Density Functional Theory and *Ab Initio* Hartree-Fock Conformational Study On Isonicotinic Acid and Its Derivatives

Güventürk Uğurlu
Department of Physics, Kafkas University, Kars, Turkey
E-mail: gugurlu@kafkas.edu.tr

Murat Beytur*
Department of Chemistry, Kafkas University, Kars, Turkey

Haydar Yüksek
Department of Chemistry, Kafkas University, Kars, Turkey

Tuba Uğurlu
Department of Medicine, Atatürk University, Erzurum, Turkey

ABSTRACT

Ab initio and DFT calculations have been performed to characterize some ground state structures of isonicotinic acid and its derivatives molecules using the 6-311++ G(d, p) basis set. Molecular structure, dipole moment, relative energies, rotational barriers, polarizability, first static hyperpolarizability, and potential energy scan of isonicotinic acid (IA), isonicotinamide acid (INA), isonicotinic acid hydrazide (INH) and 1-isonicotinyl-2-isopropylhydrazide (IHH) molecules have been calculated by using 6-311++G(d,p) basis set for both models. Also, E_{HOMO} (the highest occupied molecular orbital energy), E_{LUMO} (the lowest unoccupied molecular orbital energy) and HOMO-LUMO energy gap (ΔE_g) are investigated. The dipole moment for IA, INA, INH and IIH molecules are calculated at 1.79, 3.54, 2.08 and 2.67 with DFT/B3LYP level of the theory 6-311++G(d, p) basis set and at the HF/6-311++ G(d, p) 1.90, 3.54, 2.04 and 2.38 Debye, respectively. Dipole moment value of isonicotinic acid was seen lower value than others dipole moment values. HOMO, LUMO energy and energy gap (ΔE_g) values of title molecules compared with data in the literature. For the results of calculation at the both models, the overall order of polarizability values of studied molecules are found to be IIH > INH > INA> IA. All computational studies have been performed with the Gaussian 09W program package.

Keywords: Ab initio, DFT, HF, 6-311++ G(d, p) and Gaussian 09W

1. INTRODUCTION

Isonicotinic (IA) acid is one of important derivatives of pyridine in which the acid group is located in para-position of the heterocyclic ring. Pyridine derivatives are used in the manufacture of isoniazid (antituberculosatic drug), in many products such as vitamins, food, flavorings, plants, dyes, rubber products [1-3] and other pharmaceutically important drugs [4-6]. Hydrazine derivatives of isonicotinic acid are one of the most active drugs for the treatment of tuberculosis caused by mycobacterium tuberculosis [7-10]. Isoniazid, Hydrazine derivatives of isonicotinic acid, inhibits synthesis of mycolic acid. At the same time, intravaginal isoniazid (INH) could induce cervical ripening by increasing collagen solubility. Thus, it uses before induction labor because successful delivery needs suitable cervix [11-13]. There is a lot of study about isoniazid and its derivatives due to they have wide area of usage in medicine. In recent years, hydrazine derivatives of isonicotinic acid were developed as potential antimycobacterial agents. Consequently, numerous studies have pointed out the importance of developing novel INH hydrazides as promising anti-tubercular agents. Although several hydrazine derivatives of isonicotinic acid, most of them containing nitro groups were synthesized by researchers, and evaluated for their in vitro antibacterial activity against Mycobacterium tuberculosis [14-20]. A very few comprehensives comparative study of hydrazine derivatives of isonicotinic acid on electronic structure, non-linear properties along with the potential energy surface has been reported. The conformational behavior of structurally similar molecules with title molecules have been studied theoretically. The present work is aimed at comparing the molecular structural and non-linear properties of isonicotinic acid (IA), isonicotinamide acid (INA), isonicotinic acid hydrazide (INH) and 1-isonicotinyl-2-isopropylhydrazide (IHH) molecules in gas phase. The physical and chemical properties of a substance are strongly related to both its geometrical and electronic structures. In this work, we have studied molecular structure, dipole moment, relative energies, rotational barriers, polarizability, first static hyper polarizability, potential energy scan, the electronic structure and HOMO-LUMO energies of studied molecule. The molecular structure using numbering scheme of the isonicotinic acid molecule is given in Figure 1.

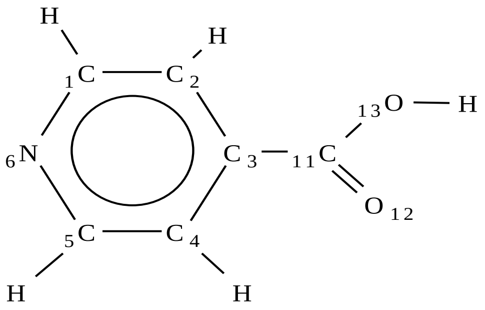

Figure 1. Molecular structure of isonicotinic acid numbering scheme.

2. COMPUTATIONAL METHODS

All geometrical parameters of the studied molecules in the ground state was optimized at the density functional theory (DFT) [18] employing the Becke's three-parameter hybrid functional [19] combined with Lee-Yang-Parr correlation [20] functional (B3LYP), ab initio- Hartree-Fock (HF) methods [21] using 6-311++G (d,p) basis set [22] to obtain stable structures. The molecular geometry was not restricted and all the calculations (geometric parameters and other molecular properties) were performed by using Gauss View molecular visualization program [23] and Gaussian 09W program package on a computing system [24]. The geometries of the most stable conformers I and II of the title molecules were optimized at the B3LYP/6-311++G (d,p) and HF/6-311++G(d,p) levels. The optimized structural parameters are used in the electronic properties, such as HOMO-LUMO energies, the HOMO- LUMO energy gap, dipole moment, polarizability and hyperpolarizability at HF and DFT levels. For the conformational analysis, individual torsion potentials were obtained for each molecule by performing a constrained geometry optimization of the structure as a function dihedral angle C2-C3-C11-O12 which was from 0˚ to 180˚ by steps of 10˚ the B3LYP/6-311G(d,p) and HF/6-311G(d,p) methods.

3. RESULTS AND DISCUSSION

3.1. *Optimized geometries*

The initial structures of the molecules were prepared with GaussView 5.0. The geometries were then fully optimized at DFT/B3LYP and HF levels in vacuum using the 6-311++G (d,p) basis.

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

				B3LYP/6-311++G(d, p)			
	Electronic Energy (a.u)	M (D)	α (a.u)	β (a.u)	E_{HOMO} (a.u)	E_{LUMO} (a.u)	$\Delta Eg\ (eV)$
IN	-436.985269556	1,79 TL	80,67	118,78	-0,278831	-0,087292	5,21197
INA	-417.108666984	3,54 TL	85,64	107,13	-0,272802	-0,074341	5,40032
INH	-472.444390504	2,08 TL	95,52	70,54	-0,275133	-0,075324	5,43700
IHH	-590.413501660	2,67 TL	133,54	318,20	-0,247701	-0,074146	4,72261
				HF/6-311++G(d, p)			
IN	-434.427694450	1,90	73,44	24,97	-0,361738	0,035913	10,82048
INA	-414.586502403	3,54	77,93	49,72	-0,361174	0,030503	10,65792
INH	-469.595537981	2,04	86,17	55,60	-0,36277	0,033965	10,79556
IHH	-586.722000622	2,38	119,67	47,46	-0,36146	0,05650	11,37311

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. The crystal structure of the isonicotinic acid is taken from the work F. TAKUSAGAWA et al [25]. The global minimum energy obtained by DFT/B3LYP structure optimization using 6-311++G(d,p) basis set for isonicotinic acid (IA), isonicotinamide acid (INA), isonicotinic acid hydrazide (INH) and 1-isonicotinyl-2-isopropylhydrazide (IHH) molecules as -436.985269556 a.u, -417.108666984 a.u, -472.444390504 a.u and -590.413501660 a.u. and these values in the HF method, -434.427694450 a.u, -414.586502403 a.u, -469.595537981 a.u and -586.722000622 a.u, respectively. The dipole moments of all molecules have been calculated at the both models, the dipole moment of isonicotinic acid hydrazide is the equal value, but values of other molecules are different. The optimized structure parameters of all molecules by HF and DFT (B3LYP) levels with the 6-311G++(d,p) basis set are listed in Table 2 in accordance with the atom numbering scheme given in Figure 1.

Table 2. Selected structural parameters of isonicotinic acid and its derivatives.

Molecule	B3LYP/6-311++G**					HF/6-311++G**			
Bond length (Å)	IA	INA	INH	IHH	Expt[a]	IA	INA	INH	IHH
C1-C2	1.3934	1.394	1.3939	1.3937	1.386(2)	1.3859	1.386	1.3861	1.386
C1-N6	1.3361	1.335	1.3351	1.3354	1.339(2)	1.3182	1.3176	1.3175	1.3177
C2-C3	1.3958	1.3966	1.3969	1.3971	1.381(3)	1.3844	1.3858	1.3858	1.3859
C3-C4	1.3955	1.3952	1.3953	1.3952	1.389(2)	1.3847	1.3848	1.3848	1.3848
C3-C11	1.4924	1.5077	1.5045	1.5045	1.506(2)	1.4952	1.507	1.5057	1.5062
C4-C5	1.3916	1.3916	1.3918	1.3919	1.382(2)	1.3838	1.3838	1.3837	1.3838
C5-N6	1.3374	1.3377	1.3376	1.3375	1.334(3)	1.3202	1.3205	1.3205	1.3204
C11-O12	1.2069	1.2184	1.2208	1.2226	1.215(2)	1.1826	1.1925	1.1944	1.1945
Bond length (Å)	**IA**	**INA**	**INH**	**IHH**	**Expt[a]**	**IA**	**INA**	**INH**	**IHH**
C11-O13	1.3541	-	-	-	1.294(3)	1.3251	-	-	-
C11-N13	-	1.3687	1.3709	1.3712		-	1.3581	1.3553	1.3589
N13-N14	-	-	1.4083	1.4135		-	-	1.3891	1.3955
C17-C19	-	-	-	1.5291		-	-	-	1.5255
C17-C20	-	-	-	1.5339		-	-	-	1.5296
Bond angle (°)									
C2-C3-C11	122.73	123.85	123.63	123.66	120.3(1)	122.43	123.29	123.31	123.24
C1-N6-C5	117.48	117.22	117.25	117.22	118.9(2)	118.12	117.82	117.83	117.83
O12-C11-N13	122.61	122.36	122.15	122.35	125.1(2)	122.77	122.61	122.68	123.16
Dihedral angle (°)									
C2-C3-C11-O12	180.00	-156.23	-153.87	155.82		-180.04	-152.89	-150.68	152.48
C2-C3-C11-N13	0.00	22.86	26.14	-24.59		-0.03	26.24	29.18	-27.74
C4-C3-C11-O12	0.00	22.47	24.67	-22.67		-0.04	26.04	28.11	-26.31
C4-C3-C11-N13	180.00	-158.44	-155.32	156.93		-180.04	-154.84	-152.03	153.47

[a]Taken from Ref. [25]

For the IA, INA, INH and IHH molecules, we calculated equilibrium dihedral (C2-C3-C11-O12) angles at the as -180.04°, -152.89°, -150.68° and 152.48°, B3LYP/6-311++G(d,p) as 180.00°, -156.23°, -153.87° and 155.82°, respectively. As seen from the results, the carboxyl group in the IA is coplanar with pyridine ring while the other group in the INA, INH and IHH are not coplanar with pyridine ring. Also at the B3LYP/6-311++G(d,p) as 1.4924, 1.5077, 1.5045 and 1.5045 HF/6-311++G(d,p) as 1.4952, 1.507, 1.5057, 1.5062. As seen from the Table 2, the C3-C11 bond length of isnicotinic acid was obtained as 1.506(2). This experimental study concludes that the theoretically calculated bond lengths and bond angles are agrees well with reference [25].

3.2. *Conformational Analysis and Torsional Barriers*

The energy barriers of rotation around the C3-C11 bond were calculated at the B3LYP and HF with 6-311++G(d, p) basis set. The potential energy surface (PES) scans for studied molecules are shown Figure 2 (a), (b), (c), and (d). In the calculation of PES, the entire geometrical parameters were simultaneously relaxed while the dihedral angle C2-C3-C11-O12 was varied from 0° to 180° by steps of 10°.

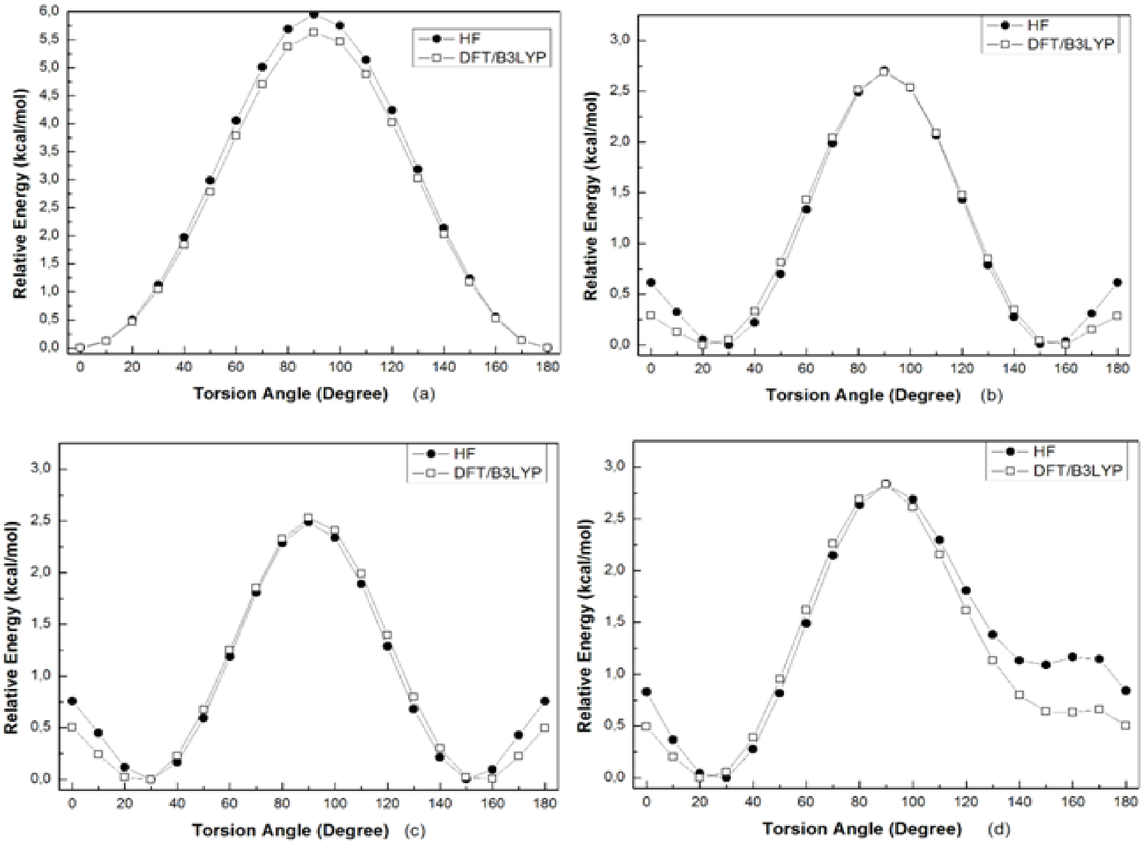

Figure 2. The potential energy surface (PES) of (a) isonicotinic acid (IA), (b) isonicotinamide acid (INA), (c) isonicotinic acid hydrazide (INH) and (d) 1-isonicotinyl-2-isopropylhydrazide (IHH).

The calculated barrier (at 90˚) high of IA, INA, INH, IHH are 5.62514, 2.68835, 2.52763, 2.83234 for DFT and 5.95101, 2.70507, 2.49239, 2.83551 (kcal/mol) for HF, respectively. In the potential energy curves of INA, INH, two- minima energy have been obtained in the range (20˚-30˚) and (140˚-150˚) as shown in Fig 2 (b) and (c) clearly demonstrates that in the range (20˚-30˚) corresponds to conformer I and in the range (140˚-150˚) corresponds to conformer II in the both models. For this value of IA has been obtained (at 0˚ and 180˚). The most stable conformer is obtained in the range (20˚-30˚) torsion angle for C2-C3-C11-O12 rotation for IHH.

4. CONCLUSION

We calculated the optimized geometries of molecules under investigation and their molecular properties such as equilibrium energy, frontier orbital energy gap, dipole moment, polarizability, and hyperpolarizability. Those properties of studied molecules have also been used to understand the properties and active sites of the drug. The C3-C11 bond length of isonicotinic acid was obtained as 1.506(2). This experimental study concludes that the theoretically calculated bond lengths and bond angles are agrees well with reference [25]. Dihedral angle C2-C3-C11-O12 at the equilibrium of isonicotinic acid is planar (at 0˚ and 180˚) while dihedral angles C2-C3-C11-O12 at the equilibrium of other molecules are non-planar.

5. References

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