Article

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

Prediction of Thermodynamic and Structural Properties of Sulfamerazine and Sulfamethazine in Water Using DFT and ab Initio Methods

Neda Hazhir[1], Farhoush Kiani[1], Hasan Tahermansouri[1], Azade Ghorbani-Hasan Saraei[2], Fardad Koohyar[3,4*]

[1] *Department of Chemistry, Faculty of science, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran.*
[2]*Department of Agriculture of Food Science Engineering, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran.*
[3]*Division of Computational Physics, Institute for Computational Science, Ton Duc Thang University, Ho Chi Minh City, Vietnam.*
[4]*Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Vietnam.*
Corresponding author e-mail: fardadkoohyar@tdt.edu.vn

Received August 16th, 2017; Accepted October 31, 2017

DOI: http://dx.doi.org/10.29356/jmcs.v62i1.575

Abstract. The acid-ionization constant (pK_a) is an important physico-chemical property of molecules. In this research work, the ab initio and density functional theory (DFT) methods, in combination with the polarized continuum model (PCM), were used to calculate the acid-ionization constant of sulfamethazine (SMZ) and sulfamerazine (SMR) solved in water. For these molecules, the calculated pK_a value is in relatively good agreement with the experimental one. Also, in these calculations some structural properties such as dihedral angle between the indicated atoms: D, bond lengths between the indicated atoms: d, Bohr radius: $a_\circ$, intermolecular hydrogen bond: IHB, and total atomic charge: au have been determined. These data can be used in nano drug modeling of sulfamethazine and sulfamerazine.
Key words: Acid-ionization constant; Sulfamethazine; Sulfamerazine; Density functional theory; Nano drug modeling.

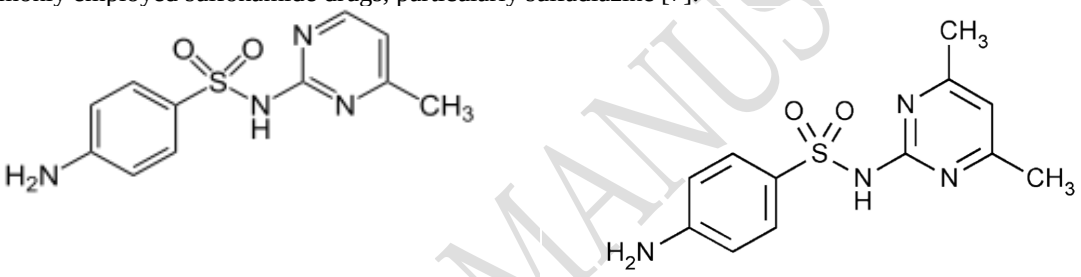
Resumen. La constante de disociación ácida (pK_a) es una propiedad fisicoquímica importante de las moléculas. In este trabajo de investigación se usaron métodos de la teoría de funcionales de la densidad (TFD), en combinación con el modelo continuo polarizado (MCP), para calcular las constantes de ionización de sulfametazina (SMZ) y sulfamerazina (SMR) solvatadas en agua. Para estas moléculas, el valor calculado de pK_a es en relativo buen acuerdo con el experimental. Además, en estos cálculos se determinaron algunas propiedades estructurales tales como ángulos diedro (D), longitud de enlace (d), radio de Bohr (a_0), enlace de hidrógeno intermolecular (EHI) y carga atómica total (au). Estos datos se pueden usar en el modelado de nano medicamentos de sulfametazina y sulfamerazina.
Palabras clave: constant de disociación ácida; sulfametazina; sulfamerazina; teoría de funcionales de la densidada; modelado de nano medicamentos.

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

Introduction

Pyrimidines comprise a relatively large, growing and most interesting group of antibacterial drugs. In the recent years, it has made a major impact on the field of antibacterial chemotherapy. Sulfamethazine (SMZ) and sulfamerazine (SMR) are classified as chemotherapeutic agents. They contain pyrimidine nucleus and have clinical use such as an antibacterial and antibiotics. Antibiotics are neutral compounds which are synthesized by living organisms to inhibit the growth of harmful microorganisms [1]. During recent decades, the use of antibiotics in animal husbandry has increased considerably. Sulfonamides are a group of synthetic antimicrobial agents with a broad spectrum of antibacterial activity. They therapeutically are used to treatment infections and prophylactically to improve feed efficiency, and to promote growth [2]. Sulfadiazine, sulfamerazine and sulfamethazine are three sulfa drugs and are commonly called triple sulfa drugs. They introduced in medical therapy because of their antibacterial activities [3]. Sulfamethazine (SMT) is widely used as an antimicrobial agent in the feed of meat-producing animals to treat infections [4]. Pyrimidines and their derivatives have a wide spectrum of biological activities such as antimicrobial, anti-inflammatory, analgesic, antiviral and anticancer activities [5]. Sulfamerazine (Fig. 1) is used as effective antimicrobial agents for the prevention and cure of several types of bacterial infections in human and veterinary therapies. Although SMR and SMT have been widely used in therapeutics, the solubility data of these drugs in co-solvent mixtures is still scarce in the literatures [6]. SMR, the mono-metyl derivative of sulfadiazine, is in fairly wide clinical use at the present time and certain advantages have been claimed for it over the other commonly employed sulfonamide drugs, particularly sulfadiazine [7].



(a) (b)

Fig. 1. Structures of sulfamerazine (a) and sulfamethazine (b).

Various experimental procedures are frequently used for the determination of acidity constants. However, there is an increasing interest for theoretical prediction of pK_a values, employing various quantum theoretical techniques during the last two decades.

A compound is defined as Bronsted acid, in aqueous solution, if it dissociates as follows:

$$HA_{aq} + H_2O_{aq} \rightleftharpoons A^-_{aq} + H_3O^+_{aq} \qquad (1)$$

pK_a equals to $\Delta G/2.303RT$, where ΔG is a free energy change of the dissociation reaction either in a gas or solution. As it can be seen, the acidity of a compound can be determined by ΔG value as the follow [8]:

$$pK_a = -\log K_a = \Delta G_{aq}/2.303RT \qquad (2)$$

On the basis of solvation free energies, the pK_a values were obtained for the compounds by using thermodynamic equations, involving the combined experimental and calculated data [9].

The pK_a is an important property of drug molecules. It is the key parameter for drug development because it governs solubility, absorption, distribution, metabolism and elimination. Moreover, the transport of drugs into cells and across other membranes is a function of this physicochemical property.

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

On the other hand, most drugs are either weak acids or weak bases, therefore, pK_a can be an important parameter in drug absorption.

A sulfonamide contains one amine group ($-NH_2$) and one amide group. Amine group is able to take a proton, while the amide group is able to release proton under specific pH conditions (Fig. 1) [10].

The drug-protein complex can serve therefore as a reservoir in the vascular space for sustained drug release to extra vascular tissues, but only for drugs that exhibit a high degree of binding. Thus, the protein-binding characteristics of a drug can play a significant role in its therapeutic effect regardless of the dosage form [11].

In addition, precise measurements of the acid-ionization constants (pK_a) of sulfamethazine and sulfamerazine can be hampered by their low solubility in water. In this case, a theoretical investigation would be an alternative way to determine the pK_a values [12]. Quantum mechanical calculations in both ab initio and DFT levels of theory have been extensively employed to the study of acidities in the solution phase and the results have been compared with the experimental values. It is well known that the calculated gas-phase acidities using a high level theory such as GAUSSIAN-2 (G2) are reliable. Some recent models of solvation such as polarizable continuum model (PCM) ignore some part of solute- solvent interactions [13]. Quantum chemical calculation has been widely used in the determination of the pK_a values in water or organic and inorganic solvents [14]. We used Tomasi's method [15] of the B3LYP/6-31+G(d) level of theory for the anion, cation, and neutral species at 298.15 K and compared them to experimental pK_a values.

Computational Methods

Two compounds were studied in this research work. These components are sulfamerazine and sulfamethazine as shown in Fig.1. The solvation was included in the calculations using the polarized continuum model (PCM) [16]. The optimization process in the solution phase was performed at the B3LYP/6-31+G(d) level on the structures obtained from solution phase [14].

To analyze the solvent effects on all species continuum model (PCM) of Tomasi et al, was used. Furthermore, to shed light on the experimental pK_a values of sulfamerazine and sulfamethazine in water, several conformers were tested by program and some of them were not further considered because the estimated error in its acidic dissociation constants was unacceptable [9]. In the other word, if the conformers aren't energetically stable, they don´t contribute to the study of sulfamerazine and sulfamethazine.

The model calculates short-range interaction energies between solvent and solute using a modified solvent accessible surface area which incorporates parameters for atomic and molecular surface tensions and hydrogen-bound acidity and basicity. It has been proven to be an effective tool to investigate on a variety of solution phase physicochemical properties. Solvation of selected species was finally considered in terms of the intermolecular hydrogen bonds (IHB_S) (see Table 1 and Fig. 2) [17].

Table 1. Values of pK_a for protonation of sulfamerazine and sulfamethazine that were obtained using the Tomasi method at the B3LYP/6-31+G(d) level of theory, at 298.15 K.

species	Selected equations	pK_a (calculated)	pK_a (experimental)	*RD* for pK_a (Relative deviation)
sulfamerazine	$H_2L^+(H_2O)_4 + OH^- \leftrightharpoons HL(H_2O)_4 + H_2O$	2.13	2.17[a]	0.01843
	$HL(H_2O)_4 \leftrightharpoons L^-(H_2O)_3 + H_3O^+$	6.70	6.77[a]	0.01034
sulfamethazine	$H_2L^+(H_2O)_4 + OH^- \leftrightharpoons HL(H_2O)_4 + H_2O$	2.31	2.37[a]	0.02532
	$HL(H_2O)_4 \leftrightharpoons L^-(H_2O)_3 + H_3O^+$	7.58	7.49[a]	0.01202

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

a: Ref [10]

$$RD_{(\ for\ pKa)} = \left| \frac{pK_{a\,(\exp erimental)} - pK_{a\,(calculated)}}{pKa_{\exp erimental}} \right|$$

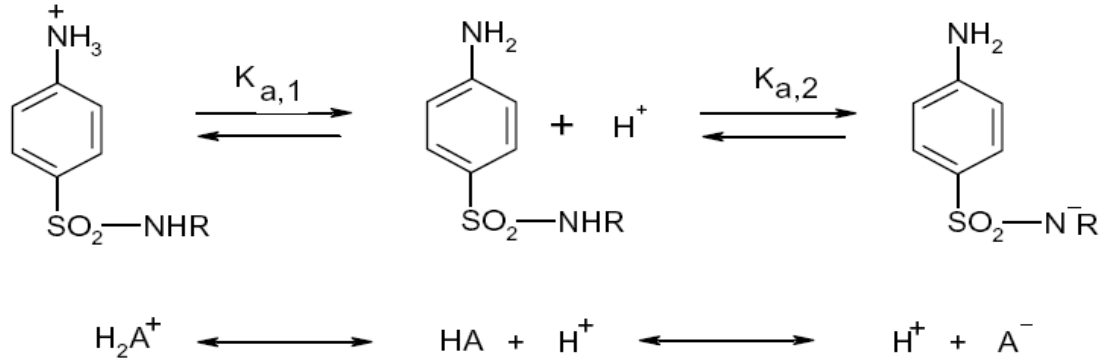


Fig. 2. Protonation scheme of sulfamerazine and sulfamethazine.

Results and Discussion

The molecular structures of sulfamerazine and sulfamethazine are shown in Fig. 1. As it can be seen in this figure, there are two sites for protonation. First site, -NH_2, which is attached to benzene ring, and second site, –NH, which is attached to –SO_2 and $N_2C_4H_3$ ring. It means that the protonated sulfamerazine and sulfamethazine can lose two acidic hydrogens. This first proton can be lost from NH_3^+ group and the second one from NH group (Fig. 1) [17].

The total free energies (Hartree and kJ·mol^{-1}) of the neutral, cation and anion species of sulfamerazine and sulfamethazine are listed in Tables 2 and 3, respectively. These values were calculated for single and solvated, in water, species at the B3LYP/6-31+G(d) level of the theory using Tomasi's method. Tables 2 and 3 show that the total free energies (Hartree) for different species of sulfamerazine and sulfamethazine increase when the number of water molecules increases in the solvation. Also, these tables (2 and 3) and Fig. 3 show that the total free energies per water molecule (kJ·mol^{-1}) decrease by increasing of the number of water molecules. All of these changes can be evidence on the endothermic nature of the reaction.

Table 2. Calculated total energies using the Tomasi method at the B3LYP/6-31+G(d) level of theory for cationic, neutral, and anionic species of sulfamerazine, at 298.15 K.

Solvated Species	G°_{sol} (Hartree)	G°_{sol}/molecule (kJ.mol^{-1})
HL	-1194.050927	-3134980.408
HL(H_2O)	-1270.489645	-1667835.121
HL(H_2O)$_2$	-1346.930916	-1178788.927
HL(H_2O)$_3$	-1423.369133	-934263.825
HL(H_2O)$_4$	-1499.808887	-787549.571
H_2L^+	-1194.486242	-3136123.327
H_2L^+(H_2O)	-1270.927236	-1668409.569
H_2L^+(H_2O)$_2$	-1347.369514	-1179172.773
H_2L^+(H_2O)$_3$	-1423.813789	-934555.6861
H_2L^+(H_2O)$_4$	-1500.262285	-787787.6502

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

L^-	-1193.586203	-3133760.275
$L^-(H_2O)$	-1270.02895	-1667230.344
$L^-(H_2O)_2$	-1346.47234	-1178387.596
$L^-(H_2O)_3$	-1422.923122	-933971.0746
$L^-(H_2O)_4$	-1499.353956	-787310.6867
H_3O^+	-76.862	-201801.1616
H_2O	-76.434	-200677.4477
OH^-	-75.952	-199411.9569
$(H_2O)_2$	-152.87	-133786.7155
$2H_2O$	-152.868	-401354.8955
$3H_2O$	-229.302	-602032.3432
$OH^-(H_2O)$	-152.4	-200063.0808

The structural properties of solvated species of sulfamerazine and sulfamethazine were shown in Tables 4 and 5, respectively. These properties are including of the distance between the indicated atoms (A°), D: dihedral angle between the indicated atoms (°), $a_.$: bohr radius (A°), *q*: total atomic charges (Mulliken) (au), d: distance of the IHB between the indicated atoms (A°), and A: H-bond angle (°).

Table 3. Calculated total energies using the Tomasi method at the B3LYP/6-31+G(d) level of theory for cationic, neutral, and anionic species of sulfamethazine, at 298.15 K.

Solvated Species	**G°_{sol} (Hartree)**	**G°_{sol}/molecule (kJ.mol^{-1})**
HL	-1233.374288	-3238223.882
$HL(H_2O)$	-1309.813128	-1719457.019
$HL(H_2O)_2$	-1386.258676	-1213207.268
$HL(H_2O)_3$	-1462.699952	-960079.5888
$HL(H_2O)_4$	-1539.129281	-808196.7079
H_2L^+	-1233.809496	-3239366.521
$H_2L^+(H_2O)$	-1310.254399	-1720036.297
$H_2L^+(H_2O)_2$	-1386.697137	-1213590.995
$H_2L^+(H_2O)_3$	-1463.139514	-960368.1063
$H_2L^+(H_2O)_4$	-1539.582285	-808434.5803
L^-	-1232.908595	-3237001.205
$L^-(H_2O)$	-1309.351274	-1718850.72
$L^-(H_2O)_2$	-1385.793694	-1212800.331
$L^-(H_2O)_3$	-1462.245273	-959781.1489
$L^-(H_2O)_4$	-1538.676529	-807958.9678
H_3O^+	-76.862	-201801.1616
H_2O	-76.434	-200677.4477

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

OH^-	-75.952	-199411.9569
$(H_2O)_2$	-152.87	-133786.7155
$2H_2O$	-152.868	-401354.8955
$3H_2O$	-229.302	-602032.3432
$OH^-(H_2O)$	-152.4	-200063.0808

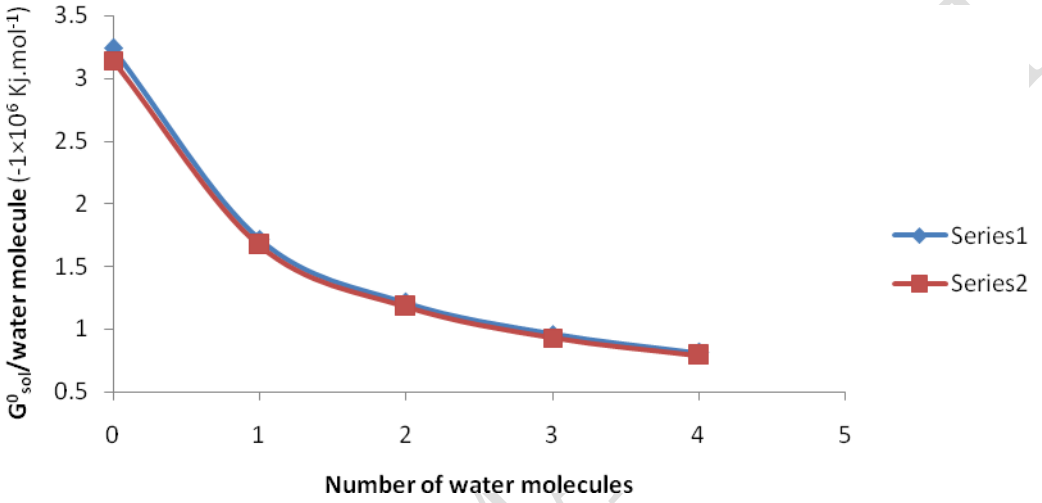


Fig. 3. The total energy (kJ · mol^{-1}) of solvated sulfamethazine (series 1) and sulfamerazine (series 2) cations per water molecule against the number of solvation water molecules.

Several factors are effective in structural properties of single and solvated species. These factors can be number and size of atoms, nature of agents (electron donor or acceptor effect), and the number of solvent molecules.

First ionization constant of sulfamerazine and sulfamethazine

In alkaline solution, the sulfamerazine and sulfamethazine undergo a reaction of partial neutralization as the below:

$$H_2L^+(H_2O)_4 + H_2O \leftrightharpoons HL(H_2O)_4 + H_3O^+ \qquad K_{C1} \qquad (3)$$

In the above reaction, $H_2L^+(H_2O)_4$ is the sulfamerazine and sulfamethazine cations solvated with four water molecules and $HL(H_2O)_4$ represents neutral sulfamerazine and sulfamethazine solvated with four water molecules. The described reaction in Eq. 3 is characterized by another equilibrium constant, K_{C1}, which was also theoretically determined.

All aqueous solutions contain hydrogen (H^+) and hydroxyl (OH^-) ions. In pure water, these ions are entirely derived from the ionization of the water molecules. The autoprotolysis reaction of two molecules water is better represented by the following reaction:

$$2H_2O \leftrightharpoons OH^- + H_3O^+ \qquad K_W \qquad (4)$$

At T = 298.15K, Kw =1.008×10^{-14} and it shows that only a few of the water molecules are ionized [18].

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

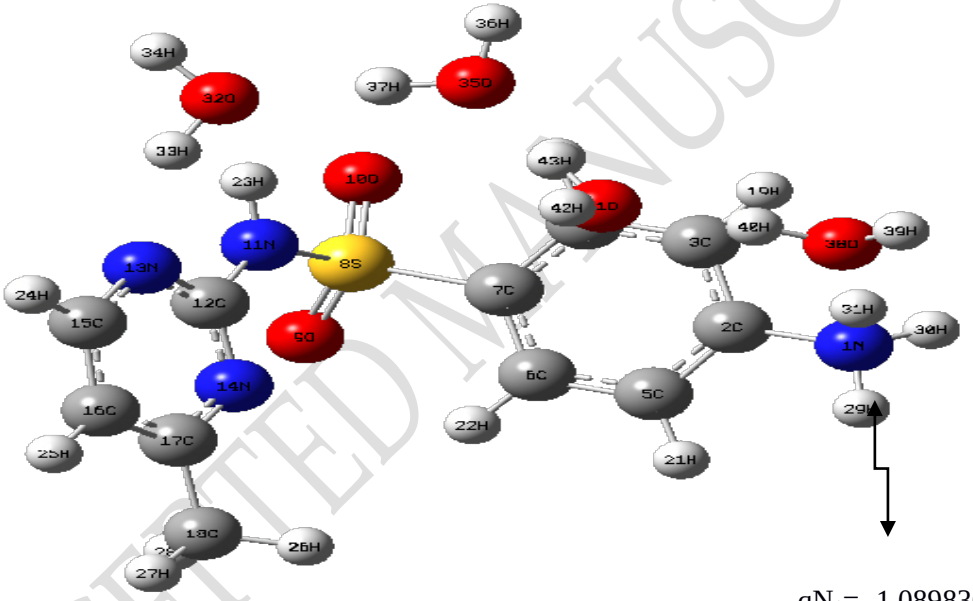
The reaction 5 is characterized by equilibrium constant, K_{al}. This reaction was theoretically obtained by incorporating of Eqs.3 and 4. The equation 5 defines the first ionization constant of sulfamerazine and sulfamethazine:

$$H_2L^+(H_2O)_4 + OH^- \leftrightharpoons HL(H_2O)_4 + H_2O \qquad K_{a1} \qquad (5)$$

It is obvious that:

$$K_{al}=K_{C1}\times K_W \qquad (6)$$

The equation 6 was used to theoretically determine the value of the first ionization constant of sulfamerazine and sulfamethazine in water. The values of structural properties for different species of sulfamerazine including, cation$H_2L^+(H_2O)_4$ (Fig. 4A), anion $L^-(H_2O)_3$ (Fig. 4B), and neutral $HL(H_2O)_4$ (Fig. 5A) have been summarized in Table 4. The formation of neutral sulfamerazine and sulfamethazine implies that the electronic density of the N_1 atom, in absolute value, significantly decreases with respect to the N_1 atom of the sulfamerazine and sulfamethazine cations. It can show the first deprotonation of sulfamerazine and sulfamethazine.

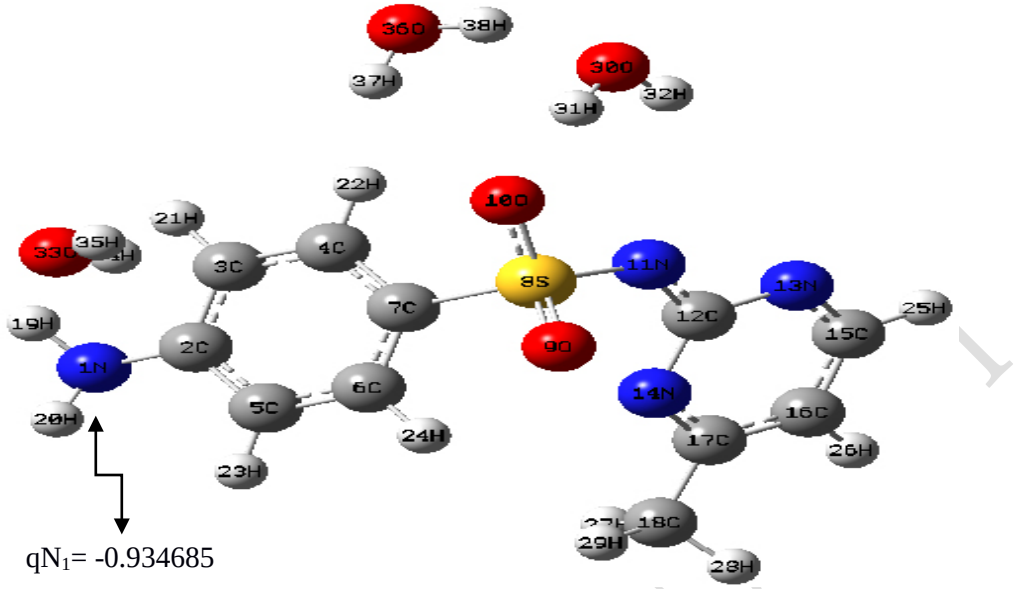


(A): $H_2L^+(H_2O)_4$

qN_1= -1.089836

J. Mex. Chem. Soc. **2018**, *62*(*1*)

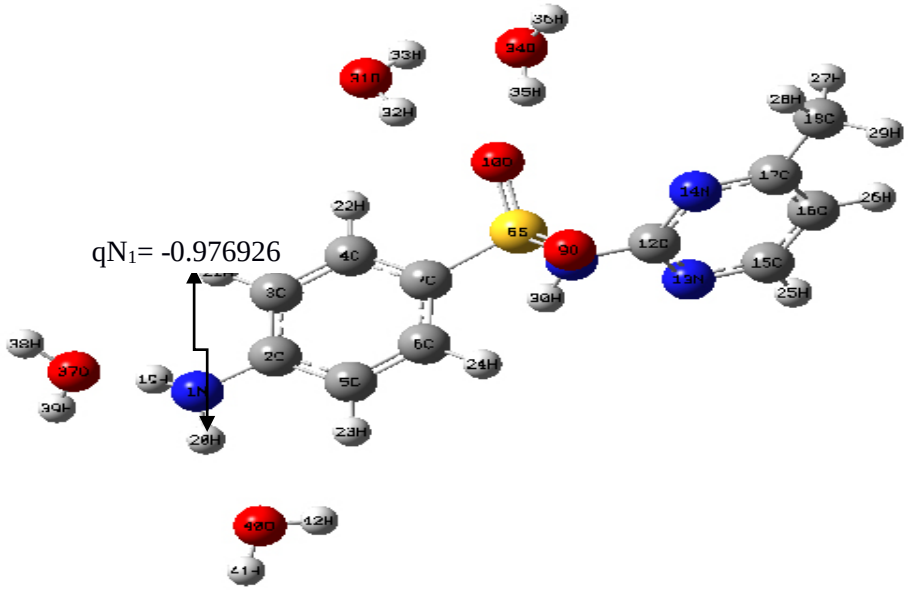
ISSN-e 2594-0317
ISSN 1870-249X



(B): $L^{-}(H_2O)_3$

Fig. 4. Calculated structure for the sulfamerazine cation (A) and anion (B) at the B3LYP/6-31+G(d) level of theory and using Tomasi's method in water at 298.15 K.

As it can be observed in Table 1, the theoretically calculated values of pK_{a1} for sulfamerazine and sulfamethazine (2.13 and 2.31) are relatively comparable with the experimentally ones (2.17 and 2.37), respectively [10].



(A):$HL(H_2O)_4$

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

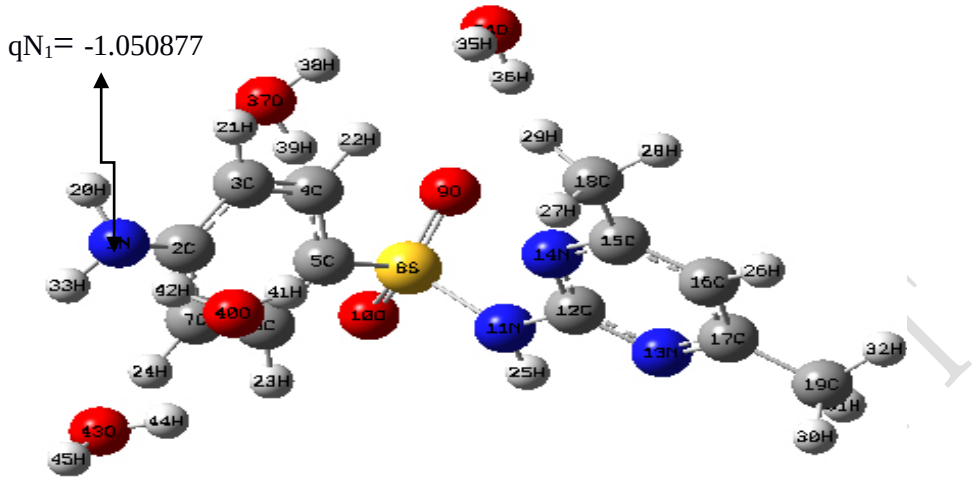


Fig. 5. Calculated structure for the neutral sulfamerazine(A) and sulfamethazine (B) at the B3LYP/6-31+G(d) level of theory and using Tomasi's method in water at 298.15 K.

Table 4. Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G(d) level of theory for the cations, anion, neutral molecule of sulfamerazine at 298.15 K.

Properties	**Species**		
	$H_2L^+(H_2O)_4$	$HL(H_2O)_4$	$L^-(H_2O)_3$
K_{c1}	1.34007E+16	–	–
K_{c2}	–	5.8912E+20	–
K_{a1}	135.079074	–	–
K_{a2}	–	5938334.061	–
a_0	5.53	5.31	5.34
qN_1	-1.089836	-0.976926	-0.934685
qN_{11}	-0.992271	-0.660839	-0.736741
$dO_{38}H_{31}$	1.58144	–	–
$dN_{13}H_{33}$	1.86876	–	–
$dO_{10}H_{35}$	–	1.81587	–
dS_8O_9	1.434483	1.443205	1.488730
$A\text{-}N_1H_{31}O_{38}$	168.23354	–	–
$A\text{-}O_{33}H_{19}N_1$	–	–	99.70419
$A\text{-}N_{11}H_{32}O_{30}$	–	–	172.09264
$A\text{-}O_{33}H_{35}O_{10}$	–	–	167.53637
$D\text{-}C_{12}N_{11}S_8C_7$	-74.089225	-175.939946	-62.278069

K_{C1} and K_{C2}, equilibrium constants of equations; K_{a1} and K_{a2}, first and second acidic dissociation constants of species in water; D, dihedral angle between the indicated atoms (°); a_0, bohr radius (Å); q, total atomic charge (Mulliken) (au); d, bond lengths between the indicated atoms; A, angles (°).

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

Second ionization constants of sulfamerazine and sulfamethazine

It is selected that the sulfamerazine and sulfamethazine suffer a total neutralization process as the below:

$$HL(H_2O)_4 + OH^- \leftrightharpoons L^-(H_2O)_3 + 2H_2O \qquad K_{C2} \qquad (7)$$

In reaction 7, $L^-(H_2O)_3$ shows the sulfamerazine and sulfamethazine anion solvated with three water molecules and $HL(H_2O)_4$ represents the neutral sulfamerazine and sulfamethazine solvated with four water molecules.

The described reaction in Eq. 7 is characterized by another equilibrium constant, K_{C2}, which was also theoretically determined. By combining Eqs.7 and 4, the second ionization reaction of sulfamerazine and sulfamethazine was obtained as the below:

$$HL(H_2O)_4 \leftrightharpoons L^-(H_2O)_3 + H_3O^+ \qquad K_{a2}$$

(8)

The second ionization constant (K_{a2}) that characterizes the above reaction is associated with the constants K_{C2} and K_w:

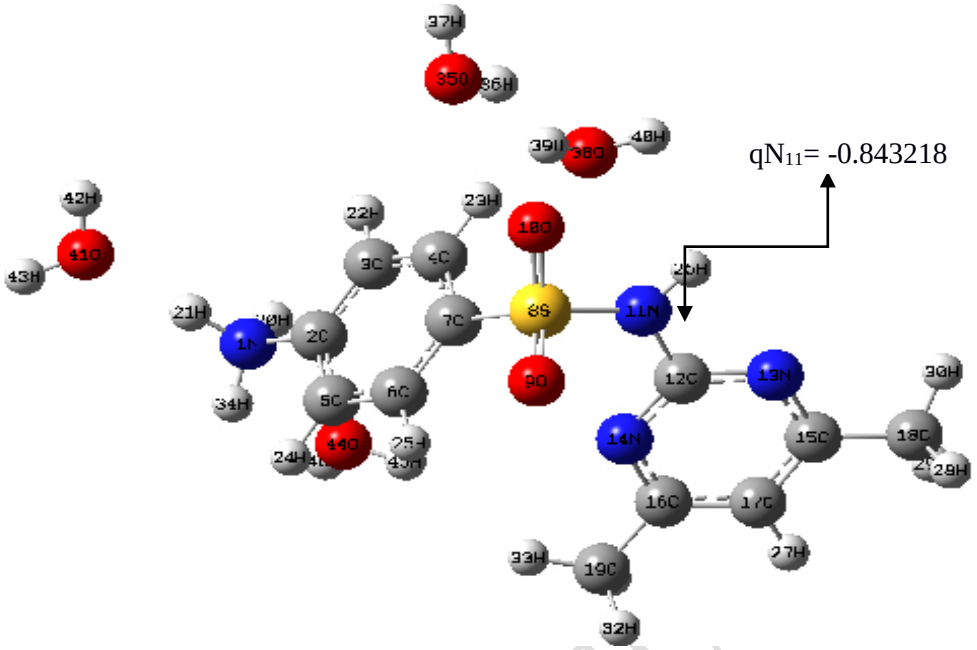
$$K_{al} = K_{C2} \times K_W \qquad (9)$$

The above equation was used to theoretically determine the value of the second ionization constants of sulfamerazine and sulfamethazine in water. The values of structural properties for different species of sulfamethazine including, neutral $HL(H_2O)_4$ (Fig. 5B), cation $H_2L^+(H_2O)_4$ (Fig. 6A), and anion $L^-(H_2O)_3$ (Fig. 6B) have been listed in Table 5. It is clear that the formation of the sulfamerazine and sulfamethazine anion implies that the electronic density of the N_{11} atom increases notably (in absolute value) with respect to the N_{11} atom of the neutral sulfamerazine and sulfamethazine. It can show the second deprotonation of sulfamerazine and sulfamethazine.

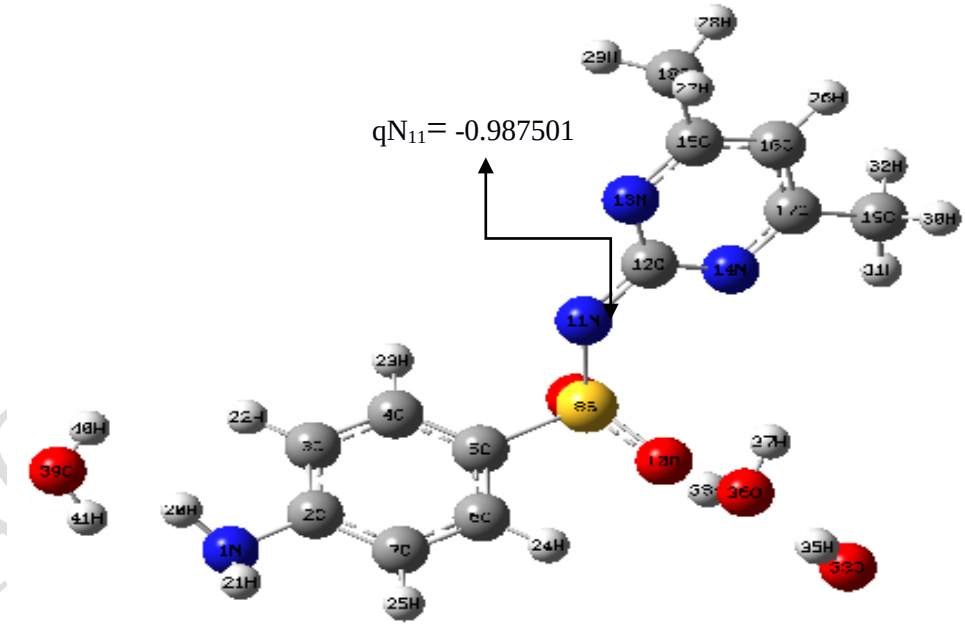
Table 1 shows that the theoretically calculated pK_{a2} values for sulfamerazine and sulfamethazine (6.70 and 7.58) are relatively comparable with the experimentally ones (6.77 and 7.49), respectively [10].

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X



(A): $H_2L^+(H_2O)_4$



(B): $L^-(H_2O)_3$

Fig. 6. Calculated structure for the sulfamethazine cation (A) and anion (B) at the B3LYP/6-31+G(d) level of theory and using Tomasi's method in water at 298.15 K.

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

Table 5. Calculated structural magnitudes using Tomasi's method at the B3LYP/6-31+G(d) level of theory for the cations, anion, neutral molecule of sulfamethazine at 298.15 K.

Properties	**Species**		
	$H_2L^+(H_2O)_4$	$HL(H_2O)_4$	$L^-(H_2O)_3$
K_{c1}	2.03497E+16	–	–
K_{c2}	3.79557E+21	–	–
K_{a1}	205.125385	–	–
K_{a2}	38259374.67	–	–
$a_\circ$	5.40	5.53	5.52
qN_1	-1.206800	-1.050877	-0.936580
qN_{11}	-0.843218	-0.846408	-0.987501
$dO_{10}H_{38}$	–	–	1.79095
$dO_{41}H_{21}$	1.79405	–	–
dN_1H_{42}	–	1.98339	–
$dO_{43}H_{33}$	–	2.72815	–
$A\text{-}O_{35}H_{20}N_1$	178.70952	–	–
$A\text{-}O_{34}H_{35}O_9$	–	166.49845	–
$A\text{-}O_{40}H_{42}N_1$	–	152.43011	–
$D\text{-}N_{13}C_{12}N_{11}S_8$	-156.177712	-157.062475	-179.250913
$D\text{-}C_{15}N_{13}C_{12}N_{11}$	-177.372055	–	179.537732
$D\text{-}C_{18}C_{15}N_{13}C_{12}$	-179.360392	–	-179.055450
$D\text{-}H_{29}C_{18}C_{15}N_{13}$	-148.901672	–	-38.252538

K_{C1} and K_{C2}, equilibrium constants of equations; K_{a1} and K_{a2}, first and second acidic dissociation constants of species in water; D, dihedral angle between the indicated atoms (°); a_0, bohr radius (Å); q, total atomic charge (Mulliken) (au); d, bond lengths between the indicated atoms; A, angles (°).

The molecule of water originated from the acid-base reaction, together with the hydration water molecule of the sulfamerazine and sulfamethazine, and these are the molecules of water that interact with the sulfamerazine and sulfamethazine molecules by means of IHBs. According to Ref 19, the properties of the weak, moderate and strong hydrogen bonds have classified. For species of this study, the distances and angles of intermolecular hydrogen bounds (IHBs) are shown in Tables 4 and 5. These values show that the all species of sulfamerazine and sulfamethazine have moderate IHBs. Data of IHBs is very important because it can be used in the design of benefit and economical nanodrugs that are very useful in the treatment of disease.

Conclusion

In this paper, we theoretically determined the pK_a of sulfamerazine and sulfamethazine. We showed the feasibility of a theoretical method that uses to determine the ionization constants of these molecules. The calculations performed at the B3LYP/6-31+G(d) levels of theory using Tomasi's method allowed us to prove that cation, anions and neutral molecules from IHB_S with sum molecules of water. The theoretical ionization constants show relatively suitable agreement with the acidity constants experimentally determined. This agreement along with the other data (the electronic density, q, structural properties, and IHB_s) help us to design nano drug modeling of sulfamerazine and sulfamethazine.

J. Mex. Chem. Soc. **2018**, *62*(*1*)

ISSN-e 2594-0317
ISSN 1870-249X

References

1. Qiang, Q.; Adams, C. *Water Res*. **2004**, *38*, 2874
2. Sternesjo, A.; Mellgren, C.; Bjorck, L. *Anal Biochem*.**1995**, *226*, 175.
3. Golzar Hossain, G.M.; Amoroso, A.J.; Banu, A.; Malik, K.M.A. *Polyhedron*. **2007**, *26*, 967.
4. Poirier, L.A.; Doerge, D.R.; Gaylor, D.W.; Miller, M.A.; Roland, S.; Lorentzen, J.; Casciano, D.A.; Kadlubar, F.F.; Schwetz, B.A.; *Regul Toxicol Pharmacol*. **1999**, *30*, 217.
5. Sridhar, S.; Prasad, Y.R.; Dinda, S.C. *Int J Pharm Sci Res*. **2011**, *2*, 2562.
6. Delgado, D.R.; Martinez. F. *Fluid Phase Equilibria*. **2013**, *360*, 88.
7. Forbes, G.B.; Perley, A.; Dehlinger, J.; Louis, S.T. *J Pediatr*. **1946**, *28*, 24.
8. Namazian, M.; Heidary, H.; *MolStruct. (Theochem)*. **2003**, *620*, 257.
9. Kiani, F.; Rostami, A.A.; Sharifi, S.; Bahadori, A.; Chaichi, M.J. *Chem Eng Data*. **2010**, *55*, 2732.
10. Babic, S.; Horvat, A.J.M.; Pavlovic, D.M.; Macan, M.K. *TrAC, Trends Anal Chem.* **2007**, *26*, 1043.
11. Rout, S.K.; Madhabkar, D. *Int. J. Pharm. Pharm. Sci*. **2015**, *2*, 25.
12. Jang, Y.H.; Hwang, S.; Chang, S.B.; Ku, J.; Chung, D.S. *Phys. Chem*. **2009**, *113*, 13036.
13. Yu, A.; Liu, Y.; Wang, Y. *Chem Phys Lett*. **2007**, *436*, 276.
14. Kheirjou, S.; Abedin, A.; Fattahi, A.; Mahmoodi Hashemi, M. *Comput Theor Chem.* **2014**, *1027*, 191.
15. Miertus, S.; Tomasi, E. *J. Chem. Phys*. **1982**, *65*, 239.
16. Young, D.C. Young, Computational Chemistry: A Practical Guide for Applying Techniques to Real-World Problems, John Wiley & Sons, Inc, USA, 2001.
17. Kiani, F.; Abbaszadeh, M.; Pousti, M.; Koohyar, F. *Braz J Pharm Sci.* **2015**, *51*, 213.
18. Atkins, P.W. Physical Chemistry, 6th ed; Oxford University Press: England, 1998.
19. Jeffrey, G.A. An Introduction to Hydrogen Bonding, Oxford University Press, Oxford, 1997.