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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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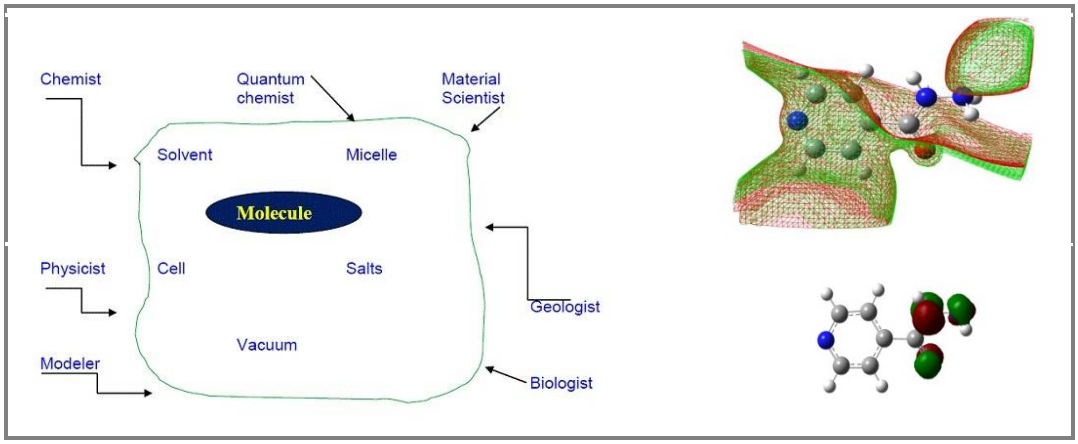
ABSTRACT

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