Crystal Packing Analysis of Picric Acid, Phthalazone and their Cocrystal using Hirshfeld Computational Studies

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Abstract

In this paper we present the investigation of crystal packing of picric acid (PA), phthalazone (PZ) and their cocrystal phthalazone-picric acid (PA-PZ) using Hirshfeld surface computational analysis. The title molecules are synthesized, crystallized and three-dimensional structures are redetermined using XRD analysis. PA exhibit intermolecular hydrogen bonds O---H…N, O---H…O and intermolecular connection N---O...π. PZ shows N---H…O molecular interaction in it. O---H…O molecular contact has been noticed in PA-PZ. These intermolecular contacts within the crystal structure are quantified, evaluated and visualized in terms of 2D-finger print plots and Hirshfeld surfaces. In all crystal structures, O...H intercontact is common. The major contacts observed are O…H in PA and PA-PZ, H…H in PZ, respectively. In addition, electrostatic potential surface mappings are drawn on Hirshfeld surfaces for all the molecules. Copyright © VBRI Press.

Keywords: Computational studies, cocrystal, hydrogen bonding, Hirshfeld surfaces.

Introduction

The development of cocrystal has attained considerable attention as an alternative form in improving the properties of an API. It is composed of two or more than two molecules combined into the same crystal lattice held together by a non-covalent interaction with a fixed stoichiometric ratio [**1**]. Rationalization of crystal structures concerning these interactions is of great interest in order to make useful predictions using computational tools.

Hirshfeld surface analysis is such a radical approach which quantifies the molecular interactions. It provides visually appealing surface which smoothly encompasses available space throughout the molecules. It is built by separating the area of crystal into regions in which electron cloud of total amount of spherical atoms for molecule influences corresponding sum over the crystal [**2**].

The hydrogen bonding interaction was chief criteria in crystal engineering which is responsible for the stabilization of molecular crystal. Chen *et al.* have explored the electron transfer nature of picric acid which is a known cocrystal former. Their studies emphasized that van der Waals, hydrogen bonding and π-π stacking are prime cause for cocrystallisation. [**3**]. Yun-Chen *et al.* synthesized nitrogen heterocyclic compound Phthalazin-1(2*H*)-one and reported its crystal structure [**4**]. Yathirajan et al. obtained phthalazin-1(2*H*)-one-

picric acid using cocrystallisation methods and reported its structural details [**5**].

Taking all these into consideration, present work focused on revisiting the crystal morphology of cocrystal by using Hirshfeld surface analysis. The study of picrate salts by Chan *et al.* [**6**] depicted Hirshfeld surface packing which is reviewed for our study with the intention of making a perfect comparison of cocrystal with its individual components. The crystals (PA and PZ) and cocrystal (PA-PZ) were synthesized with different methodology and structure was redetermined using single crystal XRD method.

Experimental section

Synthesis

Molecule PA was crystalised by using aceto nitrile and water mixture in 1:1 ratio. PZ was crystalised by using methanol (10mL). Mixture of PA (0.01M) and PZ (0.01M) was ground properly using agate mortar and pestle with few drops of methanol as solvent. Then it was completely dissolved using hot methanol solution (15mL). Single crystals of PA-PZ were acquired by slow evaporation process.

Single crystal XRD studies

The yellow colour single crystal is used for diffraction experiment and the diffracted intensities were collected

using Rigaku Satrun 724+ diffractometer (at temperature 293 K). The collected intensities were processed using CrystalClear [**7**]. Structure solution and structure refinement (full-matrix least squares method on F^2) are performed in SHELXS programs [**8**] using Olex2 as interface [**9**]. The molecular structure (ORTEP) of each molecule and their packing views were extracted from MERCURY software [**10**].

Hirshfeld surface investigation

The Hirshfeld surface computational technique is employed in the investigation of molecular interactions within crystal structure. The proximity of neighbouring atoms is examined by 3D surface analysis and 2D finger print graphs [**11, 12**]. Inter contacts are quantified in terms of percentage distribution to Hirshfeld surfaces. Affinity of intermolecular contacts can be obtained by measuring a d_{norm} (normalized contact distance: extent of space between two atoms across the surface to atomic radii of atoms) based on d_e (distance to closest nuclei outside the surface), d_i (is a distance to closest nuclei within the surface from Hirshfeld surface) and van Der Waals radii of atoms [**13**]. These were investigated using CrystalExplorer 3 and electrostatic potential is traced on Hirshfeld Surface by exerting the range +-0.030 au at wave function STO-3G basis set (Hartree-Fock theory) [**14**].

Results and discussion

Single crystal X-ray diffraction analysis

An ORTEP view of PA, PZ and PA-PZ with atomic labelling is displayed in **Fig. 1**. Packing views of the molecules are as shown in **Fig. 2**. PA shows significant O---H…O, O---H…N interactions and further stabilized by N---O…π contacts. N---H…O hydrogen bonding have been observed in PZ. O---H…O inetarctions fortifies PA-PZ.


(a)

(b)   (c)
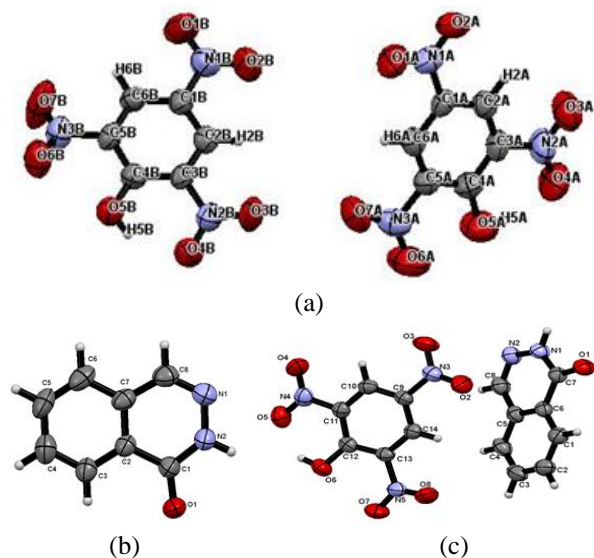
Fig. 1. ORTEP views of PA (a), PZ (b) and PA-PZ (c) with atom labelling system (displacement ellipsoids are at probability level of 50%).
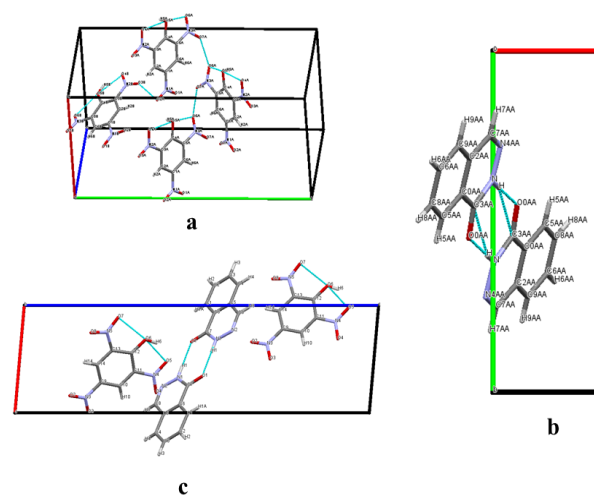
Fig. 2. Packing view of PA (a), PZ (b) and PA-PZ (c). Dotted lines indicate hydrogen bonds.
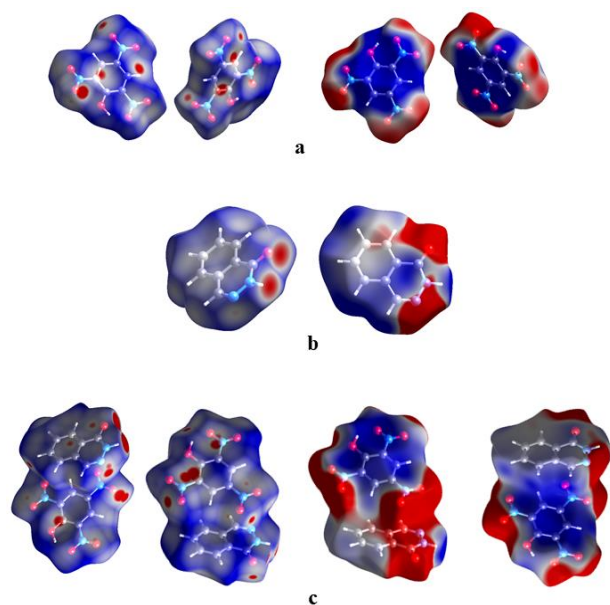
Hirshfeld surface analysis

As illustarted in **Fig. 3**., 2D finger print inetraction plots revealed that PA has C…H (0.1 %), H…H (0.8 %), O…C (25.6 %), N…C (0.2 %), H…N (1.1 %), O…H (35.5 %), O…N (11.0 %) and O…O (27.7 %). The observed intercontact for PZ are C…C (9.3 %), C…N (5.5 %), C…O (0.1 %), C…H (15 %), H…H (36.5 %), O…H (19.2 %), H…N(12.8 %), N…N (0.6 %), N…O (0.2 %), O…O (0.2 %). PA-PZ exhibits inter connections C…C (2.1 %), C…H (5.6 %), O…C (12.7 %), H…H (13.6 %), C…N (4.4 %), N…H (1.5 %), N…N (1.4 %), N…O (5.6 %), O…H (4.5 %), O…O (7.9 %). These molecular intercontacts have their significant distribution to the total surface area.
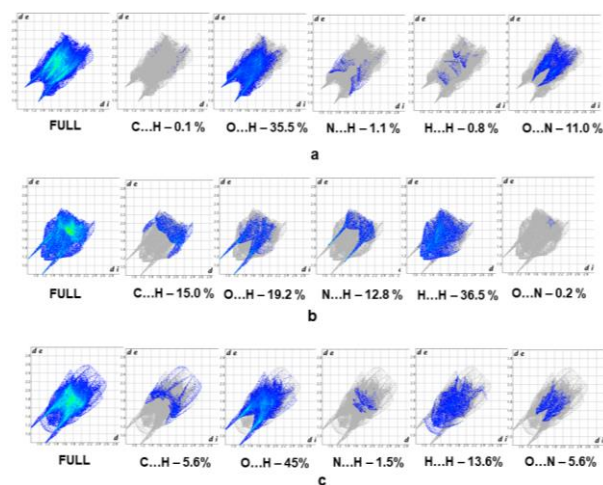
Fig. 3. Dnorm mapped on Hirshfeld surface (2D finger print plots) of the PA (a), PZ (b) and PA-PZ (c). (Color scale -0.11 auto -1.4 au). The gray area outlines full fingerprint.

3D Hirshfeld surfaces and molecular elctrostactic potential maps for each molecules were drawn and depicted in **Fig. 4**. The blue region on surface represents positive electrostatic potential (hydrogen bond donors) whereas red region represents negative electrostatic potential representing hydrogen bond acceptors.

Fig. 4. Different orientations of electrostatic potential plots on Hirshfeld surfaces with +-20 au for PA (a), PZ (b) and PA-PZ (c).

Conclusions

The crystal packing was perceptualized with regard to single crystal XRD, 2D-finger print plots and Hirshfeld surfaces and compared with its individual components. In the supramolecular architecture, major contacts observed among the molecules are O…H in PA and PA-PZ and H…H in PZ. In PA-PZ O---H…O intermolecular hydrogen bonding has been observed and percentage distribution of O...H was found to be 45%. Thus, it clearly says that O---H…O interaction between the molecules is responsible for cocrystalisation. The surface characteristics displayed the interaction between different atoms and hence supramolecular assembly in a very subtle way.

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