# ORIGINAL PAPER

# Quantitative Evaluation of C–H…O and C–H… $\pi$ Intermolecular Interactions in Ethyl-3-benzyl-1-methyl-2-oxoindoline-3carboxylate and 3-Methyl-but-2-en-1-yl-1,3-dimethyl-2oxoindoline-3-carboxylate: Insights from PIXEL and Hirshfeld Analysis

Dhananjay Dey · Santanu Ghosh · Deepak Chopra

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Abstract The X-ray crystallographic structures of two biologically active molecules, namely  $(\pm)$ -ethyl-3-benzyl-1methyl-2-oxoindoline-3-carboxylate (I) and  $(\pm)$ -3-methylbut-2-en-1-yl-1,3-dimethyl-2-oxoindoline-3-carboxylate (II) have been investigated based on the molecular conformation and supramolecular packing of the molecules in the solid state. These two structures assemble via C-H···O=C and C- $H \cdots \pi$  intermolecular interactions which contribute towards the stability of the crystal packing. In order to gain quantitative insights into the nature of non-covalent interaction between different molecules the interaction energy of the molecular pairs obtained after analysis of the crystal structures for both the molecules has been performed by using the PIXEL approach along with high level DFT+Disp calculations. Hirshfeld surface analysis and the associated fingerprint plots provide rapid quantitative insight into the intermolecular interactions in molecular solids. This article provides support to the fact that every molecule can be explored in detail for an understanding of its solid state structure via experimental and computational tools in crystal engineering.

**Keywords** Indoline carboxylates · Hydrogen bonds · PIXEL · Hirshfeld analysis

#### Introduction

Oxindole [1] has a wide range of applications and exhibits biological activities consisting of antibacterial [2], anticancer

D. Dey  $\cdot$  S. Ghosh  $\cdot$  D. Chopra ( $\boxtimes$ )

Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal, ITI (Gas Rahat) Building, Bhopal 462 023, MP, India e-mail: dchopra@iiserbhopal.ac.in [3], anti-inflammatory [4, 5], antihypertensive [6] and anticonvulsant activities [7]. Oxindole's derivatives are used to inhibit the replication of HIV and combat the infections that are caused by drug-resistance, drug-sensitive, and mutant strains of HIV [8]. Because of such important applications of this class of compounds in synthetic organic chemistry and medicinal chemistry, we have analyzed the crystal structure of these title compounds by single crystal X-ray diffraction and also subsequently explored their crystal packing and molecular conformation in both the solid state and compared with the geometry in the gas phase. PIXEL calculations were performed in order to estimate the nature and energies associated with the intermolecular interactions in the crystal lattice. The total lattice energy is divided into the corresponding coulombic, polarization, dispersion and repulsion energies [9]. All the molecular pairs involved in the crystal packing, were extracted and their energies were determined from PIXEL and finally compared with the values obtained from high level DFT+Disp calculations at the crystal geometry with BSSE [10] corrections. Hirshfeld surfaces [11] mapped with d<sub>norm</sub> using a red-white-blue color scheme, where red is used to indicate the shorter contacts, white is used for contacts around the vdW separation, and blue is for longer contacts along with the fingerprint plots [12] have been studied to evaluate the contribution of the individual types of interaction within the crystal structures. Hirshfeld surface and fingerprint plots of the title compounds also provide the essential similarities and differences between the two compounds.

# Experimental

Synthesis and crystallization

The detailed synthetic procedure for these two compounds has already been reported in the literature [13]. Scheme 1

Scheme 1 Synthetic route for the preparation of the target compounds



outlines the final step necessary for the synthesis of the two compounds of interest. Single crystals of these compounds were grown by the slow evaporation method from EtOAc+hexane solvent system at low temperature.

## X-Ray Crystallography

X-ray diffraction datasets were collected on a three circle Bruker APEX-II diffractometer equipped with a CCD area detector using Mo-K $\alpha$  radiation ( $\lambda = 0.71073$  Å) in  $\phi$  and  $\omega$  scan modes. The crystal structures were solved by direct methods using SIR92 [14] and refined by the full matrix least squares method using SHELXL97 [15] present in the program suit WinGX [16]. Empirical absorption correction was applied using SADABS [17]. The non-hydrogen atoms are refined anisotropically and the hydrogen atoms bonded to C atoms were positioned geometrically and refined using a riding model with  $U_{iso}$  (H) =  $1.2U_{eq}(C)$  for aromatic hydrogen and the hydrogen atoms connected to double bond and  $U_{iso}(H) = 1.5U_{eq}(C)$  for hydrogen atoms of the methyl and ethyl group. The molecular connectivity was drawn using ORTEP32 [18] and the crystal packing diagrams were generated using Mercury (CCDC) program [19]. Geometrical calculations were done using PARST [20] and PLATON [21]. The geometrical restrictions placed on the intermolecular H-bonds are the sum of the van der Waals radii +0.4 Å and the directionality is greater than 110° [22]. The details of the crystal data, data collection and structure refinements are shown in Table 1. Hirshfeld surfaces and the associated 2D-fingerprint plots were generated using Crystal Explorer 3.0 [23].

#### Crystallographic Modeling of Disorder

The crystal structure of compound II (containing two molecules in the asymmetric unit) at room temperature (298 K) exhibits a short  $C28(sp^3)$ – $C29(sp^2)$  bond (of distance 1.29 Å). The ideal value is 1.52 Å (default) [24]. This shortening of the bond distance is mainly due to the positional disorder of an atom over two sites. The dynamic disorder has been

Table 1 Data collection and structure refinement in I and II

Data	Ι	II
Formula	C <sub>19</sub> H <sub>19</sub> NO <sub>3</sub>	C <sub>16</sub> H <sub>19</sub> NO <sub>3</sub>
Formula weight	309.35	273.32
Wavelength (Å)	0.71073	0.71073
Solvent system	Ethylacetate + hexane	Ethylacetate + hexane
CCDC no.	941352	941353
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/n$	$Pn2_1a$
a (Å)	13.4007 (3)	17.8207 (10)
<i>b</i> (Å)	8.7952 (2)	18.3624 (8)
<i>c</i> (Å)	15.5729 (4)	9.1595 (5)
α, β, γ (°)	90, 114.1170 (10), 90	90, 90, 90
$V(\text{\AA}^3)$	1675.24 (7)	2997.3 (3)
Z	4	8
Density (g cm <sup>-3</sup> )	1.227	1.211
$\mu (mm^{-1})$	0.083	0.084
F (000)	656	1168
$\theta$ (min, max)	2.60, 27.47	2.22, 27.60
Treatment of Hydrogens	Fixed	Fixed
h <sub>min, max</sub> , k <sub>min, max</sub> , l <sub>min, max</sub>	(-17, 17), (-11, 11), (-20, 19)	(-23, 20), (-23, 23), (-11, 6)
No. of ref.	14,290	13,693
No. unique ref./ obs. ref.	3,823, 2,889	5,808, 3,335
No. of parameters	208	384
R_all, R_obs	0.0579, 0.0435	0.1182, 0.0641
wR <sub>2</sub> _all, wR <sub>2</sub> _obs	0.1274, 0.1171	0.1882, 0.1595
$\Delta\rho_{min,\ max}(e \mathring{A}^{-3})$	-0.167, 0.128	-0.165, 0.200
G. o. F.	1.056	1.004

modelled using the PART instruction by splitting the atom into two independent positions, namely C28A & C28B and C29A & C29B ('A' contains the higher occupancy for that atom). The final bond distance value refines to 1.503(7) Å. The anisotropic displacement parameter for these two sites is fixed using EADP. For equivalent bond distances, the restraints SADI and DFIX have been used. Similar treatment has been performed for the atoms C31 and C32. These have also been split up into C31A & C31B and C32A & C32B respectively. The bond distances C30–C31A and C30–C32A are 1.461(9) and 1.456(10) Å respectively.

#### Theoretical Calculations

All theoretical calculations have been performed taking the major conformer for the second molecule (subsequently referred as B), out of the two molecules in the asymmetric unit, the first molecule (referred to as A) exhibiting no positional disorder. The geometrical optimization of the molecule was performed at the B3LYP/6-31G\*\* level of calculation at the crystal geometry using TURBOMOLE [25]. The atomic coordinates of the optimized geometry were visualized with Mercury software. The selected torsion angles of compound I and II obtained from theoretical calculations (following geometrical optimization) were then compared with the experimentally obtained values. DFT+Disp calculations were done with the functional B97-D using a higher basis set aug-cc-pVTZ in TURBO-MOLE. The lattice energies of these crystal structures have been calculated by PIXEL using the Coulomb-London-Pauli (CLP) model of intermolecular coulombic, polarization, dispersion and repulsion energies. Furthermore, high level DFT+Disp quantum mechanical calculations for comparison with the pairing energies obtained from PIXEL method have been performed.

## **Results and Discussion**

Compound I (Fig. 1a) crystallizes in a centrosymmetric monoclinic space group  $P2_1/n$  with one molecule in the asymmetric unit, thus having Z = 4 whereas II (Fig. 1b and c) crystallizes in a non-centrosymmetric orthorhombic space group  $Pn2_1a$  with two molecules in the asymmetric unit, having Z = 8. The *N*-methyl 2-oxindole moiety is a common skeleton for both the molecules which are chemically and crystallographically different. In compound I, one benzyl group and ethyl ester group are connected with the carbon atom, C15, but in case of II, one methyl group and one dimethylallyl ester group are attached with C9 & C25 respectively for the molecule A and B respectively.

To gain insights into conformational differences in these molecules in the solid state, overlay diagrams are shown in Fig. 2 wherein the 2-oxindole moiety is superimposed. In case of compound I, C14–C15–C16–O2 torsion varies by  $8^{\circ}$  (Fig. 2a). In Fig. 2b and c, the conformation of molecule I is compared by overlapping with the molecular

conformation of both the molecules (IIA and IIB) separately as is present in the asymmetric unit of II. Overlay diagram between molecules IIA and IIB shows that although these two molecules are chemically same, but their configurations are different and of an opposite nature. The molecule IIB exhibits dynamic disorder in the crystal. Before modeling the disorder, the bond distance C28-C29 was 1.291(8) Å and after the crystallographic treatment for disorder, the bond distance C28A-C29A and C28B-C29B refined to a value of 1.507(8) and 1.483(14) Å, these values are closely related to those obtained from the geometrical optimization of the molecule. Furthermore, a comparison of the torsions C27-O6-C28-C29 and O6-C28-C29-C30 obtained from experimental data and a comparison with the theoretical values reveals changes in magnitude of 37.4° and 19.9° respectively. Table 2 and 3 list some selected torsion angles and bond angles for the compounds I and II.

Table 4 lists all the geometrically relevant intermolecular hydrogen bonds presented in the title compounds. In molecule I, O1 and O2 oxygen atoms act as a hydrogen bond acceptor. The hydrogen atoms present in the Nmethyl group are most acidic (due to electronegativity difference and resonance effect of the nitrogen lone pair with the adjacent carbonyl group) followed by those belonging to the ethyl ester group (due to electron with drawing inductive effect of the oxygen atom). The oxygen atom present in the 2-oxindole moiety has a strong capacity for hydrogen bond formation as is reflected in the formation of C-H···O=C hydrogen bonds (with O1 and aromatic ring hydrogen H3, H9, H11 and aliphatic hydrogen H13C). Figure 3a-f represents the different structural motifs which contribute towards the crystal packing. In compound I, the maximum stabilization comes from C–H··· $\pi$  intermolecular interactions, involving H2 (ring hydrogen) and H13B (and aliphatic hydrogen) with Cg2 (centre of gravity of C7-C8-C9-C10-C11-C12) and Cg1 (centre of gravity of C1-C2-C3-C4-C5-C6) to generate a dimer across the centre of symmetry. The energy stabilization is -9.1/-10.3 kcal/ mole (Fig. 4a) obtained using PIXEL/TURBOMOLE. One C-H···O=C hydrogen bond involving O1 with H13C forms a dimer across the centre of symmetry with an interaction energy of -6.6/-8.0 kcal/mole (Fig. 4b). Additional C–H··· $\pi$  (involving H18C and H8 with Cg2 and C3) and C-H···O=C (O1 with H3) interaction together generates a molecular pair, the pairing energy being -5.8/-6.7 kcal/ mole (Fig. 4c). Another molecular pair (Fig. 4d) (involving the bifurcated acceptor atom, O2 with H12 and H5) having similar interaction energy (-5.8/-7.5 kcal/mole) also stabilizes the crystal packing. In additional, a comparatively weak C-H··· $\pi$  (involving H17B) and C-H···O=C (involving O1 with H11) mutually forms a dimeric chain along the b axis, the energetic contribution being -4.6/-5.3 kcal/mole (Fig. 4e). Finally, there is a

**Fig. 1** a *ORTEP* of compound I drawn with 30 % ellipsoidal probability. **b** *ORTEP* of compound II, without the treatment of disorder. **c** *ORTEP* of compound II having disorder along O6–C28=C29–C30 chain of the molecule *B* in the asymmetric unit (containing two molecules *A* and *B*) drawn with 30 % ellipsoidal probability

Fig. 2 Overlay diagrams between a I (experimental) and I (theoretical), b I (experimental) and IIA (experimental), c I (experimental) and IIB (experimental) and IIB (experimental), e IIB (experimental) and IIB

(theoretical)



 Table 2
 Selected torsion angles (°) for I and II

Torsion (I)	Experimental/theoretical	Torsion (IIA)	Experimental/theoretical	Torsion (IIB)	Experimental/theoretical
C16-C15-C19-C7	177.3(10) 178.6 <sup>a</sup>	C11-O3-C12-C13	161.7(4) <i>163.3</i> <sup>a</sup>	C27-O6-C28-C29	125.0(7) 87.4 <sup>a</sup>
C19-C15-C16-O3	165.5(10) <i>164.0</i> <sup>a</sup>	O3-C12-C13-C14	117.0(5) <i>126.8</i> <sup>a</sup>	O6-C28-C29-C30	97.0(10) 116.9 <sup>a</sup>
C14-C15-C16-O2	138.3(14) 145.1 <sup>a</sup>	C12-O3-C11-C9	179.0(4) 179.3 <sup>a</sup>	C28-O6-C27-C25	175.9(4) <i>179.0</i> <sup>a</sup>
C17-O3-C16-C15	172.1(11) <i>177.9</i> <sup>a</sup>	O3-C11-C9-C10	163.9(3) <i>163.2</i> <sup>a</sup>	C26-C25-C27-O6	163.5(3) 152.18

<sup>a</sup> Italicised values obtained from theoretical B3LYP/6-31G\*\* calculations

C-H···O=C interaction (involving O1 with H9), forming a molecular chain along the crystallographic *b*-axis, the energy being -3.4/-3.4 kcal/mole (Fig. 4f; Table 5).

In the solid state, *N*-methylic hydrogen atoms in compound II do not exhibit more acidic nature compared to I in the crystal packing. In case of compound II, containing two

Table 3 Selected Bond angles (°) for I and II

Bond angle (I)	Experimental/theoretical	Bond angle (IIA)	Experimental/theoretical	Bond angle (IIB)	Experimental/theoretical
C16-O3-C17	117.8(11) <i>116.8<sup>a</sup></i>	C6-C9-C11	110.2(2) <i>109.8</i> <sup>a</sup>	C22-C25-C27	110.2(3) <i>110.0</i> <sup>a</sup>
C16-C15-C14	109.1(10) 110.7 <sup>a</sup>	C9-C11-O3	110.8(3) <i>111.3</i> <sup>a</sup>	C26-C25-C27	110.8(3) <i>109.5</i> <sup>a</sup>
C16-C15-C19	110.8(10) 109.0 <sup>a</sup>	C10-C9-C11	110.1(3) <i>110.0</i> <sup>a</sup>	C25-C27-O6	111.6(4) <i>112.3</i> <sup>a</sup>
C7-C19-C15	113.8(10) 115.2 <sup>a</sup>				

<sup>a</sup> Italicised values obtained from theoretical B3LYP/6-31G\*\* calculations

Table 4 List of Intermolecular hydrogen bonds

Ι	D–H…A	D-H(Å)	D…A(Å)	H…A(Å)	$\angle D$ –H···A(°)	Symmetry code, operation
	C12–H12…O2	1.08	3.592(2)	2.61	151	$-x + 1/2, y + 1/2, -z + 1/2, 2_1$
	C5-H5O2	1.08	3.481(2)	2.69	130	$-x + 1/2$ , $y + 1/2$ , $-z + 1/2$ , $2_1$
	C11-H11…O1	1.08	3.666(2)	2.88	130	x, y-1, z
	С9-Н9…О1	1.08	3.405(2)	2.37	160	$-x + 3/2$ , $y + 1/2$ , $-z + 1/2$ , $2_1$
	C13-H13C…O1	1.08	3.593(2)	2.62	149	-x + 1, -y, -z, i
	C3-H3O1	1.08	3.610(2)	2.83	129	x-1/2, $-y + 1/2$ , $z-1/2$ , <i>n</i> -glide
	C13–H13B…π(C2)	1.08	3.859(2)	2.83	159	-x + 1, -y + 1, -z, i
	С2-Н2…π(С9)	1.08	3.791(2)	2.85	145	-x + 1, -y + 1, -z, i
	C18-H18C…Cg2	1.08	3.827(2)	2.79	161	x-1/2, $-y + 1/2$ , $z + 1/2$ , <i>n</i> -glide
	C8–H8…π(C3)	1.08	3.772(2)	2.94	150	x-1/2, $-y + 1/2$ , $z + 1/2$ , <i>n</i> -glide
	C17–H17B…π(C4)	1.08	3.632(2)	2.86	129	x, y-1, z
Π	D–H···A	D-H(Å)	DA(Å)	HA(Å)	$\angle D-HA(^{\circ})$	Symmetry code, operation
	C20-H20-O4	1.08	3.485(5)	2.41	174	x, y, z + 1
	C26-H26BO2	1.08	3.855(6)	2.84	156	$-x + 2$ , $y + 1/2$ , $-z + 1$ , $2_1$
	C4-H4O1	1.08	3.449(5)	2.37	178	x, y, z-1
	C31-H31A···O2	1.08	3.768(8)	2.78	152	x + 1/2, y, $-z + 3/2$ , <i>a</i> -glide
	C7-H7BO2	1.08	3.430(5)	2.42	155	x-1/2, y, $-z + 3/2$ , <i>a</i> -glide
	C23-H23CO5	1.08	3.551(6)	2.52	159	x + 1/2, y, $-z + 1/2$ , a-glide
	C13-H13-05	1.08	3.763(5)	2.84	143	x + 1/2, y, $-z + 3/2$ , <i>a</i> -glide
	C32-H32CO2	1.08	3.688(7)	2.73	148	x-1/2, y, $-z + 1/2$ , <i>a</i> -glide
	C7-H7CO4	1.08	3.906(5)	2.96	147	x, y, z-1
	C23-H23BO1	1.08	3.973(5)	2.97	155	x, y, z-1
	C3–H3····Cg2	1.08	3.679(5)	2.93	127	x, y, z
	C19-H19Cg1	1.08	3.868(5)	2.91	148	x, y, z
	C5-H5····Cg2	1.08	3.774(7)	2.85	144	x-1/2, y, $-z + 1/2$ , <i>a</i> -glide
	C21-H21Cg1	1.08	3.715(5)	2.71	154	x + 1/2, y, $-z + 3/2$ , <i>a</i> -glide
	C10–H10C…π(C17)	1.08	3.813(6)	3.21	116	$-x + 2$ , $y + 1/2$ , $-z + 1$ , $2_1$
	C32– H32A…π(C20)	1.08	3.816(6)	2.86	148	-x + 3/2, y + 1/2, z + 1/2, n-glide

Cg1=C1-C2-C3-C4-C5-C6 (I, II), Cg2=C7-C8-C9-C10-C11-C12 (I), C17-C18-C19-C20-C21-C22 (II), Cg1=C13-C14 (II), Cg2=C29-C30 (II)

molecules in the asymmetric unit, there exists three types of molecular pairs A–A, A–B and B–B held via C–H···O, C–H··· $\pi$  and  $\pi$ - $\pi$  which are the key supramolecular elements contributing toward the stability of the crystal packing. Energetically A–B type molecular pairs are more stable than the A–A type and B–B type. C–H··· $\pi$  and  $\pi$ .. $\pi$  both forms molecular stacks across the centre the symmetry (involving H2, H3, H18, and H19) with a high energetic stabilization, the magnitude being -10.0/-12.5 kcal/mole (Fig. 5a) obtained from PIXEL and TURBOMOLE. In addition, one C-H···O=C (involves O2 with H32C) and one C-H··· $\pi$  (isolated double bond



Fig. 3 Packing motifs of I a showing different C-H··· $\pi$  interactions down the crystallographic ac plane. b showing C-H-O=C hydrogen bonds with the oxygen atom down the ac plane. c showing bifurcated C-H···O=C hydrogen bond with the acceptor oxygen atom (O1) down

the ab plane. d Packing diagram of II showing the array of molecules  $(A \cdots A)$  forming a tetrameric sheet down the *ac* plane. **e** and **f** depicts an alternate layer of molecules (IIA...IIB) viewed down the ab plane and ac plane respectively

present in the allyl group) intermolecular interaction holds the molecules along the a axis, having an interaction energy of -7.6/-8.7 kcal/mole (Fig. 5b). Another molecular pair along the same direction, utilizing the a glide having energy comparable to the previous one, containing two different types of C-H···O (involving O2 with H31A and O5 with H13), including one C-H··· $\pi$  (H21 with isolated double bond) with an energy stabilization of -7.2/-8.1 kcal/mole (Fig. 5c) provides additional stability. Acceptor O1 with H23B and O4 with H7C generates a dimer across the centre of symmetry having interaction energy of -5.4/-7.0 kcal/mole (Fig. 5d). Molecular pairs e (A–B), f (A–A), g (B–B) and h (B–B) having energies in the stabilization range of -2.8 to -1.8 kcal/mole also contribute towards the stability of the crystal packing. Table 6 lists the calculated lattice energies which are closely related to each other.

Thus we observe that the crystal structures of novel molecules containing complex molecular architectures are assembled via a judicious interplay of C–H···O and C–H··· $\pi$ 



Fig. 4 Molecular pairs (a-f in Table 5) of compound I in order of decreasing interaction energy obtained from PIXEL. Cg1 = C1-C2-C3-C4-C5-C6, Cg2 = C7-C8-C9-C10-C11-C12

intermolecular interaction which contribute towards the stability in the solid state. It is already well known from the literature that the C–H··· $\pi$  hydrogen bond [26, 27] has been observed in chemical [28] and biological systems [29, 30]. It has been reported that such an interaction provides an energetic stabilization of 7 kcal/mole, the donor and acceptor being both hard in nature. In the current investigation the energy values are greater signifying their increased contribution towards the stability in the crystal packing. It has been observed that the formation of a C–H $\cdots\pi$  intermolecular interaction with an isolated double bond is not a very common feature in organic crystals. Compound II contains this type of C–H··· $\pi$  hydrogen bonding with the isolated double bond of dimethyallylester moiety. An investigation of the Cambridge Structural Database [CSD version 5.34 updates (Feb 2013)] [31-35] related to an investigation of the above mentioned interaction (Scheme 2) present in compound II, has been performed. Only 11 hits (containing C, H,

N, and O) have been found to bear C–H $\cdots\pi$  interatomic distance, the distance and angle range being 2.71 to 2.94 Å and 120° to 160° respectively.

CSD code	Bond distance (Å)	Angle (°)	Molecular formula
Compound II	2.93, 2.91, 2.85, 2.71	127, 148, 144, 154	C <sub>16</sub> H <sub>19</sub> NO <sub>3</sub>
AFEWEN [36]	2.85	147	$C_{21}H_{25}N_1O_3$
BETTEZ [37]	2.86	142	$C_{42}H_{54}N_2O_9$
DACWIP [38]	2.88	151	$C_{17}H_{24}N_2O_3$
FATWAY [39]	2.90	146	$C_{31}H_{52}N_2O_1$
GIMQUP [40]	2.83	142	$C_{13}H_{12}N_2O_2$
NUBTUA [41]	2.85	142	$C_{20}H_{27}N_1O_6$
OLIZEP [42]	2.90	148	$\begin{array}{c} C_{31}H_{39}N_{1}O_{8},\\ 2.2(H_{2}O)\end{array}$
PORJEM [43]	2.89	154	$C_{23}H_{29}N_1O_4$

CSD code	Bond distance (Å)	Angle (°)	Molecular formula
SILPAF [44]	2.92	136	C <sub>18</sub> H <sub>17</sub> N <sub>1</sub> O <sub>3</sub>
VAQQOV [45]	2.86	147	$C_{31}H_{30}N_2O_4$
XENBAV [46]	2.94	147	$C_{18}H_{27}N_1O_4$

From the CSD search, all the C–H··· $\pi$  bond angles are observed in the range of 142° to 154° signifying their directional role in self assembly processes in the crystal. For compound II, similar geometrical features (both distance and directionality) are observed which is in accordance with those obtained from the CSD.

The Hirshfeld surfaces of these two compounds (I, II) are described in Fig. 6, showing surfaces that have been mapped over  $d_{norm}$  (-0.5 to 1.5 Å). It is clear that the large circular depressions (deep red) visible on the front view and back view of the surfaces are indicative of hydrogenbonding contacts. Other visible white spots on the surfaces are because of the head-to-head H…H contacts present in the crystal lattice. The dominant interactions between the C–H and carbonyl oxygen atoms in both the compounds can be seen in the Hirshfeld surface as red spots. Hydrogen bonds coming from the oxygen atom presented in the 2-oxyindole moiety are energetically stronger than those from the carbonyl oxygen atom presented in the ester group. This is depicted in the former being associated with a deeper red color compared to that in the latter case. In the

shape index, there are some red and blue triangles which denote the presence of C–H··· $\pi$  intermolecular contacts in both the molecules. The nature of the d<sub>norm</sub> (front and back views) of the molecule II provides the information about the differences between two molecules present in the asymmetric unit. Furthermore there exist a relationship of the red colored region (in the 2-oxindole moiety) between the d<sub>norm</sub> (front) of IIA and d<sub>norm</sub> (back) of IIB and vice versa. The presence of stacking is evident on the Hirsfeld surfaces, as large flat regions on both sides of the molecules, which is clearly visible on the curvedness surface (Fig. 7). In the Fig. 8, C–H··· $\pi$  intermolecular interaction for both the molecules present in the asymmetric unit of II, has been shown by the d<sub>norm</sub> and shape index together.

Each fingerprint plot of these two 2-oxyindole derivatives summarizes the contribution of the interaction present in the two molecules (Fig. 9). In addition to that, these plots highlight the similarities and differences between crystal structures in this class of compounds. There are some distinct spikes (shown by arrows) which are appearing in the 2D fingerprint plot for both the structures. These spikes indicate different interactions motifs in the crystal lattice. The molecule I contains a total of four spikes whereas II has three spikes. The middle spike for molecule IIA is a single spike but for IIB consist of double spikes. Complementary regions are visible in the fingerprint plots where one molecule acts as donor (d<sub>e</sub> > d<sub>i</sub>) and the other as an acceptor (d<sub>e</sub> < d<sub>i</sub>). In

No.	Symmetry code	Centroid– centroid distance	E <sub>Coul</sub>	E <sub>Pol</sub>	E <sub>Disp</sub>	E <sub>Rep</sub>	E <sub>Tot</sub>	DFT-Disp/ B97-D aug-cc-pVTZ	Involved interactions
I (P2	$C_1/n$								
а	-x + 1, -y + 1, -z	7.136	-3.7	-1.4	-9.9	6.0	-9.1	-10.3	С13-Н13В…π(С2); С2-Н2…π(С9)
b	-x + 1, -y, -z	7.485	-3.0	-0.9	-5.9	3.1	-6.6	-8.0	C13-H13C…O1
с	x-1/2, -y + 1/2, z + 1/2	7.935	-2.0	-0.8	-6.6	3.6	-5.8	-6.7	С3-Н3…О1; С18-Н18С…Сg2; С8-Н8…π(С3)
d	-x + 1/2, y + 1/2, -z + 1/2	7.745	-2.6	-1.0	-5.4	3.2	-5.8	-7.5	C12-H12···O2; C5-H5···O2
e	x, y-1, z	8.795	-1.2	-0.9	-5.5	3.0	-4.6	-5.3	С11-Н11…О1; С17-Н17В…π(С4)
f	-x + 3/2, y + 1/2, -z + 1/2	9.677	-1.9	-0.8	-3.2	2.5	-3.4	-3.4	С9-Н9…О1
II $(P$	$n2_1a)$								
а	x, y, z (A…B)	5.813	-3.0	-1.4	-13.7	8.1	-10.0	-12.5	Cg2…π(C2); C3–H3…Cg2; Cg1…π(C18); C19– H19…Cg1
b	$x-1/2, y,-z + 1/2 (A \cdots B)$	6.793	-2.5	-1.1	-8.2	3.9	-7.6	-8.7	C32-H32C…O2; C5-H5…Cg2
с	$x + 1/2, y, -z + 3/2 (A \cdots B)$	6.973	-3.4	-1.1	-7.9	4.1	-7.2	-8.1	C31-H31A···O2; C13-H13···O5; C21-H21···Cg1
d	x, y, z-1 (A…B)	7.077	-2.0	-0.8	-5.4	2.7	-5.4	-7.0	C7-H7C···O4; C23-H23B···O1
e	-x + 2, y + 1/2, -z + 1 (AB)	8.582	-0.4	-0.3	-3.3	1.2	-2.8	-3.9	C26–H26B…O2; C10–H10C…Cg2
f	x, y, z-1 (A…A)	9.160	-1.5	-0.7	-1.7	1.6	-2.3	-2.1	C4-H4…O1
g	$x, y, z + 1 (B \cdots B)$	9.159	-1.4	-0.7	-1.8	1.8	-2.0	-2.2	C20-H20····O4
h	-x + 3/2, y + 1/2, z + 1/2 (B···B)	10.268	-0.4	-0.2	-2.6	1.3	-1.8	-2.4	С32–Н32А…π(С20)

Table 5 PIXEL interaction energies (in kcal/mol) between molecular pairs related by a symmetry operation in the crystal



Fig. 5 Molecular pairs (a-g in Table 5) of compound II in order of decreasing interaction energy obtained from PIXEL.Cg1 = C1-C2-C3-C4-C5-C6, Cg1 = C13-C14, Cg2 = C17-C18-C19-C20-C21-C22, Cg2 = C29-C30

Table 6 Lattice energy (CLP, in kcal/mol) of compounds I and II

Comp. code	E <sub>Coul</sub>	E <sub>Pol</sub>	$E_{\text{Disp}}$	E <sub>Rep</sub>	E <sub>Tot</sub>
I	-11.2	-4.3	-32.8	18.6	-29.7
II	-8.6	-3.4	-31.5	15.8	-27.8



Scheme 2 Cambridge Structural Database (CSD) search for the occurrence of C–H··· $\pi$  intermolecular interactions with an isolated double bond

compound II, there is a slight difference in the percentage contribution of  $C \cdots H$  intermolecular interaction and other related contributions of different types of interactions are similar to each other.

## Conclusions

The field of investigation of the crystal and molecular structures has advanced to an extent wherein it is possible to decipher the role of molecular conformation and exploit the role of weak intermolecular interactions which aid crystal packing. These features have ramifications in both reactivity and ordering of molecules in the crystalline state. Studies on complex natural products is rare, the reason being that the determination of the molecular structure is of significance and importance to the organic chemist.



Fig. 6 Hirshfeld surfaces mapped with d<sub>norm</sub> (front view), d<sub>norm</sub> (back view), and Shape index for the title compounds I and II (A & B)

Fig. 7 Curvedness of compound I and II (A and B)



Fig. 8 a  $d_{norm}$ , b shape index and c molecular packing with  $d_{norm}$  and shape index between two crystallographically distinct molecules A and B in the asymmetric unit of compound II involving C-H··· $\pi$  intermolecular interaction

However, it is of interest to re-iterate the fact that forces beyond covalent bonding also play a significant role in packing the molecules and an understanding of their nature is also of interest in structural chemistry. In this study performed on oxoindoline carboxylates, it has been found that C–H··· $\pi$  intermolecular interaction and  $\pi$ - $\pi$ stacking are the most important contributors towards the crystal stability in addition to the C–H···O intermolecular



Fig. 9 Fingerprint plots **a**–**d** for I, **e**–**h** for IIA and **i**–**l** for IIB: full (*left column*) and resolved into C–H…O (*second column*), C…H (*third column*), H…H (*right*) contacts showing the percentages of contacts contributed to the total Hirshfeld surface area for the molecules

hydrogen bonds in both the molecules. The observed molecular conformation of these *N*-methyl 2-oxindole derivatives from X-ray analysis agrees well with that obtained from geometrical optimization. PIXEL and high level DFT + Disp calculation suggest the presence of molecular pairs which are the key recognition motifs instrumental for the packing of molecules. Hirshfeld surface analysis and fingerprint plots represent a unique approach for an evaluation of the contribution of individual types of interaction within the crystal structures. It is of interest to extend such studies in more complex molecular architectures and also exploit the occurrence of polymorphism in these molecules.

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