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Hirshfeld Computational Analysis and Crystal Structure of 5-[3-(4-Nitrophenyl)-4,5-dihydro-1,2-oxazol-5-yl]-Methyl-5H-dibenzo-[b,f]azepine

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ABSTRACT

The title compound 5-[3-(4-Nitrophenyl)-4,5-dihydro-1,2-oxazol-5-yl]Methyl-5H-dibenzo-[b,f]azepine, is synthesized and characterized using single crystal X-ray diffraction method. The azepine ring adopts boat confirmation and the fused benzene rings to the azepine ring makes a dihedral angle of 53.39 (7)°. In the crystal structure, molecules are stabilized with the C-H \cdots π , N-O \cdots π and $\pi\cdots\pi$ short contacts. The intermolecular contacts in the crystal structures are quantified using Hirshfeld surfaces analysis method. The results suggests that the intermolecular H \cdots H contacts contributes more to the crystal packing when compared to other contacts and the electrostatic potential surfaces are visualized.

Keywords: Dibenzoazepine, Crystal structure, Short contacts, Hirshfeld surfaces

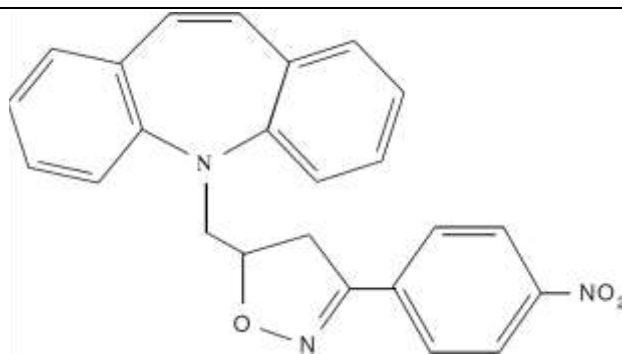
INTRODUCTION

A large number of dibenzoazepine derivatives have been synthesized and reported to have number of pharmacological activities [1-3]. Among them, dibenzo[b,f]azepine have attracted considerable attention, which shows a broad range of pharmaceutically active compounds [3-5]. Dibenzoazepine deravative, 5H-dibenzo[b,f]azepine is a common basic fused tricyclic amine. It is used as an intermediate for the synthesis of the registered anticonvulsant drug oxcarbazepine [6,7]. Dibenzo[b,f]azepine and its derivatives have been variously reported as having antiallergic activity, specifically antihistaminic, spasmolytic, serotonin antagonistic, anticonvulsive, antiemetic, antiepileptic, antiinflammatory, sedative and fungicidal action [8]. The crystallographic studies of the molecular and crystal structures of dibenzoazepine derivatives have been reported. [9-12]. In view of the above importance, the synthesis, crystal structure and Hirshfeld surfaces of the title compound 5-[3-(4-Nitrophenyl)-4, 5-dihydro-1,2-oxazol-5-yl]Methyl-5H-dibenzo-[b,f]azepine is reported herewith.

MATERIALS AND METHODS

Synthesis of the 5-[3-(4-Nitrophenyl)-4,5-dihydro-1,2-oxazol-5-yl]-Methyl-5H-dibenzo-[b,f]azepine

4-Nitro-benzaldehyde oxime (2.0 mmol) was taken in methylene dichloride (10 ml) taken in a round bottom flask. The solution was made basic using triethyl amine (5.0 mmol). N-Chloro succinimide (2.0 mmol), followed by tricyclic amine (1 mmol), were added slowly at 0°C to the stirring solution. After complete addition of the reactants the stirring was continued 6 h. After completion of the reaction (Monitored by Thin Layer Chromatography (TLC)), the reaction mixture was extracted with ethyl acetate (2 \times 25 ml). The combined organic layer was washed with 0.1 N hydrochloric acid (2 \times 20 ml), followed by brine solution (2 \times 20 ml). Then, the organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford the crude product, which was then purified by column chromatography over silica gel (60-120 mesh) using Hexane: Ethyl acetate mixture in 7: 3 ratios as eluent. The slow evaporation method using ethyl acetate and hexane gave yellow colored block shaped crystals. The schematic diagram of the molecule is shown in Scheme 1.



Scheme 1: The chemical diagram of the title compound

Single crystal X-ray diffraction

A yellow block shaped crystal of the title compound, $C_{24}H_{19}N_3O_3$ with dimensions of $0.23 \times 0.21 \times 0.22 \text{ mm}^3$ was chosen for an X-ray diffraction study using Bruker X8 Proteum diffractometer equipped with $\text{CuK}\alpha$ radiation ($\lambda=1.54178 \text{ \AA}$) at 296K. Data collections, integration, and scaling of the reflections were performed using the APEX2 program [13]. The structure was solved by direct methods using SHELXS [14]. All the non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement using SHELXL [14] with isotropic displacement parameters for all the atoms Refinement of the non-hydrogen atoms with anisotropic parameters was started at this stage. The hydrogen atoms were placed at chemically acceptable positions and were allowed to ride on their parent atoms. The details of the crystal data and structure refinement are given in Table 1. The ORTEP [15] of the molecule with thermal ellipsoids drawn at 50% probability is shown in Figures 1 and 2.

Hirshfeld surfaces analysis

The program Crystal Explorer 3.0 [16] was used to perform Hirshfeld surfaces computational analysis and to quantify the intermolecular interactions in terms of surface contribution and generating graphical representations (Figure 3a), plotting 2D fingerprint plots (Figure 3b) [17] and generating electrostatic potential (3c) [18] with TONTO [19]. The electrostatic potential is mapped on Hirshfeld surfaces using Hartree-Fock (STO-3G basis set) theory over the range of -0.020 a.u. to $+0.020 \text{ a.u.}$ (Figure 3c). The electrostatic potential surfaces are plotted with red region which is a negative electrostatic potential (hydrogen acceptors) and blue region which is a positive electrostatic potential (Hydrogen donor).

RESULTS AND DISCUSSIONS

Molecular and crystal structure

The azepine ring (Figure 1) adopts a boat conformation with the nitrogen atom showing a maximum deviation of $0.494(1) \text{ \AA}$, the puckering parameters $Q_2=0.711(1) \text{ \AA}$, $\phi_2=1.95(1)^\circ$, $Q_3=0.214(1) \text{ \AA}$ and $\phi_3=359.8(4)^\circ$ and the total puckering amplitude $Q_T=0.7431(1) \text{ \AA}$ [20]. The fused benzene rings $\text{Cg}(2):\text{C}1/\text{C}2/\text{C}3/\text{C}4/\text{C}5/\text{C}15$ and $\text{Cg}(3) \text{C}8/\text{C}9/\text{C}10/\text{C}11/\text{C}12/\text{C}13$ to the azepine motif makes a dihedral angle of $53.39(7)^\circ$. The bond lengths and bond angles of the title compound are in good agreement with the standard values. The bond lengths $\text{N}14-\text{C}13=1.434(2) \text{ \AA}$ and $\text{N}14-\text{C}15=1.434(2) \text{ \AA}$ indicates π -electron delocalization, as a result there is a difference in the bond length of $\text{C}5-\text{C}6=1.459(2) \text{ \AA}$ and $\text{C}7-\text{C}8=1.455(2) \text{ \AA}$. The torsion angles for the atoms $\text{C}1-\text{C}15-\text{N}14-\text{C}16$ and $\text{C}12-\text{C}13-\text{N}14-\text{C}16$ shows +syn-periplanar conformation with $24.8(19)^\circ$ and -syn-periplanar conformation with $-27.9(1)^\circ$ about the mean plane of fused rings respectively. The packing of the molecules (Figure 2) is stabilized with the $\pi\cdots\pi$, $\text{C}-\text{H}\cdots\pi$ and $\text{N}-\text{O}\cdots\pi$ short contacts. The $\pi\cdots\pi$ interaction exists between centroids $\text{Cg}(2)$ with a distance of $3.927(9) \text{ \AA}$ [$-x, y-1, -z$]. The $\text{C}3-\text{H}3\cdots\text{Cg}(3)$ and $\text{C}9-\text{H}9\cdots\text{Cg}(2)$ exists with distance of $3.643(2) \text{ \AA}$ [angle 142° , $(-x, y-1, -z)$] and $3.573(2) \text{ \AA}$ [angle 147° , $(x, y-1/2, z-1/2)$], respectively. In addition a short contact $\text{N}28\cdots\text{O}29\cdots\text{Cg}(3)$ exists with a distance of $3.737(2) \text{ \AA}$ [angle 102° , $(x, y-1/2, z-1/2)$].

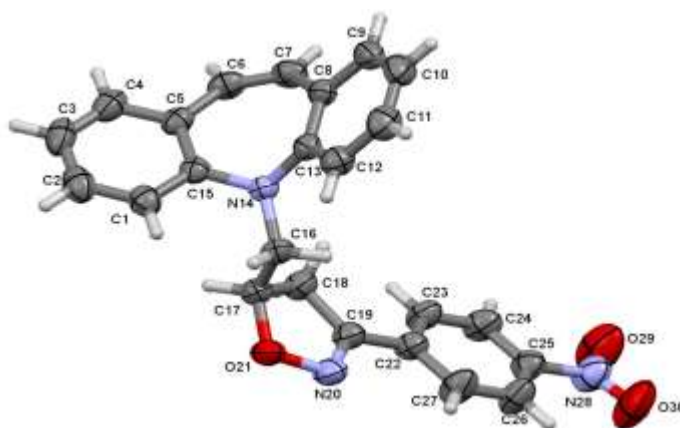


Figure 1: ORTEP of the title compound showing the atomic numbering system. Displacement ellipsoids are drawn with 50% probability

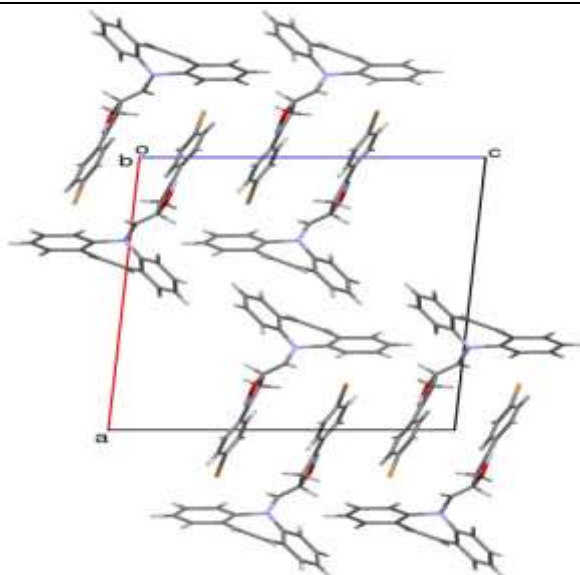


Figure 2: Crystal packing of the molecules viewed across b-axis

Table 1: Crystal data and structure refinement details for the title compound

CCDC number	1526804
Empirical formula	C ₂₄ H ₁₉ N ₃ O ₃
Formula weight	397.42
Temperature (K)	293(2)
Wavelength (K α , Å)	0.71075
Crystal system, space group	Monoclinic, <i>P21/c</i>
Unit cell dimensions (Å, °)	$a=18.8298(11)$ $b=6.9338(4)$ $c=15.1055(10)$ $\beta=95.096(2)$
Volume Å ³	1964.4(2)
Z	4
Calculated density (Mg/m ³)	1.344
Absorption coefficient (mm ⁻¹)	0.733
$F_{(000)}$	832
Crystal size mm	0.20 x 0.20 x 0.21
Theta range for data collection (°)	2.4 to 63.8
Limiting indices	$-21 \leq h \leq 21$, $-8 \leq k \leq 6$, $-17 \leq l \leq 14$
Reflections collected/unique[R(int)]	21670/3091 [0.030]
Refinement method	Full-matrix least-squares on F ²
Data/restraints/parameters	3091/0/371
R value/wR2	0.0390/0.1094
Goodness-of-fit on F ²	1.04
Largest diff. peak and hole (e. Å ⁻³)	0.26 and -0.31

Hirshfeld surface analysis

The short contacts ($\pi\cdots\pi$, C-H $\cdots\pi$ and N-O $\cdots\pi$) in the crystal structures are quantified using Hirshfeld surface analysis and the Hirshfeld surfaces are visualized (Figure 3a). The 2D-fingerprint plots of intercontacts contributing to the Hirshfeld surfaces are (i) C \cdots C-4.2%, (ii) C \cdots H-19.6%, (iii) C \cdots N-2.9%, (iv) C \cdots O - 4.7%, (v) H \cdots H-43.8%, (vi) H \cdots N -4.1%, (vii) H \cdots O-20.6% and the full plots is shown in Figure 3b, (viii) The major intercontacts contributing to Hirshfeld surfaces are H \cdots H, O \cdots H and C \cdots H. The electrostatic potential Figure 3c shows the distribution of positive and negative potential over the Hirshfeld surfaces.

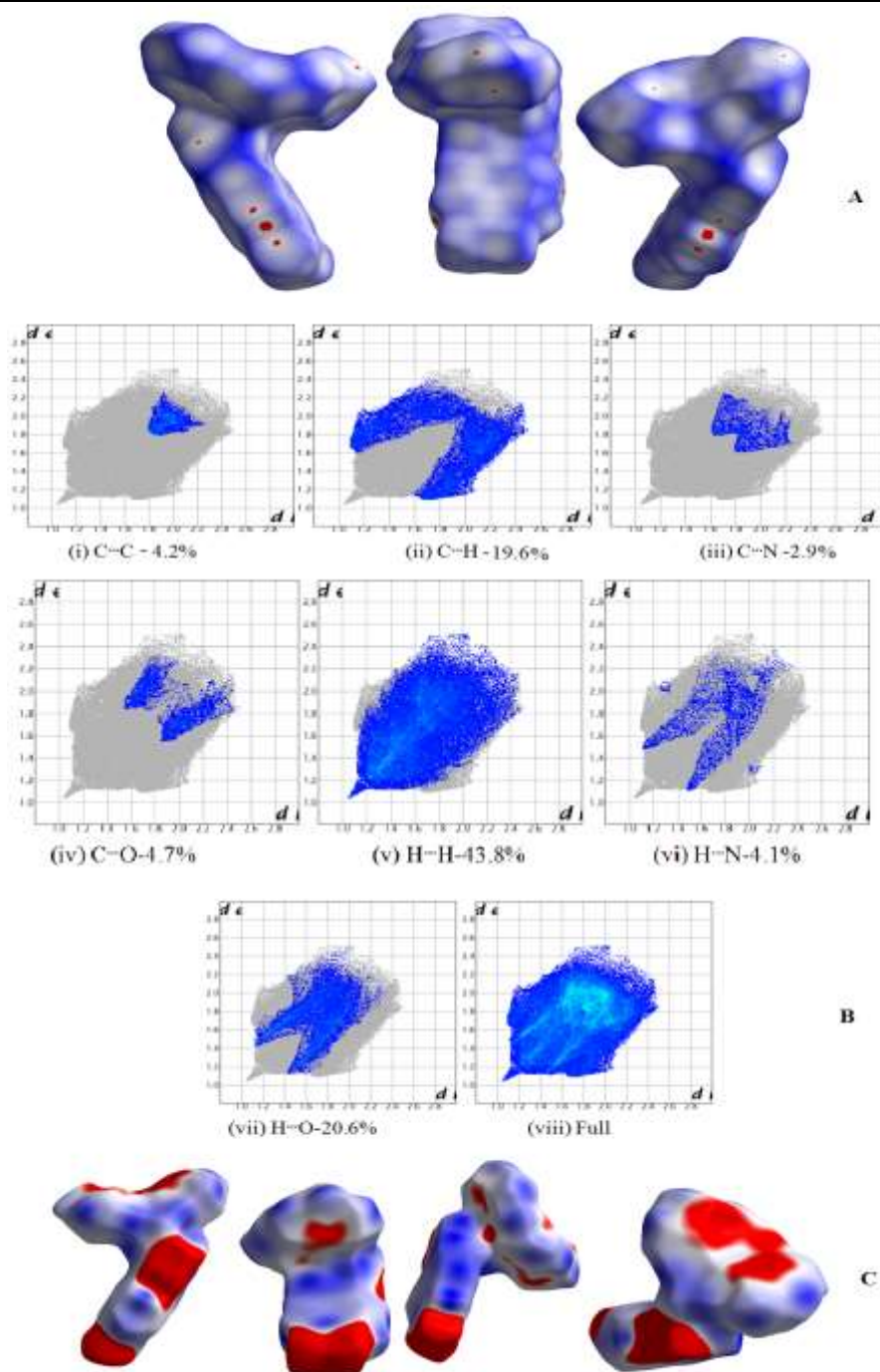


Figure 3: Hirshfeld surfaces analysis: (a) d_{norm} mapped on Hirshfeld surface for visualizing the intercontacts of the title compound. Color scale in between -0.003 au (blue) and 1.400 au (red). (b) Fingerprint plots- (i) C-C, (ii) C-H, (iii) C-N, (iv) C-O, (v) H-H (vi) H-N, (vii) H-O and (viii) full. The outline of the full fingerprint is shown in gray. This is the closest internal distance from a given point on the Hirshfeld surface and d_e is the closest external contacts. (c) Electrostatic potential mapped on Hirshfeld surface (different orientation) with ± 0.020 au. Blue region corresponds to positive electrostatic potential and red region to negative electrostatic potential

CONCLUSIONS

The title compound is synthesized, crystallized and the three dimensional molecular structure is determined using single crystal X-ray diffraction method. The azepine ring adopts boat configuration and the crystal structure is stabilized with short contacts $\pi-\pi$, C-H \cdots π and N-O \cdots π . In addition, the intercontacts C-C, C-H, C-N, C-O, H-H, H-N and H-O are contributing to the Hirshfeld surfaces.

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Supplementary materials

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications numbers 1526804.

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