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Structure, acidity and basicity of a benzene disulfonamide inhibitor of carbonic anhydrase

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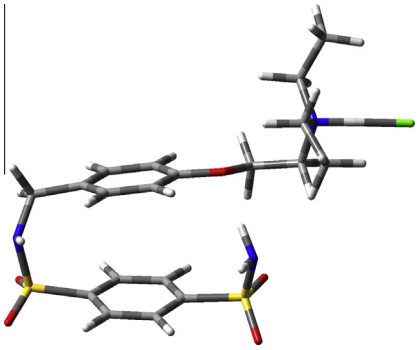
HIGHLIGHTS

- Molecular structure of CAI I-3 and its HCl salt.
- The crystal packing is stabilized by intermolecular hydrogen-bond and π–π stacking interactions.
- This structure is also present in the gas phase and/or in water solution.
- The I-3 behaves as a weak acid and/or base.

GRAPHICAL ABSTRACT

N-(4-Diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3) and its hydrochloride salt (I-3·HCl) were prepared. The X-ray molecular structure of this compound has been determined. The gas phase geometry of these ligands has been computed using Becke3LYP/6-311++G(d,p) and B97D/6-311++G(d,p) model chemistry.



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ABSTRACT

N-(4-Diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3) and its hydrochloride salt (I-3·HCl) were prepared. The X-ray molecular structure of (I-3·HCl) has been determined. The gas phase geometry of free base, its anion, cation and hydrochloride has been computed using Becke3LYP/6-311++G(d,p) and B97D/6-311++G(d,p) model chemistry. The conformational behavior of these systems in water was examined using the solvation CPCM model. In the solid state this compound possesses a sandwich-like structure. According to the density functional calculations using B97D Grimme's functional including dispersion this structure is also present in the gas phase and/or in water solution. On the other hand, the B3LYP functional calculations prefer extended conformer in gas phase. The calculated gas-phase acidity and basicity are conformationally dependent and low, indicating that I-3 behaves as a weak acid and/or base.

1. Introduction

The sulfonamide group $-SO_2NH-$ is present in many organic compounds that are known as potent inhibitors of the carbonic anhydrases (CA) [1–3]. In addition to their established role as

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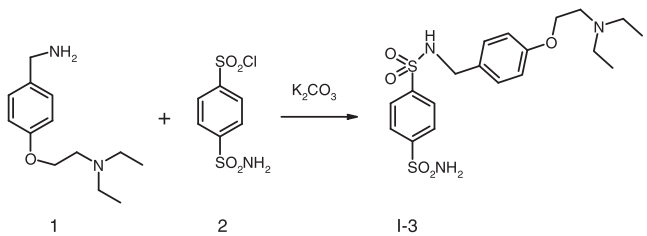
diuretics and antiglaucoma drugs, it has recently emerged that CA inhibitors could have potential as novel anti-obesity, anticancer and anti-infective drugs [4]. Furthermore, recent studies suggest that CA activation may provide a novel therapy for Alzheimer's disease [4] and antibiotic therapy [5]. Various substituted aromatic and heterocyclic sulfonamides have been synthesized and evaluated for possible therapeutic use as antiglaucoma agents [6–9]. Commonly used sulfonamide antiglaucomatics include orally administered acetazolamide, ophthalmic suspension of brinzolamide and ophthalmic solution of dorzolamide [8,9]. They bind as anions to the Zn^{2+} ion within the enzyme active site [10–12] with abnormally high affinities for isozyme CAII, ref. [13–15]. Because therapeutically useful antiglaucoma drugs are aromatic and heterocyclic sulfonamides, it is evident that for optimal *in vivo* activity the balanced hydro- and liposolubility is necessary. It is well established [16,17] that a water-soluble sulfonamide, also possessing 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 modest lipid solubility attributable to its unionized form.

In this work we report the synthesis, molecular structure, basicity and acidity of a novel drug-like aromatic sulfonamide (N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3), and its hydrochloride (N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide), I-3·HCl) with favorable biological properties comparable to those obtained for therapeutically useful acetazolamide, dorzolamide and brinzolamide [18]. The solid-state structure of novel aromatic sulfonamides has been examined by X-ray crystallography. Theoretical quantum chemical methods were applied for structural characterization of these compounds in the gas phase and water solution.

2. Experimental section

2.1. Synthesis

N-(4-Diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3) was prepared as depicted in Scheme 1 [19]. To the cold solution 4-diethylaminoethoxy benzylamine (1) in acetone (12 ml) solution of sodium carbonate 2.34 g (0.022 mol) in water (10 ml) in a small portion during 5 min was added. To this stirred mixture 4-sulfamoylbenzenesulfonylchloride (2) 5.12 g (0.02 mol) during 30 min at 10 °C was added. After then the reaction mixture was stirred 12 h at room temperature. The solid inorganic salt was filtered, washed with acetone (5 ml). The solvent from filtrate was evaporated using a vacuum rotatory evaporator. The residue was mixed three times with cold water (3 × 10 ml). The crude solid was filtered and purified by crystallization from 2-propanol. Colorless solid, yield 6.10 g (69.3%), m.p. 158 °C. TLC in acetone Rf = 0.50. Elemental analysis for $C_{19}H_{27}N_3O_5S_2$ (M.r. 441.57), calculated (found): C 51.68 (51.86), H 6.16 (6.02), N 9.52 (9.38), S14.52 (14.23). ^{1}H NMR (DMSO) 1.07 (t, 6H, CH3), 2.64 (q, 4H, CH_2-N), 2.87 (t, 2H, CH_2-N), 4.04 (t, 2H, CH_2-O), 6.89 (d, 2H, Har.), 7.12 (d, 2H, Har.-O), 7.63 (s, 2H, SO_2-NH_2), 8.00 (dd, 4H, Har.-SO_2), 8.39 (t, 1H, NH-SO_2).



Scheme 1.

Hydrochloride of N-(4-diethylaminoethoxy-benzyl)benzene-1,4-bis(sulfonamide) (I-3·HCl) was prepared by followed procedure: The solution of 20% hydrochloride in anhydrous methanol was added slowly to stirred solution of N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) 0.9 g (0.0021 mol) in methanol (10 ml) to pH = 4. After then the mixture was stirred 15 min at room temperature. The solvent was evaporated and the residue was purified by crystallization from ethanol:water (10:1). Colorless solid, yield 0.72 g (80%), m. p. 210–211 °C. TLC in acetone: Rf = 0.40. Elemental analysis for $C_{19}H_{28}ClN_3O_5S_2$ (M.r. 478.03), calculated (found): C 47.74 (47.90), H 5.90 (5.76), Cl 7.42 (7.31), N 8.79 (8.88), S 13.41 (13.19). ^{1}H NMR (DMSO) 1.24 (t, 6H, CH_3), 3.20 (m, 4H, CH_2-N), 3.47 (t, 2H, CH_2-N), 3.97 (t, 2H, CH_2-Phenyl), 4.31 (t, 2H, CH_2-O), 6.90 (d, 2H, Har), 7.16 (d, 2H, Har), 7.62 (s, 2H, SO_2-NH_2), 7.93 (d, 2H, Har), 7.98 (d, 2H, Har), 8.37 (t, 1H, SO_2NH), 10.17 (s, 1H, NH^+).

2.2. X-ray crystallographic data

The single-crystal, X-ray data collection for compound I-3·HCl was performed on an Oxford Diffraction Gemini R four circle κ-axis diffractometer equipped with a Ruby CCD detector and a graphite monochromator, using Mo-Ka radiation at 298(1) K. CrysAlis program package (Oxford Diffraction, 2012) was used for data reduction [20]. The structure was solved by direct methods using SHELXS-2008 and SHELXS-2013 programs [21,22]. Refinement was carried out on F^2, and scattering factors incorporated in SHELXL-2013 program were used. All non-hydrogen atoms were refined with anisotropic thermal parameters. Crystal data for I-3·HCl data collection procedures, structure determination methods and refinement results are summarized in Table 1. All hydrogen atoms were placed geometrically and refined using a mixed model, with Uiso(H) = 1.2 Ueq(C, or N), C–H distances fixed for CH_2 groups at 0.97 Å, for aromatic groups at 0.93 Å, for methyl group at 0.96 Å and N–H distances for NH_2 and NH groups fixed at 0.83 Å and for the N3-H3 N group at 0.97 Å. The DIAMOND program package was used for molecular structure drawing [23].

Table 1
Crystallographic data and structure refinement for compound I-3·HCl.

Compound	I-3 × HCl
Identification code	C:_1005
Empirical formula	C19 H28 Cl N3 O5 S2
Formula weight	478.01
Temperature	293(1) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P b c a
Unit cell dimensions	a = 11.2348(2) Å α = 90°
	b = 16.0525(3) Å β = 90°
	c = 25.2170(4) Å γ = 90°
Volume	4547.80(14) Å^3
Z	8
Density (calculated)	1.396 Mg/m^3
Absorption coefficient	0.387 mm^{-1}
F(000)	2016
Crystal size	0.22 × 0.08 × 0.03 mm
Theta range for data collection	2.74–26.37°
Index ranges	$-14 \leqslant h \leqslant 14$, $-20 \leqslant k \leqslant 20$, $-31 \leqslant l \leqslant 31$
Reflections collected	79865
Independent reflections	4629 [R(int) = 0.0924]
Completeness to 2Θ = 25.00°	99.5%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4629/3/283
Goodness-of-fit on F^2	1.016
Final R indices [I > 2sigma(I)]	$R1$ = 0.0445, w$R2$ = 0.0945
R indices (all data)	$R1$ = 0.0818, w$R2$ = 0.1080
Largest diff. peak and hole	0.265 and −0.300 e.Å^{-3}

Crystallization of free base N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3) did not give single crystals suitable for X-ray diffraction studies. Thus its solid-state structure is still unknown. Crystallographic data of the title compound has been deposited with the Cambridge Crystallographic Data Center as supplementary publication No.: CCDC 966739.

2.3. Computational details

The geometry (Fig. 1) of all molecular species investigated has been completely optimized with the Gaussian 09 program [24], using density functional theory [25–27] with the B3LYP hybrid functional [28–30] and B97D Grimme's functional including dispersion [31] and the polarized triple-ζ 6-311++G(d,p) basis set [32]. The enthalpies and Gibbs energies of protonation and deprotonation of base N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3) was computed by the same way as in our previous publication [33]. Solvent effects on the species studied were evaluated using the polarizable conductor calculation model (CPCM) [34–37]. The structures of all gas-phase and condensed-phase (CPCM) species were fully optimized without any geometrical constraint. The calculations of the macroscopic

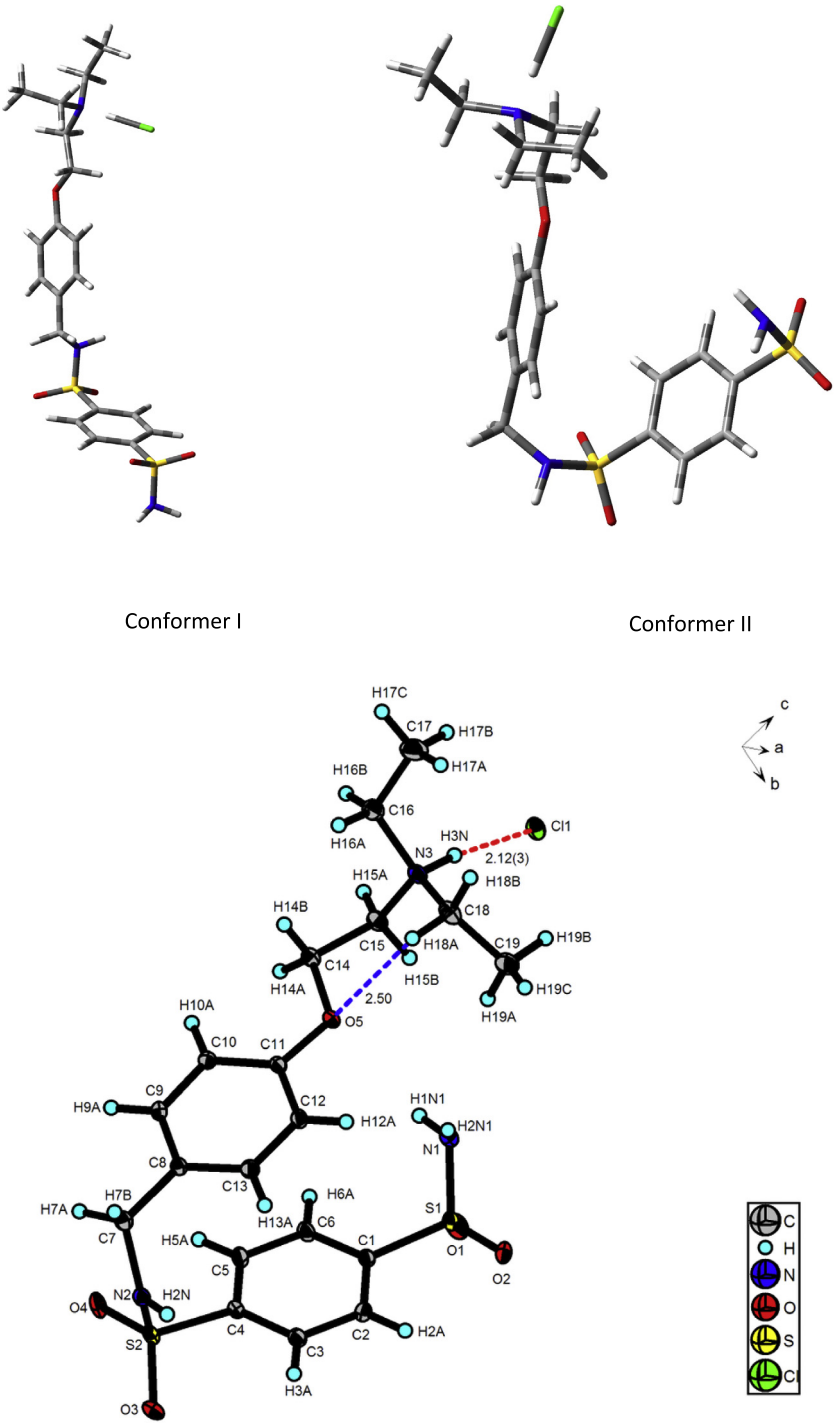


Fig. 1. Molecular structure of two stable conformers of hydrochloride of the N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) and ortep drawing of its X-ray structure. Thermal ellipsoids are drawn at 30% probability.

pK_a were performed using the program SPARC developed by Carreira et al. [38–40].

3. Results and discussion

3.1. X-ray structure

The compound investigated belongs to the effective carbonic anhydrase inhibitors and consists of common benzene-1,4-disulfonamide pharmacophoric structural unit. Extended tail of this derivative contains diethylaminoethoxybenzyl moiety and exploit the strategy of enhanced hydrophobic interactions between hydrophobic moieties of both active site of enzyme and inhibitor [18]. The diethylamino nitrogen atom of the parent base I-3 is principal basic center with the computed pK_a = 8.87, and is at physiological pH = 7.4 slightly protonated (hydrogen bond acceptor site). Two sulfonamide NH groups are slightly acidic (the computed pK_a = 9.18 and 10.14 for terminal $-SO_2NH_2$ and central $-SO_2NH-$ moieties, respectively) and provide hydrogen bond donors. The crystal packing of the molecule shows a system of four intermolecular hydrogen bonds, five hydrogen interactions and one intramolecular hydrogen interaction (Fig. 2, Table 2). Crystal structure has crystallized in the centrosymmetric *P bca* group (No. 61). There are eight molecules in the unit cell.

Chlorine anion Cl^- is bonded by three hydrogen bonds (H3 N, H2 N and H1N1, with distances 2.12(3) Å, 2.347(6) Å and 2.478(6) Å, as well) and two *Van der Waals* interactions (H6A and H14A of 2.74 Å and 2.88 Å). The sulfonamide NH_2 group is engaged in two intermolecular hydrogen bonds. One H-bond arises from the N1–H2N1···O4 interaction with adjacent SO_2 group and the other is N1–H1N1···Cl1 (2.270(11) Å and 2.478(6) Å, as well). Weak C14–H14B···O2 of 2.50 Å and C14–H14A···Cl1 of 2.88 Å contacts and π–π [centroid–centroid distance = 3.842 Å] stacking interactions also occur. Shorter distance is between carbons C4 and C8 with value of 3.361 Å.

In the molecule there are two sulfonamide groups with the distances S1–O1, S1–O2, S1–N1, S1–C1 1.422(2), 1.427(2), 1.597(2) and 1.770(2) Å, and S2–O3, S2–O4, S2–N2, S2–C4 1.427(2), 1.428(2), 1.592(2) and 1.766(2) Å, which are within the interval found for 153 crystal structures in the Cambridge Structural Database with R-value lower as 0.030. For S–O bonds in similar aromatic sulfonamides the shorter distance of 1.389 Å was found [41], refcode UKAXEK and longer of 1.500 Å [42], refcode MEZGON. For S-N bond the shorter distance of 1.542 Å [43], refcode YAZNIY and longer of 1.695 Å [44], refcode YODCUQ was found. For S-C bond the shorter distance of 1.760 Å [41] and longer of 1.838 Å [45], refcode HOFPEX was found.

An X-ray analysis of this compound showed that the proton is located on the basic nitrogen atom N3. Three intermolecular hydrogen bonds mediated by the Cl1 atoms and one hydrogen bond between O4···H2N1–N1 stabilize the crystal structure. Each Cl1 atom bridges three molecules via N–H···Cl1 hydrogen bond. Similar stabilizing effect on the structure exhibit the five intermolecular and one intramolecular C18–H18A···O5 hydrogen interaction (Fig. 3, Position 1 and 2).

The carbonic anhydrase inhibitor I-3 possesses benzene-1,4-bis(sulfonamide) functionality, connecting aromatic ring and a basic diethylaminoethoxy substituent. Their relative molecular orientation is described by sixteen dihedral angles. The relevant bond lengths, bond angles and dihedral angles for X-ray conformations and calculated values of the fully optimized structures are given in Tables 3 and 4, respectively. The bond lengths and bond angles of the sulfonamide moieties in I-3·HCl are similar. The C_{arom}–S bond length of about 1.76–1.77 Å is a single bond length between sp^2 hybridized carbon atom and sulfur since the sulfonamide group

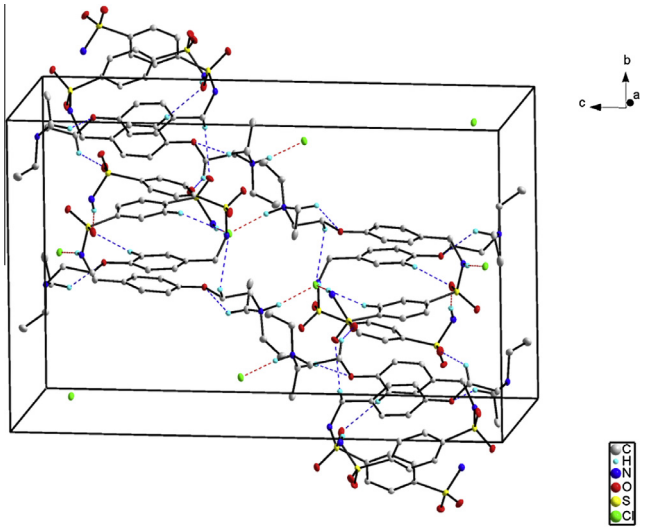


Fig. 2. Intermolecular N–H···O hydrogen bonds of I-3·HCl (dashed lines) determining the packing of molecules in the crystal structure. Only H atoms participating in hydrogen bonds are shown.

Table 2
Hydrogen bonds and hydrogen interactions for I3.HCl [Å and °].

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
C(6)–H(6A)···Cl(1)#1	0.93	2.74	3.609(3)	156.2
C(7)–H(7A)···O(1)#2	0.97	2.63	3.339(3)	130.0
C(12)–H(12A)···O(4)#3	0.93	2.60	3.504(3)	164.8
C(14)–H(14B)···O(2)#4	0.97	2.50	3.171(3)	126.4
C(14)–H(14A)···Cl(1)#1	0.97	2.88	3.447(3)	118.6
C(18)–H(18A)···O(5)	0.97	2.50	3.086(3)	118.8
N(1)–H(1N1)···Cl(1)#1	0.830(3)	2.478(6)	3.300(2)	171(3)
N(1)–H(2N1)···O(4)#3	0.830(3)	2.270(11)	3.061(3)	159(3)
N(2)–H(2N)···Cl(1)#5	0.829(3)	2.347(6)	3.169(2)	172(3)
N(3)–H(3N)···Cl(1)	0.97(3)	2.12(3)	3.082(2)	172(2)

Symmetry transformations used to generate equivalent atoms: #1 $-x+1$, $-y$, $-z+2$ #2 $-x+1$, $y-1/2$, $-z+3/2$ #3 $x+1/2$, y, $-z+3/2$ #4 $-x+3/2$, $y-1/2$, z #5 $-x+3/2$, $-y$, $z-1/2$.

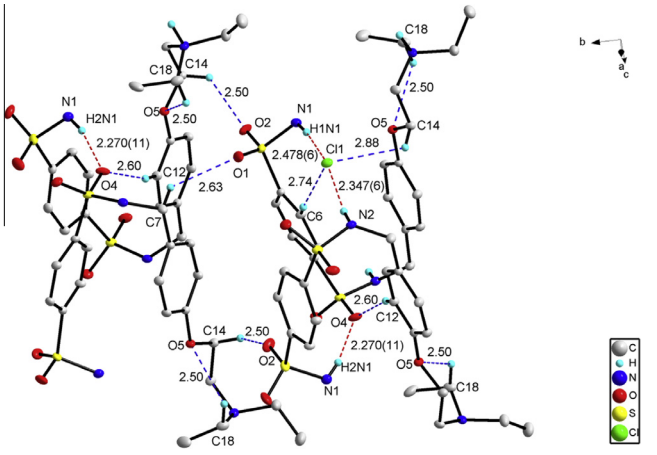


Fig. 3. Ortep drawing of crystal packing detail in two positions for I3.HCl, red-hydrogen bonds, blue-hydrogen interactions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Experimental and theoretically optimized relevant bond lengths (Å), bond angles (degrees) and dihedral angles (degrees) of the I-3·HCl.

	I-3·HCl, conformation II			I-3·HCl, conformation I			
Parameter	X-ray	B3LYP	B97D	B3LYP-CPCM	B3LYP	B97D	B3LYP-CPCM
d[C(1)–S(1)]	1.770(2)	1.8100	1.8210	1.8057	1.8027	1.8163	1.8013
d[C(4)–S(2)]	1.766(2)	1.8034	1.8210	1.8032	1.8108	1.8213	1.8082
d[C(7)–N(2)]	1.468(3)	1.4799	1.4783	1.4841	1.4753	1.4861	1.4846
d[C(7)–C(8)]	1.513(3)	1.5123	1.5209	1.5117	1.5110	1.5112	1.5098
d[C(11)–O(5)]	1.373(3)	1.3713	1.3784	1.3697	1.3688	1.3734	1.3688
d[C(14)–O(5)]	1.424(3)	1.4264	1.4477	1.4284	1.4251	1.4331	1.4271
d[C(14)–C(15)]	1.510(3)	1.5174	1.5195	1.5169	1.5271	1.5289	1.5257
d[C(15)–N(3)]	1.494(3)	1.4969	1.5001	1.5107	1.4939	1.4940	1.5022
d[C(16)–N(3)]	1.508(3)	1.5037	1.5044	1.5146	1.5040	1.5052	1.5155
d[C(18)–N(3)]	1.483(4)	1.5018	1.5037	1.5150	1.5019	1.5026	1.5144
d[N(1)–S(1)]	1.597(2)	1.6957	1.6956	1.6673	1.6886	1.7153	1.6760
d[N(2)–S(2)]	1.592(2)	1.6957	1.6999	1.6750	1.6700	1.6970	1.6664
d[O(1)–S(1)]	1.422(2)	1.4556	1.4647	1.4634	1.4597	1.4703	1.4656
d[O(2)–S(1)]	1.427(2)	1.4557	1.4705	1.4633	1.4598	1.4701	1.4664
d[O(3)–S(2)]	1.4266(18)	1.4612	1.4671	1.4672	1.4582	1.4680	1.4645
d[O(4)–S(2)]	1.4275(19)	1.4613	1.4677	1.4685	1.4586	1.4677	1.4651
Θ[C(6)–C(1)–S(1)]	118.5(2)	119.13	118.96	119.04	119.09	118.91	119.06
Θ[C(5)–C(4)–S(2)]	119.46(19)	119.33	118.77	119.24	119.36	119.18	119.01
Θ[N(2)–C(7)–C(8)]	117.3(2)	113.42	115.62	113.24	110.09	109.23	109.74
Θ[C(9)–C(8)–C(7)]	120.2(2)	120.66	121.07	120.75	120.67	120.52	120.79
Θ[O(5)–C(11)–C(10)]	124.9(2)	124.57	124.86	124.56	115.64	115.53	115.58
Θ[O(5)–C(14)–C(15)]	108.7(2)	109.45	109.15	109.05	104.53	105.05	104.58
Θ[N(3)–C(15)–C(14)]	117.1(2)	117.36	116.26	116.68	113.23	112.07	113.18
Θ[C(7)–N(2)–S(2)]	123.56(18)	118.89	120.54	119.72	120.97	117.89	120.08
Θ[C(11)–O(5)–C(14)]	117.49(18)	118.66	118.43	119.72	118.54	117.47	118.71
Θ[O(1)–S(1)–O(2)]	120.05(14)	123.36	123.11	120.59	122.70	122.87	119.66
Θ[O(1)–S(1)–N(1)]	106.82(13)	105.57	105.20	105.92	107.29	107.44	105.84
Θ[O(2)–S(1)–N(1)]	106.85(13)	105.57	105.20	105.94	107.28	107.52	111.46
Θ[N(1)–S(1)–C(1)]	107.96(12)	107.20	106.07	108.87	103.27	102.03	102.48
Θ[O(3)–S(2)–O(4)]	120.18(12)	122.25	123.69	119.67	122.82	123.06	120.55
Θ[O(3)–S(2)–N(2)]	106.83(11)	105.16	105.69	111.29	105.54	105.84	105.67
Θ[O(4)–S(2)–N(2)]	107.31(12)	109.24	104.84	105.48	106.55	106.40	106.72
Θ[N(2)–S(2)–C(4)]	107.34(11)	104.11	107.06	104.16	107.22	105.23	108.95
Φ[N(2)–C(7)–C(8)–C(9)]	129.9(3)	125.05	129.98	122.77	61.22	65.63	72.56
Φ[O(5)–C(14)–C(15)–N(3)]	−80.2(3)	−68.21	−67.60	−72.91	179.87	−176.04	−169.86
Φ[C(8)–C(7)–N(2)–S(2)]	−65.9(3)	−82.77	−70.00	−79.24	−166.37	−177.01	−166.56
Φ[C(19)–C(18)–N(3)–C(15)]	64.8(3)	54.12	59.53	57.04	−176.33	−176.02	−175.25
Φ[C(14)–C(15)–N(3)–C(18)]	65.6(3)	74.24	80.64	69.01	161.60	167.39	173.75
Φ[C(14)–C(15)–N(3)–C(16)]	−64.8(3)	−57.42	−50.80	−60.43	−67.66	−62.45	−56.92
Φ[C(17)–C(16)–N(3)–C(15)]	−159.6(3)	−163.05	−163.50	−161.66	−66.01	−64.07	−63.16
Φ[C(10)–C(11)–O(5)–C(14)]	8.0(3)	1.53	−9.07	−1.27	177.08	179.21	177.98
Φ[C(15)–C(14)–O(5)–C(11)]	−171.73(19)	−178.86	179.04	−177.96	176.19	177.92	−179.02
Φ[C(6)–C(1)–S(1)–O(1)]	−55.0(2)	−21.93	−2.20	−25.03	−22.94	−23.28	−29.36
Φ[C(6)–C(1)–S(1)–O(2)]	174.6(2)	−156.10	−136.80	−156.31	−156.59	−157.44	−160.13
Φ[C(6)–C(1)–S(1)–N(1)]	59.9(2)	90.96	109.75	89.32	90.22	89.59	82.38
Φ[C(7)–N(2)–S(2)–C(4)]	77.0(2)	103.60	67.42	93.32	−65.25	−58.99	−62.30
Φ[C(5)–C(4)–S(2)–O(3)]	143.0(2)	150.95	154.98	134.82	−20.54	−22.79	−19.82
Φ[C(5)–C(4)–S(2)–O(4)]	12.6(2)	17.86	20.14	4.66	−153.77	−157.16	−150.69
Φ[C(5)–C(4)–S(2)–N(2)]	−102.5(2)	−97.84	−92.92	−113.39	93.31	90.18	95.19

Table 4
Geometry of N···H–Cl and N–H^{+} bonds in I-3·HCl and I-3-H$^{(+)}$ species.

	I-3·HCl, conformation II				I-3·HCl, conformation I		
Parameter	X-ray	B3LYP	B97D	B3LYP-CPCM	B3LYP	B97D	B3LYP-CPCM
d[N(3)–H]	0.970	1.1329	1.1664	1.0545	1.1288	1.1609	1.0568
d[H···Cl]	2.126	1.7550	1.7043	2.0752	1.7609	1.7081	2.0469
d[N(3)···Cl]	3.089	2.8853	2.8686	3.1249	2.8897	2.8689	3.1022
d[N(1)···O(5)]	3.396	6.2658	3.0133	5.0631	13.4721	12.8740	13.4720
d[S(1)···O(5)]	4.698	6.9276	3.7550	6.0645	12.5392	11.4285	12.1885
Θ[C(15)–N(3)–H]	100.80	102.19	102.81	103.54	106.53	106.49	106.28
Θ[N(3)–H···Cl]	172.01	174.91	175.43	173.21	178.96	178.82	176.17
Φ[C(14)–C(15)–N(3)–H]	−176.43	−170.17	−163.33	−174.69	47.70	53.27	59.60
Φ[C(15)–N(3)–H···Cl]	−34.26	26.64	42.03	16.25	−63.77	−50.77	20.91
d[N(3)–H]		1.0232	1.0262	1.0237	1.0237	1.0257	1.0233
d[N(1)···O(5)]		6.0652	3.1610	7.5579	13.7993	13.0261	13.4581
d[S(1)···O(5)]		4.4547	3.8360	5.9296	12.5392	11.5928	12.1602
Θ[C(15)–N(3)–H]		104.83	104.90	104.49	106.44	106.90	106.84
Φ[C(14)–C(15)–N(3)–H]		−166.36	−169.68	−176.29	57.11	59.50	54.18

Table 5
Relative energy stability (kJ/mol) of individual conformers of N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3) and its hydrochloride salt (I-3·HCl).

Conformer	B3LYP/6-311++G(d,p)		B97D/6-311++G(d,p)	
	Gas-phase	In water (CPCM)	Gas-phase	In water (CPCM)
I-3 (**I**)	0	0.3	39.0	43.5
I-3 (**II**)	6.5	0	0	0
I-3 (**I**) NH^+	43.4	2.9	57.3	45.2
I-3 (**II**) NH^+	0	0	0	0
I-3 (**I**) SO_2NH^-	17.2	0	x	x
I-3 (**II**) SO_2NH^-	0	6.8	0	0
I-3·HCl (**I**)	0	0	31.7	41.5
I-3·HCl (**II**)	11.6	1.3	0	0

[x] Conformer (**I**) converged to the conformer (**II**).

Table 6
Computed gas-phase acidity and basicity of N-(4-diethylaminoethoxybenzyl)benzene-1,4bis(sulfonamide) (I-3).

No.	Species	B97D/6-311++G(d,p)			B3LYB/6-311++G(d,p)		
		ΔH^{298} (kJ/mol)	ΔS^{298} (J/K mol)	ΔG^{298} (kJ/mol)	ΔH^{298} (kJ/mol)	ΔS^{298} (J/K mol)	ΔG^{298} (kJ/mol)
I	I-3-SO_2NH_2 (NH-anion)	1342.40	53.46	1326.47	1390.23	119.71	1357.23
II	I-3-SO_2NH_2 (NH-anion)	1380.86	125.97	1343.32	1369.44	121.90	1333.07
I	I-3-SO_2NH_2 (N3-cation)	−975.23	−126.27	−937.56	−956.32	−132.41	−916.85
II	I-3-SO_2NH_2 (N3-cation)	−995.91	−160.39	−948.44	−1007.07	−115.69	−972.62

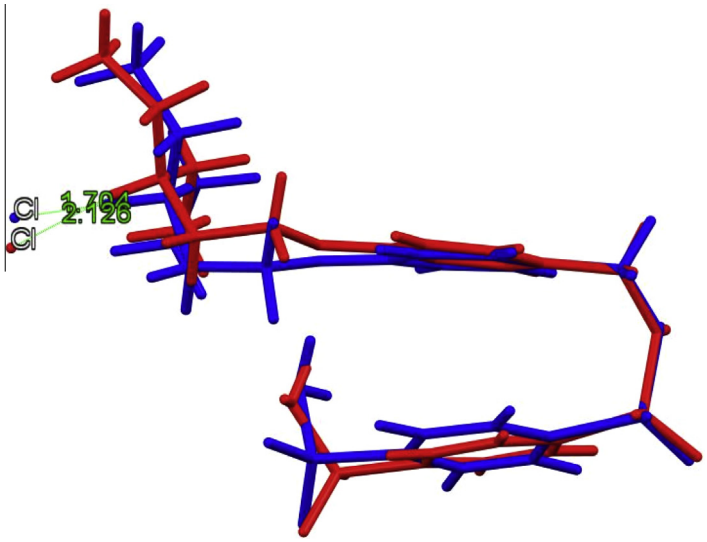


Fig. 4. Molecular superimposition of the X-ray structure of I-3·HCl (red) and its B97D/6-311++g(d,p) optimized conformer **II** (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and aromatic rings are approximately perpendicular (dihedral angles Φ[C(6)–C(1)–S(1)–N(1) and Φ[C(5)–C(4)–S(2)–N(2)], Table 3). The S–N bond length is about 1.60 Å, and is much shorter than the S–N single bond distance of about 1.75 Å [46]. The arrangement of bonds around sulfur atom is distorted tetrahedral, a common structural feature found in aromatic and heterocyclic sulfonamides [43,47]. The largest deviation of about 120° is in the O–S–O angle (Table 3). The X-ray structure of I-3·HCl provides the sandwich-like conformer in which both aromatic rings are almost in parallel arrangement (Fig. 1).

3.2. Theoretical calculations

The conformational structure of the N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) and its hydrochloride salt in the gas phase and in water solution was investigated using two functionals of the density functional theory. The hybrid Becke3LYP functional is, in combination with the triple-ζ basis set, one of the best DFT functionals for the accuracy of geometries [48]. The Grimme's B97D uses the empirical dispersion energy correction specifically designed for accurate evaluation of van der Waals interactions [31]. Two initial conformations of the N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) for use in the calculations were selected. First one, based on the our previous investigations of aromatic sulfonamides [49,50] represent "extended" conformer (**I**). A second, "sandwich-type" conformer (**II**) resulted from the X-ray structure of a solid sample of the N-(4-diethylaminoethoxybenzyl) benzene-1,4-bis(sulfonamide) hydrochloride. An analysis of the harmonic vibrational frequencies of the optimized species computed at the B3LYP and B97D levels of theory also proved that all of them are minima (zero number of imaginary frequencies). Important geometrical parameters of the

neutral molecules and ionic species investigated are given in Tables 3 and 4. The hydrochloride salt was considered as 1:1 complexes of base I-3 with hydrochloric acid. Hydrochloride was selected because it is one of the favorite counterions for the salt formation of the drugs [51]. HCl bridges the basic N(3) nitrogen atom and in the solid state the extent of proton transfer has been determined from single-crystal X-ray diffraction.

Initial conformations to use in the density functional theory calculations of the N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide), its hydrochloride salt, protonated and ionized species were build using of the Gauss View graphical interface of Gaussian. As an initial conformation of these species an "extended" structure **I** was applied (Fig. 1). However, it is common in the computational study of biologically active compounds also use available structural data obtained from X-ray crystallography as guides to the quality of theoretical computations. Thus, as a second conformer for calculations we took the "sandwich-like" conformer **II**, Fig. 1 resulted from the experimental X-ray data of the crystal structure of I-3·HCl discussed in the previous paragraph. Important geometric parameters of hydrochloride salt of the N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) and protonated species are given in Tables 3 and 4. The hydrochloride salt was considered as 1:1 complex of base I-3 with hydrochloric acid. HCl bridges basic N(3) nitrogen atom by means of proton transfer hydrogen bond of the N^+–H···Cl^- type (Table 4). In the solid state the I-3·HCl salt exists as stable sandwich-like conformer which is, besides hydrogen bonds, also stabilized by interatomic contacts resulting from the aromatic-aromatic interaction. Thus, the dispersion interaction may also play important part in stabilization of stable conformation of this salt in the gas state. The relative energies of individual conformations of the I-3, I-3·HCl, protonated and ionized I-3 species with respect to the most stable conformers computed for the gas phase and solvated molecules are reported in Table 6. Owing to the different accounting of nonbonding interactions the optimized geometry of hydrochloride I-3 using B3LYP and B97D functionals differs considerably, especially in the values of selected dihedral angles describing the mutual position of the two aromatic ring moieties (dihedral angles Φ[C(8)–C(7)–N(2)–S(2)] and Φ[C(7)–N(2)–S(2)–C(4)]). In the solid state this compound possesses a unique sandwich-like structure (conformer **II**). According to the density functional calculations using B97D Grimme's functional including dispersion the conformer **II** is the most stable species also in the gas phase and/or in water solution. The B3LYP functional calculations prefer extended conformer **I** in both gas phase and in water. The "sandwich-like" conformation **II** is less stable by 11.6 kJ/mol (Table 6). The same ordering of stability of two conformations resulting from calculations was also observed for base N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) (I-3). Protonation of the basic N3 nitrogen atom of I-3 results in an appreciable stabilization of the "sandwich-like" conformer **II.** As regards of anionic species initial geometry of conformer **I** converged to the conformer **II** (B97D functional). Conformer **II** resulted also from B3LYP calculations as the most stable species (Table 6). As it was shown previously [52] for correct theoretical description of interactions in complex molecules like DNA using the DFT method the study may include the ability to treat covalent and dispersion interactions along with treatment of solvent effects. Thus, the B97D Grimme's functional including dispersion and treatment of solvent effects within a CPCM model represents more realistic description of conformational behavior of N-(4-diethylaminoethoxybenzyl)benzene-1,4-bis(sulfonamide) studied by us. Treatment of solvent effect within B3LYP and B97D functionals produced a different relative energy stability of the species studied (Table 6). The B3LYP method shows that relative stability of both conformers in water is almost the same. However, the application of the DFT method including dispersion unambiguously prefers "sandwich-like" conformation as the most stable structure. This conformation is also most stable species in the solid state. The superposition of the 3-D structures of the I-3·HCl manifesting the overall difference in experimental solid state and gas phase geometries of this salt is shown in Fig. 4. Solvent effect did not change appreciably geometry of isolated molecule (Table 3). The sulfonamide studied contains an acidic –NH_2 group and thus it may undergo deprotonation reactions. It is well known [10,53] that the anion is bound to the enzyme active site and therefore represents the active species. Table 5 contains acidities of I-3 computed by two model chemistry methods. The absolute value of computed acidity is conformationally dependent. Average values of gas phase acidities computed by two methods (1334.9 (B97D) and 1345.2 kJ/mol (B3LYP), respectively) fit well to each other and are close to those values calculated for a series of substituted aromatic sulfonamides [33].

4. Conclusions

This study was set out to synthesize, determine stable conformations, study solvent effect, acidity and basicity of aromatic sulfonamide, potent inhibitor of carboanhydrase and its hydrochloride salt for which a relatively small amount of experimental and theoretical physicochemical data exist, considering its biological importance. Using the experimental and theoretical methods the following conclusions can be drawn.

(1) In the solid state the 3D structure of I-3·HCl provides the sandwich-like conformer in which both aromatic rings are almost in parallel arrangement. Examination of X-ray data showed that the proton resides on the base, it means that the proton transfer has occurred and the crystalline complex of I-3·HCl is a salt.
(2) According to the density functional calculations using B97D Grimme's functional including dispersion the "sandwich-like" conformer **II** is the most stable species also in the gas phase and in water solution. The B3LYP functional calculations prefer extended conformer **I** in both gas phase and in water. The "sandwich-like" conformation **II** is less stable by 11.6 kJ/mol.
(3) The calculated gas-phase acidity and basicity are conformationally dependent and low, indicating that I-3 behaves as a weak acid and/or base. In the condensed phase the diethylamino nitrogen atom of the parent base I-3 is principal basic center with the computed pK_a = 8.87, and is at physiological pH = 7.4 slightly protonated. Two sulfonamide NH groups are slightly acidic (the computed pK_a = 9.18 and 10.14 for terminal -SO_2NH_2 and central –SO_2NH– moieties, respectively) and provide hydrogen bond donors.

Supplementary data

Crystallographic data for the molecule I-3·HCl have been deposited at the Cambridge Crystallographic Data Center with the deposition number CCDC 966739. Copy of the data can be obtained free of charge via External link http://ccdc.cam.ac.uk/retrieving.html.

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