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Synthesis, crystal and molecular structure of two biologically active aromatic sulfonamides and their hydrochloride salts

Milan Remko [a,*], Jozef Kožíšek [b], Jana Semanová [b], Fridrich Gregáň [c]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University Bratislava, Odbojarov 10, SK-832 32 Bratislava, Slovakia
[b] Department of Physical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, SK-812 37 Bratislava, Slovakia
[c] Department of Chemistry, Faculty of Natural Sciences, Matej Bell University, SK-974 01 Banská Bystrica, Slovakia

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ABSTRACT

4-Sulfamoyl-N-(3-morpholinopropyl) benzamide (P10), N-(3-morpholinopropyl)benzene-1,4-disulfonamide (P20) and their hydrochloride salts (P11 and P22) were prepared. The X-ray molecular structure of these compounds was determined. The gas-phase structure of these drugs was computed using Becke3LYP/6-31G(d) and Becke3LYP/6-311 + G(d,p) model chemistries. The conformational behavior of these systems in water was examined using the solvation CPCM model. In the solid state, gas phase and in solution the conformations of the basic compounds P10 and P20 possess a characteristic L-shaped structure stabilized via an intramolecular hydrogen bonding system of the N—H···N type. This hydrogen bond is not present in P11 and P22. A network of intermolecular hydrogen bonds mediated by the Cl atoms and crystal-packing forces in P11 and P22 stabilize a more extended structure in the solid state.

1. Introduction

Compounds bearing sulfonamide groups have long been known to be potent inhibitors of the carbonic anhydrases (CA) [1,2]. In addition to their established role as diuretics and antiglaucoma drugs, it has recently emerged that CAIs could have potential as novel anti-obesity, anticancer and anti-infective drugs. Furthermore, recent studies suggest that CA activation may provide a novel therapy for Alzheimer's disease [3]. Various substituted aromatic and heterocyclic sulfonamides have been synthesized and evaluated for possible therapeutic use as antiglaucoma agents [2,4–7]. Commonly used sulfonamide antiglaucomatics include orally administered acetazolamide, an ophthalmic suspension of brinzolamide and an ophthalmic solution of dorzolamide [6,7]. They bind as anions to the Zn^{2+} ion within the enzyme active site [8–10] with abnormally high affinities for isozyme CAII [11–13]. 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 known that a water-soluble sulfonamide, also possessing relatively balanced lipid solubility, would be an effective antiglaucoma drug via the topical route [14,15]. One of the conditions [14] needed for a sulfonamide to act, as an effective intraocular pressure-lowering agent, is to possess modest lipid solubility attributable to its non-ionized form.

In this work we report the synthesis of a novel drug-like aromatic sulfonamides (4-sulfamoyl-N-(3-morpholinopropyl) benzamide (P10), and N-(3-morpholinopropyl)benzene-1,4-disulfonamide (P20) and their hydrochloride salts) with favorable biological [16] structural, physicochemical and some pharmacokinetic properties comparable to those obtained for the therapeutically useful acetazolamide, dorzolamide and brinzolamide [17]. The solid-state structure of novel aromatic sulfonamides was examined by X-ray crystallography. Theoretical quantum chemical methods were used for structural characterization of these compounds in the gas phase and in water solution.

2. Experimental section

2.1. Chemistry

2.1.1. Synthesis of 4-sulfamoyl-N-(3-morpholinopropyl)benzamide (P10)

A stirred solution of 125 g (0.865 mol.) 3-morpholinopropylamine in 1.8 l of acetone was added in small aliquots to a solution of sodium carbonate 91.5 g (0.865 mol.) in 300 ml water at 25 °C. The solution was cooled to 0 °C. To this stirred solution 190 g (0.865 mol.) of 4-sulfamoylbenzoylchloride was added in small aliquots over 45 min at 10 °C. The reaction mixture was then stirred for 1 h at 5 °C and 12 h at 25 °C. The solid product was filtered, and

* Corresponding author. Tel.: +421 2 50117225; fax: +421 2 50117100.
E-mail address: remko@fpharm.uniba.sk (M. Remko).

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washed with 100 ml acetone and 100 ml ether. The crude solid product was mixed three times with 200 ml of a 5% solution of sodium chloride in water. The solid was filtered and washed twice in 100 ml cold water and dried (yield 190 g, 67%; m.p. 198–200 °C), M.r. 327.41. Microanalysis (Elemental Analyser Model 1102, Carlo Erba) gave the following values (calc for $C_{14}H_{21}N_3O_4S$): C 51.20 (51.36), H 6.51 (6.47), N 12.71 (12.83), S 9.88 (9.79). ^{1}H NMR P10 (base) δ CH_2 (middle) 1.643, 1.666, 1.689, 1.712, 1.736 (2 H), CH_2 2.306–2.353 m (6H), CH_2 3.272–3.294 m (2 H), $(CH_2)_2$ O 3.548, 3.564, 3.580 t (4 H), SO_2—NH_2 7.477 s (2 H) Har 7.874, 7.880, 7.897, 7.903, 7.971, 7.987, 7.994 m (4 H), CO—NH 8.644, 8.662, 8.680 t (1 H).

2.1.2. Synthesis of 4-sulfamoyl-N-(3-morfolinopropyl)benzamide-hydrochloride (P11)

A stirred mixture of 168 g (0.513 mol.) 4-sulfamoyl-N-(3-morpholinopropyl)benzamide in 400 ml methanol was added to 480 ml water at 65 °C. Charcoal (20 g) and silica gel (20 g) were added and the mixture was shaken and filtered. The solution was cooled and hydrochloride acid (35%) was added in small aliquots at 25 °C to reach pH = 3. The water was evaporated by distillation at reduced pressure (20 torr) and traces of moisture were removed by repeated distillation with toluene. Purification was carried out by crystallization from ethanol: water (5:1) to give a colorless solid, yield 110 g, 59%, m.p. 200–202 °C, M.r. 363.86. Microanalysis gave the following values (calc for $C_{14}H_{22}ClN_3O_4S$): C 46.02 (46.21), H 6.13 (6.09), Cl 9.39 (9.74), N 11.38 (11.55), S 9.00 (8.81). ^{1}H NMR P11 (salt) δ CH_2 1.963–2.040 m (2 H), CH_2 2.991–3.152 m (4 H), SO_2—NH_2 7.510 s (2 H) Har 7.892, 7.923, 8.021, 8.053 dd (4 H), CO—NH 8.912, 8.933, 8.952 t (1 H), NH^+ 10.992 s (1 H).

2.1.3. Synthesis of N-(3-morpholinopropyl)benzene-1,4-disulfonamide (P20)

A mixture of 7 g (0.086 mol.) 3-morpholinopropylamine, 24 g (0.238 mol.) triethylamine and tetrahydrofurane (50 cm^3) was taken up. A solution of 4-sulfamoylbenzenesulfonylchloride in 50 cm^3 tetrahydrofurane was added to this stirred mixture at 5 °C over 30 min. The mixture was stirred for 12 h at room temperature. To this mixture 100 cm^3 of hexane was added. The solid was separated and mixed with cold water (15 cm^3) and then filtered, washed with cold water (5 $cm^{3)}$ and dried. The crude product was crystallized from water to give a colorless solid, yield 8.7 g, 51%, m.p. 121–123 °C, M.r. 363.46. Microanalysis gave the following values (calc for $C_{13}H_{21}N_3O_5S_2$): C 42.67 (42.96), H 5.91 (5.82), N 11.39 (11.56), S 17.80 (17.64). ^{1}H NMR P20 (base) δ CH_2-middle 1.533, 1.564, 1.574 t (3 H), CH_2 2.377 m (4 H), CH_2—N 2.806, 2.818, 2.829 t (2 H), CH_2 3.557 m (6 H), SO_2—NH_2 7.607 s (2H), SO_2—NH 7.865 s (1 H) Har 7.962, 7.975, 8.010, 8.023 dd (4 H).

2.1.4. Synthesis of N-(3-morpholinopropyl)benzene-1,4-disulfonamide hydrochloride (P22)

N-(3-Morpholinopropyl)benzene-1,4-disulfonamide 12 g (0.033 mol.) was dissolved in methanol (15 cm^3) at 55–60 °C. Charcoal (5 g) and silica gel (5 g) were added to this solution and after a short period of stirring the mixture was filtered. A solution of hydrogen chloride in methanol was added to this stirred solution at 5 °C to reach pH = 3. After three hours the solid was filtered, washed with acetone (10 cm^3) and dried. The crude product was crystallized from water: ethanol (1:1) to give a colorless solid, yield 8 g, 60%, m.p. 236–238 °C, M.r. 399.92. Microanalysis gave the following results (calc for $C_{13}H_{22}ClN_3O_5S_2$): C 39.32 (39.04), H 5.39 (5.54), Cl 8.31 (8.87), N 10.48 (10.51), S 16.32 (16.04). ^{1}H NMR P21 (salt) δ CH_2 1.813–1.912 m (2 H), CH_2 2.823–2.881 m (2 H), CH_2 2.953–3.102 m (4 H), CH_2 3.322–3.363 m (2 H), CH_2 3.731–3.964 m (4 H), SO_2—NH_2 7.642 s (2 H) Har 8.002, 8.011, 8.022, 8.032 dd (4 H), SO_2—NH 8.053, 8.076, 8.096 t (1 H), NH^+ 10.893 s (1 H).

2.2. X-ray crystallographic data

Crystallographic data for compounds P10, P11, P20 and P22 were obtained by GEMINI R [18] diffractometer at room temperature. A summary of the crystal and collection data is given in Table 1. All crystal structures were solved by direct methods with the program SHELXS [19] and refined by the full-matrix least-squares method on F^2 with SHELXL [19]. The non-H atoms were refined anisotropically. All hydrogen atoms were placed geometrically and refined using a riding model, with $U_{iso}(H) = 1.2\ U_{eq}$(C, or N), C—H distances fixed for CH_2 groups at 0.97 Å, for aromatic groups at 0.93 Å, and N—H distances for NH_2 groups at 0.94 Å and for the NH group at 0.97 Å. Inspection of the similar crystal structures in CSD showed that in the case of trivalent nitrogen the interatomic distances in C—N bonds are in the range of 1.339 Å [20] to 1.478 Å [21] for acyclic bonds and 1.462–1.471 Å for both cyclic ones [20,21] Our values for P10 and P20 were 1.476 Å, 1.464 Å, 1.464 Å and 1.460 Å, 1.452 Å and 1.454 Å, respectively. On the other hand in the case of tetravalent nitrogen, the C—N bonds are in the range of 1.449 Å [22] to 1.508 Å [23] for acyclic bonds and 1.496 Å and 1.500 Å for both cyclic ones [22], and 1.503 Å and 1.504 Å [23]. Our values for P11 and P21 were 1.496 Å, 1.477 Å, 1.496 Å and 1.486 Å, 1.493 Å and 1.497 Å, respectively.

2.3. Computational details

Ab initio calculations of the 4-sulfamoyl-N-(3-morpholinopropyl) benzamide (P10), and N-(3-morpholinopropyl)benzene-1,4-disulfonamide (P20) and their hydrochlorides (P11 and P22) (Fig. 1) were carried out with the Gaussian 03 computer code [24] at the density functional theory (DFT, Becke3LYP [25]) level of theory using the 6-31G(d) and 6-311 + G(d,p) basis sets. The structures of all gas-phase species were fully optimized at the Becke3LYP level of theory. In order to check the correctness of the B3LYP calculated geometries using the double-ζ basis set, we also performed calculations for the sulfonamide species, using the larger triple-ζ basis set 6-311 + G(d,p) implemented in the Gaussian 03 package of computer codes. The conformational behavior of these systems in water was examined using the CPCM solvation method [26,27]. The structures of all condensed-phase (SCRF) species were fully optimized without any geometric constraint at the B3LYP/6-31G(d) level of theory.

3. Results and discussion

3.1. X-ray structure

The compounds investigated contain a common benzene sulfonamide moiety substituted in the *para* position with a N-(3-morpholinopropyl) amide (P10 and P11) or a N-(3-morpholinopropyl)-sulfonamide (P20 and P22) substituent. The morpholino nitrogen atom of the parent P10 and P20 molecules is the principal basic center with the computed pK_a = 7.4, and is partially protonated (hydrogen bond acceptor site) at the physiological pH = 7.4 [17]. The amide and the sulfonamide N—H groups provide hydrogen bond donor functionalities. In the solid state the 3D structure of P10 and P20 is stabilized via an intramolecular hydrogen bonding system of the N(10)—H···N(4) type (Fig. 1). The prepared complexes of basic aromatic sulfonamides P10 and P20 with HCl form multicomponent crystals in the solid state. Examination of X-ray data for the corresponding hydrochloride salts showed the proton resides on the base, which means that proton transfer had occurred and that the crystalline complex of P11 and/or P22 is a salt. The hydrochloride salt of P10 is a monohydrate.

Table 1
Crystallographic data for compounds P10, P11, P20 and P22.

Compound	P10	P11	P20	P22
Molecular formula	$C_{14}H_{21}N_3O_4S$	$C_{14}H_{22}ClN_3O_4S$	$C_{13}H_{21}N_3O_5S_2$	$C_{13}H_{23}ClN_3O_5S_2$
Molecular weight	327.40	363.86	363.45	400.91
Crystal description	Colorless	Colorless	Colorless	Colorless
Size (mm)	0.361 × 0.507 × 0.517	0.051 × 0.110 × 0.684	0.129 × 0.309 × 0.493	0.219 × 0.542 × 0.861
Space group	No. 29 $Pca2_1$	No. 14 $P2_1/c$	No. 14 $P2_1/n$	No. 15 $C2/c$
a (Å)	11.014(1)	10.032(2)	11.022(1)	14.738(1)
b (Å)	8.304(1)	18.830(4)	6.0140(1)	12.129(1)
c (Å)	17.056(2)	9.839(2)	25.163(2)	21.360(2)
α (°)	90.00	90.00	90.00	90.00
β (°)	90.00	98.89(3)	97.24(2)	107.673(2)
γ (°)	90.00	90.00	90.00	90.00
V (Å^3)	1559.98(3)	1836.2(6)	1654.66(7)	3638.1(2)
Z	4	4	4	8
d_x (g cm^{-3})	1.394	1.316	1.470	1.473
F (000)	696	768	768	1688
μ (cm^{-1})	0.229	0.343	0.353	0.471
T (K)	298	298	298	298
Max θ (°)	29.57	26.37	29.38	29.44
hkl ranges	$-15 \leqslant h \geqslant 15$ $-11 \leqslant k \geqslant 11$ $-21 \leqslant l \geqslant 23$	$-12 \leqslant h \geqslant 12$ $-23 \leqslant k \geqslant 23$ $-12 \leqslant l \geqslant 12$	$-14 \leqslant h \geqslant 14$ $-8 \leqslant k \geqslant 8$ $-34 \leqslant l \geqslant 34$	$-19 \leqslant h \geqslant 210$ $-16 \leqslant k \geqslant 16$ $-29 \leqslant l \geqslant 28$
No. of reflns. measd.	49504	41069	34897	48593
No. of indep. reflns.	4138	3753	4245	4742
Rint	0.0167	0.0435	0.0296	0.0176
Refinement type	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
No. of params. refined	206	234	216	232
wR2 (all)	0.0719	0.0517	0.1247	0.0380
R1 (obs.)	0.0253	0.0468	0.0403	0.0287
No. of obsd. reflns.	3808	2597	2919	3845
Criterion	$Fo > 4\sigma(Fo)$	$Fo > 4\sigma(Fo)$	$Fo > 4\sigma(Fo)$	$Fo > 4\sigma(Fo)$
Difference peak/hole (e Å^{-3})	−0.159 0.207	−0.305 0.473	−0.417 0.317	−0.290 0.275

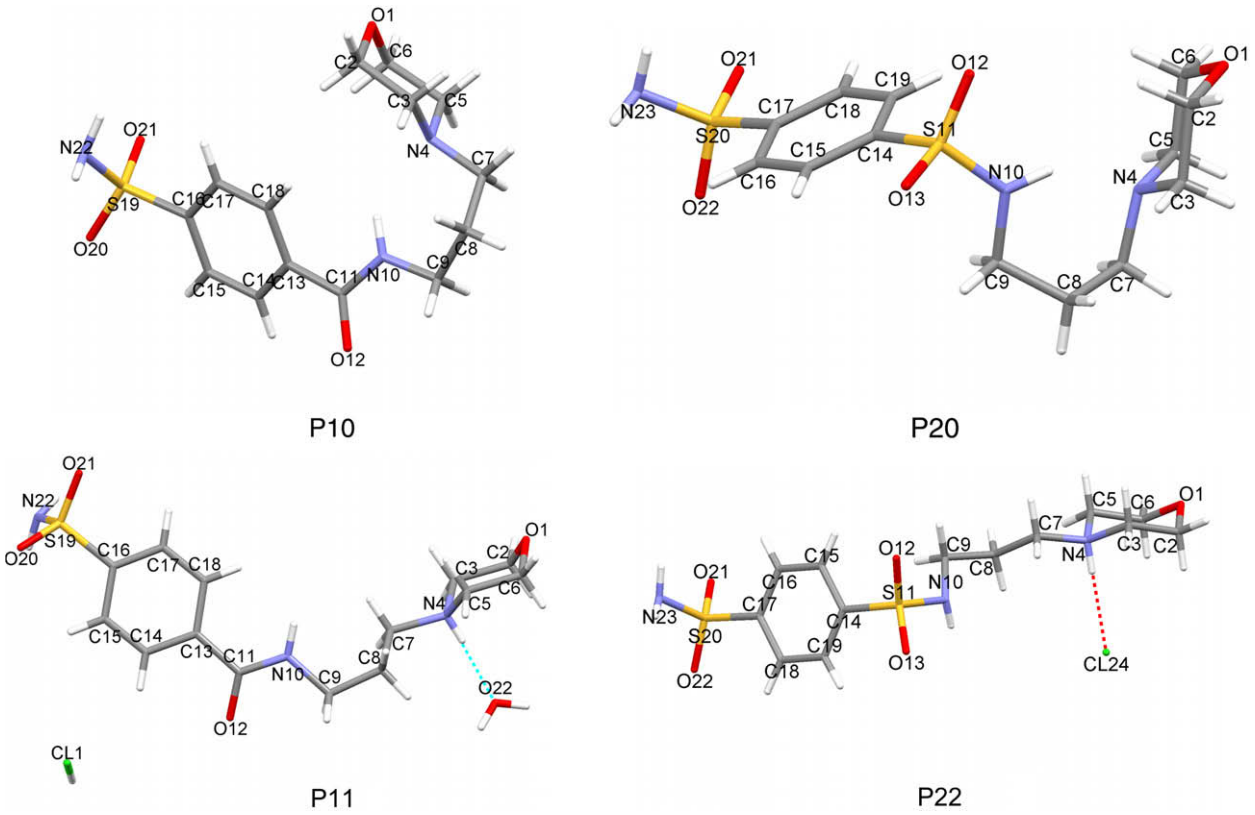

Fig. 1. Molecular drawing of compounds studied giving the crystallographic atom-numbering scheme.

The sulfonamides studied possess arylsulfonamide functionality, a connecting chain and a basic morpholino substituent. Their relative molecular orientation is described by twelve 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 2 and 3, respectively. The bond lengths and bond angles of the principal R—SO_2NH_2 moiety in P10, P20 and their hydrochloride salts are very similar. Some trends are apparent: (i) the C_{arom}—S bond length of about 1.76–1.78 Å is a single bond length between the sp^2 hybridized carbon atom and sulfur since the sulfonamide group and aromatic rings are approximately perpendicular (dihedral angles Φ[C(17)—C(16)—S(19)—N(22)] and Φ[C(18)—C(17)—S(20)—N(23)], Tables 2 and 3). (ii) The S—N bond length in all of the substituted sulfonamides investigated is about 1.60 Å, and is much shorter than the S—N single bond distance [28] of about 1.75 Å. (iii) The arrangement of bonds around the sulfur atom creates a distorted tetrahedron, a structural feature that is found in aromatic and heterocyclic sulfonamides [29]. The largest deviation of about 119° is in the O—S—O angle. The other angles are in the range of 105–108°. (iv) The protonization of the morpholine N(4) nitrogen atom (P11 and P22) is manifested by the lengthening of the neighboring N(4)—C covalent bonds by about 0.03 Å. (v) The sp^3 hybridized nitrogen atoms of the —SO_2NH_2 group have a pyramidal character. (vi) The dihedral angles for individual drugs differ, and no general conclusions about aromatic sulfonamide functionality can be deduced (Tables 2 and 3).

3.1.1. P10

The solid state conformation of 4-sulfamoyl-N-(3-morpholinopropyl) benzamide (P10) is stabilized by a system of intramolecular and intermolecular hydrogen bonds (Table 4). The geometric parameters show that P10 possesses a typical L-shaped structure stabilized by means of an intramolecular N—H···N hydrogen bond with a length of 2.178 Å. The sulfonamide NH_2 group is engaged in two intermolecular hydrogen bonds. One H-bond arises from the N—H···O interaction with the morpholine oxygen atom of the neighboring molecule and the second one (also of the N—H···O type) mediates the oxygen atom of the amide group of another molecule (Fig. 2). The carbonyl oxygen atom is coordinated with the sulfonamide group of the neighboring molecule via intermolecular H-bond of the C—O···H—N type. The oxygen atom of the morpholine moiety forms an intermolecular hydrogen bond with the sulfonamide NH_2 group of the other molecule (Fig. 2). Four surrounding molecules form the full coordination sphere of P10 (Fig. 2). In general, these hydrogen bonds generate an overall three-dimensional framework of hydrogen-bonded molecules of P10.

3.1.2. P11

The X-ray structure of P11, shown in Fig. 1, displays crystal packing that is distinct from that of its parent base P10 (Fig. 2). P10 and HCl form a 1:1:1 complex with water. The chloride anion in the crystal structure is coordinated with the basic center of the parent molecule by means of a water molecule. The proton of the P10-H^+ cation residing on the basic N(4) nitrogen is coordinated with one water molecule via an intermolecular N^+—H···OH_2 hydrogen bond with a N^+···O length of 2.716 Å. One O—H bond of this water molecule takes part in an intermolecular H-bond with the anionic Cl^- atom with an O···Cl— length of 3.201 Å. The second O—H group of the water molecule interacts by means of an H-bond

Table 2
Experimental and theoretically optimized relevant bond lengths (Å), bond angles (°) and dihedral angles (°) of the P10 and its salt.

Parameters	P10				P11			
	X-ray	DFT[a,d]	DFT-HL[b,d]	DFT-CPCM[c,d]	X-ray	DFT[a]	DFT-HL[b]	DFT-CPCM[c]
d[C(16)—S(19)]	1.777(1)	1.794	1.798	1.791	1.771(2)	1.797	1.801	1.793
d[S(19)—O(20)]	1.433(1)	1.466	1.461	1.475	1.433(1)	1.466	1.460	1.473
d[S(19)—O(21)]	1.432(1)	1.466	1.461	1.473	1.437(1)	1.465	1.460	1.473
d[S(19)—N(22)]	1.601(1)	1.699	1.693	1.678	1.596(2)	1.697	1.691	1.676
d[C(13)—C(11)]	1.502(2)	1.509	1.509	1.507	1.500(2)	1.506	1.507	1.506
d[C(11)—O(12)]	1.222(1)	1.230	1.226	1.239	1.238(2)	1.230	1.224	1.238
d[C(11)—N(10)]	1.336(1)	1.362	1.360	1.351	1.324(2)	1.367	1.365	1.357
d[N(4)—C(7)]	1.476(2)	1.476	1.475	1.478	1.496(2)	1.501	1.499	1.511
d[N(4)—C(3)]	1.464(2)	1.472	1.471	1.472	1.496(2)	1.497	1.495	1.507
d[N(4)—C(5)]	1.464(2)	1.472	1.471	1.472	1.477(2)	1.498	1.497	1.509
d[N(4)...N(10)]	2.862(1)	2.956	2.991	2.920	4.444(1)	4.590	4.562	4.530
Θ[C(17)—C(16)—S(19)]	120.18(8)	119.18	119.10	119.49	120.18(14)	119.18	119.18	119.22
Θ[C(16)—S(19)—O(20)]	105.65(6)	107.53	107.54	107.84	106.47(8)	107.48	107.45	107.65
Θ[C(16)—S(19)—O(21)]	108.78(6)	107.80	107.72	109.47	107.41(9)	107.40	107.39	107.53
Θ[O(20)—S(19)—O(21)]	119.21(7)	122.40	122.46	118.21	119.40(9)	122.64	122.67	120.06
Θ[C(16)—S(19)—N(22)]	107.63(6)	103.40	103.39	101.63	108.48(9)	103.32	103.35	103.80
Θ[C(13)—C(11)—O(12)]	121.34(10)	120.97	120.71	120.88	119.94(19)	121.29	121.19	120.65
Θ[C(13)—C(11)—N(10)]	116.64(9)	116.43	116.60	116.06	118.62(17)	116.57	116.48	116.91
Φ[C(17)—C(16)—S(19)—O(20)]	−155.78(10)	157.52	157.20	137.52	−143.23(16)	−154.05	−156.45	−157.59
Φ[C(17)—C(16)—S(19)—O(21)]	75.13(10)	23.78	23.41	7.69	−14.24(18)	−20.31	−22.72	−26.91
Φ[C(17)—C(16)—S(19)—N(22)]	−40.10(10)	-88.77	−89.26	−111.09	100.90(18)	92.83	90.21	87.50
Φ[C(18)—C(13)—C(11)—O(12)]	154.69(12)	158.05	155.47	147.48	−165.24(17)	−156.86	−153.86	−152.63
Φ[C(18)—C(13)—C(11)—N(10)]	−26.40(16)	−21.62	−23.97	−32.42	11.9(3)	22.82	26.06	27.28
Φ[C(13)—C(11)—N(10)—C(9)]	−178.83(10)	−175.66	−177.61	−176.69	−177.26(15)	173.84	175.11	176.82
Φ[C(11)—N(10)—C(9)—C(8)]	−163.05(11)	−172.56	−167.50	−175.43	170.81(18)	91.14	93.40	98.70
Φ[N(10)—C(9)—C(8)—C(7)]	−59.86(13)	−61.89	−63.88	−60.50	−61.8(2)	−71.19	−69.60	−66.83
Φ[C(9)—C(8)—C(7)—N(4)]	74.73(14)	71.75	71.88	71.94	−167.85(16)	−169.09	−170.93	−172.02
Φ[C(8)—C(7)—N(4)—C(5)]	−158.34(11)	−158.78	−158.76	−157.19	−60.5(2)	−67.54	−66.14	−63.23
Φ[C(8)—C(7)—N(4)—C(3)]	80.88(14)	78.43	78.44	80.11	175.42(16)	166.24	168.13	172.51
d[N(4)···Cl]					10.836(1)	2.909	2.898	3.018

[a] B3LYP/6-31 g(d).
[b] B3LYP/6-311 + g(d,p).
[c] B3LYP/6-31 g(d) + CPCM.
[d] Taken from the Ref. [17].

Table 3
Experimental and theoretically optimized relevant bond lengths (Å), bond angles (°) and dihedral angles (°) of the P20 and its salt.

Parameter	P20				P22			
	X-ray	DFT[a,d]	DFT-HL[b,d]	DFT-CPCM[c,d]	X-ray	DFT[a]	DFT-HL[b]	DFT-CPCM[c]
d[C(17)—S(20)]	1.775(4)	1.797	1.802	1.798	1.760(9)	1.798	1.802	1.798
d[S(20)—O(21)]	1.425(3)	1.466	1.460	1.471	1.430(4)	1.466	1.460	1.472
d[S(20)—O(22)]	1.418(5)	1.465	1.460	1.471	1.422(6)	1.465	1.460	1.472
d[S(20)—N(23)]	1.601(4)	1.695	1.689	1.674	1.601(9)	1.696	1.690	1.674
d[C(14)—S(11)]	1.777(4)	1.808	1.813	1.802	1.765(10)	1.802	1.807	1.801
d[S(11)—O(12)]	1.421(5)	1.464	1.460	1.471	1.429(6)	1.469	1.464	1.470
d[S(11)—O(13)]	1.425(4)	1.464	1.460	1.471	1.431(3)	1.467	1.462	1.469
d[S(11)—N(10)]	1.597(4)	1.661	1.658	1.665	1.611(9)	1.651	1.649	1.663
d[N(4)—C(7)]	1.460(5)	1.473	1.473	1.477	1.486(9)	1.517	1.516	1.517
d[N(4)—C(3)]	1.454(3)	1.472	1.472	1.473	1.493(9)	1.506	1.505	1.510
d[N(4)—C(5)]	1.452(4)	1.470	1.470	1.472	1.497(4)	1.505	1.504	1.507
d[N(4)···N(10)]	2.752(1)	2.863	2.895	2.864	4.327(1)	3.135	3.127	3.412
Θ[C(18)—C(17)—S(20)]	119.80(2)	119.15	119.08	119.03	120.62(29)	119.18	119.10	118.95
Θ[C(17)—S(20)—O(21)]	107.55(19)	107.43	107.40	107.39	107.41(37)	107.35	107.37	107.22
Θ[C(17)—S(20)—O(22)]	106.57(20)	107.39	107.37	107.37	108.55(44)	107.64	107.61	107.86
Θ[O(21)—S(19)—O(22)]	119.63(18)	122.57	122.59	120.28	119.46(27)	122.61	122.62	120.04
Θ[C(17)—S(20)—N(23)]	107.73(22)	103.35	103.36	103.51	106.85(41)	103.16	103.14	103.16
Θ[C(14)—S(11)—O(12)]	108.66(22)	106.64	106.71	107.01	107.29(35)	107.47	107.47	107.54
Θ[C(14)—S(11)—O(13)]	106.34(19)	106.59	106.52	107.16	108.09(33)	107.74	107.00	107.28
Θ[O(12)—S(11)—O(13)]	120.70(16)	122.79	122.62	120.27	119.96(23)	121.40	121.28	120.31
Θ[C(14)—S(11)—N(10)]	107.09(21)	107.00	107.25	108.56	106.96(43)	107.58	107.80	107.85
Φ[C(18)—C(17)—S(20)—O(21)]	−11.17(16)	23.95	23.98	25.88	−137.86(25)	−160.98	−159.64	−161.60
Φ[C(18)—C(17)—S(20)—O(22)]	118.26(16)	157.54	157.56	156.54	−7.39(13)	−27.22	−25.87	−31.03
Φ[C(18)—C(17)—S(20)—N(23)]	−127.94(23)	−89.17	−89.15	−88.67	108.57(31)	85.47	87.01	82.04
Φ[C(19)—C(14)—S(11)—O(12)]	48.66(19)	24.75	26.48	23.47	−151.13(18)	−172.44	−170.78	−160.21
Φ[C(19)—C(14)—S(11)—O(13)]	179.97(15)	157.51	159.02	153.78	−20.45(17)	−40.76	−39.23	−29.46
Φ[C(19)—C(14)—S(11)—N(10)]	−64.59(26)	−87.97	−86.54	−90.48	94.26(33)	72.52	74.22	84.43
Φ[C(14)—S(11)—N(10)—C(9)]	−58.98(23)	−67.82	−67.93	−66.44	58.75(28)	88.77	85.74	64.88
Φ[S(11)—N(10)—C(9)—C(8)]	−162.87(16)	−171.91	−171.99	−179.03	171.74(11)	135.78	139.86	165.22
Φ[N(10)—C(9)—C(8)—C(7)]	−63.12(30)	−66.13	−67.28	−66.39	−72.71(30)	−46.25	−45.59	−52.08
Φ[C(9)—C(8)—C(7)—N(4)]	58.99(30)	61.94	63.51	64.36	171.46(12)	94.06	93.13	106.61
Φ[C(8)—C(7)—N(4)—C(5)]	−166.24(17)	−163.42	−162.39	−160.55	58.96(27)	96.76	97.31	83.11
Φ[C(8)—C(7)—N(4)—C(3)]	70.70(27)	72.80	73.97	76.47	−176.66(11)	−137.63	−137.51	−161.14
d[N(4)···Cl]					3.054(1)	3.018	3.007	3.174
d[N(10))···Cl]					3.210(1)	3.138	3.122	3.260

[a] B3LYP/6-31 g(d).
[b] B3LYP/6-311 + g(d,p).
[c] B3LYP/6-31 g(d) + CPCM.
[d] Taken from the Ref. [17].

Table 4
Hydrogen bond geometry of P10 (hydrogen bond lengths in Å).

H-bond type	D—H···A	D—H	H···A	D···A
—SO_2NH_2···O=C	N—H···O[a]	0.940	1.948	2.865
—SO_2NH_2···O<	N—H···O[a]	0.755	2.214	2.965
—SO_2NH_2···O=C—NH—	N—H···O[b]	0.940	1.948	2.865
—SO_2NH_2···O<	N—H···O[b]	0.755	2.214	2.965

[a] Parent molecule as H-bond donor.
[b] Parent molecule as H-bond acceptor.

with the oxygen atom of the substituted amide group of the neighboring molecule (the O—H···O bond length is about 2.813 Å). The specific hydrogen bond interactions in the solid forms of P10 and P11 give rise to their unique overall shape. The orientation of the sulfonamide moiety in the base P10 and its salt P11 is very different (Fig. 3). The difference in dihedral angle *Φ*[C(17)—C(16)—S(19)—N(22)] can be as large as 140° (Table 1). The morpholinopropyl chain in P10 is in the L-shaped conformation, with C(9)—C(8) bound *cis* with respect to C(7)—N(4) (*Φ*[C(9)—C(8)—C(7)—N(4)] = 74.7°), whereas in P11 it is found to be *trans* (−167.6°, see Table 2).

3.1.3. P20

The X-ray structure of N-(3-morpholinopropyl)benzene-1,4-disulfonamide (P20) is also stabilized by means of a network of hydrogen bonds (Table 5). The crystal packing of the molecule shows a system of four intermolecular hydrogen bonds connecting a parent P20 with three neighboring molecules (Fig. 2). The hydrogen bonding centers are sulfonamide —SO_2NH_2 group and morpholine oxygen atoms, respectively. The central N-substituted —SO_2NH— group is involved in an intramolecular hydrogen bond only. This N—H···N hydrogen bond with a length of 2.105 Å stabilizes the structure around the flexible connecting chain —$(CH_2)_3$— in the stable L-shaped conformation.

3.1.4. P22

The hydrochloride salt of N-(3-morpholinopropyl)benzene-1,4-disulfonamide (P22) exists in an extended conformation in the solid state. The reaction of the base P20 with hydrochloric acid results in the formation of a 1:1 salt. X-ray analysis showed that the proton is located on the basic nitrogen atom of the morpholine moiety. A network of intermolecular hydrogen bonds mediated by the Cl atoms stabilizes the crystal structure. Each Cl atom bridges three molecules via N—H···Cl hydrogen bonds (Fig. 2). The different hydrogen bonding network and crystal-packing forces in P20 and its salt P22 are the reason for the large differences in dihedral angles describing both the sulfonamide functionality and *para*-substituted N-(3-morpholinopropyl) sulfonamide moiety (Table 2). The N-(3-morpholinopropyl) sulfonamide moiety in P22 is almost in the *trans* arrangement. The morpholine substituent of P22 is located, in comparison to that of P20, in the opposite position in space (Fig. 3).

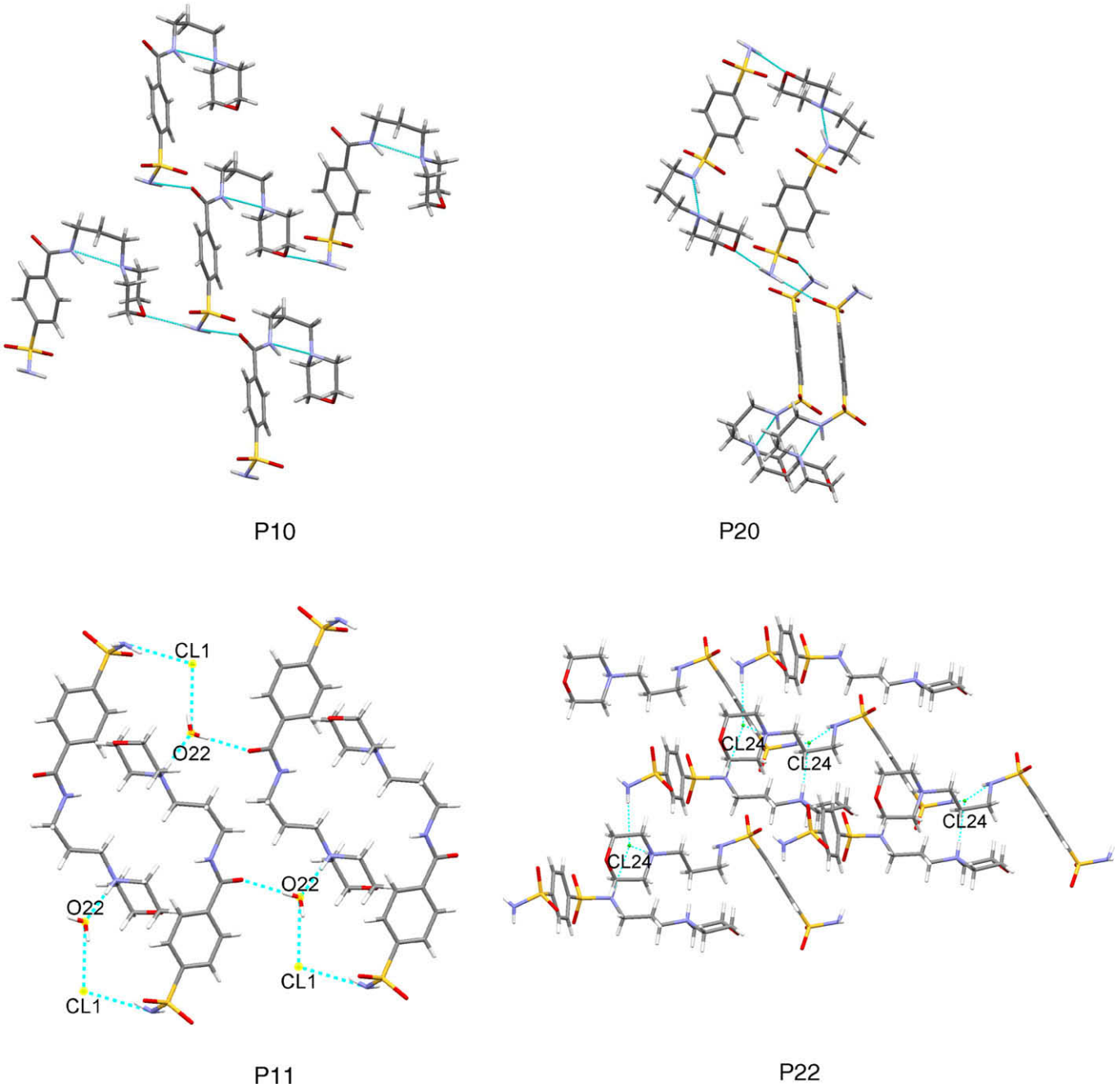

Fig. 2. Details of the three-dimensional hydrogen bonding network of P10, P11, P20 and P22 with atoms participating in the drawn hydrogen bonds represented by dashed lines.

3.2. Theoretical calculations

In order to determine the stable conformations of title compounds in the gas phase and/or in water solution we also carried out theoretical calculations. The initial conformations for use in the calculations of the aromatic sulfonamides and their salts were constructed by means of the Gauss View graphical interface. It is common in the computational study of drugs to use structural data obtained from X-ray crystallography or NMR spectroscopy as guides to the quality of theoretical computations. We took the relative orientation of the individual functional groups of the sulfonamides studied from the X-ray data of the crystal structures discussed earlier. Examination of the space models of the B3LYP computed structures using two basis sets of the drugs showed that an increase in the basis set gives essentially the same results [30–32]. Thus, for the purpose of determining reasonable geometries of large systems, B3LYP/6-31G(d) should be considered the method of choice. Important geometric parameters of the molecules investigated are given in Tables 2 and 3. In the isolated sulfonamide P10 and P20 species the absolute minimum is stabilized by an intramolecular N—H···N hydrogen bond. The hydrochloride salts were considered as 1:1 complexes of the bases P10 and P20 with hydrochloric acid. HCl bridges the basic N(4) nitrogen atom by means of proton transfer to the hydrogen bond of the N^{+}—H···Cl— type.

3.2.1. Gas phase

The gas-phase geometry of P10 and P20 was comprehensively discussed in a recent publication [17]. The connecting chain of

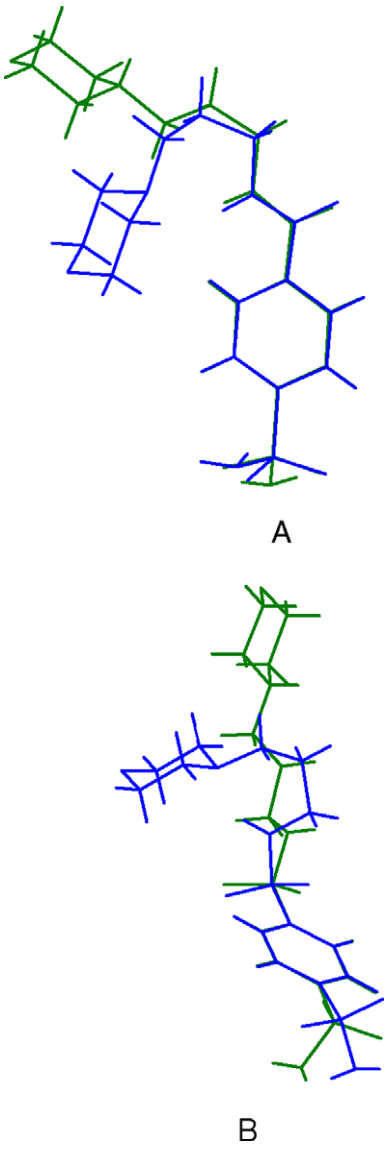

Fig. 3. (A) – molecular superimposition of the X-ray structure of P10 (blue) and its hydrochloride salt P11 (green). (B) – molecular superimposition of the X-ray structure of P20 (blue) and its hydrochloride salt P22 (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Hydrogen bond geometry of P20 (hydrogen bond lengths in Å).

H-bond type	D—H···A	D—H	H···A	D···A
$-SO_2NH_2\cdots O{=}SONH_2$	N—H···O[a]	0.810	2.103	2.909
$-SO_2NH_2\cdots O<$	N—H···O[a]	0.848	2.060	2.894
$-SO_2NH_2\cdots O{=}SONH_2$	N—H···O[b]	0.810	2.103	2.909
$-SO_2NH_2\cdots O<$	N—H···O[b]	0.848	2.060	2.894

[a] Parent molecule as H-bond donor.
[b] Parent molecule as H-bond acceptor.

three carbon atoms imparts some flexibility to the P10 and P20 structures investigated. Thus, although the conformation is stabilized in the solid state by means of an intramolecular hydrogen bond of the N—H···N type, "extended" conformations without hydrogen bonding may also exist. Thus, we also carried out calculations for two additional "trans" structures. The relative stability order of individual conformers computed by two theoretical methods at the HF and Becke3LYP levels of theory is shown in Fig. A of the Supplementary Information. In both cases the thermodynamically most stable structures are conformers possessing the characteristic L-shaped structure stabilized via an intramolecular hydrogen bonding system of the N—H···N type. It is also apparent that this intramolecular hydrogen bond is a prevailing stabilizing geometric factor in the solid state (Tables 2 and 3). To demonstrate the changes in the molecular structure of P10 and P20 in the gas-phase and solid state we used the superposition of these two structures as presented in Fig. B. It is apparent that a particularly large change in geometry occurs for the morpholinopropyl and *para*-sulfonamide moieties of these compounds.

A different situation occurs with the hydrochloride salts. In general there is, of course, no reason why the minimum-energy conformation in the gas phase should also be the minimum-energy conformation in the solid state. Extensive intermolecular hydrogen bonding as well as crystal-packing forces may influence which conformer is actually adopted in the solid state, and the gas-phase structure can also contain intramolecular hydrogen bonds. In the absence of the stabilizing effect of intermolecular hydrogen bonds mediated via chlorine atoms the most stable gas phase conformers of P11 and P22 correspond to the conformation in which the anionic chlorine atom forms a salt bridge of the N^+—H···Cl— type (Fig. 4). In P11 the chlorine atom is directly coordinated with the charged N^+—H group of the morpholine part of the molecule. For P22 the most stable conformer corresponds to the structure in which the Cl^- atom is bicoordinated and forms two intramolecular hydrogen bonds with the proton donor N—H groups of the molecule (Fig. 4).

3.2.2. In water

In order to study the influence of the surrounding medium on the relative stability of the complexes studied we also investigated

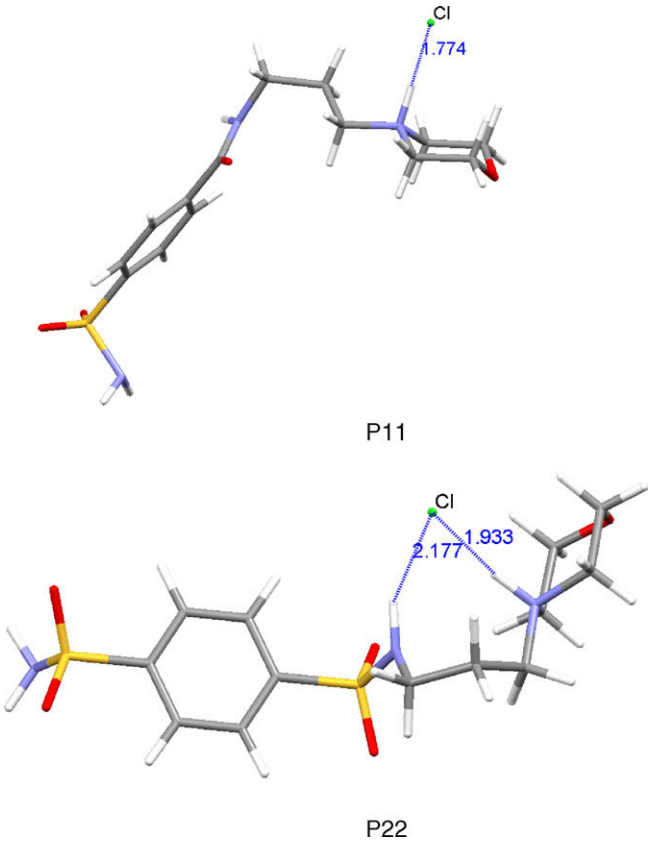

Fig. 4. B3LYP/6-311 + G(d,p) optimized structures of P11 and P22.

Table 6
Theoretically optimized hydrogen bond lengths (Å) and bond angles (°) of P11 and P20.

Parameter	P11		P22			
	$N^+(4)$—H···Cl—		$N^+(4)$—H···Cl—		N(10)—H···Cl—	
	DFT	DFT-CPCM	DFT	DFT-CPCM	DFT	DFT-CPCM
$R_{N\cdots H}$	1.126	1.060	1.082	1.053	1.034	1.031
$R_{Cl\cdots H}$	1.784	2.049	1.943	2.123	2.196	2.291
$R_{N\cdots Cl}$	2.909	3.108	3.108	3.174	3.138	3.260
⟨N—H···Cl	179.3	178.9	172.2	171.7	150.5	156.2

the environmental effects. The effect of bulk solvent was assessed using the CPCM solvation method [27,29] in combination with the B3LYP/6-31G(d) calculations. Water has a remarkable effect on the geometry and stability of the individual molecules studied, especially the ionic complexes (Tables 2 and 3). The solvent effect causes substantial structural rearrangement of the morpholinopropyl moiety in P11 and P22, and the difference in torsion angles can be as large as 20° (Tables 2 and 3). The energetic stability of the three stable solvated conformers of basic sulfonamides (P10 and P20) is not considerably altered. The most stable conformer in water solution is also the L-shaped structure with an intramolecular hydrogen bond of the N—H···N type (Fig. A). The conformational change in the basic sulfonamides P10 and P20 upon water solvation is small and related to the morpholinopropyl moiety (Fig. B).

The calculated hydrogen bond geometries of the ionic complexes in H_2O are quite different (Table 6). The difference in N···Cl bond lengths is about 0.2 Å. A proton is located on the N(4) nitrogen atom, indicating that in solution, as in the solid state, the sulfonamides P11 and P22 will be salts. The preference for proton transfer in solution can be deduced from the known pK_a values of the reactants in water. It is generally accepted that reaction of an acid with a base will form a salt (ionized complex) if the $\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$ is greater than 2 or 3 [33]. This criterion is frequently used in pharmaceutical research for the selection of appropriate counterions in a salt selection. We used ACD/Labs software [34] to compute the theoretical pK_a values of the studied structures in the condensed-phase (water). The calculated pK_a values of the morpholinopropyl moiety in the P10 and P20 are the same (7.4) and are characterized as weak organic bases [17]. For hydrochloric acid we used an experimentally determined value of $pK_a = -8.0$ [35]. For P11 and P12 the computed ΔpK_a difference is very high and the same (15.4), indicating the existence of these structures in solution in the form of an ionized complex (salt). Based on the pK_a values of the separation between P11 (P22) and HCl (15.4) and on mixing equimolar quantities in water the concentration of the ionized species is about 3×10^{15}. Therefore the concentration of the ionized species in both cases is about 15 times greater than the concentration of the non-ionized (neutral) species.

4. Conclusions

This study set out to synthesize, determine stable conformations and study the solvent effect of two aromatic sulfonamides and their hydrochloride salts for which a relatively small amount of experimental and theoretical physicochemical data exist, given their pharmacological importance. Using the experimental and theoretical methods the following conclusions can be drawn:

1. In the solid state the 3D structure of P10 and P20 is stabilized via an intramolecular hydrogen bonding system of the N(10)—H···N(4) type. The prepared complexes of basic aromatic sulfonamides P10 and P20 with HCl form multicomponent crystals. Examination of X-ray data for corresponding hydrochloride salts showed that the proton resides on the base, which means that proton transfer had occurred and that the crystalline complex of P11 and/or P22 is a salt. The hydrochloride salt of P10 is a monohydrate.
2. Calculations showed that P10 and P20 exist in their most stable conformers in the gas phase, possessing a characteristic L-shaped structure that is stabilized via an intramolecular hydrogen bonding system of the N—H···N type. The solvent effect causes substantial structural rearrangement of the morpholinopropyl moiety of these compounds, and the difference in torsion angles can be as large as 20°.
3. In polar solvents like water the computed ΔpK_a difference ($\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$) for P11 and P22, respectively, is very high and the same (15.4), indicating the existence of these structures in solution in the form of an ionized complex (salt). The concentration of the ionized species in both cases is about 15 times greater than the concentration of the non-ionized (neutral) species.

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Appendix A. Supplementary material

Crystallographic data for the molecules P10, P11, P20 and P22 have been deposited at the Cambridge Crystallographic Data Centre with the deposition numbers CCDC 760296–760299. Copies of the data can be obtained free of charge via External link http://ccdc.cam.ac.uk/retrieving.html. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2010.03.013.

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