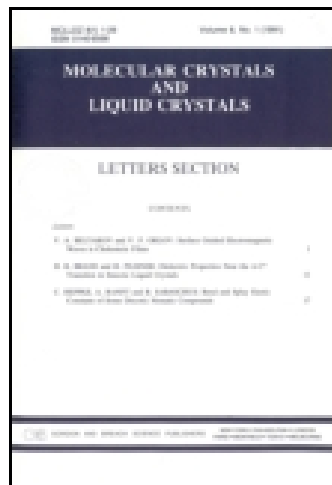


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Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:

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Published online: 26 Feb 2015.



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To cite this article: N. Latha Rani, M. P. Chakravarthy, K. N. Mohana, N. K. Lokanath & M. A. Sridhar (2015) Synthesis, Characterization and Hirshfeld Surface Analysis of a 2-thiophene Acetic Acid Derivative, *Molecular Crystals and Liquid Crystals*, 607:1, 223-231, DOI: [10.1080/15421406.2014.928978](https://doi.org/10.1080/15421406.2014.928978)

To link to this article: <http://dx.doi.org/10.1080/15421406.2014.928978>

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Synthesis, Characterization and Hirshfeld Surface Analysis of a 2-thiophene Acetic Acid Derivative

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N,N'-dicyclohexylcarbamoyl-2-(thiophen-2-yl)acetamide (C₁₉H₂₈N₂ O₂S), was prepared using 1,3-dicyclohexylurea. The compound has been characterized by IR, and single-crystal X-ray diffraction followed by a detailed Hirshfeld surface analysis. The compound crystallizes in the monoclinic space group P2₁/c, with cell parameters a = 9.0969(3) Å, b = 18.3067(5) Å, c = 11.6499(3) Å, β = 103.876(2)°, V = 1883.49(10) Å³, Z = 4. The crystal structure of the compound is stabilized by the intermolecular interactions of types N–H... O, C–H... O and intramolecular interactions of the type C–H... O.

Keywords 2-thiophene acetic acid; *Candida albicans*; fingerprint plots; FTIR spectrum; Hirshfeld surface analysis

Introduction

Organic compounds containing five-membered aromatic heterocyclic rings are widely distributed in nature and often play an important role in various biochemical processes [1]. Thiophene is one such heterocyclic compound. The compound *N,N'*-dicyclohexylcarbamoyl-2-(thiophen-2-yl)acetamide is derived from 2-thiophene acetic acid.

Derivatives of 2-thiophene acetic acid have gained remarkable importance due to their widespread biological activities. For example, thiourea derivatives (derived from 2-thiophene acetic acid) show antifungal activity [2]. Investigations were carried out to determine their antimicrobial activity. They proved to be active on fungus *Candida albicans* [3].

In this paper, we report the synthesis and structure analysis of *N,N'*-dicyclohexylcarbamoyl-2-(thiophen-2-yl)acetamide using FT-IR and single crystal X-ray diffraction. Intermolecular contacts are studied using Hirshfeld surface analysis.

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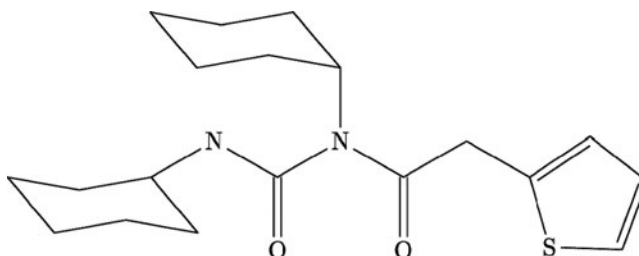
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Experimental

Synthesis and Crystal Growth

1,3-dicyclohexylurea ($C_{13}H_{24}N_2O$, Mol. Wt. 224.34 g) was synthesized by dissolving 1.43 g (10 mmol, $C_7H_{13}NO_2$, Mol. Wt. 143.18 g) of cyclohexylcarbamic acid and 0.99 g (10 mmol, $C_6H_{13}N$, Mol. Wt. 99.17 g) of cyclohexanamine in 15 mL DCM (dichloromethane, CH_2Cl_2 , Mol. Wt. 84.93 g) taken in a round bottom flask. A 4.12 g (20 mmol, $C_{13}H_{22}N_2$, Mol. Wt. 206.33 g) of DCC (N,N' -Dicyclohexylcarbodiimide) was added and the reaction mixture was refluxed for 8 h at room temperature in basic condition with the addition of 4 mL (30 mmol, $C_6H_{15}N$) of triethylamine. The solution obtained was filtered off and the filtrate was kept for drying at room temperature to get 1,3-dicyclohexylurea.

Later 1.1 g of the obtained 1,3-dicyclohexylurea (5 mmol, $C_{13}H_{24}N_2O$, Mol. Wt. 224.34 g) along with 15 mL of DCM was taken in a clean round bottom flask. To the resultant mixture 0.71 g (5 mmol, $C_6H_6O_2S$, Mol. Wt. 142.18 g) of 2-thiopheneacetic acid in 15 mL DCM was added. To this mixture 2.6 g (10 mmol, $C_{13}H_{22}N_2$, Mol. Wt. 206.33 g) of DCC was added and the reaction mixture was refluxed for 8 h at room temperature in basic condition with the addition of 2 mL (15 mmol, $C_6H_{15}N$) of triethylamine. The solution obtained was filtered off and the filtrate was kept for drying at room temperature to get N,N' -dicyclohexylcarbonyl-2-(thiophen-2-yl)acetamide. Single crystals suitable for X-ray diffraction study were obtained by a slow evaporation technique using methanol as a solvent.



Scheme 1. Scheme of N,N' -dicyclohexylcarbonyl-2-(thiophen-2-yl)acetamide.

Results and Discussion

FT-IR Spectral Analysis

Infrared spectra were recorded on a Perkin-Elmer spectrophotometer in the range $400\text{--}4000\text{ cm}^{-1}$. The FT-IR spectrum of the crystal structure is shown in Fig. 1. The peak at 3386 cm^{-1} is due to N-H stretching vibrations. The peaks observed at 1690 cm^{-1} and 1649 cm^{-1} correspond to C=O stretching. The peaks at 1452 cm^{-1} and 675 cm^{-1} are due to C-N and C-S stretching vibrations, respectively.

Single Crystal X-ray Diffraction

A yellow colored, prismatic single crystal of the synthesized compound with approximate dimensions of $0.23 \times 0.22 \times 0.21\text{ mm}$ was used for X-ray diffraction study. Data were collected on a Bruker CCD diffractometer equipped with $Cu\ K_\alpha$ radiation. Data reduction

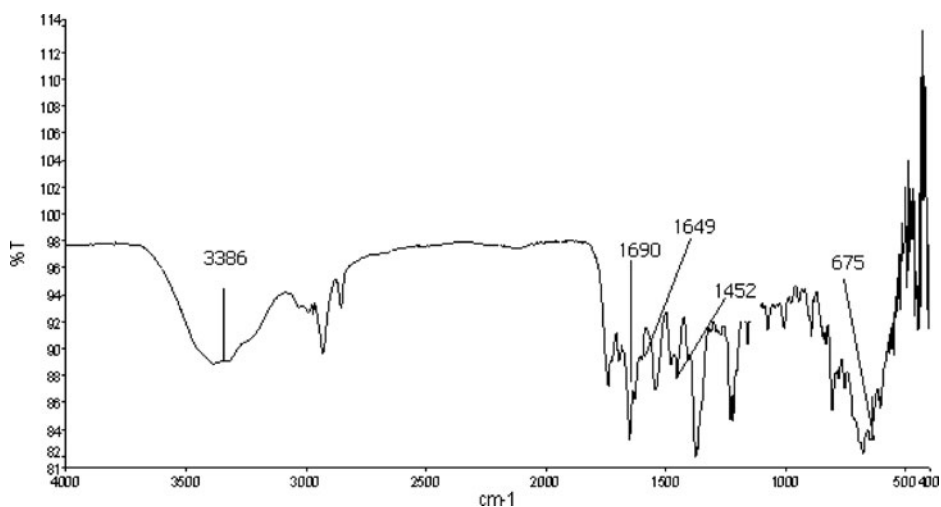


Figure 1. The FT-IR spectrum of the crystal structure.

Table 1. Crystal data and details of the structure determination

CCDC deposition number	988475
Formula	$C_{19}H_{28}N_2O_2S$
Formula weight	348.50
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 9.0969(3) \text{ \AA}$, $b = 18.3067(5) \text{ \AA}$, $c = 11.6499(3) \text{ \AA}$, $\beta = 103.876(2)^\circ$
Volume	$1883.49(10) \text{ \AA}^3$
Z	4
Calculated density	1.229 Mg m^{-3}
Absorption coefficient	1.625 mm^{-1}
$F_{(000)}$	752
Crystal size	$0.23 \times 0.22 \times 0.21 \text{ mm}$
Temperature	293 K
Radiation [CuK α]	1.54178 \AA
Theta range for data collection	$4.6^\circ - 64.4^\circ$
Limiting indices	$-4 \leq h \leq 10$, $-20 \leq k \leq 21$, $-13 \leq l \leq 13$
Reflections collected/unique	4176/3069 [$R(\text{int}) = 0.039$]
Observed data [$I > 2.0 \sigma(I)$]	2543
Data/restraints/parameter	3069/0/217
Goodness-of-fit on F^2	1.03
Final R indices [$I > 2 \sigma(I)$]	$R_1 = 0.0495$, $wR_2 = 0.1525$
Largest diff. peak and hole	0.28 and -0.42 e\AA^{-3}

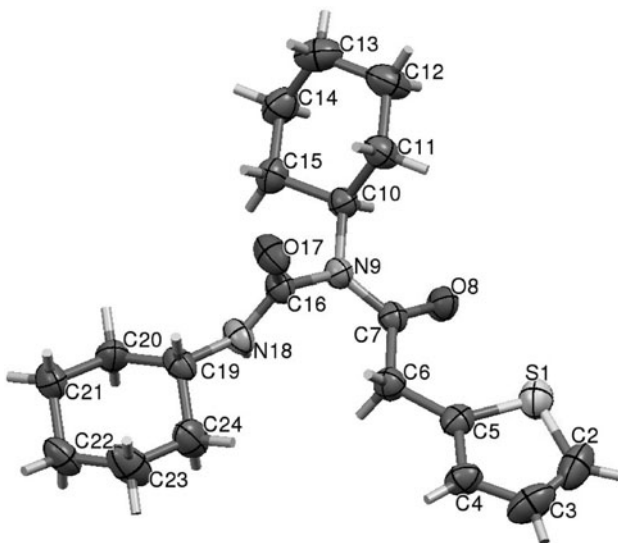


Figure 2. ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

of all the collected reflections and absorption corrections were carried out using the *APEX 2* package [4]. Crystal structure was solved by direct methods using *SHELXS-97* and was refined by full-matrix least squares refinement against F^2 using *SHELXL-97* [5]. All nonhydrogen atoms were refined anisotropically and hydrogen atoms were placed in chemically acceptable positions. Two hundred and seventeen parameters were refined with 3069 unique reflections which converged the residual to $R = 0.0495$. The bond lengths and bond angles values are within the expected range. The details of the crystal data and structure refinement are given in Table 1. Figure 2 shows the ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability. The geometrical calculations were carried out using *PLATON* [6]. The molecular and packing diagrams were generated using *Mercury* [7]. The bond distances, bond angles and torsion angles are listed in Table 2. Hydrogen-bond geometry is given in Table 3.

The 5-membered thiophene ring, S1–C2–C3–C4–C5 (ring 1) is sp^2 hybridized and is in planar conformation with a torsion angle of 0.24° . Both the cyclohexane rings, C10–C11–C12–C13–C14–C15 (ring 2) and C19–C20–C21–C22–C23–C24 (ring-3), are sp^3 hybridized. They are in chair conformation with a puckering amplitude $Q = 0.571(3)$ Å, $\theta = 3.3(3)^\circ$, $\varphi = 323(5)4^\circ$ and $Q = 0.583(3)$ Å, $\theta = 180.0(3)^\circ$, $\varphi = 237(9)^\circ$, respectively [8]. They are well described by the torsion angles 56.17° and 57.05° , respectively, which suggest that they adopt +synclinal conformations.

The torsion angle of $174.50(18)^\circ$ for N9–C16–N18–C19 shows the deviation of ring-3 (cyclohexane ring) from amide group. The bond distances of C=O (O8–C7 = $1.234(2)$ Å, O17–C16 = $1.216(3)$ Å) of amide groups agree with the distances found in the crystal structure of 1,3-dicyclohexyl-1-(4-nitrobenzoyl)urea [9]. The C–C bond length in thiophene ring (ring-1, C4–C5) is 1.408 Å. This is less than the corresponding value of 1.475 Å and greater than 1.383 Å reported for (2*Z*, 3*E*)-2,3-bis(2-thiylmethylene)-succinic acid methanol hemisolvate [10]. The structure exhibits intermolecular hydrogen bonds of the type N(18)–H(18) . . . O(8) and C(24)–H(24A) . . . O(17) whose symmetry codes are $I-x$, $I-y$, $-z$ and $-x$, $I-y$, $-z$, respectively. One can see that the molecules are interlinked by hydrogen bonds in Figs. 3, 4, and 5.

Table 2. Selected bond lengths (Å), angles (°), and torsion angles (°) of the compound

S(1)-C(2)	1.696(3)	C(10)-C(15)	1.519(3)
S(1)-C(5)	1.702(2)	O(17)-C(16)	1.216(3)
C(5)-C(6)	1.502(3)	C(19)-C(20)	1.521(3)
C(6)-C(7)	1.515(3)	O(8)-C(7)	1.234(2)
C(19)-C(24)	1.509(3)	C(4)-C(5)	1.408(3)
C(20)-C(21)	1.518(4)	C(3)-C(4)	1.388(4)
C(21)-C(22)	1.527(3)	C(2)-C(3)	1.332(5)
C(10)-C(11)	1.512(3)	C(23)-C(24)	1.524(5)
Selected bond angles (°)			
C2-S1-C5	92.58(14)	C10-C11-C12	110.19(19)
C3-C2-S1	111.9(2)	C13-C12-C11	111.8(2)
C2-C3-C4	114.0(3)	C14-C13-C12	111.7(2)
C3-C4-C5	111.8(2)	C13-C14-C15	111.5(2)
C4-C5-C6	123.6(2)	C10-C15-C14	109.23(19)
C4-C5-S1	109.69(17)	O17-C16-N18	126.2(2)
C6-C5-S1	126.66(17)	O17-C16-N9	120.67(19)
C5-C6-C7	117.10(19)	N18-C16-N9	113.13(19)
O8-C7-N9	121.20(18)	C16-N18-C19	122.82(18)
Selected torsion angles (°)			
C(3)-C(4)-C(5)-C(6)	178.0(2)		
S(1)-C(5)-C(6)-C(7)	-7.8(3)		
C(4)-C(5)-C(6)-C(7)	175.0(2)		
C(5)-C(6)-C(7)-O(8)	21.8(3)		
C(5)-C(6)-C(7)-N(9)	159.23(19)		
O(8)-C(7)-N(9)-C(10)	-9.1(3)		
O(8)-C(7)-N(9)-C(16)	-179.06(18)		
C(6)-C(7)-N(9)-C(10)	171.94(18)		
C(6)-C(7)-N(9)-C(16)	1.9(3)		
C(11)-C(10)-N(9)-C(7)	-82.5(2)		
C(11)-C(10)-N(9)-C(16)	88.0(2)		
C(15)-C(10)-N(9)-C(7)	151.60(19)		
C(15)-C(10)-N(9)-C(16)	-37.9(2)		
N(9)-C(10)-C(11)-C(12)	177.2(2)		
C(15)-C(10)-C(11)-C(12)	-57.0(3)		
N(9)-C(10)-C(15)-C(14)	-175.67(18)		
C(11)-C(10)-C(15)-C(14)	58.3(3)		
C(10)-C(11)-C(12)-C(13)	54.1(3)		
C(19)-C(20)-C(21)-C(22)	-58.1(3)		
C(22)-C(23)-C(24)-C(19)	56.2(3)		

Hirshfeld Surface Analysis

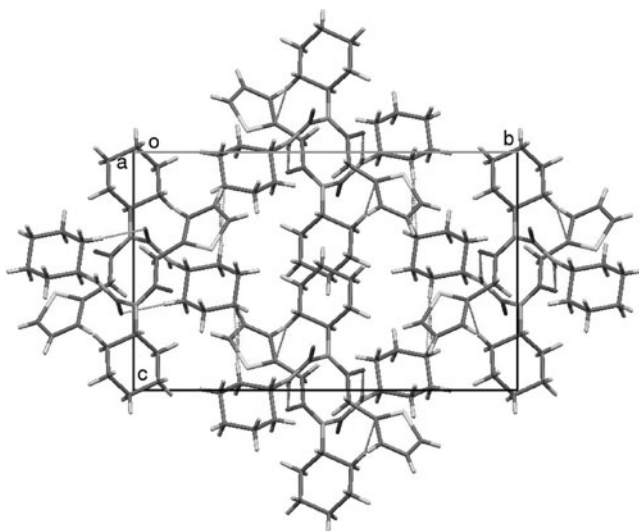
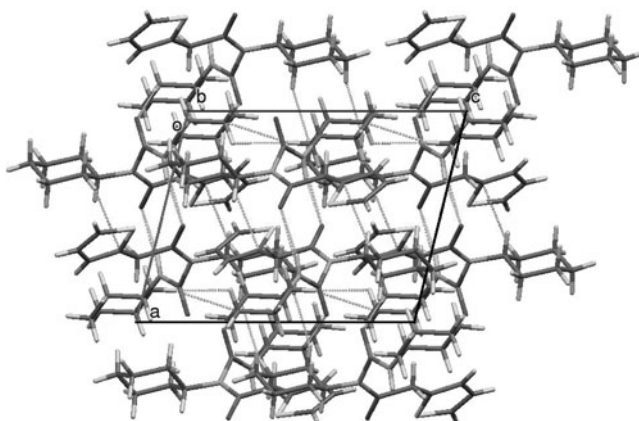
Hirshfeld surfaces and the associated 2D-fingerprint plots were calculated using Crystal-Explorer [11]. Hirshfeld surface analysis of a crystal structure is an approach wherein internuclear distances and angles, crystal packing diagrams are studied extensively [12].

Table 3. Hydrogen bond geometry [\AA , $^\circ$]

D–H... A	D–H	H... A	D... A	D–H... A
N(18)–H(18)..O(8) ^(a)	0.86	2.15	2.993(2)	168
C(10)–H(10)..O(8)*	0.98	2.40	2.740(3)	100
C(19)–H(19)..O(17)*	0.98	2.44	2.849(3)	105
C(24)–H(24A)..O(17) ^(b)	0.97	2.51	3.460(3)	165

*Intramolecular hydrogen bond interactions.

Note: Symmetry codes: (a) $1-x, 1-y, -z$; (b) $-x, 1-y, -z$.

**Figure 3.** Packing of molecules when viewed down *a*-axis.**Figure 4.** Packing of molecules when viewed down *b*-axis.

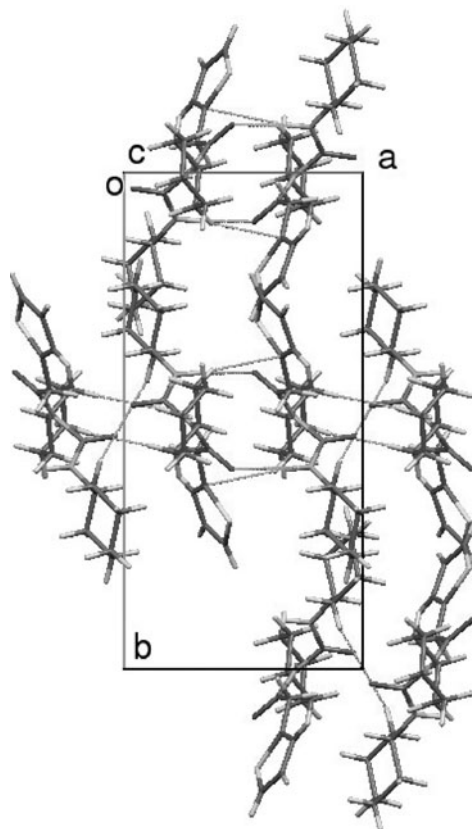


Figure 5. Packing of molecules when viewed down *c*-axis.

Table 4 shows the contributions of various intermolecular contacts to the Hirshfeld surface. The highest contributor is H...H, which is 69.1% and least is 0.3% for H...N.

Figure 6 shows surface that has been mapped over a d_{norm} . The dominant interactions between amine N–H and carbonyl O atoms can be seen in the Hirshfeld surfaces as the bright red areas.

Figure 7 shows the fingerprint plots. Figure 7a shows H...H (69.1%) contribution of intercontact to the Hirshfeld surfaces. Features along the diagonal occur due to H...H contacts. Figures 7b, 6c, and d show the intercontacts H...O (13.8%), H...C (8.3%),

Table 4. Hirshfeld surface: Percentage of various intermolecular contacts contributed to the Hirshfeld surface

Inter-contacts	Contribution (%)
H–H	69.1
H–O	13.8
H–C	8.3
H–S	8.2

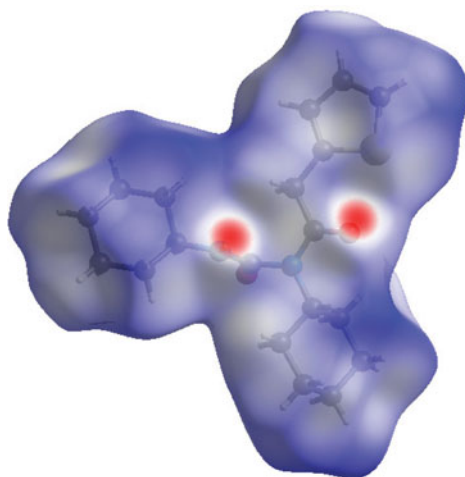


Figure 6. Hirshfeld surfaces mapped with d_{norm} for the visualization of the compound.

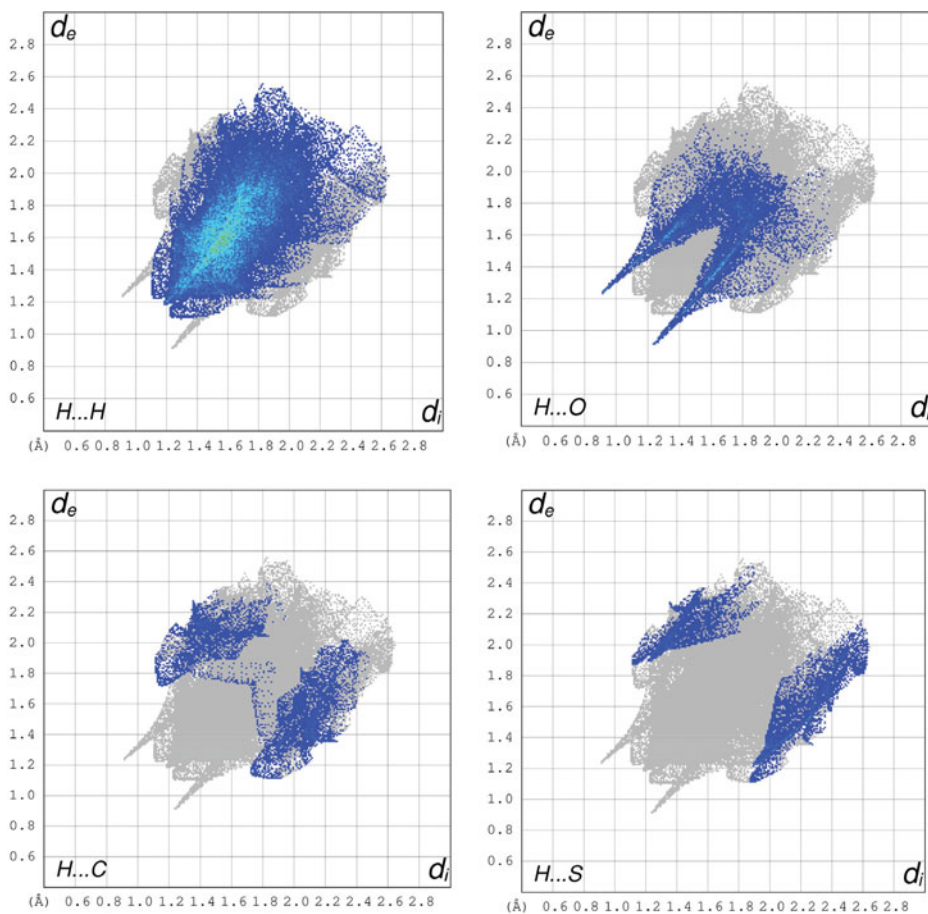


Figure 7. Fingerprint plots of the compound, (a) H... H, (b) H... O, (c) H... C, (d) H... S, showing the percentage contribution of the contacts to the total Hirshfeld surface area for the molecule.

and H... S (8.2%), respectively. The blue points on the plot indicate the contributions to the surface [13].

Acknowledgment

Authors are thankful to IOE, Vijnana Bhavan, University of Mysore, Mysore for providing the single-crystal X-ray diffraction facility.

Funding

N. Latha Rani is thankful to the UGC, New Delhi, for RFSMS fellowship.

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