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Scientific paper

Prediction of Physico-chemical Properties of Bacteriostatic N[1]-Substituted Sulfonamides: Theoretical and Experimental Studies

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Abstract

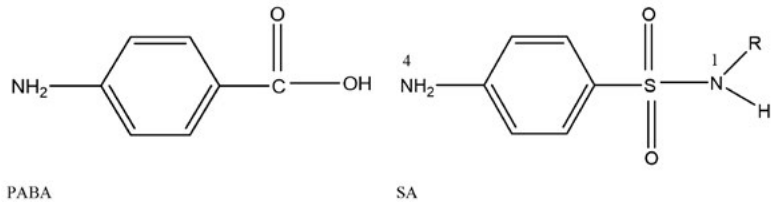
A computational study at the density functional theory (DFT) as well as electrochemical methods, was carried out on the structural and physico-chemical properties of a series of sulfonamide derivatives (SAs) as WHO essential medications in the treatment of basic health system. The B3LYP/6-311++G(d,p) level of theory carried out on sulfadiazine (SDZ), sulfathiazole (STZ), sulfaquinoxaline (SQX), sulfacetamide (SAA), and the reference unsubstituted sulfonamide (SA) was discussed and rationalized in term of the N[1]-sulfonamide substituent. The geometric structures and the electronic properties related to the bacteriostatic reactivity were revealed to be affected by the steric and "push-pull" characteristics of the substituents. Electrochemical experiments on oxidation of SAs, using cyclic voltammetry are presented. The results obtained showed that the calculated ionization potentials (IPs) could be correlated linearly with the electro-oxidation potentials. From the molecules studied it is evident that SDZ act as the most electro-active agent, possessing the highest biological activity. DFT computations carried out using the standard molar enthalpies of formation in the gas phase predicted improvements in the thermodynamic stabilization of the SDZ, SQX, and SAA molecules and an unstabilization of STZ with respect to the parent molecule SA.

Keywords: Sulfonamide, Substituent, Density functional theory, Electrochemical behavior

1. Introduction

Sulfa drugs (sulfonamides), characterized by a *p*-aminophenyl group and a sulfonamido one (-SO_2N-) in their molecular structures, are the basis of some important bacteriostatic agents. These molecules represent a substantial class of pharmaceutical compounds, which are extensively employed as chemotherapeutic agents,[1] and anti-tumor,[2] anti-thyroid,[3] anti-carbonic anhydrase,[4] anti-inflammatory,[5] hypoglycemic,[6] diuretic,[7] COX-inhibitors, and anti-impotence drugs,[8] and also have been used as azo dyes to achieve improved light stability, water solubility, and fixation to fiber. Sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthase in bacteria, and catalyze changing *p*-aminobenzoic acid into a nutrient necessary for some bacteria.[9] Some sulfonamide derivatives are still extensively used for the treatment of numerous bacterial, fungal infections, protozoal, and the first effective chemotherapeutic agents used in safe therapeutic dosage ranges.[10] Due to their biological and pharmaceutical ingredients, sulfonamide derivatives find a lot of importance in the literature related to the synthesis of new classes of compounds.[11-15]

Molecular structure of the sulfa drug is analogous to that for *p*-aminobenzoic acid (PABA) (Scheme 1). The similarity between them has been shown by the Wood-fielder theory.[16] According to Bell and Robin,[17] a structure that is comparable to the molecular structure of PABA may interfere within its biological function. The sulfonamide mechanism has been recognized at the enzyme level. In bacteria, anti-bacterial sulfonamides act as the competitive inhibitors of dihydropteroate synthetase. Hence, sulfonamide interferes with the enzyme folic acid synthetase, which is involved in changing PABA to folic acid, which results in the deficiency of folic acid, causing injury to the bacterial cell. Most bacteriostatic SAs have been derivatized basically by variation in the R-substitution linked to the N[1] atom of the sulfonamido group (Scheme 1). Substitution with a heterocyclic structure has



Scheme 1. Sketch map of PABA structure and SA structure with N atom numbering.

produced compounds more active than the parent molecule SA (R = H). More widespread experimental studies carried out by Bell,[17] Kumler,[18] Seydel,[19] and others have been devoted to the analysis of the structure-electronic effects that could be related to the pharmaceutical activities, paying special interest to the role of the acidity of the sulfonamido group.[20-22] Sulfonamides are weak acids compared to carboxylic acid amides. Their acidic nature results from the ability of the SO_2 moiety to stabilize the nitrogen anion via resonance. It has been found that their pharmaceutical activity is favored directly by the increased sulfonamide acidity (related to the lower pK_a values).

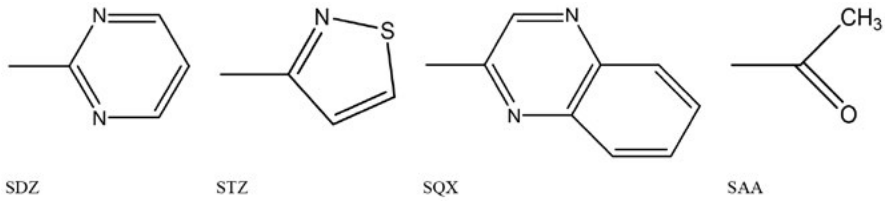
The relationship between the chemical structure and pharmaceutical activity of the SA derivatives has prompted the current experimental and theoretical investigations for new sulfa compounds that would possess a greater pharmacological activity.[23–26] In this way, sulfadiazine is one of the substantial sulfonamide antibiotics that are listed as WHO crucial medications in the cure of basic health system.[15] In comparison to the SA derivatives, it has been found that the original SA is at the lowest end of the activity spectrum. Although these drugs are clinically effective in the treatment of various medical disorders, they cause some negative side-effects, which may lead to hepatitis and arthritis. Through relocation, these drugs reach the environment and cause acute toxicity and serious public health hazards.[14]

Now we wish to report a theoretical investigation carried out on the SA derivatives including SAA, SDZ, SQX, STZ, and the original sulfonamide SA as the reference molecule, which can be used to evaluate the relevance of the physico-chemical and structural properties toward the steric and electronic influences of the N^1-substituents. The R groups were chosen by taking into account the structures of some sulfonamide-based drugs. The sketch map of the substituent structures for all the studied SAs is depicted in Scheme 2. Investigations have been carried out to identify the geometric structure, energy disparity between the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO), atomic and group Mulliken charge distribution, and some appropriate quantum descriptors. Since electrochemical methods are accurate, simple and economical in terms of both time and cost for drug residue monitoring as well as control processes, electro-oxidation behavior of SAs was initially studied on a carbon paste electrode (CPE) using cyclic voltammetry technique.

2. Methodology

2. 1. Computation Method

The ground-state geometry of each sulfonamide was fully optimized using the gradient procedure at the restricted DFT technique, as implemented in the Gaussian 09 program package.[27] A preliminary basis set test carried out for calculations on the electronic ground state for the unsubstituted reference molecule (SA), showed that that 6-311++G(d,p) was the best basis set that can be used within our available hardware/software facilities within a reasonable time. The reports by others[28,29] have also shown that the B3LYP/6-311+G(d,p) level of theory appeared notably adapted to describe sulfonamides to obtain experimental data. The fully-optimized structures by the DFT-B3LYP level[30,31] were confirmed to be the real minima through the zero imaginary frequencies. For all cases, both the radical cation and radical anion were treated as open-shell systems by UB3LYP/6-311++G(d,p). In particular, the values for the electronic chemical potential (μ), global hardness (η), electrophilicity index (ω), and maximal flow of electrons (ΔN_{Max}) were determined using the Koopman's theorem eigenvalues.[32,33] Furthermore, the standard molar enthalpies of formation in the gas phase at 298.15 K for all the studied species were estimated by the atomization energy route. The detailed description of this calculation procedure has been reported in the literature.[34]



Scheme 2. Sketch map of R group structure for all studied SAs.

2. 2. Experimental

All chemical material used for this project were reagent grade from Merck and used as received. A nano-composite modified carbon past electrode consisted of 5% reduced graphene oxide (RGO) decorated CeO_2 nano-particle was employed to study the electro-oxidation of SAs solution using cyclic voltammetry. A homemade ultra-voltammetry system designed in Center of Excellence Electrochemistry (CEE) of University of Tehran was used for the electrochemical measurements at 25.0 ± 0.1 °C. A stock solution (1mM) for each SA derivatives was prepared and kept in refrigerator. Standard solution for measurements was prepared by dilution of stock solution by phosphate buffer (pH 7.4). The external electrode surface was smoothed with a clean and soft paper. A new surface was produced by scraping out the old surface and replacing the carbon paste.

3. Results and Discussion

3. 1. Geometric Structures of SAs

Full-optimized geometrical structure of each studied sulfonamide obtained at the B3LYP/6-311 ++G(d,p) level of theory are given in Fig. S1 in the Supporting Information. In Table 1, some selected dihedral (*D*) and bond (*A*) angles of the SA derivatives are tabulated. According to this table (column 2), for the dihedral angle $D_{N4\text{-}ph}$, defining the torsion between the amino group (NH_2) and phenyl ring (ph), a value of 178° is an evidence of complete planarity, and our calculated results indicated that all SAs presented values for $D_{N4\text{-}ph}$ close to 180°. It is interesting that introduction of the selected R groups did not affect the planarity of the amino group and phenyl ring present in the parent molecule (SA). It has been found that this planarity in the SA drugs is a necessary condition for a pharmaceutical activity.[23] The dihedral angle between the SO_2 group and the phenyl ring, $D_{ph\text{-}SO2}$, was also close to 180° in all SAs (Table 1, column 3). However, for the SAA, SDZ, and SQX species, the C-S-N^1 bond angle (A_{CSN1}) displayed a value of nearby 105°, although it was found to be 100° for the STZ molecule. This may be attributed to the different steric effects resulting from the proximity of the substituent R to the sulfonamido group. Our calculated results for all SAs revealed that the bond angle for O-S-O was near 120°, indicating that introduction of the R group did not affect it considerably.

Table 1. Dihedral and bond angles (in degrees) for SA species in neutral state at the B3LYP/6-311++G(d,p) level of theory.

Species	$D_{N4\text{-}ph}$	$D_{ph.\text{-}S}$	A_{CSN1}	A_{OSO}
SA	178	–180	104	122
SAA	178	179	106	122
SDZ	178	179	105	121
SQX	178	179	105	122
STZ	178	180	100	120

In the case of the optimized structures in the ground state, some selected bond lengths (*d*) of the studied molecules are given in Table 2. As we can see in this table, for all SAs, the bond length for N^4-ph is 1.38 Å, which is in the order of the C-C bond length in the resonance structure of phenyl ring (on average, 1.39 Å). This means that the amino group is well-conjugated with the phenyl ring, and is not affected by the substituent type. In this way, the N^4-ph bond distances for both the radical anion and radical cation species, tabulated in Table S1 of the Supporting Information, indicated that the N^4-ph bond length varied in the following order: anionic (1.40 Å) > neutral (1.38 Å) > cationic (1.34 Å). It is interesting that the ph-S and S-N^1 bond lengths were not varied considerably by the R groups, where the distance between the S atom and R group changed due to the substituent steric hindrance. It has been established[23] that the sulfonamide activity is accompanied by a small distance between the N^1 atom and R group corresponding to the large bond order for $d_{N1\text{-}R}$. According to Table 2 (column 5), the SDZ molecule with a shorter N^1-R distance possesses a more bacteriostatic activity with respect to the other substituted SAs. It was concluded that the electronic and structural properties of the substituent could contribute to the bacteriostatic activity of a sulfa drug.

Table 2. Some selected bond lengths (Å) for SA species in neutral state at the B3LYP/6-311++G(dip) level of theory.

Species	$d_{N4\text{-}ph}$	$d_{ph\text{-}S}$	$d_{S\text{-}N1}$	$d_{N1\text{-}R}$
SA	1.3851	1.7835	1.7001	–
SAA	1.3803	1.7815	1.7102	1.4022
SDZ	1.3842	1.7773	1.7152	1.3846
SQX	1.3829	1.7758	1.7201	1.3916
STZ	1.3810	1.7787	1.7247	1.4127

3. 2. Electronic Properties of SAs

One of the important parameters involved in the bacteriostatic activity of a sulfa drug is the charge distribution of an atom and a group over their molecular structures. We investigated qualitatively the "push-pull" effect of the R substituents on the SA molecules by the Mulliken population analysis. Some atomic and group charge distributions obtained for the neutral and both the radical anion (–) and radical cation (+) of SAs are summarized in Table 3. In all the neutral species, linkage of the R group on the parent molecule SA did not affect the charge on the N^4 atom (Table 3, column 2). This is expected because R group is far from it (see Scheme 1). The calculated results show that the influence of substituent introduction is manifested in the increased negative charge on the N^1 atom in the SAA, SDZ, and SQX species, and an increased positive

charge on it in STZ with respect to the reference molecule SA. These are referred to the electron-withdrawing effect of the R group in the SAA, ADZ, and SQX molecules, and the electron-donating effect of the R group in the STZ molecule, respectively. The same trend was observed for the negative charge on the phenyl ring. Depending on the substituent type, the calculated charge at the SO_2 group shows a large variation. In both the experimental and theoretical works carried out by Bell *et al.*[17] and Soriano-Correa *et al.*,[23] respectively, the increase in the acidity of SAs (which is equivalent to an increase in the bacteriostatic activity) was found to be related to a reduction in the negative charge of the SO_2 group. In other words, the substituent electronegativity is an important parameter that controls the bacteriostatic activity in sulfa drug. Our calculated results showed that SDZ with a more positive charge (or a less negative charge) of the SO_2 group can have a higher reactivity (Table 3, column 5). For the case of radical cation species, the main influence of the injection of one positive charge is manifested in the increased positive charge on the N^4 atom with respect to the N^1 atom. Consequently, the N^4 atom in the *p*-amino group, which is far from the substitution position, was found to be a more reactive zone to the protonation processes than the N^1 atom that is closer to the substituent (see Scheme 1). An inverse trend was observed for the negative charge on the radical anion species. In this regards, the negative charge was distributed mainly on the N^1 atom, which provides that the deprotonation processes were take place most probability at the N^1 atom position with respect to the N^4 atom.

Table 3. Some atomic and group charge distributions of SAs in neutral and both radical cation (+) and radical anion ($^-$) states.

Species	N^4	N^1	ph	SO_2
SA	–0.29	–0.34	–0.14	–0.34
SAA	–0.29	–0.40	–0.22	0.03
SDZ	–0.29	–0.49	–0.34	0.36
SQX	–0.31	–0.36	–0.24	0.23
STZ	–0.29	–0.05	–0.07	–0.20
SA(+)	–0.18	–0.38	0.30	–0.08
SAA(+)	–0.18	–0.33	0.27	0.07
SDZ(+)	–0.20	–0.50	–0.01	0.57
SQX(+)	–0.26	–0.41	–0.11	0.53
STZ(+)	–0.25	–0.23	0.16	0.07
SA(–)	–0.23	–0.35	0.12	–0.54
SAA(–)	–0.24	–0.39	–0.22	–0.08
SDZ(–)	-0.25	–0.41	–0.30	–0.07
SQX(–)	–0.30	–0.31	0.00	0.00
STZ(–)	–0.25	–0.33	–0.34	–0.42

It is expected that the presence of a desired R substituent on the sulfonamido group could improve the electron delocalization along the molecular structure. For the case of the SA derivatives, delocalization of the π-electrons onto the molecular backbone led to satisfactory conjugation systems and improved stabilizations. The extended aromatic structure can correspond to the narrow HOMO-LUMO (H-L) gap energy, which provides a reasonable qualitative indication of the excitation properties and of the ability of electron or hole transport [35–37]. Table 4 displays the H-L gaps for all the SA molecules. According to this data, reduction in the H-L gap values for both the radical anion and radical cation species becomes more considerable with respect to the ones in the neutral state. Thus we may predict that the SA derivatives have the most reactivity in their ionic forms. It is interesting that the H-L gaps for the R substituted species are lower with respect to the reference SA molecule, which is in good agreement with the less bacteriostatic reactivity of the original SA.[23] Among the compounds studied, SDZ and SQX have the lower H-L gaps, indicating that they can be show the higher reactivity. The results obtained revealed that the HOMO-LUMO electronic transitions could be attributed to the tendency of the considered R groups to contribute the π-electrons with the molecular system.

Table 4. Calculated values for HOMO-LUMO gaps (eV) for studied species in neutral and ionic states.

Species	Neutral	Cationic	Anionic
SA	0.197	0.074	0.034
SAA	0.192	0.052	0.034
SDZ	0.174	0.050	0.025
SQX	0.166	0.049	0.034
STZ	0.193	0.054	0.034

According to density functional theory, the energy E can be expressed as a function of the electron number N and as a functional of the external potential $v(r)$. Derivatives of $E[N; v(r)]$ with respect to N and $v(r)$ produce a set of global and local quantities that allow to quantify the concept of reactivity and site selectivity, respectively. The electronic chemical potential μ, the molecular hardness η, the electrophilicity index ω, and the maximal flow of electrons that a system may accept ΔN_{Max} are defined as:[32,33]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_v \approx \frac{1}{2}(E_L + E_H) \quad (1)$$

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_v \approx \frac{1}{2}(E_L - E_H) \quad (2)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

$$\Delta N_{Max} = -\frac{\mu}{\eta} \quad (4)$$

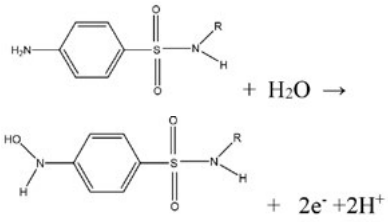
where E_H and E_L are the energies of HOMO and LUMO. These electronic that characterize the charge injection and

charge transport properties of such materials g are given in Table 5. It was found that the electronic descriptors of SAs are influenced by the electronic and steric properties of the substituent. The values for μ, ω, and ΔN_{Max} are related with the escaping tendency of electrons and stabilization energy of the system, and increase with presenting the R group to the parent SA molecule. This indicates that the escaping tendency of electrons in the structures of the SA derivatives, in particular for the deprotonation process, is stabilized by the electron-withdrawing character of the substituent. An inverse trend was observed for the molecular hardness, which points out an obvious substitution effect on the reactivity of the molecules, in particular for the SDZ, SQX, and SAA species. The less change in the electronic properties of the STZ molecule may be referred to the less contribution of its substituent to the conjugated system.

Table 5. Calculated values for electronic descriptors μ, η, ω, and ΔN_{Max} for studied SAs.

Species	μ (eV)	η (eV)	ω (eV)	ΔN_{Max}
SA	–0.136	0.098	0.187	1.377
SAA	–0.149	0.097	0.230	1.545
SDZ	–0.146	0.087	0.246	1.679
SQX	–0.151	0.084	0.271	1.798
STZ	–0.141	0.097	0.209	1.411

In order to elucidate the electrochemical behavior of the titled SA derivatives, their voltammetric responses obtained at a carbon past electrode. Owning to non-solubility of SAs in acidic rezones, a phosphate buffer solution with pH = 7.4 was used in the cyclic voltammetry measurements. These compounds can be electrochemical oxidized at the amino group (NH_2). Figure 1 shows the cyclic voltammograms of each SAs containing 1.0 mM of sulfacetamide, sulfaquinoxaline, sulfadiazine, and sulfathiazole at the CPE. In all voltammograms, just one oxidation peak was observed which could be expressed as a two-electron, two-proton process via the following reaction:



(5)

As it can be seen in Figure 1, the anodic peak current and potential at which the oxidation reaction occurs (I_{pa} and E_{pa}, respectively) are strongly dependent on the characteristic of R group (Scheme 2). Among the SAs, sulfadiazine shows a significant increase in the response current with respect to the other SAs. Under these conditions, it

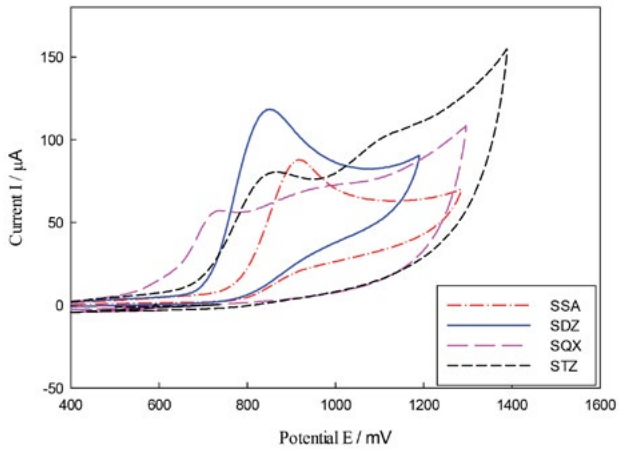


Figure 1. Electrochemical behavior of sulfacetamide (SAA), sulfadiazine (SDZ), sulfaquinoxaline (SQX), and sulfathiazole (STZ) at a CPE. All solutions were studied in concentration of 1 mM in a phosphate buffer solution (pH = 7.4) with scan rate of 0.1 V s^{-1}.

can be concluded that SDZ possesses a higher electrochemical reactivity, and so it can be considered as a desired pharmaceutical application. Since the anodic peak potential E_{pa}, where the oxidation current is maximum, is related to the ionization potential, we calculated the adiabatic IP values for SAs at B3LYP/6-311++G(d,p) level defined as:

$$SAs \rightarrow SAs^{+\circ} + e^{-} \quad (6)$$

where SAs and $SAs^{+\circ}$ stand for the neutral and radical cation states of the sulfonamide derivatives, respectively. In the case of sulfonamide derivatives, the calculated IP is an important parameter for use to estimate the energy barrier for their electro-oxidation reaction.

In Figure 2, the calculated IP values are plotted against the experimental values for E_{pa}. According to this figure, one can observe a good correlation between the IP and E_{pa} values (the correlation coefficient $r^2 > 0.90$). The observed correlation indicates that a highly delocalized

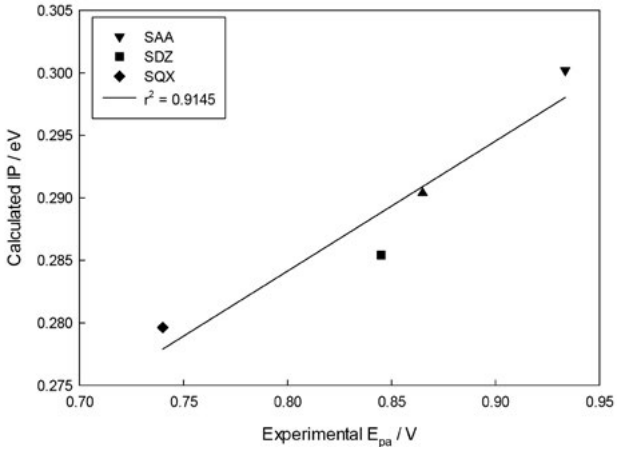


Figure 2. Correlation plot between the calculated IP (eV) and experimental E_{pa} (V) for SA derivatives.

system corresponding to a low E_{pa} value may accept a less barrier energy than a relatively more localized system (with higher E_{pa}). This trend is reasonable because a higher electron-conjugation character of the substituent stabilizes the oxidation product (Eq. 2). It can also be observed in Figure 2 that the SAA molecule with a non-cyclic group (R = $COCH_3$) has a large positive shift for E_{pa}.

3. 3. Thermodynamic Stability of SAs

Full-optimized geometrical structure of SAs were used to calculate the vibrational frequencies by means of the B3LYP/6-311 ++G(d,p) level of theory. All vibrational frequency values together some thermochemical quantities of the sulfonamide derivatives including the total energy (*E*), zero-point energy (*ZPE*), enthalpy (*H*), and thermal corrected energy (H_{corr}) at 298.15 K were tabulated in Tables S2 and S3. As mentioned in section 2, the gas-phase standard molar enthalpies of formation at 298 K, $\Delta H^{\circ}_{f,298}(g)$, for SAs were calculated through the atomization energy route, and the results obtained were displayed in Figure 3. As it can be seen in this figure, in a comparative study in the gas phase, the improvement in stability (corresponding to $\Delta H^{\circ}_{f,298}(g) < 0$) was obtained for the SAA, SDZ, and SQX species with respect to the reference molecule SA. Indeed, attachment of an electron-attracting substituent to the sulfonamido group leads to an evident decrease in the standard molar enthalpies of formation and followed by an increase in the thermodynamic stabilization. In agreement with the electronic results obtained in section 3.2, we observed that the thermodynamic stability of the STZ molecule decreased with respect to the unsubstituted parent SA. Since the thermal stability of compounds is an important factor to be considered for the standardization of drugs and pharmaceuticals, it may be concluded that the considered processor helps us to predict the relative thermodynamic stability of new SA derivatives for which the respective experimental determination has not been reported.

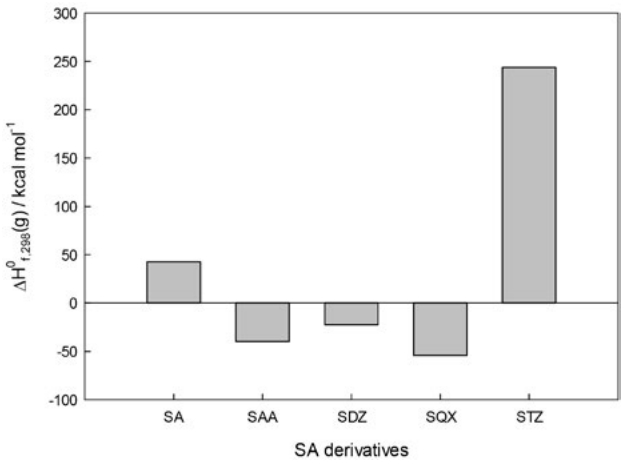


Figure 3. Gas-phase standard molar enthalpy of formation values for SA derivatives at 298 K at the B3LYP/6-311++G(d,p) level of theory.

4. Conclusion

In the current work, the B3LYP/6-311++G(d,p) level of theory was employed to investigate the influence of the N^1-sulfonamide substituent on the geometrical structure and electronic properties of the SAA, SDZ, SQX, and STZ molecules. Substituting the hydrogen atom of the sulfanamido group by four different substituents played a fine-tune effect on the physico-chemical properties and thermodynamic stabilities of the SA derivatives. In the case of the R substituted species, improvements were obtained in the HOMO-LUMO gap, charge density, and some electronic descriptors with respect to the ones in the reference SA molecule, which were in good agreement with the higher bacteriostatic reactivity of these molecules. Comparison of the cyclic voltammetry experiments for the oxidation potential of SAs obtained in this work, with the calculated ionization potential values shows a linear correlation, which corresponds to the conjugational character of the substituent. The calculations carried out on the neutral and ionic SAs as well as electrochemical measurements showed that the SDZ molecule had a more satisfactory structural and electronic characteristic for the bacteriostatic reactivity. Besides, the calculated results for the standard molar enthalpies of formation in the gas phase revealed an improvement in the thermodynamic stabilization of the SDZ, SQX, and SAA molecules with respect to the unsubstituted parent molecule. Generally, the theoretical data obtained for the efficient injection and transport of the carrier charges involving holes and electrons can be applied for the rational design of a sulfa drug of desired properties.

5. Acknowledgment

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6. References

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Povzetek

S teorijo gostotne funkcije (DFT) in z uporabo elektrokemijskih metod smo proučevali strukturne in fizikalno-kemijske lastnostih serije derivatov sulfonamida (SA), ki imajo vlogo nujnih zdravil WHO pri osnovnem zdravljenju. Izračune za sulfadiazin (SDZ), sulfatiazol (STZ), sulfakvinoksalin (SQX), sulfacetamid (SAA) in referenčni nesubstituirani sulfonamid (SA), smo izvedli na B3LYP / 6-311 ++ G (d, p) nivoju. Ugotovili smo, da geometrijske strukture in elektronske lastnosti, povezane z bakteriostatično aktivnostjo, vplivajo na sterične in „push-pull" značilnosti substituent. Predstavili smo tudi elektrokemijske eksperimente oksidacije SA z uporabo ciklične voltametrije. Izkazalo se je, da med izračunani ionizacijski potenciali (IP) in elektrooksidacijskimi potenciali lahko obstaja linearna zveza. Izmed proučevanih molekul je očitno SDZ najbolj elektroaktiven in izkazuje tudi največjo biološko aktivnost. Izračuni DFT, izvedeni s uporabo standardnih molskih tvorbenih entalpij za tvorbo v plinski fazi, so predvideli možne izboljšave pri termodinamski stabilnosti molekul SDZ, SQX in SAA ter relativno nestabilnost STZ glede na molekulo SA.