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Molecular Electrostatic Potential and Hirshfeld Surface Analysis of p-Acetamidobenzoic Acid

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Abstract: ***p-Acetamidobenzoic acid is the acetyl derivative of para-aminobenzoic acid and it is a strong oxidizing agents. The molecular geometry, the normal mode frequencies and corresponding vibrational assignments of the compound were performed by B3LYP levels of theory using the 6-31G(d, p) basis set. Molecular electrostatic potential (MESP) analysis were performed for the compound to study the possible electrophilic and nucleophilic sites. Hirshfeld surface analysis for visually analyzing intermolecular interactions in crystal structures employing surface contours and 2D fingerprint plots has been used to scrutinize molecular shapes. The Hirshfeld surface analysis and 2D fingerprint plots reveal that the molecule have stabilized intermolecular interactions.***

Keywords: p-Acetamidobenzoic acid; DFT; Hirshfeld; MESP;

I. INTRODUCTION

p-Acetamidobenzoic acid is a amidobenzoic acid that consists of benzoic acid bearing an acetamido substituent at position 4. It is derived from 4-aminobenzoic acid. It is a conjugate acid of a 4-acetamidobenzoate. p-Aminobenzoic acid was evaluated for noninvasive sampling of UDP-glucose in the liver. It has been tried to investigate p-Acetamidobenzoic acid as an alternative to glycine conjugation that facilitates the metabolism of toxic aromatic acids, capable of disrupting mitochondrial integrity. Owing to the high exposure to toxic substrates, characterization of individual glycine conjugation capacity, and its regulatory factors has become increasingly important. Aspirin and benzoate have been employed for this purpose; however, adverse reactions, aspirin intolerance, and Reye's syndrome in children are substantial drawbacks. [1-2]. p-Acetamidobenzoic acid has long been used as an indicator of the completeness of 24-h urine collection by determination of total urinary excretion and its metabolite, N-acetyl- p-Acetamidobenzoic acid. N-Acetyl- p-Acetamidobenzoic acid is formed by human arylamine N-acetyltransferase 1 (NAT1) in liver and intestine. This intestinal metabolism may reduce the urinary recovery of p-Acetamidobenzoic acid due to secretion of N-acetyl-p-Acetamidobenzoic acid into the intestinal lumen [3].

II. COMPUTATIONAL DETAILS

In the present work, the density functional theory method (DFT) has been employed using Beck's three parameters hybrid exchange functional with the Lee-Yang-Parr correlation functional [4-6] to optimize the structure of the title compound. The entire calculations were performed at DFT method using B3LYP levels at 6-31G(d, p) basis sets on a Pentium V/1.6 GHz personal computer using Gaussian 09W program package [7].

The Hirshfeld Surfaces were performed using Crystal Explorer program 2.1. The Hirshfeld Surface Analysis and subsequent fingerprint plots were calculated to quantify the intermolecular contacts present within the crystal structure of compound, which accepts a structure.

III. RESULTS AND DISCUSSIONS

A. Molecular Geometry

The optimize geometry structure of the title molecule p-Acetamidobenzoic acid with atomic numbering shown in the above Figure1

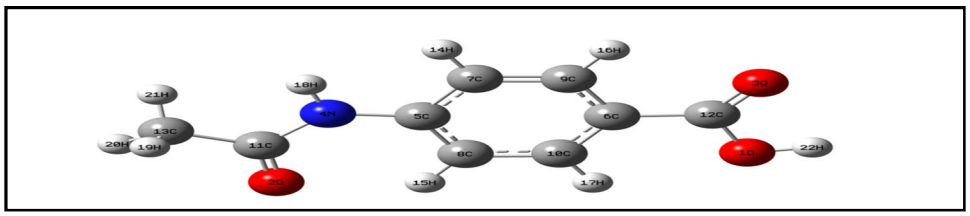

Figure 1 Optimized structure of p-Acetamidobenzoic acid

B. Molecular Electrostatic Potential

The molecular electrostatic potential V(r) at a given point r (x,y,z) in the vicinity of a molecule is defined in terms of interaction energy between the electrical charge generated from the molecule electrons and nuclei and a positive test charge (a proton) located at r. The molecular electrostatic potential (MEP) is related to the electronic density which is very useful descriptor for determining sites for electrophilic attack and nucleophilic reactions as well as hydrogen bonding reactions [8-9].To predict the reactive sites for electrophilic and nucleophilic attack fo r the title molecule, MEP is calculated at B3LYP/6-31 G(d,p) level. The negative (red) regions of MEP are related to electrophilic reactivity and positive (white) regions are related to nucleophilic reactivity as shown in Figure 2. The negative regions are mainly localized on O1and O3 oxygen atoms. A maximum positive regions is localized on hydrogen atoms indicating a possible potential sites for nucleophilic attack. The MEP map shows that the negative potential sites on electronegative atoms as well as the positive potential sites are around the hydrogen atoms. The MEP provides a visual representation of the chemically active sites and comparative reactivity of the atoms.

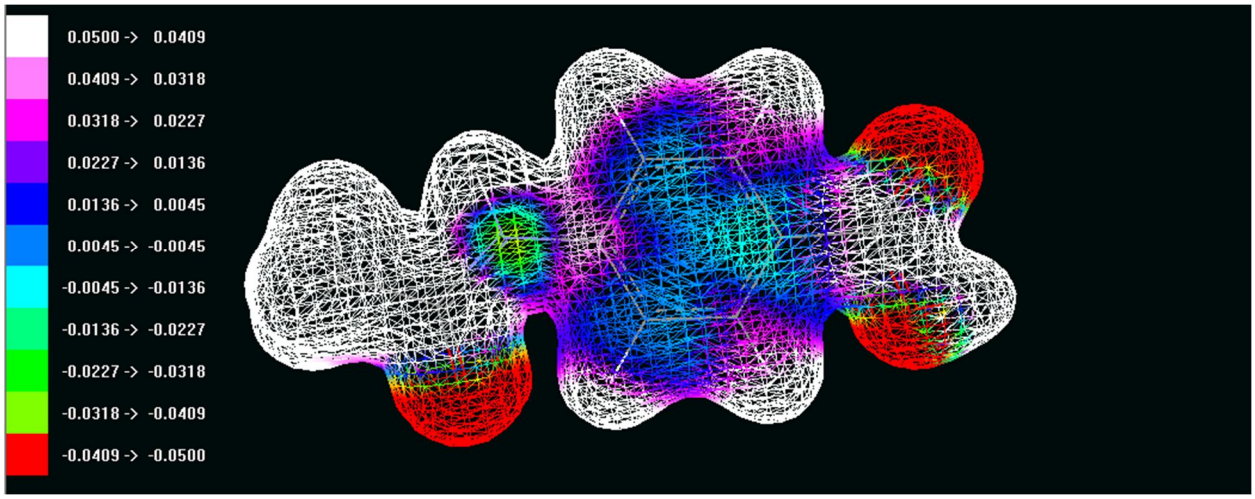

Figure 2 Molecular electrostatic potential map of p-Acetamidobenzoic acid

C. Hirshfeld Surfaces Computational Method

3D-Hirshfeld surfaces [10-12] associated with 2D finger print analysis [13-15] was performed using a powerful graphical tool Crystal Explorer 3.1 suite [16] which accept CIF as the input File. A CIF file containing complete information of the studied structure was deposited with CCDC deposition number 785060 and is freely available from the following website: www.ccdc.cam.ac.uk/data-request/cif [17]. The Single X-ray crystallographic data of the investigated compound is given in Table 1.

Table 1. Single X-ray Crystallographi data of the compound

Data	Compound
Formula	$C_9H_9NO_3$
Molecular weight	179.17 g/mol
Space Group	P1
a,b,c (Å)	5.0255(13) (Å),6.8219(13) (Å),12.196(3) (Å)
α,β,γ (Å)	89.524(7)°, 80.8047(7) °, 79.282(5) °

The 3D Hirshfeld surfaces of the title compound have been mapped over (a)d_{norm}, (b) shape index (c) and curvedness in the range of -0.7528 (red) to 1.2423 (blue), -1.0 (concave) to 1.0 Å au (convex) and -4.0 (flat) to 0.4 Å au (singular) respectively as shown in Figure 3 (a),3(b) and 3(c). In d_{norm} surface, strong hydrogen bonds and nitrogen atoms result in bright red spots near the hydrogen bonding acceptor and donor atoms while the other interactions result in faint red spots. The d_{norm} mapped surfaces of the present compound exhibit interaction between the oxygen atom and the hydrogen atom can be visualized as bright red spots and the bond distances are shown in Figure 4.

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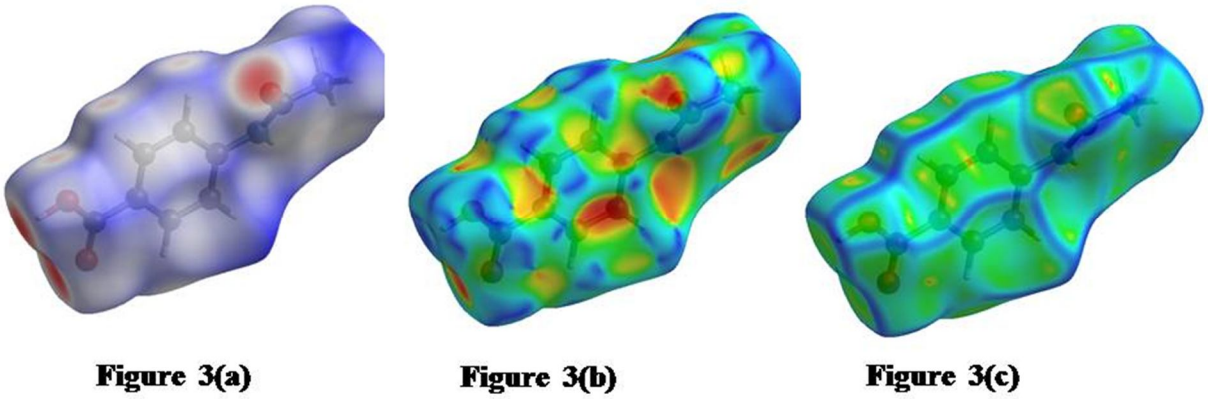

Figure 3(a) **Figure 3(b)** **Figure 3(c)**

Figure 3(a) Hirshfeld surfaces of p-Acetamidobenzoic acid d_{norm} -0.7528 (red) to 1.2423Å au. (blue)
3(b) shape index -1.0 (concave) to 1.0 Å au (convex)
3(c) curvedness -4.0(flat) to 0.4 Å au (singular)

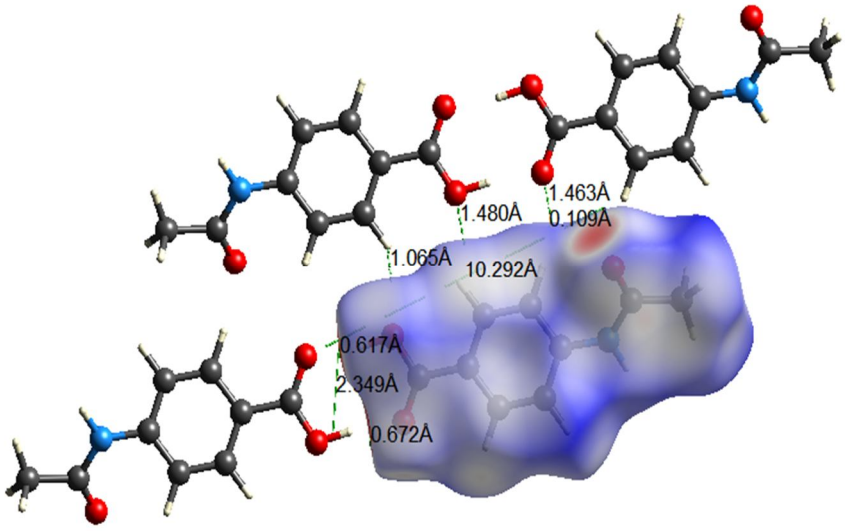

Figure 4. View of O...H contacts of d_{norm} surface of p-Acetamidobenzoic acid

From the decomposition of fingerprint plots of the investigated compound represents the major contributors contacts on the surface of Hirshfeld namely H....H, O....H and C...H contacts. The intermolecular hydrogen bonds contacts H...H have the greatest contribution to the surface of Hirshfeld (36.1%) represented by two surfaces in the two dimensional fingerprint map. The O...H contacts contribute to the surface of Hirshfeld (18%) represented by two sharp spikes in two dimensional fingerprint map and C...H contacts contribute to the surface of Hirshfeld (12.5%) and the 2D fingerplots of these contributions are shown in Figure 5. two dimensional fingerprint maps in Fig.4(c). The relative contribution of the different interactions to the Hirshfeld surface is H...H, O...H and C...H interactions have major participations in crystal structures [18-19] .

It is clear from 2D plot of interaction between H...H (36.1%) observed in the form of spike with d_i value, the distance from the surface to the nearest nucleus internal to the surface [H] is 1.2 Å au and d_e surface, the distance from the surface to the nearest nucleus external to the surface [H] is 1.2 Å au. Similarly, the interaction between O...H (18%) observed in the form of spike with d_i value, the distance from the surface to the nearest nucleus internal to the surface [O] is 1.2 Å au and d_e surface is the distance from the surface to the nearest nucleus external to the surface [H] is 0 Å au and the interaction between C...H (12.5%) observed with d_i value, the distance from the surface to the nearest nucleus internal to the surface [C] is 1.8 Å au and d_e surface is distance from the surface to the nearest nucleus external to the surface [H] is 1.2 Å au.

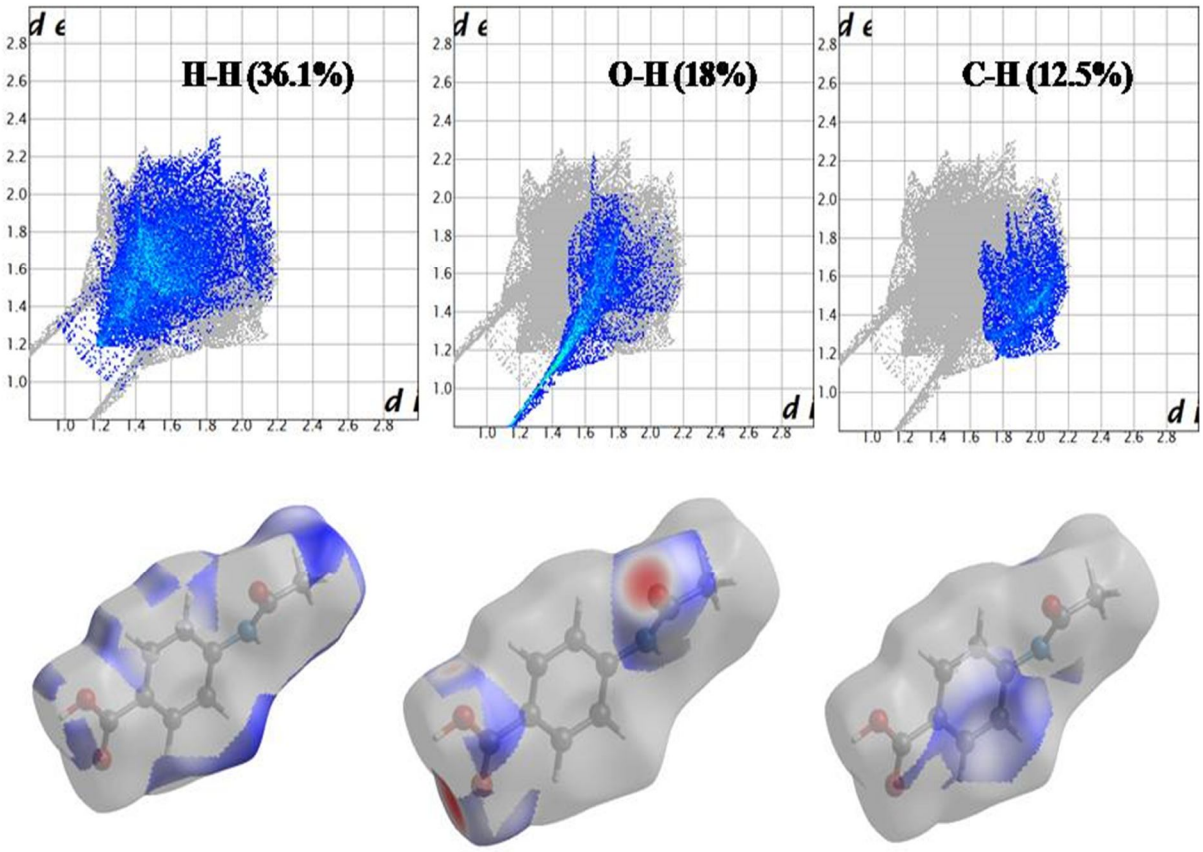

Figure 5 2DFingerprints plots of p-Acetamidobenzoic acid and various interactions are visualized with percentage of contact (a) H-H (36.1%) (b) O-H (18%) (c) C-H (12.5%)

IV. CONCLUSION

Density functional calculations have been successfully performed for the title compound and the calculated value shows that B3LYP/6-31G(d,p) method can reproduce the title compound very well. MEP was performed by DFT method. The MEP map indicates that the negative potential sites are on the electronegative atom and positive potential sites are around carbon and hydrogen atoms and it is clear that, the negative regions are associated with O1 and O3 and the weak positive region on the nearby hydrogen atoms. The Hirshfeld surface and fingerprint plot analysis, which act as a novel method of visualizing the intermolecular interactions, show that the close contacts in the title molecule dominated by the H-H, O-H, C-H interactions that have major participations in crystal structures. These interactions play a key role towards the stabilization of the molecule in the solid state and these interactions also have prominent signatures in the finger plots.

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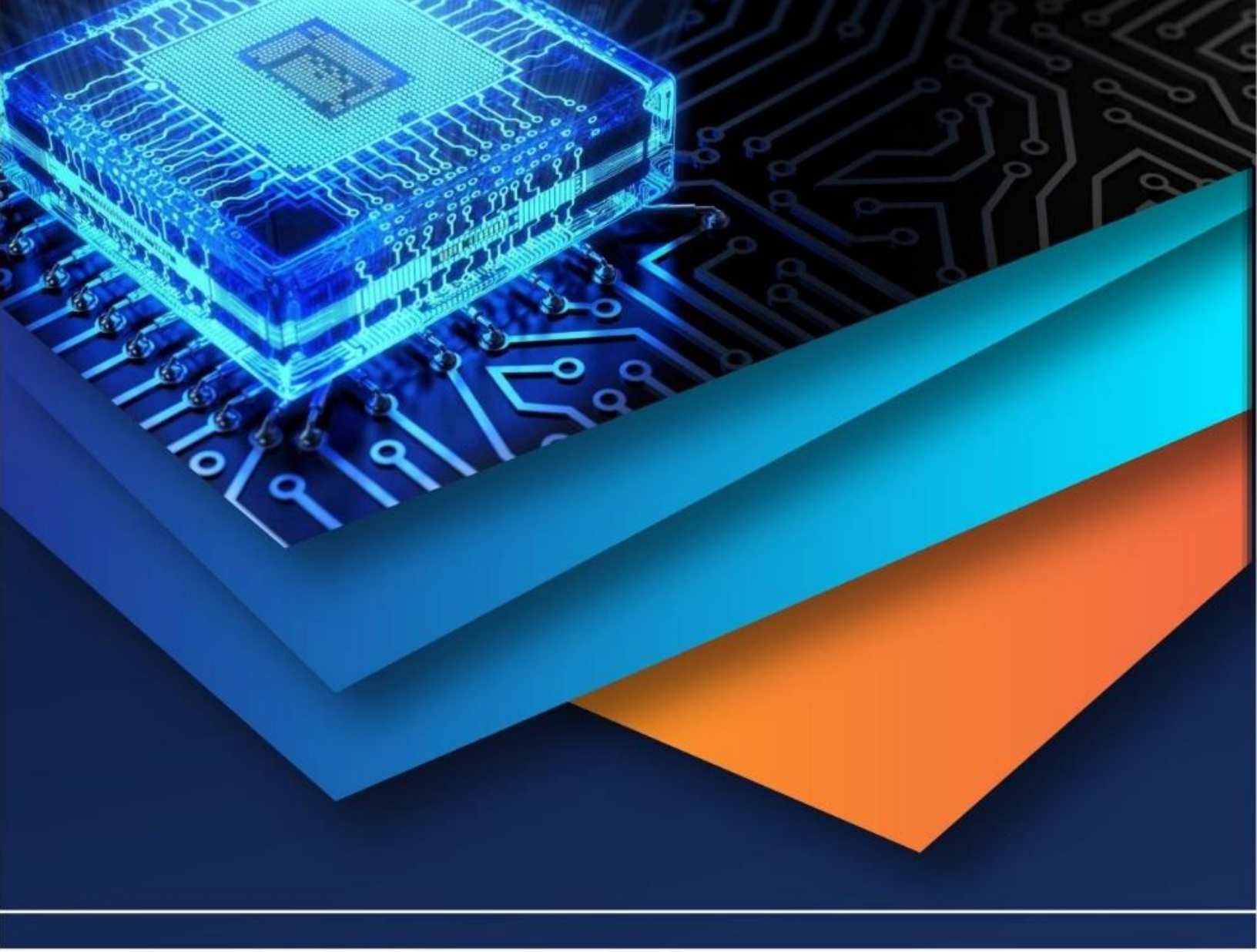

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