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Theoretical study of the conformational preference of N-[(4-aminophenyl) sulphonyl]acetamide (sulphacetamide) and its azanion

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Dedicated to Academician Ivan Juchnovski on the occasion of his 70th birthday

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The potential energy surfaces of N-[(4-aminophenyl)sulphonyl]acetamide (sulphacetamide) and its azanion have been explored with DFT calculation at the B3LYP/6-31G* level of theory. All conformational isomers have been located. Three torsion angles (C–C–S–N, C–S–N–C, and S–N–C=O) are used in describing the conformations of the species examined. The preferred structures obtained by the scan for molecule (∠C–C–S–N, 90°; ∠C–S–N–C, 60° and ∠S–N–C=O, 0°) and azanion (∠C–C–S–N, –90°; ∠C–S–N–C, 60° and ∠S–N–C=O, 0°) were optimized at the B3LYP/6-31++G** level. The results of the optimized molecular structure are presented and compared with the experimental X-ray diffraction. The geometry changes caused by the conversion of the molecule into azanion have also been estimated.

Key words: sulphacetamide, azanion, conformers, DFT.

INTRODUCTION

N-[(4-Aminophenyl)sulfonyl]acetamide (sulphacetamide) belongs to the important class of sulpha drugs, which are well-known as antimicrobial agents. The structural resemblance between the sulphanilamide grouping and *p*-aminobenzoic acid enables the sulphanilamide to block folic acid synthesis in bacteria, which accounts the antibacterial action of these drugs [1, 2]. Sulphacetamide is of considerable interest as a highly soluble sulphonamide which does not cause crystalluria, and its sodium salts are extensively used in cases of ophthalmic infections, giving solutions which do not irritate the delicate eye tissues [3]. Detailed knowledge of the structure of the species studied is an obligatory prerequisite for understanding its biological activity. Theoretical investigations were performed with the aim to provide an insight into structure-activity relationships. CNDO/2 calculations have been used to represent the changes in the electronic structure of a series of sulphanilamides on going to their anionic, imidic and amidic form and to obtain correlations between theoretically calculated values and biological activity parameters [4]. It was found that the anionic forms appear to give the dominant contributions to the biological potency of these compounds. The increase in the charge on the nitrogen atom was associated with the increase in the experimental pK_a and also in a decrease of the bacteriostatic activity [5]. It was suggested that acidity of sulphonamido group, and the factors affecting it, are key features ruling the physico-chemical properties which modulate the sulphonamide bioactivity [6]. A conformational analysis of sulphonamide-type compounds illustrates that active molecules have relatively larger torsion energy barriers [7].

The molecular structure of sulphacetamide has not received the attention one could reasonably expect. We found in the literature only one quantum chemical study where selected geometrical parameters of the sulphacetamide molecule and its anionic form were presented [6]. By single crystal X-ray diffraction was determined the crystal and molecular structure of sulphacetamide [8], sodium sulphacetamide monohydrate [9] and silver sulphacetamide [10].

Since the characterization of the most stable conformers of sulphacetamide and the factors which contribute to their relative stability are essential for a complete understanding of its biological properties, we used in this article the density functional theory (DFT) in order to perform structural analysis of both sulphacetamide and its azanionic form.

THEORETICAL AND COMPUTATIONAL METHODS

DFT computations of the studied species were performed using the GAUSSIAN-98 program

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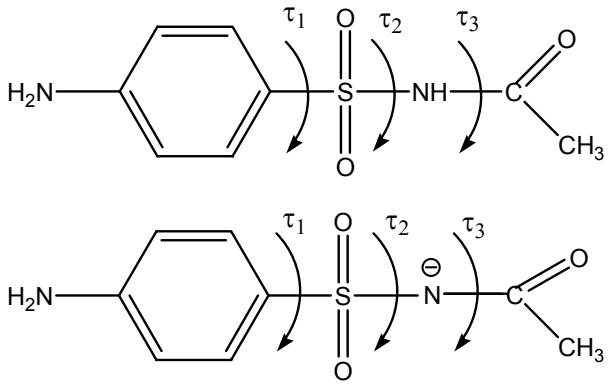
package [11]. We employed the B3LYP functional, which combines Becke's three - parameter non-local exchange with the correlation functional of Lee, Yang and Parr [12, 13], adopting a 6-31G* basis set. The conformational analysis of the molecule and its anion was carried out by varying the torsion angles τ_1, τ_2 and τ_3 from 0° up to 360° in step of 18° with relaxation of the system (see Scheme 1). The minima obtained by the scan for both species were optimized at B3LYP/6-31++G** level. For each structure, the stationary points found on the molecular potential energy hypersurfaces were characterized using standard analytical harmonic vibrational analysis. The absence of negative frequencies, as well as of negative eigenvalues of the second-derivative matrix, confirmed that the stationary points correspond to minima on the potential energy hypersurfaces.

RESULTS AND DISCUSSION

Sulphacetamide and its azanion have a large degree of conformational mobility due to the three single bonds C–S–N–C. In order to characterize conformational states, the potentional energy profiles for internal rotations around these single bonds were calculated. Three torsion angles (τ_1, τ_2 and τ_3) are used here to describe the conformations of the species examined (see Scheme 1).



Scheme 1.

The smaller of the two C–C–S–N torsion angles between the aniline ring and S–N bond is marked as τ_1. Figure 1 presents the calculated potential energy profiles for internal rotation around the Ph–S bond for sulphacetamide and its anion. B3LYP calculations predict the existence of two stable conformations both in molecule and azanion: **1** (C–C–S–N, 90°) and **2** (C–C–S–N, –90°). Comparison of the energy values of these conformers indicates that structure **1** with $\tau_1 \cong 90$ is the lowest in energy for the molecule and it is the least stable for the azanion. However, in both cases the estimated conformational energy differences are very small (0.3 kJ·mol^{-1} for molecule and 0.7 kJ·mol^{-1} for azanion). These τ_1 values lie in a characteristic range (between 70 and 120°) reported in literature by analyzing of the geometries of many independent sulphonamide fragments [14, 15]. This angle for sulphacetamide has been experimentally found to be 114.5° [8]. The calculated energy barriers (about 21 and 17 kJ·mol^{-1} for molecule and azanion, respectively) are higher than the energies of the rotation of the aromatic rings which respect to the sulphonamido group for sulphanilamide [6].

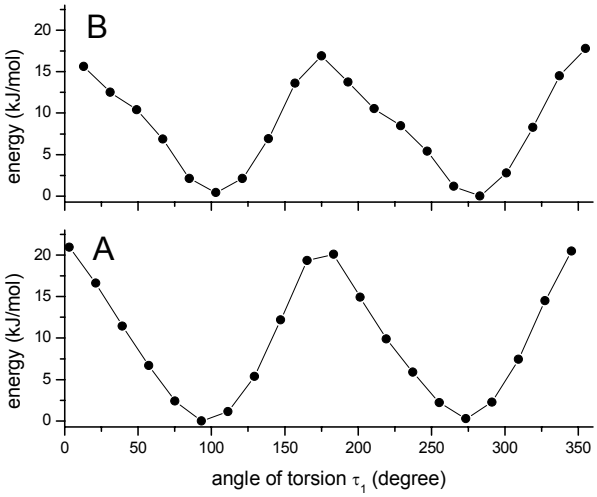


Fig. 1. Conformation potential energy curves for the rotation around Ph-S bond of sulphacetamide molecule (A) and its azanion (B).

The dependence of the total energy on the central torsion angle, C–S–N–C (called τ_2, Scheme 1) is depicted in Figure 2. Internal rotation around the S–N bond, in the molecule and in azanion, also leads to a conformational isomerism. Three stable conformers were predicted both in the molecule and azanion: **1** (C–S–N–C, 60°) and **2** (C–S–N–C, –60°) and **3** (C–S–N–C, 180°). The conformers **1** and **2** were predicted to have relative energies within *ca.* 0.3 and 0.1 kJ·mol^{-1} for molecule and azanion, respectively, and then being expected to contribute significantly to the gas-phase conformation equilibrium. Conformers **3** in both molecule and azanion were found to be of no practical interest, because their energies are higher by more than 23 and 13 kJ·mol^{-1}, respectively than the energies of **1** and **2** conformers.

Conformation potential energy curves for the rotation around N–C bond of sulphacetamide molecule and its azanion are given in Figure 3. The S–N–C=O torsion angle is referred to as τ_3. Two possible conformers were located: **1** (S–N–C=O, 0°) and **2** (S–N–C=O, 180°). In this case, however, the

estimated conformational energy differences in the molecule are very small (<1 kJ·mol^{-1}) and no conclusive answer regarding the relative stability of the different conformers can be extracted by taking into consideration only the theoretical results. According to X-ray diffraction the τ_3 value is 7.2° [8]. Comparison of the energy values of these conformers in azanion indicates that conformer **2** is less stable by 10 kJ·mol^{-1} than conformer **1** in the gas state. In general, conformations **1** are within the range of (τ_3, 0–20) observed for secondary amides [15].

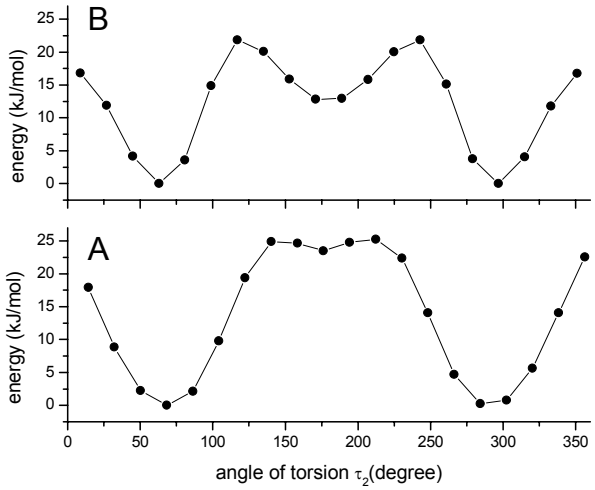


Fig. 2. Conformation potential energy curves for the rotation around S-N bond of sulphacetamide molecule (A) and its azanion (B).

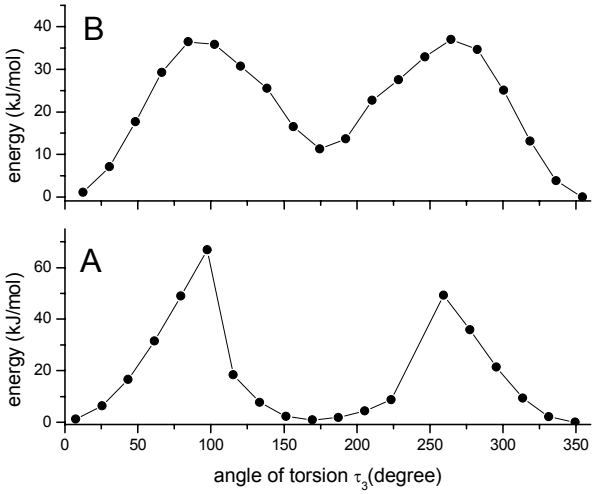
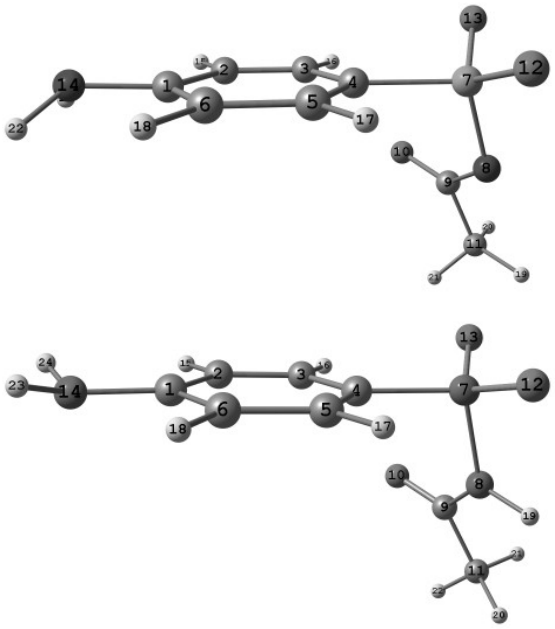


Fig. 3. Conformation potential energy curves for the rotation around N-C bond of sulphacetamide molecule (A) and its azanion (B).

The minima obtained by the scan for molecule and azanion were optimized at B3LYP/6-31++G** level. The relevant conformations are depicted in Scheme 2. All calculated geometry parameters of the most stable conformer for the molecule are presented in Table 1. The molecular structure data of sulphacetamide [8] determined by single crystal X-ray analyses are listed, too. According to X-ray data, the sulphur and amino nitrogen atoms are lying in the phenilene ring plane. The one of the sulphonyl oxygen is almost coplanar with the phenilene ring (<OSCC = 3.5), while the other is out of this plane (<OSCC = 44.7). The fragment containing S, N, C, C, O atoms is also planar and the dihedral angle between this plane and is 90.9. Similar results have been theoretically estimated for the isolated sulphacetamide molecule. As can be seen, there is a good agreement between the experimental and the theoretical structural parameters (the mean absolute deviations are 0.03Å for bond length and 1.0º for bond angle). The largest individual deviation of 0.076 Å corresponds to the S–N bond, whose N-atom participated directly in intermolecular interaction in the crystal state. The theoretical method used predicts correctly the N_8–C_9 and N_{14}–C_1 bond lengths which are in agreement with trigonal hybridization of the nitrogen atoms and with a C_9–C_{11} bond length close to the expected Csp^2–Csp^3 distances. The carbonyl distance C_9–O_{10} is equivalent to that of a partially double bond as the O atom is involved. In agreement between theory and experiment there are deviations of the phenyl ring bond lengths C_2–C_3 and C_5–C_6 from the remaining ones (Table 1). Similar partially quinoidal structures were observed in *p*-aminobenzoic acid [16], *p*-sulphanilamide [17] and *p*-sulphathiazole [18].



Scheme 2. Lowest energy conformer of neutral sulphacetamide (*down*) and its azanion (*up*) with atom numbering scheme.

Table 1. Theoretical and experimental values of bond lengths (Å), angles (degrees) and selected torsion angles (degrees) in the molecule of sulphacetamide.

Geometry parameters	B3LYP	X-ray [a]	Δ [b]
Bond lengths			
$R(C_1C_2)$	1.410	1.387(5)	0.023
$R(C_2C_3)$	1.384	1.372(5)	0.012
$R(C_3C_4)$	1.400	1.380(4)	0.020
$R(C_4C_5)$	1.400	1.385(4)	0.015
$R(C_5C_6)$	1.389	1.355(5)	0.034
$R(C_6C_1)$	1.410	1.405(4)	0.005
$R(S_7C_4)$	1.775	1.749(3)	0.026
$R(N_8S_7)$	1.729	1.653(3)	0.076
$R(C_9N_8)$	1.388	1.363(4)	0.025
$R(O_{10}C_9)$	1.219	1.216(5)	0.003
$R(C_{11}C_9)$	1.518	1.488(5)	0.030
$R(O_{12}S_7)$	1.469	1.419(5)	0.050
$R(O_{13}S_7)$	1.459	1.425(5)	0.034
$R(N_{14}C_1)$	1.384	1.366(5)	0.018
m.d. [c]	-	-	0.027
Bond angle			
$<(C_1C_2C_3)$	120.8	120.2(2)	0.6
$<(C_2C_3C_4)$	119.4	120.8(3)	1.4
$<(C_3C_4C_5)$	120.8	119.3(3)	1.5
$<(C_4C_5C_6)$	119.6	120.3(3)	0.7
$<(C_1C_6C_5)$	120.5	121.0(3)	0.5
$<(C_2C_1C_6)$	118.9	118.3(3)	0.6
$<(S_7C_4C_5)$	119.2	119.7(2)	0.5
$<(O_{12}S_7C_4)$	109.2	110.0(1)	0.8
$<(O_{13}S_7C_4)$	109.5	109.1(1)	0.4
$<(N_8S_7C_4)$	105.5	105.5(1)	0
$<(N_8S_7O_{12})$	101.1	103.2(1)	2.1
$<(N_8S_7O_{13})$	108.4	109.9(1)	1.5
$<(C_9N_8S_7)$	126.3	124.8(2)	1.5
$<(O_{10}C_9N_8)$	122.4	120.1(2)	2.3
$<(C_{11}C_9N_8)$	114.4	115.0(3)	0.6
$<(C_{11}C_9O_{10})$	123.2	124.8(3)	1.6
m.d.[c]			1.04
Torsion angle			
$<(N_8S_7C_4C_3)$	87.8	66.0	
$<(O_{12}S_7C_4C_3)$	164.2	134.8	
$<(O_{13}S_7C_4C_3)$	28.8	3.5	
$<(C_9N_8S_7O_{12})$	–47.1	–61.6	
$<(C_9N_8S_7O_{13})$	146.5	171.4	
$<(O_{10}C_9N_8S_7)$	10.1	7.2	
$<(C_{11}C_9N_8S_7)$	–169.3	–172.0	
$<(C_4S_7N_8C_9)$	68.2	55.8	

[a]Ref. 8; [b] Algebraic deviations between theoretical and experimental value; [c]Mean absolute deviation.

Certain geometry parameters (bond lengths and bond angles), calculated for the isolated azanion and sodium sulphacetamide monoxydrate determined by single crystal X-ray analyses, are compared in Table 2. The mean absolute deviation (m.a.d.) between the theoretical and experimental bond length is 0.020. This result can be considered as very good with m.a.d. values comparable to the average error for carbanions, oxyanions, azanions [19–22] and references therein. The theoretical method used predicts quite correctly also the bond angles (m.a.d. = 0.6º). The calculations predict that the largest structural deviations, caused by the molecule→azanion conversion, should be manifested as shortenings of the S–N and N–C bonds and lengthenings of the Ph–S, C=O, S=O bonds.

Table 2. Theoretical and experimental values of bond lengths (Å) and angles (degrees) in the azanion of sulphacetamide.

Geometry Parameters	B3LYP	X-ray [a]	Δ [b]
Bond lengths			
$R(C_1C_2)$	1.404	1.400(9)	0.004
$R(C_2C_3)$	1.394	1.382(9)	0.012
$R(C_3C_4)$	1.397	1.393(9)	0.004
$R(C_4C_5)$	1.396	1.392(10)	0.004
$R(C_5C_6)$	1.396	1.382(9)	0.014
$R(C_6C_1)$	1.403	1.387(9)	0.016
$R(S_7C_4)$	1.819	1.763(6)	0.056
$R(N_8S_7)$	1.641	1.603(5)	0.038
$R(C_9N_8)$	1.354	1.349(9)	0.005
$R(O_{10}C_9)$	1.247	1.247(7)	0
$R(C_{11}C_9)$	1.534	1.498(9)	0.036
$R(O_{12}S_7)$	1.484	1.444(6)	0.040
$R(O_{13}S_7)$	1.483	1.453(4)	0.030
$R(N_{14}C_1)$	1.414	1.394(8)	0.020
m.d. [c]	-	-	0.020
Bond angle			
$<(C_1C_2C_3)$	120.8	120.5(6)	0.3
$<(C_2C_3C_4)$	119.9	119.8(6)	0.1
$<(C_3C_4C_5)$	119.9	120.0(6)	0.1
$<(C_4C_5C_6)$	120.3	119.9(6)	0.4
$<(C_1C_6C_5)$	120.4	120.7(5)	0.3
$<(C_2C_1C_6)$	118.9	119.1(6)	0.2
$<(S_7C_4C_5)$	119.3	120.4(5)	1.1
$<(O_{12}S_7C_4)$	104.6	-	0
$<(O_{13}S_7C_4)$	106.3	107.7(3)	1.4
$<(N_8S_7C_4)$	108.3	107.3(3)	1
$<(N_8S_7O_{12})$	106.2	105.6(3)	0.6
$<(N_8S_7O_{13})$	114.0	113.5(3)	0.5
$<(C_9N_8S_7)$	120.0	121.5(4)	1.5
$<(O_{10}C_9N_8)$	129.5	-	0
$<(C_{11}C_9N_8)$	112.3	114.1(5)	1.8
$<(C_{11}C_9O_{10})$	118.2	119.3(3)	1.1
m.d. [c]			0.65
Torsion angle			
$<(N_8S_7C_4C_3)$	–94.9	145.0	
$<(O_{12}S_7C_4C_3)$	162.0	165.3	
$<(O_{13}S_7C_4C_3)$	37.8	22.5	
$<(C_9N_8S_7O_{12})$	–55.2	–55.2	
$<(C_9N_8S_7O_{13})$	174.7	179.2	
$<(O_{10}C_9N_8S_7)$	5.6	0.2	
$<(C_{11}C_9N_8S_7)$	–175.6	–179.3	
$<(C_4S_7N_8C_9)$	62.8	64.9	

[a] Refs. 9, 10; [b] Algebraic deviations between theoretical and experimental value; [c] Mean absolute deviation.

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ТЕОРЕТИЧНО ИЗСЛЕДВАНЕ НА КОНФОРМАЦИОННИТЕ ПРЕДПОЧИТАНИЯ НА N-[(4-АМИНОФЕНИЛ)СУЛФОНИЛ]АЦЕТАМИД (СУЛФАЦЕТАМИД) И НЕГОВИЯ АЗАНИОН

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Посветена на акад. Иван Юхновски по повод на 70-та му годишнина

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(Резюме)

Потенциалните енергетични повърхности на N-[(4-аминофенил)сулфонил]ацетамид (сулфацетамид) и неговия азанион са изследвани чрез теорията на фукционала на плътността на ниво B3LYP/6-31G*. Три торзионни ъгъла (C–C–S–N, C–S–N–C и S–N–C=O) са използвани за описанието на възможните конформациите на изследваните частици. Предпочетените структури получени при сканирането за молекулата (∠C–C–S–N, 90°; ∠C–S–N–C, 60° и ∠S–N–C=O, 0°) и азаниона (∠C–C–S–N, –90°; ∠C–S–N–C, 60° и ∠S–N–C=O, 0°), са оптимизирани на ниво B3LYP/6-31++G**. Оптимизираните структурни параметри за молекулата и азаниона за сравнени с експерименталните рентгеноструктурни данни. Установени са геометричните промени, произтичащи от превръщането на молекулата в анион.