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Theoretical Molecular Structure, NLO, NMR and HOMO-LUMO Analysis of Isonicotinic Acid (*ortho-, meta-* and *para*-Hydroxy-Benzylidene)-Hydrazides

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ABSTRACT

The present work is aimed to compare the molecular structural, non-linear optical and NMR–spectra properties of isonicotinic acid (*ortho*- *meta*- and *para*-hydroxy-benzylidene)-hydrazides, in gas phase, due to their versatile medical activities and importance. The ground state properties of the title molecules have been calculated employing DFT/B3LYP and HF level of theory using the 6-311++G(d, p) basis set. ^{1}H NMR and ^{13}C NMR chemical shifts calculations have been performed by using the DFT method with B3LYP functional, where the 6-311++G(d,p) basis set was employed. The highest occupied molecular orbital (HOMO) energy, the lowest unoccupied molecular orbital (LUMO) energy values and non-linear optical properties such as dipole moment, polarizability and first order hyper polarizability of isonicotinic acid (*ortho*- *meta*- and *para*-hydroxy-benzylidene)-hydrazides have been calculated with HF/ 6-311++G(d,p) and B3LYP/6-311++G(d,p) levels of DFT theory. The dipole moment for isonicotinic acid (*ortho*, *meta* and *para* –hydroxy-benzylidene)-hydrazides are calculated at 2.8054, 1.9882 and 3.1169 Debye, respectively with DFT/B3LYP level of theory the 6-311++G(d, p) basis set. The dipole moment value of isonicotinic acid (*ortho*–hydroxy-benzylidene)-hydrazide was seen lower value than others dipole moment values. All computational studies have been performed with the Gaussian 09W program package.

Keywords: isonicotinic acid (*ortho*-, *meta*- and *para*-hydroxy-benzylidene)-hydrazides, DFT, HF, NMR

1. INTRODUCTION

According to WHO [1-3], millions of people die every year from tuberculosis that is caused bacteria *(Mycobacterium tuberculosis)* [4]. In the last decades the incidence of microbial infections have increased because of antimicrobial resistance [5, 6]. As a result, because the medications used to treat tuberculosis are insufficient, syntheses and searching of new type complexes come into prominence against pathogenic microorganisms that put up resistance to these drugs. Isoniazide that hydrazide of isonicotinic acid that is isomer of nicotinic acid – known as B3 vitamin – is the one of five drugs used to treat tuberculosis in the recent years [7]. Isoniazide whose mechanism of action was examined on cellular [8-11] and molecular [12] levels come to researchers notice during the recent years. After knowing isoniazide derivatives have antimicrobial activity [13], a large number of isonicotinic acid hydrazide derivatives have been synthesized and its antibacterial, antiviral activities have been investigated [5, 7, 14-23]. Particularly, there is significant interest in the synthesis of substituted ***isonicotinic acid benzylidene hydrazides*** in recent years. Antimicrobial, antibacterial activities of metal complex of some isoniazide derivatives was also tested [24-29]. Crystal structures of fewer amounts of known isonicotinohydrazide compounds until now have been solved [30-38]. Particularly, there is significant interest in the synthesis of substituted ***isonicotinic acid benzylidene hydrazides (abbreviate as INBH)*** in the recent years. The physical and chemical properties of a substance are strongly related to both its geometrical and electronic structures [39]. So in this work, we have reported the electronic structure, NMR –spectra and non-linear optic calculation of isonicotinic acid (hydroxyl-benzylidene) in which the position of the hydroxyl (OH) group on the phenyl ring were changed systematically. The structure of ***isonicotinic acid benzylidene hydrazide,***isonicotinic acid (*o*-hydroxybenzylidene)-hydrazide, isonicotinic acid (*m*-hydroxybenzylidene)-hydrazide and isonicotinic acid (*p*-hydroxybenzylidene)-hydrazide have been optimized to compare the variation in electronic, NMR –spectra, and non-linear optic properties substitution of hydroxyl (OH) group at ortho, para and meta position. The optimized geometries of molecules under investigation and their molecular properties such as frontier orbital energy gap, equilibrium energy, molecular, NMR–spectra, polarizability and hyperpolarizability have been used to understand the properties and biological activities. The systematic use of polarizabitity in modeling the pharmacological activity of molecular substances and in quantitative structure-activity relationship (QSAR) approach studies has also been noted [40]. We have studied molecular structure, dipole moment, relative energies, rotational barriers, polarizability, first static hyperpolarizability, the electronic structure, and HOMO-LUMO energies of all molecules. The molecular structure using numbering scheme of the isonicotinic acid molecule is given in Figure 1.

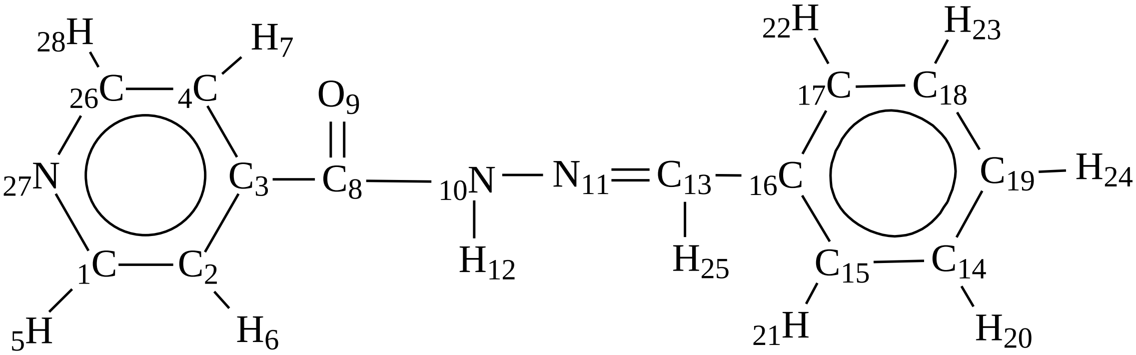

Figure 1: Molecular structure of ***isonicotinic acid benzylidene hydrazide*** numbering scheme.

2. COMPUTATIONAL METHODS

For the quantum chemical calculations, the title compounds were first optimized within the framework of Hartre Fock (HF) [41] and Density Functional Theory (DFT) with Becke's three parameter hybrid functional (B3) [42] and combined with gradient corrected correlation functional of Lee–Yang–Parr (LYP) [43,44] and employing 6-311++G (d,p) basis set [45] Gaussian 09 program package [46]. After optimization, at all optimized structures of the title compounds obtained B3LYP/6-311++G (d,p) and HF/6-311++G (d,p) level of theory, the dipole moment (μ), mean polarizability (α), the total first static hyperpolarizability (β) based on finite field approach and energy of the highest occupied molecular orbital HOMO (E_{HOMO}), energy of the lowest unoccupied molecular orbital LUMO (E_{LUMO}) were calculated in the same as level of theory. The ^{1}H and ^{13}C NMR chemical shifts were calculated by GIAO approach by using B3LYP/6-311+G (2d,p) and HF/6-31G (d) level of theory.

The molecular models of the template molecules, functional monomer and their complexations were the initial structures of ***isonicotinic acid benzylidene hydrazide,*** isonicotinic acid (*o*-hydroxybenzylidene)-hydrazide, isonicotinic acid (*m*-hydroxybenzylidene)-hydrazide and isonicotinic acid (*p*-hydroxybenzylidene)-hydrazide were prepared by GaussView, version 5.0.

3. RESULTS AND DISCUSSION

3.1. *Structural and Electronic Properties*

The numbering of atoms in ***isonicotinic acid benzylidene hydrazides*** is given in Figure 1. The optimized geometrical parameters (bond length, angles and dihedral angles) together with the labelling scheme of ***isonicotinic acid benzylidene hydrazide*** are shown in Figure 1.

The energy of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) is known as frontier molecular orbitals (FMOs). Energy difference between HOMO and LUMO orbital is called as energy gap (ΔE). These orbitals determine the way the molecule interacts with other species. The frontier molecular orbital gap helps characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier molecular orbital gap is more polarizable and generally associated with a high chemical reactivity and low kinetic stability.

The electronic, dipole moment, polarizability, hyperpolarizability, HOMO, LUMO energy and energy gap (ΔE_g) values at the ground-state equilibrium geometry of studied molecules are listed in Table 1.

Table 1. The electronic, HOMO, LUMO energy, dipole moment, polarizability, hyperpolarizability, and energy gap (ΔE_g) of equilibrium conformations of ***isonicotinic acid benzylidene hydrazide and its*** substituted derivatives.

	Electronic Energy (a.u)	μ (D)	α (a.u)	β(a.u)	E_{HOMO} (a.u)	E_{LUMO} (a.u)	$\Delta E_{g\,(eV)}$
				B3LYP/6-311++G(d, p)			
INBH	-741.643788728	2.2271	182.186	353.708	-0.246269	-0.081056	4.495611
Ortho	-816.894673175	2.8054	179.726	198.361	-0.241999	-0.085570	4.25659
Meta	-816.890867349	1.9882	186.872	650.392	-0.240292	-0.081330	4.325515
Para	-816.892700561	3.1169	190.774	1233,01	-0.234226	-0.077947	4.252508
				HF/6-311++G(d, p)			
INBH	-737.039718830	2.3336	160.642	89.1809	-0.337756	0.032974	10.08793
Ortho	-811.928207453	2.9519	161.856	188.175	-0.329028	0.030654	9.787307
Meta	-811.922653615	1.8240	163.352	221.877	-0.323612	0.032998	9.703715
Para	-811.923886381	2.6773	165.945	430.497	-0.319770	0.033034	9.600149

The dipole moment in a molecule is an important property that is mainly used to study the intermolecular interactions involving the non-bonded type dipole-dipole interaction, because higher the dipole moment will be stronger than the molecular interaction. At the /B3LYP/6-311++G(d,p) and HF/6-311++G(d,p), ***t***he dipole moments of ***isonicotinic acid benzylidene hydrazide and*** isonicotinic acid (*ortho*, *meta* and *para* –hydroxy-benzylidene)-hydrazides have been calculated as 2.2271, 2.8054, 1.9882, 3.1169, 2.3336, 2.9519, 1.8240 and 2.6773 Debye, respectively. Isonicotinic acid (*para* –hydroxy-benzylidene)-hydrazide has the biggest hyperpolarizability while isonicotinic acid (*ortho*-hydroxy-benzylidene)-hydrazide has the smallest hyperpolarizability for the both models. The difference between hyperpolarizability values of the two molecules appear to be very large. Energy gap (ΔE_g) values of ***isonicotinic acid benzylidene hydrazide and*** isonicotinic acid (*ortho*, *meta* and *para* –hydroxy-benzylidene)-hydrazides have been calculated as 4.495611, 4.25659, 4.325515 and 4.252508 (eV) at the /B3LYP/6-311++G(d,p) model, respectively.

The equilibrium geometry optimization of lowest energy conformer has been achieved by energy minimization. Full optimization of all bond lengths, bond angles, and torsional angles of ***isonicotinic acid***

benzylidene hydrazide, nicotinic acid (*o* -hydroxybenzylidene) hydrazide.Isonicotinic acid (*p*-hydroxybenzylidene) hydrazide and isonicotinic acid (*m*- hydroxybenzylidene) hydrazide were initially achieved by using HF and DFT/B3LYP with 6-311+G(d,p) basis set and are listed in Table 2. The crystal structure of ***isonicotinic acid benzylidene hydrazide*** was ***studied by*** Tajudeen et al [47].

Table 2. ***Selected structural parameters*** of ***isonicotinic acid benzylidene hydrazides and its*** *substituted derivatives.*

Molecule		B3LYP/6-311++G**				HF/6-311++G**			
Bond length (Å)	***INBH***	Ortho	Meta	Para	Expt[a]	***INBH***	Ortho	Meta	Para
C1-C2	1.394	1.3937	1.3941	1.3939	1.388 (4)	1.386	1.3859	1.3861	1.3861
C1-N27	1.3351	1.3352	1.3351	1.3351	1.338 (4)	1.3175	1.3176	1.3176	1.3175
C2-C3	1.3974	1.397	1.3972	1.3976	1.387 (4)	1.386	1.3857	1.3858	1.3861
C3-C4	1.3958	1.3955	1.3957	1.3958	1.387 (4)	1.385	1.3846	1.3849	1.385
C3-C8	1.5062	1.5015	1.5057	1.5068	1.503 (4)	1.5072	1.5038	1.5066	1.5077
C4-C26	1.3915	1.3918	1.3915	1.3915	1.384 (4)	1.3836	1.3839	1.3837	1.3836
C8-O9	1.2142	1.2228	1.214	1.2151	1.223 (3)	1.1876	1.1956	1.188	1.1877
C8-N10	1.3898	1.3781	1.3906	1.3878	1.353 (3)	1.3754	1.3633	1.3747	1.375
N10-N11	1.3971	1.4047	1.3968	1.3993	1.386 (3)	1.3929	1.3942	1.3914	1.3945
N11-C13	1.2834	1.2784	1.2824	1.2849	1.278 (3)	1.2557	1.2547	1.2547	1.2573
C13-C16	1.472	1.4864	1.4742	1.4662	1.463 (4)	1.4865	1.4922	1.4889	1.4805
C14-C15	1.3897	1.3916	1.3916	1.3844	1.387 (4)	1.3839	1.3825	1.3877	1.3770
C14-C19	1.3953	1.3954	1.3912	1.3981	1.380 (4)	1.3859	1.3869	1.3799	1.3894
C15-C16	1.4039	1.4003	1.4009	1.4071	1.390 (4)	1.390	1.3896	1.3848	1.3950
C16-C17	1.4036	1.4045	1.4023	1.4033	1.393 (4)	1.389	1.3900	1.3898	1.3866
C17-C18	1.3908	1.3947	1.3926	1.3886	1.384 (4)	1.3839	1.3857	1.3822	1.3841
C18-C19	1.3934	1.391	1.3953	1.396	1.382 (4)	1.3849	1.3823	1.3876	1.3840
C26-N27	1.3377	1.3373	1.3378	1.3377	1.338 (3)	1.3206	1.3202	1.3205	1.3206
C17-O28		1.3644					1.3506		
C18-O28			1.3681					1.3495	
C19-O28				1.3634					1.3459
Bond angle (°)									
C2-C1-N27	123.70	123.67	123.69	123.71	124.4 (3)	123.57	123.53	123.56	123.57
C1-C2-C3	118.70	118.59	118.69	118.73	118.6 (3)	118.37	118.25	118.35	118.39
C2-C3-C4	117.91	118.10	117.93	117.86	117.7 (3)	118.26	118.45	118.29	118.22
C2-C3-C8	124.06	123.54	123.99	124.15	123.6 (2)	123.50	123.08	123.40	123.59
C4-C3-C8	118.02	118.35	118.07	117.97	118.7 (2)	118.23	118.46	118.30	118.19
C3-C8-O9	122.17	121.51	122.21	122.08	121.2 (3)	121.54	121.19	121.61	121.45
C3-C8-N10	114.33	114.88	114.26	114.42	114.2 (2)	114.42	114.92	114.36	114.51
O9-C8-N10	123.50	123.61	123.53	123.49	124.7 (3)	124.04	123.89	124.03	124.03
Bond angle (°)									
C8-N10-N11	122.67	121.19	122.47	122.51	119.5 (2)	119.99	120.20	120.17	119.76
N11-C13-C16	134.76	130.37	133.90	135.22	120.8 (3)	131.71	129.75	130.97	132.91
C15-C14-C19	120.46	119.57	121.13	120.05	119.6 (3)	120.25	119.36	121.02	119.91
C14-C15-C16	120.41	120.61	119.71	121.16	120.9 (3)	120.19	120.70	119.29	121.06
C13-C16-C15	124.50	119.77	123.80	125.33	119.7 (3)	122.47	119.98	121.71	124.10
C13-C16-C17	116.84	120.56	116.88	116.81	121.6 (3)	118.16	120.34	118.15	117.68
C15-C16-C17	118.51	119.28	119.14	117.73	118.6 (3)	119.23	119.44	120.00	118.11
C16-C17-C18	121.02	120.01	120.63	121.62	120.6 (3)	120.55	119.99	120.15	121.44
C17-C18-C19	119.85	120.01	120.01	119.53	120.0 (3)	119.93	120.02	120.10	119.53
C14-C19-C18	119.72	120.46	119.34	119.89	120.3 (3)	119.82	120.47	119.41	119.92
C4-C26-N27	123.70	123.67	123.69	123.71	123.9 (3)	123.57	123.54	123.56	123.58
C1-N27-C26	117.20	117.30	117.21	117.17	116.0 (2)	117.80	117.91	117.82	117.79
Dihedral angle (°)									
C2-C3-C8-O9	155.58	154.36	155.14	156.61		153.06	150.56	152.29	153.59
C4-C3-C8-O9	-22.81	-24.32	-23.30	-21.91		-25.92	-28.46	-26.67	-25.42
H25-C13-C16-C15	155.36	103.49	148.91	159.92		135.19	102.82	128.01	145.37
H25-C13-C16-C17	-20.05	-69.24	-26.11	-15.81		-40.63	-71.50	-47.58	-30.82

[a]Taken from Ref. [47]

For all molecules for the both models, calculated geometrical parameters such as bond lengths, bond angles were compared with experimental values and comparison of the calculated and experimental structural parameters indicates that results of the optimized geometric parameters are in a good agreement with experimental data. It is observed that the various benzene ring bond distances and the pyridine bond lengths of title compound are found to be almost same at all levels of calculations. The bond lengths determined from B3LYP6-311++G(d,p) method with 6-311++G(d,p) basis set are slightly higher than that obtained from HF/6-311++G(d,p) method. In the calculations, change at the dihedral angle H25-C13-C16-C15 were shown to be greater than change at the dihedral angle C4-C3-C8-O9, for substituted derivatives.

3.2. *NMR Spectral Investigations*

We have calculated ^1H, ^{13}C NMR values of ***isonicotinic acid benzylidene hydrazides,*** isonicotinic acid (*o*-hydroxybenzylidene)-hydrazide, isonicotinic acid (*p*-hydroxybenzylidene)-hydrazide and isonicotinic acid (*m*-hydroxybenzylidene)-hydrazide and are listed in Tables 3. Where the atomic positions are numbered as given in Figure 1. Calculations performed with GIOA/DFT and GIOA/HF methods were used the B3LYP/6-311+G (2d,p) and HF/6-31G (d) level of theory.

Table 3. The theoretical ^1H, ^{13}C NMR chemical shifts values of ***isonicotinic acid benzylidene hydrazides and its*** substituted.

				B3LYP/6-311+G(2d,p)			HF/6-31G (d)		
Atoms	***INBH***	Ortho	Meta	Para	Expt^b	***INBH***	Ortho	Meta	Para
C8	165.49	168.94	165.41	165.81	162.09	156.70	162.48	157.13	156.67
C13	162.81	173.76	163.01	162.00	149.49	157.31	160.77	156.77	157.01
C26	157.77	157.80	157.73	157.82	150.82	147.41	147.45	147.35	147.48
C1	156.37	156.67	156.36	156.78	150.82	146.09	146.24	146.12	146.15
C3	147.03	146.46	146.88	147.05	140.93	139.81	138.93	139.69	139.92
C16	141.28	133.08	142.45	133.86	134.48	130.07	120.75	134.03	120.12
C17	137.24	163.05	119.57	139.84	129.37	126.82	149.32	108.35	132.63
C19	135.15	136.13	121.32	165.43	130.87	126.61	129.49	112.35	152.41
				B3LYP/6-311+G(2d,p)		HF/6-31G (d)			
C14	132.67	124.67	134.30	119.41	127.74	123.34	115.49	128.21	109.57
C15	132.43	129.55	122.43	136.42	129.37	123.31	124.95	112.92	129.40
C18	132.34	125.59	163.74	115.54	127.74	124.57	117.44	150.46	106.01
C4	127.12	127.06	126.77	127.08	122.01	118.99	118.64	118.88	119.06
C2	121.57	121.73	121.52	121.62	122.01	114.38	114.41	114.49	114.30
H5	9.0727	8.9789	9.0646	9.0421		8.7442	8.6821	8.7253	8.7826
H28	9.0692	9.0531	9.0628	9.0702		8.7602	8.7901	8.756	8.7952
H12	8.4801	8.1406	8.3461	8.3885		6.0101	6.1008	5.9979	5.9978
H21	8.2514	7.1427	7.7171	8.1699		7.8508	7.0578	7.0468	8.2453
H25	8.2088	7.2993	8.0253	7.9983		8.0014	7.0138	7.9641	7.8036
H7	7.9967	7.9381	7.8848	8.073		7.5636	7.5573	7.5413	7.6223
H23	7.6637	7.4656	3.7531	6.6932		7.3586	7.3182	2.8468	6.2085
H22	7.576	6.8831	6.7054	7.3635		7.371	4.7821	6.2811	7.3371
H24	7.545	8.6637	7.0194	3.8776		7.2759	8.3474	6.8045	2.9085
H6	7.5253	7.3311	7.5088	7.5355		7.2018	6.9741	7.1507	7.2562
H20	7.3859	7.0445	7.3066	6.9284		7.1597	6.8117	7.2305	6.6771

^{a}Taken from Ref. [48]

The calculated chemical shifts were reported in ppm relative to tetramethylsilane (TMS) for ^1H, ^{13}C NMR spectra. Relative chemical shifts were then estimated by using the corresponding TMS shielding calculated in advance at the same theoretical level as the reference.

^{13}C NMR chemical shifts of ***isonicotinic acid benzylidene hydrazide*** were ***studied by*** Raghuvanshi D S et al [48]. For all the molecules at the both models, calculated ^{13}C NMR chemical shifts of were compared with the experimental values. The theoretical results of investigated all compounds at the B3LYP/6-311+G(2d,p) and HF/631G(d) models correspond to experimental values of those compounds, except for N-H and OH proton. It has been merged a higher-than expected difference between values calculated and experimental values of N-H protons because the H-N proton may have acidic property. That is, remaining electron pair on the nitrogen atom with the carbonyl group it has been delocalized resonance results, after leaving proton.

4. CONCLUSION

The structural parameters, the electronic energy, the dipole moment (μ) , the highest occupied molecular orbital (HOMO) energy, the lowest unoccupied molecular orbital energy (LUMO), the polarizability (α), hyperpolarizability (β) values of ***isonicotinic acid benzylidene hydrazide,*** Isonicotinic acid (*p*-hydroxybenzylidene)-hydrazide and isonicotinic acid (*m*- hydroxybenzylidene)-hydrazide by **ab initio** HF and DFT methods with the B3LYP approaches, using 6-311++G(d,p) basis sets, with optimized geometries. Comparison of the calculated and experimental structural parameters indicates that results of HF/ 6-311++G (d,p) and B3LYP/6-311++G(d,p) are in a good agreement with experimental data. The values of nonlinear optical (NLO) properties for ***isonicotinic acid benzylidene hydrazide and its*** substituted derivatives obtained by B3LYP/6-311++G (d,p) were found to be higher than those by obtained by HF/ 6-311++G (d,p) method. As it is seen from the calculation results, Isonicotinic acid (*p*-hydroxybenzylidene) hydrazide has highest the dipole moment, the polarizability and hyperpolarizability.

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