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Peculiar hydrogen-bond patterns in the crystal structure of a heterocyclic aryl benzyl sulfone

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ABSTRACT

In our research on the crystal structures of many sulphur compounds (sulfides or enantiopure and racemic sulfoxides), we report now the first example of a crystal structure of an heterocyclic aryl benzyl sulfone from our chemical library. The presence of the sulfonyl and the pyridyl moieties organises a peculiar network of weak hydrogen bonds, that is unprecedented in the crystallographic database.

KEYWORDS **Sulphur compounds. X-ray diffraction. Hydrogen bond. Weak interactions.**

INTRODUCTION

Sulphur is one of the most abundant element on earth. It can be found in pure native state, but more frequently as sulfides or sulfate minerals. Organic sulphur plays also a crucial role in many biological processes. It can be found in the cysteine or methionine aminoacids, and in proteins therefrom, but also in vitamins, co-factors and so on. Sulphur is present in many drugs, the most famous being the (S)-omeprazole (Surur *et al.*, 2019). This compound is largely used against gastric diseases and is one of the best-selling drug in the world (Surur *et al.*, 2019).

Organic molecules containing sulphur can exist in different states of oxidation, the sulfides being the lowest, the sulfoxides the intermediate and the sulfones the highest (Solladié, 1991).

On the basis of previous studies on the enantioselective oxidation of aryl benzyl sulfides to enantiopure aryl benzyl sulfoxides, an innovative procedure was developed and extensively investigated, with an efficiency comparable to that of enzymatic processes (Capozzi *et al.*, 2013, 2014, 2015, 2024a, b; Naso *et al.*, 2009). A large chemical library of sulfides, racemic and enantiopure sulfoxides and sulfones was built. Many products in this chemical library were investigated for their bio-activity.

In particular, in our investigation on the synthesis of molecules connected with the omeprazole scaffold (Capozzi

et al., 2024a), we studied the enantioselective oxidation of 2-(4-bromophenylthiomethyl)-pyridine 1a with *tert*-butyl hydroperoxide in the presence of a chiral complex between titanium and (*S*,*S*)-hydrobenzoin (Capozzi *et al.*, 2024a). Small amounts (7%) of the corresponding sulfone 1c were obtained.

The crystal structures of many sulfides, racemic and enantiopure sulfoxides have been investigated with single crystal X-ray diffraction experiments (*e.g.*, Capozzi *et al.*, 2013, 2014, 2015, 2024a, b, 2025; Naso *et al.*, 2009). The main patterns of these classes of compounds were recognised and described (Capozzi *et al.*, 2014, 2024b, 2025). The discovery of new and unusual patterns in crystallography is a central research topic today, as they can be useful for predicting new crystal structures and their properties (Taylor *et al.*, 2025). In our previous research, sulfones have been often obtained as amorphous material.

METHODS

Synthesis of the product

Sulfones are usually synthesised by over-oxidation of sulfides, *meta*-chloroperoxybenzoic acid or hydrogen peroxide being the most useful reagents to this end (Solladié, 1991). In the present work, the product under investigation was obtained as a side product.

A solution of Ti(O-*i*-Pr)$_4$ 99.999% (14 mg, 0.05 mmol) in 4 mL of *n*-hexane was added to a solution of (*S*,*S*)-hydrobenzoin (21 mg, 0.1 mmol) in 8 mL of *n*-hexane. After 1 hour stirring at room temperature, a solution of 0.28 g (1 mmol) of 2-(4-bromophenylthiomethyl)-pyridine 1a in 8 mL of *n*-hexane was added. The stirring was continued for 30 minutes. After this time, 0.14 mL (1.1 mmol) of a commercial solution of *tert*-butyl hydroperoxide was added and the stirring was continued for two days. After this time, the solvent was evaporated and the residual was subjected to column chromatography (silica gel, eluent ethyl acetate/*n*-hexane 7:3). Example: Following the methodology of Capozzi *et al.* (2024a), 2-(4-Bromophenylsulfinylmethyl)-pyridine 1b was the main reaction product, but also small amounts of 2-(4-bromophenylmethylsulfonyl)pyridine 1c (7% yield) were obtained. The separated sulfone 1c was purified by crystallisation (ethanol). This product had been also obtained in the oxidation of 2-(4-bromophenylthiomethyl)-pyridine 1a with *m*-chloroperoxybenzoic acid (Haviv *et al.*, 1983).

2-(4-bromophenylmethylsulfonyl)pyridine (1c) Mp 149-150 °C (Lit. (Haviv et al., 1983) 141-143 °C). ^{1}H-NMR (500 MHz, $CDCl_3$) 8.48-8.44 (m, 1 H), 7.88-7.82 (m, 1 H), 7.65-7.54 (m, 5 H), 7.40-7.34 (m, 1 H), 4.68 (s, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$) 148.3, 147.9, 138.4, 137.1, 132.4, 130.0, 129.5, 126.5, 124.0, 63.3.

RESULTS

Crystal structure determination

The methodology used for the crystal structure determination is the so called "direct methods" (Giacovazzo *et al.*, 1998, 2011), where the phases of the structure factors (F's) are derived from the magnitudes measured experimentally. The program used for carrying out the calculations was SHELX (Sheldrick, 2015). Subsequently, the crystal structure was refined by full matrix least-squares methods on F^2 for all reflections (Sheldrick, 2015).

X-ray diffraction experiments

A suitable single crystal was mounted on a Bruker D8 Venture automatic diffractometer using monochromated Cu Kα radiation at 219 K temperature. The intensities were corrected for Lorentz and polarization effects as well as for absorption (Krause, 2015). Data corresponding to the measurements are collected in Table 1.

Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions with isotropic displacement parameters fixed at 1.2 times the U_{eq} of the corresponding carbon atoms. Methylene hydrogen atoms (H1A and H1B) and the aryl hydrogen atoms involved in a hydrogen bonding (H5, H6 and H8) were located by means of difference Fourier synthesis. The crystallographic .cif file was deposited in the Cambridge Structural Database (CSD) with the number 2498417. ORTEP plot for 50% probability level was represented in Figure 1.

Crystal data and structure refinements for sulfone 1c are collected in Table 1.

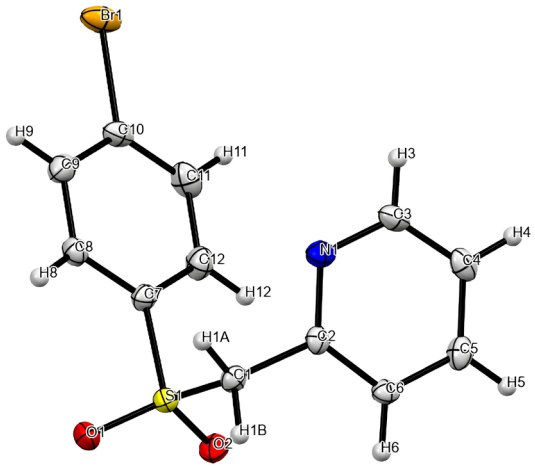

FIGURE 1. ORTEP plot for 2-(4-bromophenylmethylsulfonyl)pyridine (1c).

TABLE 1. Crystal data and structure refinement for sulfone (1c)

Empirical formula		$C_{12}H_{10}BrNO_2S$
Formula weight		312.18
Temperature		219(2) K
Wavelength		1.54178 Å
Crystal system		Orthorhombic
Space group		P b c a
Unit cell dimensions	a = 11.9713(3) Å	a= 90°
	b = 7.8506(2) Å	b= 90°
	c = 25.6619(5) Å	g = 90°
Volume		2411.75(10) $Å^3$
Z		8
Density (calculated)		1.720 Mg/m^3
Absorption coefficient		6.182 mm^{-1}
F(000)		1248
Crystal size		0.080 x 0.060 x 0.060 mm^3
Theta range for data collection		3.444 to 68.271°.
Index ranges		-14<=h<=14, -9<=k<=9, -30<=l<=30
Reflections collected		26898
Independent reflections		2214 [R(int) = 0.0807]
Completeness to theta = 25.000°		99.5 %
Absorption correction		Semi-empirical from equivalents
Max. and min. transmission		0.71 and 0.60
Refinement method		Full-matrix least-squares on F^2
Data / restraints / parameters		2214 / 0 / 169
Goodness-of-fit on F^2		1.026
Final R indices [I>2sigma(I)]		R1 = 0.0329, wR2 = 0.0787
R indices (all data)		R1 = 0.0429, wR2 = 0.0855
Extinction coefficient		n/a
Largest diff. peak and hole		0.558 and -0.641 $e.Å^{-3}$

DISCUSSION

The main interactions building up the crystal structures of sulfones had been investigated and reviewed (Brondel *et al.,* 2010). According to Brondel *et al.,* (2010), a network of hydrogen bond usually builds up the crystal structures. Due to the presence of the sulfonyl moiety, the methylene hydrogen atoms are more acidic than the same corresponding hydrogen atoms of the sulfoxides and they behave as the typical hydrogen bond donors.

However, at variance with generic aryl benzyl sulfones, the case of sulfone 1c is peculiar. First, we found that the particular fragment of 2-pyridylmethylsulfonyl is very rare among the crystal structures collected in the CSD. In fact, we found only the DOHKET crystal structure, that is the 2-(((pyridin-2-yl)methyl)sulfonyl)pyridine (Qin *et al.,* 2019), in which two 2-pyridyl moieties are present.

Second, the 2-pyridyl moiety adds complexity to the crystal structure, due to the possibility that the nitrogen atom behaves as a hydrogen bond acceptor together with the sulfonyl oxygen atoms. Therefore, a model of hydrogen bond based upon only the sulfonyl oxygen atoms (Brondel *et al.,* 2010) cannot be used to account for the complexity of the present crystal structure.

Finally, the hydrogen atoms involved in these hydrogen bonds are not only the weakly acidic methylene hydrogen atoms, but also three aryl hydrogen atoms. In Figure 2, we represented the network of some weak hydrogen bonds in

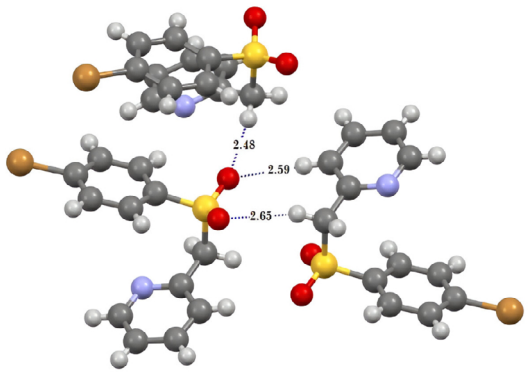

FIGURE 2. Network of weak hydrogen bonding in the crystal structure of sulfone (1c).

TABLE 2. Characteristics of main intermolecular hydrogen bonds in sulfone (1c)

	Angle (°)	H···O/N (Å)	C···O/N (Å)	H-C (Å)
C1-H1A···O1	172(3)	2.48(3)	3.412(3)	0.94(4)
C6-H6···O1	178(3)	2.59(3)	3.505(4)	0.91(3)
C1-H1B···O2	159(3)	2.65(3)	3.577(4)	0.97(4)
C5-H5···O2	148(3)	2.50(3)	3.314(4)	0.92(4)
C8-H8···N1	154(3)	2.57(4)	3.412(4)	0.91(4)

the crystal structure of sulfone 1c, in which the oxygen atoms behave as the acceptors.

The characteristics of the main hydrogen bonds are summarised in Table 2. The hydrogen bond donor or acceptor can be graphically identified by decorating the Hirshfeld surface (Spackman *et al.,* 2021) with the electrostatic potential (Fig. 3).

The contemporary presence of the sulfonyl and the pyridyl moieties allow the formation of two cyclic patterns, according to the reported classification (Bernstein *et al.,* 1995). These two pattern are characteristic of the present structure.

The first pattern is a nine-membered cycle, consisting of the S1-O1-H1A-C1-C2-N1-H8-C8-C7 atoms, with two weak hydrogen bonds C8-H8···N1 and C1-H1A···O1, as represented in Figure 4, in which only the framework of the involved atoms is represented. According to the classification of Bernstein *et al.,* (1995), it is indicated as a $R^2_2(9)$ (a ring of 9 terms with two donors and two acceptors).

The next eight-membered cycle, consisting of the S1-O2-H1B-C1-C2-C6-H6-O1 atoms, is by far more interesting. It is indicated as a $R^2_2(8)$ (a ring of 8 terms with two donors and two acceptors) according to Bernstein *et al.,* (1995). As shown in Figure 4, in which only the cited atoms were represented, this pattern is based upon the weak C6-H6···O1 and C1-H1B···O2 hydrogen bonds. The head-to-tail scheme of these two weak hydrogen bonds is duplicated by the presence of two oxygen atoms in the sulfonyl moiety, giving rise to the pattern represented in Figure 5.

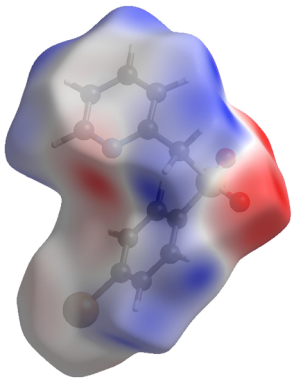

FIGURE 3. Hirschfeld surface of sulfone (1c) decorated with electrostatic potential (red colour for hydrogen bond acceptors; blue colour for hydrogen bond donors).

A similar pattern is seldom found in the CSD crystallographic database of organic compounds such as the CIBTUB (Miles *et al.,* 2007), IBABET (Mehta and Pallavi, 2004), LUDJIE (Acuña *et al,* 2009), PUJXUG (Chen *et al,* 2020) and TAJNIB (Estrada and López-Castro, 1991) crystal structures. These five molecules are poly-oxygenated cyclic compounds and the unusual pattern is built up due to the rigidity of the cycles. On the other hand, sulfone 1c is the first non-cyclic framework showing the peculiar pattern represented in Figure 5, based upon the sulfonyl moiety.

CONCLUSIONS

The crystal structure of 2-(4-bromophenylmethylsulfonyl) pyridine was established by X-ray single crystal diffraction experiments. This compound is a further example of a 2-pyridylmethylsulfonyl molecule beyond the only precedent up to now reported. The crystal structure is built up by a network of many weak hydrogen bonds, arranged in a peculiar

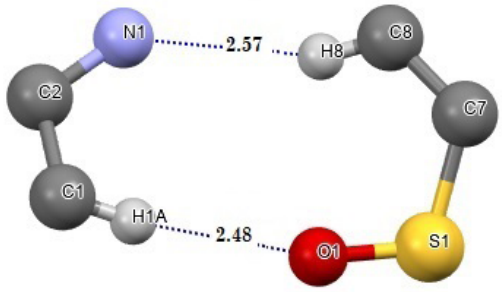

FIGURE 4. Nine-membered pattern of double hydrogen bonds.

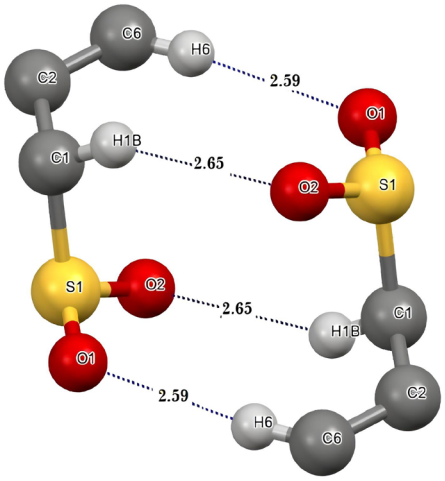

FIGURE 5. Eight-membered pattern of duplicated double hydrogenbonds in sulfone (1c).

interlaced pattern, organised around the sulfonyl moiety. Only cyclic compounds showed similar patterns and, in this regard, this is the first example of a non-cyclic framework that can originate it.

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