Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2024, 13 (1): 1-10

(International Peer Reviewed Journal)

Model Chemistries of Hydrazides V. Bio-physico-chemical parameters derived from SEMO Computational Quantum Chemical (CQC-SEMO) studies of mono substituted INH

K. Somasekhara Rao[1], K. Ramadevi[2] and R. Sambasiva Rao[3]*

1. Dept. of Chemistry, Acharya Nagarjuna Univ., Dr. M.R.Appa Rao Campus, Nuzvid-521 201, **INDIA**
2. PG Department of Chemistry, Sir C.R. Reddy College for Women, Eluru-534001, **INDIA**
3. Department of Chemistry, Andhra University, Visakhapatnam 530 003, **INDIA**

Email: sraokaza1947@gmail.com, rsr.chem@gmail.com

Accepted on 10th January, 2024

ABSTRACT

The effect of substituents on the electronic structure and physicochemical/biochemical properties of isonicotinic acid hydrazide (INH), an antitubercular drug is studied in gas phase at SEMO level. The quantum chemical computations are performed using PM3 Hamiltonian with AMPAC 6.7 software package, which accepts the chemical structure of a molecule through Graphics User Interface (Agui). The substituents attached to the pyridine ring of INH investigated are halogens (F, Cl, Br, I), fluoromethane (CH_2F, CHF_2, CF_3), groups like CH_3, NH_2, OMe- and CN-. The stability of INH based on total electronic energy and heat of formation (HoF) in gas phase substantially increases with the halogen atom or increases with the number of F atoms in fluoro methane group. Both electron pushing and pulling groups enhance the static dipole moment and linear polarizability of INH. The electron withdrawing NO_2 in INH results in a maximum dipole moment of 4.4 Debye. The second order non-linear hyperpolarizability (β, γ) is enhanced by two to three fold with iodo substituent rendering it to be a non-linear-optic (NLO) material. The log of octanol partition coefficient reflecting hydrophobicity increases by changing the substituent from F to I or with di- or tri-fluro methane group. 2-Amino INH has greater hydrophilic function compared to even unsubstituted compound. The results of SEMO procedures offer complimentary /supplementary/additional information in probing into contradictory trends in physico-chemical/biological response of hydrazides.

Keywords: Isonicotinic acid hydrazide, SEMO, PM3-Hamiltonian, substituent effect, Polarizability, hydrophobicity, AMPAC-software, NLO-material

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INTRODUCTION

In general, aromatic and aliphatic hydrazides find application in chemical industry besides biological activity [1-4]. Isonicotinic acid hydrazide (INH) is the constituent of isoniazid [4], a popular antitubercular drug with slight carcinogenicity. Probing into antitubercular and carcinogenic mechanisms is vital to prepare guidelines in the design of molecules with desired range of therapeutic activity and free of side effects. Introducing substituents in a compound affect shape and/or energy of frontier molecular orbitals (FMOs), total electron density (TED), electro-static-potential (ESP), atomic net charge, soft-hard character, Fuki's hybrid parameters (nucleophilicity, electrophilicity, radical activity) and molar volume. The consequences have been advantageously exploited in many fields viz. molecular electronic devices, lasers, toxicology, drugs and chemical/biological activities.

Effect of substituents on chemical reactivity and application devices

Historical perceptive: In 1863, it was observed that toxicity of alcohols to mammals increased with decrease in their solubility in water. Later in 1890 this effect was attributed to lipophilicity. Hammett [5, 6] explained the chemical reactivity (ionization, rate of reaction) of meta- and para- substituted aromatic acids in terms of substituent constant (σ). Taft extended this idea to ortho-substituted aromatic and aliphatic analogues. Hansch modelled biological response (ED_{50}, LD_{50}) with hydrophobicity measured as partition coefficient of the compound between n-octanol and water. Second order terms in multi-linear equations accounted for the non-linear trend. Hansch and his group applied the quantitative structure activity relationship (QSAR) model to drugs and agro-chemicals etc. Free and Wilson proposed binary regression model indicating the presence or absence (yes/no or 1/0) of an atom (N, O, S), group (C=O, NH2) or sub-structure (n-membered ring) in a compound. In Hansch like models, this concept was independently proposed as indicator variable. It resulted in increased correlation between X and response (y) and decrease in standard deviation of y.

Mathematical chemistry opened new vistas in understanding structure within the framework of connectivity, geometry and electrostatic descriptors. Wiener index of 1940's still finds use in sorting out similar structures in a large pool of silicon (virtual) library. Although, significant modifications have been proposed over years, electrostatic indices of Kier and Hall and WHIM series of descriptors employ 3D- geometry of a conformer and charges. The number of descriptors grew from a single digit to over 4000 making use of quantum chemical and graph theoretical approaches. The quality of molecular descriptors derived from Quantum and Mathematical chemistry depends on the level of theory employed in geometry optimization. The two popular software packages CODESSA and DRAGON accept geometry from the output of GUASSAN, HYPERCHEM, AMPAC etc.

CQC studies of substituent effects

Conformer preferences: Dapporto *et.al.*, [7] investigated model compounds for low molecular weight scaffolds for which information in crystallographic database is not available. The conformations and energetics of the three 3, 5-trans disubstituted (fluoro and hydroxy) piperidenes are studied by theoretical (global MMX force field and Monte Carlo – metropolis methods) and X-ray procedures. The energetics of experimentally isolated conformers is discussed with the results of ring and/or nitrogen inversion. Freitas [8] computed energy differences between conformers of mono halo cyclohexanes at DFT level of quantum chemistry to probe into conformational equilibria. This study on a series of dihalo substituted cyclohexanes and cyclohexanones revealed orbital interactions between n_{halo} and π^{*}_{co} are important for 2-halocycohexanones while classical steric and electrostatic contributions are essential for 1-3’, 1-4’, disubstituted cyclohexanes.

Charge transfer complexes: Fomine et. al. modeled interaction between substituted biphenyl diacetylenes using B3LYP/6-31G(d) at DFT level. The resulting complexes are inferred to be mainly due to dipole-dipole forces between the substituents in ground state whereas a strong charge transfer occurs from the triple bond of the donar to the nitro group of an acceptor molecule.

Reactivity: Analysis of Fuki function of 27 disbubstituted (X : CH_3, NH_2 and Y : F, CN, CH_3) compounds of benzene at DFT level of theory using B3LYP/6-311G** basis set was employed to predict the reactive site for soft-soft electrophilic interactions. Zheng et al investigated the active sites of substituted (OH, F) of Ru(II) poly pyridyl complexes at DFT level.

Orbital based interactions: Erkov *et al.*, studied the effect of halogen atoms (F, Br, I) on the energetics, charge and FMOs of cornone. The molecule $C_{24}F_{12}$ has D_{6h} planar symmetry; while bromo and iodo substituted molecules ($C_{24}Br_{12}$, $C_{24}I_{12}$) have D_{3d} non-planar symmetries. It is obvious that symmetries are clearer from optimized geometries rather than from chemical structures. All these molecules have no dipole moments and $C_{24}F_{12}$ alone is exothermic. The accumulation of negative charge of fluoride, while positive charge on bromide/iodide indicates electron accepting and slightly electron donating nature respectively. The HOMOs and LUMOs of fluorinated coronene have lower energy levels compared to bromo and iodo analogues.

Biological activity: Honorio et al inferred that substitution at C4 in cannabinoid molecule results in E_{LUMO} to be 0.3ev which renders it to be psychoactive. However, E_{LUMO} is not a distinguishing descriptor for substituents like -OH, -COOH, -F, -Me, -Et, -Acetyl, -COOMe and acetoxyl group.

The excitation energies of mono substituted ($-COCH_3$, $-NO_2$, -CN, $-NH_2$ and -NO) benzenes obtained with an ab initio method (CASPT2-CASSCF) are nearer to the experimental data from ion cyclotron resonance spectroscopy [9] studies. This QC procedure is crucial to obtain reliable energies wherein protonation results in significant reorganization of charge.

Electronic devices: Jansen de [10] reported a set of organic chromophores with beta values (30 to $120*10^{-30}$ esu) for application in non-linear optics with modulated thermal stability. In an elongated molecule, electrons flow easily from one end to the other. It functions as a molecular wire, which is the simplest molecular electronic device. Majumder investigated electronic structure of substituted ($–NH_2$, $-CH_3O$, –CN and $–NO_2$) compounds containing three benzene rings with intervening acetylene moieties. Nitro group resulted in conducting HOMO and LUMO levels which leads to the engineering of tailor made molecular devices with specific conducting characteristics.

In continuation of our computational quantum chemical studies on aliphatic, five membered [1, 2] and aromatic hydrazides [3], the results of effect of substituents on charges, electron densities on atoms, 3D- surface of total electron density and ESP of the whole molecule are presented in this communication.

MATERIALS AND METHODS

Computer system and software: All computations are performed on DELL XPS model lap top with an Intel® core(TM) i7-2670QM CPU @2.20 GHz with 8 logical processors, 8.00 GB RAM. The system has an auxiliary storage capacity of 650GB and with R/W DVD. SEMO computations in gas phase are performed with AMPAC 6.7 software package from Semichem Inc. It has a provision for MNDO, AM1, PM3 type of SEMO procedures in addition to a hybrid SAM-Hamiltonian. The powerful graphics user interface, Agui (**A**mpac**g**raphics **u**ser **i**nterface) enables the user to input the chemical structure directly from fragment library. The software computes Z-matrix or Cartesian coordinates as per the user's choice and the file can be exported in G03 input format. It produces 3D-graphics of TED, ESP, FMOs etc and can be exported in jpeg format. The keywords restrict the computations of the tasks like geometry optimization, frequency calculation, IR spectra, ESP and so on.

MATLAB from Maths works, USA [1] is a powerful numerical high performance computation and visualization environment which adopts white box approach. Executable modules in C and C++ generated from MATLAB run in Windows OS. It consists of an arsenal of numerical, graphical, statistical /mathematical modules in a white box open-ended mode. Third party software for chemometrics and computational tasks are also available and is one of the acceptable software running on PCs, workstation and mainframes. Object oriented (OO) Matlab (Oom) m-functions (oomm read as o! om !m; O! object-mfile-in-MATLAB) developed in this laboratory are used as front end and back end functional modules for AMPAC. The om-function, inp_amp.m, automatically generates input files for AMPAC and a batch file directly implementable with OS itself from a z-matrix file and a set of options. This approach has been in use in this decade in our laboratories [1-3] and relieves the drudgery of preparing ASCII files for different Hamiltonians, convergence in SCF, QC parameters and tasks like frequency analysis, IRC etc. The tabular summary with trends and graphic display from AMPAC output files for a set of runs with different compounds, Hamiltonians and parameters is a useful tool for a detailed study with a large number of compounds.

RESULTS AND DISCUSSION

A study of the effect of substituents in the 2-position with C_2H_5, Cl, NH_2, OH and CN is made on 3-NH_2-INH. It is aimed to observe the changes in electronic properties and also orbital based interactions. The shapes, extent of spread of HOMO, LUMO, their energies and quantitative measure of percentages of occupancy on the neutral molecules in the gas phase is a preamble to probe into the reactivity in presence of a solvent electric/magnetic field and (hypothetical) sparkles. The information derived from it is useful to predict the reactivity with other small molecules, proton, protein or an active site in a macro molecule under biological/ environmental/ exotic terrestrial and intra-stellar conditions.

Computational Methods: The local optimization algorithm used in AMPAC is BFGS modification of DFP algorithm. The stationary point on the energy profile of the molecule is a function of geometric coordinates.

SCF convergence tests: The first convergence test, in the battery of SCF convergences, checks for a difference between electronic energy. It should be less than threshold in the two successive iterations. In spite of the fact it ensures energy to be stationary on potential energy (PE) surface, the density matrix still may be oscillating. Testing the diagonal elements of the density matrix to be below a limiting value circumvents this difficulty. Thus the multiple convergence criteria guarantees self-consistence of the model both in energy and electron density. The default SCF convergence value 1e-08 and it can decrease to a lowest possible value of 1e–11 with the option SCFCRT=0 and frequency calculation is automatically performed.

The second step in the hierarchical convergence test is for calculated value of heat of formation (HoF). Here, the convergence of RMS gradient norm, relative change in geometry and change in HoF are tested for successive iterations. AMPAC has an arsenal of optimization tools with versatility, computational time and utility. But it employs a BFGS modification of DFP procedure as a default. A slow, but reliable geometry is possible by minimizing gradient norm with full Newton algorithm. In 'LTRD' option of AMPAC, full Hessian is calculated at each step.

Frequency Analysis: For all mono-substituted compounds of INH studied, second derivatives of energy with respect to all pairs of atoms (coordinates) in X, Y and Z-axes are calculated. An analysis of force constants and vibrational frequencies revealed that there are no imaginary or negative frequencies (or negative numbers even for Eigen values). The fact that all the first six frequencies are zero, confirms that the optimum geometries arrived correspond to a local minimum energy (stable) structure. The Key word ‘FORCE’ of AMPAC performs frequency analysis in Cartesian coordinates while 'LTRD' carries out optimization of geometry and invokes the module 'FORCE'. The prime objective of the harmonic frequency analysis is detection of a transition state corresponding to on maximum on the potential energy (PE) surface and higher order saddle points with more than one imaginary frequency. The physicochemical parameters computed at any point other than minimum on the PE map are undefined and unreliable/meaningless if calculated. The transition state (TS) structure is confirmed by IRC analysis of reactant and product in both the directions. The simulation of IR spectrum, zero-point energy (ZPE) and thermodynamic parameters without resorting to experimental methods is a beneficial direct consequence of computational chemistry. The nature, number and position of substituents induce different effects on stability, charge, and spectral properties of a compound. It may induce pi-electron delocalization inside a ring [11].

Stability of substituted hydrazides: Increasing the number of fluorine atoms from 1 to 3 increases the stability of mono substituted INH based on the decrease of Hof and TE. The substitutent -OMe increases the stability compared to -OH and -CN from the point of view of TE. Electronic energy follows the same trend as TE, while core-core repulsion energy exhibits a reverse trend as expected. Table 1 incorporates the information bits regarding the effect of substituents of QC derived energies reflecting the stability. The information frames obtained from data massaging (mining) lead to knowledge bits (Table 1b).

Table 1. HoF and energies for mono-substituted INH

Compound	HoF	HoF	ee	cc	te
	kcal	kJ	kJ	eV	eV
-H	17.51		-7607.2916	6009.4143	-1597.8771
-F	-30.8677	-129.1815	-9094.9081	7203.0084	-1891.8998
-Cl	10.7193	44.8602	-8944.6823	7045.3913	-1899.291
-Br	25.1681	105.3285	-8934.0439	6998.1321	-1935.9118
-I	38.7445	162.1455	-8833.0422	6961.996	-1871.0462
-H	17.51		-7607.2916	6009.4143	-1597.8771
-Me	14.8977	62.3469	-9235.2504	7274.8062	-1960.4442
$-CH_2F$	-30.9448	-129.504	-10482.5363	8310.2489	-2172.2874
$-CHF_2$	-80.0934	-335.191	-12253.9042	9656.4818	-2597.4223
$-CF_3$	-138.7555	-580.6916	-14250.1824	11227.2126	-3022.9698
-H	17.51		-7607.2916	6009.4143	-1597.8771
-Me	14.8977	62.3469	-9235.2504	7274.8062	-1960.4442
-OH	-30.8677	-129.1815	-9094.9081	7203.0084	-1891.8998
-OMe	-22.129	-92.6098	-10533.013	8492.1866	-2040.8264
-CN	54.892	229.7229	-9307.8408	7445.7633	-1862.0775
$-NO_2$	11.7884	49.3343	-11723.1022	9393.9461	-2329.1561

Table 1(b). Information bits for the trend in HoF and energies

Property	Increasing order				Increasing order					Increasing order				
HoF	OH	OMe	Me	H	F	Cl	H	Br	I	H	CF3	CHF_2	CH_2F	Me
EE	OMe	Me	OH	H	F	Cl	Br	I	H	CF_3	CHF2	CH_2F	Me	H
CC	H	OH	Me	OMe	H	I	Br	Cl	F	H	Me	CH_2F	CHF_2	**CF_3**
TE	OMe	Me	OH	H	Br	Cl	F	**I**	H	CF_3	CHF2	CH_2F	Me	H

Dipole Moment: It is the first derivative of energy with respect to applied electric field and is a measure of asymmetry in the molecular charge distribution [12]. The total dipole moment increases with the introduction of a An increase from 15% for methyl to approximately 400% for nitro substituted INH. The order is OH <OMe<Me. In the case of halo substituents, bromine atom has highest effect whereas iodine atom has least with the trend Br<Cl<F<I. A comparison of fluromethyl groups with methyl is normal i.e. $CF_3<CHF_2 \cong CH_2F<CH_3$. Increasing the number of fluorine atoms in the substitutent ($-CH_3$) enhance the dipole moment considerably. The substituent 2-CH_2F exerts less effect compared to 2-F due to the intervening –CH_2 group. Cyano or nitro groups substantially increase μ and nitro-INH has highest dipole moment (4.38) in the substituted compounds studied. The information derived from the chemical group wise trend analysis of the magnetic properties is given in the table 2. Introduction of iodo group increased γ about 250%. The substantial increase of α and γ by introduction of iodo group suggests the use of the substituted INH for further investigation for non-linear optical properties (NLO). Keeping this in view, multi-substituted INHs are studied and tetra-iodo compound has γ around 50, the details of which will be published. The total dipole moment of NO_2-INH is highest (4.4) while γ for CN-INH is 6.9.

Table 2. Total dipole moments and polarizabilities for mono-substituted INH

Substituent	Tot dipole moment	Alpha ESU(x10-24)	Beta ESU(x10-30)	Gamma ESU(x10-36)
H	**1.13**	**20.70**	**0.88**	**4.79**
Me	1.3090	24.2969	0.2876	5.0694
OH	1.5800	22.3129	0.2547	4.2479
OMe	1.5390	25.0058	0.6263	5.8701
F	1.5800	22.3129	0.2547	4.2479
Cl	1.6070	24.0065	-0.8177	0.9795
Br	1.8130	24.7868	1.0663	5.7352
I	1.4480	***26.8469***	0.3177	***12.3747***
CH_2F	*2.8400*	*23.2875*	1.1604	5.0743
CHF_2	*2.8400*	*23.2875*	1.1604	5.0743
CF_3	3.5540	23.2568	**1.3493**	4.8434
CN	3.9080	25.6048	1.1732	6.9252
NO_2	**4.3830**	25.1025	-0.4578	5.0239

Table 2 (b). Information bits for the trend in dipole moment and polarizabilities

Property		Increasing order				Increasing order					Increasing order				
Dipole moment	μ	H	Me	OMe	OH	H	I	F	Cl	Br	H	Me	$CH_2F \cong$	CHF_2	CF_3
Polarizability	α	H	OH	Me	OMe	H	F	Cl	Br	**I**	H	CF_3	$CH_2F\cong$	CHF_2	Me
	β	OH	Me	OMe	H	Cl	F	I	H	Br	H	Me	CH_2F	CHF_2	**CF_3**
	γ	OH	H	Me	OMe	Cl	F	H	Br	**I**	Me	H	$CH_2F\cong$	CHF_2	CF_3

Charge on atoms: The trend in atomic charges is related to active site in electrophilic and nucleophilic reaction and charge based interactions between molecules. A complete picture of electronic charge density of the molecule are viewed through NPA and is useful to study the stability of the molecule [12]. Substituents on the phenyl ring influence the charges on atoms, the change being significant on the neighboring atoms and it being diminished with distance. The charges on the atoms farther away are practically unaltered (<1e-4 angstroms) due to polarity interference and law of polarity alteration. The atomic and ESP of pyridine N are markedly affected with the substituent. From a perusal of the charges as well as the differences with those for INH suggest trends in the compounds studied. The atomic charges on nitrogen of pyridine increase from fluorine to iodine. The negative charges increased markedly with OMe, me followed OH. The charges on C of CO, O of CO, N of NH and N of NH_2 are not affected (Table 3).

The electrophilic character of N of Py decreases with the halo groups (Cl, Br, I) and substantially enhances with electron donating groups like -OH or OMe- and σ donors (Me-). The electron withdrawing fluromethyl and cyano groups markedly decrease this nature. The approximate constancy of ESP charges on O of CO, N of NH and N of NH_2 of hydrazide moiety indicate weak charge based interactions with nucleophiles.

FMOs: The shapes of FMOs for F, Cl and Br substituted INH exhibit a trend while, iodo compound gives distinct shapes. The LUMO spreads on N of pyridine (py) and O of CO with 's' shape for all compounds but the extent of coverage is very small. Nitrogen atom of NH has a small 's' shaped MO only for F and Br substituted compounds. Further, the atoms in the ring C1-C2, C4-C5 and C3(py)-C of CO of fragment have 'p' shape in all halo substituted INH, except iodo analogue. For the iodo compound, LUMO spreads with 's' shape on indicated atoms viz. all carbon atoms in the ring. The shapes of FMOs for iodo substituted INH are distinctly different from other halides (F, Cl, Br). But, shapes of MOs on O of CO are ‘s’ shape for F, Cl, Br compounds. The shape for N of NH changes from ‘s’ for F, Cl to ‘p’ for bromo derivative. For N of NH_2, ‘p’ shape for F, Cl, Br, but present on two atoms viz. N of NH and N of NH2. However, for iodide analogue, ‘s’ shape persists on N of Py, C1, C2 and C4 only. For Br-INH four atoms are covered (N of NH, Hof NH, N of NH_2 and H of NH_2 by HOMO with ‘p’ shape. The spreading of HOMO for fluoro analogues of CH3-INH is mostly confined to the hydrazide fragment. In INH and 2-methyl derivative, it is on the heterocyclic ring. HOMO is ‘s’ shape on O of CO, N of NH and N of NH2 for all compounds. Except for CF3, H of NH and H of NH2 are in ‘p’ shape. In CF3-INH, three atoms (N of NH, H of NH and H of NH_2) are covered with p-character. In all the compounds N of py has ‘s’ shape and C (of CO) has ‘p’ shape. With increasing number of F in CH2F to CF3, ‘s’ character increases on ring carbon atoms.

Table 3. Charges for mono-substituted INH

Sub1	**N (Py)**		**C(CO)**		**O(CO)**		**N(NH)**		**N(NH2)**	
	At	**ESP**	**At**	**ESP**	**At**	**ESP**	**At**	**ESP**	**At**	**ESP**
H	-0.059	-0.542	0.2779	0.4526	-0.349	-0.348	-0.077	-0.241	-0.022	-0.516
F	-0.073	-0.544	0.2728	0.5201	-0.343	-0.363	-0.074	-0.278	-0.02	-0.500
Cl	-0.047	-0.539	0.2751	0.4574	-0.346	-0.351	-0.075	-0.273	-0.020	-0.492
Br	-0.008	-0.537	0.2758	0.4662	-0.345	-0.352	-0.076	-0.270	-0.021	-0.493
I	-0.003	0.3817	0.2762	0.3255	-0.346	-0.417	-0.076	-0.238	-0.020	-0.462
Me	-0.125	-0.396	0.305	0.3141	-0.348	-0.306	-0.310	-0.398	-0.192	-0.540
CH_2F	-0.024	-0.490	0.2762	0.4812	-0.351	-0.349	-0.075	-0.277	-0.020	-0.519
CHF_2	0.0044	-0.428	0.2746	0.4755	-0.349	-0.344	-0.074	-0.278	-0.019	-0.509
CF_3	0.0018	-0.453	0.2724	0.5394	-0.340	-0.355	-0.073	-0.288	-0.018	0.4965
Me	-0.125	-0.396	0.305	0.3141	-0.348	-0.306	-0.310	-0.398	-0.192	-0.540
OH	-0.157	-0.586	0.2746	0.5843	-0.075	-0.380	-0.075	-0.293	-0.022	-0.498
Ome	-0.080	-0.554	0.2749	0.3998	-0.354	-0.331	-0.075	-0.267	-0.021	-0.511
CN	-0.024	-0.495	0.2727	0.4809	-0.343	-0.354	-0.073	-0.268	-0.018	-0.499
NO_2	0.0032	-0.37	0.27	0.4208	-0.339	0.853	-0.068	-0.266	-0.020	-0.479

HOMO is spread on C1-C2, C3-C4 and N of CH-C of CN with ’p’ shape for CN-INH. For 2-NO2, ‘s’ shape is observed with O of CO, N of NH and N of NH_2. But an extended ‘p’ character is observed with H of NH-N, NH_2-H of NH_2. LUMO for CN substituted INH ring atoms C1, C5, C4, N of py and N of CN and O (of CO) are covered with ‘s’ character. But, C3-C of CO exhibits ‘p’ character. A very small patch of ‘s’ character is observed on N of NH. For NO2-INH, LUMO is of ‘s’ character on N of py, C1, C3, C4 with a small magnitude on O of CO and C of CO. With substitution of second position in INH with -OH and –OMe, the resulting FMOs are similar. The oxygen of the substituent has ‘s’ shape. The atoms in the ring C1-C2-N of py and C4-C5 are covered with ‘p’ shape. By replacing H by methyl in OH, HOMO slightly extends to C3 atom. For LUMO, N of py and O of CO have ‘s’ shape while C4-C5, C1-C2 and C3-C (of CO) exhibit ‘p’ shape. A distinct feature however is that of N of NH2 in 2-OH-INH is covered by LUMO while LUMO is present on N of NH in OMe-INH. FMO energies of halogen-substituted compounds depend primarily on inductive rather than mesomeric effect.

TED of Mono Substituted INH: The limit of electron density of the optimized structure of the substituted hydrazides and their shapes are analyzed from 2D total density (TED) contours mapped on 3D surfaces. There is a vivid change in the shape of unsubstituted hydrazide with a rod like protrusion with the introduction of –OMe, –CN, –Br and –I substituents adjacent to pyridine nitrogen. A neutral electron density zone appears as a patch on H9 atom (attached to C5), C2 and also on Nl4–H16 (NH of terminal NH_2) with all substituents. The neutral zone in the case of chloro-substituted hydrazides extends as a long patch along Cl l7– Cl–N6.

The symmetric shape and TED on TED of benzene is flattened in pyridine with a result of pushing along the C3-H7 bond. The hydrazide group further distorts, resulting in an elliptical contour. The substituents of electron donating/withdrawing and those with mesomeric and resonance effects altogether alters the shapes, reactivity and steric hindrance of the molecules. Near one fluorine atom (Fl8) of fluoro methane substituted (CF_3, CF_2H, CH_2F) compounds, a neutral zone appears in 3D surface of the TED diagram. There is a remarkable change in shape with increase in size of protrusion along C-X with the change in halo substituents (F<Cl<Br<I).

Bio-physico-chemical parameters derived from computational quantum chemical output: The physicochemical response of compounds, electronic/mechanical properties of materials and biological/drug likeliness characteristics of toxic/pharmaceutical preparations are related to the macroscopic and microscopic parameters [**13**]. The partition coefficient of a compound between n-octanol and water (LogP), Henry's solubility parameter, dielectric constant and molar refractivity/volume are the typical bulk properties employed during the last 50 years. Quantum chemical descriptors (Mullikan/chelpG,charge, ESP), derived reactivity parameters (Fuki, global/local softness, hardness) and topological/electrostatic/hybrid molecular descriptors are the candidates now available. Around 1500 to 4200 descriptors are calculable from DRAGON CODESSA etc packages.

Table 4. log P, MR and Henry's constant for mono-substituted INH

Subst	**log P**	**MR**	**Henry Constant**
H	-0.95	**37.04**	**4.06**
F	-0.02	38.52	7.29
Cl	0.26	42.81	7.49
Br	0.59	45.93	7.76
I	0.59	**50.43**	7.99
CH_2F	-0.09	42.25	7.68
CHF_2	0.05	42.21	7.68
CF_3	**0.7**	42.93	7.68
OH	-0.32	39.09	8.11
ome	-0.05	44.52	7.86
CN	-0.19	42.52	**9.37**
NO_2	-0.5	NaN	7.67
Me	0.06	42.32	7.68
NH_2	**-1.32**	39.31	**4.06**

LogP calculated by an additive model of fragment contribution procedure shows a wide range (-1.32 to 0.7) of hydrophilic to hydrophobic character with electron donating and withdrawing substituents (Table 4). The hydrophobic character increases in INH with the substitution of H by F to I. MR as well as Henry's constant also increase and the trend is H< F< Cl< Br< I. Increase in number of atoms of fluoro methyl substituent markedly changes log P while MR and Henry's constant are little affected. Henry's constant calculated as the ratio of vapor pressure to solubility in water has a maximum for CN-INH while a minimum value for NH_2-INH. Electron donating groups like -OH, -NH_2 and -OMe result in negative values of logP. Henry's constant is highest for 2-CN INH while it is minimum for 2-NH_2 INH.

Essentials

- The stability of halo substituted INH increases from F to Br inferred from HoF as well as TED. Increase in number of fluorine atoms in fluoromethane also increases the stability compared to the unsubstitued methyl analogue.

- The dipole moment of 2-nitro-INH has highest value (4.4) amongst the substituted compounds of INH studied rendering it to be more soluble in polar solvents. There is an increase in μfrom F to Br substituent with a trend reversal at Iodine analogue. The second order hyper polarizability (γ) increases by 2 to 3-fold by introducing iodo group in INH, where as for the tetra iodo compound the magnitude of γ is more than tenfold. The effect of organic polar substituents deserves attention to probe into non-linear-optical (NLO) properties.

- 2-amino-INH has lowest logP (-1.3) while 2-triflouromethane INH has the maximum (0.7) value. Henry's constant, a function of reciprocal of water solubility shows a similar trend for halo compounds.

ACKNOWLEDGMENT

We thank DRDE, Gwalior for financial support in procuring AMPAC 6.7 package.

Supplementary information (SI): Graphics output and input/output files in this study are available from authors.

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