

Hirshfeld Surface Analysis of Phthalyl Sulfacetamide

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ABSTRACT: Phthalyl Sulfacetamide is an antibiotic sulfonamide used as a leprostatic agent to treat urinary tract infections. The title compound crystallizes in monoclinic crystal system with $P2_1/n$ space group and $Z=4$. The presence of quite a good number of potential donor and acceptor groups facilitate the formation of intra and intermolecular interactions like $O-H\cdots O$, $N-H\cdots O$, $C-H\cdots O$, $\pi-\pi$ and $C-H\cdots\pi$ which play prominent role in the stability of molecular structure. The 3-D Hirshfeld surface analysis and 2-D fingerprint analysis are performed to study the nature of interactions and their quantitative contributions towards the crystal packing. 'Crystal Explorer' provides a new way of visualizing interactions in molecular crystals using the full suite of Hirshfeld surface tools.

KEYWORDS: Phthalyl Sulfacetamide, Hirshfeld analysis, Intermolecular interactions, 2-D fingerprint plots.

I. INTRODUCTION

Sulfonamide is an important class of biologically active heterocyclic compounds. Sulfonamides are the first antimicrobial agent having wide spread applications as anti bacterial, anti fungal and anti viral drugs [1-3]. Sulfacetamide, a highly soluble sulfonamide which does not cause crystalluria, and its sodium salt are extensively used in ophthalmic infections, giving solutions which are non-irritating to the delicate tissues of the eye. Crystal structure of sulfacetamide sodium monohydrate (Ghosh, Basak & Mazumdar, 1987) [4] have already been reported. Along with this, the crystal structure of 2-((4-([Acetylamino]sulfonyl)phenyl)amino)carbonyl)benzoic acid (Phthalyl sulfacetamide) is also reported by T. P. Singh et al. [5]. The chemical structure of Phthalyl sulfacetamide is shown in Fig. 1.

Crystal design and crystal engineering, prediction and computation of molecular crystal structure through intermolecular interactions also have aroused attention [6-8]. The main approach is through Hirshfeld surfaces, a powerful tool for elucidating molecular crystal structures [9]. Hirshfeld surface is a space partitioning construct that summarizes the crystal packing into a single 3-D surface, and the surface can be reduced to a 2-D fingerprint plot, which summarizes the complex information on intermolecular interactions present in molecular crystals. The present work brings a complete study on Hirshfeld surface analysis of Phthalyl sulfacetamide.

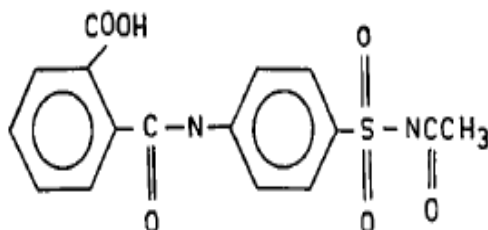


Fig. 1. Chemical structure of 2-((4-([Acetylamino]sulfonyl)phenyl)amino)carbonyl)benzoic acid

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II. MATERIALS AND METHODOLOGY

The title compound, Phthalyl sulfacetamide, is procured from Sigma Aldrich. Transparent rectangular needle shaped diffraction quality single crystals of the title compound are grown by slow evaporation technique using methanol (Loba Chemie) solvent at room temperature.

Molecular Hirshfeld surfaces [10] in the crystal structure have been constructed based on the electron distribution calculated as the sum of spherical atom electron densities [11]. For a given crystal structure and set of spherical atomic electron densities, the Hirshfeld surface which is unique [12] suggests the possibility of gaining additional imminent into the intermolecular interactions of molecular crystals. Hirshfeld surfaces and the associated 2-D fingerprint plots are generated using the Crystal Explorer 3.1 [13]. When the CIF file is read into the Crystal Explorer program for analysis, all bond lengths to hydrogen are automatically modified to typical standard neutron values (C–H = 1.083 Å and N–H = 1.009 Å). The 2-D fingerprint plots displayed by using the standard 0.6–2.8 Å view with the d_e and d_i distance scales displayed on the graph axes. The normalized contact distance (d_{norm}) based on both d_e , d_i and the vdw radii of the atom, given by Eq. (1) enables identification of the regions of particular importance to intermolecular interactions. Because of the symmetry between d_e and d_i in the expression for d_{norm} , where two Hirshfeld surfaces touch, both will display a red spot identical in color intensity as well as size and shape.

$$d_{norm} = (d_i - r_i^{vdw})/r_i^{vdw} + (d_e - r_e^{vdw})/r_e^{vdw} \quad (1)$$

III. RESULTS AND DISCUSSION

Hirshfeld Surface Analysis: The Hirshfeld surface enclosing a molecule is defined by points where the contribution to the electron density from the molecule of interest is equal to the contribution from all the other molecules. For each point on that isosurface two distances are defined: d_e (the distance from the point to the nearest nucleus external to the surface), and d_i (the distance to the nearest nucleus internal to the surface). The molecular Hirshfeld surfaces of the title molecule generated using a standard (high) surface resolution with the 3-D d_{norm} surfaces mapped over a fixed color scale of -0.738 (red) to 1.813 Å (blue), shape index mapped in the color range of -1.00 to 1.00 and curvedness in the range of -4.0 to 0.4. The molecular Hirshfeld surfaces (d_{norm} , curvedness, d_i , d_e and shape index) of the title molecule are shown in Fig. 2.

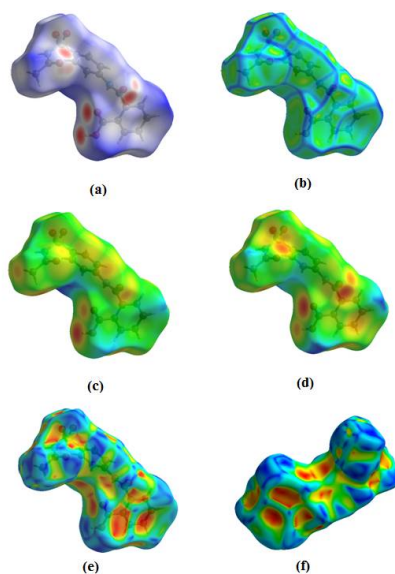


Fig. 2. Hirshfeld surfaces mapped with (a) d_{norm} , (b) curvedness, (c) d_i , (d) d_e , (e) front view of shape index (f) back view of shape index

For comparison of intermolecular interactions scheme in crystal structure, the normalized contact distances, d_{norm} , based on van der Waals radii, are mapped into the Hirshfeld surfaces. In the color scale, negative values of d_{norm} are visualized by the red color, indicating contacts shorter than the sum of van der Waals radii. The white color denotes intermolecular distances close to van der Waals contacts with d_{norm} equal to zero. In turn, contacts longer than the sum of van der Waals radii with positive d_{norm} values are indicated by blue. The O–H and C–H contacts in the molecule can be seen in the Hirshfeld surface as the bright red areas. The other visible spots on the surface correspond to H–H contacts. Shape index is a measure of “which shape” and it can be sensitive to very subtle changes in surface shape, particularly in areas where the total curvature is very low. The curvedness is the measurement of “how much shape”, the flat areas of the surface correspond to low values of curvedness, while sharp curvature areas correspond to high values of curvedness and usually tend to divide the surface into patches, indicating interactions between neighboring molecules.

2-D fingerprint plots: The 2-D fingerprint plots can be decomposed to highlight particular atom pair close contacts. This decomposition enables separation of contributions from different interaction types, which overlap in the full fingerprint. The 2-D fingerprint plots, which analysis all of the intermolecular contacts at the same time, revealed that the main intermolecular interactions in the molecules are H··H, H··O, H··C, H··N and C··C intermolecular interactions shown in Fig. 3. The 2-D fingerprint plot of the title compound for all intermolecular contacts are shown in Fig. 3a. The H–H contacts, which are reflected in the middle of scattered points and cover most area in the 2-D fingerprint plots, have a most significant contribution to the total Hirshfeld surfaces (32.4%) shown in Fig. 3b. The H–O contacts appear as distinct spikes shown in Fig. 3c. Complementary regions are visible in the fingerprint plots where one molecule act as donor ($d_e > d_i$) and the other as an acceptor ($d_e < d_i$). The proportion of O–H/H–O contacts comprising 38% of the total Hirshfeld surfaces for each molecule of the compound which is also supported experimental data. At bottom left of the fingerprint plot, there are characteristic “wings” which are identified as a result of H–C contacts shown in Fig. 3d. The decomposition of the fingerprint plot shows that C–H/H–C contacts comprise 16.8% of the total Hirshfeld surface area. The proportion of N–H/H–N contacts comprising 1.4% of the total Hirshfeld surfaces shown in Fig. 3e. The C–C contact on the fingerprint plot is presented as characteristic stacking kite, which is mainly assigned to π – π interaction. This is reflected by red–blue triangles on the shape index surface of the title compound shown in Fig. 2e and Fig. 2f. The C–C contact includes only 0.8% of the total Hirshfeld surfaces area shown in Fig. 3f. Thus the nature of the interplay of the molecule is more easily understood using Hirshfeld surface, with the results further highlighting the power of the technique in mapping out the interactions within the crystal and this methodology has very important promise in crystal engineering [14]. Undoubtedly, the Hirshfeld surface allows a much more detailed scrutiny by displaying all the intermolecular interactions and by quantifying them in 2-D fingerprint plot within the crystal. In fact it is a novel tool in crystal structure prediction.

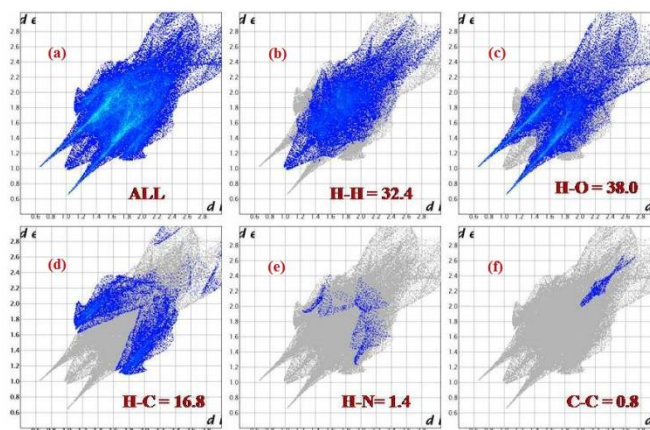


Fig. 3. 2-D fingerprint plots of Phthalyl sulfacetamide: (a) All (b) H–H (c) H–O (d) H–C (e) H–N (f) C–C contacts showing the percentages of contacts contributed to the total Hirshfeld surface area of molecule

Strong intermolecular and weak but significant intramolecular interactions are responsible for the stability of the crystal structure. The carbonyl oxygen and hydroxyl oxygen atom form a significant O–H···O intermolecular interactions with pseudo ring of dimension $R_2^2(8)$ shown in Fig. 4.

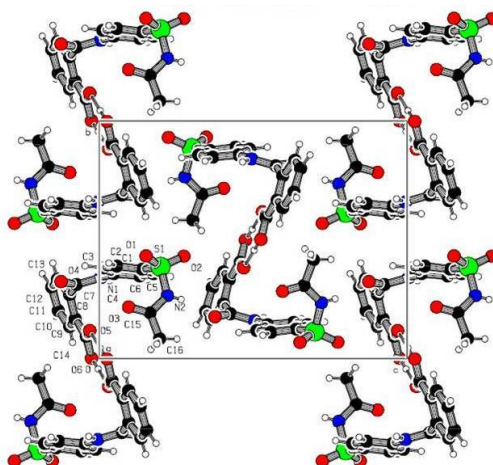


Fig. 4. O–H···O intermolecular interactions of Phthalyl sulfacetamide

One of the C–H···O intramolecular interactions is formed between aromatic carbon and sulfonamido oxygen atom. Second C–H···O intramolecular interactions is formed between aromatic carbon and hydroxyl oxygen atom. The ORTEP view showing C–H···O intramolecular interactions are depicted in Fig. 5.

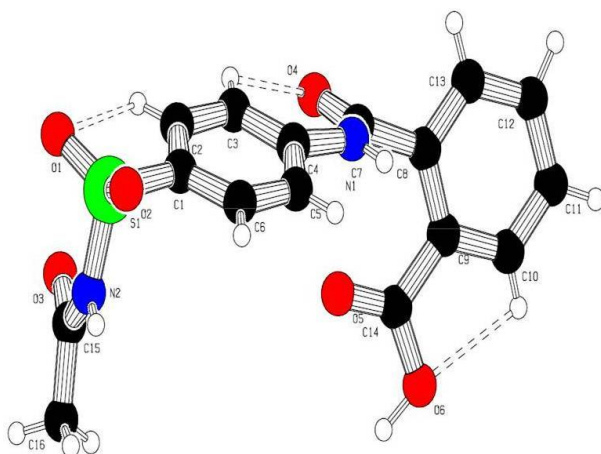


Fig. 5. C–H···O intramolecular interactions of Phthalyl sulfacetamide

The strongest O6–H6A···O5 interaction represented by comparatively dark red region in d_{norm} Hirshfeld surface. The presence of red spot on front view reflects the N2–H2A···O4 interaction and C16–H16A···O4 intermolecular interaction is presented on back view of d_{norm} surface at the distance of Vander wall separation (white region). The intermolecular interactions mapped with d_{norm} Hirshfeld surfaces are shown in Fig. 6.

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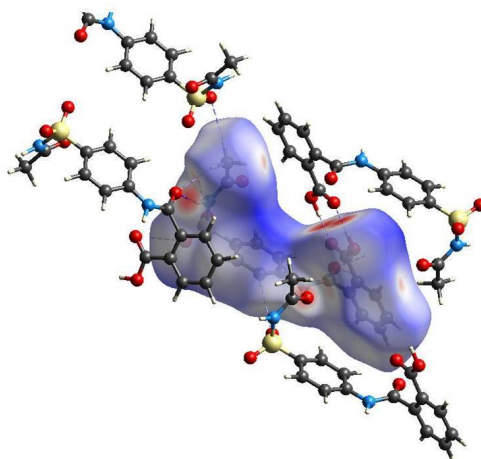


Fig. 6. d_{norm} Hirshfeld surface showing O–H···O intermolecular interactions

IV. CONCLUSION

In the crystalline phase of the title compound, the O–H···O interaction forms a pseudo ring of dimension $R_2^2(8)$ which is also observed in d_{norm} Hirshfeld surface. The highest contribution of H···O interactions in the molecular stability are confirmed by 2-D fingerprint analysis and experimental data from X-ray.

V. ACKNOWLEDGMENTS

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