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Theoretical study of gas-phase acidity, pK_a, lipophilicity, and solubility of some biologically active sulfonamides

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Abstract—The geometries of 19 biologically active substituted sulfonamides (including clinically useful acetazolamide, methazolamide, ethoxzolamide, dichlorophenamide, dorzolamide, and brinzolamide) in both neutral and deprotonated forms, were optimized using Becke3LYP/6-311+G(d,p) method (compounds **1**–**6**) and two-layered ONIOM (B3LYP 6-311+G(d,p): MNDO) method (compounds **7**–**19**). The investigated sulfonamides are weak acids with calculated acidity of about 1320–1420 kJ mol^{-1}. Of acids studied the highest gas-phase acidity (1324 kJ mol^{-1}) possesses methazolamide. This drug is, according to the computed pK_a value (5.9), also in water solution the most acidic compound of the sulfonamides investigated. The computed pK_a values varied between 5.9 and 12.6 and correlate well with the available experimental pK_a's found in the literature. Cancerostatic aromatic sulfonamides **16**–**19** are generally weak acids with the acidity comparable or slightly lower than the lead sulfanilamide. The available experimental partition coefficients of sulfonamides investigated are best reproduced by the IA LOGP method. Computed partition coefficients for antiglaucoma sulfonamides **1**–**13** varied between −0.47 and 2.61 (IA LOGP). Thus these compounds are only slightly or moderate lipophilic. The lipophilicity of the cancerostatic sulfonamides **14**–**18** is from relatively narrow interval between −0.07 and 1.68 (IA LOGP). The most potent CAI **10**–**13** are also the most lipophilic compounds among the antiglaucomatics studied. The available experimental solubilities are best reproduced by the IA LOGS method. The computed solubilities qualitatively correlate with the corresponding lipophilicities, log S increasing as log P declines. The analysis of molecular descriptors defined by Lipinski have been shown that all of the sulfonamides studied obey 'Rule of 5'. Therefore, in the early stages of the design of antiglaucoma sulfonamides, it is becoming more important to determine the pK_a, lipophilicity, water solubility, and other physicochemical properties associated with a drug, before synthetic work is undertaken, with the aim of avoiding the synthesis of compounds that are predicted to have poor biopharmaceutical characteristics.

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 antitumor drugs, and number of other biological activities.[1–3] Many sulfonamides with the general formula R–SO_2NH_2 constitute an important class of inhibitors of the zinc enzyme carbonic anhydrase[4] (CA) due to their use in antiglaucoma therapy.[5–8] They bind as anions to the Zn^{2+} ion within the enzyme active site[9–11] (with abnormally high affinities of around 10^6–10^9 M^{-1} for isozyme CA II, Refs. 12–14). Sulfonamides are weak organic acids.[15] Because medicinally useful antiglaucoma drugs are aromatic sulfonamides, it is evident that for optimal in vivo activity the balanced hydro- and liposolubility is necessary. Simple aliphatic sulfonamides exhibit good water solubility.[15] Aromatic sulfonamides possessing large hydrophobic domains are generally substantially less soluble.[15] It is well established[16,17] 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[16] 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). Therefore, in the early stages of the design of antiglaucoma sulfonamides, it is becoming more important to determine the pK_a lipophilicity, water solubility, and other physicochemical properties associated with a drug, before

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synthetic work is undertaken, with the aim of avoiding the synthesis of compounds that are predicted to have poor biopharmaceutical characteristics.

The physicochemical characteristics of some of the prepared antiglaucoma sulfonamides were experimentally determined.[4] Unfortunately, not much is known about the theoretical determination of molecular structure, ionization, and complexation with metal ions of medicinally useful sulfonamides. Murcko[18] carried out conformational analysis of methane sulfonamide anion using ab initio methods. In a recent work[15] large-scale theoretical quantum chemical methods were used to determine stable conformations, gas-phase acidity, lipophilicity, and hydrophilicity of 11 aliphatic and aromatic sulfonamides for which a relatively small amount of experimental physicochemical data exist, considering their pharmacological importance. Thermodynamics of binding of Zn(II) to carbonic anhydrase inhibitors was also investigated.[19] Computational chemistry was also used for screening of novel inhibitors of human carbonic anhydrase.[20–22] Klebe and co-workers[20,21] used several methods for virtual screening of compound libraries. On the basis of predicted affinity 13 new compounds was prepared and experimentally tested. Of these 13, four compounds were shown to be nanomolar or subnanomolar inhibitors.[21] Shakhnovich and co-workers[22] used combinatorial computational method for prediction of new ligands for hCA II. One of the designed ligands is the best-known inhibitor[22] with experimentally verified binding affinity $K_d \approx 30\,pM$.

In this paper we have used theoretical methods for the study of stable geometries of 19 biologically active aromatic and heteroaromatic sulfonamides in both neutral and anionic forms. All structures of these most representative sulfonamides investigated are shown in Figure 1. Of particular interest are the molecular geometries, gas-phase acidities, pK_a, solubilities, and lipophilicities of the species. The results of theoretical studies of sulfonamides were compared with the available experimental data and discussed with the present theories of action of these inhibitors of carbonic anhydrase.

2. Results and discussion

2.1. Geometries

An analysis of the harmonic vibrational frequencies at the DFT level of theory of the optimized species revealed that all the structures obtained were minima (no imaginary frequencies). In the sulfonamides investigated there are two rotational degrees of freedom, which correspond to the X–S (X = N, C, O) and N–S bond rotations (Fig. 1). Thus several rotamers we can identify for rotations about these bonds. According to the recent high-lever ab initio calculations[23] 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 to the $-SO_2$ group. The *syn* isomer of the sulfonamide $HS(O)_2NH_2$ was found to be the most stable structure.[23] Thus the calculations of acidities for sulfonamides studied were carried out for *syn* structures only.

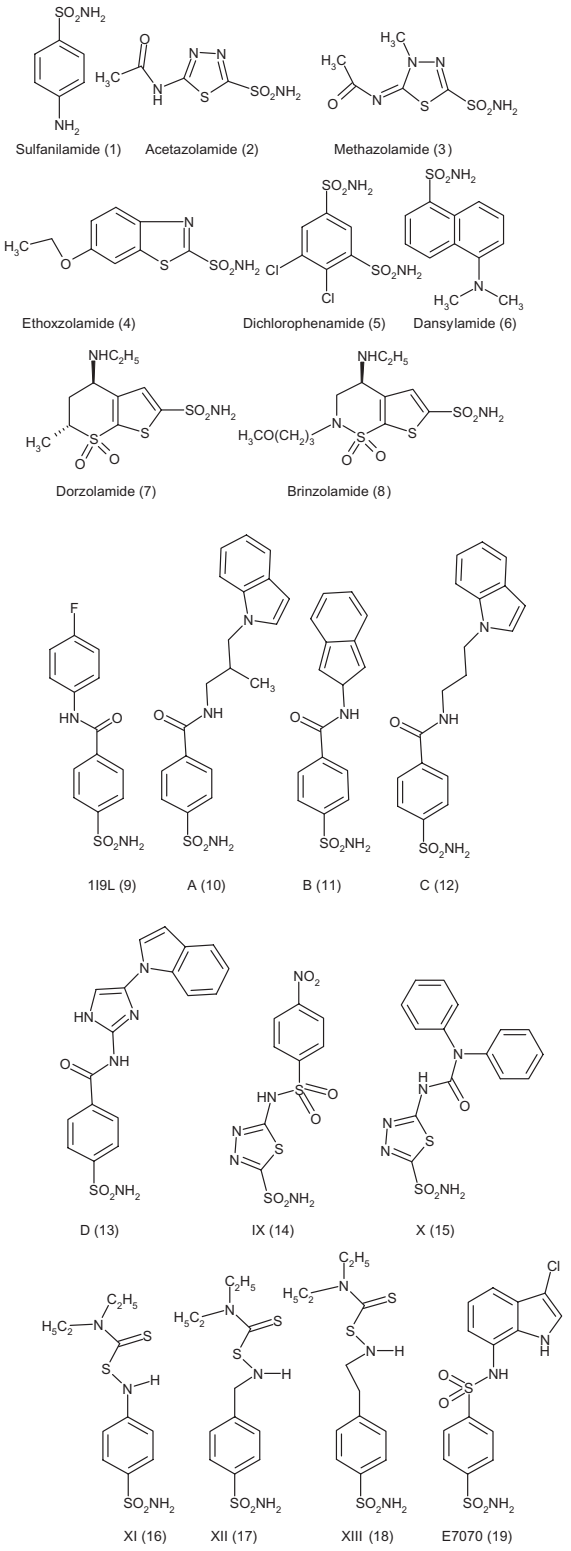

Figure 1. Structure of the sulfonamide species studied.

The structural characteristics of the sulfonamide moiety of the compounds **1**, **2**, and **7**–**9** were discussed in detail elsewhere.[15] Some trends are apparent. (i) The S–N

bond length in sulfonamides studied (about 1.68–1.70 Å) is much shorter than the S–N single bond distance[24] of about 1.75 Å. (ii) In aromatic and heterocyclic sulfonamides the C_{arom}–S bond length of about 1.78–1.80 Å is a single bond length between sp^2 hybridized carbon atom and sulfur since the sulfonamide group and aromatic rings are approximately perpendicular. (iii) The sp^3 hybridized nitrogen atoms of the $–SO_2NH_2$ group show pyramidal character. Compared to the parent free acids of the sulfonamides, the C_{arom}–S bond of the *N*-anions is longer by about 0.02–0.1 Å. The S–N distance is in anions substantially shorter (by about 0.1 Å). Thus, upon ionization of the parent sulfonamides, this bond gains double bond 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 and stabilized by means of a weak intramolecular hydrogen bond (the H···O bond length is about 2.51–2.60 Å).

2.2. Gas-phase acidities

The sulfonamides studied contain an acidic $–NH_2$ group and thus they may undergo deprotonation reactions. It is well known[9–11] 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.[25,26] The gas-phase proton affinities of simple aliphatic sulfonamides (methane sulfonamide and 1,1,1-trifluoromethanesulfonamide) have been determined.[27]

Table 1 contains acidities of sulfonamides studied. Previous high-level ab initio calculations[15] of the simpler substituted sulfonamides using various levels of model chemistry have been shown that density functional theory performs quite well and can thus be used as relatively inexpensive method for investigation of acidity of larger sulfonamides. 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.[15] The compounds investigated exhibit from the pharmacological point of view different mechanism of action. Sulfonamides **1**–**6** are orally active systemic antiglaucoma drugs, compounds **7**–**13** are topically acting antiglaucoma sulfonamides, and structures **14**–**19** represent potent cancerostatic sulfonamides.[28,29] It is therefore interesting to examine whether or not the physicochemical properties of these compounds could be rationalized with respect to their different biological activities. The simplest of the sulfonamides examined, sulfanilamide, may be considered as a lead. Its gas-phase acidity was computed to be 1418.5 kJ mol^{-1} and is the weakest acid of the compounds studied. The substituents on the aromatic ring of the benzene sulfonamide moiety in compounds **5**, **6**, **9**–**13**, and **16**–**19** in various degrees increase the acidity of the lead compound. The acidity of the potent dichlorophenamide is by 75 kJ mol^{-1} higher than the parent sulfanilamide (Table 1). On the other hand, the acidity of the micromolar inhibitor dansylamide is comparable in strength with the lead sulfanilamide. The acidities of the topical aromatic sulfonamides **9**–**13** are from a relatively narrow energy interval of 1360–1375 kJ mol^{-1}. Thus these compounds are in the vapor state practically equally acidic. *para*-Substituents of the aromatic sulfonamides **16**–**18** do not generally influence the acidity of the $–SO_2NH_2$ group. The acidity of those cancerostatic sulfonamides is by about 20 kJ mol^{-1} lower than that in the topically acting antiglaucoma sulfonamides

Table 1. Computed gas-phase acidities (in kJ mol^{-1}) of sulfonamides studied

No.	Compound	B3LYP/6-311+G(d,p)		K_i, nM	Ref.
		ΔH^{298}, kJ mol^{-1}	ΔG^{298}, kJ mol^{-1}		
1	Sulfanilamide	1449.2	1418.5	300	35
2	Acetazolamide	1392.8	1360.7	10	28
3	Methazolamide	1361.5	1323.5	8	28
4	Ethoxzolamide	1399.2	1362.8	0.7	28
5	Dichlorophenamide	1381.3	1343.8	30	28
6	Dansylamide	1428.3	1390.0	930[b]	21
7	Dorzolamide	1379.9[a]	1349.6[a]	9	28
8	Brinzolamide	1365.3[a]	1335.1[a]	3	28
9	1I9L	1397.4[a]	1366.4[a]	2.4[b]	30
10a	A-(*R*)	1402.7[a]	1373.7[a]	0.030[b]	22
10b	A-(*S*)	1406.9[a]	1362.3[a]	0.230[b]	22
11	B	1411.1[a]	1374.8[a]		
12	C	1403.9[a]	1375.6[a]		
13	D	1395.0[a]	1367.6[a]		
14	IX	1362.4[a]	1325.4[a]	0.1	31
15	X	1390.0[a]	1353.4[a]	8	31
16	XI	1434.7[a]	1396.5[a]	48	32
17	XII	1431.3[a]	1391.1[a]	13	32
18	XIII	1430.7[a]	1395.6[a]	11	32
19	E7070	1374.6[a]	1339.2[a]	15	32

[a] ONIOM(B3LYP/6-311+G(d,p):MNDO) method.
[b] K_d values.

9–**13**. The acidity of the compound E7070 is, owing to the electron-withdrawing effect of the secondary sulfonamide moiety, considerably increased (Table 1). However, the computed gas-phase acidities do not correlate with the in vitro inhibition constants against hCA II (Table 1).

Sulfonamide carbonic anhydrase inhibitors studied bind in the active site of carbonic anhydrase in deprotonated state.[9–11] The neutral sulfonamides **1**–**19** are weak acids (Table 1) with high pK_a values. In the definition of the acidity of sulfonamides in water the proton as the product of deprotonation is associated with water. In proteins, the proton is not solvated but associated with a nearby basic residue,[33] which can affect the protonation state of zinc ligands in proteins. It is therefore conceivable that these acids are deprotonated when coordinating to zinc in carbonic anhydrase in which the basic amino acid sites can serve as a proton acceptor. The acidity of these compounds considerably increases upon chelation.[19] The presence of other zinc ligands, the residues in the higher zinc coordination shells, and the electrostatic field of the protein may influence the absolute acidities of the ligands in their complexes with specific proteins. However, the previous calculations made by El Yazal and Pang[33] has shown that these influences on acidities of test ligands can be canceled out.

2.3. Dissociation constants

The calculations of gas-phase acidities of sulfonamides studied (Table 1) have shown that these compounds are weak acids. However, in solution dissociation constant or the pK_a is a measure of the strength of an acid or a base. Therefore this parameter is very useful in understanding the behavior of drug molecules at the site action. We used the pK_a predictor[34] module of Jaguar 4.2 program to compute dissociation constants of substituted sulfonamides. In pK_a calculations we used quantum mechanically optimized most stable isomers of the species studied. The calculated pK_a values are listed in Table 2. The computed pK_a values correlate well with the available experimental pK_a values found in the literature. Using the regression analysis with pK_a^{exp} as the independent variable the following regression equation was obtained: $pK_a^{exp} = 0.84 pK_a^{calc} + 0.75$ (correlation coefficient, 0.9892; SD of pK_a^{exp} from linear fit, $\sigma = 0.48$). An intercept of 0.84 pK_a units shows that experimental pK_a's are higher than corresponding computed dissociation constants. The difference between theoretical value and experiment may be partly due by the fact that a predicted pK_a value is obtained from the raw pK_a (computed quantum chemically) with an empirical correction $pK_a = A * pK_a(raw) + B$. In the case of substituted sulfanilamides the empirical parameters were obtained from a relatively small number of compounds.

Although the gas-phase acidities of sulfonamides do not correlate with the computed pK_a values (Tables 1 and 2), some trends in acidities are common for both vapor state and water phase. In both phases heteroaromatic inhibitors are more acidic. Aromatic inhibitors **9**–**13** are in the water solution by about 1–2 pK_a units less acidic than heteroaromatic inhibitors (dorzolamide, brinzolamide, and compound X). The calculations indicate that methazolamide is also in water solution the most acidic drug of the sulfonamides investigated. Potent systemic antiglaucoma sulfonamides **2**–**5** are by about 2–4 units more acidic than the sulfanilamide. The pK_a's of these drugs, however, do not correlate with their biological activities (pK_i). Maren and Conroy[35] also experimentally showed lack of relation between pK_a and pK_i for four aromatic sulfonamides. However, linear relation between acid pK_a and sulfonamide-enzyme (CA-II) dissociation constant pK_i was observed

Table 2. The pK_a values of the sulfonamides studied

No.	Compound	pK_a, calc	pK_a, exp	Ref.	pK_i, exp
1	Sulfanilamide	10.1	10.1	35	6.92[b]
2	Acetazolamide	6.5	7.4	28	8
3	Methazolamide	5.9	7.2	28	8.09
4	Ethoxzolamide	6.8	8.0	28	9.16
5	Dichlorophenamide	7.8	8.3	28	7.52
6	Dansylamide	9.6		21	6.03[b]
7	Dorzolamide	7.8	8.4	28	8.05
8	Brinzolamide	7.2		28	8.52
9	1I9L	8.8		30	8.62[b]
10a	A-(*R*)	9.0		22	10.52[b]
10b	A-(*S*)	9.1		22	9.63[b]
11	B	8.8			
12	C	8.8			
13	D	8.6			
14	IX	17.1[a]			
15	X	7.2		31	8.09
16	XI	10.9		32	7.32
17	XII	12.6		32	7.89
18	XIII	9.2		32	7.96
19	E7070	8.5		32	7.82

pK_i and pK_d is corresponding negative logarithm of inhibition and dissociation constants against hCA II, respectively.

[a] Unrecognized functional group, unreliable results.

[b] pK_d values.

in a homologous series of nine aliphatic compounds,[35] which possess little lipophilicity. Cancerostatic aromatic sulfonamides **16**–**19** are generally weak acids with the acidity comparable or slightly lower than the lead sulfanilamide. The different lipophilicity of aromatic and heterocyclic sulfonamides is in this case also important factor in their activity.

2.4. Lipophilicity

Poor solubility and poor permeability are among the main causes for failure during drug development.[36–38] It is therefore important to determine these physicochemical properties associated with a drug, before synthetic work is undertaken. The computed log *P* values (*P* is the partition coefficient of the molecule in the water–octanol system), together with the experimental data, are shown in Table 3. The ALOGPs and ALOGpS methods are part of the ALOGPS 2.1 program[39] used to predict lipophilicity[40] and aqueous solubility[41] of compounds. The lipophilicity calculations within this program are based on the associative neural network approach and the efficient partition algorithm. The IA LOGP and IA LOGS predictors are another methods based on neural network algorithms.[42] KoWWIN program is based on an atom/fragment contribution method.[43] CLOGP is another fragment-based method.[44]

The available experimental partition coefficients of sulfonamides investigated are best reproduced by the IA LOGP method (correlation coefficient, $R = 0.9945$; SD of $\log P_{exp}$ from linear fit, $\sigma = 0.15$). Other three theoretical methods perform also fairly well (Table 3). Greater discrepancy between experiment and theory exists in the case of acetazolamide only. Its experimental partition coefficient is well reproduced by the IA LOGP and ALOGPs methods based on neural networks only. However, there are large differences among the theoretical methods used in the reproduction of lipophilicity of sulfonamides studied (Table 3) and the mutual correlation of the calculated log *P* values for individual compounds was not observed. The observed discrepancies in the calculated values of log *P* for the same class of compounds are probably due by the different sets of compounds used in development process of methods applied. It is well known[45] that one of the features of all of the log *P* calculation routines is the fact that many of them perform very well for certain classes of compounds but will then fail for another series. The calculated values by the IA LOGP method are remarkably close to the measured data but this method fails, due to the missing of some molecular indices, in calculations of sulfonamides containing >N(C=S)SN(H)– moiety. Computed partition coefficients for antiglaucoma sulfonamides **1**–**13** varied between −0.47 and 2.61 (IA LOGP), −0.98 and 2.83 (CLOGP), and between −0.72 and 2.75 (KoWWIN), respectively. Thus these compounds are only slightly or moderate lipophilic. The lipophilicity of the cancerostatic sulfonamides **14**–**18** is from relatively narrow interval between −0.07 and 1.98. One exception is compound E7070 with computed log *P* between 2.2 and 3.5 is the most lipophilic one (Table 3). The highly active CAI **10**–**13** are also the most lipophilic compounds among the antiglaucomatics studied. Their lipophilicity is considerably higher than the lipophilicity of the clinically useful topically acting antiglaucoma sulfonamides dorzolamide and brinzolamide. The more lipophilic compounds **4**, **6**, **9**–**13** 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.

2.5. Solubility

Log *S*—an intrinsic solubility in neutral state is indicative of a compound's solubility. The computed solubility

Table 3. Calculated partition coefficients of the sulfonamides studied

No.	Compound	Log *P* (exp.)	ALOGPs	IA LOGP	CLOGP	KoWWIN
1	Sulfanilamide	−0.62	−0.16	−0.47	−0.57	−0.55
2	Acetazolamide	−0.26	−0.39	−0.25	−0.98	−0.72
3	Methazolamide	0.13	−0.20	−0.08	0.09	0.33
4	Ethoxzolamide	2.01	1.87	2.00	2.05	2.08
5	Dichlorophenamide		0.95	−0.04	0.24	1.06
6	Dansylamide	2.01	1.92	2.07	1.80	1.72
7	Dorzolamide		−0.50	0.71	−0.43	0.37
8	Brinzolamide		−0.65	0.22	0.33	0.33
9	1I9L		1.88	1.67	1.67	1.49
10a	A-(*R*)		2.71	2.61	2.83	2.75
10b	A-(*S*)		2.71	2.61	2.83	2.75
11	B		1.77	1.45	1.39	1.78
12	C		2.53	2.31	2.43	2.33
13	D		2.72	2.26	2.64	1.53
14	IX		0.48	1.66	−0.07	−0.07
15	X		1.88	1.68	1.37	1.23
16	XI		2.59[a]	0.48	1.78	0.88
17	XII		2.23[a]	0.22	2.11	0.79
18	XIII		2.54[a]	0.10	1.98	1.28
19	E7070		2.22	2.37	2.37	3.53

[a] Unreliable log *P*: some molecular indices were missed in training set.

together with the experimental values of log *S* is given in Table 4. Theoretical values were obtained using ALOGpS and IA LOGS predictors. Both methods use E-state indices as descriptors and a neural network[41,42] as the modeling 'engine'. The available experimental solubilities are best reproduced by the IA LOGS method. ALOGPS results are also remarkably similar to the experimental values of log *S*. Thus both methods can be used for prediction water solubility of new biologically active sulfonamides. The highest solubility possesses parent sulfanilamide. Both, experimental and computed values of log *S* of the rest of compounds indicate that these potent carbonic anhydrase inhibitors are generally slightly soluble or insoluble in water. Oral carbonic anhydrase inhibitors acetazolamide and methazolamide are slightly soluble in water.[37] Dichlorophenamide is less acidic than the acetazolamide and methazolamide (Table 2) and it has extremely slight solubility in water.[37] Computed solubilities for these systemic drugs (Table 4) well reproduce the experimental findings. Clinically useful topical drug dorzolamide has been computed slightly more soluble than the brinzolamide. Due to its insolubility, in clinic aqueous suspension of brinzolamide is used only. The computed solubilities qualitatively correlate with the corresponding lipophilicities (Tables 3 and 4), log *S* increasing as log *P* declines. Sulfonamides containing large hydrophobic domains (compounds **9**–**19**) are substantially less soluble in water (the IA LOGS of about −2.9–(−4.7)) than parent sulfanilamide.

2.6. 'Rule of 5' properties

Properties of molecules such as bioavailability or membrane permeability have often been connected to simple molecular descriptors such as log *P*, molecular weight (MW), or counts of hydrogen bond acceptors and donors in molecule.[46] These molecular properties have been used by Lipinski et al.[47] in formulating his 'Rule of 5'. The rule states, that most molecules with good membrane permeability have $\log P \leqslant 5$, molecular weight $\leqslant 500$, number of hydrogen bond acceptors $\leqslant 10$, and number of hydrogen bond donors $\leqslant 5$. Klebe and co-workers used Lipinski rules for preliminary preselection of chemical databases in their virtual screening program[21] for novel inhibitors of human carbonic anhydrase. Table 5 contains calculated Lipinski parameters of the sulfonamides investigated. All compounds studied satisfy these rules. The number of hydrogen bond donors (any NH group) is relatively constant (about 2–4). Less active ($K_d \approx$ mM) sulfanilamide and dansylamide possess substantially less proton accepting sites (any O and N atoms). It is therefore probable that the number of hydrogen bond acceptor groups is one of the important factors for designing of highly-active ($K_d \approx$ nM) inhibitors of given isoform of carbonic anhydrase. These groups may make polar interactions[48] with anchoring polar groups of active site, fixing the ligand via hydrogen bonding. The presently known most active ($K_d \approx$ pM) hCA II inhibitor **10** possesses relatively low hydrogen bonding capacity (six hydrogen bond acceptors and three hydrogen bond donors) and moderate lipophilicity. It is therefore probable that for the extremely large in vitro activity of both stereoisomers of this ligand the extensive van der Waals interaction of the indole group with hydrophobic residues on the wall of the active site cavity is mainly responsible. However, the possible differences in the nature of the active site of the various CA isoenzymes can also play important part in the selectivity of binding of these CAI to individual isoenzyme forms of carbonic anhydrase.

3. Conclusions

This theoretical study was set out to determine stable conformations, gas-phase acidity, pK_a, lipophilicity,

Table 4. Calculated solubilities of sulfonamides investigated

No.	Compound	Log *S* (exp.)	ALOGpS	IA LOGS
1	Sulfanilamide	−1.36 (7.52 g/l)	−1.21 (10.52 g/l)	−1.40 (6.86 g/l)
2	Acetazolamide	−2.36 (0.97 g/l)	−1.89 (2.85 g/l)	−2.19 (1.43 g/l)
3	Methazolamide	−1.83 (1.49 g/l)	−2.12 (1.78 g/l)	−1.94 (2.71 g/l)
4	Ethoxzolamide	−3.81 (40.0 mg/l)	−2.57 (10.7 g/l)	−3.69 (52.7 mg/l)
5	Dichlorophenamide		−2.87 (0.41 g/l)	−3.18 (0.20 g/l)
6	Dansylamide		−3.06 (0.22 g/l)	−3.06 (0.22 g/l)
7	Dorzolamide		−2.67[a] (0.70 g/l)	−2.68 (0.68 g/l)
8	Brinzolamide		−2.73 (0.71 g/l)	−2.92 (0.46 g/l)
9	1I9L		−3.96 (34.06 mg/l)	−3.84 (44.57 mg/l)
10a	A-(*R*)		−3.95 (41.49 mg/l)	−4.67 (8.01 mg/l)
10b	A-(*S*)		−3.95 (41.49 mg/l)	−4.67 (8.01 mg/l)
11	B		−4.09 (25.63 mg/l)	−3.47 (0.11 g/l)
12	C		−3.80 (56.88 mg/l)	−4.54 (10.34 mg/l)
13	D		−3.79 (64.73 mg/l)	−3.75 (3.18 mg/l)
14	IX		−3.45 (0.11 g/l)	−3.77 (67.59 mg/l)
15	X		−4.11 (29.1 mg/l)	−4.33 (17.5 mg/l)
16	XI		−3.80[a] (50.1 mg/l)	−3.19 (0.21 g/l)
17	XII		−4.00[a] (33.0 mg/l)	−2.87 (0.45 g/l)
18	XIII		−4.20[a] (21.8 mg/l)	−2.94 (0.40 g/l)
19	E7070		−4.25 (21.6 mg/l)	−3.55 (0.11 g/l)

[a] Unreliable log *S*: some molecular indices were missed in training set.

Table 5. Calculated Lipinski parameters of the sulfonamides studied

No.	Compound	No. of hydrogen bond acceptors	No. of hydrogen bond donors	Log *P*, calcd[a]	Formula weight
1	Sulfanilamide	4	4	−0.16–(−0.57)	172
2	Acetazolamide	7	3	−0.25–(−0.98)	222
3	Methazolamide	7	2	−0.08–0.09	236
4	Ethoxzolamide	5	2	1.87–2.08	258
5	Dichlorophenamide	6	4	−0.04–1.06	305
6	Dansylamide	4	2	1.72–1.92	250
7	Dorzolamide	6	3	−0.43–0.71	324
8	Brinzolamide	8	3	−0.65–0.33	383
9	1I9L	5	3	1.49–1.88	308
10a	A-(*R*)	6	3	2.15–2.83	371
10b	A-(*S*)	6	3	2.15–2.83	371
11	B	5	3	1.39–1.78	314
12	C	6	3	1.86–2.53	357
13	D	8	4	1.53–2.72	381
14	IX	10	3	−0.07–1.66	365
15	X	8	3	1.23–1.88	375
16	XI	5	3	0.48–1.78	319
17	XII	5	3	0.22–2.11	333
18	XIII	5	3	0.10–1.98	347
19	E7070	7	4	2.37–3.53	385

[a] Range of log *P* values obtained by four theoretical methods (Table 3).

and solubility of 19 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) The investigated sulfonamides are in gas-phase weak organic acids with calculated acidity of about 1320–1420 kJ mol^{-1}. Of acids studied the highest gas-phase acidity (1324 kJ mol^{-1}) possesses methazolamine.
(2) The computed pK_a values correlate well with the available experimental pK_a values found in the literature. Aromatic inhibitors **9**–**13** are in the condensed phase by about 1–2 pK_a units less acidic than heteroaromatic inhibitors (dorzolamide, brinzolamide, and compound X). The calculations showed that methazolamide is also in water solution the most acidic drug of the sulfonamides investigated. Potent systemic antiglaucoma sulfonamides **2**–**5** are by about 2–4 units more acidic than the parent sulfanilamide.
(3) The ALOGPs, IA LOGP, ALOGpS, and IA LOGS 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.
(4) The sulfonamides studied obey Lipinski 'Rule of 5' properties.
(5) In the early stages of the design of antiglaucoma sulfonamides, it is becoming more important to determine the pK_a, lipophilicity, water solubility, and other physicochemical properties associated with a drug, before synthetic work is undertaken, with the aim of avoiding the synthesis of compounds that are predicted to have poor biopharmaceutical characteristics.

4. Computational details

The geometry of 19 aromatic and heteroaromatic sulfonamides (Fig. 1) in both neutral and deprotonated forms were completely optimized with the GAUSSIAN98 program,[49] using Becke3LYP/6-311+G(d,p) method[50–52] (compounds **1**–**6**) and two-layered ONIOM (B3LYP 6-311+G(d,p): MNDO) method[53–55] (compounds **7**–**19**). The model system and real molecule (R) used for the two-layer ONIOM calculations are shown in Figure 2. The real systems are full molecules **7**–**19**. The model systems (MS) are represented by 1,3,4-thiadiazole-2-sulfonamide, 4-formylbenzenesulfonamide, benzenesulfonamide, 4-aminobenzenesulfonamide, 5-(formylamino)-1,3,4-thiadiazol-2-sulfonamide, 5-[(dioxidosulfanyl)amino]-1,3,4-thiadiazole-2-sulfonamide, and 4-(aminomethyl)benzenesulfonamide, respectively. The two levels of theory used for energy calculations are density functional theory (DFT) at the Becke3LYP level[50–52] with the polarized triple split valence 6-311+G(d,p) basis set (the High level, H) and the semi-empirical MNDO method[56] for the Low level (L) of theory.

The integrated energy for the two-layered ONIOM approach is defined as[53]

$$\begin{aligned} E(\text{ONIOM2}) &= E(\text{High},\ \text{Model}) + E(\text{Low},\ \text{Real}) \\ &\quad - E(\text{Low},\ \text{Model}) \\ &= E(\text{High},\ \text{Model}) \\ &\quad + \Delta E(\text{Low},\ \text{Real} \leftarrow \text{Model}) \end{aligned} \tag{1}$$

where

$$\begin{aligned} &\Delta E(\text{Low},\ \text{Real} \leftarrow \text{Model}) \\ &\quad = E(\text{Low},\ \text{Real}) - E(\text{Low},\ \text{Model}) \end{aligned}$$

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

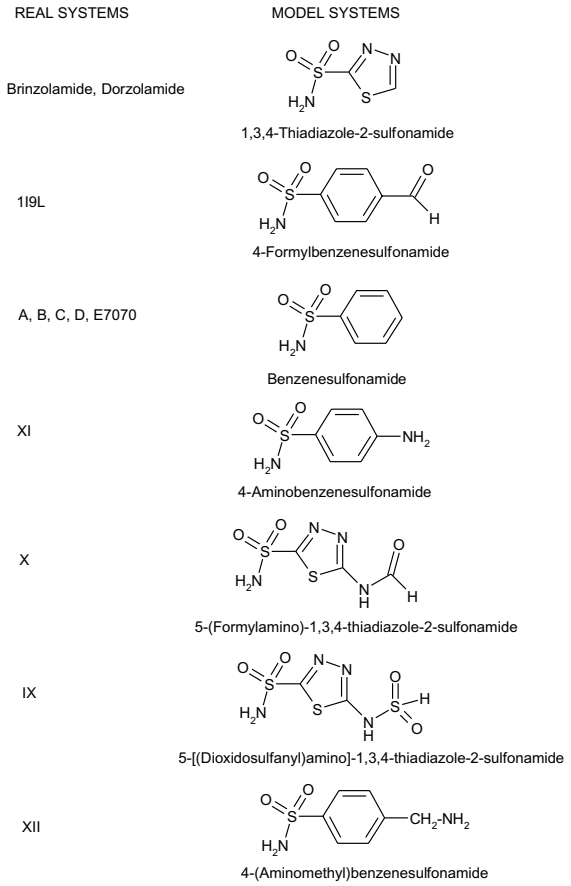

Figure 2. The two sites of systems used for the ONIOM-2 prediction. The full (real) systems (**1**–**19**), and the model systems (1,3,4-thiadiazole-2-sulfonamide, 4-formylbenzenesulfonamide, benzenesulfonamide, 4-aminobenzenesulfonamide, 5-(formylamino)-1,3,4-thiadiazole-2-sulfonamide, 5-[(dioxidosulfanyl)amino]-1,3,4-thiadiazole-2-sulfonamide, 4-(aminomethyl)benzenesulfonamide).

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

The energy of deprotonation, ΔE, at T = 0 K was computed using Eq. (2),

$$\Delta E(\mathrm{A}) = E(\mathrm{A^-}) - E(\mathrm{AH}) \qquad (2)$$

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 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),

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

$$\Delta E^{298} = [E^{298}_{\mathrm{ONIOM}}(\mathrm{A^-}) + 3/2RT] - E^{298}_{\mathrm{ONIOM}}(\mathrm{AH}) \qquad (4)$$

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 $\Delta(pV) = RT$ (1 mol of gas is obtained in the reaction (A)). The gas-phase Gibbs energy, ΔG^{298}, of the proton abstraction reaction (gas-phase acidity) may be calculated from

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

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

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

For $T = 298$ K at the standard pressure, the second term $TS(\mathrm{H^+}) = 32.5\ \mathrm{kJ\,mol^{-1}}$, Ref. 57. Thus,

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

Notice that there is an inverse relationship between the magnitude of ΔG (gas-phase acidity) and the strength of the acid. The more positive the value of the ΔG, the weaker is the acid. Ab initio calculations were carried out with the aid of the GAUSSIAN98 (Ref. 49) and JAGUAR 4.2 (Ref. 58) packages of computer codes. Lipophilicity and water solubility calculations were performed using the web-based tools.[59]

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