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Model Chemistries of Hydrazides: Part IV. Computational Quantum Chemical (CQC) Studies of Isonicotinic acid hydrazide, its valence isomers and their Isopropyl Derivatives

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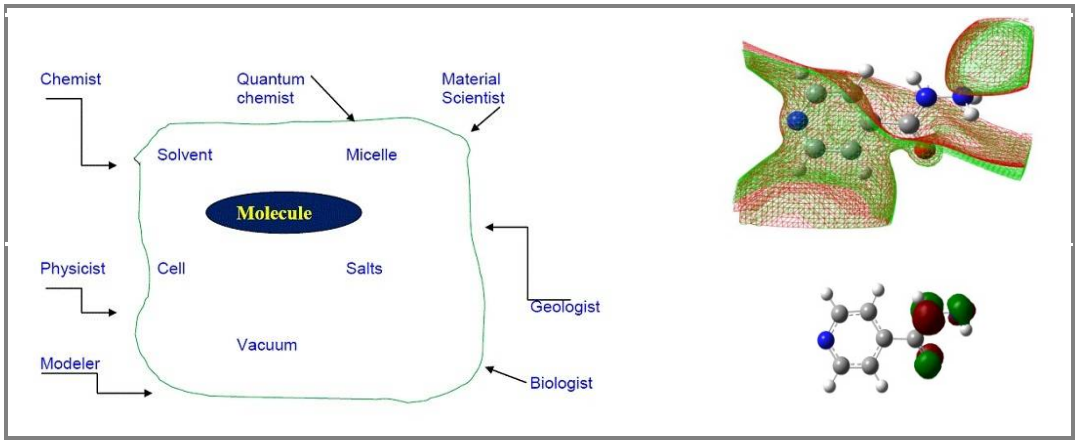
ABSTRACT

The optimum geometries, single point energies, electronic properties and chemical reactivities of isonicotinic acid hydrazide (INH), picolinic acid hydrazide (PAH), a valence isomer of INH and benzoic acid hydrazide (BAH) without a hetero atom in the aromatic ring and their isopropyl derivatives are studied by ab initio and DFT methods using G03 software package. The basis set 6-311G is used both for ab initio (RHF-SCF) and DFT (hybrid functional, B3LYP) in geometry optimization as well as frequency analysis. The presence of hetero atom N (of pyridine ring) in PAH and INH enhanced the stability compared to BAH containing only a phenyl ring based on single point (electronic, nuclear repulsion and zero point vibrational) energies of the geometries at the stationary point. Iso-propyl derivatives substantially increased the stability of the compounds following the trend of parent compounds.

*In the case of nicotinic acid hydrazide (NAH), a meta isomer of INH, DFT and ab initio methods resulted in one imaginary value for the optimized geometry and thus, further investigation could not be done. PAH is found to be more polar compared to INH and BAH, from static dipole moment values. The iso-propyl group enhanced μ of INH by about 70%. On the other hand non-linear (second order) hyper polarizablity (β) of INH is higher than PAH and BAH. The electrophilic nature of pyridine N, N15 of hydrazide fragment and orbital-based interactions are inferred from Mullikan population analysis and FMO energies. The differences in the TD and ESP contour maps indicate the shapes and interaction potential of hydrazides. A few physics-based and chemical parameters of biological relevance like molar volume, log P, Henry's solubility parameters, and Fukui- reactivity-parameters are reported. An in-depth study of electronic structure of INH was attempted with CC and MP2 –Post HF procedures— using higher-level basis sets 6-311++G** to take into account polarization and diffusion contributions. The computational bond characteristics are in agreement with experimental values from x-ray crystallographic studies.*

[$] ***Dedicated to "J. Applicable Chemistry" during end of first decadal (2012-2022) publication era***

Graphical Abstract:



Ab initio and DFT chemical models of an anti tubercular drug (isonicotinic acid hydrazide) and its isomers are studied. Biologically relevant electron density, ESP and Fuki parameters are probed

Novelty: The study of antitubercular drugs continues to be fascinating research focus due to the development of resistance of Mycobacterium tuberculosm bacillus for INH containing drugs. Also tuberculosis is an opportunistic infection and a major cause of fatal health problems in developing/developed nations. INH, its isomers and isopropyl derivatives are investigated with high level quantum chemical computations. The results reported here is a subset of our ongoing project. The effect of water molecules, metal ions, thorough conformational search are in progress. MD in gas phase and low dielectric media, follow to probe into energetics.

Highlights:

- The physico-chemical and quantum chemical parameters of biological relevance are computed from computational quantum chemical studies using abinitio and DFT theory.
- Gaussian-03, popularly known as G03 with its GUI software, Gaussian-5 is used.
- The bond lengths/angles and dihedral angles are in agreement with X-ray data indicating the adequacy of QC-model.
- The probes (TED, ESP, atomic charges on the atom, group, and moiety of molecule) for chemical-, physical-, biological- and life- processes are calculated.
- The basis sets (6-311++G**) account for polarization and diffusion contributions of electrons in nitrogen and oxygen atoms on energetics of molecule.

Keywords: Antitubercular drug, Computational QC, 3D-optimized geometries, Total Electron Densities, Fukui reactivity, bio-chemical properties

INTRODUCTION

Isonicotinic acid hydrazide (INH) is an antitubercular drug [**1**]. The pharmaceutical preparations like isoniazid, isonex contain INH as active ingredient. The isopropyl derivative called iproniazid and copper complex of INH have considerable activity. However, the other two valence isomers picolinic (PAH) and nicotinic acid hydrazides (NAH) do not exhibit therapeutic activity. Bagchi *et. al*. reported a MLR (Multiple linear regression) model for nineteen 2-substituted isonicotnic acid hydrazides with 2 to 5 explanatory variables viz. structural information content, Van der waal volume, pKa, Wiener index and number of bonding pi-electrons [**2**]. The biological response in the model is logarithm of reciprocal of minimum inhibitory concentration of the compound. Dias et al. employed a third parametric model (PM3) implemented in AMPAC to correlate anti-tubercular activity of 28

biflavonoid compounds with heat of formation and hydration energy [**3**]. Speciation studies of proton-ligand and metal–ligand complexes (in aquo–organic media) of anti-tubercular (INH) [**4**], anti-hypertensive (labitalol) drugs, pharmaceutical preparations for Parkinson disease (DOPA) [**5, 6**] and electronic structure were reported earlier from this laboratory [**7-9**]**.** These investigations were aimed at probing into drug/protein – small molecule interactions within the thermodynamic, kinetic and statistical thermodynamic framework [**10-13**].

Drug design [**14, 15**] is an interdisciplinary inverse problem of finding a chemical compound in a suitable matrix to cure a target disease in presence of viruses, living cells etc involving dynamic in-vivo processes. The computational design of drugs/lead molecule/drug like structures with optimal characteristics is a multi-objective task to be explored in chemical structural/ constitutional/ conformational/ pharmacological/ biochemical-reaction space [**16**]. These spaces are correlated, complementary, with large unexplored patches. The number of molecules available range from 10^{60} to 10^{100} and recent attempts in covering drug-like molecular space extended to 5 million and up to a maximum of 35 million entities. Thus, it is a hard non-polynomial complete problem with conflicting multiple objectives having no unique solution. The pragmatic way is intelligent pruning of search space into prospective islands adhering to Pareto optimality. A point of view of critics is that no drug was introduced with computational science alone. Yet, in the recent past, every phase of life cycle of drug discovery[**17, 18**] to abandoning stage through clinical trials invariably involves computational quantum chemistry, QSAR, virtual high throughput screening etc. The interaction of a drug with protein, active site of the target and another drug in different environments viz. blood plasma, cells etc. play a vital role in the function of a compound as a drug. A detailed knowledge of the conformers and their optimized geometries are pre-requisite in this pursuit. Experimental approaches -- X-ray studies of single crystals, multi-dimensional NMR in solution, time delayed excitation emission fluorescence -- and computational quantum chemistry of a single molecule in gas phase or in presence of a solvent are sought after tools. Since, experimental elucidation of structure for millions of compounds even in the focused target virtual library is out of reach, SEMO (semi empirical molecular orbital) methods or quantum chemical–molecular mechanics (QC-MM)/ONIOM are widely used in filtering undesired molecules. Molecular dynamics yielded realistic energy of the system unlike traditional QC studies. The desirable properties of a compound for accepting it to be a lead are, aqueous solubility, permeability through membranes, bio-availability, moderate binding constant of drug-protein complex in blood plasma, excretion, favorable pharmaco-kinetics/dynamics, while undesirable characteristics include metabolism, toxicity, interaction with another drug, passing through BBB etc. As the experimental determination of these properties is time-consuming and costly, molecular descriptors derived from computational QC (CQC) and other paradigms along with QSAR (quantitative structure activity relationship) studies [**19**] are integral parts of drug design. Pharmacophore mapping, ligand based drug design, combinatorial chemistry, parallel synthesis, (focused) virtual libraries, (experimental/virtual) HTS (high throughput screening), bio-isosterism, scaffold hopping and accumulated common sense/knowledge bases accelerated the movement towards prospective drug launching. It is well known that chemical behavior of an amino acid in its free form, peptide and protein are similar for strong interactions, but diverse in weak (low energy) bonding.

Further, biological activity is a composite of several factors including structure based chemical response. A detailed theoretical reactivity of INH, an anti tubercular drug paves way to probe into its plight in bio-systems. The model chemistries at different levels of theory (SEMO, ab initio and DFT) and molecular descriptors of anti tubercular drug INH is envisaged with variation in the sizes of the ring (5 to 8 members), change of hetero atom (S, N, O or Se), derivatives with iso-propyl group on the terminal NH_2 of the hydrazide, length of the fragment and substituents on aromatic ring. In this communication, the results of model chemistries and the quantum chemical (QC) parameters at ab initio and DFT levels in gaseous phase are reported for INH, its valence isomers (NAH and PAH), BAH and their iso-propyl derivatives.

MATERIALS AND METHODS

Hardware & software: Ab initio and DFT computations are performed on DELL Inspiron/6000 model with 504 MB RAM with a CPU of clock speed 1.86 GHz and a hard disk of 74.4 GB. All computations were performed with G03 package (Frisch et al., 2004). The force constants/ vibrational frequencies, ESP charges, hyperpolarazabilities and molecular volume are calculated with the key word FREQ pop=ChelpG volume= tight polar=enonly options.

Theory and implementation: The origin, existence and extinction of life processes are in striking balance between energetics in dynamic surrounding/environment. The scientific/philosophical frame concentrates first on dominant forces. But, after a significant progress, look for relatively smaller, yet cumulatively significant interactions. Information science and knowledge bases deal with Physical/Chemical/Biological and Mathematical models figure 1.

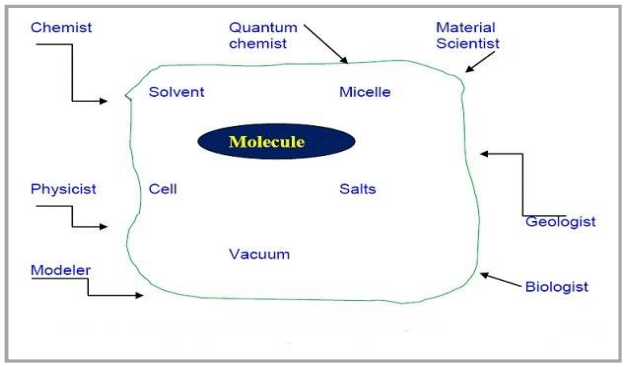


Figure 1. Different perceptive viewpoints of chemical species from scientist's experimental probes and theoretical models.

Laboratory/industrial scale syntheses of organic/inorganic materials and bio-/geo-/environmental-transformations involve chemical reactions in different phases/interfaces. The interactions and properties of nano- to macro-molecular systems are key factors in the life cycle of mankind, eco-balance and interstellar events. The focus now is around non-bonded interplay of moieties, opening new vistas in chemical biology. The non-bonded interactions include electrostatic interaction between permanent and induced charged species, dispersion/hand shake/H-bond forces. Computational chemistry encompasses classical /theoretical (statistical /thermodynamic /chemical dynamics /spectroscopy) chemistry, QSAR and quantum chemistry. The progress of computational science (CS) is closely associated with physical/biological experiments and also with numerical mathematics. The advances of physico-chemical-biological and mathematical laws (including statistical, fuzzy concepts, nature inspired approaches etc) were iterative. The outcome of integration/loose coupling/fusion of chemistry with biology, computer science, pharmacy resulted in emerge of interfacial disciplines viz. chemometrics, chemoinformatrics, pharmacometrics, dietetometrics, speciometrics and qualimetrics, proteomics, genomics, computational quantum chemistry. The energetics and geometry of macro molecules of biological/industrial importance and of even small molecules in condensed phase are indispensable.

Molecular mechanics employing Hooks and Newton's second law is feasible. And, quantum chemical calculations with full swing are impracticable with even today's hardware speeds. In molecular mechanics, a force field which implicitly represents E_{el} is calculated. Thus, the output is approximate geometry and energy of the system. Quantum mechanics, a physicist tool, revolutionized chemistry, although the initial application was restricted to one-electron systems. It comprises of ab initio and semi empirical (SEMO) methods. Ab initio method now can be viewed to comprise of Hart-Fock (HF), post_HF and density functional theory (DFT) paradigms.

Quantum chemistry (QC) goes around the motion of electrons under the influence of electromagnetic forces of nuclear (protons') charges. The energetics of electrons in molecules is quantified based on QM principles. It is the heart of conformer geometric structure, isomerisation process, chemical reactions in all phases and organic photo-/electro-/radiation- chemistries and spectroscopy. Classical quantum chemistry could not even deal with hetero atoms and metal ions' electronic spectra. The efforts during the last three decades render QC into a powerful paradigm competing even advanced experimental instrumental probes. Yet, the limitation is in dealing with non-covalent bonds [Nobel gas (aerogen), Halogen, Chalcogen, Pnicogen (or Pnictogen), Tetrel, Triel , Spodium, Regium (or Coinage), alkali, alkaline earth, Hydrogen [{strong, weak}, dihydrogen, hydride], catch bonds, stacking interactions, Van der waal forces, and low-energy solvent-solvent interactions].

Molecular quantum chemistry is the application of quantum chemical principles amenable to hydrogen like atoms for a molecular system. A battery of tools implemented in the solution of Schrodinger wave equation (SWE) from bare hydrogen atom to complex chemical reactions is the realm of computational quantum chemistry (CQC). The concerted efforts during the last two decades are to achieve high quality results adopting the recent advances in optimization, chemical knowledge, algorithms for integro-differential equations and modeling the electron density with mathematical functions (basis sets).

QC models: Quantum chemistry, evolved from principles of quantum mechanics, is one of the well-nurtured quantitative tools of the present times. The ab initio (HF to post HF), DFT, time-dependent-DFT (TD-DFT) and prefixed set of encapsulated (G3, G3B3,G4, etc) procedures rendered the dream of last century quantum chemists in solving Schrödinger wave equation for chemical moieties in different phases and also in presence of solvents into a reality. The basis of the two methods is mathematically significant ψ (in ab initio) and physically meaningful ψ^2 (in DFT).

DFT models freezing process, multi-component systems and superconductivity It is extended to Bosons and their mixture with fermions.

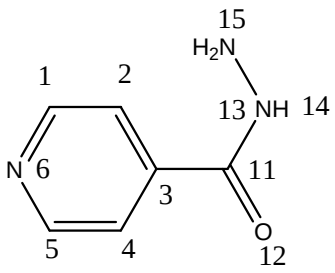
RESULTS AND DISCUSSION

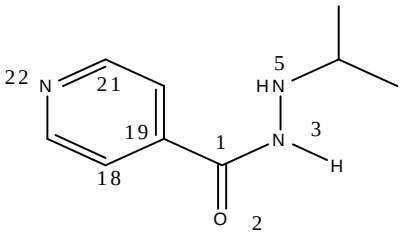
In this study, geometric optimization and vibrational frequency analysis are carried out at the same level of theory (ab initio and DFT) with the basis sets, 6-31G and 6-311G. For DFT method, B3LYP correlation exchange functional is adopted. The optimized geometric parameters (bond length BL, bond angle, BA and dihedral angle, DH) for all six compounds are summarized in Table 1a-d. Figure 2-5 displays the stable geometry, total electron density and ESP of INH at DFT level of theory with 6-311G basis set.

Table 1. Optimized geometric parameters of hydrazide fragment of INH and its isopropyl derivative

(a) Bond lengths

Bond	HF/6-311G		B3LYP/6-311G		Experimental (x-ray data)
	INH	Isop-INH	Isop-INH	INH	INH
O-C	1.227	1.228	1.254	1.252	1.235
N-C	1.353	1.353	1.371	1.371	1.346
H-N	0.986	0.987	1.005	1.005	0.86
N-N	1.393	1.397	1.419	1.412	1.426
H-N	0.997	0.998	1.019	1.015	1.05
H-N	0.997	---	--	1.015	0.86





INH | Isop-INH

Numbering scheme of atoms in G03

(b) Bond angles

	HF/6-311G		B3LYP/6-311G		Experimental (x-ray data)
	INH	Isop-INH	INH	INH	INH
O-C-N	121.7	121.7	121.2	121.4	122.1
C-N- N	122.2	121.7	121.2	122.1	121.1
N-N-H	112.3	109.5	107.5	110.4	113.0

(c) Dihedral angles

INH	HF/6-311G		B3LYP/6-311G	
	INH	Isop-INH	INH	Isop-INH
C-C-N-H	9.9	14.8	9.9	14.4
C-C-N-N	-179.4	179.2	-179.9	177.2
O-C-N-H	-169.1	-163.8	-169.1	-163.9
O-C-N-N	1.7	0.6	1.1	-1.1
C-N-N-H	-56.6	-45.6	53.0	-35.7
C-N-N-H	68.6	----	69.1	----
H-N-N-H	114.7	119.7	117.8	128.1
H-N-N-H	-120.1	---	-120.2	----

(d) Comparison of optimized geometric parameters of INH at different levels of theory and basis sets

Geometric parameter	Ab initio				DFT			
	HF		Post_HF		B3LYP			
	6-31G	6-311G	CC PVDZ	CC PVTZ	6-31G	6-311G	6-311++G**	LANL2DZ
O12-C11	1.228	1.227	1.197	1.193	1.253	1.252	1.218	1.259
N13-C11	1.353	1.353	1.359	1.352	1.372	1.371	1.367	1.3831
H14-N13	0.989	0.986	0.997	0.989	1.008	1.005	1.006	1.011
N15-N13	1.391	1.393	1.391	1.388	1.409	1.412	1.407	1.417
H16-N15	0.997	0.997	1.007	0.999	1.018	1.015	1.017	1.022
H17-N15	0.997	0.996	1.006	0.998	1.017	1.015	1.015	1.021
O12-C11-N13	121.7	121.7	122.5	122.7	121.3	121.4	122.13	121.6
C11-N13-N15	122.2	122.1	120.7	121.5	121.9	122.1	120.9	122.4
N13-N15-H16	112.3	111.6	108.6	109.2	110.9	110.4	107.5	110.9
N13-N15-H17	112.1	111.4	108.0	108.8	110.9	110.5	108.2	110.9
C03-C11-N13-H14	8.3	9.9	23.2	18.5	8.8	9.9	20.7	8.11
C03-C11-N13-N15	-179.1	-179.4	173.9	175.0	180.0	-180.0	173.1	-180.0
O12-C11-N13-H14	-170.8	-169.1	-157.1	-161.6	-170.3	-169.1	-159.3	-170.3
O12-C11-N13-N15	1.9	1.5671	-6.5	-5.1	0.9	1.1	-6.9	0.9
C11-N13-N15-H16	-58.8	-56.6	-39.0	-42.7	-54.5	-54.0	-28.7	-54.5
C11-N13-N15-H17	68.8	68.6	75.5	74.0	68.9	69.1	85.6	68.9
H14-N13-N15-H16	114.3	114.7	112.9	114.9	117.3	117.8	125.6	117.3
H14-N13-N15-H17	-118.1	-120.1	-132.6	-128.4	-119.4	-120.2	-120.7	-119.4

The electronic energy, nuclear repulsion energy, zero point vibrational energy (ZVPE), rotational constants are summarized in Table 2. Post HF procedures -- MP2 and CC -- have been employed for

the typical compound INH. Further, the basis sets 6-311++G and 6-311++G** are also used to study the effect of diffusion and polarization on energies (Table 2c). The typical critical properties are tabulated (Tables 3-7).

Table 2. Electronic energies for optimized stable[#] geometric structures of hydrazides

(a) HF and DFT/B3LYP level of theory

Molecule	Electronic energies in Hartrees			
	HF		DFT/B3LYP	
	6-31G	6-311G	6-31G	6-311G
BAH	-453.2990624	-453.3944953	-456.1436992	-456.255634
INH	-469.2653863	-469.3679936	-472.1589599	-472.2764432
PAH	-469.2609315	-469.3636822	-472.154144	-472.2718546
Isop- PAH	-586.3124026	-586.4354554	-590.0725602	-590.2072532
Isop-INH	-586.3188679	-586.4419078	-590.0725126	-590.2138969
Isop-BAH	-570.352474	-570.4683633	-574.0572254	-574.1930818

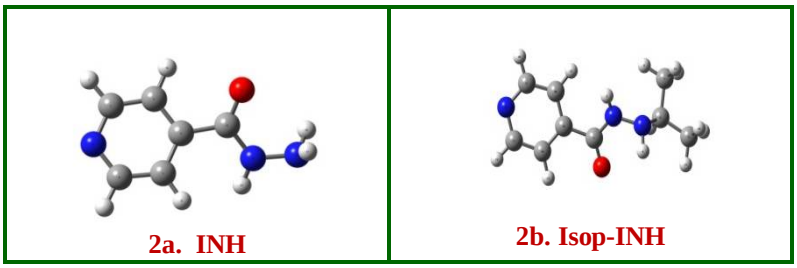
(b) NRE and ZPEs

Molecule	NRE (Hartrees)		ZPE (Kcal/Mol)	
	HF/6-311G	B3LYP/6-311G	HF/6-311G	B3LYP/6-311G
BAH	486.0731294644	486.0731740481	91.17329	91.17332
INH	488.5320872780	488.5320967062	83.49919	83.49920
PAH	489.5455402878	489.5495979860	83.36636	83.36281
Isop-BAH	766.8045073815	759.3136381400	154.55414	144.23339
Isop-INH	769.9933432832	761.8047460854	146.64910	136.57980
Isop- PAH	789.9229164556	780.3796229521	146.30251	136.28350

(c) Diffuse and Polarization effects in post HF and DFT methods

INH					
Level		Exchange/ Correlation	Basis set	Electronic energy	mu
Ab initio	HF		6-31G	-469.2653863	
			6-311G	-469.357404	
	Post HF	MP2	6-311G	-470.4086811	2.38
		CC	pvdz	-469.5145026	1.93
		CC	pvtz	-469.639858	2.05
DFT		B3LYP	6-311G	-472.2764432	
			6-311++G	-472.2888049	2.34
			6-311++G(**)	-472.4791506	2.10
			LANLZDZ	-472.2288166	2.40

Number of imaginary frequencies (Nimag) = 0



2a. INH **2b. Isop-INH**

Figure 2. Optimised Geometries at B3LYP/6-311G (a) INH (b) isop-INH.

Second order harmonic frequency analysis is performed for the geometric structures optimized by Berny algorithm of G03 package. The atomic charges are obtained from Mulliken population analysis

and CHelpG charges for INH. The linear (α) and second order non-linear (β) polarizabilities computed with 'POLAR' option are summarized in Table 4.

Optimized geometric structure: The optimized chemical moieties are the stable stationary structures (Figure 2) as the number of imaginary frequencies (Nimag) is zero for each of the hydrazides at different levels of theory. BLs, BAs for the stable optimized geometries of the all compounds (INH, PAH, BAH, iso-propyl derivatives) are almost same at DFT level of theory using B3LYP, exchange correlational functional under 6-311G basis set (table 1a-c). Finally, convergence is tested against criteria for the maximum force component, root-mean square force, maximum step component, and root-mean-square step. The step is the change between the most recent point and the next to be computed (the sum of the linear and quadratic steps).

Item	Value	Threshold	Converged?
Maximum Force	0.000089	0.000450	YES
RMS Force	0.000018	0.000300	YES
Maximum Displacement	0.000419	0.001800	YES
RMS Displacement	0.000152	0.001200	YES
Predicted change in Energy	-5.416092D-08		
Optimization completed.			
-- Stationary point found.			

A perusal of dihedral angles (DAs) revealed that two hydrogens on the terminal NH2 are in different planes for INH (117.8, -120.15), PAH (-67.10, 54.52) and BAH (-50.34, 70.98). In PAH, O-C-N-H dihedral angle reveals that there is scope for hydrogen bond. The bond length, bond angle of hydrazide fragment at different levels of theory with basis sets incorporating diffuse and polarization contribution are investigated. The BLs and BAs for INH (Table 1) are comparable with x-ray structure. The diffuse and polarization function has no effect on BLs and BAs, but a small influence on DAs at both ab initio and DFT levels. However, a close inspection infers that 6-311G is adequate (from cpu time) to compute geometric parameters of the hydrazides. The iso-propyl substituent at the terminal nitrogen influences the DAs in the fragment**.**

The optimized structure of nicotinic acid hydrazide (NAH) in the gas phase at all levels of theory (ab initio and DFT) with many basis sets is found to be a transition state (TS). It is inferred from one imaginary (Nimag = 1) value in harmonic frequency analysis. A detailed study is in progress to find a stable conformer at least in presence of one or a few solvent molecules.

Stability of compounds: Benzoic acid hydrazide (BAH) is least stable amongst the compounds studied. INH and PAH with nitrogen as hetero atom in the ring have very similar total energy (TE), but more stable compared to BAH at all levels of theory (Table 2). The components of TE, nuclear-nuclear repulsion, electronic, vibrational modes reveal that nuclear repulsion energy increases in the order BAH > INH ≅ PAH, while the electronic component decreases in the same order.

Substitution of one of the hydrogens on the terminal nitrogen of hydrazide fragment with iso-propyl group substantially increases the stability of the molecules. Total energy as well as the contributing components increased approximately by about 50% compared to unsubstituted compounds. A detailed study of the effect of nature of substituent group on the stability and nuclephilic/electrophilic/radical reactivity of the hetero atoms enables one to probe into complex biological responses of these molecules.

Atomic and ESP charges: Mullikan and Lowden population analysis (MPA, NPA) are popular theoretical procedures to calculate atomic charges based on overlapping AOs and symmetrically orthgonalising the basis [**20**].

Charges on atoms of the molecule: Although fractional charges are present on each atom of a neutral molecule, they sum up to zero for the entire molecule in commensuration with broad classical principle of electro-neutrality. The QC based calculation of charges using the results of population

analysis are Mullikan, ESP (=MAC), CHelp, CHelpG etc. MPA is a partition technique. The algorithms for calculating charges using Mullikan population analysis (MPA) and the advantages/ limitations are incorporated. In MPA, wave function is partitioned in terms of basis function.

Atom	Mulliken atomic charges	Hydrogen summed into
O	-0.81	0
H	0.40	0
H	0.40	0

Mullikan_charge

\+ Trend is good enough for closely related compounds

\- It is not very reliable

\- Differs from those from Bader using topological approach

☏ Remedy : Corrected Mullikan charge

Corrected_Mullikan_charge

\+ Reproduces calculated dipole moments for planar molecules in contrast to Mullikan charges

\+ Similar to those from ESP charge

\- Limited to planar molecules

\- It is not invariant to rotation

☏ Remedy : CHelpG charge

CHelpG: Breneman model of calculation of charges is popularly known as CHelpG (**CH**arge **el**ectrostatic **p**oint **G**rid). It fits point charges with ESP near Van der wall surface grid. The Broneman radii are used.

CHelpG

\+ Superior to Mullikan charges

\+ Invariant to rotation

\+ Does not depend upon the orientation of the molecule in a coordinate system since uniform grid of points is used to sample ESP

\- Assignment of grid points does not reach satisfactorily for burried atoms (SP3 hybridization). Ex. sterically crowded environment in bulkier secondary and tertiary ammonium ion

\- Does not sample points far away from vander waal surface

The Mulliken and CHelpG charges for hetero atoms of INH and its isopropyl derivatives are given in figure 3. In CHelpG method, the point charges are fitted with ESP on a grid using Breneman radii [21].

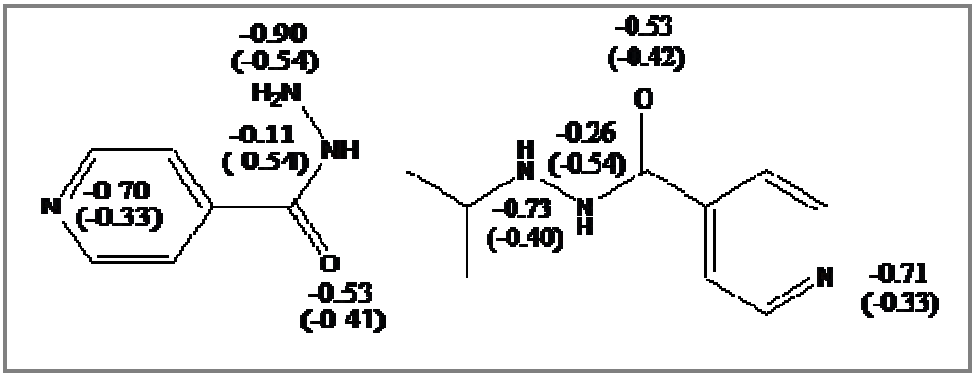
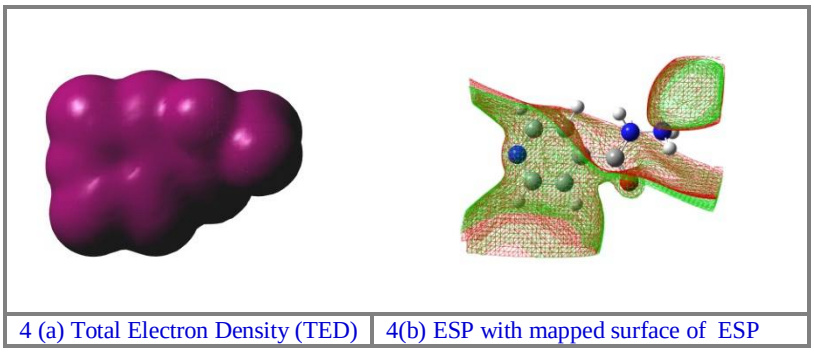


Figure 3. CHelpG charges on (a) INH (b) isopropyl-INH

The negative charges on N of NH_2 of the hydrazides considered are far greater than O of CO and N of NH. Isoproppyl group at the terminal N increases its negative charge and the effect is less pronounced on the penultimate N. The difference in charges of the two nitrogens of the fragment is 0.47 for iso-INH while it is 0.79 for INH. CHelpG charges are superior and invariant to orientation of the molecule in a co-ordinate system in contrast to other ESP based ones.

Total electron density (TED) and ESP surfaces/contours: The contour of electron density and that mapped on a 3-D surface represents the shape of the optimized molecule in the gas phase (Figure 4). The small white patches around H10, N16, H9-H14, both for INH and its iso-propyl derivative indicate that the electron density is very low compared to other regions. A similar small region of negligible electron cloud is found on the proton of isopropyl group, while the electron density on N16 is significant.



4 (a) Total Electron Density (TED)	4(b) ESP with mapped surface of ESP

Figure 4. Graphical output at ab initio HF/6-311G model (a) TED (b) 2D contours of ESP.

Dipole moment: The total static dipole moments (μ) and their components of BAH, INH and PAH and their iso-propyl derivatives are computed at ab initio and DFT levels of theory and with varying basis sets accounting for the effects of diffuse and polarization. The typical values are incorporated in Table 3. PAH has highest μ (5.22 Debye) and the order for the compounds investigated is INH < BAH <PAH. INH or PAH has a pyridine ring and the hydrazide fragment (-$CONHNH_2$) is attached in 4- and 2- positions respectively. The dipole moment of BAH (containing only a phenyl ring) is higher than INH. The lower value for INH is as a result of compensation effect of dipole of pyridine and –CONHNH2 group in the para position. The largest μ of PAH among the unsubstituted compounds arises due to cumulative effects of the components rendering it to be a highly polar. But, the change for isopropyl derivatives of BAH and PAH is relatively less and $\mu_{isop\text{-}BAH} < \mu_{isop\text{-}PAH}$.

The total dipole moment of a molecule is equal to the contributions in X, Y and Z directions and the component in each direction is due to contribution from the net charge located at the atomic site and that from hybridization of atomic [**22, 23**]. From the table 3, it is clear that the dipole moments calculated at different levels of theory differ in magnitude significantly. It appears that there is not much change in μs with basis sets. However, it is important to note that the trend remains the same. Inspections of in different μ directions reveal interesting features. The contribution in Y direction is high in magnitude, while it is least for Z component. It is reported [**24, 25**] that μs at DFT level of theory with B3LYP are usually in good agreement with high level ab initio calculation and are also with experimental ones, especially when basis sets of spdf quality are employed.

Polarizabilities: The linear polarizability (α), second order non-linear hyper polarizabiltiy (β) are computed using static frequencies at the optimized geometries i.e. stationary point. The trend (Table 4), in α is BAH > INH > PAH, whereas for β it is PAH > BAH ≈ INH. Introduction of isopropyl group at the terminal -NH2 has a profound influence. The effect is quite significant for BAH (β : 0.27 to 1.23, α : 5332 to 7813). The substituents will drastically either increase rendering materials suitable for non-linear optical properties or decrease making them devoid of polar interactions. The numerical

values of β for unsubstituted PAH and all isopropyl derivatives are greater than that for urea (0.39). Thus, they can be prospective compounds with non-linear optical susceptibilities on introducing the substituents in the pyridine ring also.

Table 3. Static dipole moments of hydrazides

(a) Total μ

	Dipole moment (Debye)			
	HF		B3LYP	
	6-31G	6-311G	6-31G	6-311G
BAH	3.28	3.27	2.76	2.83
INH	2.38	2.38	2.27	2.33[#]
PAH	5.32	5.22	4.71	4.73
Isop- PAH	4.14	4.16	4.19	3.64
Isop-INH	2.59	2.54	2.57	2.59
Isop-BAH	3.19	3.16	2.78	2.83

([#])2.3427 6-311++G

(b) Components of μ in X, Y and Z directions

	HF/6-311G			B3LYP/6-311G		
	X	Y	Z	X	Y	Z
BAH	-1.66	-2.21	-0.62	-1.65	-2.22	-0.41
INH	1.25	-1.89	-0.54	1.26	-1.91	-0.34
PAH	-2.38	4.02	-0.74	-2.39	4.42	-0.72
Isop-BAH	-1.59	2.59	0.86	-1.24	2.47	0.61
Isop-INH	1.37	1.86	1.05	1.71	1.79	0.76
Isop- PAH	-0.42	-4.03	0.93	-0.52	-3.50	0.86

Table 4. Linear and Hyper polarizabilities at DFT (B3LYP) and ab initio (HF) levels with 6-311G basis set

Hydrazide	Polarizabilities					
	HF/6-311G			DFT/B3LYP/6-311G		
	α	Δα	β *1e30	α	Δα	β *1e30
BAH	4248.51	82.186	0.19	5332.25	87.56	0.27
INH	2846.29	74.82	0.18	4040.20	82.22	0.17
PAH	2739.53	77.59	0.91	3448.87	82.63	1.58
Isop-BAH	5220.56	112.99	0.91	7813.08	124.86	1.23
Isop-INH	2502.46	107.63	0.79	4430.56	119.23	0.77
Isop- PAH	1300.09	106.92	0.90	2046.57	118.50	0.96

Frontier Molecular Orbitals (FMOs): The HOMO and LUMOs of INH are depicted in figure 5. Ionization potential (IP) exhibits a decreasing trend (INH < BAH <PAH) at ab initio and DFT levels of quantum chemical computations. Iso- propyl group at NH_2 of -$CONHNH_2$, a σ donor, decreases the IP compared to the unsubstituted ones and follows the order Isop-INH < Isop-BAH < Isop-PAH.

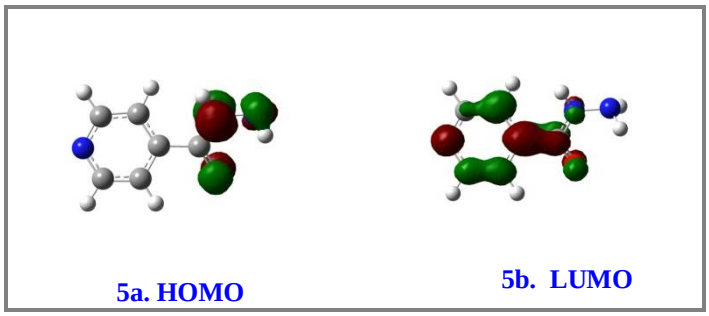


Figure 5. FMOs of INH (ab initio HF/6-311G) (a) HOMO (b) LUMO..

The difference between E_{LUMO} and E_{HOMO}, called E_{gap} is a crucial factor in electronic spectroscopy, exhibits the pattern PAH > INH >BAH. There is a slight increase in E_{gap} for iso-propyl derivatives**.**

Fukui Descriptors: Fukui descriptors [**26**] are calculated as the difference between gross charges of the atoms in the neutral molecule and the corresponding cationic and anionic species. They distinguish electrophilic/ nucleophilic/ radical reaction sites (atoms) in the molecule without knowing the other reactant. These are also called additional indicators to determine relative softness of each atom. In fact for a set of analogous molecules Fukui indices offer a good comparison. Condensed

local softness indices are related to condensed Fukui values. For frontier orbital controlled soft-soft interactions, Fukui values are very large. From the three input vectors containing charges on cation, neutral and anion moieties of the molecule, Fukui chemical reactivity parameters are calculated from optimized geometries of cationic and anion form of all the compounds at DFT(B3LYP) level with 6-311G basis set. The nitrogens of –CONHNH2 fragment are nucleophilic character whereas oxygen is a electrophilic center (Table 5). The valence isomers INH and PAH have similar Fukui chemical reactivity parameters different from BAH.

Table 5. Fuki reactivity parameters for INH

No	Atom	N	E	R
6	N	0.061	0.047	0.054
11	C	-0.043	**0.125**	0.041
12	O	0.020	**0.139**	0.079
13	N	**0.122**	-0.011	0.056
14	H	0.037	0.059	0.048
15	N	**0.154**	0.063	**0.109**
16	H	0.112	0.028	0.070
17	H	0.089	0.043	0.065
N Nucleophillicity E Electrophililcity R Radical				

Physics-based and chemical parameters relevant to drug/biological activity: Macroscopic physico chemical parameters popular during the last fifty years are partition coefficient of the compound between n-octanol and water (log P), Henry's solubility parameter, dielectric constant of the surrounding and/or medium etc. A glance at the values for the hydrazides given in table 6, calculated by summing up the fragment contributions as enunciated by Crippen, Rikker and Mannhold and Viswarnathan [27-29] reveals that log P (representing hydrophobic property which indicates the passage of compound into the cell) follows the order INH > PAH > BAH.

Table 6. Typical physics based and chemical parameters of biological relevance

Molecule	Log P	Henry's Constant	Molar volume # (cm^3 mol^{-1})
INH	-0.60	7.36	109.115
PAH	-0.22	7.36	100.012
BAH	0.21	4.48	104.722
Isop- PAH	0.87	7.36	140.569
Isop-INH	0.64	7.36	141.446
Isop-BAH	1.75	4.48	155.055
#: DFT/B3LYP/6-311G			

The isopropyl group enhances log P value and exhibits the trend **isop-BAH > isop-PAH > isop-INH**. The molecular volume calculated from electron density exhibits the order BAH > INH> PAH for parent compounds as well as isopropyl derivatives.

CONCLUSION

- PAH and INH with hetero cyclic pyridine ring are stable compared to BAH based on total or electronic energy calculated at ab initio and density function theory. Iso- propyl derivatives of the hydrazides are substantially more stable.

- Dipole moment of INH is enhanced by more than 70% on introduction of a σ donor, an iso-propyl group. Among the unsubstituted hydrazides PAH is more polar than INH and BAH based on static permanent dipole moments.

- In iso-propyl INH, HOMO and LUMO spread on either side, which enhances the possibility for orbital-based interactions. However, in the case of INH, LUMO extends over the pyridine ring while HOMO concentrated on the hydrazide fragment. Fukui chemical reactivity parameters indicate nucleophilic character of the nitrogens and electrophilic nature of oxygen of –CONHNH2 fragment.

- ESP on ESP, ESP on TD and atomic/Mulliken charges on the heteroatoms reveals electrophilic nature of the pyridine nitrogen and N15 of hydrazide moiety. On the other hand, N13 has a less chance to involve in charge-based reactions. The difference in energy of LUMO and HOMO and shapes of FMOs are distinct. Iso-propyl group decreases the hardness and IP. These are good probes in monitoring and controlling bio-chemical interactions in vivo.

- The non-linear optical activity inferred from second order hyper polarizability (β) is higher for INH compared to PAH. Linear polarizability (α) increases while β decreases in the case of iso-propyl derivatives. The electrophilic centers of the hydrazides are pyridine nitrogen (N6) and terminal nitrogen (N15) of hydrazide fragment

- The isopropyl derivatives of hydrazides are highly hydrophobic facilitating the passage of molecules through the cell. Nucleophilic pyridine nitrogen and electrophilic oxygen of –CONHNH2 are susceptible for interaction with biomolecules.

- Optimization of NAH, meta isomer, by DFT/ab initio methods even with 6-311G basis set resulted in only a transition state with one imaginary value in the frequency analysis.

- DFT/B3LYP with 6-311G basis set is adequate for geometric optimization and frequency analysis of the hydrazides from the stand point of view of accuracy versus cpu time

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