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Quantitative Insights into the Crystal Structures of Nitro Derivatives of Ethyl (2*E*)-2-cyano-3-phenylprop-2-enoate: Inputs from X-Ray Diffraction, DFT Calculations and Hirshfeld Surface Analysis

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Abstract Two nitro substituted ethyl (2*E*)-2-cyano-3-phenylprop-2-enoate with molecular formula $C_{12}H_{10}N_2O_4$ have been synthesized and characterized by single-crystal X-ray diffraction. These two structures assemble via weak C–H···O=C/O (nitro group), C–H···N, and π – π intermolecular interactions which contribute towards the stability of the crystal packing. The lattice energies have been calculated using the PIXEL approach. Furthermore, high level DFT + Disp calculations for comparison with the pairing energies obtained from PIXEL method have been performed. An analysis of Hirshfeld surfaces and fingerprint plots facilitates a comparison of intermolecular interactions, which are the key elements in building different supramolecular architectures.

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Introduction

(2*E*)-2-cyano-3-phenylprop-2-enoate [1] derivatives are of significance as they can act as inhibitors of mitochondrial pyruvate transport [2]. Pyruvate is the key substance controlling the formation of diacetyl, acetaldehyde and acetate during alcoholic fermentation [3]. The mitochondrion is an organelle that plays a central role in oxidative respiration including ageing [4] and recent studies suggest that it is also involved in various biological and chemical processes in addition to oxidative respiration, biogenesis of the iron-sulfur cluster protein assembly [5], apoptosis [6], diauxic shift [7] and the metabolism of lipids [8, 9].

We report here the synthesis of two nitro derivatives of (2E)-2-cyano-3-phenylprop-2-enoate. These compounds are characterized by FT-IR, ¹H-NMR spectroscopy and single crystal X-ray diffraction. Subsequently, the compounds were analysed for their crystal packing, and the molecular conformation in the solid state was compared with the geometry in the gas phase. In order to evaluate the nature and energetics associated with intermolecular interactions in the crystal packing, PIXEL calculations were performed. The total lattice energy is partitioned into the corresponding Coulombic, polarization, dispersion and repulsion energies.

Similar partitioning is also evaluated for the corresponding molecular pairs, which contribute towards the understanding of the crystal packing for both the molecules [10, 11] and these have been compared with values from DFT calculations using higher basis sets for the elements





C, H, N, O at the crystal geometry. Furthermore, molecular Hirshfeld surfaces [12, 13], mapped with d_{norm} (defined using Eq. 1), using a red-white-blue colour scheme, where red is for the shorter contacts, white is used for contacts around the vdW separation, and blue is for longer contacts along with the fingerprint plots [14] have been analysed as these represent a unique approach for the assessment of the contribution of the individual types of interaction within the crystal structures. This also includes emphasizing significant similarities and differences between the various types of packing motifs in crystal engineering.

$$d_{norm} = \frac{d_i - r_i^{vdw}}{r_i^{vdw}} + \frac{d_e - r_e^{vdw}}{r_e^{vdw}}, \qquad (1)$$

where d_e is the distance from the Hirshfeld surface to the nearest nucleus outside the surface, d_i is the distance from Hirshfeld surface to the nearest nucleus inside the surface and the normalized contact distance (d_{norm}) are defined in terms of d_e and d_i , and the vdW radii of the atom.

Finally, infra-red (IR) vibrational frequency analysis for some selected functional groups has been performed in the gaseous state, and the results were compared with those in the solid state. It is of interest to compare the variations in the vibrational frequencies when a molecule in the isolated gaseous state is bought into the crystal environment. These changes are usually due to the prevalence of different noncovalent interactions, which control the packing of molecules in the solid state.

Experimental

Synthesis and Crystallization

A round bottom flask was charged with a mixture of *p*nitrobenzaldehyde (10 mmol) and ethylcyanoacetate (10 mmol) in ethanol. In presence of a catalytic amount of

sodium ethoxide the above reaction mixture was stirred for 2 h and kept overnight. After that the solid product (I) was filtered from the reaction mixture (Scheme 1) and recrystallized from ethanol (yield 95 %, m.p.13²C). The second nitro derivative, II was synthesized by the same procedure using *m*-nitrobenzaldehyde (yield 92 %, m.p.133 °C).

Spectroscopic Characterization (FTIR, ¹H NMR) of the Synthesized Compounds

I: FTIR (in solid state, cm⁻¹: KBr): $2,225(C \equiv N \text{ str.})$, 1,720(C=O str.), 1,617(C=C str.), 1,514(O–N–O asym. str), 1,347(O–N–O sym. str). ¹H NMR (400 MHz, CDCl₃): δ 8.34 (d, *ortho*- position 2H), 8.30 (s, =CH), 8.13 (d, *meta*-position 2H), 4.44 (q, –CH₂), 1.43 (t, –CH₃).

II: FTIR (in solid state, cm⁻¹: KBr): 2,230(C \equiv N str.), 1,722(C=O str.), 1,615(C=C str.), 1,522(O–N–O asym. str.), 1,350(O–N–O sym. str.). ¹H NMR (400 MHz, CDCl₃): δ 8.68 (s, =CH), 8.39 (t, *meta*-position and *para*position 2H), 8.29 (s, *ortho*-position 1H), 7.72 (t, *ortho*position 1H), 4.41 (q, –CH₂), 1.41 (t, –CH₃).

X-Ray Crystallography

Single crystal X-ray diffraction data for the two crystals were collected with a Bruker APEX- II diffractometer equipped with a CCD area detector using Mo-K α radiation ($\lambda = 0.71073$ Å) in φ and ω scan modes. The crystal structures were refined by least-squares methods on the basis of all observed reflections using SHELXL-97 [15] present in WinGx (version 1.80) [16]. An empirical absorption correction was applied using SADABS [17]. The non- hydrogen atoms were 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 and sp² carbon atom and U_{iso} (H) = $1.5U_{eq}(C)$ for hydrogen atoms of the ethyl

 Table 1 Crystallographic and refinement data of I and II

Data	I	П
Formula	$C_{12}H_{10}N_2O_4$	$C_{12}H_{10}N_2O_4$
Formula Weight (amu)	246.22	246.22
Wavelength (Å)	0.71073	0.71073
Solvent system	Ethanol	Ethanol
CCDC no.	932606	932607
Crystal system	Monoclinic	Triclinic
Space group	$P2_{1}/c$	P-1
a (Å)	15.452(7)	4.0490(5)
b (Å)	4.1836(19)	10.7699(14)
<i>c</i> (Å)	20.985(9)	13.8840(18)
$\alpha(^{\circ})$	90	103.980(12)
$\beta(^{\circ})$	121.21(3)	96.908(8)
γ(°)	90	91.065(8)
V (Å ³)	1160.2(9)	582.53(13)
Z	4	2
Density (g cm ⁻³)	1.410	1.404
$\mu (mm^{-1})$	0.108	0.108
F (000)	512	256
θ (min, max)	1.54, 25.00	2.78, 22.60
Treatment of hydrogens	Fixed	Fixed
$h_{min,max},\ k_{min,max},\ l_{min,max}$	(-17, 18), (-4, 4), (-24, 24)	(-4, 4), (-12, 12), (-16, 16)
No. of ref.	10093	7279
No. unique ref./obs. ref.	2021, 1040	1979, 1297
No. of parameters	164	164
R_all, R_obs	0.1210, 0.0515	0.1179, 0.0943
wR2_all, wR2_obs	0.1673, 0.1259	0.2715, 0.2536
$\Delta \rho_{min,max}(e ~ {\rm \AA}^{-3})$	-0.217, 0.191	-0.271, 0.443
G. o. F	0.932	1.089

group. The molecular connectivity was drawn using OR-TEP32 [18] and the crystal packing diagrams were generated using Mercury [19]. Geometrical calculations were done using PARST [20] and PLATON [21]. 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 [22].

Theoretical Calculations

Geometrical optimization of all the isolated molecules were performed using the basis set 6-31G** at the DFT/ B3LYP level in TURBOMOLE [23, 24]. DFT + Disp calculations were done with the functional B97-D using a higher basis set aug-cc-pVTZ in TURBOMOLE. Vibrational frequencies for both of the molecules in the gas phase have been calculated at the B3LYP/6-31G** level using the program TURBOMOLE and compared with those obtained in the solid state. All the obtained vibrational frequencies for the optimized geometries are positive.



Fig. 1 ORTEP of the synthesized compounds **a I** and **b II** drawn at 50 % probability. *Bending arrows* are showing the significant torsion angles in the asymmetric unit

Result and Dicussion

Compound I (Fig. 1a) crystallizes in $P2_1/c$ and compound II (Fig. 1b) crystallizes P-1.

The change in the position of the nitro group on the phenyl ring from *para* to *meta* results in minor variations in the bond angle and torsion angle [Table S1 and S2]. From the overlay diagram [Fig. S4] it is clear that these two molecular structures are nearly planar. The theoretical B3LYP/6-31G** calculations, after geometrical optimization of the molecule, reveal torsion angles, which are similar to the experimental values. It is of interest to note that the torsion angles for the optimized geometry of both I and II are similar. The values are close to 180 indicating planarity of the entire molecule. It is of interest to note that the c4–C5–C7–C8 (in I) and O2–C3–C4–C6 (in II) torsion angle in the solid state have similar values with those from the optimized geometry.

Table S3 lists the intermolecular hydrogen bonding in I and II. 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° [25]. Table 2 lists the calculated lattice energy using the PIX-ELC module in the CLP package. Table 3 shows all the contribution energies (Coulombic, polarization, dispersion and repulsion energies) towards the interaction energy for a given molecular pair. We have compared the total energy for each pair from PIXEL and with values from quantum mechanical DFT + Disp methods.

Compound I contains the cinnamic acid moiety and the acidic hydrogen of the carboxylic acid group is substituted

 Table 2
 Lattice energy CLP (in kcal/mol) of compounds I and II

Comp. Code	E _{Coul}	E _{Pol}	E _{Disp}	E _{Rep}	E_{Tot}
I	-12.3	-4.0	-30.0	16.1	-29.7
II	-11.3	-4.0	-31.0	16.8	-29.4

the nitro group with the phenyl ring results in an enhancement of the acceptor ability of C–H···O hydrogen bonding. These interactions have been recognized as key elements for supramolecular association in the solid state. The principal packing motifs (also referred to as molecular pairs) for compound I are represented in Fig. 2, the pairs being depicted from (a) to (e) and for compound II in Fig. 3 from (a) to (f). Two weak but directional C–H···O=C (involving H5 and H8 with O2 being the bifurcated acceptor) (Figs. 2b and 3a) hydrogen bonds generate a dimer in the crystallographic *ac* plane (Fig. 2) and *bc* plane (Fig. 3) acting across the centre of symmetry for both the

No.	Symmetry code	Centroid– centroid distance (Å)	E _{Coul}	E _{Pol}	E _{Disp}	E _{Rep}	E _{Tot}	DFT-Disp/ B97-D aug-cc- pVTZ	Involved interactions
I(P2	1/c)								
а	x, y + 1, z	4.184	-1.0	-1.1	-11.7	5.8	-8.1	-9.9	Molecular stacking
b	-x, -y + 1, -z	6.448	-5.8	-2.0	-6.0	6.4	-7.5	-7.0	С5– Н5…О2
									С8– Н8…О2
с	-x, 1/2 + y,	5.643	-3.0	-1.1	-5.2	3.0	-6.4	-6.5	C12– H12…N1
	-z + 1/2								C11– H11…N1
									C1– H1C…O4
d	-x + 1, y + 1/2, -z + 1/2	13.032	-2.5	-0.6	-1.8	2.0	-3.0	-3.0	C9– H9…O3
e	x + 1, - y + 1.5,	13.534	-1.0	-0.3	-1.7	0.9	-2.2	-2.2	C1– H1B…O4
	z + 1/2								C1– H1B…O3
II(P-	1)	6.056	0.2	0.1	0.1	7.0	11.5	10.4	05
а	-x + 1, -y, -z	6.056	-8.3	-2.1	-8.1	7.0	-11.5	-10.4	C5– H5…O2
	+ 1								C8– H8…O2
b	x-1, y, z	4.047	-0.7	-1.0	-12.9	6.2	-7.8	-9.8	Molecular Stacking
c	2-x, -y, -z + 1	5.206	-1.5	-0.7	-7.0	2.5	-6.8	-7.4	C2– H2B…O3
d	-x + 3, -y + 1,	7.390	-5.0	-1.6	-3.6	4	-6.0	-6.2	C11– H11…N1
	-z + 1								C12– H12…N1
e	x-3, - y + 1, -z + 2	13.259	-3.2	-0.7	-2.5	2.0	-4.3	-4.3	C10– H10…O4
f	-x + 2, -y + 1, -z + 1	5.747	-0.7	-1.0	-5.5	2.8	-4.3	-5.6	Molecular stacking

energies (in kcal/mol) between molecular pairs related by a symmetry operation and the associated intermolecular interactions in the crystal

Table 3 PIXEL interaction



Fig. 2 Packing diagram for I showing C–H···O=C/O and C–H···N intermolecular hydrogen bonding motifs in the ac plane and selected molecular pairs in order of decreasing interaction energy

compounds I and II. The interaction energy for these dimers is -7.5/-7.0 kcal/mol for I and -11.5/-10.4 kcal/ mol for **II** respectively obtained from energy calculations performed using PIXEL and TURBOMOLE. In addition the atom, N1 also acts as a bifurcated acceptor interacting with two hydrogen atoms (involving H11 and H12) for both the structures, forming a chain motif utilizing the 21-screw axis of symmetry in I and a dimeric motif across the center of symmetry in II (Figs. 2c and 3d). It is of interest to note that the C-H-O and C-H-N dimers (as indicated by molecular pairs Fig. 3a, d) exist alternately in the crystal lattice forming a sheet-like structure in II. Adjacent sheets are held via weak C-H...O (involving O4 with H10); (the energy is -4.3/-4.3 kcal/mol) that generates a dimer in the bc plane (Fig. 3e). In addition, in I, additional C-H...O-N H-bonds with the nitro group, as revealed by the presence of molecular pairs Fig. 2d, e provide additional stability to the crystal packing (the energies range from 2.2 to 3.0 kcal/mol as obtained from PIXEL/TURBOMOLE). In II, a weak and directional C-H…O (involving H2B with O3) intermolecular hydrogen bond generates a dimer in the crystallographic bc plane (Fig. 3c). The characteristic packing feature in both the molecules consists of π - π stacking interactions [26] namely $\pi(\text{carbonyl}) - \pi(\text{cyano})$ (Fig. 2a) and $\pi(\text{nitro}) - \pi(\text{cyano})$ π (aromatic) (Fig. 3b), the interaction energies being -8.1/-9.9 and -7.8/-9.8 kcal/mol respectively via inputs from PIXEL/TURBOMOLE. π - π stacking in these molecules is responsible for the increased stability of the crystal packing. These energies are higher in magnitude when compared to related molecular pairs containing intermolecular hydrogen bonds in the crystal lattice.

The Hirshfeld surfaces of the title compounds (**I**, **II**) are illustrated in Fig. 4, showing surfaces that have been mapped over d_{norm} (-0.5-1.5 Å). It is clear that the large circular depressions (deep red) visible in the front and back views of the surfaces are indicating hydrogen- bonding contacts. The dominant interactions between the C-H (C8 and C5) and carbonyl O (O2) atoms in both the compounds can be seen in the Hirshfeld surface as red areas. The small light red colour on the surface, denotes weaker and longer contact. Some significant π - π interactions are observed in both compounds. In Fig. 4c, f there are red and blue triangles representing the presence of π - π stacking.

There are three distinct spikes (marked with arrows), which are appearing in the 2D fingerprint plot (Fig. 5a, e) for both structures. These spikes indicate different interactions that can occur between two chemically and crystallographically distinct molecules. Complementary regions are visible in the fingerprint plots where one molecule acts as donor $(d_e > d_i)$ and the other as an acceptor $(d_e < d_i)$. The fingerprint plots can be decomposed to highlight a particular type of atomic pair contacts. This decomposition leads the separation of the contributions towards the total interaction from different interaction types, which overlap in the full fingerprint. The C-H-··O intermolecular interactions appear as one spike in the 2D fingerprint plots for both molecules. Similar behaviour is observed for the corresponding C-H...N intermolecular interaction. A greater value of d_i ($d_e = 1.00$ Å and $d_i = 1.30$ Å for I and $d_e = 1.05$ Å and $d_i = 1.36$ Å for II) indicates the presence of the nitro group and carbonyl group, which are acting as good acceptors (Fig. 5b, f) of H-bonds. In case of the C-H...N intermolecular interaction, a greater value of d_i is indicating the presence of the cyano (CN) group where the N1 atom is acting as a good acceptor (Fig. 5c, g).

The packing of molecules in **II** has a greater contribution of O···H intermolecular interaction in comparison to molecule **I** by 1.2 %. But the contribution of N···H intermolecular interaction is slightly higher for **I** compared to that in compound **II**.

In Table 4 we have compared the vibrational frequencies of some selected functional groups involved in noncovalent interactions [27] in the solid phase with those in the gaseous phase, obtained from B3LYP/6-31G** calculations using TURBOMOLE. It is noteworthy that the O atoms of the $-NO_2$ group are involved in the formation of intermolecular interactions in the crystal packing in comparison to the other functional groups present in the molecule. The changes in vibrational frequency between the gas phase and the solid state (for both O–N–O asymmetric stretching and symmetric stretching) is 156 and 159 cm⁻¹



Fig. 4 Hirshfeld surfaces mapped with d_{norm} (front view and back view) and shape index for the title compounds I (a, b, c) and II (d, e, f)

for both of the molecules respectively. The changes in vibrational frequency for the $C \equiv N$ and C=O groups are similar to each other (in the range of 80–100 cm⁻¹) for similar reason as mentioned previously. Figure 6 depicts the overlay diagram for the IR spectrum obtained in the gaseous state for the two molecules. The IR spectra are similar for same functional groups in both the molecules. This analysis contributes to a quantitative understanding of the changes in vibrational frequencies, which result from

packing the molecule in the solid state, thereby highlighting the significant role of intermolecular interactions in the crystal.

In order to evaluate the influence of the solid state environment on the vibrational frequency, we have evaluated these values for one such dimer in unoptimized, solidstate geometry and compared them to the gas phase optimized values of this dimer for all the functional groups of interest. In Fig. 7a, it has been shown that the four Table 4 Comparison of the



Fig. 5 Fingerprint plots of I (a, b, c, d) and II (e, f, g, h): full (left) and resolved into C-H···O (middle) and C-H···N (right) contacts showing the percentages of contacts contributed to the total Hirshfeld surface area of molecules

Table 4 Comparison of the vibration frequencies (in cm ⁻¹) between solid state and gaseous state (optimized geometry) of the synthesized compounds	Bond	Solid state IR frequency (I)	Gaseous state IR frequency	Shift	Solid state IR frequency (II)	Gaseous state IR frequency	Shift
	$C \equiv N(str)$	2225	2329	104	2230	2329	99
	C=O (str)	1720	1804	84	1722	1805	83
	C=C(str)	1617	1655	38	1615	1653	38
	O-N-O(asym. str)	1514	1670	156	1522	1681	159
	O–N–O(sym. str.)	1347	1609	262	1350	1634	284



Fig. 6 The calculated IR spectrum of isolated I and II (in the gaseous state) obtained from calculations at the B3LYP/631G** level

independent asymmetric molecules with different colours (gray, green, yellow and pink) in the unit cell of compound I, are connected with each other by non-covalent interactions or via other symmetry related molecules present in the crystal. Similarly, in Fig. 7b, two independent asymmetric molecules with different colour codes (gray and yellow) of compound II have been shown in the unit cell. We have focussed on a common molecular pair between I (b pair) and **II** (a pair) where the bifurcated acceptor O2 is interacting with hydrogen atoms H5 and H8. The theoretical interaction energy for the molecular pair Ib (-7.5/-7.0 kcal/mole) is less than IIa (-11.5/-10.4 kcal/mole). In these molecular pairs only one functional group C=O group is involved. From Table 5 it is clear that there is no change in the vibrational frequency of the carbonyl group calculated for the solid state unoptimized dimer as well as the optimized gaseous state dimers between **Ib** and **Ha**. Figure 8 It is also of interest to note that the vibrational frequency for the unoptimized solid state dimer corresponding to all the functional groups is greater than the experimental vibrational frequency in the solid state, thereby indicating the role of crystal forces in relaxing these to lower values.



Fig. 7 The unit cells containing independent asymmetric molecules represented by different colours for a compound I and b II respectively

Table 5 Comparison of the vibrational frequencies (in cm ⁻¹) between solid state dimer (unoptimized) and gaseous state dimer (optimized) of the synthesized compounds									
	Bond	Solid state IR frequency (Ib)	Gaseous state IR frequency	Shift	Solid state IR frequency (IIb)	Gaseous state IR frequency	Shift		
	$C \equiv N(str)$	2489	2330	159	2472	2328	144		
	C=O(str)	1939	1781	158	1938	1781	157		
	C=C(str)	1705	1654	51	1690	1647	43		
	O–N– O(asym. str)	1754	1669	85	1784	1677	107		
	O–N– O(sym. str)	1477	1396	81	1501	1402	99		



Fig. 8 Theoretical IR spectrum of dimers **Ib** and **IIa** (solid state unoptimized and gaseous state optimized) obtained from calculations at the B3LYP/6-31G** level

Conclusion

In this study, the role of intermolecular interactions of two biologically active compounds have been analyzed through single crystal studies. These compounds demonstrate the formation of primary structural motifs, which constitute the key supramolecular motifs essential for the formation of the crystal structure. The arrangement of the molecules is determined by the formation of hydrogen bonds and also a relatively greater contribution from the π - π stacking. The observed molecular conformation of these two nitro derivatives compounds from X-ray analysis agrees well with that obtained from the quantum mechanical calculation. The analysis of the interaction energy of the molecular pairs via PIXEL and DFT + disp calculation suggests the presence of considerable stabilization from the weak interactions in the crystal packing. Hirshfeld surface and fingerprint plot analyses provide rapid quantitative insights into the intermolecular interaction in molecular solids. It differentiates the molecular packing of these two chemically and crystallographically distinct compounds. Close O…H, N…H and H…H contacts have clear signatures in the fingerprint plots. The differences in IR spectroscopic values for the vibrational frequencies for both the molecules in the gas phase and solid state have been analysed to demonstrate the pivotal role of non-covalent interactions in the formation of the crystal. It is of interest to investigate polymorphism in such solids and screen such compounds for differences in their biological function.

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