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Crystal Structure, Hirshfeld Surface Analysis, Energy Frameworks and DFT Studies of 1-methylindoline-2, 3-Dione

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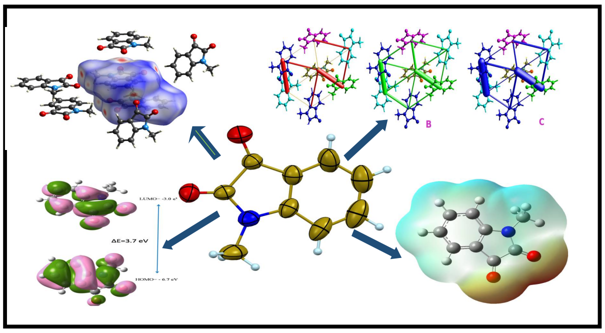
ABSTRACT

Isatin derivative, 1-methylindoline-2,3-dione single crystals were grown by slow evaporation method using methanol solvent and the structure was determined by single crystal X-ray diffraction. The title compound is crystallized in the monoclinic space group $P2_1/c$*, which exhibits various intra and intermolecular hydrogen bond interactions along with C-H…Cg and Cg…Cg interactions. Intermolecular hydrogen bond interactions C9A-H2B...O2B and C4A-H16…O1B combines to form supramolecular ring motif* $R_2^2(11)$ *along crystallographic ab plane. Hirshfeld surface analysis revealed that C-H…O(30.4%), H…H(25%) and C-H(18%) interactions are dominantly contribute in the crystal packing leading to the structural stability. Further the coordinates were optimized by DFT calculations with basis set of 6-311+G(d,p).The optimized structural parameters showed very good correlation with those determined by XRD method. The Mulliken charge, molecular electrostatic potential map, frontier molecular orbitals were investigated and the HOMO and LUMO energy gap was found to be 3.7 eV. The interaction energies were also calculated and energy frames were explored using Crystal Explorer, which confirm that the dispersion energy framework is dominant over the electrostatic energy frameworks.*

Graphical Abstract



Keywords: Crystal structure, Hirshfeld surface, Energy frameworks, DFT calculation.

INTRODUCTION

Heterocyclic compounds play an important role in medicinal and pharmaceutical field. 1-methylindoline-2,3-dione, isatin derivative is an important class of indole derivative. These are very useful precursor for the synthesis of variety of heterocyclic compounds which gained more attention of chemist. There are several methods to synthesize isatin derivatives for its versatile applications [**1**]. Isatin was first identified by Erdmann and Laurent in 1840 as a product in the oxidation of indigo carmine [**2**]. Isatin is an endogenous compound was also identified in humans, which possesses a wide range of biological activities [**3**], such as antimicrobial, antianalesgic, anti-inflammatory, anticonvulsant [**4**], anticancer activities [**5**]. In addition, isatin is a core constituent of many alkaloids, drugs, dyes, pesticides and analytical reagents [**6**]. The isatin and their Schiff bases show high affinity towards transition metals lead to broad spectrum of applications [**7**].

In view of the significant interest of isatin derivatives, 1-methylindoline-2,3-dione was crystallized and determined its crystal structure. In addition, Hirshfeld surface analysis and DFT studies were also carried out to explore extensive intermolecular interactions and chemical parameters. Further, interaction energy frameworks including electrostatic, polarizability, dispersion and repulsion energies were calculated and compared.

MATERIALS AND METHODS

Suitable single crystals of the isatin derivative compound were grown in the room temperature by slow evaporation method using methanol solvent.

Crystallographic studies: Single crystals of title compound with suitable dimensions were used for X-ray intensity data collection. Diffraction intensities were collected on a RigakuXtaLAB mini CCD diffractometer with Mo-Kα (λ = 0.71073 Å) radiation source and X-ray generator operating at 50 kV and 12 mA, keeping the scan width of 0.5°, exposure time of 3 s and the sample to detector distance of 50 mm. A complete data set was processed using *CRYSTALCLEAR* [**8**]. The structure was solved by direct method using *SHELXS* program and all the coordinates were refined with *SHELXL* [**9**] refinement package using least squares minimization. The geometrical calculations were carried out using *PLATON* [**10**] and diagrams were generated using *MERCURY* [**11**]. The crystal data and the structure refinement details are given in table 1.

Table 1. Crystal data and structure refinement details of the isatin derivative compound

Parameter	Value	Parameter	Value
Empirical formula	$C_{18}H_{14}N_2O_4$	Absorption coefficient	0.100 mm^{-1}
Formula weight	161.16	F_{000}	672
Temperature	293 K	θ range for data collection	3.14° to 27.48°
Wavelength	0.71073Å	Index ranges	$-10 \le h \le 10$
Crystal system	Monoclinic		$-13 \le k \le 10$
Space group	$P2_1/c$		$-22 \le l \le 13$
Cell dimensions		Reflections collected	6712
a	8.329(1) Å	Independent reflections	3344 [R_{int} = 0.0469]
b	10.779(1) Å	Refinement method	Full matrix least-squares on F^2
c	17.63(3) Å	Data / restraints / parameters	3344 / 0 / 219
β	103.32(1)°		
Volume	1540(4) $Å^3$	Goodness-of-fit on F^2	1.047
Z	8	Final [$I>2\sigma(I)$]	$R1$ = 0.050, $wR2$ = 0.1368
Density(calculated)	1.390 Mg m^{-3}	*R* indices (all data)	$R1$ = 0.0663, $wR2$ = 0.1527

Hirshfeld surface analysis: The Hirshfeld surface were generated for the isatin derivative compound using a high surface resolution and mapped with the d_{norm} of shape index functions 2D fingerprint plots and energy frameworks were constructed using *Crystal Explorer* [**12, 13, 14**].

DFT studies: The coordinates were optimized for the isatin derivative compound in gas phase using density functional theory (DFT) with B3LYP hybrid functional at 6-311+G (d,p) level basis set [15-17]. The Mulliken charges, Kohn-Sham molecular orbitals, their energy gap the related global and local indexes (electro negativity, chemical potential, hardness, softness, electrophilicity) were estimated with Koopman's approximation.

RESULTS AND DISCUSSION

Crystal structure of 1-methyl-1H-pyrrole-2,3-dione: In the figure 1 emphasize the *ORTEP* of 1-methyl-1H-pyrrole-2,3-dione which is crystallizes as centrosymmetric dimer, in the monoclinic crystal system with the space group $P2_1/c$. The molecular structure of the title compound is highly planar, evidenced by the dihedral angles of 1.2(3)° between oxygen substituted pyrrole and benzene ring and 1.0(3)° between methyl moiety and benzene ring. The carbon atoms in the pyrrole attached benzene ring are sp^2 hybridized with an average bond separation of 1.38 Å (Table 2).

Crystal structure of the 1-methyl-1H-pyrrole-2,3-dione is stabilized by several types of inter and intramolecular interactions followed by C-H... π and Cg-Cg interactions. Inter molecular hydrogen bond interaction of type C9A-H2B...O2B (donor acceptor distance 2.44 Å, C-H...O angle 135° and symmetry code 1-*x*,1/2+*y*,3/2-*z*) significantly contribute in the crystal packing by forming supramolecular ring motif $R_2^2(11)$ where as C2A-H14...O2A (donor acceptor distance 2.55 Å, C-H...O angle 153° and symmetry code 1-*x*,2-*y*,1-*z*) hydrogen bond interaction engage in connecting those motif to plate the twisted chain along crystallographic *b*-axis (Fig. 2). Apart from these interactions, inter dimer short interactions between adjacent oxygen and carbon atoms of pyrrole rings with an average distance of 3.1 Å (Fig. 3a) play a vital role in stabilization of the crystal structure. These two interactions combined with intermolecular hydrogen bond interactions lead to the zig-zag molecular grid chains (Fig. 3b).

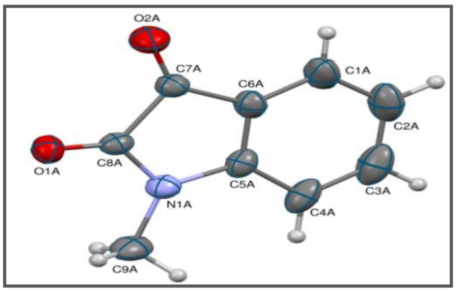


Figure 1. ORTEP of isatin derivative compound with thermal ellipsoid is drawn at 30% probability.

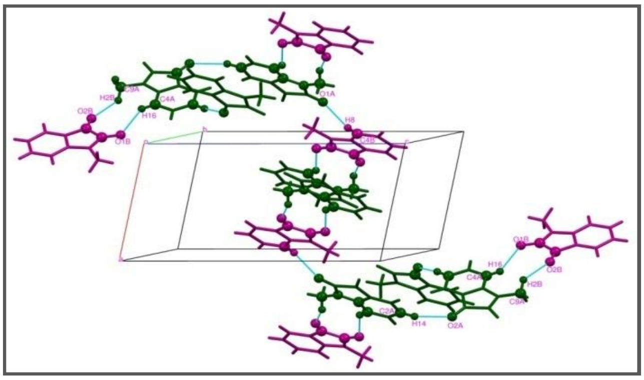


Figure 2. Intermolecular hydrogen bond interaction between adjacent molecules forming twisted molecular chain along *b*-axis.

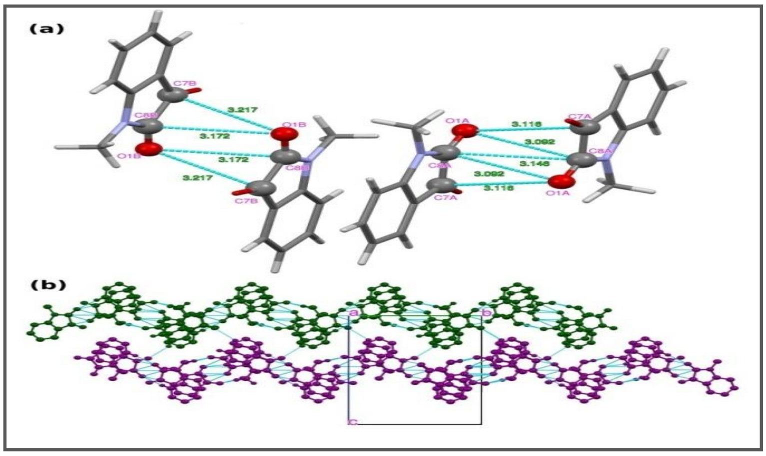


Figure 3. (a) Inter molecular short interactions between adjacent oxygen and carbon atoms of pyrrole rings and (b) Zig-zag molecular grid packing of title compound along *a*-axis.

Structural stability of title compound is also promoted by inter molecular C8A-O1A...Cg1 (where Cg1 is the centroid of the ring N1A/C5A/C6A/C7A/C8A, with a symmetry code 1-*x*,1-*y*,1-*z* having O–Cg distance of 3.141(6) Å and C–O…Cg angle of 104.15^o) and C8B-O1B...Cg4 (where Cg4 is the centroid of the ring N1B/C5B/C6B/C7B/C8B, with a symmetry code -*x*,2-*y*,1-*z* having O–Cg distance of 3.431(6) Å and C–O…Cg angle of 112.51^o) interactions between oxygen atom and π-system of adjacent inter dimer pyrrole rings (Fig. 4a). The molecular structure also exhibits Cg...Cg interaction between adjacent pyrrole rings (Cg1...Cg4 with centroid to centroid distance of 3.57 Å) and π-system of the same pyrrole ring interact with the centroid of benzene ring with an aromatic-aromatic distance of 3.870 Å (Fig. 4b).

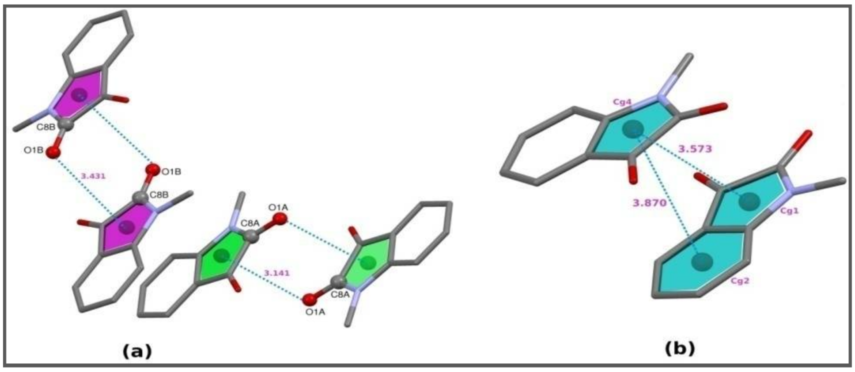


Figure 4. (a) C-O... π and (b) π-π stacking interactions of the isatin derivative compound.

Hirshfeld surface analysis: Three dimensional Hirshfeld surfaces mapped on $d_{norm,}$ shape index and curvedness are illustrated in figure 5. The deep red circular spots on the Hirshfeld surfaces mapped with d_{norm} indicate intermolecular hydrogen bond interactions and the relatively small red dots on the surfaces represent the C–O…Cg and Cg...Cg intermolecular interactions. Two dimensional fingerprint plots of the title compound are shown in figure 6. C-H... O intermolecular interactions (30.4 %) appeared as two sharp spikes in the upper and lower left of the 2D fingerprint plot have significant contribution to the total Hirshfeld surfaces, whereas H... H interactions which are reflected by single sharp peak between C-H... O spikes have relatively significant contribution (25.3 %) to the total Hirshfeld surfaces. C-H/H-C interactions viewed as sharp wings in the upper and lower middle of the 2D fingerprint plot comprised of 18% and C-O/O-C interactions appeared in middle of the 2D fingerprint plot comprised of 12.9%. Apart from these interactions C-C (9.8%), N-H (1.5%) is also observed in the total Hirshfeld surfaces (Fig 6).

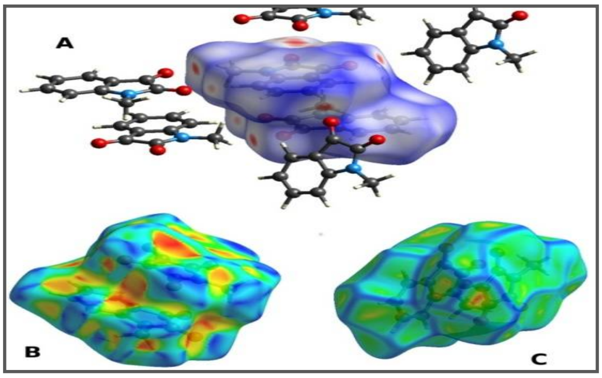


Figure 5. (a) d_{norm}, (b) shape index and (c) curvedness mapped on Hirshfeld surface for visualizing the intermolecular contacts.

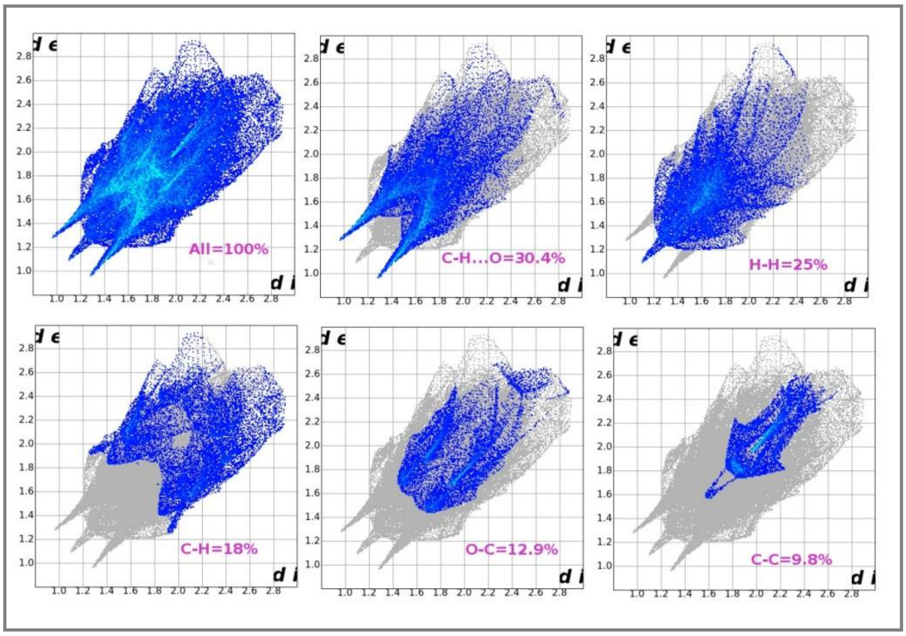


Figure 6. Two dimensional fingerprint plots indicate the major contributions of intermolecular interactions in the isatin derivative compound.

Energy frameworks: Molecular packing in the crystal is envisaged and examined using energy frameworks [18]. The interaction energies for the isatin derivative compound were calculated and the values are tabulated in table 2 and 3. D-topology of the predominant interactions in molecular packing were generated and are visualized in figure 7. The molecular pair-wise interaction energies, electrostatic (E_{ele}=-26.63 kJ mol^{-1}), polarization (E_{pol}=-7.84 kJ mol^{-1}), dispersion (E_{dis}=-47.73 kJ mol^{-1}), repulsion (E_{rep}=23.11 kJ mol^{-1}), total interaction energy (E_{tot}=-59.5 kJ mol^{-1}) are calculated. Energy frameworks are constructed for these calculated interaction energies which confirms that dispersion energy is dominated over the electrostatic energy of the title compound.

Table 2. Molecular interaction energies (centroid distances R in Å, interaction energies in kJ mol^{-1})

S.No.	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_re	E_tot
1	*-x, -y, -z*	9.02	B3LYP/6-31G(d,p)	3.6	-0.5	-0.8	0.0	2.7
2	*x, -y+1/2, z+1/2*	10.68	B3LYP/6-31G(d,p)	-2.0	-0.1	-0.5	0.0	-2.6
1	*-x, -y, -z*	5.21	B3LYP/6-31G(d,p)	-22.8	-6.4	-28.7	23.1	-39.6
2	*x, -y+1/2, z+1/2*	8.87	B3LYP/6-31G(d,p)	1.0	-0.7	-6.2	2.6	-3.3
2	*-x, y+1/2, -z+1/2*	8.14	B3LYP/6-31G(d,p)	-6.8	-1.7	-6.1	7.0	-9.4
1	*-x, -y, -z*	6.92	B3LYP/6-31G(d,p)	1.8	-1.2	-12.5	4.7	-7.0

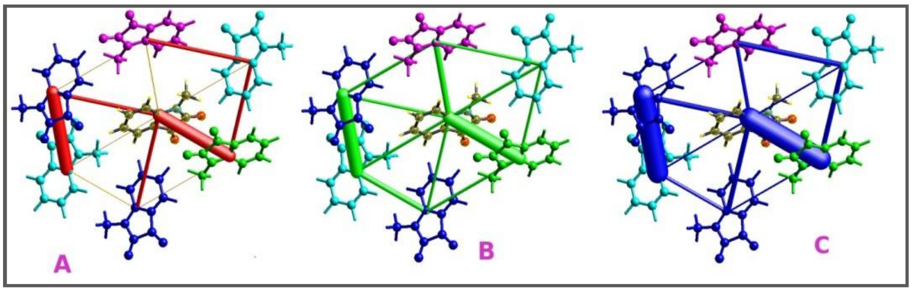


Figure 7. Energy-framework diagrams of the isatin derivative compound for E_{ele} (A), E_{dis}(B) and E_{tot}(C). All diagrams use the same cylinder scale of 200 for energies.

Density functional theory studies: The molecular structure of the isatin derivative compound was optimized by DFT calculations using B3LYP hybrid functional with 6-311+G(d,p) basis sets. In the table 3 anticipate the comparison between selected bond lengths, bond angles and torsion angles with those resulted from XRD studies. Optimized geometrical structure is in good agreement with the determined XRD structure, confirmed by the correlation coefficients. The frontier molecular orbitals and molecular electrostatic potential map (MEP) were generated for the title compound (Fig.8). The HOMO-LUMO energy gap calculated by DFT calculations is 3.7 eV. Further the Mulliken charges were calculated for the compounds show that the Mulliken charges on C6 and C5 is 1.546 and -0.907 in title compound.

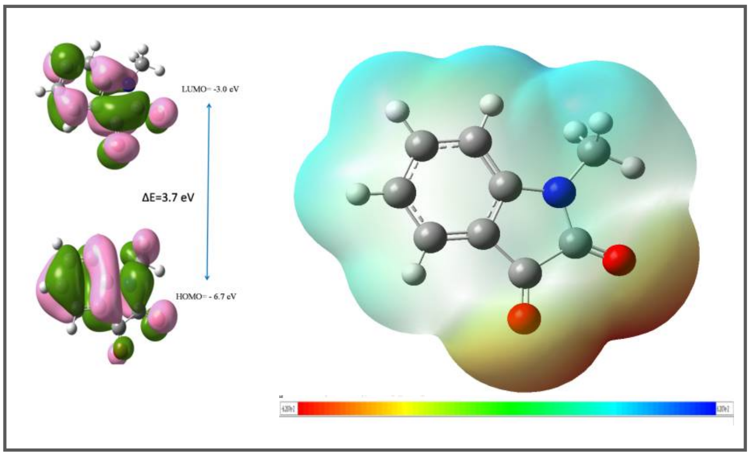


Figure 8. Frontier molecular orbitals and MEP surface of the isatin derivative compound.

Table 3. Selected experimentally and theoretically determined bond lengths, angles and torsion angles

Bond lengths (Å)			Bond Angles (°)			Torsion Angles (°)		
Atoms	**XRD**	**DFT**	**Atoms**	**XRD**	**DFT**	**Atoms**	**XRD**	**DFT**
O1-C8	1.1962	1.2059	C8-N1-C5	110.79	111.12	C5-N1-C8-O1	-179.2	179.98
N1-C8	1.3620	1.3856	C8- N1-C9	121.76	123.76	C9-N1-C8-C7	-178.69	-179.94
N1-C5	1.4127	1.4054	C5-N1- C9	127.41	125.11	C8-N1-C5-C4	179.51	-180.00
N1-C9	1.4702	1.4505	C8- C7- C6	104.51	104.70	C6-C7-C8-O1	179.00	-179.98
C7-C8	1.5691	1.5713	C8- C7-O2	121.91	124.53	O2-C7-C8-N1	-178.28	-179.98
C7-C6	1.4780	1.4706	C6- C7-O2	133.56	130.77	C8-C7-C6-C5	-0.06	-0.01
C7-O2	1.1907	1.2042	O1- C8-N1	127.18	126.89	C8 -C7-C6-C1	179.89	179.99
C5-C6	1.3576	1.4080	O1- C8-C7	127.58	127.53	O2-C7-C6-C5	178.39	179.99
C5-C4	1.3785	1.3882	N1- C8-C7	105.23	105.59	N1-C5-C6-C7	-0.3	0
C6-C1	1.3705	1.3886	N1- C5-C6	112.24	110.99	N1-C5-C6-C1	179.74	-180
C4-C3	1.3770	1.4011	N1- C5-C4	124.60	128.15	C4-C5-C6 -C7	-179.22	-179.99
C2-C1	1.3684	1.3963	C6-C5-C4	123.15	120.86	N1-C5-C4-C3	-179.78	180.00
C2-C3	1.4330	1.3970	C7- C6- C5	107.23	107.60	C7-C6-C1-C2	179.43	179.99
Correlation coefficient		0.9799	Correlation coefficient		0.9769	Correlation coefficient		0.9999

Table 4. The energy values and global reactive descriptors of the compound

Parameter	Value
E_{HOMO} (eV)	-6.7
E_{LUMO} (eV)	-3.0
ΔE (eV)	3.7
Electronegativity (χ) (eV)	4.9
Chemical Potential (μ) (eV)	-4.9
Global hardness (η) (eV)	1.9
Global softness (s) (eV-1)	0.5
Electrophilicity index (ω) (eV)	6.3

APPLICATION

In this study, isatin derivative compound, 1-methylindoline-2,3-dione is very useful for the optimum crystal growth of desired product and to synthesize a core constituent of many alkaloids, drugs, dyes, pesticides and analytical reagents. This isatin derivative compound is beneficial for human health, which possesses a wide range of biological activities, antimicrobial, antianalesgic, antiinflammatory, anticonvulsant and anticancer activities.

CONCLUSION

Isatin derivative compound,1-methylindoline-2,3-dione has been crystallized by slow evaporation method and single crystal structure was elucidated by X-ray diffraction technique. The crystal structure is stabilized by several intra and intermolecular interactions. Inter dimer hydrogen bond interactions promote the formation of supramolecular synthon $R_2^2(11)$, which strengthen the molecular packing. These intermolecular interactions are evidenced by Hirshfeld surface analysis, C-H…O and H…H interactions showed significant contribution to the total Hirshfeld surfaces. The structures of the title compound were optimized using density functional theory calculations. Excellent correlation coefficients were obtained between the optimized geometrical parameters and their counterparts from XRD studies. The 3D-topology of the crystal packing is analyzed and visualized in terms of electrostatic (E_{ele}), dispersion (E_{dis}) and total energies (E_{tot}). The average total interaction energy found to be -59.5 kJ mol^{-1}. Energy framework calculations conclude that the contribution of dispersion energy is greater than the electrostatic energy for the crystal packing.

ACKNOWLEDGEMENTS

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