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Hirshfeld surface, charge density and site selectivity studies of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone

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ABSTRACT

Extensive quantum chemical calculations were carried out for the molecule with B3LYP/6311G++(d,p) level of theory. The molecular packing of the crystal is stabilized by C—H...N and C—H...O interactions and those interactions were investigated through Hirshfeld surface analysis. Aspherical distribution of charges was estimated using Hansen-Coppens multipole formalism and the effect of temperature on charge density was analyzed. Bader's AIM theory was used to perform the topological analysis of electron density which disclose the strength and nature of atom-atom interaction. Stability of the molecule arising from hyper conjugative interactions and charge delocalization was examined using Natural Bond Orbital analysis and it also confirms the existence of C—H...N and C—H...O hydrogen bonds. Frontier Molecular Orbital analysis was carried out and the molecule is found to be a good electrophile with the electrophilicity index of 9.7349 eV. Molecular Electrostatic Potential was used to identify the possible reactive locations of the molecule.

1. Introduction

Ever since the discovery of imidazol, the research and developments of imidazol based compounds have turn out to be a rapidly increasing active field due to their extensive applications in natural products, medicinal chemistry, non linear optical applications, catalysts, corrosion inhibitors and so on [1-6]. Even though it has enormous number of applications, imidazol derivatives attained a great progress in medicinal chemistry and it played a crucial role in the treatment of different types of diseases. The phenomenon that nature selects this distinctive type of imidazol ring in various bio molecules such as cobalamin, histamine and hemoglobin shows that the imidazol ring is essential for the physiological action in many biological activities. These specific physiological properties gained special attention in imidazol based medicinal chemistry [7-9]. The presence of imidazol ring in certain compounds enhances the water solubility to some extent due to its ability to form hydrogen bonds. On the other hand imidazol has an attractive binding site that could interact well with the bio molecules in the human body. All the above mentions show the immense potentiality of imidazol based compounds in medicinal chemistry and a lot of increasing work has been carried out for its practical applications.

The compound 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone is an

imidazol derivative with anti bacterial property. The structure of the compound was already reported earlier and the crystal belongs to a monoclinic system $(P2_1/n)$ with the following lattice parameters: a = 4.7548 Å, b = 12.3971 Å, c = 14.8580 Å, $\alpha = \gamma = 90^{\circ}$, $\beta = 97.35^{\circ}$ and volume, $V = 868.62 \text{ Å}^3$ [10]. Due to the wide applications of imidazol derivatives in medicinal chemistry, the title compound was chosen for investigation. The present work deals with the exploration of structure, electronic and molecular properties of the molecule at DFT level of theory [11]. The intermolecular interactions present in the crystal were studied through Hirshfeld and fingerprint plot analysis [12]. The aspherical distribution of charges were determined from the Hansen-Coppens multipole formalism [13] and the topological analysis of bond critical points were carried out using Bader's AIM theory [14]. Laplacian, ELF and LOL map were used to quantify the nature of interaction. Frontier Molecular Orbital studies were carried out to understand the reactive nature of the molecule. In addition to that, the Molecular Electrostatic potential studies were done to understand the chemical reactivity and to identify the region of electrophilic and nucleophilic attack [15].

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2. Computational details of quantum chemical calculations

The DFT calculations for the isolated molecule were performed using GAUSSIAN 09 W [16]. The X-ray diffraction data of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone was used to optimize the structure [10]. The geometry of the molecule was fully optimized using the hybrid exchange correlation functional B3LYP with a double numeric plus polarization basis set [11,17]. Hirshfeld Surface calculations and fingerprint plot analysis were done using the package Crystal Explorer 2.1 [18]. Analysis of electron density by Bader's theory of atoms in molecules was performed using *Multiwfn 3.3.9* (MWF) program [19]. The NBO calculations were executed using NBO program as implemented in Gaussian 09W package at the DFT/B3LYP level in order to understand the intra molecular delocalization or hyper conjugation.

3. Multipole model

Understanding the real distribution of charges in a crystal is essential to study the elaborate details of charge derived parameters including the expansion/contraction of atoms during the bond formation. This can be made possible by constructing the electron density model by Hansen and Coppens multipole formalism [13] which allows the refinement of population parameters at various orbital levels. In this model, the atomic density is defined as,

$$\rho_{atom}(\overrightarrow{r}) = P_C \rho_{core}(\overrightarrow{r}) + P_V \kappa^3 \rho_{valence}(\kappa r) + \sum_{l=0}^4 \kappa^3 R_l(\kappa r) \sum_{m=-l}^l P_{lm} Y_{lm}(\overrightarrow{r}/r)$$

where P_C , P_V and P_{lm} are the population coefficients. The first two terms describe the spherically symmetric core and valence density while the third term describes the non spherical distribution of valence shell density due to chemical bonding. The R_l represent the Slater type radial functions and Y_{lm} represent the real spherical harmonic angular functions. The parameters ρ_{core} and $\rho_{valence}$ were constructed using canonical Hartree-Fock atomic orbitals and the valence function is allowed to expand or contract by adjusting the variable parameter κ and κ' The software JANA 2006 [20] was used for multipole refinement of core, valence and pseudo atomic electron occupancies. Here the neutral atom wave functions with, $n_l = 2,2,2,3,4$ for O/N/C and $n_l = 1,1$ for H are used with $l \leq 4$. For all the atoms in molecule, the valence expansion/ contraction parameter κ is refined to see the effect of asphericity while bonding.

4. Results and discussions

4.1. Geometry optimization and molecular structure

The spatial coordinates of the molecule as obtained from the crystallographic information file [10] were used as the initial coordinates for theoretical calculations. The optimized molecular structure of the title molecule along with the numbering scheme is shown in Fig. 1. In the optimized molecule the electrons are delocalized in the heterocyclic aromatic imidazol ring. In the imidazol ring 4N is bonded with 7C, 10C and 15C while 5N is bonded with 8C and 10C with a bond length of 1.391, 1.365, 1.453, 1.354 and 1.329 Å which indicates that the bonding between 4N-10C, 5N-8C and 5N-10C are delocalized while the bonding between 4N-15C and 4N-7C is a single bond. But the single bond between 4N-15C and 4N-7C has different bond length which reveals that the carbon 15C is sp³ hybridized while 7C is sp² hybridized. Similarly the bonding between 6N and 7C is a single bond with a bond length of 1.419 Å and it again confirms that the carbon atom 7C is sp^2 hybridized. The bond length of 7C and 8C is 1.377 Å which shows the bonding between 7C and 8C is double bond and it also confirms that, both the carbon atoms were involved in sp^2 hybridization. The title molecule has three C-C single bonds 15C-18C, 18C-19C and 10C-11C with a bond



Fig. 1. Optimized molecular structure and the atom labeling scheme of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone.

length of 1.540, 1.507 and 1.490 Å which shows that those atoms undergo sp³-sp², sp²-sp² and sp-sp³ hybridization. The carbonyl 18C = 30 bond has a bond length of 1.206 Å which is nearer to the standard value of 1.22 Å and the hybridization is termed as sp² = 0. The bond length of 6N-10 and 6N-20 bond in the nitro group is 1.226 and 1.238 Å which clearly reveals the delocalization of electrons in N—O bond. The C—H bond length in methyl group ranges from 1.088 to 1.095 Å which agrees well with a typical bond length of 1.09 Å [21]. The bond angle between 4N-7C–8C (106.70°) and 5N-8C–7C (109.65°) indicates the better delocalization in the former. The optimized bond lengths and bond angles obtained from theory and experiment were compared and listed in Tables 1 and 2.

4.2. Hydrogen bonding interactions

It is a fundamental task to analyse the hydrogen bonding interactions in order to understand their biological role [22,23]. Fig. 2 shows the hydrogen bonding interactions in 1-(2-Methyl-5-nitro-1H-imidazol-1yl)-acetone molecule. The structure of the molecule is stabilized by the strong as well as the weak intermolecular interactions present in the crystal. The intermolecular interactions observed in this molecule are C—H...N ⁽ⁱ⁾ and C—H...O ^{(ii), (iii)} type and the molecules are linked by 8C-9H...5N, 15C-17H...2O and 19C-21H...3O intermolecular interactions to form a three dimensional network. In addition to that, the 15C-16H group in the molecule also forms an intra molecular 15C-16H...2O interaction, where the H...A distance is 2.420 Å and the angle is 102.28° which reveal that the interaction is weak. The existence of the intra molecular hydrogen bond can be agreed if the H...A distance is less than the sum of the van der Waal radii. The distance between the hydrogen and the acceptor in 15C-16H...2O is found to be 2.42 Å which is less than the sum of van der Waal radii of $\mathrm{H}...\mathrm{O}$ (2.72 Å) which confirms the existence of intra molecular hydrogen bonding. The hydrogen bonding geometries of the title molecule is listed in Table 3.

4.3. Hirshfeld surface and fingerprint analysis of intermolecular interactions

The Hirshfeld surface of the molecule is used to explain the intermolecular interactions present in the crystal. The Hirshfeld surface analysis [12,24] was performed using the software Crystal Explorer [18]. Fig. 3 shows the Hirshfeld surface of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone molecule mapped over d_{norm} and shape index. The Hirshfeld surface mapped with d_{norm} ranges from -0.5 to 1.5 Å and shape index ranges from -1.0 to 1.0 Å. The d_{norm} values were mapped on the Hirshfeld surface using red, blue and white color scheme, where

Table 1

Comparison of Theoretical and Experimental Bond lengths.

Bond	Bond Bond length (Å)		Bond	Bond length (Å)		
	DFT 6311G++(d,p)	MultipoleAnalysis		DFT 6311G++(d,p)	MultipoleAnalysis	
10-6N	1.226	1.239 (2)	10C-11C	1.490	1.471 (4)	
20-6N	1.238	1.226 (9)	11C-12H	1.088	0.954 (2)	
30-18C	1.206	1.210(1)	11C-13H	1.093	0.956 (5)	
4N-7C	1.391	1.377 (2)	11C-14H	1.094	0.970 (2)	
4N-10C	1.365	1.364 (7)	15C-16H	1.088	0.979(1)	
4N-15C	1.453	1.459 (3)	15C–17H	1.093	0.986 (1)	
5N-8C	1.354	1.339 (3)	15C-18C	1.540	1.498 (8)	
5N-10C	1.329	1.336 (2)	18C-19C	1.507	1.480 (5)	
6N-7C	1.419	1.407 (2)	19C-20H	1.088	0.951 (3)	
7C-8C	1.377	1.357 (8)	19C-21H	1.095	0.965 (2)	
8C-9H	1.077	0.930 (1)	19C-22H	1.094	0.962 (2)	

Table 2

Comparison of Theoretical and Experimental Bond Angles.

Angle Between Atoms Angle (°)			Angle Between Atoms	Angle (°)	
	DFT 6311G++(d,p) Multipole Analysis			DFT 6311G++(d,p)	
7C-4N-10C	105.33	105.64(12)	12H–11C-13H	108.55	110.26(12)
7C-4N-15C	128.14	126.99(10)	12H–11C-14H	108.36	109.17(13)
10C-4N-15C	126.39	125.89(14)	13H–11C-14H	108.32	108.93(12)
8C-5N-10C	106.34	106.29(12)	4N-15C-16H	110.02	108.98(12)
10-6N-20	124.36	122.85(9)	4N-15C-17H	108.05	108.52(12)
10-6N-7C	117.30	116.95(13)	4N-15C-18C	112.67	114.28(12)
20-6N-7C	118.32	120.19(15)	16H–15C-17H	107.91	105.79(7)
4N-7C-6N	124.90	124.57(12)	16H-15C-18C	110.17	109.68(10)
4N-7C-8C	106.70	106.92(11)	17H-15C-18C	107.83	109.22(7)
6N-7C-8C	128.38	128.23(12)	30-18C-15C	120.87	120.25(15)
5N-8C-7C	109.65	110.29(13)	30-18C-19C	123.82	123.25(11)
5N-8C-9H	123.16	125.04(14)	15C-18C-19C	115.29	116.48(13)
7C-8C-9H	127.17	124.66(12)	18C-19C-20H	110.07	109.81(9)
4N-10C-5N	111.94	110.83(12)	18C-19C-21H	108.26	108.98(7)
4N-10C-11C	124.00	124.20(11)	18C-19C-22H	111.47	109.21(7)
5N-10C-11C	124.05	124.88(7)	20H-19C-21H	109.35	109.88(7)
10C-11C-12H	107.90	109.54(13)	20H-19C-22H	110.25	110.06(7)
10C-11C-13H	111.53	109.76(12)	21H-19C-22H	107.33	108.84(7)
10C-11C-14H	112.05	109.13(7)			



Fig. 2. Hydrogen bonding in 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone. The three intermolecular hydrogen bonding are shown by pink dashed lines and the intra molecular hydrogen bond as green dashed line.

the red region represent the region of close contacts and blue longer contacts. The C—H...N and C—H...O interactions of the molecule appear as dark red spots. Other visible spots on the surface correspond to H...H contacts. From the mapping of shape index, it is obvious that the crystal structure of the title molecule do not exhibit any π ... π stacking interaction since there is no evidence of the adjacent red and blue triangles on the shape index surface. The two dimensional fingerprint plots

that decomposed to highlight particular atoms close pair contact is shown in Fig. 4.The fingerprint plot of full contact and the relative contributions of individual intermolecular interactions to the Hirshfeld surface are depicted in Fig. 5. In Fig. 4(a), the two small spikes on the left and right sides indicate the O...H/H...O inter molecular interactions whereas the sets of diffuse points between the spikes form H...H contacts and are shown in Fig. 4 (b). The interior wing shaped feature can be recognized for N...H/H...N interactions and the upper wing shaped structure for C...H/H...C interactions can be visualized from Fig. 4 (c) and 4 (d). The butterfly shaped region in the inner part represents the O...O contacts while the set of diffuse points in the innermost region of fingerprint plots represent the C...N/N...C contacts. The contribution of inter-contacts to the Hirshfeld surface for O...H/H...O, H...H, N...H/ H...N, C...H//H...C, O...O, C...N/N...C, C...O/O...C, N...N, C...C, N... O/O...N was found to be 42.4%, 30.3%, 13.2%, 6.4%, 2,2%, 1.9%, 1.6%, 1.1%, 0.6% and 0.3% which revealed that the main inter molecular interaction is O ... H/H ... O interactions and next to O ... H/H ... O interactions the H...H contacts are dominant and it is shown in Fig. 5 (b).

4.4. Asphericity of atoms and charge density maps

The initial step in modeling the aspherical electron density is structure refinement, in which, the X-ray data was refined to produce the desired molecular structure and from which the bond lengths and bond angles were estimated and listed in Tables 1 and 2. To model the aspherical electron density the refined structure factors were transferred to the multipole refinement program MOLLY [13] incorporated in JANA

Table 3

Hydrogen Bonding Geometries of Inter and Intra molecular hydrogen bonds.

D – H A	D - H (Å)		HA (Å)	HA (Å)		D – A (Å)		A – H…D (°)	
	Theory	Exp	Theory	Exp	Theory	Exp	Theory	Exp	
8C–9H5N ⁽ⁱ⁾	1.083	0.93	2.438	2.55	3.361	3.349	142.30	143.97	
15C–17H20 ⁽ⁱⁱ⁾	1.083	0.99	2.464	2.57	3.527	3.536	166.89	167.36	
19C–21H30 ⁽ⁱⁱⁱ⁾	1.083	0.96	2.389	2.49	3.340	3.349	145.79	147.93	
15C-16H20 (a)	1.083	0.98	2.420	2.45	2.828	2.821	100.66	102.28	

Symmetry codes: (i) -x - 1, -y + 1, -z + 1; (ii) -x + 1/2, y + 1/2, -z + 1/2; (iii) x + 1, y, z; (a) intra molecular hydrogen bond.



Fig. 3. Hirshfeld surface mapped with (a) d_{norm} and (b) shape index.

2006 [20]. The results extracted from the multipole refinement were listed in Table 4. The refined κ values in Table 4, evidently reveals the expansion or contraction of atoms. The k for the atoms 11C, 15C and 19C are less than one, which clearly shows all these atoms undergo expansion during bonding and hence the valence charge increases while for the remaining atoms the κ is greater than one and it undergoes contraction during bonding. The allowed multipole deformation functions for the monoclinic $P2_1/n$ site symmetry are P20, P22+, P22-, P40, P42+, P42-, P44 + and P44- and they are listed in Table 4. To validate the quality of the data, difference Fourier maps (DFM) were constructed. The DFM in Fig. 6 is plotted with a positive and negative contour of \pm $0.05 \text{ e}\text{\AA}^{-3}$ and it shows negligible positive residual density, which clearly reveals that, the modeled electron density is more precise and it can be used to quantify the interaction. To see the effect of temperature on charge density, static and multipole deformation density maps (SMD & DMD) were constructed and presented in Fig. 7. Both the SMD and DMD maps depicts the accumulation of charge density in the bonding and lone pair regions of the molecule and the effect of temperature was deconvoluted from SMD while it is convoluted in DMD. Hence the SMD map is free from thermal smearing and the lone pair electrons of oxygen atoms are obviously visible.

4.5. Analysis of (3, -1) bond critical points and electron density

The topological view of charge distribution offers a quantitative description of bonding and this can be obtained using Bader's quantum theory of atoms in molecules [14]. According to Bader, "two atoms are bonded if they are connected by a line of maximum electron density called bond path on which lies a bond critical point where the first derivative of the electron density is equal to zero ($\nabla \rho = 0$)" and the critical points are the characteristics of the bond existing between the two atoms. In the present study, the charge density distribution obtained from DFT and multipole model were analyzed. A critical point search was made between every pair of atoms and a (3,-1) bond critical point was found between every pair of nuclei. Fig. 8 shows the molecular graph of the molecule which shows the bond path, bond critical point and two ring critical points (RCP) – one for the heterocyclic imidazol

ring and the other one for the quasi ring formed by intra molecular hydrogen bond [25]. Thus the existence of intra molecular hydrogen bond leads to the creation of quasi ring where the RCP is not at the center of the ring because of the lack of symmetry while in the imidazol ring the RCP lies at the center due to the symmetry constraints. The experimental and theoretical electron density at the bond critical point of the selected bonds in the 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)acetone molecule was calculated and listed in Table 5. The experimental electron density of the 7C-8C bond in the imidazol ring is 0.3154 e/ Bohr³ (2.128 $e/Å^3$), which is almost equal to the electron density of similar C—C bonds reported by Kubicki et al., [26]. The value for other C—C bonds in the title molecule ranges from 0.2003 to 0.2134 e/Bohr³ which shows that the C-C bond with a density of 0.3154 e/Bohr³ is a double bond while all other C-C bonds are single bonds. The electron densities at the critical points of the N-C bonds are unequal and exhibit different values. The electron density of the N-C bonds in the imidazol ring ranges from 0.2495 to 0.3326 e/Bohr³ while for other N—C bonds the electron density ranges from 0.2143 to 0.2429 e/Bohr³, which clearly shows that in the imidazol ring the bond with lowest density is the 4N-7C bond while all other bonds are delocalized and it has higher density compared to 4N-7C. Similarly the lower density of other N-C bonds in the molecule shows the single bond nature of 4N-15C and 6N-7C. The density of the O-C bond is little less compared to the density of O—N bonds where the C atom is involved in sp² hybridization. The electron densities of the hetero nuclear O—N bonds of the NO₂ group are $0.4621 \ (\rho_{(10-6N)} = 3.118 \ e/Å^3) \ and \ 0.4468 \ e/Bohr^3 \ (\rho_{(20-6N)} = 3.105 \ e/$ $Å^3$), these densities agree with the reported electron density of the NO₂ group reported by Zhurova et al., [27]. The similar trend was observed in theoretical electron density for C-C, O-N, O-C and N-C bonds. In the hetero nuclear O-N, O-C and N-C bonds, the bond critical point lies significantly closer to the N atom in the O-N bond and C atom in both O-C and N-C bonds because the atoms with high electronegativity have more affinity to electrons. But in the case of homo nuclear C-C bond the difference in electronegativity of two carbon atoms is zero and the bond critical point is found at the midpoint of two atoms. This is evident from the d_1 and d_2 values of (3, -1) critical points and it is shown in Table 5.



Fig. 4. Fingerprint plots resolved into (a) O...H/H...O, (b) H...H/H...H, (c) N...H/H...N, (d) C...H/H...C, (e) O...O/O...O and (f) C...N/N...C contacts.

4.6. Laplacian of electron density

Laplacian is the remarkable property of the bond critical point which gives the information about the charge concentration or depletion. A

positive Laplacian is a measure of depletion of charges and it is typical for closed shell or any other interactions like van der Waals and mediumweak hydrogen bonds while the closed shell interactions have a negative Laplacian [28]. In the present analysis, the Laplacian of O—N bond



Fig. 5. (a) Fingerprint plot of full contacts (b) Pie Chart showing the percentage of contacts contributed to the total Hirshfeld surface area.

 Table 4

 Population Coefficients of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone.

	P_C		P_{ν}		к	Deformatio	on Density Mu	ltipole Popula	ations				
Atoms	THEO	EXP	THEO	EXP	EXP	P20	P22+	P22-	P40	P42+	P42-	P44+	P44-
10	1.999	1.995	6.361	5.930	1.007	0.251	-0.157	-0.402	0.016	-0.001	0.101	0.007	0.026
20	1.999	1.995	6.413	5.875	1.012	-0.027	-0.179	-0.079	0.015	-0.021	0.023	0.002	0.001
30	1.999	2.014	6.521	5.829	1.017	0.272	0.017	-0.336	0.074	-0.084	-0.007	0.068	-0.059
4N	1.999	1.98	5.382	4.975	1.094	0.053	0.120	0.061	-0.118	-0.058	-0.012	-0.079	-0.033
5N	1.9994	2.006	5.472	4.957	1.093	0.046	0.006	-0.174	0.015	-0.082	-0.010	-0.059	0.036
6N	1.999	1.995	4.477	4.796	1.012	0.248	0.146	-0.157	-0.035	-0.098	0.146	0.004	0.238
7C	1.998	1.984	3.762	3.940	1.001	0.088	0.207	0.155	-0.033	-0.015	-0.014	0.031	0.037
8C	1.999	1.992	3.949	3.963	1.0031	0.131	0.113	0.038	0.065	0.007	0.045	-0.003	-0.070
9H	0	0	0.773	0.985	1.138	0.001	0.119	-0.050	-0.053	-0.055	0.056	-0.045	-0.047
10C	1.999	1.993	3.521	3.805	1.020	0.065	0.025	-0.064	0.001	-0.081	0.024	-0.065	0.053
11C	1.999	2.001	4.622	4.445	0.972	0.128	0.139	-0.242	0.238	-0.047	0.096	0.006	-0.008
12H	0	0	0.752	0.909	1.126	-0.121	0.262	0.026	-0.125	-0.210	-0.157	0.065	-0.023
13H	0	0	0.771	0.841	1.288	-0.137	0.441	0.102	-0.039	-0.011	-0.080	0.203	0.050
14H	0	0	0.781	0.726	1.148	0.192	0.017	-0.097	-0.128	0.042	-0.032	-0.283	0.054
15C	1.999	1.989	4.249	4.037	0.992	-0.055	0.047	0.110	-0.078	0.029	0.008	0.126	0.216
16H	0	0	0.754	0.941	1.327	0.0419	-0.008	-0.087	-0.004	0.154	-0.002	0.140	0.078
17H	0	0	0.771	0.902	1.239	0.0238	0.099	-0.009	0.014	-0.105	0.118	0.016	0.024
18C	1.999	1.998	3.378	3.676	1.019	0.052	0.014	-0.011	-0.239	-0.022	0.112	0.072	-0.104
19C	1.999	1.995	4.668	4.340	0.968	-0.092	-0.001	0.072	0.028	0.048	0.024	-0.088	0.155
20H	0	0	0.765	0.850	1.212	-0.246	-0.024	-0.128	-0.021	0.193	0.087	0.042	0.059
21H	0	0	0.753	0.845	1.291	-0.075	0.014	0.091	-0.147	0.227	-0.012	0.087	-0.213
22H	0	0	0.783	0.956	1.166	-0.077	0.157	-0.199	-0.035	-0.120	0.125	0.114	-0.112

ranges from -0.9557 to -1.0225 e/Bohr⁵ while for O-C bond it is -0.0222 e/Bohr⁵. The N-C bonds involved with 4N and 6N have the Laplacian of -0.6359 to -0.7796 e/Bohr⁵ while for 5N-8C and 5N-10C the Laplacian is -0.9755 and -1.1011 e/Bohr⁵ which shows that 5N is the non Huckle lone pair Nitrogen in the imidazol ring. Similarly the Laplacian of all C—C and C—H bonds ranges from -0.5623 to -0.8986 e/Bohr⁵ and -0.8897 to -0.9843 e/Bohr⁵. Negative Laplacian observed in O-N, O-C, N-C, C-C and C-H bonds show that the electron density is locally concentrated and it is a strong evidence of shared shell interaction and the magnitude of Laplacian expose the strength of interaction. This can also be visualized from the contour plot of Laplacian. The contour plot of Laplacian along the aromatic ring and O3-C18-C19 plane of a molecule is shown in Fig. 9. The shared shell interaction of C--C, N--C, O--N, C--H and O--C bonds can be visualized from Fig. 9 (a) and (b). Similarly the lone pairs around the nitrogen atom and oxygen atom can be visualized from Fig. 9 (a) and (b). Among the lone pair atoms, the oxygen atom shows a spherical distribution of charges which indicates an even distribution of electrons while the nitrogen atom shows more deformation in the valence region than in the core region. [29,30].

4.7. Quantification of interaction

Cremer and Kraka proposed the use of energy density functions to quantify the atom-atom interaction. According to them, the local kinetic (G) and potential energy density (V) functions were defined by the first order density matrix and the total density (H) is expressed as the sum of potential and kinetic energies [31,32] and these values are presented in Table 6. When H < 0, the interaction is termed as shared shell while the interaction is closed shell or van der Waals, when H > 0. It is also observed that when G_{cp}/ρ (amount of K.E per electron) > 1 a.u., the interaction is closed shell. The estimated G_{cp} / ρ value of O–N, N–C, C-C and C-H bonds lie between 0.1094 and 0.8336 a.u and it reveals the shared shell character of bonds. Whereas the O-C bond alone shows the G_{cp}/ρ value of 1.67 a.u. that reveals the interaction as closed shell. But in the view point of cremer and Kraka, the closed shell interaction have H > 0. The H values obtained from the topological analysis for O-N, O-C, N-C, C-C and C-H is negative and it ranges from -0.1950 to -0.6279 a.u. Thus it is not possible to predict the interaction between O and C as closed shell as the value of H is negative. Hence to understand the nature of interaction between O and C, the quantity (|V|/ G), proposed by Epinosa et al., was used [33]. Based on this quantity the



Fig. 6. Difference Fourier map of imidazol ring. Solid lines indicate positive contour and dashed lines negative contour.

interaction is classified as closed shell when |V|/G < 1 and H > 0 whereas the interaction is shared shell when |V|/G > 2 and H < -G. Hence the interaction between O and C is termed as shared shell and not as closed shell, as the value of |V|/G is 2.008. This suggests that even though the bonding between O and C is shared shell the percentage of covalent character is less in O—C bond compared to O—N, N—C, C—C and C—H bonds.

4.8. Electron localization function and its variant

Electron Localization Function (ELF) is a popular function for highlighting regions with high degree of electron localization and it can be used to reveal electron delocalization paths [34–37]. The excess kinetic energy density caused by Pauli repulsion, D(r) and the Thomas-Fermi kinetic energy density, D₀(r) were used to estimate ELF and hence it can be defined as $\left[1 + (D(r)/D_0(r))^2\right]^{-1}$ [38]. Both energy densities were evaluated from the occupation number of orbitals and the wavefunction. Several functions were closely related to ELF and show similar distribution character. One among them is Localized Orbital Locator (LOL) and it was defined by Schmider and Becke [39]. Similar to ELF, the LOL also depends on kinetic energy density and it reveals the electronic shell structure of compounds. A low value of LOL is an evidence for ionic interaction while a large value of LOL is covalent and it shows the greater localization of electrons. Even though the chemically significant regions that are highlighted by ELF and LOL are qualitatively comparable, Jacobsen pointed out that LOL conveys clearer picture compared to ELF [40]. Figs. 10 and 11 shows the ELF and LOL map of the molecule along the aromatic ring and O1-N6-O2 plane. The shared shell interaction between C—C, N—C and O—N bonds can be visualized from the above maps and the strength of the interaction is in the order of C—C > N—C > O—N. The lone pairs are clearly visible in the LOL map than the ELF map and among the two nitrogen atoms in the imidazol ring the atom 5N is identified as the Non-Huckle lone pair electron and it is clearly visible in the LOL map.

4.9. Natural bond orbital analysis

The Natural Bond Orbital (NBO) Analysis has proved to be an efficient tool for chemical interpretation of hyper conjugative interaction. DFT level computations were used to explore the various second order interaction between the filled orbitals of one subsystem and vacant



Fig. 8. Molecular graph of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone. Here the large violet, small orange and yellow spheres represent the NCP, BCP and RCP. Brown lines represent the bond path.



Fig. 7. (a) Static deformation density map of 10-6N-2O plane (b) Dynamic deformation density map of 10-6N-2O plane.

Table 5

(31) Bond Critical Points from DFT and Multipole Ai	-1) Bond Critica	l Points from	DFT and	Multipole	Analysis.
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Bond (A1-A2)	B3LYP/ 6311G++(d,p)				Multipole Analysis				
	d (Å)	d _{1 (A1-CP)} (Å)	d _{2 (CP-A2)} (Å)	P (e/Bohr ³)	d (Å)	d _{1 (A1-CP)} (Å)	d _{2 (CP-A2)} (Å)	ρ (e/Bohr ³)	
10-6N	1.2268	0.6408	0.5859	0.4969	1.2263	0.6454	0.5809	0.4621	
20-6N	1.2387	0.6466	0.592	0.4826	1.2392	0.6443	0.5949	0.4468	
30-18C	1.2061	0.7954	0.4106	0.413	1.2097	0.7869	0.4228	0.3962	
4N-7C	1.3914	0.8744	0.5181	0.2958	1.3772	0.8299	0.5473	0.2495	
4N-10C	1.3655	0.8762	0.4893	0.3101	1.3641	0.8657	0.4984	0.2926	
4N-15C	1.4539	0.9091	0.5448	0.2555	1.4593	0.9589	0.5004	0.2143	
5N-8C	1.3547	0.8332	0.5216	0.3319	1.3391	0.823	0.5161	0.3059	
5N-10C	1.3294	0.8122	0.5176	0.3561	1.3355	0.8445	0.491	0.3326	
6N-7C	1.4189	0.8914	0.5276	0.2871	1.4069	0.8316	0.5753	0.2429	
7C-8C	1.3771	0.7225	0.6549	0.3196	1.3565	0.6983	0.6582	0.3154	
10C-11C	1.4903	0.7819	0.7084	0.2592	1.4709	0.7355	0.7354	0.2134	
15C-18C	1.54	0.7737	0.7663	0.2455	1.4983	0.7791	0.7192	0.2003	
18C-19C	1.5075	0.7785	0.7289	0.2561	1.4799	0.7547	0.7252	0.2092	



Fig. 9. Contour plot of Laplacian along (a) Aromatic ring and (b) 30 –18C –19C plane of a molecule. Blue and red lines represent the positive and negative contours.

Table 6

Energy Density Functions of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone.

Bond	G (a.u)	V (a.u)	H (a.u)	G/ρ (a.u)	V /G	Bond	G (a.u)	V (a.u)	H (a.u)	G/ρ (a.u)	V /G
10-6N	0.3723	-1.0002	-0.6279	0.7492	2.686	10C-11C	0.0637	-0.2882	-0.2244	0.2457	4.524
20-6N	0.3544	-0.9477	-0.5933	0.7343	2.674	11C-12H	0.0393	-0.3137	-0.2744	0.1413	7.982
30-18C	0.6914	-1.3884	-0.6970	1.6740	2.008	11C-13H	0.0415	-0.3089	-0.2674	0.1520	7.443
4N-7C	0.1996	-0.5894	-0.3898	0.6747	2.952	11C-14H	0.0426	-0.3087	-0.2661	0.1569	7.246
4N-10C	0.2585	-0.6975	-0.4390	0.8336	2.698	15C–16H	0.0363	-0.3187	-0.2823	0.1275	8.779
4N-15C	0.1484	-0.4559	-0.3074	0.5808	3.072	15C–17H	0.0391	-0.3136	-0.2745	0.1404	8.020
5N-8C	0.2062	-0.6564	-0.4501	0.6212	3.183	15C-18C	0.0544	-0.2495	-0.1950	0.2215	4.586
5N-10C	0.2203	-0.7160	-0.4956	0.6186	3.250	18C-19C	0.0615	-0.2778	-0.2163	0.2401	4.517
6N-7C	0.1749	-0.5447	-0.3698	0.6091	3.114	19C-20H	0.0395	-0.3128	-0.2732	0.1424	7.918
7C-8C	0.1163	-0.4573	-0.3409	0.3638	3.932	19C–21H	0.0414	-0.3052	-0.2638	0.1531	7.371
8C-9H	0.0316	-0.3209	-0.2892	0.1094	10.155	19C-22H	0.0430	-0.3089	-0.2653	0.1587	7.183

orbitals of another subsystem, which is a measure of delocalization or hyper conjugation. The analysis is carried out by investigating all possible interactions between filled Lewis type NBO's (donors) and empty non Lewis type NBO's (acceptors). Delocalization of electron density between bonding and anti bonding orbitals corresponds to a stabilizing donor–acceptor interaction and the second order perturbation theory can be used to estimate the strength of interaction. The stabilization energy E ⁽²⁾ connected with the delocalization between the Lewis type donor NBO (i) and Non Lewis type acceptor NBO (j) is estimated as $E^{(2)} = (q_i F_{i,j}^2)/(\varepsilon_j - \varepsilon_i)$, where q_i represents the orbital occupancy, ε_i , ε_j are diagonal elements and $F_{i,j}$ represent the off diagonal NBO Fock matrix element. The lowering of orbital energy due to interaction between doubly occupied orbitals and unoccupied ones is used to interpret the molecular structure. In energetic terms, hyper conjugation is an imperative effect in which an occupied Lewis type orbital is stabilized by overlapping with a non Lewis type orbital [41,42]. Table 7 shows the second order perturbation energy and the overlap integral of most important interactions between the Lewis and non Lewis orbitals. In the title molecule the intra-molecular interaction is formed by the orbital overlap between π (10-6N) $\rightarrow \pi$ *(10-6N) which results into intra-molecular charge transfer causing stabilization of the system. The interaction between the bonding and anti bonding orbitals π (5N-10C) $\rightarrow \pi^*$ (7C–8C) and π (7C–8C) $\rightarrow \pi^*$ (10-6N) results into the stabilization energy of 28.02 and 30.50KJmol⁻¹ and hence they give stronger stabilization to the structure. The electrons donated from the lone pair to anti bonding orbitals were represented as LP (3)2O $\rightarrow \pi^*$ (10-6N), LP (2)3O



Fig. 10. ELF map of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone along the (a) Aromatic ring and (b) O1 -N6 - O2 plane of the molecule.



Fig. 11. LOL map of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone along the (a) Aromatic ring and (b) O1 –N6 – O2 plane of the molecule.

Table 7Second order perturbation theory analysis of Fock matrix in NBO basis obtainedat B3LYP/6311G++ (d,p) level.

Donor NBO (i)	Acceptor NBO (j)	E(2) (kJ/mol)	E(j)-E(i) a.u	F(i,j) a.u
π (1O-6N)	π*(1O-6N)	8.44	0.31	0.056
π (5N-10C)	π*(7C–8C)	28.02	0.32	0.087
π (7C–8C)	π*(1O-6N)	30.50	0.15	0.068
LP(2) 20	σ*(15C–17H)	1.04	0.67	0.024
LP(1) 5N	σ*(8C–9H)	1.95	0.80	0.036
LP(3) 20	π*(10-6N)	141.71	0.14	0.133
LP(2) 30	σ*(15C–18C)	23.78	0.62	0.109
LP(1) 4N	π *(5N-10C)	52.06	0.28	0.110
LP(1) 4N	π *(7C–8C)	29.67	0.29	0.084

→ $\sigma^*(15C-18C)$, LP (1)4N → π *(5N-10C), LP (1) 4N → π *(7C-8C) which leads to the stabilization energy of 141.71, 23.78, 52.06 and 29.67 KJ mol⁻¹ which shows the larger delocalization of electrons. The importance of hyper conjugative interaction and charge density transfer from filled lone pair electrons of the Lewis base into the unfilled anti bond $\sigma^*(X-H)$ of the Lewis acid X-H in X-H...Y hydrogen bonding systems were formerly reported for innumerable molecular systems [43]. The intermolecular C—H...N hydrogen bonding is formed due to the orbital overlap between LP (1) 5N and $\sigma^*(8C-9H)$ which results in charge transfer causing stabilization of the hydrogen bonded systems.

The stabilization energy associated with hyper conjugative interaction LP (1) 5N and $\sigma^*(8C-9H)$ is obtained as 1.95 KJmol $^{-1}$, which quantify the hydrogen bonding between LP (1) 5N and $\sigma^*(8C-9H)$. Similarly the intermolecular C—H…O hydrogen bond is formed by the orbital overlap of LP (2) 2O and $\sigma^*(15C-17H)$ which results in the stabilization energy of 1.04 KJmol $^{-1}$. These energy values are chemically significant and they can be used as a measure of the intermolecular C—H…N and C—H…O hydrogen bonding interaction between the lone pair atoms (5N and 2O) and the anti bonding orbitals.

4.10. Frontier molecular orbital analysis

The highest occupied and lowest unoccupied molecular orbitals (HOMO & LUMO) are the most important frontier molecular orbitals and these orbitals determine the interaction of one molecule with another molecule. The HOMO is a donor with π character whereas the LUMO is an acceptor with π * character and thus the energy of HOMO and LUMO indicates the nucleophilicity and electrophilicity nature of the compound [44]. Fig. 12(a) and (b) shows the frontier molecular orbitals of the title compound in which, the electron charge cloud is spread over the nitro fragment and imidazol ring for LUMO while it is located over the acetone fragment for HOMO. The HOMO and LUMO energies of 1-(2-Methyl-5-nitro-1H-imidazol-1-yl)-acetone are found to be -7.9801 eV and -4.1817 eV giving rise to a HOMO-LUMO energy



Fig. 12. Molecular Orbital representation (a) HOMO (b) LUMO.

gap of 3.7984 eV. Since the frontier orbital gap of the molecule is found to be very small, the molecule is termed as more polarizable and soft molecule with high chemical reactivity. Using Koopman's theorem [45] within DFT scheme, the ionization energy and electron affinity were expressed as $I = -\varepsilon_{HOMO}$ and $A = -\varepsilon_{LUMO}$. Based on this, the chemical reactivity concepts like electronegativity (*X*), absolute hardness (η), chemical potential (μ) and the global electrophilicity index (ω) were determined and it is found to be 6.0809, 1.8992, -6.0809 and 9.7349 eV. The high values of electronegativity and electrophilicity indicates the molecule has strong attraction for electrons and it is a good electrophile.

4.11. Molecular Electrostatic potential and reactivity site

Molecular Electrostatic Potential (MESP) around a molecule gives an indication of the net electrostatic effect produced by the total charge distribution of the molecule. It can be used for interpreting and predicting the relative reactive sites for electrophilic and nucleophilic attack [46]. It is obtained from B3LYP/6311G++(d,p) level of theory and is shown in Fig. 13. The red colored region in the molecule represents the negative electrostatic potential while the blue color indicates the region of positive electrostatic potential and these regions are prone to electrophilic and nucleophilic attack. In the title molecule, the region of negative electrostatic potential is spread over the non Huckle lone pair nitrogen atom of imidazol ring and also on the carbonyl and nitro groups. Hence atoms 10, 20, 30 and 5N were identified as the reactive locations of the title molecule. Thus when the title molecule comes in the vicinity of the bio molecule, the bio molecule is attracted towards the reactive site and a charge transfer takes place between the two molecules [15]. This process continues until the electrophilicity of the two molecules gets equal and after that there will be no interaction or transfer of charges.

5. Conclusion

In the present study the equilibrium geometry of the molecule was estimated using DFT level of theory employing the basis set 6311G++(d, p). The systematic analysis of structure using Hirshfeld surfaces helps to identify the common features which would be more difficult to recognize using common methods of structure analysis. The close contacts are dominated by O...H/H...O and H...H contacts and these weak interactions have clear signature in the fingerprint plots. The (3,-1) bond critical points were analyzed using Bader's AIM theory. Laplacian and Energy density functions were used to quantify the interaction and it was found that in the title molecule the interaction between O and C is shared shell but the percentage of covalent character is less in O—C compared to O—N, N—C, C—C and C—H bonds. Similar to Laplacian,



Fig. 13. Molecular Electrostatic Potential showing the electrophilic and nucleophilic site of the molecule.

the ELF and LOL maps were used to identify the nature and strength of interaction, which clearly reveals that the interaction between C—C, N—C and O—N is shared shell and the strength of the interaction is in the order of C—C > N—C > O—N. The NBO analysis was used to understand the charge transfer in hydrogen bonds. The transfer of electron density from the lone pair O and N atoms to the anti bonding orbital of $\sigma^*(15C-17H)$ and $\sigma^*(8C-9H)$ produces strong evidences for hydrogen bonds. The frontier orbital gap of the molecule is calculated as 3.7984 eV which shows that the molecule is a soft molecule with high chemical reactivity and this molecule is identified as a good electrophile since the value of the electrophilicity index is 9.7349 eV. The molecular electrostatic potential map clearly reveals that the region around the atoms 10, 20, 30 and 5N were identified as the reactive site of the molecule and those regions are prone to electrophilic attack.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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C. Anzline et al.

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Computational and Theoretical Chemistry 1191 (2020) 113044

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