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

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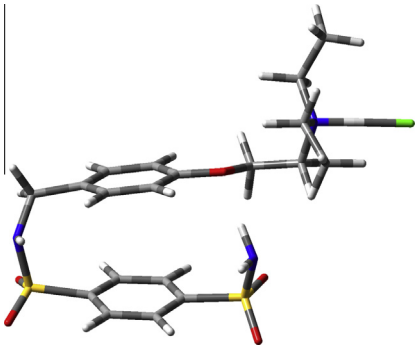
HIGHLIGHTS

- 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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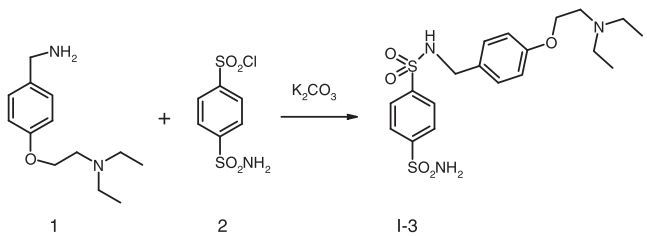
diuretics and antiglaucoma drugs, it has recently emerged that CA inhibitors could have potential as novel anti-obesity, anticancer and anti-infective drugs [4]. Furthermore, recent studies suggest that CA activation may provide a novel therapy for Alzheimer's disease [4] and antibiotic therapy [5]. 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}