Determination of Molecular Structure, Electronic and Non-Linear Optical Properties of Hydralazine Molecule

[1]G.Babaji, [1]A.S Gidado and [2]Abdulbaki M.Aliyu

Department of Physics, Bayero University Kano PMB 3011.

Abstract

Hydralazine ($C_8H_8N_4$) is an antihypertensive drug used as a vasodilator for the treatment of severe hypertension.In this work,computational methods were employed to determine the most stable conformer, optimized parameters, frontier molecular orbital energies (HOMO and LUMO), energy gap, chemical hardness, chemical softness, chemical potential, electrophilicity, polarizability, dipole moment and Natural Bond Orbital (NBO)of Hydralazine. Conformational search was performed usingwindow version ofConflex 7 based on molecular mechanics force field (MMFF) where four conformers with minimum energyare reportedand the most stable one was found to have sterric energy of 85.42kcal/mol. This value agreed with a previously reported work where 84.57kcal/mol. was obtained.Other calculations were carried out at two levels of theory, theabintio[Restricted Hatree-Fock]/ (RHF) and Density Functional Theory (DFT) [LSDA & B3LYP] using windows version of Gaussian 03 software with different basis sets. The results obtained show thatat both levels of theory, the N1-H4 bond in Hydralazine is the strongest because it has the shortest bond length (Average 1.0124 Å for DFT and 0.9921Å for RHF) while C3-C6 is the weakest due to its longer bond lengths (Average 1.4399Å for DFT and 1.4446Å for RHF). The HOMO-LUMO energy gap was found to be4.11eV which was closer to4.52eV as previously reported. NBO analysis was carried out where the highest values ofstabilisation energy $\left(E^{(2)}\right)$ were obtained in the lone-pair N5 as 10.42kJ/mol for DFT and 13.18kJ/mol for RHF which implies more intense interaction between donors and acceptors. This work specifically contributed in the calculations of chemical hardness, chemical softness, chemical potential, electrophilicity, NBO analysis, average polarizability and first order hyper polarizability which have not been reported previously. In a nutshell, this work sheds more light into the molecular structure and electronic properties of hydralazine which will be useful in drug design.

1.0 Introduction

Hypertension (high blood pressure) is define as having a blood pressure higher than 140 over 90mmHg with a consensus across a medical guidelines. Blood pressureis the force exerted by the blood against the walls of blood vessels, and the magnitude of this force depends on the cardiac output and the resistance of the blood vessels. Hydralazine is widely used in the long term treatment of hypertension The cellular response to hydralazine includes production of free radicals and induction of DNA damage [1]. Hydralazine is also known as Apresoline (HP) and is used in the treatment of hypertension because of its peripheral vasolidatoreffect[2].

The World Health Organisation (WHO) identified hypertension as the leading cause of cardio vascular mortality. As the momentum picks up every year, the WHO is confident that almost the estimated 1.5 billion people are affected by elevated

Corresponding author: A.S. Gidado, E-mail: asgidado.phy@buk.edu.ng, Tel.: +234802827621

blood pressure can be reached [3]. Hydralazine is a vasodilator used to treats severe hypertension, congestive heart failure, myocardial infarction and preeclampsia.Hydralazine thought to reduce peripheral resistance directly by relaxing the smooth muscle cell lyre in arterial vessels[4]. Hydralazine is a centrally acting anti-hypertensive agent, find use in the treatment of all grades of hypertension. It is also known to act peripherally, partly by blocking alpha-adrenegic receptors and partly by decreasing vascular reactivity [5-6]. The 3–dimentionalquantitative structure activity relationship provides the valuable information about the nature of the receptor helps to describe new drug candidates and to improve in vitro potency [7].An investigation of the relative stability, thermodynamic properties, HOMO-LUMO energy and dipole moment of hydralazine and its metabolites has been reported [1].Similarly, the anticorrosion potential of hydralazine was studied and reported by [8]. Hydralazine and nitrate when combined, reduces morbidity and in some trials of chronic heart failure (CHF) [9].
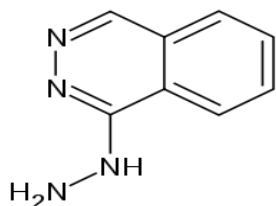

Figure 1.0: Chemical structure of Hydralazine

It is the purpose of this work to investigate some of the molecular, electronic and non-linear optical propeties of hydralazine and compare the results with previously reported works and also to compute chemical hardness, chemical softness, chemical potential, electrophilicity, NBO analysis, average polarizability and first order hyper polarizability which have not been reported previously.

2.0   Theoretical Background

Geometry Optimization

Geometry optimization is a name for the procedure that attemptsto find the configuration of minimum energy of the molecule. Theprocedure calculates the wave function and the energy at a startinggeometry and then proceeds to search a new geometry of a lower energy.This is repeated until the lowest energy geometry is found. Theprocedure calculates the force on each atom by evaluating the gradient (first derivative) of the energy with respect to atomic positions [10].

Conformational Analysis

All classical and quantum mechanics geometry optimization methods typically find a minimumenergy conformation near the starting geometry. This minimum is not necessarily the true globalminimum energy structure. Hence, there is often a need to compare all possible conformations ofa molecule to find the true global minimum, or several of the lowest minima. This process is known as conformational searching[10].

Conformational analysis of molecule is based on molecular mechanics, it is a method for the calculation of molecular structures,conformational energies and other molecular properties using concept from classical mechanics. A molecule is considered as a collection of atoms held together by classical forces. These forces are described by potential energy function of structural features like bond lengths,bond angles and torsion angles [5].

Furthermore, molecular mechanics deals with the changes in a molecule's electronic energy due to bond stretching (V_{str}), bond-angle bending (V_{bend}), out-of-plane bending (V_{oop}), internal rotation (torsion) about bonds (V_{tors}), interactions between these kinds of motion which produce cross terms (V_{cross}), van der Waals attractions and repulsion between non-bonded atoms (V_{vdw}) and electrostatic interactions between atoms (V_{es}). The sum of these contributions gives the molecular mechanics potential energy V (called the sterric energy) for motion of the atoms in the molecule (or molecules if the system being calculated has more than one molecule) [10].

$$V = V_{str} + V_{bend} + V_{oop} + V_{tors} + V_{cross} + V_{vdw} + V_{es} \qquad (1)$$

Bond stretching: V_{str}

V_{str}, the first term of the equation, represents the potential energy of stretching a bond, like a spring, from its minimum energy equilibrium length.Itrepresents the energy required to stretch or compress a bond between two atoms. In the simplest force fields, the potential energy of stretching may be approximated by the harmonic oscillator potential.

$$V_{str,ij} = \frac{1}{2}K_{IJ}\left(r_{ij} - r_{IJ}\right)^2 \qquad (2)$$

Here, r_{ij} represents the distance between atoms i and j , K_{IJ} represents the force constant between the atoms, and r_{IJ}represnts a reference bond length between the atoms.

Angle bending: V_{bend}

The second term of equation (1)V_{bend} represents the potential energy associated with bending the angle between three atoms. Itis the energy required to bend a bond from its equilibrium angleθ_{jkl}.

This system can be modelled by a spring, and the energy is given by the Hookian potential with respect to angle. The simplest representation of this interaction is a quadratic [10].

$$V_{bend,ijk} = \frac{1}{2}K_{IJK}(\theta_{ijk} - \theta_{IJK})^2 \qquad (3)$$

θ_{ijk}, K_{IJK} and θ_{IJK} each hold analogous definitions as in equation (2), except they represent an interaction between three immediately adjacent bonded atoms and are referenced and measured by the angle formed by these atoms and not by any distances.

Out-of-plane bending: V_{oop}

V_{oop} Is the energy required to deform a planar group of atoms from its equilibrium angle, usually equal to zero. An out-of-plane angle bending coordinate arises when the local molecular structure consists of four atoms with three valence bonds formed to one centre atom. Out-of-plane bending, sometimes called improper torsion, simply gives quantitative value to deviation from planarity, and may also, in simplest form, be written as a quadratic [10].

$$V_{oop,ijk} = \frac{1}{2}K_{IJKL}\chi_{ijkl}^2 \qquad (4)$$

where χ_{ijkl} represents the angle by which an atom deviates from planar.

Torsion angle: V_{tors}

V_{tors} is the energy of torsion needed to rotate about bonds. Torsional energies are usually important only for single bonds because double and triple bonds are too rigid to permit rotation. Potential energy changes due to torsional bending of four-atom groups bonded in a chain-like configuration are represented by the term V_{tors} in equation (1) and is given by [10].

$$V_{tors,ijkl} = \frac{1}{2}[V_1(1 + cos\phi)] + V_2(1 - cos2\phi) + V_3(1 - cos2\phi) \qquad (5)$$

where ϕ is the torsion angle (θ_{ijkl}) and $V_1, V_2 and V_3$ are parameters whose values depend on the atom types *i,j,k* and *l*.

Van der Waals interactions: V_{vdw}

Variations in the potential energy of the system due to van der Waals interactions among atoms are accounted for by the V_{vdw} term of equation (1). Van der Waals forces, or London dispersion forces, exist between non-bonded atoms, and are typically regarded as influential among atoms separated by roughly three bond lengths or more. The Lennard-Jones 6-12 potential is particularly useful in this case [10].

$$V_{vdW,ij} = \varepsilon_{IJ}\left[\left(\frac{R_{IJ}^*}{r_{ij}}\right)^{12} - 2\left(\frac{R_{IJ}^*}{r_{ij}}\right)^6\right] \qquad (6)$$

Here, r_{ij} is the distance between atoms i *and* j, ε_{IJ} is called the well-depth parameter, and $R*_{IJ}$ is the distance between atoms *i* and *j* when the van der Waals potential energy is at a minimum.

Electrostatic interactions: V_{es}

The V_{es} term of equation (1) represents electrostatic interactions between atoms and, like van der Waals forces; they are usually taken into account for non-bonded atoms. In its simplest incarnation, the electrostatic term appears as Columbic [10].

$$V_{es,ij} = \frac{Q_iQ_j}{\varepsilon_r r_{ij}} \qquad (7)$$

Atoms are assigned partial charges in determining the values of Q_i and Q_j. ε_r is a dielectric constant, and r_{ij} is the distance between atoms *i* and *j*.

Interactions between different modes of conformations V_{cross}

V_{cross} is a quantification of the interactions which may exist between different modes of conformation. For example, stretching bonds will change the van der Waals force between atoms, which in turn will change the force needed to bend an angle in question. The potential function that can model this interaction is given as [10].

$$V_{cross,ij} = \frac{1}{2}K_{IJ}(\Delta r_1 - \Delta r_2)\Delta\theta \qquad (8)$$

where Δr's and $\Delta\theta$ are deviations from bond lengths and angle, respectively.

Density Functional Theory (DFT)

This is a very powerful method in computation and it has low cost as well as good accuracy for many problems [11]. DFT makes use of electron probability density instead of the electron positions, which reduces the computation cost. In DFT, the ground state energy can be determined by the relationship given as [12].

$$\rho(r) = \sum_{i=1}^{n}|\psi_{i(r)}|^2 \qquad (9)$$

where $\rho(r)$ is the electron density and $\psi_{i(r)}$ is the wave function of the electrons.

Further description of DFT can be found in [13-16]

Global Quantities

Chemical hardness(η) measures the resistance of an atom to charge transfer, it is estimated by using the equation [17].

$$\eta = \frac{I-A}{2} \qquad (10)$$

Chemical softness (*S*) is a property of molecules that measures the extent of chemical reactivity. It is estimated by using the equation [17].

$$S = \frac{1}{\eta} \tag{11}$$

Chemical potential (μ) measures the escaping tendency of an electronic cloud of the atoms, ions or molecules and can be calculated using the following relation[17].

$$\mu = \frac{I+A}{2} \tag{12}$$

where I= -E_{HOMO} and A= -$E_{LUMO.}$

I and A are the ionization potential and electron affinity of the molecule.

Electrophilicity (ω) is a measure of energy lowering of the chemical species due to maximum electron flow between donor and acceptor. It is defined as [18].

$$\omega = \frac{\mu^2}{2\eta} \tag{13}$$

Further, to define global descriptors for a given molecule one may use Koopmans, theorem within Hatree-Fock to get IP and EA in the form of molecular orbital energies and also define μ,ηand χas in the following equations [18].

$$I = -E_{HOMO} \tag{14}$$

$$EA = -E_{LUMO} \tag{15}$$

$$\eta = \frac{1}{2} \left(E_{LUMO} - E_{HOMO} \right) \approx \frac{1}{2} \left(IP - EA \right) \tag{16}$$

$$\chi = \frac{1}{2} \left(IP + EA \right) \tag{17}$$

$$\mu = \frac{1}{2} \left(E_{LUMO} + E_{HOMO} \right) \approx \frac{1}{2} \left(IP + EA \right) \tag{18}$$

In addition, according to Koopmans' theorem, the energy gap, E_{gap}, defined as the difference between HOMO and LUMO energy is given by [18].

$$E_{gap} = \left(E_{LUMO} - E_{HOMO} \right) \approx IP - EA \tag{19}$$

Natural Bond Orbital (NBO) Analysis

The NBO analysis is already proved to be an effective tool for the chemical interpretation of hyperconjugative interaction and electron density transfer from the filled lone pair electron [19]. The hyperconjugative interaction energy can be calculated from the second-order perturbation approach as given by [20].

$$E^{(2)} = -n_\sigma \frac{\langle \sigma|F|\sigma \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{F_{ij}^2}{\Delta E} \tag{20}$$

Where$\langle \sigma|F|\sigma \rangle^2$ or $F_{ij}{}^2$is the Fock matrix elements between i and j NBO orbitals, $\varepsilon_{\sigma^*} \; and \; \varepsilon_\sigma$ are the energies of σ* and σ NBOs and n_σ is the population of the donor σ orbital.

Nonlinear optical properties

The study of nonlinear optical properties involves the calculation of dipole moment (μ), polarizability (α$_{tol}$) and first hyperpolarizability (β_{tol}) tensor. First hyperpolarizability is a third rank tensor which can be described by a 3×3×3 matrix. Due to the Kleinman symmetry, the 27 components of the 3-D matrix can be reduced to 10 components. Using the *x*, *y* and *z* components and the magnitude of the total static dipole moment (μ), isotropic polarizability (α$_{tol}$) and first-order hyperpolarizability β_{tol}tensor can be calculated using the following equations [21] respectively,

$$\mu_{tol} = \left(\mu_x^2 + \mu_y^2 + \mu_z^2 \right)^{\frac{1}{2}} \tag{21}$$

$$\alpha_{tol} = \frac{1}{3} \left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz} \right) \tag{22}$$

$$\beta_{tol} = \left(\beta_x^2 + \beta_y^2 + \beta_z^2 \right)^{\frac{1}{2}} \tag{23}$$

where

$$\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz} \; ,$$
$$\beta_y = \beta_{yyy} + \beta_{xxy} + \beta_{yzz}$$
$$\beta_z = \beta_{zzz} + \beta_{xxz} + \beta_{yyz}$$

3.0   Methodology

The molecular structure ofthe title molecule was obtained from ligand Expo database and was used as obtained.Ligand expo (formerly Ligand Depot) is an online database which provides chemical and structural information about small molecules (so-called ligand) within the structure entries of the protein Data Bank (PDB). In order to obtain the most stable structure of the title molecule, conformational analysis was carried out using Complex 07 [22] based on molecular mechanics force field (MMFF).

This computation was performed using Newton Raphsonoptimization method. After the most stable conformer of the molecule was determined, geometry optimization of this molecule wasperformed using the window version of Gaussian 03 program package [23].Density functional theory (DFT) has been proved to be extremely useful intreating electronic structure of molecules[24]. Also DFT methods are now standard in virtually all of the most popular software packages[25]. The

structure of the most stable conformer was used as the initial structure for quantum calculations. The entire quantum chemical calculations have been performed at DFT (B3LYP and LSDA) and ab initio methods [26] using the basis sets LSDA/3-21G*, LSDA/6-31G*, LSDA/6-311G*, B3LYP/3-21 G*, B3LYP/6-31 G*, B3LYP/6-311 G*, RHF/3-21G*, RHF/6-31G* and RHF/6-311G*. Finding a good geometry is called geometry optimization, so "OPT" was used as the keyword.The calculation generatedan output file called "filenameout". The output file (filename.out) contains a lot of information about the calculation and the results.The HOMO-LUMO analysishas been carried out to explain the charge transfer within the molecule. The energy gap which is the difference between HOMO and LUMO was calculated. The chemical hardness, chemical softnes, chemical potential and electrophilicity were also calculated using the HOMO and LUMO energy. NBO analysis stresses the role of intermolecular orbital interaction in the compounds, particularly charge transfer. This was carried out by considering all possible interaction between filled donor and empty acceptor NBOs and estimating their energetic importance by secondorder perturbation theory. For each donor NBO (i) and acceptor NBO (j), the stabilization energy associated with electron delocalization between donor and acceptor $E^{(2)}$ was calculated.

4.0   Results and Discussion
4.1   Conformational Stability
Since molecular geometry plays a very important role in determining the structure-activity relationship, conformational analysis of the molecule provides meaningful information, relevant to drug action [24]. To find the most stable conformer a conformational analysis was carried out for the title molecule usingConflex 07D. Table 1 shows the sterric energy of the four conformers with minimum energy. The conformer with ID number 0001 has the smallest value of sterric energy (85.42kcal/mol) which is in agreement with 84.57kcal/mol reported by [1].

Table 1: Sterric Energy of Conformers

S/N	ID	Sterric Energy (kcal/mol)	Conformer with minimum energy	(Zaheed and Fazlul, 2006) Kcal/mol
1	00001	85.4208		
2	00002	86.8449	85.4208	84.57
3	00003	87.3493		
4	00004	87.9595		

4.2   Optimized Parameters of Hydralazine
Optimized Bond Lengths (Å) For Hydralazine Molecule
Bond length is the average distance between the canters of two atoms bonded together in any given molecule[25].Tables 2 and 3 show the calculated bond lengths at RHF and DFT levels of theory using different basis sets. The bond length in R(1,4), R(2,7), R(2,8), R(11,15), R(13,19), R(14,18) and R(15,20) respectively are found to be the least for both levels of theory. The strongest bond was formed at B3LYP/6-311G* level of theory for R (1, 4) which was 1.002Å while the weakest bond existed at B3LYP/3-21G* level of theory which was calculated to be 1.4503. On comparing the calculated values of bond length with experimental values, the bond lengthR(5, 9) at LSAD/3-21G* which was (1.3915 Å) was found to be in agreement with experimental value of (1.392 Å) in magnitude.

Table 2: Optimized Bond Lengths of Hydralazine (Å) For RHF

Bond Lengths	RHF			[27]
	3-21G*	6-31G*	6-311G*	Experimental
R(1,2)	1.423	1.3927	1.3927	1.353
R(1,3)	1.4015	1.3629	1.3645	1.488
R(1,4)	1.006	0.9864	0.984	1.348
R(2,7)	0.9999	0.9986	0.9976	1.410
R(2,8)	1.0022	0.9986	0.9976	1.346
R(3,5)	1.2847	1.3058	1.306	1.393
,R(3,6)	1.4416	1.4468	1.4454	1.486
R(5,9)	1.4015	1.3636	1.3643	1.392
R(6,10)	1.3903	1.3989	1.397	1.394
R(6,11)	1.4042	1.4099	1.4094	1.396
R(9,14)	1.2843	1.2902	1.2893	1.400
R(10,12)	1.4042	1.4091	1.4086	1.397
R(10,14)	1.4311	1.4321	1.4305	1.401
R(11,13)	1.365	1.3714	1.369	1.080
R(11,15)	1.0693	1.0717	1.0696	1.080
R(12,16)	1.3645	1.3698	1.3674	1.080
R(12,17)	1.0723	1.0735	1.0712	1.080
R(13,16)	1.4061	1.4078	1.4074	1.080
R(13,19)	1.0716	1.0727	1.0704	1.000
R(14, 18)	1.0715	1.0709	1.0691	1.000
R(16,20)	1.0716	1.0728	1.0705	1.000

Table 3: Optimized Bond Lengths of Hydralazine (Å) for DFT

Bond Lengths	LSDA			B3LYP			[27]
	3-21G*	6-31G*	6-311G*	3-21G*	6-31G*	6-311G*	Experimental
R(1,2)	1.4278	1.3862	1.4007	1.4408	1.4107	1.4124	1.353
R(1,3)	1.3615	1.361	1.3587	1.3753	1.3742	1.3742	1.488
R(1,4)	1.0247	1.0169	1.017	1.009	1.0048	1.002	1.348
R(2,7)	1.0371	1.0278	1.0251	1.0288	1.0189	1.0165	1.410
R(2,8)	1.0512	1.0278	1.0363	1.0288	1.0189	1.0165	1.346
R(3,5)	1.3412	1.3419	1.3417	1.3373	1.341	1.34	1.393
R(3,6)	1.4318	1.4337	1.4289	1.4503	1.4483	1.4467	1.486
R(5,9)	1.3915	1.3655	1.3643	1.4214	1.385	1.3872	1.392
R(6,10)	1.4151	1.4189	1.4152	1.4177	1.423	1.4204	1.394
R(6,11)	1.4034	1.407	1.4024	1.4139	1.417	1.415	1.396
R(9,14)	1.3222	1.3235	1.3204	1.3195	1.3227	1.3202	1.400
R(10,12)	1.4066	1.4089	1.4052	1.4147	1.4177	1.4157	1.397
R(10,14)	1.4214	1.4188	1.4175	1.4326	1.4308	1.4287	1.401
R(11,13)	1.383	1.384	1.3798	1.3861	1.388	1.3841	1.080
R(11,15)	1.097	1.0965	1.0937	1.0847	1.0851	1.0817	1.080
R(12,16)	1.381	1.3816	1.3777	1.3837	1.3855	1.3817	1.080
R(12,17)	1.0969	1.0964	1.0933	1.0859	1.0861	1.0826	1.080
R(13,16)	1.4064	1.4084	1.4037	1.4132	1.4156	1.4127	1.080
R(14,18)	1.096	1.0953	1.0923	1.0853	1.0847	1.0816	1.000
R(16,20)	1.0954	1.095	1.0918	1.085	1.0853	1.0817	1.000

4.3   Optimized Bond Angles

Bond angle is defined as an angle formed between three atoms across at least two bonds. Molecular geometry is associated with the specific orientation of bonding of atom;whichcan be specified in terms of bond angles.The bond angles were calculated at RHF/3-21G*, RHF/6-31G*, RHF/6-311G*, LSDA/3-21G*, LSDA/6-31G*, LSDA/6-311G*, B3LYP/3-21G*, B3LYP/6-31G* and B3LYP/6-311G* levels of theoryas shown in Tables 4 and 5.The values obtained at both levels of theory

are close with one another.It can be seen that the bond angleA (3, 1, 4) at LSDA/6-31G* level which was 121.7865^0 corresponds with experimental value 121.5^0. AlsoA (5, 6, 14) at B3LYP/6-31G* and B3LYP/6-311G* levels which were 119.7806^0 and 119.757^0 respectively closely agreed with experimental value of 119.7^0.Similarly the bond angle A (6, 10, 12) at LSDA/6-311G* which was 119.2695^0 is similar with experimental value of 119.2^0. In a nutshell, the calculated results are in agreement with experimental values.

Table 4: Optimized Bond Angles (º) for Hydralazine Molecule in RHF

Bond Angles	RHF			[27]
	3-21G*	6-31G*	6-311G+	Experimental
A(2,1,3)	115.9534	122.7097	122.7021	118.5
A(2,1,4)	115.7658	114.8565	114.9385	120.5
A(3,1,4)	114.1879	122.4336	122.3594	121.5
A(1,2,7)	110.6805	111.5601	111.1548	121.0
A(1,2,8)	114.024	111.5349	111.1568	117.4
A(7,2,8)	115.3816	110.9296	110.4008	123.0
A(1,3,5)	119.5463	116.8813	116.91	120.0
A(1,3,6)	117.117	120.5744	120.534	106.1
A(5,3,6)	123.3145	122.5443	122.556	122.9
A(3,5,9)	120.019	120.7523	120.6794	120.6
A(3,6,10)	116.4495	115.6958	115.7268	119.7
A(3,6,11)	123.7376	124.9575	124.927	119.0
A(10,6,11)	119.7985	119.3467	119.3462	121.9
A(5,9,14)	119.529	120.6928	120.6437	119.7
A(6,10,12)	119.9227	119.8655	119.8249	119.2
A(6,10,14)	116.786	117.6014	117.6195	119.6
A(12,10,14)	123.2709	122.5331	122.5556	119.4
A(6,11,13)	119.6568	120.1002	120.1182	120.3
A(6,11,15)	119.29	120.9339	120.9022	119.2
A(13,11,15)	121.0341	118.9659	118.9796	120.4
A(10,12,16)	119.7087	120.0559	120.0923	121.3
A(10,12,17)	119.4118	119.257	119.2206	120.4
A(16,12,17)	120.8786	120.6871	120.6871	119.3
A(11,13,16)	120.5243	120.444	120.4375	121.4
A(11,13,19)	120.0872	119.9368	119.9479	119.3
A(16,13,19)	119.3839	119.6192	119.6146	119.3
A(9,14,10)	123.8082	122.7134	122.7746	119.3
A(9,14,18)	116.8859	116.7172	116.6919	120.3
A(10,14,18)	119.302	120.5694	120.5335	106.1
A(12,16,13)	120.3513	120.1877	120.181	109.5
A(12,16,20)	120.2031	120.2302	120.2497	109.5
A(13,16,20)	119.4396	119.5821	119.5693	109.5

Table 5: Optimized Bond Angles (º) for Hydralazine Molecule in DFT

Bond Angles	LSDA			B3LYP			[27]
	3-21G*	6-31G*	6-311G+	3-21G+	6-31G*	6-311G+	Experimental
A(2,1,3)	117.6963	122.2429	118.7772	122.3634	123.0051	123.058	118.5
A(2,1,4)	114.7816	115.9706	115.1139	114.4129	114.7199	114.6626	120.5
A(3,1,4)	120.6775	121.7865	119.9868	123.2237	122.275	122.2793	121.5
A(1,2,7)	109.2395	111.4973	110.8915	108.3441	110.6392	110.2683	121.0
A(1,2,8)	104.3014	111.5024	106.6011	108.3333	110.6382	110.2692	117.4
A(7,2,8)	110.1862	109.9557	110.7753	108.0981	109.7113	109.2661	123.0
A(1,3,5)	115.0902	115.5355	115.1547	115.7916	115.8376	115.8859	120.0
A(1,3,6)	121.325	120.982	121.6452	120.4533	120.8335	120.8678	106.1
A(5,3,6)	123.5818	123.4825	123.1831	123.7551	123.3289	123.2462	122.9
A(3,5,9)	120.0548	119.891	120.2941	119.4915	119.9891	119.9385	120.6
A(3,6,10)	115.6634	115.492	115.5775	115.7816	115.576	115.6841	119.7
A(3,6,11)	124.5797	125.0358	124.7464	124.9376	125.2038	125.1171	119.0
A(10,6,11)	119.7516	119.4723	119.6693	119.2808	119.2202	119.1989	121.9
A(5,9,14)	118.6236	119.9129	119.5403	118.8183	119.7806	119.757	119.7
A(6,10,12)	119.4284	119.5133	119.2695	119.7482	119.6396	119.5616	119.2
A(6,10,14)	117.7255	117.6354	117.7492	117.7487	117.6406	117.6773	119.6
A(12,10,14)	122.8455	122.8513	122.9805	122.5032	122.7199	122.7611	119.4
A(6,11,13)	119.9791	120.1151	120.0779	120.1899	120.2383	120.2846	120.3
A(6,11,15)	120.5634	120.8118	120.461	120.8933	120.8735	120.8208	119.2
A(13,11,15)	119.4466	119.073	119.4518	118.9168	118.8882	118.8947	120.4
A(10,12,16)	120.1437	120.2271	120.3009	120.1515	120.2567	120.3109	121.3
A(10,12,17)	118.9747	118.8071	118.8492	119.1451	119.0372	119.0445	120.4
A(16,12,17)	120.8815	120.9658	120.8498	120.7034	120.7062	120.6446	119.3
A(11,13,16)	120.382	120.4465	120.3824	120.4604	120.4909	120.4731	121.4
A(11,13,19)	119.9927	119.8678	119.9233	119.9196	119.8356	119.8566	119.3
A(16,13,19)	119.624	119.6857	119.6932	119.62	119.6735	119.6704	119.3
A(9,14,10)	124.3388	123.5863	123.6431	124.4049	123.6848	123.697	119.3
A(9,14,18)	115.6524	115.7904	115.741	115.7169	115.7382	115.7184	120.3
A(10,14,18)	120.0088	120.6234	120.6159	119.8782	120.577	120.5847	106.1
A(12,16,13)	120.3024	120.2258	120.2901	120.1693	120.1545	120.171	109.5
A(12,16,20)	120.1189	120.1485	120.0992	120.2172	120.1981	120.1954	109.5
A(13,16,20)	119.5773	119.6257	119.6096	119.6135	119.6474	119.6336	109.5

4.4   Homo-Lumo Energy of Hydralazine

The word HOMO means Highest Occupied Molecular Orbital while LUMO stand for Lowest Unoccupied Molecular Orbital. The calculated values of HOMO and LUMO energy in atomic unit (a.u) of different basis set at different levels of theory are reported in Table 6.Both HOMO and LUMO are the main orbital taking part in chemical reaction. HOMO energy characterizes the capability of electron giving; LUMO characterizes the capability of electron accepting. The frontier orbital gap helps to characterize the chemical reactivity, optical polarizability, chemical hardness and softness of a molecule. The HOMO-LUMO gap is an important stability index. A large HOMO-LUMO gap implies high electronic stability for the molecule in chemical reaction and low reactivity, when low values imply that it will be easier to remove an electron from the HOMO orbital to LOMO one which can result in good reactivity.However for this work, there are some discrepancies in the results for both levels of theory. These discrepancies may be as a result of the theoretical approximation and probably the type of basis set used. Despite these discrepancies the results for RHF/6-31G* and DFT/6-31G* have been found to be the same value of 4.11eV which is approaching a value of 4.52eV as reported by [1].

Table 6: Homo-Lumo Energy Gap

Method	Basis Sets		HOMO (a.u)	LUMO (a.u)	HOMO-LUMO Gap (a.u)	HOMO-LUMO Gap (eV)	[1]
RHF	6-31G+		-0.20708	-0.05620	0.15088	4.10574656	
	6-311G+		-0.21474	-0.06553	0.14921	4.06030252	
	LSDA	6-31G+	-0.18788	-0.10531	0.08257	2.246894	4.52Ev
		6-311G+	-0.19744	-0.11585	0.08159	2.22022708	
	B3LYP	6-31G+	-0.20708	-0.05620	0.15088	4.10574656	
DFT		6-311G+	-0.21474	-0.06553	0.14921	4.06030252	

4.5   Global Quantities of Hydralazine

The chemical hardness of the molecule was determined by Equation (10). The calculated values are listed in Table 7.In addition, softness, (*S*) accounts to measure the chemical reactivity of molecules, and it is the reciprocal of hardness as shown in Equation (11). The results are shown in Table 8. On the other hand, chemical potential of the title compound was determined from Equation (12)and the results calculated at different levels of theory are shown in Table 9. It can be observed that at LSDA/3-21G and LSDA/3-21G* the chemical potentials arethe same.Soft molecules are more reactive than hard ones because they can easily offer electrons.The electrophilicity was calculated using Equation (13) and the results is shown in Table 10.Electrophilicity index measures the propensity or capacity of a species to accept electrons. It is a measure of the stabilization in energy after a system accepts additional amount of electronic charge from the environment. More stable molecule corresponds to lesser electrophilicity.

Table 7: Chemical Hardness of Hydralazine

Method		Basis Sets	I= - E_{HOMO}	EA = -E_{LUMO}	Chemical Hardness (η) [eV]
RHF		6-31G+	0.20708	0.05620	0.07544
		6-311G+	0.21474	0.06553	0.074605
DFT	**LSDA**	6-31G+	0.18788	0.10531	0.041285
		6-311G+	0.19744	0.11585	0.040795
	B3LYP	6-31G+	0.20708	0.05620	0.07544
		6-311G+	0.21474	0.06553	0.074605

Table 8: Chemical Softness of Hydralazine

Method		Basis Sets	I= - E_{HOMO}	EA = -E_{LUMO}	Chemical Softness (S) [eV⁻¹]
RHF		6-31G+	0.20708	0.05620	13.2556
		6-311G+	0.21474	0.06553	13.4039
DFT	**LSDA**	6-31G+	0.18788	0.10531	24.2219
		6-311G+	0.19744	0.11585	24.5128
	B3LYP	6-31G+	0.20708	0.05620	13.2556
		6-311G+	0.21474	0.06553	13.4039

Table 9: Chemical Potential of Hydralazine

Method		I= - E_{HOMO}		A = -E_{LUMO}	Chemical Potential (μ) [eV]
RHF		6-31G+	0.20708	0.05620	0.13164
		6-311G+	0.21474	0.06553	0.140135
DFT	**LSDA**	6-31G+	0.18788	0.10531	0.146595
		6-311G+	0.19744	0.11585	0.156645
	B3LYP	6-31G+	0.20708	0.05620	0.13164
		6-311G+	0.21474	0.06553	0.140135

Table 10: Electrophilicity of Hydralazine

Method		Basis Sets	μ^2	2η	Electrophilicity (ω) [eV]
RHF		6-31G+	0.0173290896	0.15088	0.114853
		6-311G+	0.01963781823	0.14921	0.131612
DFT	**LSDA**	6-31G+	0.02149009402	0.08257	0.260265
		6-311G+	0.02453765603	0.08159	0.300743
	B3LYP	6-31G+	0.0173290896	0.15088	0.114853
		6-311G+	0.01963781823	0.14921	0.131612

4.6   Natural Bond Orbital (NBO)Analysis

The NBO analysis is proved to be an effective tool for the chemical interpretation of hyperconjugative interaction and electron density transfer from the filled lone pair electro [19]. In order to investigate the various second - order interaction between the filled orbitals of one subsystem and vacant orbitals of another subsystem, the DFT/B3LYP/6-31G* and RHF/6-31G* levels have been used to predict the   hyperconjugation energy $E^{(2)}$. The hyperconjugative interaction energy was calculated from the second-order perturbation approach as shown in Equation (20). The results obtained for both DFT and RHF are shown in Tables11and 12. The larger $E^{(2)}$ value, the more intensive is the interaction between electron donors and acceptor. That is to say the more donation tendency from electron donors to electron acceptors, the greater the extent of conjugation of the whole system.From the results obtained at DFT, the highest values of $E^{(2)}$was recorded in the lone-pairs N5 interacting with anti-bonding C3 - C6 which was 10.42kJ/mol hence this give stronger stabilization of the structure. On the other hand for RHF the highest values was obtained inthe lone-pairs N5 interacting with anti-bonding C3 - C6 with values of 13.18kJ/mol which shows larger delocalization in RHF method.Comparing DFT and ab initio, it can be seen that in RHF the interaction is more intense.

Table 11: Second-order Perturbation Theory Analysis of Fock Matrix in NBO basis Corresponding to the Intermolecular of the Title Compound at B3LYP/6-31G* Level of Theory.

Donor NBO(i)	Acceptor NBO(j)	$E^{(2)}$(kJ/mol)	E(j)-E(i)(a.u)	F(i,j) (a.u)
σ (N1 - N2)	σ*(N1 - C3)	0.59	1.26	0.025
σ (N1 - C3)	σ*(N2 - H7)	1.11	1.23	0.033
σ(N1 - H4)	σ*(C3 - N5)	2.38	1.18	0.047
σ(N2 - H7)	σ*(N1 - C3)	4.45	1.05	0.062
σ(C3 - N5)	σ*(N1 - H4)	1.22	1.25	0.035
σ (C3 - C6)	σ*(N1 - N2)	2.55	1.09	0.047
σ (C3 - C6)	σ*(C11 - C13)	1.64	1.29	0.041
LP (1) N1	σ*(N2 - H7)	1.57	0.72	0.031
LP (1) N1	σ*(N2 - H8)	6.62	0.72	0.065
LP (1) N1	σ*(C3 - C6)	0.93	0.84	0.026
LP (1) N2	σ* (N1 - C3)	0.83	0.75	0.022
LP (1) N2	σ*(N1 - H4)	8.27	0.77	0.071
LP (1) N5	σ*(N1 - C3)	3.08	0.77	0.044
LP (1) N5	σ*(C3 - C6)	10.42	0.93	0.088
LP (1) N9	σ*(C3 - N5)	8.82	0.88	0.079

Table 12: Second-order Perturbation Theory Analysis of Fock Matrix in NBO Basis Corresponding to the Intermolecular of the Title Compound at RHF/6-31G* Level of Theory.

Donor NBO(i)	Acceptor NBO(j)	$E^{(2)}$(kJ/mol)	E(j)-E(i)(a.u)	F(i, j) (a.u)
σ (N1 - N2)	σ*(N1 - C3)	0.63	1.77	0.030
σ (N1 - C3)	σ*(N2 - H7)	1.43	1.76	0.045
σ(N1 - H4)	σ*(C3 - N5)	3.10	1.66	0.064
σ (N2 - H7)	σ*(N1 - C3)	6.00	1.53	0.086
σ(C3 - N5)	σ*(N1 - H4)	1.53	1.80	0.047
σ (C3 - C6)	σ*(N1 - N2)	3.06	1.63	0.063
σ (C3 - C6)	σ*(C11 - C13)	1.80	1.80	0.051
LP (1) N1	σ*(N2 - H7)	2.13	1.15	0.046
LP (1) N1	σ*(N2 - H8)	9.45	1.15	0.096
LP (1) N1	σ*(C3 - C6)	1.20	1.27	0.036
LP (1) N2	σ* (N1 - C3)	1.04	1.21	0.032
LP (1) N2	σ*(N1 - H4)	11.05	1.24	0.104
LP (1) N5	σ* (N1 - C3)	4.35	1.25	0.066
LP (1) N5	σ*(C3 - C6)	13.18	1.40	0.122
LP (1) N9	σ*(C3 - N5)	10.86	1.36	0.109

Nonlinear Optical Properties(The Average Polarizability ($α_{tol}$),first Order Hyperpolarizability (β_{tol}) and Dipole Moment (μ)) Values of Hydralazine Analysis

The calculated values of average polarizability ($α_{tol}$), first order hyperpolarizability(β_{tol}) and dipole moment (μ) calculated at DFT and RHF levels of theory are shown in Table 12. Higher value of dipole moment, molecular polarizability and first order hyperpolarizability are important for more active non-linear optical(NLO) properties. The large value of hyperpolarizability (β) which is a function of the NLO activity of the molecular system is associated with the intra molecular charge transfer.The results at both levels of theory agreed with each other.For example the calculated average polarizability for DFT and RHF are1.922 x $10^{-23}$and 1.759 x 10^{-23}esu respectively. For the first order hyperpolarizability, the value obtained for DFT and RHF are 0.7971 x 10^{-30} and 0.7066 x 10^{-30} esu respectively and that of dipole moment for both levels were found to be 6.6579 and 6.2535D respectively.

Table 13: The Average Polarizability ($α_{tol}$), First Order Hyperpolarizability (β_{tol}) and DipoleMoment (μ) Valuesof Hydralazine

Parameters	LSDA/6-31G*	RHF/6-31G*
$α_{xx}$	178.592	156.634
$α_{xy}$	-0.107	5.132
$α_{yy}$	145.053	134.345
$α_{xz}$	1.416	1.314
$α_{yz}$	-1.100	-0.523
$α_{zz}$	65.428	65.156
$α_{tol(esu)}$	1.922 x 10^{-23}	1.759 x 10^{-23}
β_{xxx}	6.6316	5.1111
β_{xxy}	-43.4966	-38.1152
β_{xyy}	-8.6786	-8.0425
β_{yyy}	-45.5593	-40.8244
β_{xxz}	17.7682	15.4991
β_{xyz}	-2.2367	-2.0303
β_{yyz}	1.0836	1.4426
β_{xzz}	9.0112	11.6747
β_{yzz}	-0.6330	-0.8210
β_{zzz}	1.6519	1.7817
$\beta_{tol\ (esu)}$	0.7971 x 10^{-30}	0.7066 x 10^{-30}
$μ_x$	-2.8034	-3.2152
$μ_y$	-5.7817	-5.1285
$μ_z$	1.7440	1.5709
μ (D)	6.6579	6.2535

5.0 Conclusion

In this work, the most stable structure of Hydralazine was found to have sterric energy of 85.42kcal/mol by MMFF calculation which agreed with the value 84.57kcal/mol as reported by[1]. The optimized parameters (bond lengths and bond angles) calculated using DFT and ab initio with different basis sets mostly agreed with experimental values. The HOMO-LUMO energy gap calculated show that at both levels of theory, the basis sets 6-31G* and 6-311G* give closer results to the one reported by (Zaheed andFazlul, 2006). For example, RHF/6-31G* and DFT/6-31G* results show that a value of 4.11eV was obtained as compared to 4.52eV reported by [1]. Chemical hardness, chemical softness, chemical potential and electrophilicity have been calculated using the values of HOMO and LUMO energies and the results agreed with different basis sets. NBO analysis shows the calculated value of hyperconjugative energy $E^{(2)}$ in which the highest value of 10.42kJ/mol for DFT and 13.18kJ/mol for RHF which implies that the interaction will be more intense at these values. Values obtained for average polarizability, hyperpolarizability and dipole moment using different basis set strongly agreed.The results indicate that the DFT and RHF are valuable tools for predicting biological activity of hydralazine phytochemical. The HOMO-LUMO energy gap reveals the stability index of compounds.

6.0 References

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