Molecular Docking Studies and Wave Functional Analyses of 3-Fluoro Benzoic Acid

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ABSTRACT

The wave function files of 3-Fluoro benzoic acid were generated and thereby all the computational analyses were performed by Gaussian 09W software using DFT with B3LYP/6-311++G(d,p) level of theory. The ESP map predicts the distribution of potential energy on the surface and ELF & LOL evaluate the probability density of the electrons at bonding and non-bonding sites. Further, anti-bacterial activity of this molecule was studies using molecular docking.

Keywods: LOL, ELF, Docking, Wavefunction.

1. INTRODUCTION

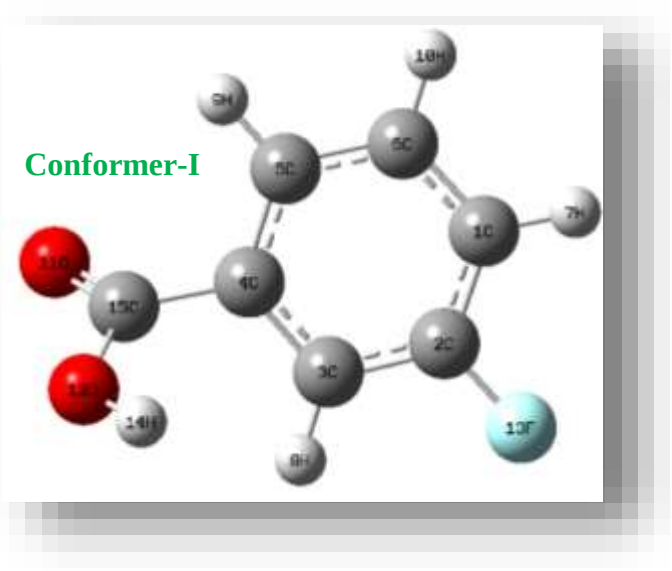
Benzoic acid and their salts are permitted food preservatives [1], as they prevent bacterial growth. Even though they prevent or delay nutritional losses due to the microbiological, enzymatic or chemical changes of foods during its shelf life, they are harmful at higher than permitted safety levels.Benzoic acid is generally extracted from plants and is used as aborticide, for destroying foetus within the uterus. Benzoic acid derivatives are used in medicine as a protective drug against UV radiation in the diagnosis of gastrointestinal disorders and therapeutically in fibrotic skin disorders [2]. Fluorobenzoic acids are suitable water tracers in oil reservoirs and in ground water sources [3].The major advantage of these acid tracers is due to their similar chemical and physical behaviour and possibility of conducting several simultaneous studies without interference [6]. It is also used as an important intermediate in the synthesis of anti-bacterial drugs [4], and currently tested as indicators in leaching studies for carbon sequenstrationtechiniques [5]. Hence, some works [1-9] have been reported on Fluoro benzoic acid derivatives [1-9]; however DFT studies, particularly in docking analysis was also carried out using Auto-dock software to understand the biological activity of the compound.

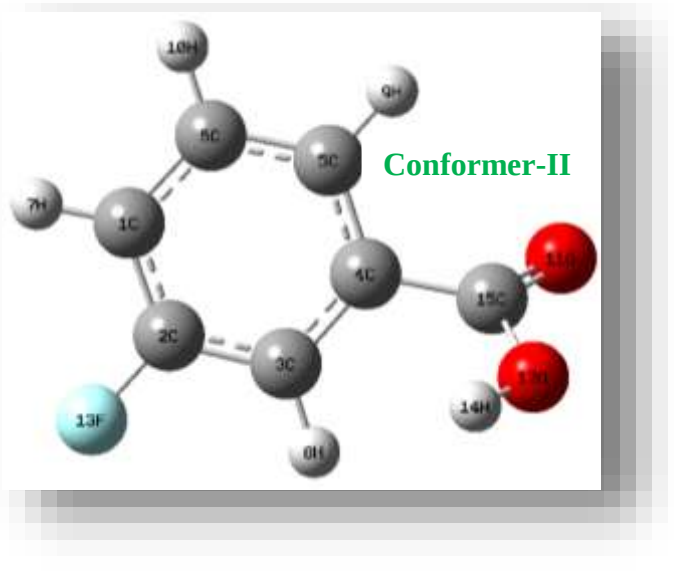
2. THEORETICAL

All the Theoretical calculations of this study were done using Gaussian 09 software package [10]. The minimum energy conformer has been simulated usingB3LYP (Beck's three-parameter hybrid functional with the non-local correlation form the Lee, Yang and parr) functional [11], using the basis set 6-311++G(d,p). The polarization functions on heavy atoms "d" and the polarization functions on hydrogen atoms "p" were joined to for better describing the polar bands of the molecules [12]. The ELF and docking analysis were carried out for understanding the antibacterial activity of the molecule.

3. RESULTS AND DISCUSSION

Energy conformers





The Conformational analysis was performed for the 3-Fluoro benzoic acid by potential energy surface (PES) scan technique with DFT/B3LYP functional by varying the torsion angle O11-C15-C4-C5 in the steps of 10° over one complete rotation 0-360° as recommended in the previous work on a similar molecule[13]. The graphical result, total energy verses scan coordinatesfor different conformers is presented in Fig.1. The graph clearly shows that there are two conformers with the same minimum energy-0.1672 Hartree, one is at 50^0 and the second is at the 300^0 respectively. These conformers are structurally identical, serve as the most stable conformer of the compound. The maximum energy is observed for the conformer at $190^0$with energy value is -0.1657 Hartree, there is one more next level maximum at 350^0 with energy value -0.1664 Hartree, these are the highly unstable conformers of the compound. One of the most stable conformer of the compound was optimised and the same is used for all the further computational analyses in this study.

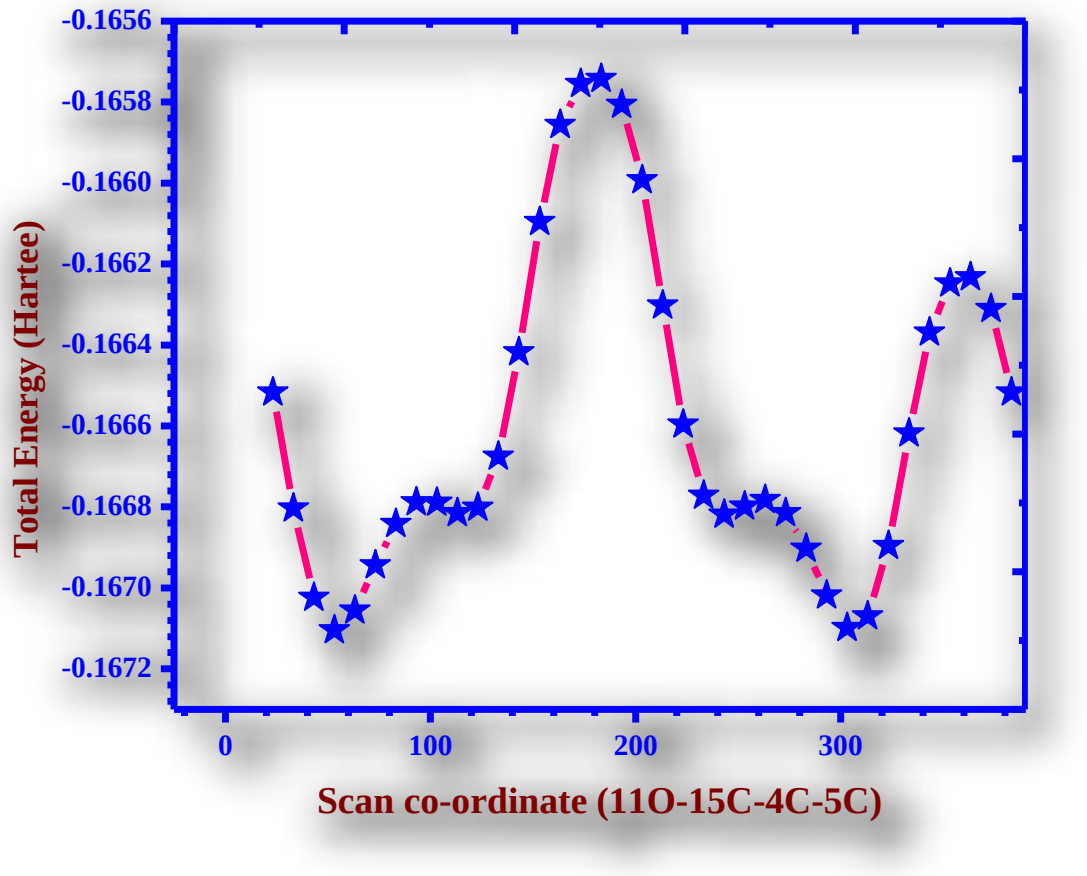


Fig.1.Minimum energy conformer for 3-Fluoro benzoic acid

Topology analyses

a. ELF and LOL:

The surface topology, performed based on the covalent bonds, provides electron localisation function (ELF) and localized orbital locator (LOL) maps. They are executed for the present molecule using Multiwfn program [14] and the obtained ELF and LOL which mostly depend on the kinetic-energy density and electron pair density [15] are shown in Fig.2 and 3 respectively.

The Fig.10 shows ELF value in the y axis, ranging from -4.6 to 4.6 with 0.5 intervals, and distance along molecular axis along x axis. The title molecule occupies the regions from -1.56 to 1.56 which include all bonding and non-bonding localized electrons. The real ELF value is expected within 1 as it indicates the probability density value, which is expressed in terms of colour codes in the diagram, the red and orange colours represent the electrons within the valence shells for which the values obtained between 0.520 to 0.650, the green colours may represent the electrons in bonding and non- bonding orbitals whose ELF value lie in the region 0.260 to 0.455 and the blue colour for which the value lie between 0.000 to 0.195 may denote the electrons in anti bonding orbitals.

Fig 3, shown above represents the localised molecular orbital locator (LOL) pictorially, it gives the same information as ELF that is seen in Fig.2, along with clear details of the location of bonds and their electron density pictorially. It shows all covalent bonds in red colours where the probability of finding the electrons is marked in between 0.8 to 0.72. The green colour indicates the regions where the electrons are distributed as

clouds with probability value between 0.56 to 0.32 and the blue colour region indicates the vacancies or the anti bonding regions where the probability values lie between 0.000 to 0.195 depletion regions between valence shell and inner shell are shown by the blue colour around the carbon and oxygen nuclei. LOL conveys a more decisive and clearer picture than ELF.

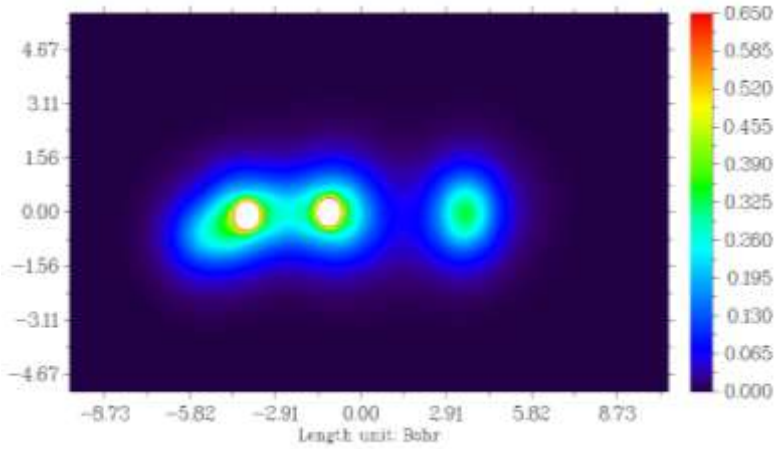


Fig.2. Pictorial representation of ELF for 3-Fluoro benzoic acid

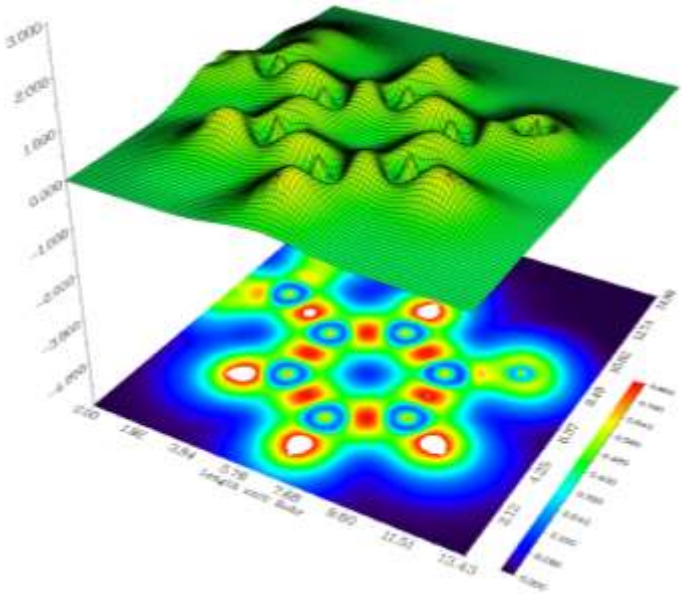


Fig.3. Pictorial representation of LOL for 3-Fluoro benzoic acid

b. Electrostatic Potential:

Fig.4 shows the pictorial representation of molecular electrostatic potential (MEP) distributed over the surface which provide a visual view of molecular shape, size and dipole moments of the molecule [16]. MEP

mapping is also useful in understanding the relationship of physio-chemical properties of the molecule with its structure [17-18], particularly the chemically reactive sites of the molecule. Here the red colour represents the negative potential region which is generally known as nucleophilic region as they can attract positive charges and induce reactions. In this molecule, the red region is found spread over the oxygen atoms strongly in the carboxylic acid group which paves way for the hydrogen bond formation with any target proteins. The blue colour represents the positive potential region which can attract electrons and thereby cause electrophilic reactions. In this molecule the electrophilic region is found only over the hydrogen atoms in the benzene ring adjacent to the F atoms. The green colour, the neutral region, is found over almost the entire central part of the molecule. Fig. 5 shows the region where only the negative potential is distributed. In this molecule, it is found in two regions; one is over the COOH group and another is over the F atom. It is to be noted that the ESP over the F atom was not seen clearly in MEP.

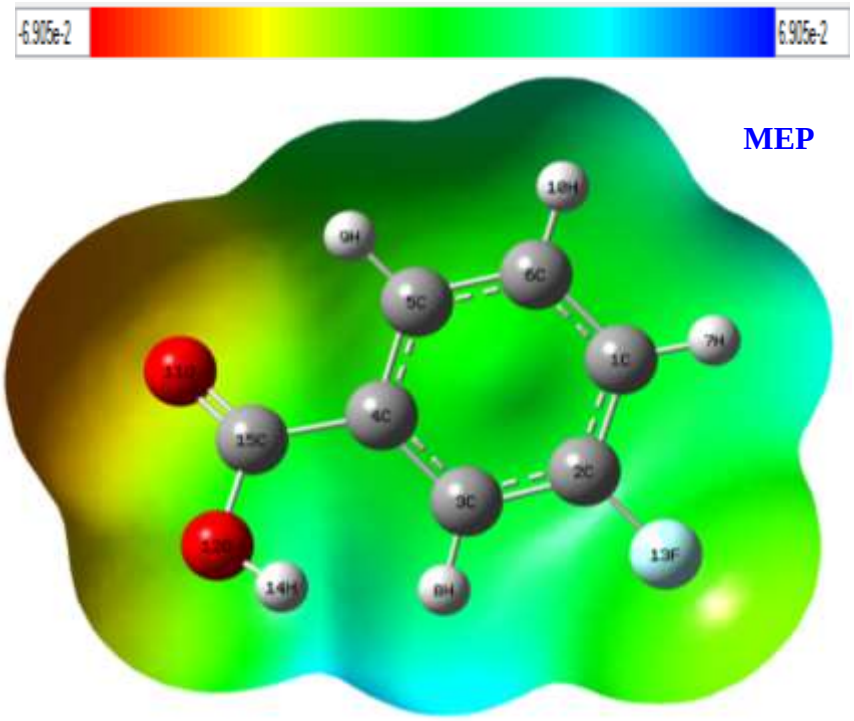


Fig.4.MEP for 3-Fluoro benzoic acid

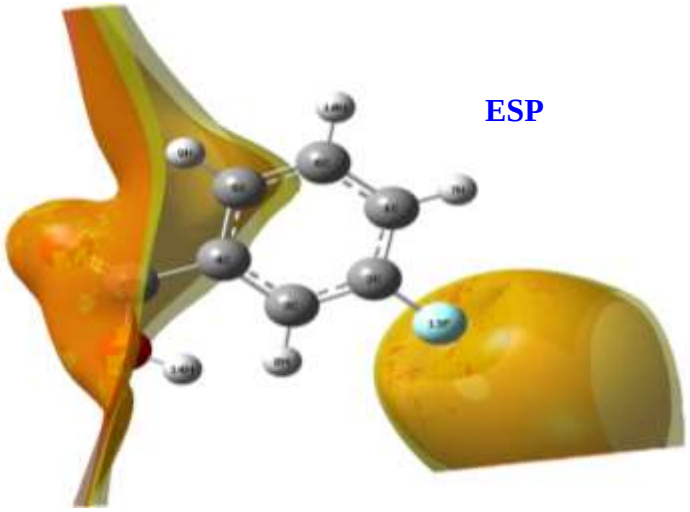


Fig.5. ESP for 3-Fluoro benzoic acid

Docking Analysis:

Molecular docking is an innovative technique for predicting clearly how the molecule under study interacts with macromolecules and change the properties. In this study, the molecule is made to dock with many proteins, as ligand – protein interactions, using Auto Dock program 4.0 [19]. The resulting binding, sites at which the binding take place and the binding energy are determined. The structure after binding was also identified using Activity Spectra (PASS) [20] program and other online tools. The residual structure of the target bacteria is downloaded from RCSB (Research Collaboratory for Structural Bioinformatics) protein data bank (http://www.rcsb.org/pdb/home/home. do). The detail of the ligand-protein docking is shown in Table.8 and the graphical representation is shown in Fig.6.

The auto dock Tools (ADT) graphical user interface was used to prepare the protein by removing water and adding polar hydrogens along with charges. The analysis shows that the docking take place at three sites SER 3, LUE 326 and LUE 4 using Hydrogen bonds at C-O_{12}, OH_{14} (hydroxyl group) and O_{12} of title ligand molecule with the bacteria 3SHO, with bond length of 1.6, 2.1 and 2.5 Å respectively. The last two bonds are stronger and stable while the first bond is relatively weak and unstable. The total binding energy of the molecule 5.5 kcal/mol which indicates the docking is quite strong. The binding of the molecule with the bacteria completely alter the nature or the functioning of the said bacteria and thereby the molecule serve as the antibacterial. The inhibition constant is found to be 89.53 micro mole which means 89 micro mole ligand will suppress half of the vitality of bacteria. The calculated RMSD the root mean square deviation of the residues of the target protein is 1.36Å, which indicates it is one of the normally occurring strong docking. Thus, the present docking study indicates that the title molecule may be used for synthesis of anti-bacterial (3SHO) drug.

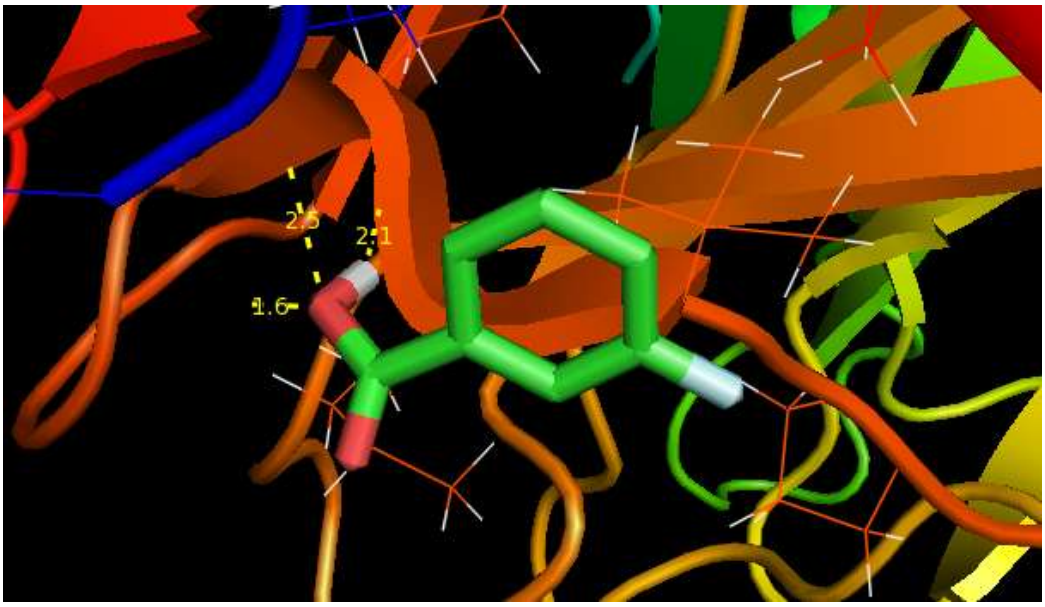


Fig.6.Docking analysis for 3-Fluoro benzoic acid

Table : 1.

Binding pose analysis for 3-Fluoro benzoic acid

Protein ID	Binding energy	Inhibition constant (micro	RMSD (Å)	Intermolecular energy (kcal/mol)	Bond Residue	Distance (Å)

	(kcal/mol)	**molar)**				
3SHO	5.52	89.53	1.36	5.52	SER 3	1.6
					LUE 326	2.1
					LUE 4	2.5

4. CONCLUSION

Detailed conformational analyses were carried out for the title molecule 3-Fluoro benzoic acid, all of which clearly indicate there is considerable change in electronic distribution in the benzene ring due to the substitutional groups COOH and F atom. The docking analysis of the molecule against various proteins leads to the finding that the molecule can be used for anti-malarial activity.

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