A quantitative study of weak noncovalent interactions in two pyridine isomers containing nitrile and thiophene moieties: a combined X-ray and theoretical investigation

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Abstract. Single crystals of two pyridine isomers containing cyano and thiophene moieties {systematic names: (Z)-2-(pyridine-2-yl)-3-(thiophen-2-yl)acrylonitrile, C₁₂H₈N₂S, **I** and (Z)-2-(pyridine-3-yl)-3-(thiophen-2-yl)acrylonitrile, C₁₂H₈N₂S, **II**} were obtained from ethanol-cyclohexane mixture. The thiophene ring was found to be disordered over two orientations (*syn* and *anti*) in **II**. The potential energy surface scan of thiophene ring rotation suggests that the *syn* conformer is more stable by ≈ 4 kcal mol⁻¹ than that of the *anti*-conformer. The optimized structures obtained using the DFT method (M06-2X/cc-pVTZ level of theory) show a high degree of similarity with the experimental structures. A detailed experimental and theoretical analysis on the intra- and intermolecular interactions observed in these structures is reported. The molecules arranged in the crystalline state are completely different in **I** and **II**. Intermolecular interactions are qualitatively analyzed using Hirshfeld surface and its associated 2D fingerprint plots. The intermolecular interaction energies of different molecular pairs are calculated using the PIXEL method. Several weak non-covalent interactions such as C–H $\cdots$ N, C–H $\cdots$ π , C–H $\cdots$ S, $\pi \cdots \pi$ and S $\cdots$ N contacts play a vital role in the stabilization of crystal structures. These interactions are further explored by the topological analysis of the electron density based on the quantum theory of the atoms-in-molecules approach.

Keywords. Pyridine; nitrile; thiophene; PIXEL; QTAIM; MESP.

1. Introduction

An understanding of weak noncovalent interactions in the context of crystal packing is an important aspect of crystal engineering. Such an understanding will help us to design new solids with desired physicochemical properties.¹ The hydrogen bonds and π - π interactions are well-acknowledged in crystal engineering, structural chemistry and structural biology among other weak noncovalent interactions.^{2–6} To understand the role of weak noncovalent interactions especially in the absence of a strong donor group, we synthesized two pyridine

isomers, which contain cyano and thiophene functionalities, and determined their crystal structures at low temperature.

Many pharmaceuticals contain a cyano(–CN) functionality and are prescribed for a diverse variety of medicinal indications.⁷ The cyano functionality was used as a substructure to search the drug bank (www.drugbank.ca),⁸ which revealed 243 compounds, most of which are approved drugs. Further, the drugs for type 2 diabetes, namely, rosiglitazone and pioglitazone, contain pyridine nucleus.⁹ Interestingly, one of the approved drugs, i.e., milrinone, contains both pyridine

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and cyano functionalities, which is used for treating heart failure.¹⁰ Thiophene scaffold is also present in many drugs, which have proven to be toxic for humans and animals.¹¹

On the other hand, the conjugated organic compounds with cyano substituent display excellent optical and electrical properties due to their high electron affinities.¹² Some of the poly(*p*-pyridine)- and poly(*p*-pyridylvinylene)-based polymers have been reported as emitting chromophores^{13–15} and some nitrile containing polymers have been reported as semiconductors.¹⁶ In view of this, we have studied the optical properties and crystal structures of several acrylonitrile derivatives earlier.^{13,17–20}

We present herein the crystal and molecular structures of two pyridine isomers featuring cyano and thiophene moieties. A detailed investigation of weak non-covalent interactions present in them is carried out using the PIXEL method^{21–23} along with the Bader's quantum theory of atoms-in-molecules (QTAIM) approach.²⁴ This study helps to understand the nature of various non-covalent interactions and their roles in the solid state. The Hirshfeld surface analysis²⁵ and the two-dimensional fingerprint plots^{26,27} are performed to delineate the differences and similarities in terms of non-covalent close contacts between these two pyridine isomers.

2. Experimental

2.1 Synthesis and crystallization

A mixture of 2-thiophencarboxaldehyde (0.23 mL, 2.0 mmol), 10 mL of ethanol and 2.0 mmol (0.25 mL) of 2-pyridylacetonitrile was prepared. This mixture was maintained at room temperature, and KOH (3.0 mmol, 0.168 g) was added to it. The resultant reaction mixture was kept for 5 h until the formation of white powder (compound **I**). Compound **II** was prepared similarly except that 3-pyridylacetonitrile (2.0 mmol, 0.249 mL) was used instead of 2-pyridylacetonitrile (Scheme 1). These two compounds were characterized by ¹H-NMR, ¹³C-NMR and FT-IR spectroscopy. Single crystals of **I** and **II** were obtained from the recrystallization using a mixture of ethanol:cyclohexane (2:1 v/v). The spectral details are given in the supplementary section (Figures S1–S6, Supplementary Information).

2.2 Structure solution and refinement

Suitable crystals of **I** and **II** were chosen for single crystal X-ray diffraction study. Both compounds were solved by the direct methods using the program SHELXS-2013.²⁸ All the non-hydrogen atoms were refined anisotropically using SHELXL-2014/7.²⁹ The H atoms were fixed at the calculated

Scheme 1. Synthesis of the title compounds.

positions with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$. In **II**, the thiophene ring was disordered over two orientations with a refined occupancy ratio of 0.838(3):0.162(3). The crystal of **II** was found to be non-merohedrally twinned and the twin relationship corresponds to a twofold axis. The BASF scale factor was refined to be 0.383(2). Only the major disordered component (hereafter **IIA**) is considered for further analysis. The crystal data and structure refinement parameters are presented in Table 1. The ORTEP diagrams and the interacting dimeric structures were drawn using the programs PLATON³⁰ and MERCURY,³¹ respectively.

2.3 Hirshfeld surface analysis (HS)

To visualize and quantify various intermolecular interactions present in **I** and **IIA**, we performed HS analysis to obtain 2D fingerprint plots using the program CrystalExplorer17.³² The X-ray geometries after resetting the bond lengths involving H atoms were ($\text{C}-\text{H} = 1.083 \text{ \AA}$) used for the calculation. The HS was mapped with various properties such as d_{norm} ,²⁷ shape index,³³ and deformation density.

2.4 PIXEL energy calculation

The lattice energy for the crystal structures of **I** and **IIA** and intermolecular interaction energies (E_{tot}) for different dimers in these structures were calculated using the PIXELC module in the CLP package (Version 3.0, November 2015).²³ For a comparative purpose, the intermolecular interaction energy for different dimers (at their crystal structure geometry) identified from the PIXEL method was computed using the M06-2X-D3/cc-pVTZ level of theory. These energies (ΔE_{CP}) were corrected for basis set superposition error (BSSE) using the counterpoise method.³⁴

2.5 Structural optimization and rigid potential energy surface scan

The structural optimization was performed for both **I** and **IIA** without any geometrical constraints using the Gaussian09 program³⁵ at M06-2X/cc-pVTZ level of theory.³⁶ The empirical dispersion correction (D3) was included as proposed.³⁷ The optimized structures were further subjected to the vibrational frequency calculation to assess the minimum energy conformer on the potential energy surface (PES). Since the thiophene ring was disordered over two orientations (*syn* and *anti* conformers are defined based on the rotation of thiophene

Table 1. Crystal data and refinement parameters for compounds **I** and **II**.

	I	II
Crystal data		
Chemical formula	C ₁₂ H ₈ N ₂ S	C ₁₂ H ₈ N ₂ S
Mr	212.26	212.26
Crystal system, space group	Orthorhombic, <i>Pbca</i>	Monoclinic, <i>P2₁/n</i>
Temperature (K)	110(2)	110(2)
<i>a</i> , <i>b</i> , <i>c</i> (Å)	6.8798(3), 13.8842(7), 20.9606(9)	13.6152(8), 4.7297(3), 16.2431(10)
α , β , γ (°)	90, 90, 90	90, 105.293(6), 90
<i>V</i> (Å ³)	2002.17(16)	1008.95(11)
<i>Z</i>	8	4
Radiation type	Mo <i>K</i> α	Cu <i>K</i> α
μ (mm ⁻¹)	0.285	2.54
Crystal size	0.36 × 0.23 × 0.19	0.46 × 0.09 × 0.06
Data collection		
Diffractometer	SuperNova, Dual, Cu at zero, Atlas	SuperNova, Dual, Cu at zero, Atlas
Absorption correction	Analytical	Analytical
<i>T</i> _{min} , <i>T</i> _{max}	0.935, 0.960	0.489, 0.880
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	8098, 2296, 1905	6405, 2209, 1915
<i>R</i> _{int}	0.031	0.033
(sin θ/λ) _{max} (Å ⁻¹)	0.650	0.616
Refinement		
<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.040, 0.102, 1.07	0.043, 0.117, 1.07
No. of reflections	2296	2209
No. of parameters/restraints	136/0	174/160
Δρ _{max} , Δρ _{min} (e Å ⁻³)	0.36, -0.36	0.46, -0.31
CCDC No.	1892110	1892109

ring) in **II**, we performed rigid PES scan using B3LYP/6-31G(d) level of theory³⁸ for the C7–C8–C9A–C10A torsion angle from 0 to 360° with an increment of 5° to identify the stable conformer.

2.6 QTAIM analysis

The topological properties were calculated for all the dimers in **I** and **IIA** using AIMALL package (T. Keith, AIMAll version 16.05.18, 2016). From the calculation, we obtained electron density (ρ), Laplacian of electron density (∇² ρ), potential energy density (*V*_b) and kinetic energy density (*G*_b) and total energy density (*H*_b) for noncovalent interactions present in different molecular dimers in these two structures. In order to evaluate the strengths of different interactions, we computed the dissociation energy (*DE*_{int}) for the interaction based on the empirical approach proposed earlier.³⁹

3. Results and Discussion

3.1 General description of structures of **I** and **II**

In the present investigation, we examined crystal structures of two pyridine isomers to study the role of weak

noncovalent interactions in the solid state and to identify the similarities and differences in the crystal packing. Both compounds crystallize in the centrosymmetric space groups and one molecule per asymmetric unit in each of this compound. From the X-ray analysis, we found that the structure of **I** is well-ordered. The thiophene ring is disordered over two orientations in **II** (Figure 1). The major disordered component (labeled as A) of the thiophene ring is in *syn* conformation concerning the orientation of S and CN group, while the minor component (labeled as B) adopts *anti* conformation. To identify the stable conformer of **II**, we performed rigid PES scan for the torsion angle C7–C8–C9A–C10A. The result suggests that the *syn* conformer is found to be more stable than the *anti* conformer (Figure S7, Supplementary Information). The relative energy difference between *syn* and *anti* conformers is found to be 4.7 kcal mol⁻¹.

The selected torsion angles that describe the conformations of molecules **I** and **IIA** are given in Table S1 (Supplementary Information). In **I**, the thiophene ring is slightly twisted (8.22(4)°) with respect to the mean plane of the 2-pyridyl ring. The central moiety formed by atoms C1–C7–C8–C9 makes dihedral angles

Figure 1. ORTEP representation of (a) compound **I**, (b) the major disordered component of compound **II** (**IIA**), and (c) the minor disordered component of compound **II** (**IIB**). Displacement ellipsoids are drawn at the 50% probability level with the atom-labelling scheme.

of 6.04(1) and 13.97(1)° with the mean planes of thiophenyl and 2-pyridyl rings, respectively. In **IIA**, the orientation of the thiophene ring is similar to that in **I** with respect to the mean plane of the 3-pyridyl ring.

3.2 Quantitative molecular electrostatic potential map (MESP)

The molecular electrostatic potential maps were generated for **I** and **IIA** at their crystal structure geometries from the corresponding wave functions using WFA-SAS program.⁴⁰ The locations of the most positive ($V_{s,max}$, black hemisphere) and negative potentials ($V_{s,min}$, blue hemisphere) are shown in Figure S8 (Supplementary Information). We found that the distribution of electrostatic potentials is varied in the central region of the molecule. It is noted that the cyano N2 atom has a more electronegative potential ($V_{s,min} = -37.59 \text{ kcal mol}^{-1}$) in **I** than in the structure of **IIA**. In contrast, the pyridyl N1 atom has a greater electronegative potential in **IIA** as compared to the structure of **I**. In the case of **I**, the more positive potential is located on the hydrogen atoms H12 and H5 with $V_{s,max}$ values of 25.03 and 23.21 kcal mol^{-1} , respectively. This supports the involvement of these atoms in the formation of intermolecular C–H $\cdots$ N_{nitrile} and C–H $\cdots$ π interactions in **I**. In **IIA**, the most positive potentials are observed near the surface of H8 and H12A atoms. Again, this

endorses the participation of these atoms in the intermolecular C–H $\cdots$ N_{pyridine}, C–H $\cdots$ N_{nitrile} and C–H $\cdots$ π interactions.

3.3 Intramolecular interactions in **I** and **IIA**

The molecules of **I** and **IIA** adopt a slightly distorted planar conformation as observed in many closely related structures.^{17,18,41,42} To characterize the intramolecular interactions present in these structures, we performed QTAIM analysis for both X-ray and optimized molecules (Figure S9, for topological properties, see Table S2, Supplementary Information). The results suggest that there is a (3, –1) bond critical point (BCP) observed between C13 $\equiv$ N2 bond and S1 atom with the electron density (ρ) of 0.076 $\text{e \AA}^{-3}$ and the Laplacian of the electron density ($\nabla^2 \rho$) of 0.951 $\text{e \AA}^{-5}$ in the X-ray structure of **I**. This interaction is retained in the optimized structure with similar ρ and $\nabla^2 \rho$ values. The above contact is also observed in the X-ray structure of **IIA** in addition to a short H2 $\cdots$ H8 contact with the bond path (R_{ij}) of 1.980 Å. The topological analysis indicates that the dissociation energy for this H $\cdots$ H contact is higher as compared to C $\equiv$ N $\cdots$ S contact. A similar type of close H $\cdots$ H contact is observed earlier in different systems as non-electrostatic stabilizing interaction.^{43–46} In the optimized structure of **IIA**, the pyridyl ring is slightly rotated to avoid this short

Figure 2. Crystal structures of (a) compound **I** and (b) the major disordered component **IIA**.

contact. This observation suggests that the formation of a short intramolecular $H \cdots H$ contact is pre-optimized in the crystal. Overall, the presence of conjugation and the existence of intramolecular $C \equiv N \cdots S$ contact may assist molecules to adopt a distorted planar conformation in the crystal.

3.4 Crystal packing of **I** and **IIA**

In the crystalline state, the basic pattern that is observed is that the molecules of **I** and **IIA** form double layers in a head (pyridine)-to-tail (thiophene) fashion (Figure 2). The way the molecules are arranged in the solid state is completely different in **I** when compared to **IIA**. For instance, the molecules are oriented in the same direction for the head and tail groups in the double layers (basic pattern) and the adjacent double layers are arranged in an anti-parallel orientation in **I**. In contrast, molecules are oriented in an anti-parallel configuration in the double layers. One of the layers in the double layers is also oriented in an anti-parallel mode with the neighbouring layers in **IIA**. The adjacent double layers are interlinked through cyano groups. Analysis of lattice energies suggests that the dispersion energy contributes more towards the stabilization of the crystal structure (Table 2). It is to be noted that the Coulombic contribution is slightly better in **IIA**.

3.5 Qualitative analysis of intermolecular interactions: Hirshfeld surface analysis (HS) and 2D fingerprint plots (FP)

The HS analysis has been performed to understand the nature and the extent of intermolecular interactions

Table 2. Lattice energy (in kcal mol^{−1}) for compounds **I** and **IIA**.

Compound	E_{Coul}	E_{pol}	E_{disp}	E_{rep}	E_{tot}
I	−12.5	−5.6	−34.2	24.8	−27.5
IIA	−15.1	−5.8	−33.5	26.1	−28.3

observed in the crystal structures of **I** and **IIA** and to qualitatively analyze the intermolecular interactions. The relative contributions of various non-covalent interactions in these structures were computed using the 2D fingerprint plots. The brightness of the red spots on the HS implies that the interactions seem to be close contacts. The analysis indicates that the intermolecular $C-H \cdots N_{\text{nitrile}}$ and $S \cdots N_{\text{nitrile}}$ interactions are clearly seen on the HS of **I** (Figure S10 (a), Supplementary Information). It is to be noted that the pale red spots for $H8 \cdots H10$ contact as compared to the other two. In **IIA**, at least five intermolecular contacts are ($C8 \cdots C11A$, $C-H \cdots N_{\text{pyridine}}$, $C-H \cdots N_{\text{nitrile}}$ and $C-H \cdots \pi$) visible on the HS (Figure S10 (b), Supplementary Information).

The relative contributions of various non-covalent interactions are depicted in Figure 3. The distributions of various non-bonded contacts in the FP plots are remarkably different in **I** and **IIA**, and these variations are also reflected on the crystal packings. In both **I** and **IIA**, the intermolecular $H \cdots H$ interactions have a major contribution to the total HS area and these contacts are 3.2% higher in **IIA** when compared to **I**. This small difference is manifested in the FP (Figure 3). In **I**, the $H \cdots H$ interactions appear as double spikes with the shortest $d_i + d_e$ distance $\cong 2.2 \text{ \AA}$, while there are three

Figure 3. The decomposed two-dimensional fingerprint plots for (a) compound **I** and (b) compound **IIA** and (c) the relative contributions of various noncovalent interactions in **I** and **IIA**.

spikes in which the center spike is more concentrated in **IIA** with the closest $d_i + d_e$ distance $\cong 2.6$ Å. The next significant contributions come from both $\text{H} \cdots \text{C}/\text{C} \cdots \text{H}$ (26% in **I** and 17.6% in **IIA**) and $\text{H} \cdots \text{N}/\text{N} \cdots \text{H}$ (21.1% in **I** and 24.2% in **IIA**). The $\text{H} \cdots \text{C}/\text{C} \cdots \text{H}$ contacts that are characteristic for $\text{C}-\text{H} \cdots \pi$ interactions, which turn out in the form of wings in **I**. Further, the $\text{H} \cdots \text{C}/\text{C} \cdots \text{H}$ contacts are slightly longer (shortest $d_i + d_e$ distance = ~ 2.9 Å) in **I**. The corresponding contacts are observed as a pair of sharp spikes (crescent shape) around 2.6 Å in **IIA**. The intermolecular $\text{H} \cdots \text{N}/\text{N} \cdots \text{H}$ contacts appear as double spikes in both **I** and **IIA**. However, these contacts are shorter ($\cong 2.4$ Å) in **IIA** than that of **I** ($\cong 2.6$ Å).

These two structures also feature the presence of $\text{C} \cdots \text{C}$ contacts (7.6% in **I** and 12.9% in **IIA**), which correspond to $\pi \cdots \pi$ interactions and these contacts appear in pale blue and green colour on the diagonal regions around $d_i = d_e = 1.7\text{--}1.8$ Å. Furthermore, the existence of $\pi \cdots \pi$ interactions is also confirmed from the shape index diagram (presence of concave red and convex blue triangles on the surface; Figure S11,

Supplementary Information). Further, the existence of intermolecular $\text{C}-\text{H} \cdots \text{S}$ interaction is clearly seen from the wings in the FP for **I** (10.9%) and the absence of corresponding interaction in **IIA** (5.1%). It is of interest to note that these contacts are observed around 2.9 Å in **I**, while it is ca. 3.4 Å in **IIA**.

3.6a Quantitative analysis of intermolecular interactions in I: PIXEL and QTAIM: The energetically significant dimers were extracted from the PIXEL calculation. The interaction energies for these dimers (dimeric motifs: M1-M7) ranging from -6.4 to -2.4 kcal mol $^{-1}$ (Table 3 and Figure 4). Motif M1 is formed by intermolecular $\text{C}-\text{H} \cdots \text{N}$ interaction (involving H10 and N1) along with one $\text{C}-\text{H} \cdots \text{C}$ and an intermolecular $\text{C10}-\text{H10} \cdots \text{H8}-\text{C8}$ contact with an E_{tot} of -6.4 kcal mol $^{-1}$. The dispersion contribution (65%) is more significant when compared to the electrostatic contribution (sum of Coulombic and polarization) towards the stabilization of this molecular pair. Further, the existence of these contacts is evaluated by QTAIM analysis (Table 4), and the molecular graphs

Table 3. Intermolecular interaction energies (in kcal mol⁻¹) for various dimers in **I** and **III A**. The *Cg1* and *Cg2* are centroids of the pyridyl and thiophenyl rings, respectively. ^aNeutron values are given for all D-H...A interactions.

Motifs	centroid-centroid distance (Å)	Symmetry code	<i>E</i> _{Coul}	<i>E</i> _{pol}	<i>E</i> _{disp}	<i>E</i> _{rep}	<i>E</i> _{tot}	Δ <i>E</i> _{CP}	Possible Interactions	Geometry (Å, °) ^a
Compound I										
M1	6.407	$x + 1/2, y, -z + 1/2$	-2.7	-1.6	-7.9	5.8	-6.4	-4.51	C10-H10...N1 C11-H11...C10 C10-H10...H8-C8	2.64, 154 2.86, 141 2.24, 141
M2	8.872	$-x + 2, -y + 1, -z + 1$	-3.7	-1.2	-3.6	2.9	-5.5	-4.77	C5-H5...N2	2.55, 159
M3	5.271	$-x + 1, -y + 1, -z + 1$	-1.6	-1.2	-7.2	4.9	-5.2	-5.37	N2 ≡ C13...C13 ≡ N2	3.403(2)
M4	6.880	$x - 1, y, z$	-1.8	-0.6	-7.2	4.7	-4.8	-6.72	Cg1...Cg2 (π...π)	3.740(1)
M5	7.867	$-x + 3/2, y + 1/2, z$	-1.9	-1.1	-4.3	4.3	-3.1	-2.94	C4-H4...S1	2.94, 122
M6	7.636	$-x + 1/2, y + 1/2, z$	-0.6	-0.6	-4.3	3.0	-2.5	-2.54	C12-H12...π	2.67, 136
M7	8.265	$x - 1/2, -y + 3/2, -z + 1$	-1.7	-1.1	-2.2	2.7	-2.4	-2.54	S1...N2	3.236(2)
Compound III A										
M8	4.730	$x, y - 1, z$	-3.3	-1.3	-13	10.7	-6.9	-11.01	C8...C11A	3.326(1)
M9	6.795	$-x - 1/2, y - 1/2, -z + 1/2$	-5.0	-2.0	-5.1	5.8	-6.3	-5.67	C2-H2...N1 C8-H8...N1	2.48, 177 2.39, 166
M10	8.801	$-x, -y + 2, -z$	-2.9	-1.1	-3.6	2.7	-4.8	-3.65	C5-H5...N2	2.57, 157
M11	7.261	$-x, -y + 1, -z$	-1.5	-0.8	-2.9	1.6	-3.6	-3.16	C6-H6...N2	2.84, 113
M12	7.786	$-x + 1/2, y + 1/2, -z + 1/2$	-2.0	-0.8	-2.2	1.8	-3.2	-3.12	C12A-H12A...N2	2.73, 115
M13	9.485	$x - 1/2, -y + 3/2, z - 1/2$	-1.1	-0.5	-2.8	2.1	-2.3	-1.72	C4-H4...C12A C4-H4...C11A	2.87, 137 2.72, 164
M14	9.360	$x + 1/2, -y + 1/2, z + 1/2$	-0.8	-0.6	-3.0	2.3	-2.1	-1.58	C12A-H12A...C5	2.61, 146

Figure 4. (a–g) Various motifs observed in **I** and (h) with the deformation density is showing the existence of intermolecular N...S contact in **I**.

show the intermolecular interactions at the BCP in different molecular pairs of **I** (Figure S12, Supplementary Information). We note that the destabilization energy for $\text{H10} \cdots \text{H8}$ and $\text{H} \cdots \text{N}_{\text{pyridine}}$ interactions is comparable.

Inversion-related molecules form the molecular dimer (M2, E_{tot} : $-5.5 \text{ kcal mol}^{-1}$), which is held by intermolecular $\text{C}-\text{H} \cdots \text{N}$ interaction in which the N atom of the cyano group acts as an acceptor. In this case, the electrostatic contribution (58%) is more than dispersion (42%) towards the stabilization. The strength of this interaction ($DE(\text{int}) = 1.21 \text{ kcal mol}^{-1}$) is the same as compared to $\text{C}-\text{H} \cdots \text{N}$ interaction in M1. The cyano group of one molecule stacks with the cyano group of

the adjacent molecule with the shortest distance between two C13 atoms being $3.403(2) \text{ \AA}$ in M3. This interaction is predominantly dispersive (72%) in nature. From the QTAIM analysis, we found that there is a BCP formed between $\text{C} \equiv \text{N}$ bonds rather than between two C atoms (Figure S12, Supplementary Information). In M4, the 2-pyridyl and thiophenyl rings are involved in the formation of the $\pi \cdots \pi$ interaction with the E_{tot} value of $-4.8 \text{ kcal mol}^{-1}$.

Molecules of **I** are self-assembled by an intermolecular $\text{C4}-\text{H4} \cdots \text{S1}$ interaction (M5; E_{tot} : $-3.1 \text{ kcal mol}^{-1}$). This interaction links the molecules into a zigzag chain, which runs parallel to the *b* axis. From the topological analysis, we found that there are two BCPs observed

Table 4. Topological parameters for different intermolecular interactions in **I** and **IIA**. R_{ij} : Bond path (Å), ρ : electron density ($\text{e}/\text{\AA}^3$); $\nabla^2 \rho$: Laplacian of electron density ($\text{e}/\text{\AA}^5$); V_b : potential energy density (a.u.); G_b : kinetic energy density (a.u.); H_b : total energy density ($\text{kJ mol}^{-1} \text{ bohr}^{-3}$) and $DE(\text{int})$: dissociation energy: $-V_b \times 0.5$ (kcal/mol).

Interacting atoms	R_{ij}	ρ	$\nabla^2 \rho$	V_b	G_b	$\frac{ -V_b }{G_b}$	H_b	$DE(\text{int})$
Compound I								
M1								
H10...H8	2.421	0.050	0.601	−0.00393	0.005079	0.77	3.1	1.23
H10...N1	2.668	0.052	0.584	−0.00387	0.004965	0.78	2.9	1.21
H11...C10	3.051	0.037	0.426	−0.00254	0.003477	0.73	2.5	0.80
M2								
H5...N2	2.576	0.051	0.657	−0.00386	0.005339	0.72	3.9	1.21
M3								
N2...N2	4.647	0.037	0.441	−0.0026	0.003587	0.72	2.6	0.82
M4								
C1...C11	3.688	0.036	0.398	−0.00231	0.003221	0.72	2.4	0.73
C5...C9	4.092	0.032	0.343	−0.00184	0.002699	0.68	2.3	0.58
M5								
H4...S1	2.986	0.050	0.562	−0.00375	0.004787	0.78	2.7	1.18
H5...S1	3.094	0.043	0.480	−0.00297	0.003978	0.75	2.7	0.93
M6								
H12...C6	3.077	0.038	0.450	−0.00271	0.003688	0.73	2.6	0.85
H11...C3	2.905	0.037	0.439	−0.00266	0.003607	0.74	2.5	0.83
M7								
S1...N2	3.252	0.052	0.695	−0.000401	0.005610	0.72	4.2	1.26
Compound IIA								
M8								
C8...C11A	3.354	0.043	0.485	−0.00293	0.003980	0.74	2.8	0.92
C9...C2	4.461	0.038	0.431	−0.00231	0.003390	0.68	2.9	0.72
S1A...C7	3.667	0.035	0.383	−0.00223	0.003102	0.72	2.3	0.70
C5...C7	3.539	0.035	0.389	−0.00218	0.003104	0.70	2.5	0.68
M9								
H8...N1	2.410	0.085	1.018	−0.00726	0.008910	0.81	4.4	2.28
H2...N1	2.508	0.070	0.830	−0.00579	0.007201	0.80	3.7	1.82
M10								
H5...N2	2.592	0.050	0.637	−0.00372	0.005163	0.72	3.8	1.17
M11								
H6...N2	2.965	0.035	0.450	−0.00249	0.003577	0.69	2.9	0.78
M12								
H12A...N2	2.840	0.045	0.597	−0.00339	0.004790	0.71	3.7	1.06
M13								
H4...C11A	2.905	0.050	0.538	−0.00342	0.004499	0.76	2.9	1.07
M14								
H12A...C5	2.634	0.054	0.608	−0.00403	0.005166	0.78	3.0	1.26

(H4...S1; $DE(\text{int})$: 1.18 kcal mol^{−1} and H5...S1; $DE(\text{int})$: 0.93 kcal mol^{−1}). We note that the latter contact is slightly longer than the sum of vDW radii of H and S. Motif M6 is stabilized by the intermolecular C–H... π interaction (involving H12 and Cg1; $DE(\text{H12} \cdots \text{C6})$: 0.85 kcal mol^{−1} and $DE(\text{H11} \cdots \text{C3})$: 0.83 kcal mol^{−1}) with the E_{tot} of −2.5 kcal mol^{−1}. As shown in Figure 4, the motif M3 is flanked on both sides by motif M6.

The least stabilized dimer in **I** is formed by a non-bonded contact between S1 and N2 atoms with a

distance of 3.236(2) Å (M7, E_{tot} : −2.4 kcal mol^{−1}). The computed deformation density plot around these two atoms is clearly showing that the charge is concentrated at N2, while the charge is found to be depleted at atom S1. (Figure 4(h)). The topological analysis of S1...N2 interaction reveals that the magnitudes of the topological parameters ($\rho = 0.052 \text{ e}/\text{\AA}^{-3}$ and $\nabla^2 \rho = 0.695 \text{ e}/\text{\AA}^{-5}$) at the BCP are slightly higher as compared to other interactions observed in **I**. This clearly suggests that the S...N interaction has a special role in the stabilization of the crystal structure of **I**.

Figure 5. Various motifs observed in **IIA** and red small spheres are centroid positions of rings and C7 = C8 bond.

3.6b Quantitative analysis of intermolecular interactions in IIA: PIXEL and QTAIM: As depicted in Figure 5, there are seven energetically significant dimers identified in **IIA** from the PIXEL analysis. In the strongest dimer (M8; E_{tot} : $-6.9 \text{ kcal mol}^{-1}$), molecules are stacked with each other in a displaced parallel mode in which pyridyl and thiophenyl rings are stacked against the vinylic group. The topological analysis confirms the existence of stacking interactions with $DE(\text{C8} \cdots \text{C11A}) = 0.92 \text{ kcal mol}^{-1}$; Table 4 and Figure S13, Supplementary Information). In the next strongest dimer (M9; E_{tot} : $-6.3 \text{ kcal mol}^{-1}$; 58% of electrostatic contribution), pyridine N1 atom acts as an acceptor for two different donor atoms (H2 and H8). The dissociation energies for these intermolecular C8–H8 $\cdots$ N1 and C2–H2 $\cdots$ N1 interactions are calculated to be 2.28 and 1.82 kcal mol^{-1} , respectively. The only similarity observed between structures **I** and **IIA** is the formation of a closed loop motif through C–H $\cdots$ N interactions (M2 in **I** and M10 in **IIA**). The evaluation of the strength of these interactions by the QTAIM analysis suggests that the dissociation energies for these interactions are found to be very similar.

The motif M11 is also formed by the intermolecular C–H $\cdots$ N interaction (involving H6 and N2) with the E_{tot} value of $-3.6 \text{ kcal mol}^{-1}$. The contact between H and N is slightly longer (by 0.09 Å) than the sum of the vDW radii of H and N atoms. It is noted that the dispersion contribution (56%) is slightly better than the electrostatic

Figure 6. Part of the crystal structure showing a helical chain in **IIA**.

contribution towards the stabilization of this dimer. The DE for these interactions is found to be $0.78 \text{ kcal mol}^{-1}$ for each. Motif M12 (E_{tot} : $-3.2 \text{ kcal mol}^{-1}$; 56% of electrostatic contribution) is formed by intermolecular C–H $\cdots$ N (involving H12A and N2 interaction). This interaction links the molecules into a helical $C(8)$ chain, and there is a stacking interaction formed between i and $i+2$ molecules in a displaced parallel mode within this chain (Figure 6).

As can be seen from Table 3, motifs M13 and M14 are formed by intermolecular C–H $\cdots$ π interactions.

The former motif has an E_{tot} of $-2.3 \text{ kcal mol}^{-1}$ and the dispersion energy contributes 64% towards the stabilization, while the latter motif has an E_{tot} of $-2.1 \text{ kcal mol}^{-1}$ and the dispersion energy contributes 68% towards the stabilization. Though these two motifs have similar intermolecular interaction energies (E_{tot}) and dissociation energies, they differ in terms of the donor group. The donor group in the former motif is the pyridyl ring, while the corresponding group in the latter motif is the thiophenyl ring.

Overall, it should be noted that the positive value of the Laplacian for different non-covalent interactions at the BCP indicates these interactions are considered as closed-shell interactions in **I** and **IIA** (Table 4). Moreover, the ratio of $\frac{|1-V_b|}{G_b}$ appeared to be less than one, which supports the weak nature of non-covalent interactions. Further, the magnitude of electron density values for these interactions in different molecular pairs lies in the range $[0.013 < \rho (\text{e } \text{\AA}^{-3}) < 0.236]$ proposed by Koch-Popelier for H-bonds.^{47,48} It is to be noted that the magnitude of the Laplacian for C–H $\cdots$ N_{nitrile}, C–H $\cdots$ N_{pyridine}, H $\cdots$ H and S $\cdots$ N interactions falls within the proposed limit $[0.580 < \nabla^2 \rho (\text{e } \text{\AA}^{-5}) < 3.355]$ in **I**. In the case of **IIA**, the intermolecular C–H $\cdots$ N_{nitrile}, C–H $\cdots$ N_{pyridine} and C–H $\cdots$ π interactions lie within the suggested limit.

Among various non-covalent interactions observed in these structures (Table 4), the S $\cdots$ N interaction is found to be strongest ($4.2 \text{ kJ mol}^{-1} \text{ bohr}^{-3}$) based on the total energy density followed by C–H $\cdots$ N_{nitrile}, H $\cdots$ H, C–H $\cdots$ N_{pyridine}, C–H $\cdots$ S interactions in **I**. The theoretical topological parameters for the C–H $\cdots$ S interaction in **I** are also comparable with the experimental topological parameters for this interaction.^{49–51} For instance, the ρ values obtained from the experiment for the C–H $\cdots$ S interaction are in the range of $0.033\text{--}0.041 \text{ e } \text{\AA}^{-3}$. In **IIA**, the C–H $\cdots$ N_{pyridine} interaction is found to be the strongest ($4.4 \text{ kJ mol}^{-1} \text{ bohr}^{-3}$) followed by C–H $\cdots$ N_{nitrile} and C–H $\cdots$ π interactions.

4. Conclusions

Two pyridine isomers containing acrylonitrile and thiophene moieties have been synthesized and their crystal structures determined at low temperature by single crystal X-ray diffraction. The thiophenyl ring in the 3-pyridine isomer is disordered over two orientations. Analysis of rigid potential energy scan of thiophenyl ring rotation suggests that the *syn* conformation is more stable. Though the lattice energies of these isomers are comparable, the molecules are arranged in different ways in the crystalline state. In both cases, the dispersion

energy contributes more to the stabilization of the crystal structure. The molecular electrostatic potential map reveals the key regions involved in the intermolecular interactions. In this study, we found that the cyano group plays an important role in linking adjacent double layers in the crystal structure. The qualitative analysis from Hirshfeld surface suggests that the intermolecular H $\cdots$ H, H $\cdots$ C and H $\cdots$ N interactions are the most important contributors to the crystal packing. The non-covalent interactions in these structures are quantified using QTAIM and Koch-Popelier criteria. From this analysis, it can be noted that the S $\cdots$ N contact is the strongest among other weak non-covalent interactions in **I**, while the C–H $\cdots$ N_{pyridine} interaction is the strongest in **IIA**. The second strongest interaction is formed by the intermolecular C–H $\cdots$ N_{nitrile} interaction in both **I** and **IIA**. It can also be seen that there is an intramolecular C $\equiv$ N $\cdots$ S contact, which is found to be important for maintaining the conformation of the molecule.

Supplementary Information (SI)

The supplementary information includes the following: spectral data (FT-IR and $^1\text{H}/^{13}\text{C}$ NMR; Tables S1–S6) for compounds **I** and **II**, Table S1 contains the selected torsion angles, Table S2 summarizes topological parameters of intramolecular interactions (both X-ray and optimized geometries) and S7–S11 show PES for thiophene ring of **IIA**, molecular graphs of intra- and intermolecular interactions in **I** and **IIA** and shape index surface of **IIA**. Supplementary Information is available at www.ias.ac.in/chemsci.

CCDC-1892110 and 1892109 contain the supplementary crystallographic data for the title compounds **I** and **II**, respectively. These data can be obtained freely via http://www.ccdc.cam.ac.uk/data_request/cif or by e-mailing to data_request@ccdc.cam.ac.uk or by contacting directly the Cambridge Crystallographic Data Centre (12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033).

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References

- Desiraju G R 1989 *Crystal Engineering: The Design of organic solids Materials science monographs* 1st edn. (Oxford, UK: Elsevier Science)
- Aakeröy C B, Champness N R and Janiak C 2010 Recent advances in crystal engineering *CrystEngComm* **12** 22

3. Arunan E, Desiraju G R, Klein R A, Sadlej J, Scheiner S, Alkorta I, Clary D C, Crabtree R H, Dannenberg J J, Hobza P and Kjaergaard H G 2011 Definition of the hydrogen bond (IUPAC Recommendations 2011) *Pure Appl. Chem.* **83** 1619
4. Arunan E, Desiraju G R, Klein R A, Sadlej J, Scheiner S, Alkorta I, Clary D C, Crabtree R H, Dannenberg J J, Hobza P and Kjaergaard H G 2011 Definition of the hydrogen bond (IUPAC Recommendations 2011) *Pure Appl. Chem.* **83** 1637
5. Desiraju G R 2011 A bond by any other name *Angew. Chem. Int. Ed.* **50** 52
6. Desiraju G R and Steiner T 1999 *The Weak Hydrogen Bond* (Oxford, UK: Oxford University Press)
7. Fleming F F, Yao L, Ravikumar P C, Funk L and Shook B C 2010 Nitrile-containing pharmaceuticals: efficacious roles of the nitrile pharmacophore *J. Med. Chem.* **53** 7902
8. Wishart D S, Feunang Y D, Guo A C, Lo E J, Marcu A, Grant J R, Sajed T, Johnson D, Li C, Sayeeda Z and Assempour N 2017 DrugBank 5.0: a major update to the DrugBank database for 2018 *Nucleic Acids Res.* **46** 1074
9. Baumann M and Baxendale I R 2013 An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles *Beilstein J. Org. Chem.* **9** 2265
10. Bayram M, De Luca L, Massie M B and Gheorghiade M 2005 Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes *Am. J. Cardio.* **96** 47
11. Gramec D, Peterlin Mašič L and Sollner Dolenc M 2014 Bioactivation potential of thiophene-containing drugs *Chem. Res. Toxicol.* **27** 1344
12. Peng Z and Galvin M E 1998 Polymers with high electron affinities for light-emitting diodes *Chem. Mater.* **10** 1785
13. Percino M J, Chapela V M, Cerón M, Soriano-Moro G, Castro M E and Melendez F J 2013 Fluorescence improvement of pyridylacrylonitrile by dimethylaminophenyl-substitutions: The effect of packing modes of conjugated compounds *J. Mol. Struct.* **1034** 238
14. Epstein A J, Wang Y, Jessen S W, Blatchford J W, Gebler D D, Lin L B, Gustafson T L, Swager T M and Macdiarmid A G 1997 Pyridine-based conjugated polymers: Photophysical properties and light-emitting devices *Macromol. Symp.* **116** 27
15. Liu M S, Jiang X, Liu S, Herguth P and Jen A K Y 2002 Effect of cyano substituents on electron affinity and electron-transporting properties of conjugated polymers *Macromolecules* **35** 3532
16. Wang C, Dong H, Hu W, Liu Y and Zhu D 2011 Semiconducting π -conjugated systems in field-effect transistors: a material odyssey of organic electronics *Chem. Rev.* **112** 2208
17. Percino J, Cerón M, Venkatesan P, Ceballos P, Bañuelos A, Rodríguez O, Siegler M A, Robles F, Chapela V M, Soriano-Moro G, Pérez-Gutiérrez E, Bonilla-Cruz J and Thamotharan S 2017 Two Different Emissions of (Z)-2-(4-Bromophenyl)-3-[4-(dimethylamino) phenyl] prop-2-enenitrile Due to Crystal Habit and Size: Synthesis, Optical, and Supramolecular Characterization *Cryst. Growth Des.* **17** 1679
18. Venkatesan P, Cerón M, Thamotharan S, Robles F and Percino M J 2018 Quantitative analysis of weak non-covalent interactions in (Z)-3-(4-halophenyl)-2-(pyridin-2/3/4-yl) acrylonitriles *CrystEngComm* **20** 2681
19. Percino M, Chapela V, Montiel L F, Pérez-Gutiérrez E and Maldonado J 2010 Spectroscopic characterization of halogen-and cyano-substituted pyridinevinyls synthesized without catalyst or solvent *Chem. Pap.* **64** 360
20. Percino M, Chapela V, Pérez-Gutiérrez E, Cerón and Soriano G 2011 Synthesis, optical, and spectroscopic characterisation of substituted 3-phenyl-2-arylacrylonitriles *Chem. Pap.* **65** 42
21. Gavezzotti A 2002 Calculation of intermolecular interaction energies by direct numerical integration over electron densities. I. Electrostatic and polarization energies in molecular crystals *J. Phys. Chem.* **B106** 4145
22. Gavezzotti A 2003 Calculation of intermolecular interaction energies by direct numerical integration over electron densities. 2. An improved polarization model and the evaluation of dispersion and repulsion energies *J. Phys. Chem.* **B107** 2344
23. Gavezzotti A 2011 Efficient computer modeling of organic materials. The atom-atom, Coulomb–London–Pauli (AA-CLP) model for intermolecular electrostatic-polarization, dispersion and repulsion energies *New J. Chem.* **35** 1360
24. Bader R F 1991 A quantum theory of molecular structure and its applications *Chem. Rev.* **91** 893
25. Spackman M A and Jayatilaka D 2009 Hirshfeld surface analysis *CrystEngComm* **11** 19
26. Spackman M A and McKinnon J J 2002 Fingerprinting intermolecular interactions in molecular crystals *CrystEngComm* **4** 378
27. McKinnon J J, Jayatilaka D and Spackman M A 2007 Towards quantitative analysis of intermolecular interactions with Hirshfeld surfaces *Chem. Comm.* **37** 3814
28. Sheldrick G M 2008 A short history of SHELX *Acta Cryst.* **A64** 112
29. Sheldrick G M 2015 Crystal structure refinement with SHELXL *Acta Cryst.* **C71** 3
30. Spek A L 2003 Single-crystal structure validation with the program PLATON *J. Appl. Cryst.* **36** 7
31. Macrae C F, Edgington P R, McCabe P, Pidcock E, Shields G P, Taylor R, Towler M and Streek J V D 2006 Mercury: visualization and analysis of crystal structures *J. Appl. Cryst.* **39** 453
32. Turner M J, McKinnon J J, Wolff S K, Grimwood D J, Spackman P R, Jayatilaka D and Spackman M A 2017 CrystalExplorer17 University of Western Australia.
33. McKinnon J J, Spackman M A and Mitchell A S 2004 Novel tools for visualizing and exploring intermolecular interactions in molecular crystals *Acta Cryst.* **B60** 627
34. Boys S F and Bernardi F 1970 The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors *Mol. Phys.* **19** 553
35. Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Mennucci B, Petersson G A, Nakatsuji H, Caricato M, Li X, Hratchian H P, Izmaylov A F, Bloino J, Zheng G, Sonnenberg J L, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery Jr. J A, Peralta J E,

- Ogliaro F, Bearpark M, Heyd J J, Brothers E, Kudin K N, Staroverov V N, Keith T, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant J C, Iyengar S S, Tomasi J, Cossi M, Rega N, Millam J M, Klene M, Knox J E, Cross J B, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann R E, Yazyev O, Austin A J, Cammi R, Pomelli C, Ochterski J W, Martin R L, Morokuma K, Zakrzewski V G, Voth G A, Salvador P, Dannenberg J J, Dapprich S, Daniels A D, Farkas O, Foresman J B, Ortiz J V, Cioslowski J. Fox, D J 2013 Gaussian 09, Revision D. 01, Gaussian Inc., Wallingford CT
36. Zhao Y and Truhlar D G 2008 The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals *Theo. Chem. Acc.* **120** 215
37. Grimme S, Antony J, Ehrlich S and Krieg H 2010 A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu *J. Chem. Phys.* **132** 154104
38. Becke A D 1993 Density-functional thermochemistry. III. The role of exact exchange *J. Chem. Phys.* **98** 5648
39. Espinosa E, Molins E and Lecomte C 1998 Hydrogen bond strengths revealed by topological analyses of experimentally observed electron densities *Chem. Phys. Lett.* **285** 170
40. Bulat F A, Toro-Labbé A, Brinck T, Murray J S and Politzer P 2010. Quantitative analysis of molecular surfaces: areas, volumes, electrostatic potentials and average local ionization energies *J. Mol. Model.* **16** 1679
41. Percino M J, Cerón M, Rodríguez O, Soriano-Moro G, Castro M E, Chapela V M, Siegler M A and Pérez-Gutiérrez E 2016 Conformational and Molecular Structures of α , β -Unsaturated Acrylonitrile Derivatives: Photophysical Properties and Their Frontier Orbitals *Molecules* **21** 389
42. Percino M J, Cerón M, Ceballos P, Soriano-Moro G, Castro M E, Chapela V M, Bonilla-Cruz J, Reyes-Reyes M, López-Sandoval R and Siegler M A 2014 Important role of molecular packing and intermolecular interactions in two polymorphs of (Z)-2-phenyl-3-(4-(pyridin-2-yl)phenyl) acrylonitrile Preparation, structures, and optical properties *J. Mol. Struct.* **1078** 74
43. Matta C F, Hernández-Trujillo J, Tang T H and Bader R F 2003 Hydrogen-hydrogen bonding: a stabilizing interaction in molecules and crystals *Chem. Eur. J.* **9** 1940
44. Al-Wahaibi L H, Sujay S, Muthu G G, El-Emam A A, Venkataramanan N S, Al-Omary F A, Ghabbour H A, Percino J and Thamotharan S 2018 Theoretical investigations of two adamantane derivatives: A combined X-ray, DFT, QTAIM analysis and molecular docking *J. Mol. Struct.* **1159** 233
45. Thamotharan S, Kothandapani J, Ganesan S S, Venkataramanan N S, Kumar S M, Byrappa K, Percino J and Robles F 2018 Quantitative analysis of intermolecular interactions in 2, 2'-((4-bromophenyl)methylene) bis (3-hydroxy-5, 5-dimethylcyclohex-2-en-1-one): insights from crystal structure, PIXEL, Hirshfeld surfaces and QTAIM analysis *J. Chem. Sci.* **130** 20
46. Udayakumar M, Jagatheeswaran K, Ganesan S S, Venkataramanan N S, Kumar S M, Byrappa K and Thamotharan S 2017 Investigation of 9-(2-hydroxy-4, 4-dimethyl-6-oxocyclohex-1-en-1-yl)-3, 3-dimethyl-2, 3, 4, 9-tetrahydro-1H-xanthen-1-one: Crystal structure, AIM and NBO analysis *J. Mol. Struct.* **1133** 510
47. Popelier P L 1998 Characterization of a dihydrogen bond on the basis of the electron density *J. Phys. Chem.* **A102** 1873
48. Koch U and Popelier P L 1995 Characterization of CHO hydrogen bonds on the basis of the charge density *J. Phys. Chem.* **99** 9747
49. Munshi P, Thakur T S, Guru Row T N and Desiraju G R 2006 Five varieties of hydrogen bond in 1-formyl-3-thiosemicarbazide: an electron density study *Acta Cryst.* **B62** 118
50. Munshi P and Guru Row T N 2006 Intra-and intermolecular interactions in small bioactive molecules: cooperative features from experimental and theoretical charge-density analysis *Acta Cryst.* **B62** 612
51. Munshi P, Cameron E, Guru Row T N, Ferrara J D and Cameron T S 2007 Investigation of inter-ion interactions in *N,N,N',N'*-tetramethylethylenediammonium dithiocyanate via experimental and theoretical charge density studies *J. Phys. Chem.* **A111** 7888