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Computational Studies of the Role of Substituents on the Reactivity and Biological Activities of Naphthoic Acid

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Abstract: Substituents play a major role in influencing the reactivity and biological activity of aromatic compounds. Substituents affect the conductivity of molecular electronic and photoresponsive switches, light harvesting dye-sensitized solar cells and organic electroluminescent devices. A number of quantum mechanical methods corresponding to stabilization energy, charge of substituent active region, energy dispersive analysis, and molecular electrostatic potential help in the description of substituent effect in aromatic systems. In the present work we carried out computational studies for the estimation of chemical and structural properties of a chemical library of nine *ortho* substituted naphthoic acids. The chemical reactivity of the selected substituted naphthoic acids was assessed from a number of physicochemical properties such as total energy, HOMO-LUMO gap, chemical hardness, binding energy, ionization potential, electron affinity, electronegativity, electrochemical potential, global softness, electrophilicity and dipole moment. The effect of the electron-donor groups on conjugation of *ortho* substituted naphthoic acid was investigated by correlating the calculated rotational barriers of transition state of *cis* and *trans ortho*-substituted naphthoic acids to observe change in single bond length, double bond length, bond angle, dihedral angle, and rotational frequency of carboxylic group of substituted napthoic acids. The rotational barrier correlated with the geometric, atomic, molecular, and spectroscopic parameters. Moreover, quantitative structure–activity relationship (QSAR) analyses was performed and the obtained structural properties were linked with biological activities.

Keywords: *Ortho*-substituted Naphthoic Acids, Rotational Barrier, Substituent Effect, Quantitative Structure–Activity Relationship

1. Introduction

The study of naphthoic acid-based xenobiotics is necessary for understanding their transformative pathways and exploring their pharmaceutical antagonist properties [1]. Literature survey reveals that extensive research has been carried out on naphthoic acid to improve its application as an intermediate for the synthesis of pharmaceuticals, photochemicals, plant growth hormones, dyes and other useful organic compounds [2, 3]. There is growing evidence that the reactivity of a substituted molecule can be enhanced for a specific application by structural modification. For instance the triplet energy state of naphthoic acid functionalized with polymer can be tuned to match the energy level of a transition metal to enhance fluorescence emission of the complex formed when electron donating groups are substituted on the aryl conjugated system [4]. A report on naphthoic acid derivatives suggests that COOH group, methyl and halogen substituents are required to be in the right configuration for exerting a biological action [5]. Another

study reveals that the optimized activity and binding of the substrate depend on the COOH group, the ring system and the substituents in naphthoic acid derivatives [6]. Similarly the pH of naphthoic acid, its hydrophilicity and hydrophobicity can be changed by changing the substituent. Hence, probing conformational changes induced by substituents on different rings systems with their relation to substrate is mandatory for tuning the reactivity of active sites of substituted aromatic compounds.

Investigations carried out through computational methods are less time and efforts consuming and also save expenditures consumed on purchasing expensive chemicals and sophisticated instruments. Computational study of the steric effects of different substituents at the neighboring position and structural modification of a molecule to fit into active site for effective interaction by virtue of its position and bulkiness are very important for understanding quantitative structure–activity relationships (QSAR). The influence of substituents in altering properties of naphthoic acid can be correlated with the electronic state of the ring at definite positions. Similarly stability of naphthoic acid derivatives depends on favorable configuration of the acid group in relation to substituents. The presence of substituents cause to modify the electronic structure, physicochemical features such as hardness and global softness, electrophilicity indexes, atomic charges, dipole moments and electrostatic potential, and chemical reactivity of the molecule which are critical for understanding and predicting the activity and stability of the compound [7]. Moreover, molecular structure and properties depend on the nature of the ring substituents [8]. Therefore, the present work is an attempt to assess the role of all these factors on the structure and reactivity of naphthoic acid.

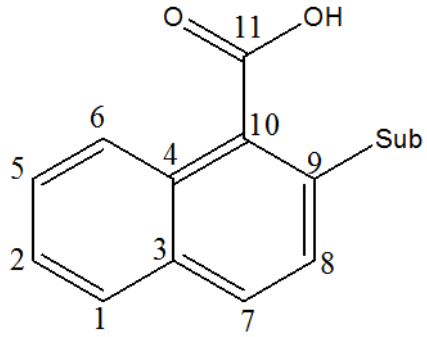

Figure 1. *Molecular structures of ortho substituted naphthoic acid.*

Herein we describe the variation in properties of naphthoic acid by modifying nine substituents at the *ortho* position. The ability of substituent groups to conjugate with naphthalene and ability of donor groups i.e. $-OCH_3$, $-OC_2H_5$, -OH, $-NH_2$, $-CH_3$, $-C_2H_5$, $-SO_3H$, -F and -Cl to conjugate with the acceptor -COOH has been examined and described in the present work. For a better understanding of the quantitative predictions of the substituent effect on naphthoic acid (COOH-$C_{10}H_6$-X), we divided the molecular structure into three parts: naphthalene, the substituents, and the carboxylic acid functional group of naphthoic acid (see Figure 1). Structure and properties of a molecule are deducted from solution of Schrodinger wave equation of its electrons, and hence, molecular descriptors can be linked to properties [9-12]. With this consideration we studied the relationship of the descriptors with the structures, and biological activities of naphthoic acid derivatives.

2. Computational Method

Chemical and structural properties of nine *ortho* substituted ($-OCH_3$, $-OC_2H_5$, $-OH$, $-NH_2$, $-CH_3$, $-C_2H_5$, $-SO_3H$, $-F$ and $-Cl$) naphthoic acids were studied theoretically using DFT method with B3LYP functional and 6-31G basis sets. The Gauss view 05 computational package was employed to perform geometrical optimization and energy calculations for all the selected naphthoic acid derivatives. Quantitative structure–activity relationships (QSAR) were calculated using HyperChem 8.0 Software. To quantify the effect of substituents the geometries of naphthoic acid derivatives were optimized using semi-empirical calculations by employing molecular modeling program Hyperchem 8.0. The structure of naphthoic acid was taken from invoke database by single point calculations. The energy and the gradient for the assumed molecular geometry were set and then geometrical optimization was done to find the most stable conformation. DFT methods including Becke's three parameters exchange functional, the lee-Yang-Parr correlation functional (B3LYP) and 631+G basis set were employed using Gaussian 09 program.

3. Results and Discussion

3.1. Substituent Effect on Geometrical, Molecular, and Spectroscopic Properties of Ortho Substituted Naphthoic Acids

For predicting the reactivity of organic molecules differing only in the substituent, it is important to investigate the substituent effect. In this regard computational studies were carried out to analyze how substituents affect the properties of naphthoic acid. The pictorial representation of charge distribution, HOMO and LUMO of o-Amino naphthoic acid are represented in Figure 2 and Figure 3. The values of frontier molecular orbital energies (HOMO and LUMO), energy band gap (E_{gap}), electron affinity (EA), ionization energy (IE), dipole moment (μ), hardness (η), softness (σ), electronegativity (χ), electrophilicity index (ω), charge distribution, bond angles (θ) and bond lengths (Å) of nine *ortho* substituted naphthoic acids were calculated as listed in Tables 1 - 3. An observation of the tabulated values reveals that the reactivity of naphthoic acid is enhanced after substitution of electron-donating groups at the *ortho* position. These donor groups shift electronic density towards the ring by conjugation leading to activation of the ring as expected.

Table 1. *Theoretical values of energy, HOMO, LUMO, Dipole moments, charge and bond lengths of ortho-naphthoic acids.*

Compounds	Energy	HOMO	LUMO	Dipole Moment	Charge		
	Kcal/mol	Kcal/mol	Kcal/mol	Debye	O12	C11/C10	Cl/O/N/S/C/F
Naphthoic acid	−3.60E+05	−1.46E+02	−4.8E+01	5.2561	−0.398	0.055 0.472	0
o-Hydroxy naphthoic acid	−4.08E+05	−1.51E+02	−4.20E+01	6.738	−0.419	0.503 0.022	−0.643
o-Methoxy naphthoic acid	−4.32E+05	−1.49E+02	−4.14E+01	6.869	−0.420	0.502 0.00	−0.573
o-Ethoxy naphthoic acid	−4.57E+05	−1.46E+02	−5.71E+01	7.401	−0.418	0.505 0.007	−0.558
o-Amino naphthoic acid	−3.95E+05	−1.35E+02	−3.83E+01	5.779	−0.395	0.433 0.007	−0.823
o-Methyl naphthoic acid	−3.83E+05	−1.24E+02	−7.59E+01	9.171	−0.443	0.483 0.058	−0.505
o-Sulpho methyl naphthoic acid	−6.35E+05	−1.48E+02	−4.33E+01	6.916	−0.419	0.481 0.072	−0.382
o-Chloro naphthoic acid	−6.49E+05	−1.49E+02	−3.89E+01	3.707	−0.347	0.346 0.114	−0.139
o-Fluoro naphthoic acid	−4.20E+05	−1.72E+02	−11.4E+01	4.895	−0.382	0.500 -0.055	−0.241
o-Ethyl naphthoic acid	−4.10E+05	−1.39E+02	−3.39E+01	1.267	−0.392	0.362 0.029	−0.280

Table 1. *Continued.*

Compounds	Bond Length (Å)		Bond Length (Å)	
	C11-C10	C11-O12	C-Cl/O/N/S/C/F	C11-O13
Naphthoic acid	1.499	1.233	1.085	1.389
o-Hydroxy naphthoic acid	1.540	1.258	1.430	1.430
o-Methoxy naphthoic acid	1.540	1.258	1.430	1.430
o-Ethoxy naphthoic acid	1.540	1.258	1.430	1.430
o-Amino naphthoic acid	1.487	1.234	1.397	1.399
o-Methyl naphthoic acid	1.419	1.305	1.506	1.312
o-Sulpho methyl naphthoic acid	1.540	1.258	1.780	1.430
o-Chloro naphthoic acid	1.359	1.199	1.813	1.359
o-Fluoro naphthoic acid	1.540	1.258	1.350	1.430
o-Ethyl naphthoic acid	1.485	1.207	1.534	1.360

Table 2. *Theoretical values of bond angles, HOMO-LUMO gap, ionization energy, electron affinity, electronegativity, electrochemical potential, hardness, softness and electrophilicity of ortho-naphthoic acid structures.*

Compounds	Bond Angle (θ)	Bond Angle (θ)	Bond Angle (θ)	HOMO-LUMO Energy Gap	I.E	E.A
	C10-C11=O12	C10-C11-O13	C11-O13-H14	Kcal/mol	Kcal/mol	Kcal/mol
Naphthoic acid	125.388	118.399	115.342	9.80E+01	1.46E+02	4.8E+01
o-Hydroxy naphthoic acid	120	120	109.471	1.09E+02	1.51E+02	4.20E+01
o-methoxy naphthoic acid	120	120	109.471	1.08E+02	1.49E+02	4.14E+01
o-Ethoxy naphthoic acid	120	120	109.471	8.91E+01	1.46E+02	5.71E+01
o-Amino naphthoic acid	126.381	116.385	112.622	9.66E+01	1.35E+02	3.83E+01
o-methyl naphthoic acid	126.89	113.811	108.660	9.98E+01	1.39E+02	3.89E+01
o-Sulpho methyl naphthoic acid	120	120	109.471	1.05E+02	1.48E+02	4.33E+01
o-Chloro naphthoic acid	126.422	112.292	111.138	1.10E+02	1.49E+02	3.89E+01
o-Fluoro naphthoic acid	120	120	109.471	5.84E+01	1.72E+02	11.4E+01
o-Ethyl naphthoic acid	126.129	114.471	110.501	1.05E+02	1.39E+02	3.39E+01

Table 2. *Continued.*

Compounds	Electronegativity χ = I.E+E.A/2	Electrochemical Potential (μ) $\mu = -\chi$	Hardness (η) η = I.E-E.A/2	Softness (σ) $\sigma = 1/\eta$	Electrophilicity Index $\omega = \mu^2/2\eta$
	Kcal/mol	Kcal/mol	Kcal/mol	Kcal/mol	Kcal/mol
Naphthoic acid	9.70E+01	−9.70E+01	4.90E+01	2.04E-02	9.60E+01
o-Hydroxy naphthoic acid	9.66E+01	−9.66E+01	5.46E+01	1.83E-02	8.53E+01
o-methoxy naphthoic acid	9.54E+01	−9.54E+01	5.40E+01	1.85E-02	8.41E+01
o-Ethoxy naphthoic acid	1.02E+02	−1.02E+02	4.46E+01	2.24E-02	8.91E+01
o-Amino naphthoic acid	8.66E+01	−8.66E+01	4.83E+01	2.07E-02	9.66E+01
o-methyl naphthoic acid	8.91E+01	−8.91E+01	5.00E+01	2.00E-02	7.97E+01
o-Sulpho methyl naphthoic acid	9.60E+01	−9.60E+01	5.24E+01	1.91E-02	8.66E+01
o-Chloro naphthoic acid	9.35E+01	−9.35E+01	5.49E+01	1.82E-02	8.16E+01

Compounds	Electronegativity χ = I.E+E.A/2	Electrochemical Potential (μ) μ = -χ	Hardness (η) η = I.E-E.A/2	Softness (σ) σ =1/η	Electrophilicity Index ω = $\mu^2/2\eta$
	Kcal/mol	Kcal/mol	Kcal/mol	Kcal/mol	Kcal/mol
o-Fluoro naphthoic acid	1.43E+02	−1.43E+02	2.93E+01	3.41E-02	3.49E+02
o-Ethyl naphthoic acid	8.66E+01	−8.66E+01	5.27E+01	1.90E-02	7.09E+01

Table 3. *Theoretical calculation of parameters for Transition states of different ortho-naphthoic acid structures using DFT method and 631+-G basis set with Gaussian software.*

Compounds	Dihederal angle θ	Energy Kcal/mol	Bond Angle (θ) C10-C11=O12	Bond Angle (θ) C10-C11-O13	Bond Angle (θ) C11-O13-H14
Naphthoic acid	0	−3.60E+05	125.388	118.399	115.342
o-Hydroxy naphthoic acid	84.097	−4.08E+05	125.456	114.946	112.019
o-Methoxy naphthoic acid	84.390	−4.32E+05	125.588	114.911	111.909
o-Ethoxy naphthoic acid	83.922	−4.57E+05	125.577	114.939	111.838
o-Amino naphthoic acid	147.787	−3.95E+05	126.381	116.385	112.623
o-Methyl naphthoic acid	88.029	−3.85E+05	126.427	112.114	109.865
o-Sulpho methyl naphthoic acid	87.270	−6.35E+05	125.417	114.8941	112.219
o-Chloro naphthoic acid	86.505	−6.49E+05	126.249	115.411	108.301
o-Floro naphthoic acid	88.595	−4.20E+05	124.173	115.223	113.284
o-Ethyl naphthoic acid	88.361	−4.10E+05	126.458	112.141	109.853

Table 3. *Continued.*

Compounds	Charge			Bond Length (Å)		Bond Length (Å)	
	O13	C11/C10	Cl/O/N/S/C/F	C11-C10	C11-O12	C-Cl/O/N/S/C/F	C11-O13
Naphthoic acid	-0.398	0.055 0.472	0	1.499	1.233	1.085	1.389
o-Hydroxy naphthoic acid	-0.362	0.474 −0.088	−0.611	1.503	1.224	1.389	1.388
o-Methoxy naphthoic acid	-0.365	0.474 −0.116	−0.557	1.503	1.224	1.388	1.389
o-Ethoxy naphthoic acid	-0.418	0.505 0.007	−0.558	1.503	1.224	1.387	1.388
o-Amino naphthoic acid	-0.395	0.433 0.007	−0.823	1.486	1.232	1.397	1.399
o-Methyl naphthoic acid	-0.391	0.362 0.047	−0.480	1.493	1.234	1.513	1.382
o-Sulpho methyl naphthoic acid	-0.365	0.441 −0.064	0.326	1.505	1.225	1.850	1.387
o-Chloro naphthoic acid	-0.427	0.437 0.098	0.144	1.512	1.221	1.807	1.378
o-Floro naphthoic acid	-0.341	0.485 −0.078	−0.285	1.511	1.221	1.379	1.378
o-Ethyl naphthoic acid	-0.388	0.334 0.010	−0.328	1.494	1.234	1.525	1.382

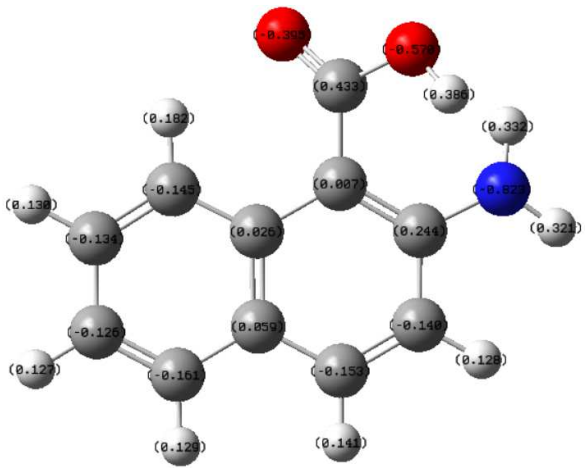

Figure 2. *Charge distribution of o-Amino naphthoic acid.*

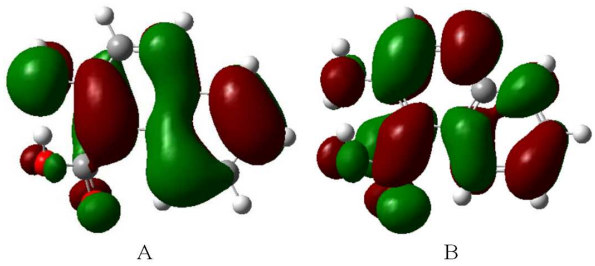

Figure 3. *Pictorial representation of (A) HOMO and (B) LUMO Molecular orbitals for o-amino naphthoic aci.*

The presence of substituents with the maximum number of lone pair of electrons, results in enhanced electron-donating ability to the ring leading to enhancement in conjugation as verified from the decrease in length of C10-C11 single bond, increase in the length of C11=O12 double bond character, decrease in bond angle of C10-C11=O12, and shift of the natural charge of C11 to less positive and O13 to more

negative values. An examination of the tables further reveals the influence of substituents on bond lengths (C11-C10-C11-O12, C-Cl/O/N/S/C/F and C11-O13-H14) and bond angles (C10-C11=O12, C10-C11-O13 and C11-O13-H14) of *ortho* substituted naphthoic acids. With the increase in the strength of electron donating group bond angle decreases (because of accumulation of electrons) and bond length of C10-C11 decreases owing to increase in π character while bond length of C11=O12 increases due to reduction in π character. As expected, bond strength of C10-C11 increases as due to shortening of bond length, while the strength of C11=O12 double bond reduces as the length of C=O bond becomes larger. Bond angle is affected by the presence of lone pair of electrons at the central atom (lone pair repulsion).

A decrease in the electronegativity of the central atom results in lowering of the bond angle. The electronegativity value of F is greater than O, N and C, hence, with the presence of F as a substituent, the bond angle reduces to 120˚ because of lone pairs availability. In case of ethyl and methyl groups as substituents, the bond angle increases due to less electron donating ability to the ring. Bond length depends inversely on bond strength and bond dissociation energy, hence, shorter bond length results in a stronger bond as expected.

Dipole moment is the index of net polarity of a molecule. Polar molecules exhibit a large difference in electrical charges due to significant difference in electronegativity of bonded atoms. Apart from electronegativity difference geometrical configuration of overall molecule also matters in its net dipole moment. The presence of electron donating OH, OCH_3, and OCH_2CH_3 groups at the *ortho* position of naphthoic acid leads to increase in the magnitude of charges on C11 (0.503), C10 (0.022), and O (0.419). More positive charge on carbon and more negative charge on oxygen leads to more separation of ends of dipole and this character is maximum in these groups (OH, OCH_3, and OCH_2CH_3) as compared to other groups studied in the present work.

DFT was used to determine HOMO, LUMO, I.E, E.A, E.N, molecular softness and hardness, electrochemical potential and electrophilicity index according to reported literature [13-16]. The HOMO and LUMO of a chemical species are used to assess the reactivity. A molecule with higher value of HOMO tends to donate electrons to the accepter molecule of lower energy. LUMO is responsible for accepting electrons. Increased values of HOMO results in decreased LUMO with enhanced binding ability of molecules. The gap (ΔE) between HOMO and LUMO is another index of reactivity of molecules. A lower ΔE of molecules points to increased reactivity and decreased stability of a molecule. In case of fluoro naphthoic acid, the HOMO and LUMO energy gap with a value of 58.4 Kcal/mol is less as compared to other groups which can be attributed to its higher reactivity and less stability than other substituted naphthoic acids. The larger value of ΔE is linked to the hardness of the molecule with enhanced stability and decreased reactivity as reported in literature [17, 18]. Results of our computational calculations show that fluoro-naphthoic acid is more softer and consequently less harder than other studied substituted naphthoic acids of the present work. Its hardness and softness values are 29.3 Kcal/mol and 13.39E+03 Kcal/mol. Smaller HOMO-LUMO energy gap suggests softness, less stability or more reactivity of a molecule. The larger HOMO-LUMO gap of hydroxy and methoxy-naphthoic acids (109 Kcal/mol and 108 Kcal/mol) are indicative of their comparatively larger hardness and less reactivity. The chemical hardness values of hydroxy-naphthoic acid and methoxy-naphthoic acid (54.6 Kcal/mol and 54.0 Kcal/mol) are higher than other substituted naphthoic acids investigated in the present work.

Parr *et al*., introduced electrophilicity index ($\omega = \mu^2/2\eta$) as a reactivity descriptor of the electrophilic nature of a molecule [19]. The electrophilicity index is a measure of energy lowering owing to electronic flow between the donor and the accepter. It measures the capacity of a species to accept electrons. Table 2 reveals that the electrophilicity index of fluoro naphthoic acid is the maximum (3.5E+02 Kcal/mol) among the studied naphthoic acid derivatives, so the capacity of accepting electron from the ring is more for fluorine in comparison to other substituents. Stabilization in energy can be measured after a system accepts additional amount of electronic charge from the environment [20]. More stable molecule corresponds to lesser electrophilicity. Hence, fluoro naphthoic acid is the most reactive among the studied compounds.

The energy gap between HOMO and LUMO is responsible to assess chemical reactivity, kinetic stability, polarizability, and chemical softness-hardness of a compound [21-23]. According to Koopman's theorem [23] the energy of HOMO and LUMO has the following relationship with IE and EA:

$$\text{Ionization energy (I.E)} = -E_{HOMO}$$

$$\text{Electron affinity (E.A)} = -E_{LUMO}$$

$$\text{Electro negativity } (\chi) = (\text{I.E} + \text{E.A})/2$$

$$\text{Electronic chemical potential } (\mu) = -\chi$$

$$\text{Chemical hardness } (\eta) = (\text{I.E} - \text{E.A})/2$$

$$\text{Chemical softness } (\sigma) = 1/\eta$$

$$\text{Electrophilicity index } (\omega) = \mu^2 / 2\eta$$

3.2. QSAR Properties

Naphthoic acid is a fungal xenobiotic metabolite. Substitution of various functional groups at the *ortho* position of naphthoic acid greatly affects its physicochemical properties. To quantify the effect of substituents the geometries of naphthoic acid derivatives were optimized. The energy and the gradient for the assumed molecular geometry were set and then geometrical optimization was done to find the most stable conformation. The QSAR proprieties including molecular volume, molecular area, hydration energy, polarizability (Pol), molar refractivity, octanol-water partition coefficient (log P), and molar mass [24-29] were theoretically calculated as listed in Table 4.

Table 4. *Quantitative structure activity relationship analyses of ortho substituted naphthoic acids.*

Parameters	Naphthoic acid	o-Hydroxy naphthoic acid	o-Methoxy naphthoic acid	o-Ethoxy naphthoic acid	o-Amino naphthoic acid
Surface area (approx.) (Å^2)	265.22	263.32	308.18	332.86	303.12
Surface area (Grid) (Å^2)	333.79	342.06	372.94	400.34	372.36
Volume (Å^3)	521.5	543.17	597.69	651.77	600.06
Hydration energy (kcal/mol)	−7.64	−9.92	−6.24	−4.48	−7.11
Refractivity (Å^3)	55.15	56.76	61.53	66.27	63.48
Polarizability (Å^3)	19.17	19.81	21.65	23.48	22.36
Log P	1.06	0.03	0.06	3.21	−0.25
Mass (amu)	172.18	188.18	202.21	216.24	201.22

Table 4. *Continued.*

Parameters	o-Methyl naphthoic acid	o-Sulpho methyl naphthoic acid	o-Chloro naphthoic acid	o-Floro naphthoic acid	o-Ethyl naphthoic acid
Surface area (approx.) (Å^2)	284.61	338.46	285.3	265.68	311.80
Surface area (Grid) (Å^2)	351.14	407.44	351	337.33	385.46
Volume (Å^3)	560.9	658.30	556.28	527.38	622.95
Hydration energy (kcal/mol)	−4.66	−6.73	−5.47	−6.23	−5.84
Refractivity (Å^3)	59.43	68.82	59.87	55.28	64.04
Polarizability (Å^3)	21.01	22.15	21.10	19.08	22.84
Log P	1.21	−0.54	0.83	0.46	1.61
Mass (amu)	186.21	250.27	206.63	190.17	200.24

Polarizability (α) shows the virtual propensity of electric charge distribution. It is the ratio ($\alpha = P/E$) of the induced dipole moment (P) of an atom to the electric field strength (E) that produces this dipole moment. Polarizability demonstrates competence of electronic cloud distortion of a molecule by external field and plays an important role in modeling several properties and biological activities of molecules. It is a descriptor of molecular solubility and the attractive part of the Van der Waals interaction is a good measure of the polarizability of molecules. Among the selected compounds ethoxy-naphthoic acid displayed the highest polarizability. This property can also be linked with molar refractivity as governed by the Snell's Law. Molar refractivity (MR) reveals the electronic shells arrangement of atoms in molecules and gives information about the electronic polarization of atoms. The MR of solutions shows the change in various properties of ions because of deformation or polarization of electron shells by the electric field of nearby ions. MR is a standard measure of the steric factor. It is normally assigned as a measure of the volume occupied by an individual atom or a group of atoms. Polarizability and refractivity increase with the increase in molar weight and volume according to Lorentz-Lorenz's formula. The highest values of volume and molar mass of *o*-sulpho methyl naphthoic acid suggest its maximum polarizability and refractivity. On the other hand, *o*-hydroxy o-methyl and o-floro naphthoic acids have lower molar refractivity and polarizability values as evidenced from their lower volume and molar mass values.

Bond cleavage energetics are useful for the estimation of physico-chemical properties. In this regard hydration energy of the selected naphthoic acids was evaluated. Hydration of solutes involves three enthalpy changing steps. In the first step which is endothermic, water molecules overcome the attractive forces of solute molecules and cause breakdown of its chemical bonds. In the second step which is also endothermic, water molecules create vacancies for accommodating solute particles. In the third step (exothermic) new bonds are formed between solute and water molecules. The sum of enthalpy changes during all these three solution forming steps is the hydration energy [30, 31] which decides the hydrophilicity or hydrophobicity of solutes. The presence of hydrophilic functionalities in the molecules enhances the hydration energy, while hydrophobic functionalities decreases the hydration energy of molecules [32]. Among the selected naphthoic acids those possessing strongly polar substituents such as hydroxy, amino and sulpho methyl at the ortho position of naphthoic acid have the higher hydration energy. While methyl, ethyl and ethoxy substituted naphthoic acids have lower hydration energy as expected.

The hydrophobic character of molecules is an important indicator for estimating the ability of a molecule to pass through cell membrane. It is also useful for getting estimate of the antifungal activity and interaction of a molecule to a receptor. The hydrophobicity can be measured by testing the relative distribution of molecules in octanol/water mixture [33]. Greater hydrophobicity of molecules leads to their solubility in octanol layer while hydrophilic molecules get solubilized in water layer of octanol/water mixture. This relative distribution of molecules is characterized as partition coefficient (P).

P = Concentration of molecules in octanol/Concentration of molecules in water

The value of P was found to change with the change of substituents on naphthoic acid. Log P (octanol-water partition coefficient) is a hydrophobicity indicator that depends strongly on the solubility, distribution, metabolism, absorption, and excretion properties of molecules in addition to their

pharmacological activity. For effective bioavailability of drug molecules, the log P values must fall in the range ($0 < \log P < 4$). Higher log P value suggests lower solubility of drugs and their easy penetration through the lipid membrane. Thus methyl, ethyl and ethoxy substituted naphthoic acids have more lipid transport propensity owing to their higher hydrophobic character as validated from their higher log P values. This result is also consistent with the hydration energy trend of the selected naphthoic acids. Conversely lower log P values indicate more solubility and difficult penetration of drug molecules through the lipid membrane. Among the selected compounds o- hydroxy, methoxy, amino and sulpho methyl naphthoic acids have lower log P values, thus they are more water soluble as authenticated from their polar nature and hydration energy values.

Antioxidants play a crucial role in protection against oxidative stress. Epidemiological studies reveal that antioxidants can impede cancer growth. Antioxidants provide electrons to free radicals that cause oxidation of biomolecules. In this regard antioxidants prevent biomolecules by sacrificial oxidation. Naphthoic acid derivatives have drawn attention as promising antioxidants owing to their low cytotoxicity and stability in various pH media [34]. Metabolites of hydroxy naphthoic acid were found to be stable not only in acidic pH of 3.0, but also in media of neutral pH [35]. This stability in a wide pH range is a value added advantage in the application of naphthoic acid derivatives as promising antioxidants in physiological environment. Below the toxicity level, naphthoic acid-based compounds exert antioxidant activity by the donation of a hydrogen atom through a proton coupled electron transfer reaction, resulting in the formation of a resonance stabilized carboxyl radical [36]. Addition of various electron donating substituents can boost up the activity of these compounds by stabilizing the resonance stabilized structure through their electron donating effect [37]. The antioxidant activity of substituted naphthoic acid can be related to the number of electron donating groups and their position on the aromatic ring. Among our studied naphthoic acid derivatives o-chloro naphthoic acid is the best donor as reflected from its C10-C11 and C11-O13 bond lengths. Next is o-methyl naphthoic acid in which the methyl group is inducing double bond character in C10-C11 bond and equal bond strength character in C11-O12 and C11-O13. Thus, its carboxyl radical will be resonance stabilized with equal contribution from both these bonds between carbon and oxygen. The key mechanism of the action of naphthoic acid derivatives is the formation of resonance stabilized structure. Hence, based on this consideration naphthoic acids can be screened for their antioxidant activities.

The oxidative cleavage of phenanthrene in the presence of Fe^{2+} oxygenase and aldolase type enzyme has been reported to result in cleaving phenanthrene into 1-hydroxy-2-naphthaldehyde [38]. This molecule further oxidizes in the presence of NAD specific dehydrogenase to 1-hydroxy-2-naphthoic acid which undergoes oxidative decarboxylation to 1,2-dihydroxynaphthalene by soil pseudomonads. This further mineralizes to CO_2 and H_2O. Thus, mode of attack is the end-ring attack which is oxidized in the same fashion as naphthalene as evidenced from the isolation of 1-hydroxy-2-naphthoic acid [38, 39]. Bacteria have been found to oxidize aromatic hydrocarbon systems to smaller molecules by O_2 uptake [40]. Mechanistic insights reveal that polycyclic HC attach to the bacterial enzyme via localized doubly bonded C9-C10 that have high electron density and block hydroxylation at this point which then directs the bacterial oxidation by activating other sites. This ring splitting in the substrate molecule dictates the bond fission based on steric as well as electronic configurations [41]. Thus, antibacterial activity relates to the substituent based variation in electronic and steric factors that play an important role in binding the substrate to the enzyme for bacterial oxidation.

4. Conclusion

Computational studies revealed that conformational changes are induced by substituents on naphthoic acid. The rotational barrier showed a strong correlation with the decrease of the naphthyl-carboxyl bond, increase of carbonyl bond, increase of electron density at the carboxyl group and increase of stabilization energy. The findings of this study demonstrated rotational barrier as a useful quantum mechanical parameter for quantifying the electron-donating substituent effect in naphthoic acids. A number of theoretically evaluated molecular descriptors helped in predicting membrane penetration ability, reactivity, antioxidant activity and receptor responsiveness of a chemical library of series of nine ortho-substituted naphthoic acids.

These are preliminary findings. Follow-up work is in progress.

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