizing hydrogen bonds between those groups has been found through NBO analysis. When solvent effect is taken into account through the IEF-PCM method, staggered conformer is preferred; in fact, eclipsed conformation changed when explicit solvent molecules were included. Conformational analysis of all derivatives has shown two global minima which are specular images. Five out of the seven derivatives studied adopted a particular minimum energy conformation with very similar geometries.

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E. G. Vega-Hissi (✉) · M. F. Andrada · G. N. Zamarbide · M. R. Estrada
Departamento de Química, Facultad de Química, Bioquímica y Farmacia, Universidad Nac. de San Luis,
Chacabuco 917,
5700 San Luis, Argentina
e-mail: egvega@unsl.edu.ar

F. Tomás-Vert
Departament de Química Física, Universitat de València, Campus Burjassot-Paterna,
46100 Burjassot, València, España

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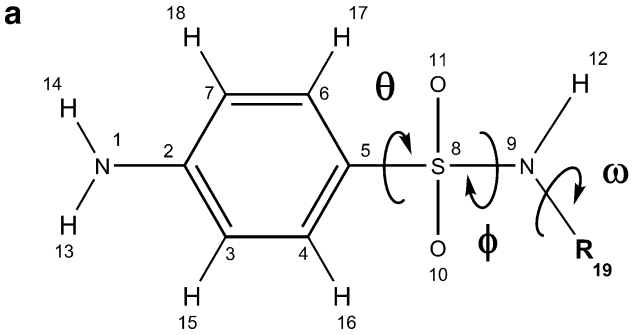
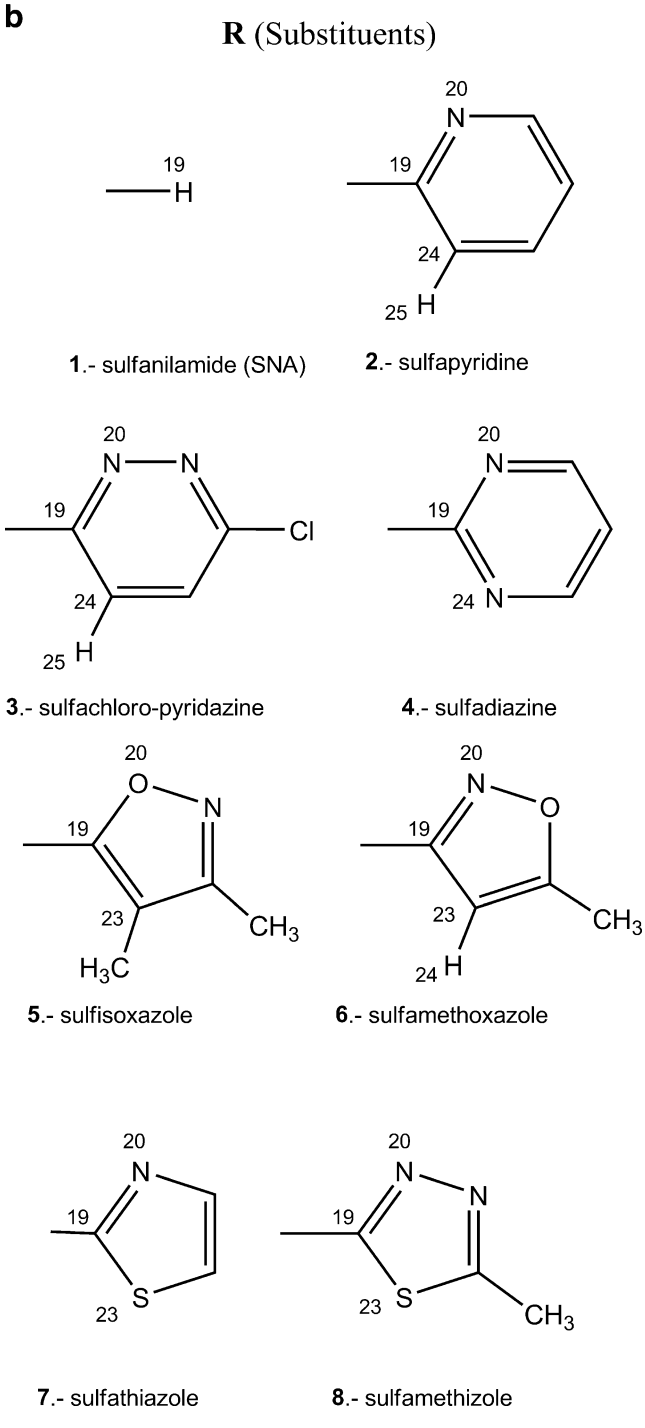
Introduction

The sulfonamide group ($R\text{-}SO_2\text{-}NR_2$) is found in several classes of biologically active compounds such as carbonic anhydrase inhibitors, HIV inhibitors [1], anti-tumor agents [2] and antimicrobials [3], among others. These important bioactive properties are affected by features of sulfonamide group and intramolecular mobility in its proximity.

Antibacterial sulfonamides inhibit microbial growth (bacteria and protozoa) by competitive antagonism of p-aminobenzoic acid in the biosynthesis of folic acid. Due to the structural similarity between sulfonamides and p-aminobenzoic acid, they take its place in the active site of the enzyme dihydropteroate synthetase blocking the metabolic pathway, which results in the inability of the microorganism to synthesize nucleotides and other metabolites essential for growth [4, 5]. Because biological properties correlate strongly with the structure and conformational properties of a compound, the analysis of the latter would provide useful information for designing new effective drugs.

Recent gas-phase studies on benzene sulfonamide [6], p-methylbenzene sulfonamide [7] and other compounds with sulfonamide group [8, 9] have shown a conformation sterically unfavorable with the amide NH_2 group eclipsing the SO_2 entity. However it has been proposed that intramolecular hydrogen bonds stabilize the conformer. A similar behavior would be expected for sulfanilamide (SNA, 1, Fig. 1).





◀ **Fig. 1** (a) Sulfanilamide N-substituted. Numbering and dihedral definitions: θ=($C_4C_5S_8N_9$), ϕ=($C_5S_8N_9H_{12}$) and ω=bond (N_9-R_{19}). (b) Numbering of important atoms and nomenclature of the substituents studied

The aim of this article is to analyze the structural and electronic properties of SNA and derivatives with antimicrobial activity (Fig. 1: sulfapyridine, 2; sulfachlorpyridazine, 3; sulfadiazine, 4; sulfisoxazole, 5; sulfamethoxazole, 6; sulfathiazole, 7; and sulfamethizole, 8) in order to find any conformational relationship between the latters and to explore electron delocalization and charge transfer in these sulfonamide type compounds. This study is performed through quantum chemical calculations (gas-phase and solution) and natural bond orbital (NBO) analysis [10].

Quantum chemical calculations

SNA relaxed potential energy surface (PES) was calculated at HF/6-31+G(d) level of theory. Complete geometry optimization of sulfanilamide conformers have been performed at HF/6-31+G(d), B3LYP/6-31+G(d) and B3LYP/6-311++G(d,p) level of theory. Geometry optimizations of unsubstituted sulfonamide group, (E)-1-propensulfonamide, benzene sulfonamide and para-methylbenzene sulfonamide were carried out at B3LYP/6-311++G(d,p) level. The choice of the latter basis set (valence split triple zeta basis set augmented by polarized and diffuse functions) is justified by previous studies [11, 12], which have shown that polarized and diffuse atomic functions provide a good description of the structure and properties of third row species. Single-point calculations were then performed on the optimized structures at B3LYP/6-311++G(3df,2p) level of theory. Frequency calculations, carried out at the same level employed for geometry optimizations, were used to characterize each stationary point as a minimum and to obtain zero point vibrational energies (ZPE).

B98 and B1B95 functionals methods were also evaluated based on a survey performed by Riley et al. [13] to estimate the performance of different density functionals (combined with different basis sets) for calculating atomic and molecular properties of small molecules.

To investigate the solvent effect of water on conformational stability, single point calculations were performed using the integral equation formalism polarizable continuum model (IEFPCM) with atomic radii invoked via the solvent keyword RADII=UFF. Although continuum solvation models represent an approach of the averaged behavior of solvent molecules, the models have been revised and improved resulting efficient and robust to be applied to the same systems studied in gas-phase [14, 15]. We also performed geometry optimizations with explicit solvent molecules (solvating

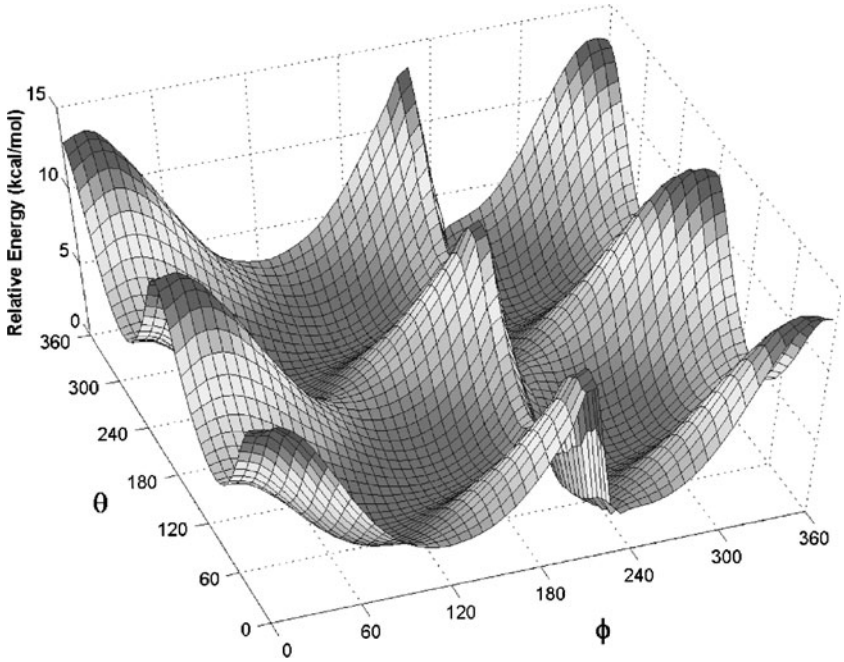


Fig. 2 SNA potential energy surface of the type E=f(θ,ϕ) computed at HF/6-31+G(d) level of theory

randomly the sulfonamide group) to account for chemical interactions between solute and solvent molecules in the first solvation shell.

SNA derivatives conformational search was performed through exploratory PESs computed at HF/3-21G* level of theory. Minimum energy conformers were further optimized at B3LYP/6-311++G(d,p) level. Most stable conformers where superposed using the program PyMOL [16].

All calculations were carried out using Gaussian 03 [17]. The NBO 3.1 program [18], implemented in Gaussian 03 package, was used to analyze charge transfer stabilization energies associated with hydrogen bonds and lone-pair delocalization.

Results and discussion

SNA conformational analysis

As can be seen in Fig. 2, four minimum energy conformers can be found on the potential energy surface of SNA. The most stable structures present the hydrogen atoms of p-amino group and oxygen atoms of sulfone group oriented to the same side of the phenyl ring plane, and the sulfonamide group can be found in two conformations (Fig. 3): 1-e, eclipsed (amide N-H bonds eclipse S-O bonds) or 1-s, staggered (amide NH_2 group staggers the S-C bond). These two conformers have also been found in other compounds containing sulfonamide group [6–9]. Important geometrical parameters of these structures are collected in Table 1. It can be noted that increasing the

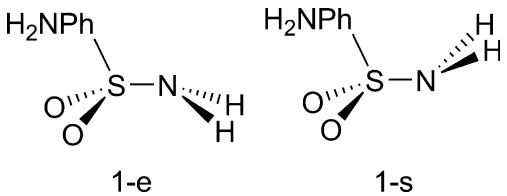


Fig. 3 Most stable conformers of sulfanilamide showing the orientation of the amido NH_2 group with respect to the SO_2 group

Table 1 Geometric parameters of eclipsed and staggered conformers of SNA computed at different levels of theory. Bond lengths are in Å and angles in degrees

Parameters	HF/6-31+G (d)		B3LYP/6-31+G (d)		B3LYP/6-311++G (d,p)	
	1-e	1-s	1-e	1-s	1-e	1-s
Bonds						
S_8-C_5	1.758	1.765	1.783	1.791	1.783	1.792
N_9-S_8	1.654	1.644	1.710	1.693	1.700	1.687
S_8-O_{10}	1.433	1.429	1.470	1.465	1.463	1.458
S_8-O_{11}	1.433	1.429	1.470	1.465	1.463	1.458
Angles						
N_9-S_8-O_{10}	106.5	105.4	106.5	104.9	106.6	105.0
N_9-S_8-O_{11}	106.4	105.4	106.4	104.9	106.5	105.0
N_9-S_8-C_5	105.5	107.9	104.4	108.0	104.4	107.9
Dihedrals						
H_{12}-N_9-S_8-C_5	−116.6	65.7	−118.7	63.4	−118.1	64.1
H_{13}-N_9-S_8-C_5	117.6	−65.7	119.6	−63.4	119.1	−64.2

Table 2 Atomic charges (NPA) obtained at B3LYP/6-311++G (3df,2p) level

Atom	1-e	1-s
S_8	2.310	2.317
N_9	−1.067	−1.049
O_{10}	−0.958	−0.951
O_{11}	−0.958	−0.951
C_5	−0.345	−0.355

basis set complexity only leads to a small change in geometrical parameters values.

N-S bond length lies between S-N single bond distance (1.733 Å) and double bond distance (1.596 Å). Its value is rationalized by $n_N \rightarrow \sigma_{C\text{-}S}^*$ anomeric π interactions, sulfur d-orbital participation and electrostatic interactions between S and N (see NPA charges on Table 2) according to previous studies on unsubstituted sulfonamide group [8].

Conformer 1-e has an eclipsed arrangement and 1-s has a staggered arrangement so 1-s is expected to have lower energy. Gas-phase results show that eclipsed conformer is preferred, but ΔE between 1-e and 1-s decreases with the increase of the complexity of the quantum mechanical level and conformer 1-s is 1.60 kcal mol^{-1} more stable than 1-e when continuum solvent model is applied (Table 3). The same behavior is obtained for analog sulfonamide compounds: sulfonamide group, (E)-1-propenesulfonamide, benzenesulfonamide and p-methyl-benzenesulfonamide. When explicit solvent molecules are added, staggered conformation is maintained in all of these compounds but eclipsed conformation changes; for instance, sulfonamide group eclipsed conformer goes through inversion at nitrogen changing to the staggered conformation. Probably this is because the latter geometry has a more proper orientation to form a stable hydrogen bond network between the sulfonamide group and the solvent.

Results obtained with B98 and B1B95 functionals (collected in Tables S1 and S2 of Online Resource) are in perfect agreement with B3LYP results.

SNA NBO analysis

NBO analysis reveals only one bond between sulfur and each oxygen and that the oxygens have three unshared pairs of electrons. It indicates as in $DMSO_2$ coordinate covalent single S-O bonds, in which both shared electrons come from the sulfur, $S^+ \rightarrow O^-$ [19]. In fact, each oxygen atom has more than 0.94 units of negative charge and sulfur has more than 2.26 units of positive charge (Table 2).

Table 4 summarizes important interactions in sulfonamide group of SNA. Anomeric $n_{N9} \rightarrow \sigma_{C5\text{-}S8}^*$ interaction follows the same trends found for unsubstituted sulfonamide group [8], i.e., staggered conformer interaction energy is higher than interaction energy of the eclipsed conformer because of N_9 lone pair is better orientated for the interaction in the staggered conformation. However, overall values are lower, perhaps due to the electron donating group (NH_2) attached at phenyl ring. It is important to note at this point the influence of anomeric effect on S_8-C_5 and S_8-N_9 distances. As charge transfer stabilization energy increases (stronger anomeric effect), S_8-N_9 bond shortens and S_8-C_5 bond lengthens. This can be seen comparing SNA conformers and the later in all the SNA derivatives studied.

The energy of $n_{N9} \rightarrow \sigma_{S8\text{-}O10}^*$ and $n_{N9} \rightarrow \sigma_{S8\text{-}O11}^*$ interactions is the same for both conformers because of their symmetry.

The second order energy analysis reveals that lone pair (oxygen and nitrogen atoms) electron density is delocalized over the O_2S-N moiety and there is no charge transfer energy from oxygen lone pairs neither to $\sigma_{N9\text{-}H11}^*$ nor to

Table 3 Relative energies (ΔE) of SNA and other sulfonamide compounds. Zero point energy corrected values are given in parentheses. All values are in kcal mol^{-1}

Method	e → s ΔE				
	sa[a]	psa[b]	bzsa[c]	pm-bzsa[d]	SNA(1)
Gas-phase					
HF/6-31+G(d)//HF/6-31+G(d)	–	–	–	–	0.79 (0.91)
B3LYP/6-31+G(d)//B3LYP/6-31+G(d)	–	–	–	–	0.66 (0.95)
B3LYP/6-311++G(d,p)//B3LYP/6-311++G(d,p)	1.05 (1.01)	1.28 (1.34)	0.66 (0.86)	0.65 (0.85)	0.55 (0.81)
B3LYP/6-311++G(3df,2p)//B3LYP/6-311++G(d,p)	0.83 (0.79)	0.68 (0.74)	0.04 (0.24)	0.02 (0.22)	−0.05 (0.22)
Aqueous solution(IEF-PCM)					
B3LYP/6-311++G(3df,2p)//B3LYP/6-311++G(d,p)	−0.96 (−1.00)	−1.23 (−1.17)	−1.77 (−1.57)	−1.80 (−1.60)	−1.86 (−1.60)

[a] unsubstituted sulfonamide group
[b] (E)-1-propenesulfonamide
[c] benzenesulfonamide
[d] p-methyl-benzenesulfonamide

Table 4 Gas-phase charge transfer stabilization energies of various anomeric interactions in sulfanilamide

Interaction	$\Delta E^{(2)}$ (kcal mol^{-1})	
	1-e	1-s
$n_{N9} \rightarrow \sigma_{C5\text{-}S8}^{*}$	3.80	6.68
$n_{N9} \rightarrow \sigma_{S8\text{-}O10}^{*}$	2.17	1.71
$n_{N9} \rightarrow \sigma_{S8\text{-}O11}^{*}$	2.07	1.71
$n_{O10(2)} \rightarrow \sigma_{C5\text{-}S8}^{*}$	15.46	16.75
$n_{O10(2)} \rightarrow \sigma_{S8\text{-}N9}^{*}$	14.31	12.17
$n_{O10(2)} \rightarrow \sigma_{S8\text{-}O11}^{*}$	1.05	1.83
$n_{O10(3)} \rightarrow \sigma_{C5\text{-}S8}^{*}$	2.41	1.68
$n_{O10(3)} \rightarrow \sigma_{S8\text{-}N9}^{*}$	10.63	12.34
$n_{O10(3)} \rightarrow \sigma_{S8\text{-}O11}^{*}$	21.30	20.60
$n_{O11(2)} \rightarrow \sigma_{C5\text{-}S8}^{*}$	15.44	16.75
$n_{O11(2)} \rightarrow \sigma_{S8\text{-}N9}^{*}$	14.34	12.17
$n_{O11(2)} \rightarrow \sigma_{S8\text{-}O10}^{*}$	1.03	1.84
$n_{O11(3)} \rightarrow \sigma_{C5\text{-}S8}^{*}$	2.44	1.67
$n_{O11(3)} \rightarrow \sigma_{S8\text{-}N9}^{*}$	10.56	12.35
$n_{O11(3)} \rightarrow \sigma_{S8\text{-}O10}^{*}$	21.32	20.59

$\sigma_{N9\text{-}H12}^{*}$. That kind of charge transfer is observed in hydrogen bonds, so we think that it is not probable that intramolecular hydrogen bonds could stabilize the eclipsed conformation. The same results (absence of charge transfer and thereby of hydrogen bonds) were obtained for benzene sulfonamide and p-methylbenzene sulfonamide in spite of what has been rationalized previously [6, 7].

SNA derivatives conformational analysis

Conformational space analysis of all SNA derivatives was performed through PESs of the type $E=f(\phi,\omega)$ and are shown in Figs. S1 and S2 of Online Resource. Two global minima with the same absolute values of dihedral angles ϕ and ω but opposite signs were found for each SNA derivative: they are specular images. Because of the analysis of both minima gave the same results we show only one for simplicity.

All the structures present a staggered conformation, except for compound 4 where hydrogen atom on the amido group eclipses the oxygen atom of SO_2 entity. Staggered conformers have also been reported for N-sulfonyl morpholines compounds with double substitution of amido N of sulfonamide [20].

Although all derivatives show S_8-N_9 bond distance larger (Table 5) than distance present in SNA, values are lower than S-N single bond length, i.e., amide N substitution shortens this distance. Due to the conjugated nature of all substituents studied, sum of angles around N_9 show low pyramidal character with values higher than those founded for unsubstituted sulfonamide group (336.7º) [8] and for SNA (337.5º).

In order to analyze the relative orientation of the substituent and molecular similarity between the different compounds studied here, we have aligned them using as a template the pharmacophore group of these drugs. A trend was found in SNA derivatives 2, 3, 6, 7, and 8: there is a large overlap between global minima structures as can be seen in the superposition of the structures that is depicted in Fig. 4 and can be checked numerically comparing φ and ω dihedral values (Table 5).

Table 5 Geometry of minimum energy conformers of sulfanilamide derivatives. Bond lengths are in Å and angles in degrees

Parameters	2	3	4	5	6	7	8
Bonds							
C_5-S_8	1.785	1.781	1.777	1.780	1.783	1.781	1.780
N_9-S_8	1.703	1.714	1.715	1.731	1.709	1.716	1.720
S_8-O_{10}	1.458	1.456	1.462	1.458	1.457	1.457	1.456
S_8-O_{11}	1.459	1.459	1.455	1.457	1.458	1.457	1.457
N_9-C_{19}	1.412	1.403	1.387	1.391	1.397	1.394	1.389
Angles							
N_9-S_8-O_{10}	103.41	103.27	101.37	103.07	103.32	103.2	103.11
N_9-S_8-O_{11}	106.6	105.8	109.62	105.32	105.63	105.08	104.92
N_9-S_8-C_5	107.32	107.13	105.27	107.35	107.51	107.43	107.29
Dihedrals							
S_8-N_9-C_{19}-$X^{a}_{20}(\omega)$	−136.7	−134.07	−26.13	−102.63	−134.42	−134.09	−133.46
C_5-S_8-N_9-$C_{19}(\varphi)$	61.73	63.22	80.44	60.28	63.95	62.79	64.05
Sum of angles around N_9	347.22	346.5	353.75	344.77	347.13	346.92	346.96
Conformation[b]	s	s	e	s	s	s	s

[a] Corresponding atom of SNA derivative structure

[b] Arragement of sulfonamide group either staggered (s) or eclipsed (e)

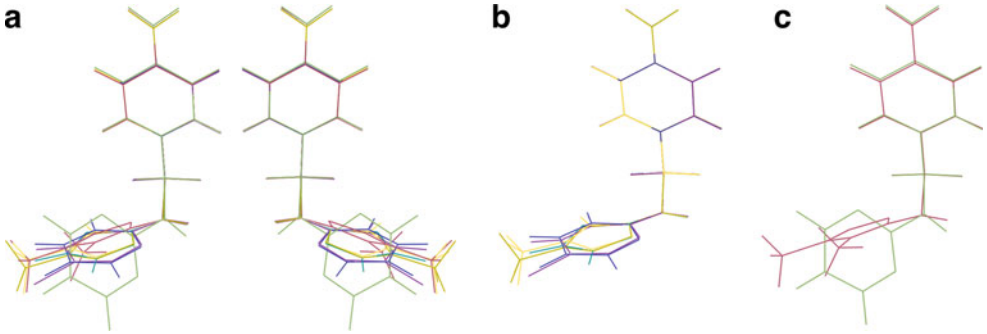


Fig. 4 (a) Superimposition of most stable conformers of all SNA derivatives; (b) Compounds 2, 3, 6, 7 and 8; (c) Compounds 4 and 5

SNA derivatives NBO analysis

As can be seen in Table 6, N_9 atom has less negative charge whereas S_8 has slightly more positive charge compared to SNA (Table 2), but charge difference between these atoms is almost the same for all the SNA derivatives. The strong electrostatic interactions between S and N persist (only slightly reduced) although the presence of a substituent on N_9.

Energy values of $n_{N9} \rightarrow \sigma_{S8\text{-}O10}^{*}$ and $n_{N9} \rightarrow \sigma_{S8\text{-}O11}^{*}$ interactions is different because of the particular orientation of the substituent in the minimum energy conformers.

In all SNA derivatives, amide N lone pair is delocalized not only over the O_2S-N moiety but to the substituent. In fact N_9 lone pair interacts strongly with substituent π-system. This is justified by a reduction on n_{N9} occupancy (Table 6) and a series of interactions of lone pair with substituent antibonding orbitals, many of which have higher energy values (Table S3) than $n_{N9} \rightarrow \sigma_{C5\text{-}S8}^{*}$ interaction energy. Due to the above, we expected, and found, a lower energy value for the latter anomeric interaction compared to the same interaction in SNA. This rationalization also explains why S_8-N_9 distances are longer (and S_8-C_5 distances are shorter) in every derivative studied. We observe the same behavior when compound 4 values were compared with SNA eclipsed conformer values.

Compounds 2 and 3 present one hydrogen bond between O_{11} and H_{25} with a low charge transfer stabilization energy value (less than 0.7 kcalmol^{-1}, Table S3). We think that this interaction could not be decisive for the stability of the conformer, although it contributes to it. This rationalization is based upon minimum energy conformers of SNA derivatives 6, 7, and 8 present almost the same geometry (close ϕ and ω dihedral values) but lack of this stabilizating interaction.

Conclusions

Gas-phase quantum chemical calculations predict that sulfonamide group of SNA could exist either in an eclipsed or staggered arrangement. As has been found for other sulfonamide-type compounds [6–9], eclipsed conformer is more stable but NBO analysis performed at a high level of theory predict that no hydrogen bond stabilizes this conformation, so this could not be a valid criterion to explain gas-phase conformational preference. When solvent effect was taken into consideration, staggered conformer was more stable than eclipsed one in all the studied systems. So, any stabilizing force important in gas-phase, is minimized in bulk water represented by the IEF-PCM method. In the presence of solvent molecules sulfonamide moiety eclipsed conformation changes probably to optimize the intermolecular hydrogen -bonded interactions in the hydrated complex.

All the functionals employed in this paper gave acceptable results with almost negligible differences between them.

Table 6 Common NBO analysis parameters of SNA derivatives

Parameters	2	3	4	5	6	7	8
Atomic charges							
S_8	2.295	2.292	2.294	2.281	2.293	2.289	2.289
N_9	−0.853	−0.849	−0.845	−0.858	−0.845	−0.860	−0.858
Δ_{SN}[a]	3.15	3.14	3.14	3.14	3.14	3.15	3.15
Occupancy[b]							
n_{N9}	1.823	1.823	1.783	1.861	1.835	1.825	1.824
$\sigma_{C5\text{-}S8}^{*}$	0.190	0.187	0.180	0.186	0.189	0.188	0.186
$\Delta E^{(2)}$[c]							
$n_{N9} \rightarrow \sigma_{C5\text{-}S8}^{*}$	6.45	5.93	3.71	5.54	6.17	5.91	5.72
$n_{N9} \rightarrow \sigma_{S8\text{-}O10}^{*}$	1.39	1.50	–	1.11	1.47	1.49	1.56
$n_{N9} \rightarrow \sigma_{S8\text{-}O11}^{*}$	2.54	2.24	5.85	2.42	2.38	3.19	2.24

[a] Charge difference between S_8 and N_9 atoms

[b] SNA n_{N9} occupancy is 1.921

[c] Charge transfer stabilization energy

We have found that all SNA derivatives present two global minima which are specular images and that compounds 2, 3, 6, 7, and 8 show a large similarity degree (pharmacophore and substituent) which may be related to a better electron density delocalization and/or to the binding mode to active site of dihydropteroate synthetase. Substitution does not change the strong electrostatic interactions between S and N of the O_2S-N moiety, however it allows more delocalization of N_9 lone pair electron density. The distance of C_5-S_8 bond changes directly with the strength of the anomeric $n_{N9} \rightarrow \sigma_{C5\text{-}S8}^{*}$ interaction while the distance of S_8-N_9 bond changes inversely.

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