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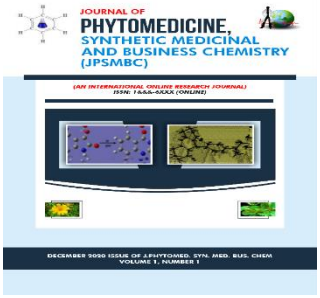

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Synthesis and single crystal X-ray analysis of Bis-[(4-ammoniobenzene-1-sulfonyl)ammonium] sulfate from the attempted synthesis of 4-[[(3-hydroxyphenyl)methylidene]amino]benzene-1-sulfonamide

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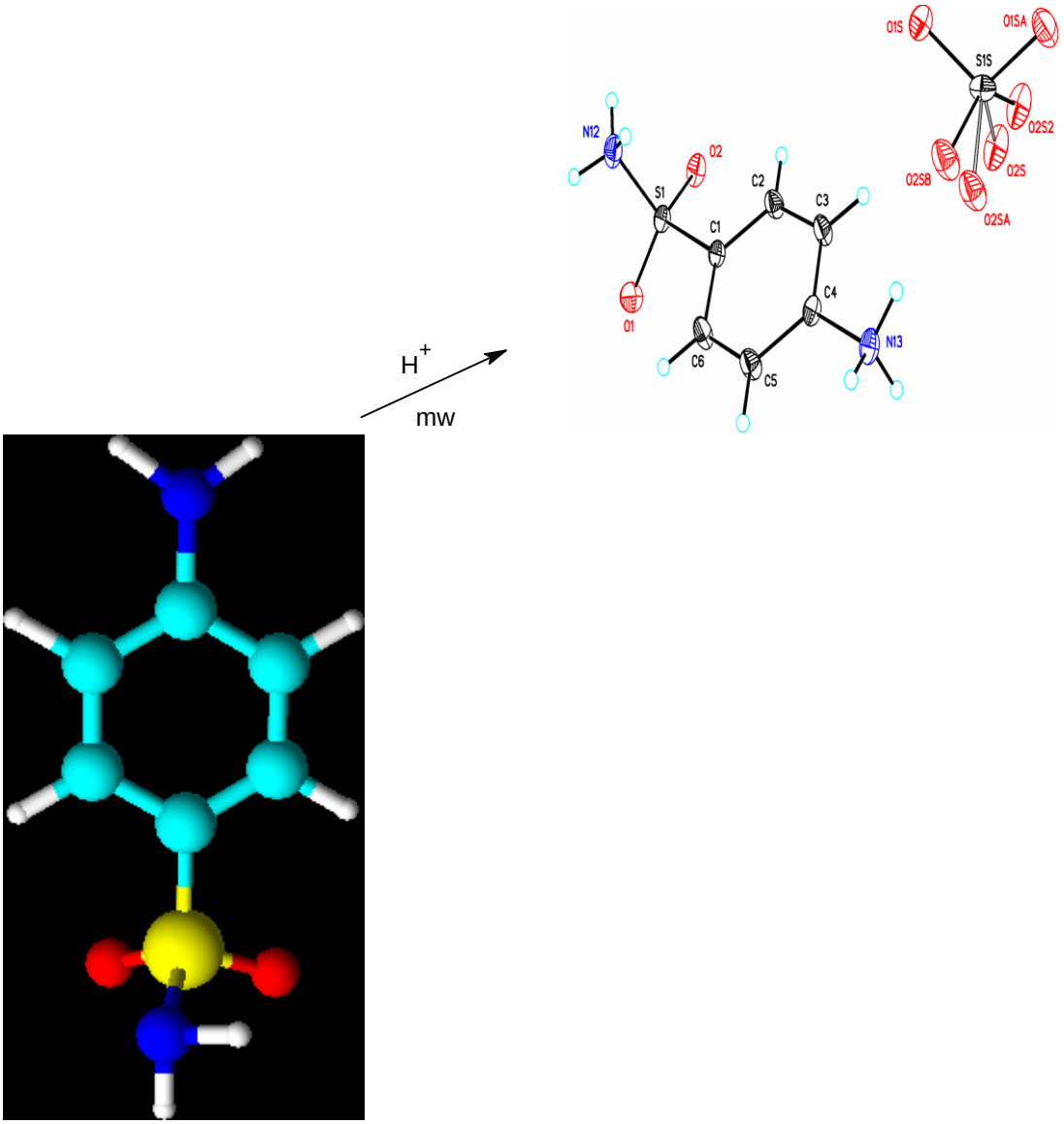
Graphical abstract



Abstract

The title compound bis-[(4-ammoniobenzene-1-sulfonyl)ammonium] sulfate has been prepared by microwave chemical synthesis in ethanol, from 4-aminobenzenesulfonamide and 3-hydroxybenzaldehyde. Its crystal and molecular structure was confirmed using single crystal X-ray diffraction analysis. The X-ray structure showed that the studied compound crystallizes in the orthorhombic system with the space group Pbcn and Z = 4. The unit cell parameters are a =

9.7339(3) Å, b = 9.6038(3) Å, c = 18.4128(6) Å and V = 1721.27(9) Å3. The structure is stabilized by oxygen-bound complexes via an intermolecular interaction of type N-H···O=S and the sulfate anions are sandwiched between layers of the di-protonated sulfanilamide cations by way of S=O···H-N interactions, building up a three-dimensional network.

Keywords: crystallization, single crystal X-ray structure, hydrogen bonds and intra-intermolecular interactions, bis-[(4-ammoniobenzene-1-sulfonyl) ammonium] sulfate

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1. Introduction

Sulfonamides, of general formula R-$SO_2NR'_2$ (where R may be an aliphatic, aromatic or heterocyclic moiety are generally easy to prepare, stable and bioavailable and the sulfonamide NH_2 group may be primary, secondary or tertiary), constitute an important class of pharmacophores having a wide range of therapeutic applications, including use as antibacterial, anticancer, anti-carbonic anhydrase, anticonvulsant, antidiabetic, anti-inflammatory, antileishmanial, antimalarial, antimicrobial, anti-obesity, antithyroid , antitubercular, antitumor, antiviral, diuretic, hypoglycemic, and other medicinal agents [1,2].

Currently, there are more than 150 sulfonamide-containing drugs on the market, including the blockbuster anti-inflammatory drug, celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide) [3]. As antimicrobial drugs, they have been widely used in human and veterinary medicine on the basis of their low cost and efficiency in the treatment of bacterial diseases [4,5].

Folic acid is synthesized by bacteria from para-aminobenzoic acid (PABA), and bacterial cells (in fact, all cells) require folic acid for growth. Sulfonamides inhibit the growth and reproduction of bacteria by a bacteriostatic effect. This activity is based on their competition with PABA which is used for the synthesis of folic acid [6].

The progenitor of the family of sulfa drugs, 4-aminobenzenesulfonamide (commonly called sulfanilamide), is still used today mainly for treatment of vaginal yeast infections. The sulfanilamide compound is reported to be more active in the protonated form. Theoretical calculations have shown that the proton affinity of nitrogen in sulfonamides is higher than

oxygen. The phenyl group in benzenesulfonamide increases the basicity of both heteroatoms, but more strongly of the nitrogen [7]. For sulfanilamide, the sulfonamide NH_2 group was identified as the protonation site in the gas phase, which is in contrast to the situation in solution, where the aniline NH_2 group is protonated [8].

2.0 Materials and Methods

2.1 General

Sulfanilamide and 3-hydroxybenzaldehyde (Sigma-Aldrich) and solvents (of analytical grade) were used as received without further purification. The FTIR spectrum was recorded on a Buck M500 infrared spectrophotometer.

2.2 Attempted synthesis of H_2SO_4-catalyzed Schiff base, 4-[[(3-hydroxyphenyl)methylidene]amino]benzene-1-sulfonamide **2**

5 drops of concentrated sulfuric acid were added to a mixture of 4-aminobenzenesulfonamide (sulfanilamide) (1.5 g, 8.7 mmol) and 3-hydroxybenzaldehyde (8.7 mmol) in ethanol (80 ml), in a 250 ml beaker, covered and subjected to microwave irradiation in a domestic microwave oven, at an emitted power of 400 W (at 30 s intervals) for a total of 5 min. The clear reaction solution was left on the bench at room temperature. After 3 weeks, colorless single crystals of the product **1** were obtained. (0.21 g, 11 % yield), code-named **OBAF-6.**

It is worth noting that most aromatic aldehydes we used reacted with the sulfanilamide under the above reaction conditions to form the expected sulfanilamide-imines derivatives (4-(benzylidene-amino)-benzenesulfonamides), which crystallized out of solution within 24 h.

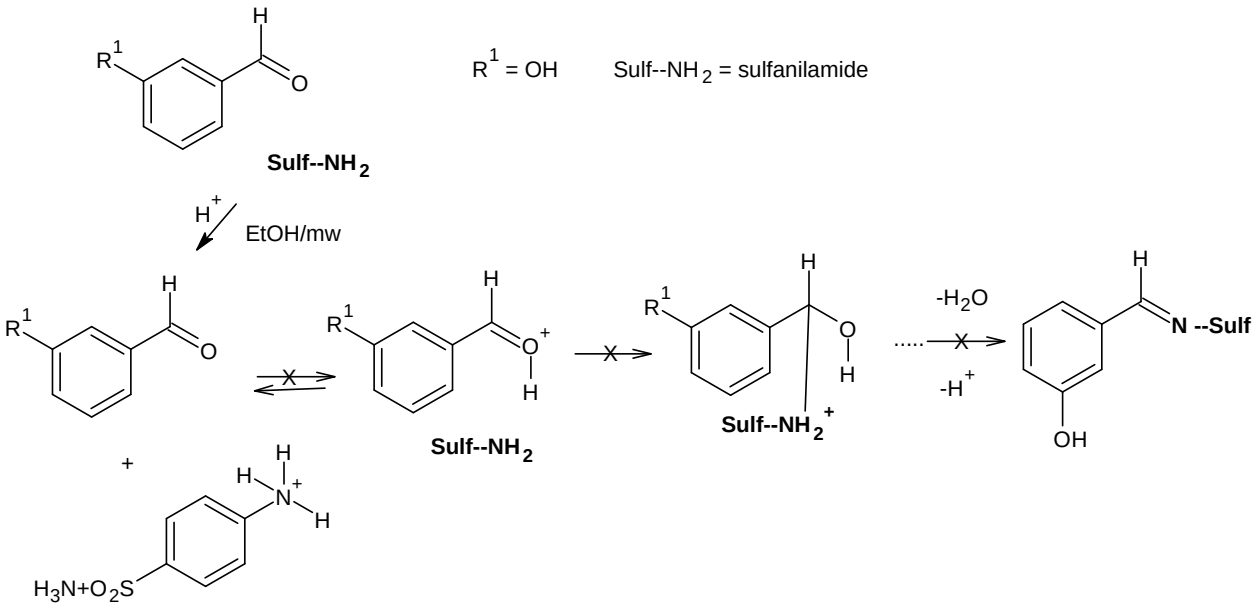
2.3. Solution and refinement of the crystal structures

Single crystals of $C_{12}H_{20}N_4O_8S_3$ **[OBAF-6]** were obtained by slow evaporation of the compound in ethanol at room temperature. A suitable crystal was selected and placed on a **Polymer** Loop on a Rigaku-Oxford Diffraction, Gemini, Eos X-ray diffractometer [9], using graphite monochromated Cu-Ka radiation (l ¼ 1.5418 Å). The crystal was kept at 293(2) K during data collection. Using Olex2 [10], the structure was solved with the ShelXT [11] structure solution program using Direct Methods and refined with the ShelXL [12] refinement package using Least Squares minimization.

Crystal Data for $C_{12}H_{20}N_4O_8S_3$ (*M* =444.50 g/mol): orthorhombic, space group Pbcn (no. 60), *a* = 9.7339(3) Å, *b* = 9.6038(3) Å, *c* = 18.4128(6) Å, *V* = 1721.27(9) Å^3, *Z* = 4, *T* = 293(2) K, μ(CuKα) = 4.445 mm^{-1}, *Dcalc* = 1.715 g/cm^3, 10974 reflections measured (9.606° ≤ 2Θ ≤ 142.978°), 1663 unique (R_{int} = 0.0576, R_{sigma} = 0.0298) which were used in all calculations. The final R_1 was 0.0536 (I > 2σ(I)) and wR_2 was 0.1500 (all data). Details of the crystal data collections and structure determinations are given in Table 1.

3. Results and discussion

It is noteworthy that the reaction of sulfanilamide with most aromatic aldehydes, under microwave irradiation, gave the expected sulfanilamide-imine derivatives as major products [13]. However, in our reaction of sulfanilamide with 3-hydroxybenzaldehyde, the expected product did not crystallize out of solution for 3 weeks. IR and X-ray crystallographic studies of the crystals formed after 3 weeks show that the expected 4-[[(3-hydroxyphenyl)methylidene]amino]benzene-1-sulfonamide did not form. Instead, the sulfanilamide got protonated to form its salt (Scheme 1).



Scheme 1. Preparation of sulfanilamide salt.

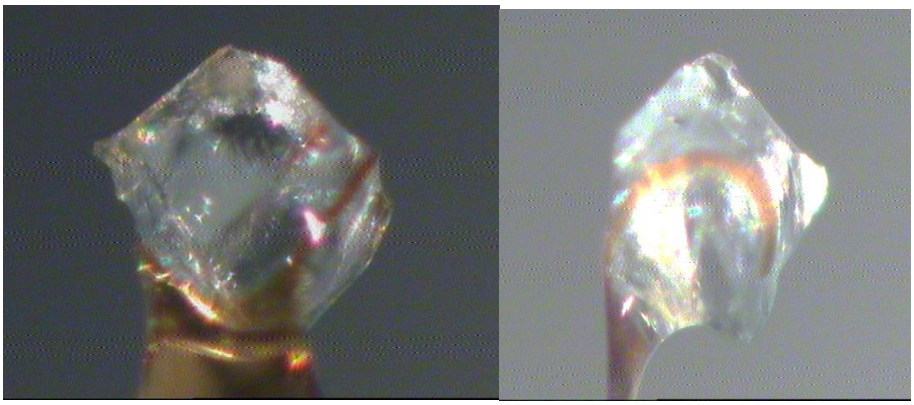
Table 1. Selected Crystal data and structure refinement for OBAF-6.

Identification code	OBAF-6
Empirical formula	$C_{12}H_{20}N_4O_8S_3$
Formula weight	444.50
Temperature/K	293(2)
Crystal system	Orthorhombic
Space group	Pbcn
a/Å	9.7339(3)
b/Å	9.6038(3)
c/Å	18.4128(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1721.27(9)
Z	4
ρ_{calc}g/cm^3	1.715
μ/mm^{-1}	4.445
F(000)	928.0
Crystal size/mm^3	0.46 × 0.42 × 0.38
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.606 to 142.978
Index ranges	$-11 \leq h \leq 11$, $-11 \leq k \leq 9$, $-19 \leq l \leq 22$
Reflections collected	10974
Independent reflections	1663 [R_{int} = 0.0576, R_{sigma} = 0.0298]
Data/restraints/parameters	1663/0/129
Goodness-of-fit on F^2	1.103
Final R indexes [I>=2σ (I)]	R_1 = 0.0536, wR_2 = 0.1454
Final R indexes [all data]	R_1 = 0.0572, wR_2 = 0.1500
Largest diff. peak/hole / e Å^{-3}	0.70/-0.61

The infrared spectrum of the compound shows absorption band at 3230 cm^{-1}, due to the asymmetric stretching vibration of the -$[NH_3]^+$ group, while its symmetric stretching vibration was observed as a weak band around 2800 cm^{-1}. Absorptions due to the asymmetric and symmetric stretching modes of the sulfonyl group (-SO_2-) appeared at 1366 and 1165 cm^{-1}, respectively, in agreement with literature reports [14, 15].

The crystal structure of bis-[(4-ammoniobenzene-1-sulfonyl)ammonium] sulfate contains a cation with a protonated 4-amino group (-$^{+}NH_3$) and protonated sulfonamide group (-SO_2-$^{+}NH_3$) and a sulfate anion, $C_{12}H_{20}N_4O_4S_2^{4+}.SO_4^{2-}$. The sulfur atom in the sulfate anion (S1S) sits on a symmetry element and contains a disordered oxygen atom (O2S, O2S2) with occupancies 0.51119 and 0.48881, respectively. This compound crystallizes in the orthorhombic Pbcn space group. An image of the single crystal used in data collection and the molecular structure of the compound is presented in Figure 1. Table 1 shows a summary of the crystal data and X-ray analysis information for the compound, while relevant bond lengths and angles are listed in Table 2.

Figure 2 shows weak N–H···O=S and S=O···H-N interactions with two inverted parallel molecules and unit cell arrangement of the dimeric compound. That is, intra and intermolecular hydrogen bonding which is responsible for building the molecular assembly and packing of the molecules in the unit cell.



Single crystals of OBAF-6

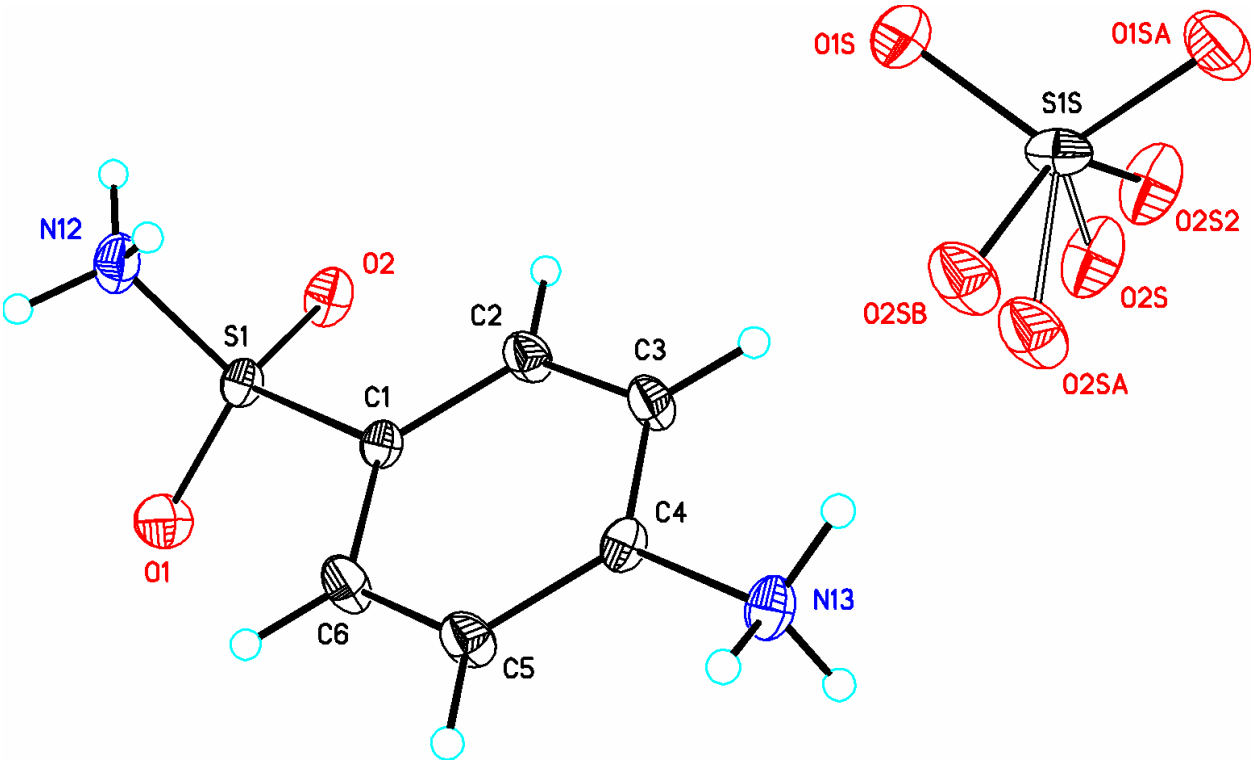


Fig. 1. Single crystal and X-ray crystallographic structure of the title compound, $C_{12}H_{20}N_4O_8S_3$, OBAF-6

In addition, the sulfate anions are sandwiched between layers of 4-ammoniobenzene-1-sulfonylammonium cations by way of hydrogen bonds and weak intra- intermolecular interactions between a sulfur-oxygen bond and anilinium N-H and a sulfur-oxygen bond and sulfonylammonium N-H (S-O·····H-N-Ar and S=O·····H-N-S=O), leading to supramolecular associations of molecules in the crystal structure (Fig. 3).

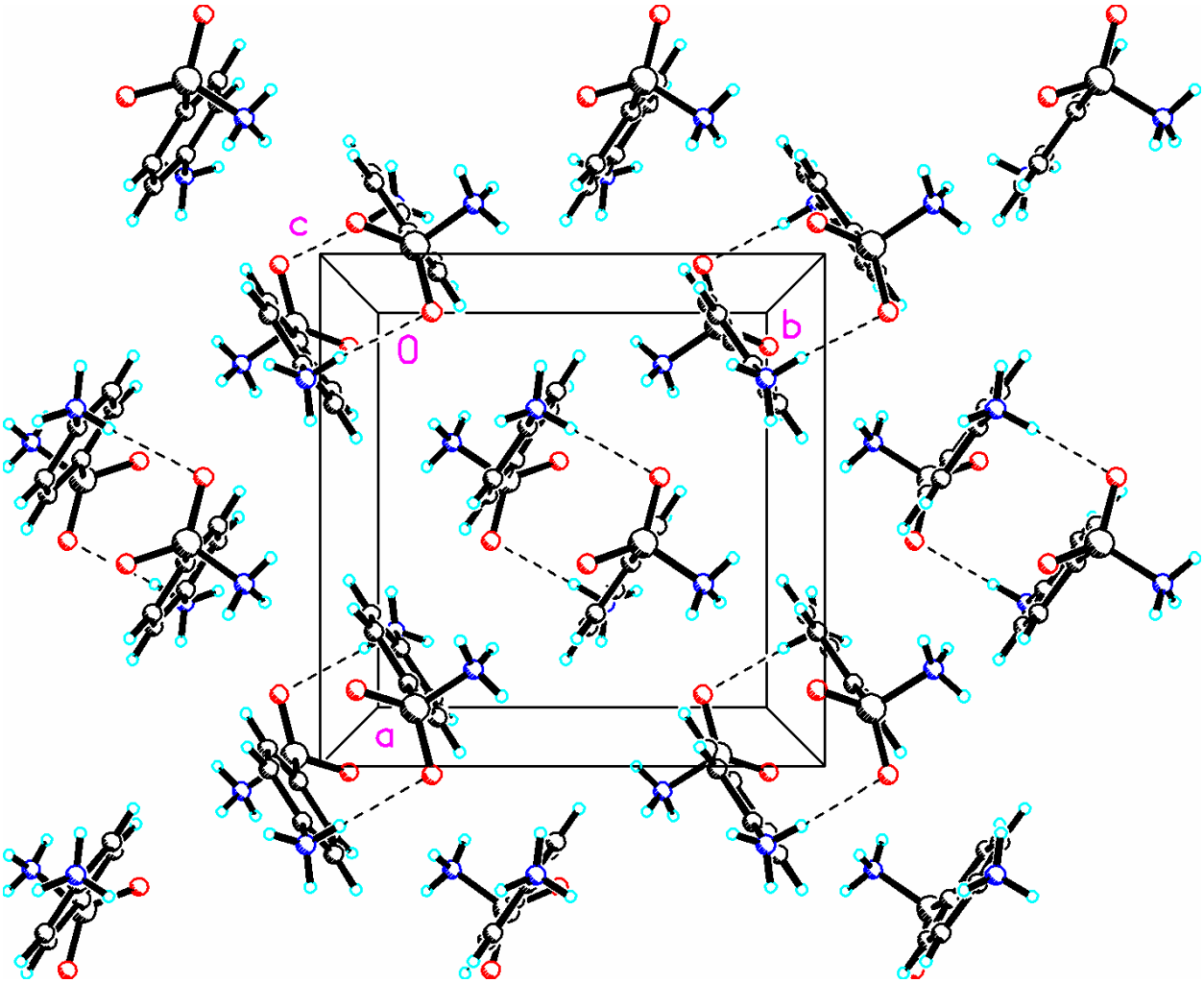


Fig. 2. Packing diagram for $C_{12}H_{29}N_4O_8S_3$ viewed along the c-axis, showing weak intermolecular interactions between two parallel, but inverted molecules, with Cg1---Cg1 ring stacking in planes [Cg1 = C1/C3/c4/C5/C6; 3.7428; 1-x, 1-y, 1-z] creating cage-like structures forming chains along the a, b and c axes. Dashed lines indicate weak N-H·----O=S intermolecular interactions.

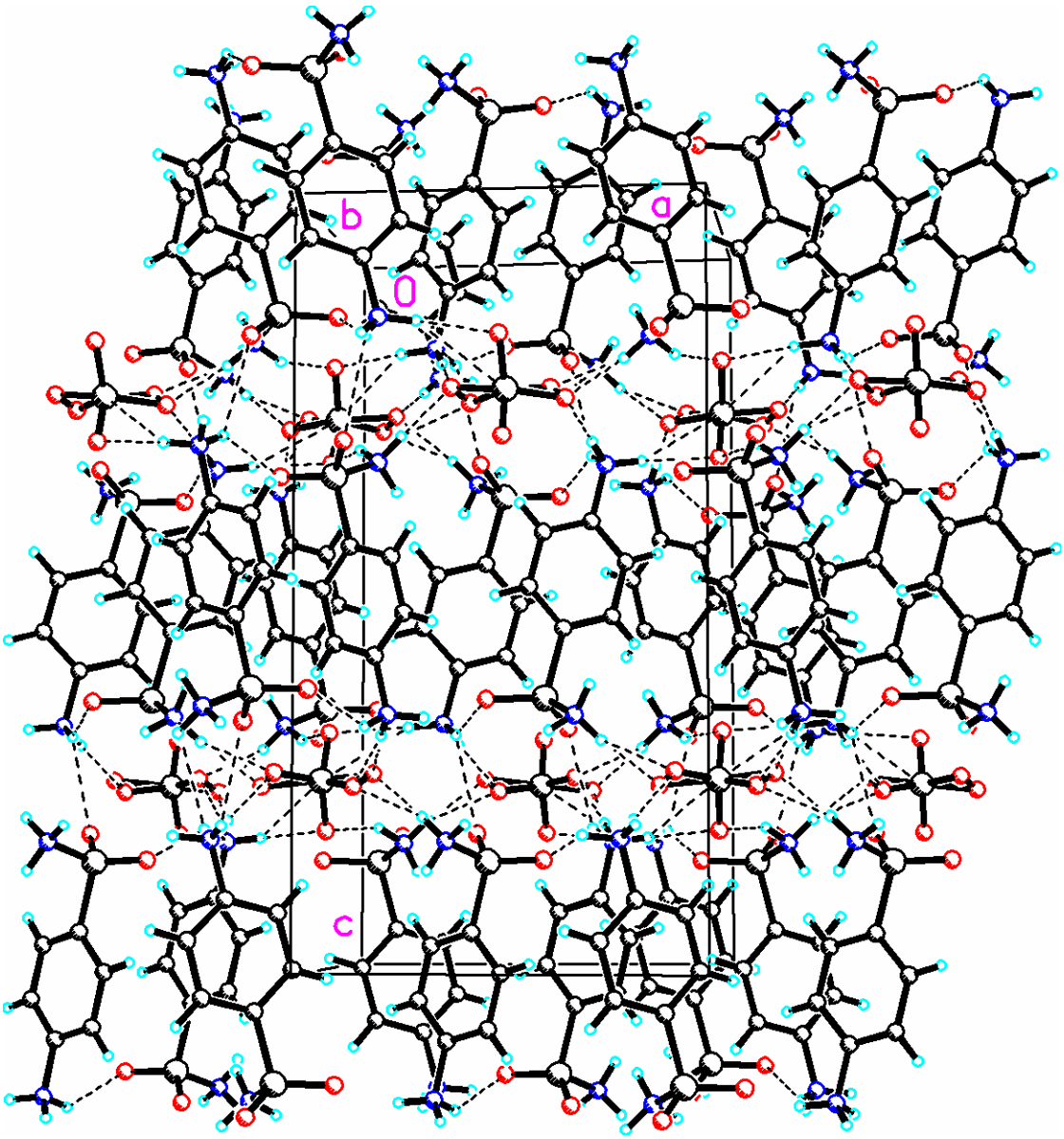


Figure 3. The crystal packing diagram of $C_{12}H_{20}N_4O_8S_3$ viewed along the b-axis. Intra and intermolecular interactions (Table 3) are drawn as dashed lines forming a 3-D supramolecular network array.

Table 2. Bond lengths (Å) and bond angles (°) for bis-[(4-ammoniobenzene-1-sulfonyl)ammonium] sulfate, OBAF-6.

Bond lengths

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O1	1.434(2)	C4	C5	1.380(4)
S1	O2	1.436(2)	C5	C6	1.388(4)
S1	N12	1.584(3)	S1S	O1S[1]	1.461(3)
S1	C1	1.778(2)	S1S	O1S	1.461(3)
N13	C4	1.465(3)	S1S	O2S[1]	1.455(7)
C1	C2	1.382(4)	S1S	O2S[1]	1.455(7)
C1	C6	1.388(4)	S1S	O2S2	1.502(7)
C2	C3	1.386(4)	S1S	O2S2[1]	1.502(7)
C3	C4	1.374(4)			

Bond Angles

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	S1	O2	118.42(15)	C5	C4	N13	119.0(2)
O1	S1	N12	110.43(15)	C4	C5	C6	119.4(3)
O1	S1	C1	106.62(13)	C1	C6	C5	119.0(3)
O2	S1	N12	108.18(15)	O1S	S1S	O1S[1]	111.5(2)
O2	S1	C1	107.06(12)	O1S	S1S	O2S2[1]	96.3(3)
N12	S1	C1	105.32(13)	O1S[1]	S1S	O2S2	96.3(3)
C2	C1	S1	119.0(2)	O1S	S1S	O2S2	108.9(3)
C2	C1	C6	121.2(2)	O1S[1]	S1S	O2S2[1]	108.9(3)
C6	C1	S1	119.9(2)	O2S[1]	S1S	O1S	119.6(3)
C1	C2	C3	119.6(3)	O2S[1]	S1S	O1S[1]	109.5(3)
C4	C3	C2	119.1(3)	O2S	S1S	O1S	109.5(3)
C3	C4	N13	119.2(2)	O2S	S1S	O1S[1]	119.6(3)
C3	C4	C5	121.8(2)	O2S2	S1S	O2S2[1]	134.7(7)

[1]1-X,+Y,1/2-Z

Torsion Angles for OBAF-6.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	C1	C2	C3	179.0(2)	N13	C4	C5	C6	-178.5(3)
S1	C1	C6	C5	-178.9(2)	C1	C2	C3	C4	0.6(5)
O1	S1	C1	C2	149.3(2)	C2	C1	C6	C5	0.9(5)
O1	S1	C1	C6	-30.9(3)	C2	C3	C4	N13	178.5(3)
O2	S1	C1	C2	21.6(3)	C2	C3	C4	C5	-0.4(5)
O2	S1	C1	C6	-158.6(3)	C3	C4	C5	C6	0.5(5)
N12	S1	C1	C2	-93.3(3)	C4	C5	C6	C1	-0.7(5)
N12	S1	C1	C6	86.5(3)	C6	C1	C2	C3	-0.8(5)

Table 3. Hydrogen Bonds for OBAF-6.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N12	H12B	N13[1]	0.89	2.90	3.453(3)	122.2
N12	H12B	O2S[2]	0.89	1.93	2.776(7)	157.4
N12	H12B	O2S2[2]	0.89	1.89	2.767(8)	169.6
N12	H12C	O1S[3]	0.89	2.01	2.821(4)	150.9
N13	H13A	O2S[4]	0.89	1.88	2.749(7)	166.4
N13	H13A	O2S2[4]	0.89	1.92	2.807(8)	171.7
N13	H13B	O1[5]	0.89	2.86	3.413(4)	121.5
N13	H13B	O1[6]	0.89	2.54	3.115(3)	122.8
N13	H13B	O2[5]	0.89	2.27	3.008(3)	140.1
N13	H13C	O1S[7]	0.89	2.07	2.915(4)	157.9
C3	H3	O2S2[4]	0.93	2.88	3.454(8)	120.8

[1]3/2-X,3/2-Y,1/2+Z; [2]1/2+X,3/2-Y,1-Z; [3]1-X,2-Y,1-Z; [4]1-X,+Y,1/2-Z; [5]1-X,1-Y,1-Z; [6]+X,1-Y,-1/2+Z; [7]3/2-X,-1/2+Y,+Z

Conclusions

The synthesis and single crystal X-ray structure of, $C_{12}H_{20}N_4O_8S_3$, OBAF-6 is described as an unexpected product for the synthesis of Bis-[(4-ammoniobenzene-1-sulfonyl)ammonium] sulfate from the attempted synthesis of 4-[[(3-hydroxyphenyl)methylidene]amino]benzene-1-sulfonamide. For sulfanilamide, the sulfonamide NH_2 group was identified as the protonation site in the gas phase, which is in contrast to the situation in solution, where the NH_2 group of the aminobenzene is protonated [8]. The titled compound crystallized in the orthorhombic Pbcn space group. ((no. 60), a = 9.7339(3) Å, b = 9.6038(3) Å, c = 18.4128(6) Å, V = 1721.27(9) Å^3, Z = 4, T = 293(2) K) and displays hydrogen bonding and weak intra and intermolecular interactions between two parallel, but inverted molecules, with Cg1---Cg1 ring stacking in planes [Cg1 = C1/C3/c4/C5/C6; 3.7428; 1-x, 1-y, 1-z] creating cage-like structures forming chains along the a, b and c axes forming a supramolecular network. One of the oxygen atoms (O2S2) is disordered with occupancies 0.51119 and 0.48881, respectively.

Further details of the crystal structure investigations may be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif on quoting the depository number CCDC 2076286.

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