Theoretical Study of Molecular Structure and Gas-Phase Acidity of Some Biologically Active Sulfonamides

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The geometries of substituted sulfonamides [sulfonamide (**I**) sulfamic acid (**II**), sulfamide (**III**), methane sulfonamide (**IV**), 1,1,1-trifluoromethanesulfonamide (**V**), 4-aminobenzenesulfonamide (**VI**), 1,2-benzisothiazol-3-(2H)-one-1,1-dioxide (saccharin) (**VII**), *N*-(5-sulfamoyl-1,3,4-thiadiazol-2yl)acetamide (acetazolamide) (**VIII**), 4-(aminosulfonyl)-*N*-[(4-fluorophenyl)methyl]-benzamide (1I9L) (**IX**), (*R*)-(+)-4-(ethylamino)-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,-dioxide (brinzolamide) (**X**), and (4*S-trans*)-(+)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide (dorzolamide) (**XI**)] in both neutral and deprotonated forms, were optimized using CBS-QB3 theory (compounds **I**−**IV**), the Becke3LYP/6-311+G(d,p) method (compounds **I**−**VIII**), and the two-layered ONIOM-(B3LYP 6-311+G(d,p): MNDO) method (compounds **VIII** - **XI**). Sulfamic acid behaves in the gas phase as O-acid. The investigated acids are weak acids with calculated acidity of about 1320−1420 kJ mol^{-1}. Of the N-acids studied, saccharin possesses the highest gas-phase acidity (1324 kJ mol^{-1}). The acidities of phenyl-substituted derivatives computed using the hybrid ONIOM (B3LYP/6-311+G(d,p): MNDO) method are in good agreement with the full DFT ones, and this method can be adopted to model large substituted sulfonamides.

1. Introduction

The sulfonamide $-SO_2NH-$ group occurs in numerous biologically active compounds, which include antimicrobial drugs, saluretics, carbonic anhydrase inhibitors, insulin-releasing sulfonamides, antithyroid agents, and a number of other biological activities[1]. Many sulfonamides with the general formula $R-SO_2NH_2$ constitute an important class of inhibitors of the zinc enzyme carbonic anhydrase[2] (CA) because of their use in antiglaucoma therapy.[3−6] They bind as anions to the Zn^{2+} ion within the enzyme active site[7−9] (with abnormally high affinities of around 10^6-10^9 M^{-1} for isozyme CA II, refs 10−12). The active site zinc cation is located at the bottom of a deep, conical cavity, where it is coordinated by three histidine ligands and a hydroxide ion with tetrahedral geometry.[13] When bound, the ionized sulfonamide nitrogen displaces a zinc-bound hydroxide from the active site to form a stable inhibitor-enzyme complex.[14−18] The structures of HCA II and many enzyme−inhibitor complexes have been solved using X-ray crystallography[17−20] and explored in structure-based drug design and modeling.[21−24] Various interactions between substrate and carbonic anhydrase have been modeled using theoretical chemistry methods.[25−33] Unfortunately, not much is known about the molecular structure, ionization, and complexation with metal ions of medicinally useful sulfonamides. Murcko[34] carried out conformational analysis of methane sulfonamide anion using high level ab initio methods.

In this paper, we have used large-scale theoretical quantum chemical calculations for the study of stable geometries of selected biologically important substituted sulfonamides in both neutral and anionic forms. All structures investigated are shown in Figure 1. Of particular interest are the molecular geometries, acidities, and lipophilicities of the species. The results of theoretical studies of sulfonamides were discussed with the present theories of action of these inhibitors of carbonic anhydrase.

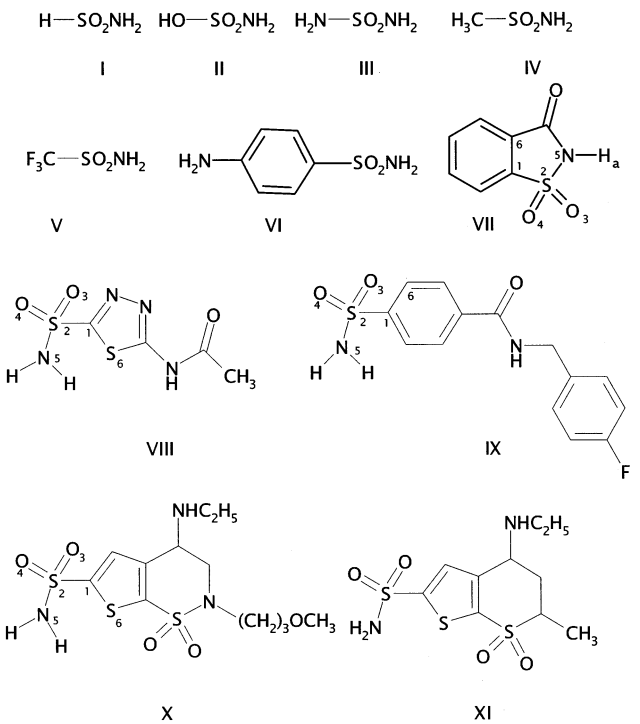

Figure 1. Structure and atom labeling in the sulfonamide species studied.

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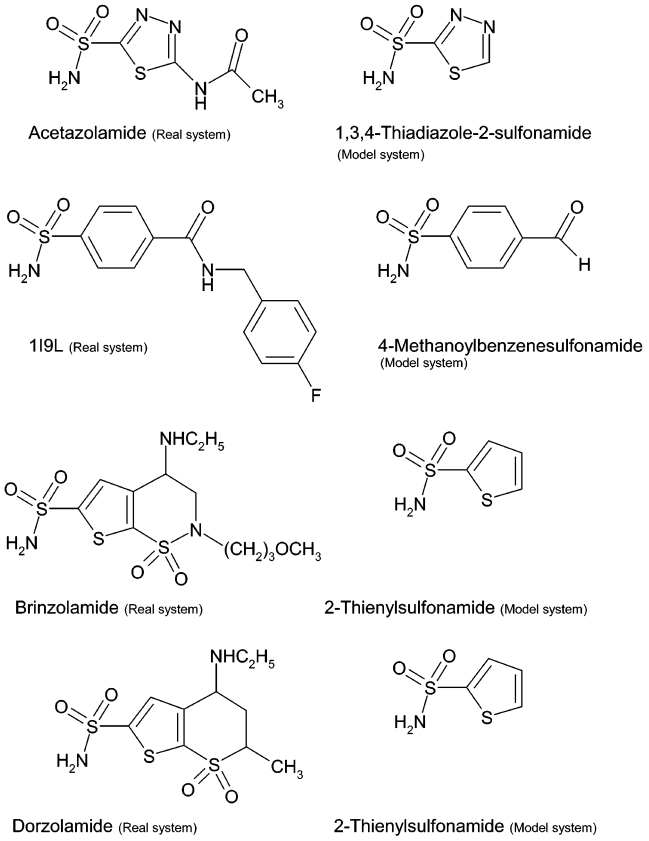

Figure 2. Two sites of systems used for the ONIOM-2 prediction. The full (real) systems (acetazolamide, 1I9L, dorzolamide, brinzolamide) and the model systems (1,3,4-thiadiazole-2-sulfonamide, 2-methanoylbenzenesulfonamide).

2. Computational Details

The geometry of sulfonamide (**I**), sulfamic acid (**II**), sulfamide (**III**), methane sulfonamide (**IV**), 1,1,1-trifluoromethanesulfonamide (**V**), 4-aminobenzenesulfonamide (**VI**), 1,2-benzisothiazol-3-(2H)-one-1,1-dioxide (saccharin; **VII**), *N*-(5-sulfamoyl-1,3,4-thiadiazol-2yl)acetamide (acetazolamide) (**VIII**), 4-(aminosulfonyl)-*N*-[(4-fluorophenyl)methyl]-benzamide (1I9L) (**IX**), (*R*)-(+)-4-(ethylamino)-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,-dioxide (brinzolamide; **X**), and (4*S*-*trans*)-(+)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide (dorzolamide; **XI**) in both neutral and deprotonated forms were completely optimized with the Gaussian 98 program,[35] using CBS-QB3 theory[36] (compounds **I**−**IV**), the Becke3LYP/6-311+G(d,p) method[37−39] (compounds **I**−**VIII**), and the two-layered ONIOM(B3LYP 6-311+G(d,p): MNDO) method[40−42] (compounds **VIII**−**XI**).

The model system and real molecule (R) used for the two-layer ONIOM calculations are shown in Figure 2. The real systems are full acetazolamide, 1I9L, brinzolamide and dorzolamide molecules. The model systems (MS) are represented by 1,3,4-thiadiazole-2-sulfonamide, 4-methanoylbenzenesulfonamide, and 2-thienylsulfonamide, respectively. The two levels of theory used for energy calculations are density functional theory[43] (DFT) at the Becke3LYP level[37−39] with the polarized triple split valence 6-311+G(d,p) basis set (the high level, H) and the semiempirical MNDO method[44] for the low level (L) of theory.

The integrated energy for the two-layered ONIOM approach is defined as[40]

$$E(\text{ONIOM2}) = E(\text{high, model}) + E(\text{low, real}) - E(\text{low, model}) = E(\text{high, model}) + \Delta E(\text{low, real} \leftarrow \text{model}) \quad (1)$$

where

$$\Delta E(\text{low, real} \leftarrow \text{model}) = E(\text{low, real}) - E(\text{low, model})$$

The gas-phase acidity ΔE(A) was defined as the energy of deprotonation ΔE for reaction (A):

$$\text{AH(g)} \rightarrow \text{A}^-\text{(g)} + \text{H}^+\text{(g)} \quad \text{(A)}$$

The energy of deprotonation, ΔE, at $T = 0$ K was computed using eq 2

$$\Delta E(\text{A}) = E(\text{A}^-) - E(\text{AH}) \quad (2)$$

where E stands for the total energies of the stable conformations of acid and its anion. For calculation of the deprotonation energies by means of the ONIOM method, the values of ONIOM extrapolated energies (E_{ONIOM}) were used. The enthalpy of deprotonation, ΔH,[298] was computed using eqs 3 and 4

$$\Delta H^{298}(\text{A}) = \Delta E^{298}(\text{A}) + \Delta(pV) \quad (3)$$

$$\Delta E^{298} = \left[E^{298}_{\text{ONIOM}}(\text{A}^-) + \frac{3}{2}RT\right] - E^{298}_{\text{ONIOM}}(\text{AH}) \quad (4)$$

where E^{298} stands for the total energies of the stable conformations of acids and their anions (including the thermal energy correction at $T = 298.15$ K). In eq 3, we substituted $\Delta(pV) = RT$ (one mol of gas is obtained in the reaction (A)). The gas-phase Gibbs energy, ΔG,[298] of the proton abstraction reaction may be calculated from

$$\Delta G^{298} = \Delta H^{298} - T\Delta S^{298} \quad (5)$$

The enthalpy of deprotonation was calculated using expression 3. The entropy contribution is given by

$$-T\Delta S^{298} = -T[S(\text{A}^-) + S(\text{H}^+) - S(\text{AH})] \quad (6)$$

For $T = 298$ K at the standard pressure, the second term $TS(\text{H}^+) = 32.5$ kJ mol^{-1}, ref 45. Thus

$$\Delta G^{298} = \Delta H^{298} - T[S(\text{A}^-) - S(\text{AH})] - 32.5 \quad (7)$$

Notice that there is an inverse relationship between the magnitude of ΔG and the strength of the acid. The more positive the value of ΔG, the weaker the acid.

3. Results and Discussion

Geometries. An analysis of the harmonic vibrational frequencies at the DFT and CBS-QB3 levels of theory of the optimized species revealed that all of the structures obtained were minima (no imaginary frequencies). In the sulfonamides investigated (one exception is saccharin), there are two rotational degrees of freedom, which correspond to the X−S (X = N, C, O) and N−S bond rotations (Figure 1). Thus, several rotamers we can identify for rotations about these bonds.

According to the recent high-level ab initio calculations[46] of the sulfonamide $HS(O)_2NH_2$ and its $-CH_3$, $-F$, and $-Cl$ substituted derivatives, these compounds exist in two stable forms. The basic difference between these two structures arises from the arrangement of $-NH_2$ group syn or anti with respect

TABLE 1: Becke3LYP/6-311+G(d, p) Optimized Relevant Bond Lengths (Å), Bond Angles (Degrees), and Dihedral Angles (Degrees) of the Sulfonamides Studied

	I	II	III	IV	IV, exp.[c]	V	VI	VI, exp.[d]	VII	VIII	VIII, exp[e]	XI[b]	X[b]	XI[b]
d[X(1)-S(2)]	1.370	1.656	1.680	1.798	1.750	1.889	1.783	1.750	1.793	1.800	1.774	1.802	1.786	1.781
d[S(2)−O(3)]	1.452	1.446	1.456	1.461	1.437	1.450	1.463	1.439	1.456	1.459	1.426	1.460	1.457	1.457
d[S(2)−O(4)]	1.452	1.446	1.456	1.461	1.437	1.450	1.463	1.431	1.456	1.452	1.425	1.460	1.457	1.457
d[S(2)−N(5)]	1.657	1.648	1.680	1.695	1.609	1.662	1.700	1.609	1.717	1.677	1.593	1.690	1.687	1.688
θ[X(1)-S(2)−O(3)]	106.4	108.0	104.9	108.0	107.8	105.9	107.6	107.4	111.9	105.3	105.3	107.4	105.7	106.1
θ[X(1)-S(2)−O(4)]	106.4	107.8	113.2	108.0	107.8	105.9	108.3	107.8	111.9	108.0	106.6	107.4	108.3	107.9
θ[X(1)-S(2)−N(5)]	104.8	100.1	97.9	102.1	108.0	100.2	104.1	110.7	90.4	102.4	106.6	103.2	102.9	103.1
ϕ[Y(6)−C(1)−S(2)−O(3)]							−161.1	−171.6	−111.7	6.2	20.7	155.3	−172.9	−168.2
ϕ[Y(6)−C(1)−S(2)−O(4)]							−27.3	−43.3	111.7	139.2	150.7	21.6	−39.5	−34.8
ϕ[Y(6)−C(1)−S(2)−N(5)]							84.7	71.5	0.0	−105.3	−94.4	−91.4	72.2	76.8

[a] X =H, N, C, O; Y = C, S. [b] ONIOM (Becke3LYP/6-311+G(d,p):MNDO) method. [c] Reference 49. [d] Reference 50. [e] Reference 51.

TABLE 2: Becke3LYP/6-311+G(d,p) Selected Structural Parameters of the Neutral and Anionic Species Studied[a,b]

species	X(1)−S(2) distance	S(2)−N(5) distance	X(1)−S(2)−N(5) angle	S(2)−N(5)−H angle	Y(6)−C(1)−S(2)−N(5) torsion angle	H−N(−)−S=O torsion angle
I	1.370	1.657	104.8	116.2		
I(N anion)	1.391	1.574	108.3	106.0		−25.6
II	1.656	1.648	100.1	113.4		
II(N anion)	1.746	1.555	105.0	106.5		−35.6
III	1.680	1.680	97.9	111.7		
III(anion)	1.773	1.570	106.2	105.6		14.9
IV	1.798	1.695	102.1	110.2		
IV(anion)	1.842	1.580	108.3	105.8		−23.5
V	1.889	1.662	100.2	113.2		
V(anion)	1.915	1.559	106.5	106.7		25.7
VI	1.783	1.700	104.1	110.3	84.7	
VI(anion)	1.841	1.576	108.1	106.2	76.3	−30.5
VII	1.793	1.717	90.4	121.0	0.0	
VII(anion)	1.815	1.637	96.4		0.0	
VIII	1.800	1.677	102.4	110.8	−105.3	
VIII(anion)	1.866	1.550	107.9	106.8	−117.6	31.6
IX[c]	1.802	1.690	103.2	110.7	−91.4	
IX(anion)	1.840	1.574	106.4	106.6	−99.6	−26.0
X[c]	1.786	1.687	102.9	109.7	72.2	
X(anion)	1.882	1.562	107.8	107.1	68.6	−27.5
XI[c]	1.781	1.688	103.1	109.7	76.8	
XI(anion)	1.875	1.560	108.0	107.0	79.6	−28.4

[a] Bond lengths are in Å, and bond angles and dihedral angles are in degrees. [b] X = H, N, C, O; Y = C, S. [c] ONIOM (Becke3LYP/6-311+G(d,p): MNDO) method.

to the $-SO_2$ group. The syn isomer of the sulfonamide $HS(O)_2NH_2$ was found to be the most stable structure.[46] Thus, the calculations of acidities for sulfonamides studied were carried out for syn structures only.

Important geometrical parameters of the sulfonamide moiety are given in Table 1. Some trends are apparent: (i) The smallest central S(2)−N(5) bond length of 1.648 Å was computed for the sulfamic acid $HOS(O)_2NH_2$ which is apparently the result of attractive interaction of the $-NH_2$ and $-OH$ groups in the most stable syn conformer of this compound. The S−N bond length in the rest of the substituted sulfonamides investigated is about 0.014−0.069 Å longer (Table 1). However, the S−N bond length in sulfonamides studied is much shorter than the S−N single bond distance[47] of about 1.75 Å (Table 1). (ii) The C(1)−S(2) single bond in the 1,1,1-trifluoromethanesulfonamide (**V**) is by about 0.09 Å longer than that bond in the parent methane sulfonamide (**IV**). The strong electron withdrawing nature of the CF_3 substituent in (**IV**) is apparently responsible for the destabilization of the C−S bond. In aromatic and hetrocyclic substituted compounds (**VI** and **VIII**−**XI**), the C(1)−S(2) bond length of about 1.78−1.80 Å is a single bond length between the sp^2 hybridized carbon atom and sulfur because the sulfonamide group and aromatic rings are approximately perpendicular (dihedral angle Φ[Y(6)−C(1)−S(2)−N(5)], Table 1). (iii) The valence angles of the $R-SO_2NH_2$ moiety change considerably upon substitution R. (iv) The sp^3 hybridized nitrogen atoms of the $-SO_2NH_2$ group show pyramidal character. (v) The five-member heterocyclic ring in saccharin is coplanar with the aromatic ring.

In the absence of gas-phase data, the geometry of the parent sulfonamides only can be compared with published[48] X-ray data of compounds **IV**,[49] **VI**,[50] and **VIII** (Table 1).[51] Although both methods are based on different models, the computed geometry for compounds **IV**, **VI**, and **VIII** is in good agreement with the experimentally determined X-ray structures of these compounds.

Sulfonamides exhibit interesting solid-state properties, among which is the ability for many of these compounds to exist in two or more polymorphic forms.[52] The solid-state properties of these compounds are influenced by their propensity for hydrogen bonding[53,54] which can give rise to polymorphism. Because the geometries of the sulfonamides in the crystalline phase are controlled by intermolecular hydrogen bonds, they are not exactly comparable with those of the free molecules.

The ionization of the parent compounds changed their geometry especially in the vicinity of reaction centers (Table 2). Compared to the parent free acids of the sulfonamides, the X(1)−S(2) (X = N, C, O) bond of the N anions is longer by about 0.02−0.1 Å. The S(2)−N(5) distance is in anions substantially shorter (by about 0.1 Å). Thus, upon ionization of the parent sulfonamides, this bond gains double bond

TABLE 3: Computed Gas-Phase Acidities of Sulfonamides Investigated

		CBS-QB3			B3LYB/6-311+G(d,p)			ONIOM (B3LYP/6-311+G(d,p): (MNDO)			ΔG^{298}
no.	compound	ΔH^{298} [a]	ΔS^{298} [b]	ΔG^{298} [a]	ΔH^{298} [a]	ΔS^{298} [b]	ΔG^{298} [a]	ΔH^{298} [a]	ΔS^{298} [b]	ΔG^{298} [a]	exp[a]
I	$H-SO_2NH_2$ (N-anion)	1427.4	102.0	1397.0	1427.5	99.9	1397.7				
II	$HO-SO_2NH_2$ (N-anion)	1419.9	86.6	1394.1	1407.3	100.7	1377.3				
II	$HO-SO_2NH_2$ (O-anion)	1322.9	85.6	1297.4	1324.6	96.1	1296.0				
II	$HO-SO_2NH_2$ (O, N-dianion)	3288.8	165.4	3239.5	3274.7	179.9	3221.1				
III	$H_2N-SO_2NH_2$	1445.8	109.3	1413.2	1441.9	108.4	1409.6				
IV	$CH_3-SO_2NH_2$	1447.0	101.2	1416.8	1449.3	100.3	1419.4				1418±8.4
V	$CF_3-SO_2NH_2$				1367.6	102.3	1337.1				1344±8.4
VI	p-Aminobenzenesulfonamide				1449.2	103.0	1418.5				
VII	Saccharin				1349.1	83.7	1324.1				
VIII	Acetazolamide				1391.2	108.7	1358.8	1392.8	107.5	1360.7	
IX	1I9L							1397.4	104.0	1366.4	
X	Brinzolamide							1365.3	101.3	1335.1	
XI	Dorzolamide							1379.9	101.7	1349.6	

[a] Values in kJ mol^{-1}. [b] Values in J K^{-1} mol^{-1}. [a] Values taken from ref 57 (in kJ mol^{-1}).

character. The short N−S distances observed in these anions can be mainly attributed to the electrostatic attractions between sulfur and negatively charged nitrogen atoms. The N−H and S═O groups in anions of the primary sulfonamides are in mutual *syn-periplanar* conformation [the dihedral angle $H-N^{(-)}-S=O$, Table 2] and stabilized by means of a weak intramolecular hydrogen bond (the H···O bond length is about 2.51−2.60 Å). The electrostatic interaction via this intramolecular hydrogen bond is apparently responsible for the substantial increase (by about 5°) of the valence angle X(1)−S(2)−N(5) (X = N, C, O) and reduction of the S(2(−N(5)−H angle (by 3−7°). The perpendicular arrangement of the $-SO_2NH^{(-)}$ groups and aromatic systems is also preserved in the corresponding anions of **VI** and **VIII**−**XI** [dihedral angle Y(6)−C(1)−S(2)−N(5), Y = C, S)].

Gas-Phase Acidities. The sulfonamides studied contain an acidic $-NH_2$ group, and thus, they may undergo deprotonation reactions. It is well-known[7−9] that the anion is bound to the enzyme active site and therefore represents the active species. However, the deprotonation reactions of sulfonamides in condensed phase have not been intensively investigated experimentally.[55,56] The gas-phase proton affinities of simple aliphatic sulfonamides (methane sulfonamide and 1,1,1-trifluoromethanesulfonamide) have been determined.[57]

Table 3 contains acidities of sulfonamides studied. At all of the levels of theory applied, the same order of acidity of sulfonamides was found. The density functional Becke3LYP enthalpies and free energies are closer to the CBS-QB3 results. The largest discrepancy occurs for sulfamic acid (**II**) for which the Becke3LYP value (1377.3 kJ mol^{-1}) is by about 16.8 kJ mol^{-1} lower than CBS-QB3 computed acidity (Table 3). The CBS-QB3 method approximates a high-level calculation with a very large basis set. The comparison of the B3LYP results with this very accurate method shows that density functional theory performs quite well and can thus be used as a relatively inexpensive alternative for investigation of acidity of larger systems. The acidity of acetazolamide (**VIII**) computed using the hybrid ONIOM (B3LYP/6-311+G(d,p): MNDO) method is in very good agreement with the full DFT ones (Table 3), and this method can be adopted to model large aromatic sulfonamides. Koppel et al.[57] have experimentally examined the acidity of methane sulfonamide (**IV**) and 1,1,1-trifluoromethanesulfonamide (**V**). The computed enthalpy and Gibbs energy is, within the range of targeted accuracy of 10 kJ mol^{-1}, in good agreement with experimentally estimated quantities (Table 3).

For the N acids studied, the acidities increase in the order: $CH_3SO_2NH_2$ ≤ *p*-aminobenzensulfonamide < $NH_2SO_2NH_2$ < HSO_2NH_2 < $HOSO_2NH_2$ (N acid) < 1I9L < acetazolamide < dorzolamide < brinzolamide < $CF_3SO_2NH_2$ < saccharin (Table 3). The electronegative trifluoromethyl substituent increases the acidity by about 82 kJ mol^{-1} in comparison with the parent methane sulfonamide. The greater acidity of 1,1,1-trifluoromethanesulfonamide can be attributed, in part, to the extra electron-attracting inductive effect of the electronegative fluorine atoms. It also stabilizes the 1,1,1-trifluoromethanesulfonamide anion by dispersing its negative charge. The negative charge is more spread out in the 1,1,1-trifluoromethanesulfonamide ion than in the parent methane sulfonamide anion. Dispersal of charge always makes species more stable.[58,59] The increased stabilization of the conjugate base of 1,1,1-trifluoromethanesulfonamide increases the strength of the acid (Table 3). Electron donation by the $-CH_3$ group in methane sulfonamide destabilizes the anion of this acid and reduces its acidity in comparison with the unsubstituted sulfonamide (HSO_2NH_2). The similar acidity decrease upon amino substitution (in $NH_2SO_2NH_2$) is apparently caused by the prevailing electron-donating mesomeric effect of the $-NH_2$ group. The aromatic group by means of its inductive effect disperses the negative charge in the anions of aromatic sulfonamides less effectively than the $-CF_3$ substituent, and aromatic sulfonamides are more acidic than the unsubstituted sulfonamide (HSO_2NH_2; Table 3).

In the case of sulfamic acid (**II**), the reaction for O ionization was also studied (Table 3). Sulfamic acid is by about 90 kJ mol^{-1} more acidic acting as an O acid. Thus, sulfamic acid behaves in the gas phase as O acid. The different computed acidity of sulfamic acid and sulfamide well correlates with the experimental pK_a values[60] of these compounds (1.2 and 12.5, respectively).

The sulfonamides investigated are weak organic acids (Table 3). However, their acidities are about 200−250 kJ mol^{-1} larger than that for natural substrate water[61] (ΔG^{298}exp = 1607.1 kJ mol^{-1}). The presence of ionizable group of appropriate pK_a is one of the conditions needed for the sulfonamide to act as an effective intraocular pressure lowering agent.[62,63] The protonation−deprotonation equilibrium in biologically active sulfonamides is characterized by the experimental pK_a value[63] (in aqueous system); this quantity, however, is not proportional to the electron density at the nitrogen atom of the SO_2NH_2 group. A quantity, which is related to the electron densities at nitrogen atoms, is the protonation/deprotonation energy in the gaseous state.[64] For antiglaucoma sulfonamides, the experimental values of acidities are unknown. The computed gas-phase acidities of the clinically useful drugs acetazolamide, brinzolamide, and dorzolamide span a rather narrow energy interval (1335−1360

TABLE 4: Calculated Partition Coefficients of Sulfonamides Investigated

no.	compound	log P (exp.)	IA log P	log P (Crippen)
I	$H-SO_2NH_2$		−0.87	−1.0
II	$HO-SO_2NH_2$		−1.79	−0.42
III	$H_2N-SO_2NH_2$		−1.64	−1.28
IV	$CH_3-SO_2NH_2$		−1.37	−0.75
V	$CF_3-SO_2NH_2$		0.21	1.19
VI	Sulfanilamide	−0.62	−0.47	0.15
VII	Saccharin	0.91	0.44	0.43
VIII	Acetazolamide	−0.26	−0.30	−0.61
IX	1I9L		1.67	1.93
X	Brinzolamide		0.22	−0.99
XI	Dorzolamide		0.71	−0.28

TABLE 5: Calculated Solubilities of Sulfonamides Investigated

no.	compound	log *S*, exp.	IA log *W*
I	$H-SO_2NH_2$		0.19 (124.5 g/l)
II	$HO-SO_2NH_2$		0.18 (148.0 g/l)
III	$H_2N-SO_2NH_2$		0.06 (111.1 g/l)
IV	$CH_{3-SO2}NH_2$		0.54 (327.14 g/l)
V	$CF_{3-SO2}NH_2$		−0.38 (62.03 g/l)
VI	Sulfanilamide	−1.36 (7.52 g/l)	−1.52 (5.26 g/l)
VII	Saccharin		−2.06(1.611 g/l)
VIII	Acetazolamide	−2.36 (0.97 g/l)	−2.15 (1.59 g/l)
IX	1I9L		−3.84 (0.04 g/l)
X	Brinzolamide		−2.92 (0.46 g/l)
XI	Dorzolamide		−2.68 (0.67 g/l)

kJ mol^{-1}) which means that the acidity of sulfonamides is one of the important factors by their proper coordinating to the Zn^{2+} ion in the active site of CA.

Lipophilicity and Solubility. It is well established[62,63] that a water-soluble sulfonamide, also possessing a relatively balanced lipid solubility, would be an effective antiglaucoma drug via the topical route. One of the conditions[62] needed for a sulfonamide to act as an effective intraocular pressure lowering agent is to possess a modest lipid solubility (attributable to its unionized form).

Lipophilicity of a drug is usually measured as *P*, the partition coefficient of the molecule in the water−octanol system. Table 4 contains computed log *P* values of sulfamide drugs under study. Calculation of log *P* was carried out using atomic parameters derived by Ghose et al/.[65,66] implemented in program HyperChem 5.0[67] and the IA log *P* predictor based on neural network algorithms.[68] The calculated partition coefficients using these two methods are different for most of the sulfonamides studied (Table 4). The comparison with the available experimental partition coefficients shows that the IA log *P* method reproduced the observed log *P* much better than Ghose et al.'s atom contribution method. However, the general applicability of the Ghose et al. approach is limited because of missing parametrization.[69] The situation is less critical for the IA log *P* method which is based on the highly predictive generalized neural network algorithm capable accurately predict completely new structures.[68] The more lipophilic compounds **VI**−**XI** contain a large hydrophobic domain in their aromatic rings. Because medicinally useful antiglaucoma drugs are aromatic sulfonamides, it is evident that for optimal in vivo activity the balanced hydro- and liposolubility is necessary. The computed solubility together with the experimental values of log *S* is given in Table 5. Theoretical values were obtained using IA log *W* predictor based on neural network algorithms.[68] Simple aliphatic sulfonamides exhibit good water solubility. Aromatic sulfonamides possessing large hydrophobic domains are generally substantially less soluble. The computed solubilities are in good agreement with the available experimental values of log *S*; thus, IA log *W* can be used for prediction water solubility of new biologically active sulfonamides.

4. Conclusions

This theoretical study set out to determine stable conformations, gas-phase reactivity, lipophilicity, and hydrophilicity of eleven biologically active sulfonamides for which a relatively small amount of experimental physicochemical data exist, considering their pharmacological importance. Using the theoretical methods the following conclusions can be drawn.

(1) Sulfamic acid behaves in the gas phase as O acid. The investigated sulfonamides are weak organic acids with a calculated acidity of about 1320−1420 kJ mol^{-1}. Of the N acids studied, saccharin possesses the highest gas-phase acidity (1324 kJ mol^{-1}).

(2) The acidity increases in the order $CH_3SO_2NH_2 \leq$ *p*-aminobenzensulfonamide < $NH_2SO_2NH_2$ < HSO_2NH_2 < $HOSO_2NH_2$ (N acid) < 1I9L < acetazolamide < dorzolamide < brinzolamide < $CF_3SO_2NH_2$ < saccharin.

(3) The ONIOM (B3LYP/6-311+G(d,p): MNDO) level of treatment can provide acidities in very good agreement with the results computed at the full Becke3LYP level, at a fraction of computational cost.

(4) The IA log *P* and IA log *W* predictors based on neural network algorithms reproduce well the experimental lipophilicity and solubility of studied compounds and can be used for calculation of these parameters of new biologically active sulfonamides.

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