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Synthesis, Single Crystal X-ray and Hirshfeld Surface Analysis of (2-(methylthio) thiophen-3-yl)(thiophen-2-yl)methanone

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ABSTRACT

The title compound of (2-(methylthio)thiophen-3-yl)(thiophen-2-yl)methanone, was synthesized and confirmed by spectroscopic techniques such as Fourier Transform Infrared (FTIR), Proton Nuclear Magnetic Resonance (^{1}H-NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR), mass spectra and element analysis. Single crystals obtained by slow evaporation technique and the crystal structure were determined by single crystal X-ray diffraction method. The compound crystallizes in the monoclinic crystal system with the space group P2(1), unit cell parameters a=5.6236(6) Å, b=12.8026(13) Å, c=7.2117(7) Å, β=92.971(5)° and Z=2. The structure exhibits intermolecular hydrogen bonds of the type C-H…S. Hirshfeld analysis was carried out to understand the packing pattern and intermolecular interactions.

Keywords: Thiophene, Crystal structure, Hirshfeld surfaces, C-H…S interaction

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INTRODUCTION

Heterocyclic molecules containing the five-membered thiophene nucleus possess a variety of useful biological applications. Recently, the thiophene chemistry has been developed extensively and is on still developing with promising properties. Most of the drugs are used clinically, which comprises thiophene moiety in association with several heterocyclic rings, which are synthetically useful and biologically active. Literature survey revealed that thiophenes are related to a wide range of pharmacological activities and find its large application in material science [1-3] and in coordination chemistry [4,5] and as intermediate in organic synthesis [6,7]. A large number of thiophene derivatives have been reported to possess significant and diverse biological activities such as antimicrobial [8], antioxidant [9], analgesic [10], anti-inflammatory [11], antitumor [12] and local anesthetic [13] activities. In view of this background, we have synthesized and characterized the title compound, and further discussed with Hirshfeld analysis representing 2D Fingerprint plots.

MATERIALS AND METHODS

All the chemicals were purchased from Sigma Aldrich Chemical Company. ^{1}H-NMR spectra was recorded on a Bruker 400 MHz in Deuterated Chloroform ($CDCl_3$) and the chemical shifts were recorded in parts per million downfield from Tetramethylsilane (TMS). Mass spectra were obtained with a VG70-70H spectrophotometer. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyzer. The results of elemental analyses were within ± 0.4% of the theoretical values.

General procedure for the preparation of (E)-3-((2,2-diethoxyethyl)thio)-3-(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (3a)

Bromoacetaldehyde diethyl acetal 2 (1.9 g, 0.01 mol) was added slowly to β-oxodithioates 1a (0.01 mol) in dry Dimethylformamide (DMF) (10 ml) in the presence of anhydrous potassium carbonate (1.2 g). The oil bath temperature was maintained at 80°C for 1.5-2 h. The progress of the reaction was monitored by Thin Layer Chromatography (TLC) using EtOAc-Petroleum ether (2:8) as the eluent. After the completion of reaction the mixture was extracted with EtOAc (3 × 10 ml). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give crude (E)-3-((2,2-diethoxyethyl)thio)-3-(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (3a) in around 85 to 90% yield. The crude product was taken to the next step without purification.

General procedure for the synthesis of (2-(methylthio)thiophen-3-yl)(thiophen-2-yl)methanone (4a)

The mixed acetals 3a (0.01 mol) were suspended in a round bottomed flask and mixed with 5 ml dry ethanol followed by orthophosphoric acid (5 ml) and the reaction mixture was heated for a period of 1-1.5 h at 80°C. The progress of the reaction was monitored by TLC (EtOAc: Petroleum ether, 2:8) and the reaction mixture was concentrated in the rotary evaporator. Further, the concentrated reaction mixture was poured into ice cold water and extracted with ethyl acetate, dried (Na_2SO_4) and the solvent was distilled out in the rotary evaporator. The residue obtained was purified by passing through silica gel and eluted with 5% ethyl acetate and petroleum ether to yield the pure product (2-(methylthio)thiophen-3-yl)(thiophen-2-yl)methanone (4a). Solid. m.p. 83-86°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.71-7.69 (dd, J=3.6Hz, 1H), 7.67-7.64 (dd, J=4.8Hz, 1H), 7.56-7.54 (d, J=5.4Hz, 1H), 7.22-7.19 (d, J=5.4Hz, 1H), 7.16-7.13 (dd, J=5Hz, 1H), 2.61 (s, 3H). ^{13}C-NMR (75MHz, $CDCl_3$): 180.87, 152.69, 144.38, 134.38, 133.06, 132.77, 129.31, 127.71, 122.33, 19.13. HRMS (ESI): Calcd for $C_{10}H_8OS_3$ $[M+H]^+$ 241.9695 found 240.9841.

Single crystal structure determination

A colorless rectangle shaped single crystal of dimensions 0.290 × 0.250 × 0.220 mm of the title compound was chosen for X-ray diffraction study. The X-ray intensity data were collected at the temperature of 296 K on Bruker Proteum2 CCD diffractometer equipped with a X-ray generator operating at 45 kV and 10 mA, using CuKα radiation of wavelength 1.54178 Å. Data were collected for 24 frames per set with different settings of φ (0° and 90°), keeping the scan width of 0.5°, exposure time of 2 s, the sample to detector distance of 45.10 mm and 2θ value at 46.6°. A complete data set was processed using SAINT PLUS [14]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using SHELXS and SHELXL programs [15]. The geometrical calculations were carried out using the program PLATON [16]. The molecular and packing diagrams were generated using the software MERCURY [17].

RESULTS AND DISCUSSION

In the molecular structure of the title compound Figure 1, the dihedral angle between the mean plane of the thiophene rings, (S1/C2/C3/C4/C5) and (C10/C14/C113/C12/S11), is 36.6(3)°. The methylthio group is present in -syn-periplanar conformation with respect to the thiophene moiety, as indicated by the torsion angle value of -4.9(4)° (S1-C2-S6-C7). The thiophene rings are connected via carbonyl group, exhibiting anti-periplanar conformation between them, as indicated by the torsion angle of value of (S11-C10-C8-C3) is -158.2(4)°. There are no classical hydrogen bonds. The crystal structure is stabilized by weak C-H…S intermolecular interactions. The packing of the molecules exhibit stacking feature down c-axis. The details of the crystal structure and data refinement are given in Table 1. Tables 2-5 gives the list of bond lengths, bond angles, torsion angles and hydrogen bond geometry. Figure 2 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability (Figure 3).

Table 1: Crystal data and structure refinement details of molecule 1

Parameter	Value
CCDC deposit No.	CCDC 1486612
Empirical formula	$C_{10}H_8OS_3$
Formula weight	240.34
Temperature	296(2) K
Wavelength	1.54178 A
Reflns. for cell determination	1566
θ range for above	7.890° to 64.071°
Crystal system	Monoclinic
Space group	P2(1)
Cell dimensions	a=5.6236(6) A˚
	b=12.8026(13) A˚
	c=7.2117(7) A˚
	β=92.971(5)°
Volume	518.52(9) $Å^3$
Z	2
Density(calculated)	1.539 Mg m^{-3}
Absorption coefficient	6.217 mm^{-1}
F_{000}	248
Crystal size	0.290 × 0.250 ×0.220
θ range for data collection	7.890°-64.071°
Index ranges	-6 < =h < =3
	-14 < =k< =14
	-8 < =l< =8
Reflections collected	1525
Independent reflections	1566
Absorption correction	none
Refinement method	Full-matrix least-squares on F_2
Data/restraints/parameters	1566/1/128
Goodness-of-fit on F^2	1.007
Final [I>2σ(I)]	R1=0.0455, wR2=0.1194
R indices (all data)	R1=0.0462, wR2=0.1205
Largest diff. peak and hole	0.313 and -0.560 $eA^{˚-3}$

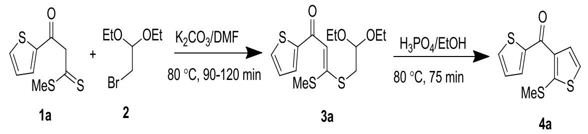

Figure 1: Synthesis of (2-(methylthio)thiophen-3-yl)(thiophen-2-yl)methanone

Table 2: Bond lengths (Å)

Atoms	Length	Atoms	Length
S1-C2	1.715(6)	C5-H5	0.9300
S1-C5	1.717(7)	C7-H7A	0.9600
S6-C2	1.741(6)	C7-H7B	0.9600
S6-C7	1.793(7)	C7-H7C	0.9600
S11-C12	1.673(6)	C8-C10	1.478(8)
S11-C10	1.711(6)	C10-C14	1.506(8)
O9-C8	1.227(7)	C12-C13	1.482(9)
C2-C3	1.374(8)	C14-H14	0.9300
C3-C4	1.433(8)	C13-C14	1.358(10)
C3-C8	1.477(8)	C13-H13	0.9300
C4-C5	1.333(10)	C12-H12	0.9300
C4-H4	0.9300	-	-

Table 3: Bond angles (°)

Atoms	Angle	Angle	Length
C2-S1-C5	91.4(3)	S6-C7-H7C	109.5
C2-S6-C7	101.5(3)	H7A-C7-H7C	109.5
C12-S11-C10	92.0(3)	H7B-C7-H7C	109.5
C3-C2-S1	111.6(4)	O9-C8-C3	120.4(5)
C3-C2-S6	126.9(4)	O9-C8-C10	119.2(5)
S1-C2-S6	121.5(3)	C3-C8-C10	120.5(5)
C2-C3-C4	111.5(5)	C8-C10-C14	128.5(5)
C2-C3-C8	121.1(5)	C8-C10-S11	116.9(4)
C4-C3-C8	127.3(5)	C14-C10-S11	114.2(4)
C5-C4-C3	112.9(5)	C13-C14-C10	103.3(5)
C5-C4-H4	123.5	C13-C14-H14	128.3
C3-C4-H4	123.5	C10-C14-H14	128.3
C4-C5-S1	112.5(5)	C12-C13-C14	115.9(5)
C4-C5-H5	123.8	C12-C13-H13	122.0
S1-C5-H5	123.8	C14-C13-H13	122.0
S6-C7-H7A	109.5	C13-C12-S11	114.4(5)
S6-C7-H7B	109.5	C13-C12-H12	122.8
H5A-C7-H7B	109.5	S11-C12-H12	122.8

Table 4: Torsion angles (°)

Atoms	Angle	Atoms	Angle
C5-S1-C2-C3	2.5(5)	C2-C3-C8-C10	-165.8(5)
C5-S1-C2-S6	-176.8(4)	C4-C3-C8-C10	16.7(8)
C7-S6-C2-C3	176.0(5)	O9-C8-C10-C14	-151.1(6)
C7-S6-C2-S1	-4.9(4)	C3-C8-C10-C14	28.9(8)
S1-C2-C3-C4	-2.9(6)	O9-C8-C10-S11	21.9(7)
S6-C2-C3-C4	176.4(5)	C3-C8-C10-S11	-158.1(4)
S1-C2-C3-C8	179.2(4)	C12-S11-C10-C8	-176.9(5)
S6-C2-C3-C8	-1.6(8)	C12-S11-C10-C14	-2.9(5)
C2-C3-C4-C5	1.8(8)	C8-C10-C14-C13	176.3(6)
C8-C3-C4-C5	179.6(6)	S11-C10-C14-C13	3.2(6)
C3-C4-C5-S1	0.1(8)	C10-C14-C13-C12	-1.9(7)
C2-S1-C5-C4	-1.5(6)	C14-C13-C12-S11	0.0(8)
C2-C3-C8-O9	14.3(8)	C10-S11-C12-C13	1.7(6)
C4-C3-C8-O9	-163.3(6)		

Table 5: Hydrogen-bonding geometry details of molecule (1) (Å), (°)

D-H…A	D-H	H-A	D-A	D-H…A
C14-H14…S6[(i)]	0.9300	2.8000	3.697(6)	163.00

Symmetry code: (i) x, y, 1+z

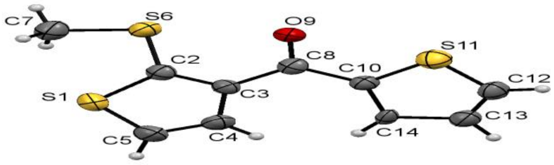

Figure 2: ORTEP of the molecule with thermal ellipsoids drawn at 50% probability

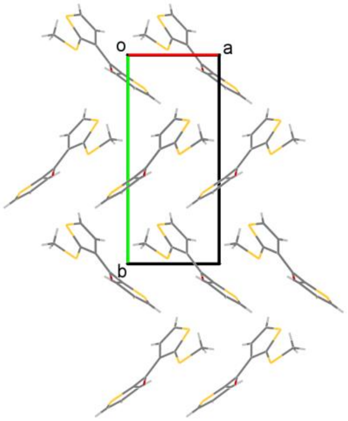

Figure 3: Packing diagram of the molecules when viewed down along the [a] axis

Molecular Hirshfeld surfaces

The Hirshfeld surfaces analysis and 2-D fingerprint plots were performed to study the intercontacts and their quantitative contributions towards the crystal packing [18-22]. The Hirshfeld surface volume and area calculated were 253.41Å^3 and 243.88 Å^3, respectively.

The Hirshfeld surface for the title compound is shown in Figure 4 and has been mapped over d_{norm} range from -0.167-1.021Å. The normalized contact distance (d_{norm}) is based on both d_i and d_e. In Figure 5, the negative value indicates red color for intermolecular contacts shorter than r^{vdW} (van der Waals (vdW) radii), positive value indicated blue color when intermolecular contacts are longer than r^{vdW} and the white regions corresponded to the distances of contacts with exact vdW separation having d_{norm} value of zero.

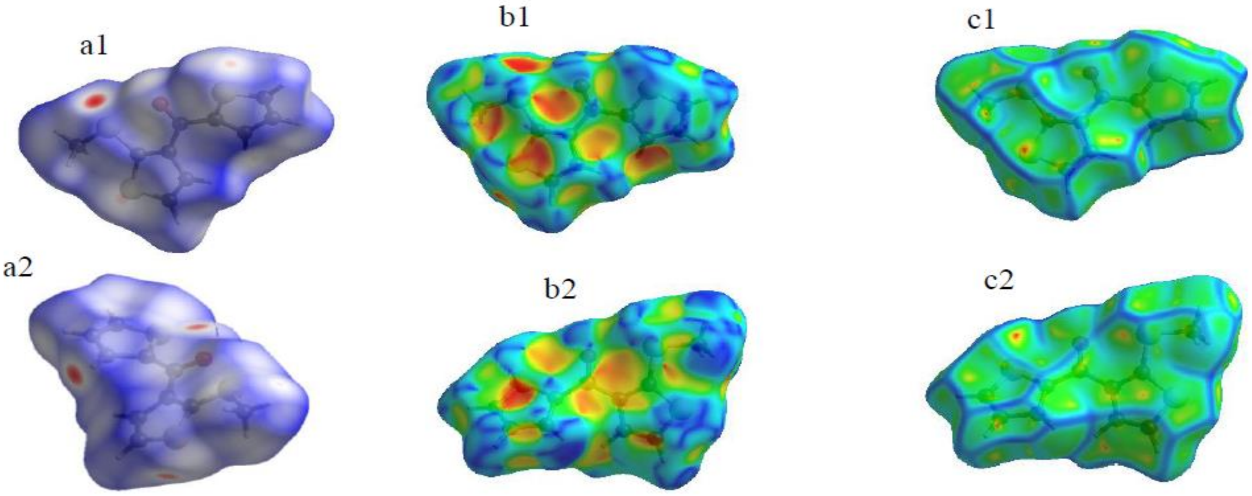

Figure 4: Hirshfeld surfaces mapped with d_{norm} with front view (a1) and back view (a2). Shape index with front view (b1) and back view (b2). Curvedness with front view (c1) and back view (c2)

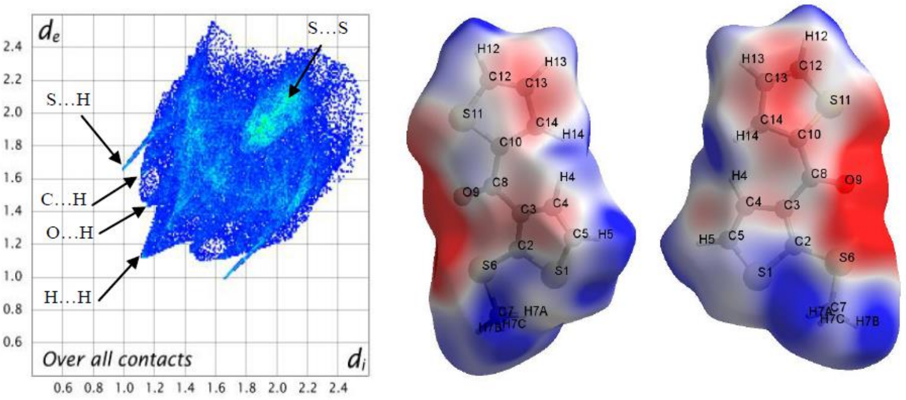

Figure 5: Fingerprint plot of the title compound with overall contacts

The breakdown of the 2D fingerprint plots identifies the patterns associated with individual contributions of all the intermolecular contacts and with the help of the electrostatic potential surface [23] illustrating surface patches that contribute to individual pattern.

The most significant contribution to the total Hirshfeld surface area is H…H contacts, appears as stacking kite which are reflected with higher concentration in the middle representing with the equal d_e and d_i distances Figure 6 covering 32.3% area of the total Hirshfeld surfaces. We can identify only three electrostatic potential regions on the surface around hydrogen atoms; one in electropositive regions (in blue color) with the hydrogen atoms acting as donors, another in electronegative regions (in red color) with the hydrogen atoms acting as acceptors and finally in isoelectrostatic potential regions (in white color) for the hydrogen atoms showing neutral character.

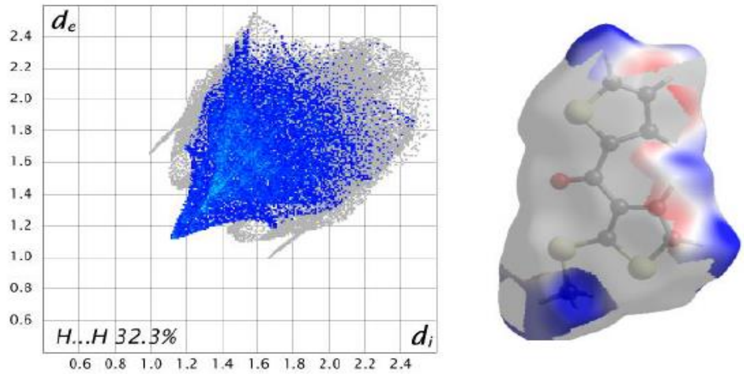

Figure 6: Fingerprint plot of H…H contact and electrostatic potential surface

The 2D fingerprint plots (Figure 5) analyzes the quantitative contributions for the all intermolecular contacts at the same time.

The wings are identified at the regions (d_e=1.74Å, d_i=1.04Å) and (d_e=1.04Å, d_i=1.74Å) in the fingerprint plot shown in Figure 7, are due to C…H\H…C contacts with 20.3% contribution to the total Hirshfeld surfaces. The electropositive (blue) regions around the methyl group and hydrogen (H5) atom in the upper thiophene ring are complementary to the electronegative (red) regions on the surface at C10, C12, C13 and C14 of the upper thiophene ring as well as C4 in the downward thiophene ring. This electrostatic complementarity is an evident for the C…H contact. It is noticeable that the acceptor carbons appears more than donors hydrogen, which explains the asymmetry pattern in fingerprint plot as represented in Figure 7.

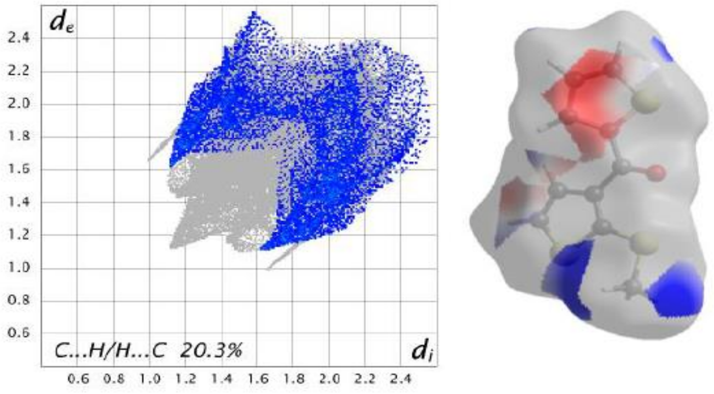

Figure 7: Fingerprint plot of C…H contact and electrostatic potential surface

S…H\H…S contacts are represented as characteristic sharp spikes in the top and lower parts of fingerprint plot as shown in Figure 8, thereby comprising 15.6 % of the total Hirshfeld surfaces with clear identification of electropositive (blue) regions on the surface above H14 donor complementing to the electronegative (red) regions on the surface above S6 acceptor.

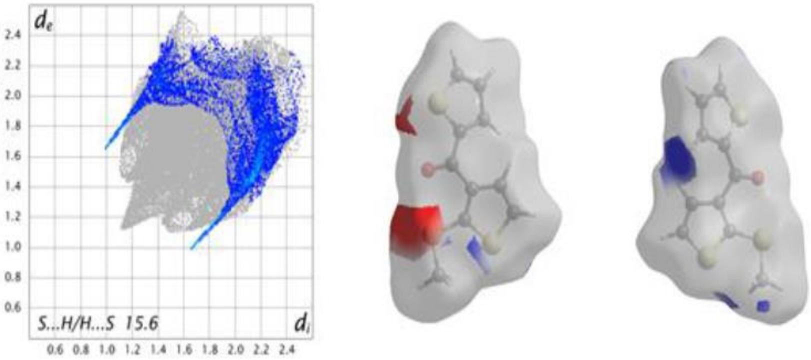

Figure 8: Fingerprint plot of S…H contact and electrostatic potential surface

O…H\H…O contacts shown in Figure 9, comprises 11.5 % of the total Hirshfeld surfaces, where O9 appears with electronegative (red) regions on the surface acting as acceptor to H13 in neighbor molecule and similarly H13 with electropositive (blue) regions on the surface acts as donor to O9 with another neighbor molecule.

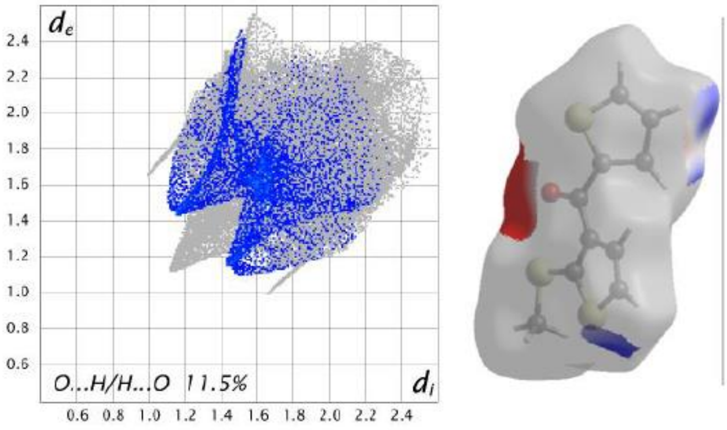

Figure 9: Fingerprint plot of O…H contact and electrostatic potential surface

Hirshfeld surface analysis also reveals the short contact S…S interactions comprising 4.8% of the total Hirshfeld surfaces as shown in Figure 10. Here, S11 with electronegative (red) regions on the surface act as acceptor and S1 with electropositive (blue) regions on the surface acts as donor.

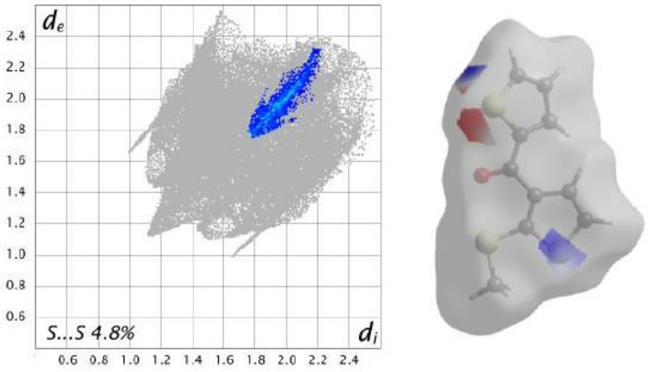

Figure 10: Fingerprint plot of S…S contacts and electrostatic potential surface

S…O\O…S contacts contributes only 3.5% to the total Hirshfeld surfaces Figure 11, showing clear identifiable electropositive (blue) regions on the surface above S1 complementing to the electronegative (red) regions on the surface above O9. This electrostatic complementary character also explains the short contacts from X-ray results, where the O9 and S1 atoms are acting as good acceptors and donors, respectively, which play a significant role in the crystal packing and stability.

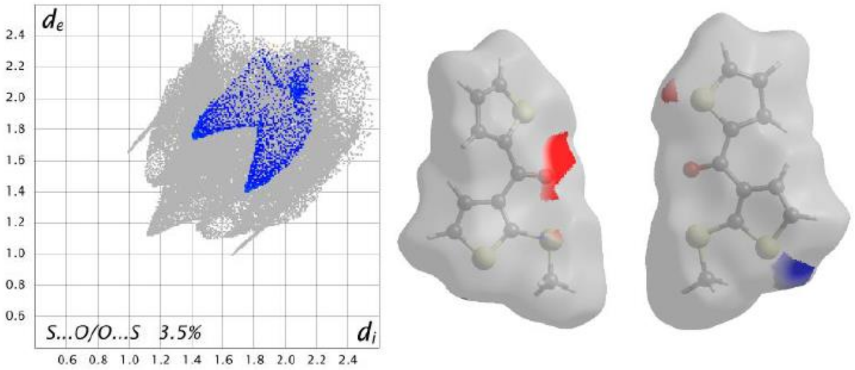

Figure 11: Fingerprint plot of S…O contact and electrostatic potential surface

The π···π interactions are not responsible for stacking contact due to very less significant contribution of C…C contact that is only 1.1% contributing to the total Hirshfeld surfaces. In Figure 4b, shape index confirms that there are no distinct red and blue triangles for representing π···π interactions. The presence of all contacts has been observed, analyzed and displayed in pie chart as shown in Figure 12.

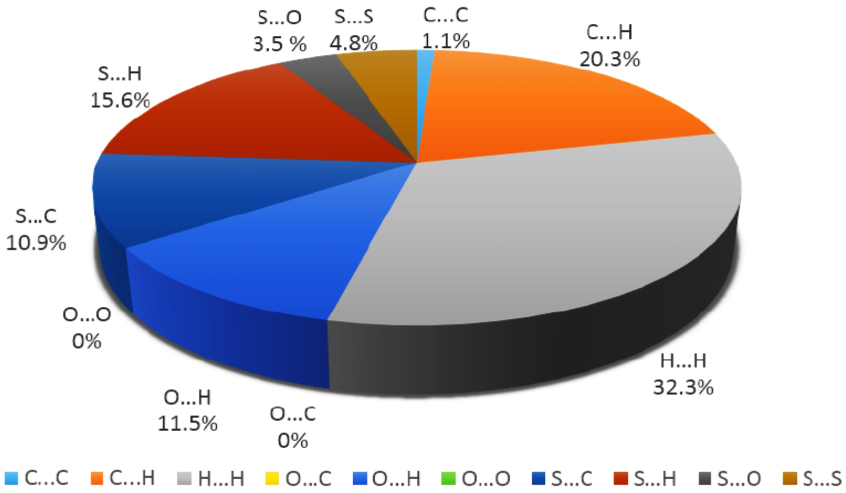

Figure 12: Pie chart for the presence of all contacts

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