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DFT calculations of effective reactive sites of inositol

D Jeevitha[a], K Sadasivam[a,] * & R Praveena[b]

[a]Department of Physics, [b]Department of Chemistry, Bannari Amman Institute of Technology (Autonomous), Sathyamangalam, Erode 638 401, Tamil Nadu, India

Email: dftsada@gmail.com

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Computational investigation of the naturally occurring compound, inositol, is evaluated to find the most reactive site and also its electron donating ability. Structural and molecular characteristics of inositol are analyzed using DFT/B3LYP/ 6-311G(d.p). Radical 2-OH is found to be the appropriate reactive site for hydrogen abstraction which is supported by the computed values of bond dissociation enthalpy, HOMO-LUMO and molecular electrostatic potential. Molecular descriptors like ionization potential, electron affinity, hardness, softness, electronegativity and electrophilic index are also calculated. Natural bond orbital analysis is carried out to identify the strong and weak intramolecular hyperconjugative interactions.

Keywords: Theoretical chemistry, Density functional calculations, Bond dissociation enthalpy, HOMO-LUMO, Natural bond orbitals, Inositol

Inositol, a carbocyclic polyol, is a naturally occurring sugar-like carbohydrate structurally similar to glucose with $C_6H_{12}O_6$ formula. Inositol is present in dietary sources such as plants, animals, fruits and predominant in whole grains[1]. In different biological forms inositol intake is approximately 1g per day[2]. People with depression possess the inositol content lower than normal levels in the cerebrospinal fluid[3]. Interestingly, kidney synthesizes inositol around 2 g per day in humans[4]. Inositol has numerous experimentally proven health benefits; it is potentially attractive therapeutic for neural tube defects (NTDs) where NTDs are birth defects of brain[5] also it contributes to the development of central nervous system[6]. Further, inositol is capable of significantly stimulating the production of lung surfactant and also it aids in reproduction[7]. In human cells, inositol is a very important growth factor in tissue culture[8]. Diabetic neuropathy is the nerve damage caused by diabetes, the oral administration of inositol valuable in the treatment of diabetic neuropathy[9].

Inositol derivatives showed anti-inflammatory activity[10]. Anti-depressant effect of inositol is experimentally evidenced[11], besides it is effective against the panic disorder[12]. Patients with obsessive-compulsive disorder are controlled by inositol[13]. Cancer is referred as deadly disease where inositol possessing anti-cancer activity[14] and with inositol hexaphosphate, it shows effective treatment for colon, breast cancer and metastatic lung cancer[15]. These findings raised the possibility that inositol has radical scavenging capability. So far no computational investigation of the compound inositol is reported regarding the most reactive site. In the present study, structure, electron donating ability and reactive site of inositol are analyzed.

Structure of inositol contains cyclohexane nucleus with six hydroxyl groups attached in 1, 2, 3, 4, 5 and 6 positions of the ring (cyclohexane-1, 2, 3, 4, 5, 6-hexol) as shown in Fig. 1. The electron donating ability and radical scavenging ability of the inositol are discussed using density functional theory (DFT). An attempt is made with the aid of DFT to identify the most reactive site of inositol compound through the computation of bond dissociation enthalpy (BDE) and ionization potential (IP). Further, electron affinity (EA), hardness (η), softness (*S*), electronegativity (χ) and electrophilic index (ω) are simulated and analyzed. In addition to that frontier molecular orbitals (FMOs) of inositol and energy gap are constructed and discussed. To estimate the appropriate reactive site for

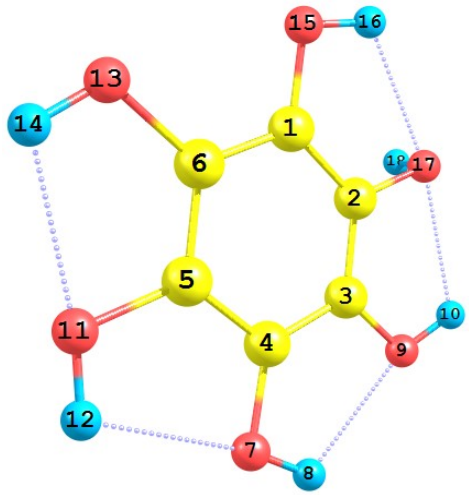

Fig. 1 — Optimized structure and atom numbering of inositol compound.

electrophilic and nucleophilic activity, molecular electrostatic potential (MEP) is simulated. Charge delocalization due to hyperconjugative interaction is characterized using natural bond orbital (NBO) analysis.

Computational details

Molecular structures of inositol were performed with Chemcraft program where the calculations were carried out with the aid of density functional theory (DFT) methods implemented in the computational GAUSSIAN 03W package[16]. In DFT methodology, the hybrid functional used B3LYP comprised Becke's three parameters exchange functional B3[17] in conjugation with non-local gradient corrected correlation functional of Lee-Yang-Parr (LYP)[18]. Besides, throughout the program the standard triple split valence basis set 6-311G together with a set of (d,p) polarization functions on heavy and hydrogen atoms were used. Using the same level of theory, optimization and harmonic vibrational frequency analysis of neutral, radicals, anion and cation species of the compound were studied.

Bond dissociation enthalpy (BDE) was calculated at 298.15 K as follows, BDE = $H_r + H_h - H_n$, where H_r is the enthalpy of radical generated through the removal of H-atom, H_h is the enthalpy of hydrogen atom (–0.49765 Hartree) and H_n is the enthalpy of neutral compound[19].

Ionization potential and electron affinity were calculated as IP=-E_{HOMO} and EA=-E_{LUMO}, respectively. Using these calculations, other parameters electronegativity (χ), hardness (η), softness (S) and electrophilic index (ω) were computed [20-23]as follows:

Electronegativity (χ): $\mu \approx - \chi = - (IP + EA)/ 2$
Hardness $\eta \approx (IP-EA)/2$
Softness $S = 1/ (2\eta)$
Electrophilic index $\omega = \mu^2/2\eta$

MEP analysis was performed and viewed by Gauss View visualization program. NBO [24] method was implemented by Gaussian03 package to characterize the electronic structure of the compound.

Results and discussion

The electronic components such as IP, EA, χ, η, S and ω give information on the influence of inositol on the radical scavenging activity[25]. IP calculated from the HOMO eigen value is 5.34 eV, which denotes its electron donating ability. The radical scavenging ability of a compound increases with high IP value. EA generated from LUMO (0.20 eV) corresponds to its ability to accept electrons. Higher the EA value indicates that the corresponding compound does not accept electrons easily which show its radical scavenging ability. The molecular descriptor values are displayed in Table 1. Hardness and softness of the compound inositol are 2.57 eV and 1.28 eV respectively. These values are useful for the prediction of types of the molecule such as soft or hard molecule. Molecules with low hardness (soft molecule) are sensitive to charge transfer and are more reactive. Electronegativity refers to the ability of an atom to attract electrons and the value is 2.77 eV for inositol.

The protective role of inositol is mainly due to its ability to donate H-atom or function as electron donor. BDE and IP of inositol are evaluated to find the most desired mechanism that supports radical scavenging ability[26].

Structural optimizations are performed for the radical species, 1-OH, 2-OH, 3-OH, 4-OH, 5-OH and 6-OH by means of H-atom removal from C1,C2,C3,C4,C5 and C6 positions respectively, from the most stable structure of inositol. The computed BDE values of inositol radicals are listed in Table 2. On comparing the BDE magnitudes of all the radicals of inositol, it is observed that the hydrogen abstraction is easier from 2-OH radical species. BDE of 1-OH is higher by 8.99 kcal/mol, 3-OH is higher by 0.44 kcal/mol, 4-OH is higher by 3.55 kcal/mol, 5-OH is higher by 14.78 kcal/mol also 6-OH is higher by 3.58 kcal/mol than the radical 2-OH. Hence, BDE

Table 1 — Molecular descriptors of inositol calculated at B3LYP/6-311G(d,p) level of theory (eV)

Molecular descriptors	Inositol
Ionization potential (IP)	5.34
Electron affinity(EA)	0.20
Hardness(η)	2.57
Softness (S)	1.28
Electronegativity(χ)	2.77
Electrophilic index (ω)	1.49

Table 2 — Calculated bond dissociation enthalpy values (BDE) (kcal/mol) at 298.15 K in the gas phase for inositol at the B3LYP/6-311G(d,p) level of theory.

Radicals	BDE
1-OH	70.53
2-OH	61.54
3-OH	61.98
4-OH	65.09
5-OH	76.32
6-OH	65.12

sequence of inositol is specified as 2-OH<3-OH<4-OH<6-OH<1-OH<5-OH.

It is shown that hydrogen abstraction is easier from 2-OH site than any other radicals and it is the most reactive site of inositol. Lower the BDE implies easier hydrogen abstraction resulting good radical scavenging ability.

Every molecule consists of a highest occupied molecular orbital (HOMO) and a lowest unoccupied molecular orbital (LUMO). The HOMO is logically considered as nucleophilic or electron donating, where as LUMO is electrophilic or electron accepting component. The hard and soft nucleophiles and electrophiles concepts are associated with the relative energies of the HOMO and LUMO orbitals. Hard and soft nucleophiles have a low energy HOMO and high energy HOMO respectively. Hard and soft electrophiles are related to high energy LUMO and low energy LUMO respectively[27].

The HOMO-LUMO frontier orbital compositions computed by DFT method for inositol are depicted in Fig. 2. To effectively evaluate the reactivity of the compound inositol, the second highest and highest occupied orbitals (HOMO-1 and HOMO), the second lowest and the lowest unoccupied orbitals (LUMO+1, and LUMO) are carried out.

Analysis of the HOMO compositions shows that the HOMO orbital of inositol presents charge distribution localized on the all radicals. It can be observed that the charge density concentration for HOMO structure is stronger on 2-OH radical when compared with 1-OH, 3-OH, 4-OH, 5-OH and 6-OH radicals. This interesting fact reveals that 2-OH forms a stable radical and is the most reactive site. Considering the HOMO-1 orbital, the atomic contributions come from all the radicals. It can be noticed from the LUMO and LUMO+1 orbitals of the inositol compound, the charge density is spread throughout the compound also does not involve in the radical scavenging ability. HOMO-LUMO gap (energy gap) is the energy difference between the HOMO and LUMO and the energy gap value is 5.14 eV as given in Table 3.

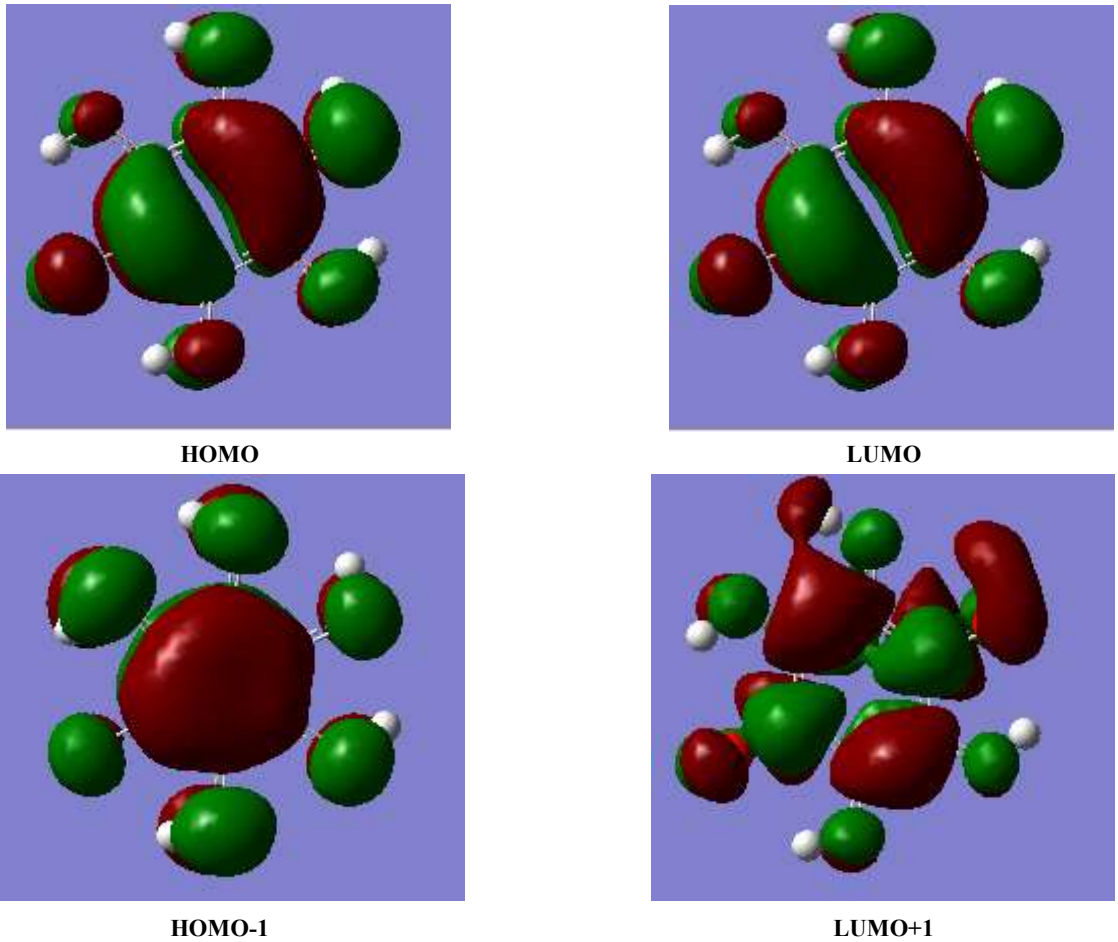

Fig. 2 — Frontier molecular orbital distribution for inositol.

The charge density of the HOMO at 2-OH radical is a measure of relative reactivity. This is in good agreement with the results obtained from BDE calculations. Higher HOMO eigen value implies higher radical scavenging activity.

MEP is a very useful descriptor for evaluating the reactivity of electrophile approaching towards the active region, where the electron density of the compound is dominant. In most of the MEP surfaces, negative region is related to electrophilic reactivity and is indicated in red color whereas positive region is related to nucleophilic reactivity which is denoted as blue color. 3D plot of MEP surface shows molecular size, shape besides electrostatic potential regions in terms of different colors which is very useful in the research of molecular modeling[28,29]. MEP plot of the compound inositol is illustrated in Fig. 3. Electron density are indicated by different colors and the increasing order of electron density is: Red > Orange > Yellow > Green > Blue.

The color code of the MEP map for inositol is ranges from –0.06640 a.u. (deepest red) to 0.06640 a.u. (deepest blue). While blue characterizes the strongest attraction, red is responsible for greatest repulsion. In inositol, the MEP plot indicates that the regions with negative potential are distributed over oxygen atoms and regions with positive potential are concentrated over hydrogen atom. It is evident from the mapped surface that the presence of red color or specifically electrophilic activity is high on radical 2-OH. This is a proof that electron donating ability is favorable from 2-OH radical and hence exhibiting good radical scavenging activity than any other radicals in inositol as it is proved from BDE and HOMO-LUMO investigations.

NBO analysis is performed in order to shed light on the intramolecular interaction and delocalization of electron density within the compound. E(2) values of each hyperconjugative interactions are used as a measure of the intramolecular delocalization. Larger E(2) value gives more intensive interaction between electron donors and acceptors.

More intensive intramolecular interactions take place between the overlap of bonding (C-C), (C-O), (O-H), (O-H…O) and anti-bonding (C-C), (C-O), (O-H) orbitals. The labeling of atoms of inositol is represented in Fig. 4. The strong intramolecular interaction obtained from aromatic carbon atoms are given as σ(C1-C2) → σ*(C3-C4) (21.11 kcal/mol) and σ(C5-C6) →σ*(C3-C4)(19.34 kcal/mol). This greater hyperconjugative interaction energy leads the electron delocalization to whole system is given in Table S1 (Supplementary Data). Lower energy comes from the weak interactions existing between electron donors and acceptors π(C1-C2) → π*(C3-O9) (3.37 kcal/mol), π(C4-C5) → π*(C3-O9) (3.23 kcal/mol), π(C5-O11) → π*(C5-C6) (0.89 kcal/mol) and π(C1-O15) → π*(C1-C2) (1.28 kcal/mol).

The interaction of (C-C) bonding with (O-H) anti-bonding orbitals exhibits lower energy, π(C4-C5) → π*(O7-H8) (1.27 kcal/mol) and σ(C1-C2) → π*(O17-H18) (2.27 kcal/mol) than the interaction

Table 3 — Frontier orbital energies and band gap energies of inositol

$-\varepsilon_{HOMO}$/ (eV)	5.34
$-\varepsilon_{LUMO}$/ (eV)	0.20
Energy gap/(eV)	5.14

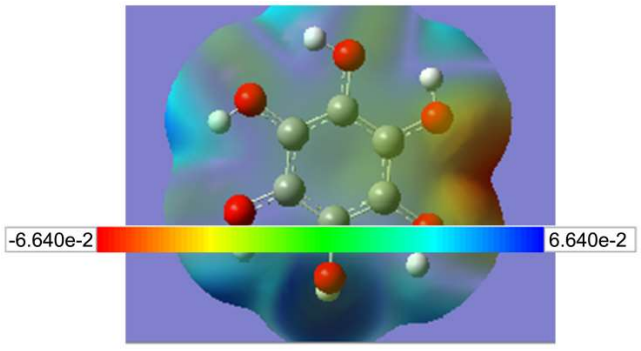

Fig. 3 — MEP plot of inositol using B3LYP/6-311(d,p) by DFT model chemistry.

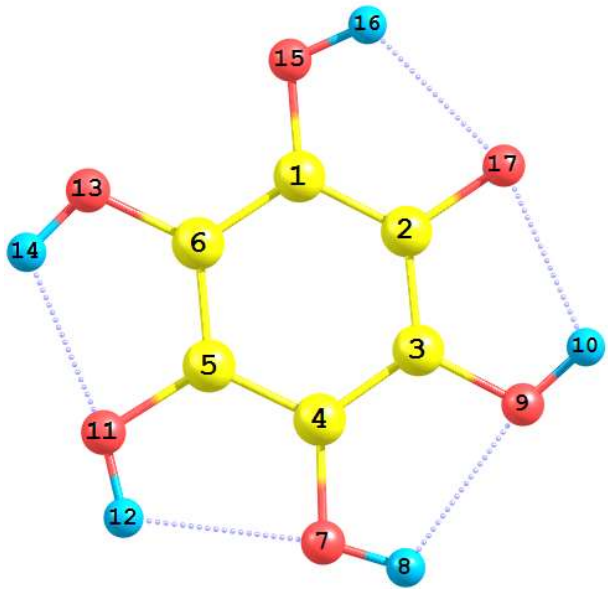

Fig. 4 — Numbering of atoms of inositol for NBO analysis. Dotted lines represent weak hydrogen bonds.

found between (O-H) bonding to (C-C) anti-bonding orbitals π(O7-H8) → π*(C4-C5) (4.17 kcal/mol) and π(O11-H12) → π*(C5-C6) (4.08 kcal/mol). It reveals that the intramolecular charge transfer is energetic from (O-H) to carbon atoms of the ring implies the conjugation of whole system held within the molecule.

Oxygen lone pair and O-H anti-bonding orbital forms weak intramolecular O…..O-H hydrogen bond interaction, which are LP(1)O7 → π*(O11-H12) (0.54 kcal/mol), LP(1)O11→ π*(O13-H14) (0.69 kcal/mol) and LP(2)O17 → π*(O15- H16) (1.22 kcal/mol). However, in the case of O….C-C interaction, LP(2)O15 → σ*(C1-C2) (26.69 kcal/mol), LP(2)O11 → σ*(C5-C6) (23.38 kcal/mol) and LP(2)O9 → σ*(C3-C4) (22.16 kcal/mol), oxygen lone pair and C-C anti-bonding orbital furnishes strong intramolecular bond. It is clear that the interaction of oxygen lone pair towards (C-C) anti-bonding orbital contributes more intensive than with the orbital of hydrogen atom. This major contribution led to study the significance of biological system regarding radical scavenging activity.

In the present study, the most reactive site and radical scavenging ability of the compound inositol are analyzed using DFT computational method. Based on the obtained results of BDE, the most stable radical is found to be 2-OH since the electron donating ability is easier from 2-OH than from other radicals of inositol. From MEP analysis, the most electron-donor system is characterized by the radical 2-OH, for which the BDE magnitude is found to be minimum. Theoretical approach from MEP map reproduces the result of BDE. HOMO structure of inositol confirms that charge density concentration is high on 2-OH radical, implying that the radical scavenging ability is higher for the 2-OH radical. It is concluded that 2-OH is the most reactive site of inositol. These theoretical findings confirm that the high electron donating ability of 2-OH radical makes inositol a good radical scavenger. The NBO results show that the charge transfer is mainly due to (O-H) and (C-C) groups. Oxygen lone pair bonding-orbital and C-C anti-bonding orbital form a strong intramolecular bond. The study shows that the interaction of oxygen lone pair → (C-C) anti-bonding orbital contributes more intensively than oxygen lone pair → (O-H) anti-bonding orbital.

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