GAS-PHASE DFT STUDIES, QUANTUM CHEMICAL CALCULATIONS, NBO ANALYSIS, FIRST HYPER POLARIZABILITY AND DOCKINGS STUDIES OF (E)-N'-(4-BROMO-3- HYDROXYBENZILIDINE)-2-METHYL-3-NITROBENZOHYDRAZIDE HYDRATE

Khushbu K. Lalvani[1*], Urmila H. Patel[1], Bhavesh N. Socha[1, 4], Sahaj Gandhi[2], Bharat D. Patel, V. M. Barot[3], Mukesh Patel[3].

[1*]X-ray Laboratory, Department of Physics, Sardar Patel University, Vallabh Vidyanagar, Gujarat, India

[2] Bhavan Shri I. L. Pandya Arts-science and Smt. J. M. Shah commerce college, Dakor, Gujarat, India

[3] P.G Center in chemistry, Smt. S. M. Panchal Science college, Talod, Gujarat, India.

[4]Department of Materials Science, Sardar Patel University, Vallabh Vidyanagar, Gujarat, India

*Corresponding author : khushbulalvani.8992@gmail.com, patelurmila324@gmail.com

Abstract - The theoretically optimized structure of the molecule in gaseous phase matches the X-ray dataquite well. The hydrazide derivative; chemical properties like stability, reactivity and binding affinity can be examined using quantum chemical calculations, and the HOMO-LUMO energies demonstrate that charge transfer happens within the molecule. The individual atomic charge values are derived from the Mulliken population analysis (MPA), which reveals the hydrazide derivative binding site. Natural bond orbital (NBO) analysis was used to investigatethe stability of the hydrazide derivative as a result of hyper-conjugative interactions and chargedelocalization, The binding energy of the hydrazide derivative with the protein molecule was additionally conveyed by thought polarizability and first hyperpolarizability.

Keywords: Gas-Phase optimization, Quantum chemical parameter, Natural bond orbital (NBO) analysis, Docking studies.

I. INTRODUCTION

Hydrazides[1, 2] belong to an exclusive class of Schiff base substances, distinguished itself by the existence of -C=N-NH-C- or -C=N-N-C-, whereas hydrazide includes, an azomethine N-CH proton. The hydrazide–hydrazones -CO-NH-N=C- are product of acid hydrazides -CO-NH- NH2 and carbonyl compounds, and in general known as hydrazones. The coordination chemistry of hydrazones is quite interesting. Both the nitrogen atoms and hydrazones (hydrazine derivatives) group have both electrophilic as well as nucleophilic character. Increasing attention in medicinal chemistry, pharmaceutical industry and toxicology of hydrazine derivatives are due to better chemical reactivity of this class of compound imparting a wide spectrum of biological actions, some of which have found application in therapeutics. We attempted to study theoretical analysis such as quantum chemical parameters to check its stability and reactivity toward the biomolecule, charge transfer, binding energy with protein molecule, and docking studies with different-different biomolecules in light of the significanceof these group of compounds as well as the versatile chemistry due to the flexible hydrazide moiety[3, 4].

1. Computational studies

DFT studies have been performed using Schrodinger software package[5], with B3LYP/LAV2P (Becke three parameter Lee-Yang-Parr) basis set to develop an optimize structure. The molecular properties of the optimized molecule like HOMO-LUMO, MEP, MPA and NBO analysis are carried out using LAV2P basic set[6, 7].

II. RESULT AND DISCUSSION

1.1 Geometry optimizations

Optimized model of the bromo hydrazide molecule is developed by Schrodinger software using the B3LYP approach with LAV2P base set. Since experimental data is

in the crystalline state while theoretical data is in the gaseous state, the differences between theoretical data (B3LYP)to experimental data (X-ray data) are primarily due to intermolecular interactions in the crystalline state. **SI 1** shows a comparison of experimental and theoretical data, and aspredicted, most of the optimised bond lengths and bond angles are slightly greater than those of experimental data[8, 9]. The correlation coefficient values for bond length and bond angle as obtained from the linear fittings of experimental and theoretical data result in as 0.93 and 0.95 respectively.

$$y = -0.05703 + 1.04884x$$
$$R = 0.9393$$

$$y = 4.09545 + 0.96555x$$
$$R = 0.95179$$
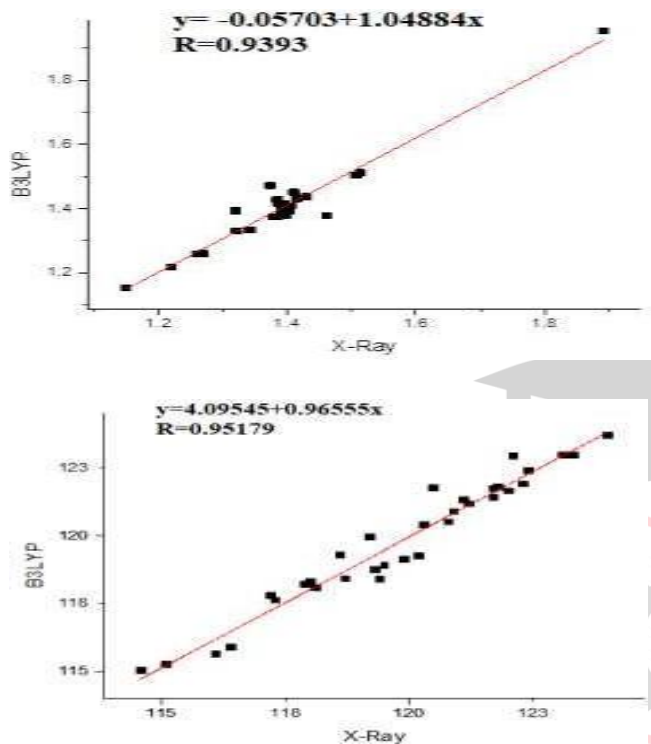
SI 1. Linear fitting of experimental and theoretical data of bond length and bond angle

1.2 Molecular electrostatic potential (MEP)

To predict the binding site and the hydrogen bonding interactions of ligand with the biomolecules the molecular, electrostatic potential (MEP) is calculated to identify the electrophilic and nucleophilic sites of the molecule[10, 11]. The calculated electron density cloud encompasses all atoms in the molecule's crystal structure electrostatic potential, as seen in **Figure 1**. The red spots in this figure relate to locations with positive potential, whereas the blue areas are indicated by the color blue. The nitrogen (N2) atoms with larger negative potentials are often located over the blue areas (negative potential), making them morevulnerable to an intense electrophilic assault. The red regions correspond to a strong nucleophilic reactivity. Average local ionization energy, density laplacian, electro-static potential, electron density, interaction strength, reduced density gradient of bromo hydrazide derivative depicted in **Figure 1**.
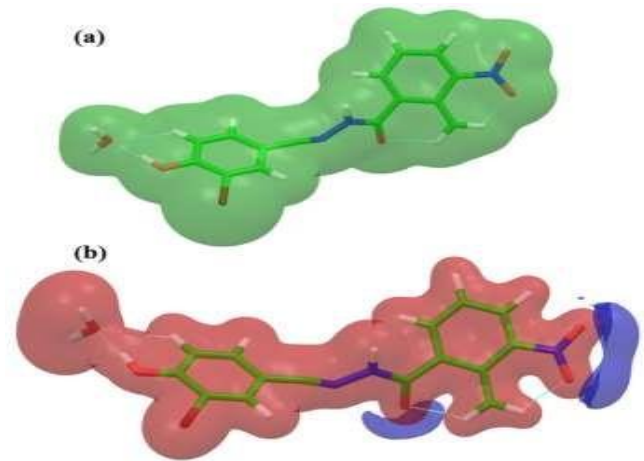

Figure 1. (a) Electron density cloud and (b) Electrostatic potential of title molecule

The knowledge of the parameters of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very important for quantum chemical calculations since they determined the way the molecule interacts with other species. The LUMO represents the ability to obtain an electron and HOMO represents ability to donate an electron within themolecule. The molecule with a large energy gap is known as hard molecule and having a small energy gap is known as soft molecule. The hard molecule is less polarizable than the soft onesbecause they require immense energy for excitation and its less active compared to soft one[12, 13]. The HOMO-LUMO energy surface are displayed in **Figure 2.** and data are tabulated in **Table1.** The LUMO energy surrounded by bromo-hydroxy phenyl ring of hydrazide derivative and most of HOMO energies are surrounded by nitro-methyl phenyl ring of hydrazide derivative. The central hydrazide moiety group are taking part in both the HOMO and LUMO energy. Theenergy band gap of hydrazide derivative is 0.64eV, which is smaller than that of pyrazole derivative(3.8eV)[14] and phenoxy-phenyl derivative(4.7eV)(6) stated data, indicating that the hydrazide derivative is highly soft in nature with high reactivity when compared to reported data.

1.3 HOMO-LUMO energy and Quantum chemical parameter

The energy gap between HOMO and LUMO a critical parameter, help to determine molecular electric transport properties, kinetic stability, optical polarizability and chemical reactivity descriptors of the molecule: hardness(η), chemical potential(μ), softness(S), electronegativity (χ), electrophilicity index (ω) and maximum charge transfer (ΔNmax.) and there data are tabulated in **Table 1**. The Global reactivity descriptor parameters are calculated using Koopman's theorem. These parameters are useful to explain the stability and binding capacity of biomolecule. The electrophilicity data ω indicated that the electronic accepting nature is more in title molecule compared to those of reported data (**Table 1**), also from the softness andhardness index

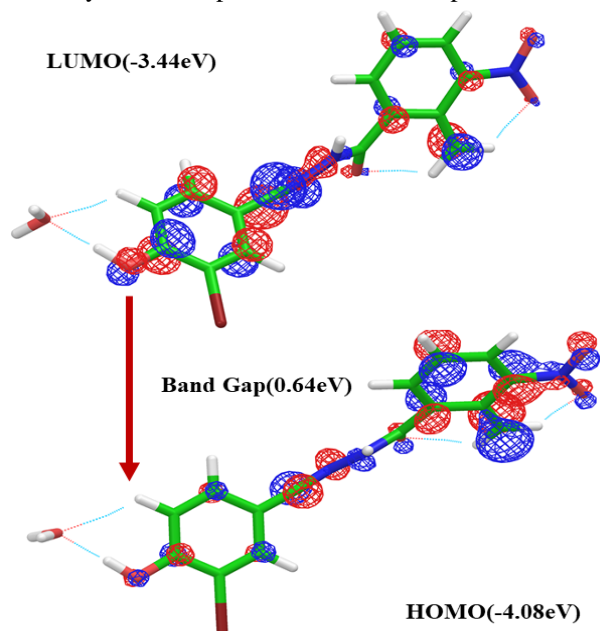indicated that the title molecule is soft in nature with high reactivity compared to reported data.

LUMO(-3.44eV)

Band Gap(0.64eV)

HOMO(-4.08eV)

Figure 2. HOMO-LUMO energy distribution

Table 1. HOMO-LUMO energy and Global quantum parameters

	Title molecule	(12)	(5)
HOMO(I)	-4.08eV	-5.7eV	-5.94eV
LUMO(A)	-3.44eV	-1.9eV	-1.57eV
Energy gap(A-I)	0.64eV	3.8eV	4.39 eV
Electronegativity χ = (I+A)/2	-3.76eV	3.8eV	3.75eV
chemical hardness η = -(I-0.32eV A)/2		1.9eV	2.18eV
chemical softness s = 1/η	3.12eV^{-1}	0.52eV^{-1}	0.45eV^{-1}
Electrophilicity ω = $\mu^2/2\eta$	9.04eV^{-1}	2.8eV^{-1}	3.22eV^{-1}
Chemical potential μ =(I+A)/2	-3.76eV	-3.29eV	-3.75eV
(ΔNmax) = - μ/ η	1.20	1.73	1.72

1.4 Mullikan Charge Distributions

Table 2. summarize the Mulliken charge distribution of each atom of bromo hydrazide derivative calculated using B3LYP/LAV2P*level. It reveals that all oxygens have negative charge with the order of OW>O3. Water oxygen OW have the highest negative charge and thecorresponding hydrogen atoms have higher positive charge, enabling it to take part in maximum number of inter molecular interactions established by X-Ray data[15]. The halogen Br is neutral with atomic charge of bromine atom (Br) is 0.082. The nitrogen atom N3 has Positive charge and all the other

nitrogen have negative charge in the molecule. The carbon atoms C2, C5, C8, C7, C13 have positive charge and other carbon atoms have negative charges in the molecule[14].

Atom	Charge	Atom	Charge
C15	-0.24955	O1	-0.50948
H15A	0.12048	H12	0.35304
H15B	0.14497	C2	0.42146
C11	-0.10454	N2	-0.17739
H11	0.09417	C3	-0.14749
OW	-0.59384	H1	0.13132
O3	-0.41267	C6	-0.0013
N3	0.38713	H3	0.14909
O4	-0.42505	C8	0.50881
Br1	0.082	C13	0.18407
C12	-0.13148	N1	-0.40086
C4	-0.08492	H5B	0.09221
H1A	0.1308	C14	0.04247
C1	-0.36043	C7	0.20939
C5	0.03781	HW1	0.34176
C10	-0.12133	HW2	0.34156

1.5 Natural Bond orbital analysis

NBO analysis, a useful method for studying molecular bonding and interaction amongst bonds, for understanding delocalization of electron density from occupied Lewis-type (donor) NBOs to properly unoccupied non- Lewis type (acceptor) NBOs within a molecule is carried out using Schrodinger software. The stabilization of orbital interaction gives information about energy difference between interacting orbitals E(2). The Stabilizing energy E(2) associated with i(donor)I (acceptor) delocalization is estimated from a second order perturbation approach as given in equation below and tabulated in Table E$^{(2)}$ given in **Table 3**. For each donor NBO (L)and acceptor NBO (NL), the stabilization energy E$^{(2)}$ is given as:

Stabilizing Energy: $E^{(2)} = \Delta E_{NL,L} = q_l(F(L,NL) / E(NL)-E(L))$

The higher value of E$^{(2)}$ reveals the intense interaction between electron donors and electron acceptors, i.e. the greater donating tendency from electron donors to electron acceptors NBO and the greater extent of conjuation of the whole system. The decreasing order of energy E2 for the interactions LP(2)O1 (donor)►LV(1)C2(acceptor), LP(1)C13►π*C11-C12, πC3- C4►LV(1)C2, πC6-C1►LV(1)C2, LP(1)C13►π*C2-C14 interactions are 116.56, 113.93,75.65, 69.38, 63.73 kcal/mol respectively.

Table 3. Second-order perturbation analysis of Fock matrix in NBO basis

Donor (L)	Acceptor(NL)	E(2) kcal/mol	E(NL)-E(L) a.u	F(L,NL) a.u.
LP(2)O2	σ*C8-N1	32.81	0.63	0.129
LP(2)O2	σ*C8-C9	18.78	0.69	0.102

LP(2)O3	σ*N3-O4	20.62	0.69	0.106
LP(2)O4	σ*O3-N3	19.39	0.69	0.103
LP(2)O1	LV(1)C2	116.56	0.19	0.31
LP(1)N2	π*C5-C7	40.91	0.4	0.115
LP(1)C13	π*C2-C14	63.73	0.17	0.092
LP(1)C13	π*C11-C12	113.93	0.15	0.116
LP(1)N1	π*O2-C8	38.1	0.32	0.099
LP(1)N1	π*N2-C7	29.69	0.31	0.086
πC15-C14	π*C9-C10	17.18	0.27	0.061
πC11-C12	π*C9-C10	25.4	0.27	0.074
πC3-C4	LV(1)C2	75.65	0.14	0.091
πC6-C1	LV(1)C2	69.38	0.15	0.091
πC9-C10	π*O2-C8	17.44	0.29	0.063

The polarizability α and first hyper polarizability (β)

The behaviour of the title molecule in presence of applied electric filed is analysed by NLO analysis (dipole moment, polarizability and first hyper polarizability). The calculated values ofelectronic dipole moment (μ), polarizability (α) and the first hyperpolarizability (β) for the titlemolecule are μ (8.38 Debye), α (194.8556 $Å^3$) and β (17.20 x 10-31 cm^5 esu^{-1}) [**Table 4**] respectively. Urea is a traditional molecule which is used for comparative analysis in NLO, forurea α is 4.28 $Å^3$ and β is 1.52 x 10^{-31} cm^5 esu^{-1}. Comparatively higher value of the polarizability(α) and the first hyperpolarizability (β) of the bromo hydrazide derivative predicts a stronger binding of the receptor molecules than those of the standard molecule(urea). The binding energy between two molecules, (title molecule and biomolecule) ligand and receptor, is proportional to their polarizability magnitude and the moment of dipole. The higher polarizability value of the title molecule suggests higher protein (receptor) binding energy[16].

dipole moment $(\mu) = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2}$

polarizability $(\alpha) = 1/3\ (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$

first hyperpolarizability (β) =
$[(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{zyy})^2]^{1/2}$

Table 4. Dipole moment, Polarizability ($Å^3$) and Hyperpolarizability (a.u).

Dipole (Debye)   Hyperpolarizability (AU)

u_x 0.93403		β_{xxx} 2.8681	
u_y -6.71509		β_{yyy} 1.9936	
u_z -4.93121		β_{zzz} -1.6228	
u_{total} 8.38342		β_{xyy} -2.7571	
Polarizability ($Å^3$)		β_{xzz} 8.7626	
a_{xx} 129.989		β_{yxx}	9.1534
a_{yy} 186.018		β_{yzz}	3.5318
a_{zz} 268.560		β_{zxx}	1.9142
a_{xy} 104.377		β_{zyy}	1.1110
a_{xz} 23.374		β_{xyz}	1.5299
α_{yz} 205.744		**Beta(β0)** 17.20 x 10^{-31} cm^5 esu^{-1}**Alpha (α)**	

194.8556 $Å^3$ **Urea(β0)**   1.52   x 10^{-31} cm^5 esu^{-1} **Urea(α)**   4.28 $Å^3$

docking studies:

Molecular docking study as an imperative computational tool played an important role in understanding the drug and nucleic acid interactions. To correlate structure function relationship of the molecule, molecular docking studies are carried out to identify the primarybinding site of the molecule to receptor. The data of crystalline structure of 1DNA, as receptorof docking studies, was downloaded from Protein Data Bank (ww.rcsb.org/pdb) with PDB format. The molecular dynamic simulation is carried out with hex software. **Figure 3** representsthe docking with 1DNA of title molecule(ligand) the docking score is -270.10.
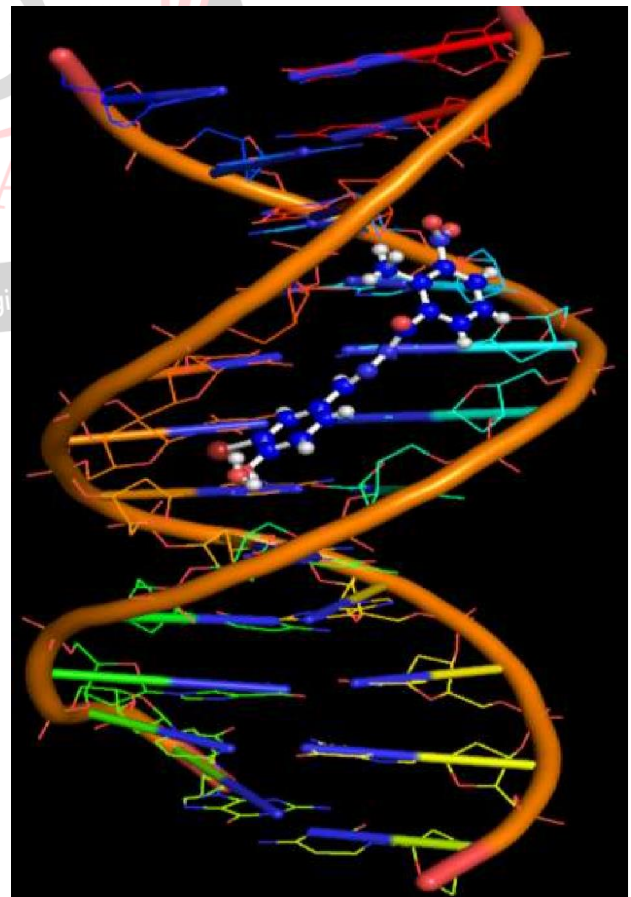

Figure 3. molecular docking with 1DNA

III. CONCLUSION

Bond lengths and bond angles are closely correlated between theoretical (B3LYP) and experimental (X-ray) data, with strong R-square values shows that the experiment data strongly correlated with theoretic. The reason for the slight differences is that the B3LYP data are in a gaseous state, where intermolecular interactions are not taken into account, whereas the X-ray data are in a solid form. Energy gap of the title molecule is 0.64eV, so we conclude that our molecule is a soft molecule with low kinetic stability and high chemical reactivity with biomolecule is more than the reported derivatives of Hydrazides derivative. According to the Mulliken population study, both N and O atoms participated in intra- and intermolecular interactions and carried more negative charges than other atoms. Comparatively higher value of the polarizability (α) and the first hyperpolarizability (β) of the bromo hydrazide derivative predicts a stronger binding of the receptor molecules than those of the standard molecule(urea) also title molecule shows the good binding energy toward the 1BNA(DNA)[17].

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