International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-1, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Theoretical Studies of Stability, and Local Molecular Properties of Allopurinol Isomers by Density Functional Theory

N. Surendra Babu[1], Sisay Tadeasse[1], T. A. Lelisho[1], Nimmagadda Padmaja[2]

[1]*College of Natural and Computational Science (CN & CS), Department of Chemistry Hawassa University, Hawassa, Ethiopia.*

[2]*Department of chemistry, Anil Neerukonda Institute of Technology and Sciences (ANITS).*

Manuscript No: IJPRS/V3/I1/00087, Received On: 19/02/2014, Accepted On: 24/02/2014

ABSTRACT

Density functional theory (DFT) were used to determine the relative energies, electronegativity(χ), hardness (η), softness(S), electrophilicity index (ω) and local reactivity descriptors such as Fukui function, for the Allopurinol isomers (A1, A2, A3, A4, A5 and A6). For this purpose, the DFT/B3LYP method, with the 6-311++G (d,p) basis set was utilized. The local reactivity has been analyzed through the condensed Fukui function using natural population analysis (NPA). The most stable isomer is A5 and A1 has lowest energy, with relative energy about 5.97 kcal mol^{-1} and other four isomers (A2, A3, A4 and A6) have highest energy, with relative energy about 11.58-37.40 kcal mol^{-1}. On the frontier orbital energy gap, the reactivity order of the isomers are A1 > A4 > A5 > A3 > A2 > A6 respectively. The preferred site for nucleophilic attack, and electrophilic in all isomers are N3, N8, N8, N3, O1 and N5, C2, N9, N9, N9, C9, and N6, for the isomers A1, A2, A3, A4, A5, and A6 respectively.

KEYWORDS

Allopurinol, DFT, HOMO-LUMO, Hardness, Softness, Fukui Function

INTRODUCTION

Allopurinol is the mainstay of urate-lowering therapy for patients with gout and impaired renal function. Although rare, a life-threatening hypersensitivity syndrome may occur with this drug. The risk of this allopurinol hypersensitivity syndrome (AHS) is increased in renal impairment. The recognition that AHS may be because of delayed-type hypersensitivity to oxypurinol, the main metabolite of allopurinol, and that oxypurinol concentrations are frequently elevated in patients with renal impairment prescribed standard doses of Allopurinol has led to the widespread adoption of allopurinol-dosing guidelines[1,2]. However, several people have developed serious allergic reactions, called Allopurinol Intolerance Syndrome (AIS), which is characterized by fever, renal and hepatic compromising, erythematous lesions and other symptoms associated with the secondary metabolite oxypurinol (which has a half-life markedly longer than the allopurinol[3]. The allopurinol molecule has structural similarity with hypoxanthine and xanthine. So, it is a powerful competitive inhibitor of the Xanthine oxidase (XO) enzyme[4]. It is converted by xanthine oxidase to alloxanthine, which binds tightly to the active site by chelation with Mo^{4+}. This greatly reduces reoxidation of Mo^{4+} to Mo^{6+} and affects catalytic activity This type of inhibitor, in which a substrate analogue is converted to an

***Address for Correspondence:**
Dr. N. Surendra Babu
Department of Chemistry,
College of Natural and Computational Science (CN & CS),
Hawassa University, Hawassa,, Ethiopia.
E-Mail Id: nsbabusk@gmail.com

inhibitor and not released from the active site, is known as a suicide enzyme-inactivator or a mechanism based inhibitor.

As part of our research program, we have performed theoretical studies of allopurinol, because of its pharmacological relevance and isomeric character with respect to hypoxanthine. The rationalized common features and differences in the physicochemical and chemical behavior between neutral hypoxanthine and allopurinol, prompted us to extend the theoretical studies of these heterocycles in different protonation levels. In this communication, several theoretical properties for the energetically most favored monocationic allopurinol isomers are presented and discussed.

Computational Methods

Allopurinol has six isomers among four enol and two keto isomeric forms altogether. Considering the orientation of the hydroxyl hydrogen (it is in the same or opposite direction with the C=N bond of the enol), the number of the isomers ascends to six, Fig. 1, illustrates the six isomers. The Becke's three parameter hybrid exchange functional[5] with Lee-Yang-Parr correlation functionals (B3LYP)[6,7] of the density functional theory[8] with 6-311++G (*d*,*p*) basis set were chosen to optimize the structures of the Allopurinol isomers under investigation. All the calculations were performed using the Gaussian 09 program[9]. Positive values of all the calculated vibrational wave numbers confirmed the geometry to be located at true local minima on the potential energy surface. Single point calculations are further done to evaluate the energies of the $N \pm 1$ electron systems by adopting the geometries of the corresponding N electron systems optimized at the B3LYP/6-311+G(d) level of theory. The hardness (η) and electrophilicity (ω) are computed using the Eq. 2 and 8 respectively. A Natural population analysis (NPA) scheme is adopted to calculate the atomic charges (q_k) and the corresponding Fukui functions $(f(\bar{r}))$ on the atom centers. The frontier molecular orbital pictures are obtained through the GAUSSVIEW 05 package[10].

Theoretical Background

Density functional theory (DFT)[11] has been found to be successful in providing theoretical insights into the chemical reactivity and selectivity, in terms of popular qualitative chemical concepts like electronegativity (χ), hardness (η), softness(S), electrophilicity index (ω) and local reactivity descriptors such as Fukui function $(f(\bar{r}))$.

The basic relationship of the density functional theory of chemical reactivity is precisely, the one established by Parr, Donnelly, Levy and Palke[12], that links the chemical potential of DFT with the first derivative of the energy with respect to the number of electrons, and therefore with the negative of the electronegativity (χ).

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} = \chi \quad \text{---------- (1)}$$

Where μ is the chemical potential, E is the total energy, N is the number of electrons, and ν(r) is the external potential of the system.

Hardness (η) has been defined within the DFT as the second derivative of the E with respect to N as (v_r) property which measures both the stability and reactivity of the molecule[13].

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} \quad \text{---------- (2)}$$

Where, $v(r)$ and μ are, respectively, the external and electronic chemical potentials.

According to, the Koopmans' theorem[14] for closed-shell molecules, ionization potential (*I*) and electron affinity (*A*) can be expressed as follows in terms of E(HOMO) and E(LUMO) the highest occupied molecular orbital energy, and the lowest unoccupied molecular orbital energy, respectively:

$$I = -E_{HOMO} \quad \text{---------- (3)}$$

$$A = -E_{LUMO} \quad \text{---------- (4)}$$

When the values of *I* and *A* are known, one can determine through the following expressions[15] the values of the absolute electronegativity χ,

the absolute hardness η and the softness S (the inverse of the hardness):

$$\chi = \frac{I + A}{2} \quad \text{---------- (5)}$$

$$\eta = \frac{I - A}{2} \quad \text{---------- (6)}$$

The global softness(s) is the inverse of the global hardness[16]

$$s = \frac{1}{\eta} \quad \text{---------- (7)}$$

The electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale. Parr have proposed electrophilicity index as a measure of energy lowering due to maximal electron flow between donor and acceptor and defined electrophilicity index (ω) as follows[17].

$$\omega = \frac{\mu^2}{2\eta} \quad \text{---------- (8)}$$

According to the definition, this index measures the propensity of chemical species to accept electrons. A good, more reactive, nucleophile is characterized by lower value of μ, ω and conversely a good electrophile is characterized by a high value of μ, ω. This new reactivity index measures the stabilization in energy when the system acquires an additional electronic charge ΔN_{max} from the environment[17].

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad \text{---------- (9)}$$

The maximum charge transfer ΔNmax towards the electrophile was evaluated using Eq. (9). Thus, while the quantity defined by Eq. (8) describes the propensity of the system to acquire additional electronic charge from the environment; the quantity defined in Eq. (9) describes the charge capacity of the molecule.

Very recently, Ayers and coworkers[18,19] have proposed two new reactivity indices to quantify nucleophilic and electrophilic capabilities of a leaving group, nucleofugality ΔE_n and electrofugality ΔE_e, defined as follows,

$$\Delta E_n = -A + \omega = \frac{(\mu + \eta)^2}{2\eta} \quad \text{---------- (10)}$$

$$\Delta E_e = I + \omega = \frac{(\mu - \eta)^2}{2\eta} \quad \text{---------- (11)}$$

Fukui Functions (FF)

The condensed Fukui functions indices allow us to distinguish each part of the molecule on the basis of its distinct chemical behavior due to the different substituent functional groups. It is known that the Fukui indices were widely used as descriptors of site selectivity for the soft–soft reactions[20]. Parr and Yang proposed that larger value of Fukui function indicate more reactivity[21,22,23]. Hence greater the value of condensed Fukui function, the more reactive is the particular atomic centre in the molecule. The f_k^+, measures the changes of density when the molecules gains electrons and it corresponds to reactivity with respect to nucleophilic attack. On the other hand, f_k^- corresponds to reactivity with respect to electrophilic attack or when the molecule loss electrons. The calculated Fukui functions for the Allopurinol isomers are presented in Tables 4.

The hard/soft acid-base principle has long been known to be an excellent predictor of chemical reactivity[24,25]. The Fukui functions can be defined in terms of the ionisation potential, I, and the electron affinity, A, which lead to:

$$f^+(r) = \rho_{N+1}(r) - \rho_N(r)$$

(For nucleophilic attack) ---------- (12a)

$$f^-(r) = \rho_N(r) - \rho_{N-1}(r)$$

(For electrophilic attack) ---------- (12b)

$$f^0(r) = \frac{1}{2}\left[f^+(r) - f^-(r) \right]$$

(for radical attack) ---------- (12c)

where, ρ_{N-1}, ρ_N and ρ_{N+1} are the electron density of cationic, neutral and anionic species, respectively. They are calculated under the frozen core approximation[26] which means a single calculation is done for the neutral species without any changes in the calculation method for the charged species, especially anions, under the Natural population analysis approach. The condensation of this Fukui function, to an individual atomic site k in a molecule gives rise to the following expressions in terms of electron population, q_k[27].

$$f_k^+ = q_k(N+1) - q_k(N)$$

for nucleophilic attack ---------- (13a)

$$f_k^- = q_k(N-1) - q_k(N)$$

for electrophilic attack ---------- (13b)

$$f_k^0 = \frac{1}{2}\left[q_k(N-1) - q_k(N)\right]$$

for radical attack ---------- (13c)

where, $q_k(N+1)$, $q_k(N)$, and $q_k(N-1)$ stand for the gross NPA charges on atom k in a molecule with N + 1, N, and N - 1 electrons, respectively.

$$f^{(2)}(r) = \Delta f(r) \approx \rho_{N+1}(r) - \rho_{N-1}(r) - 2\rho_N(r)$$
$$= f^{+(r)} - f^{-(r)} \quad (14)$$

The reactivity descriptor $\Delta f(r)$ provides useful information on both stabilizing and destabilizing interactions between a nucleophile and an electrophile and helps in identifying the electrophilic/ nucleophilic behavior of a specific site within a molecule. Since the dual descriptor has been very versatile for describing the regional stereo selectivity of a chemical reaction, it seems interesting to be used for assessing of the nucleophilicity of the nitrogen and oxygen atoms in a biological system.

RESULTS AND DISCUSSION

Energies and Relative Stability

The equilibrium geometry optimization for the isomers has been achieved by energy minimization, using DFT at the B3LYP level, employing the basis set 6-311++G(*d*,*p*). The optimized geometry of the isomers of Allopurinol under study are confirmed to be located at the local true minima on potential energy surface, as the calculated vibrational spectra has no imaginary frequency. Optimized structures of the allopurinol predicted isomers are shown in Fig. 1. First, we will discuss the relative stability of the six possible isomer forms (Fig. 1) in gas phase. The total and relative energies of isomers of Allopurinol are presented in Table 1(A1, A2, A3, A4, A5, and A6). The most stable isomer A5 is taken as reference to obtain the relative energetic stability of other isomers respectively. It can be seen from the results Table1.,that one enol isomer (A1) has lowest energy, with relative energy about 5.97 kcal mol^{-1} and other four enol isomers (A2, A3, A4 and A6) have highest energy, with relative energy about 11.58-37.40 kcal mol^{-1}.Because of the possibility of migration of hydrogen atoms, and eliminating the simultaneous transfers little likely of more than atom, only the exchange of hydrogen atom between heteroatom spatially close and separate by more than two atoms can be carried out. The energy difference of the isomers of same isomeric form that differs in the orientations of hydroxyl hydrogen's, varies for specific systems. The order of relative stabilities for isomers in gas phase with respect to stable isomer for as following order respectively: A1 > A4 > A6 > A2 > A3.

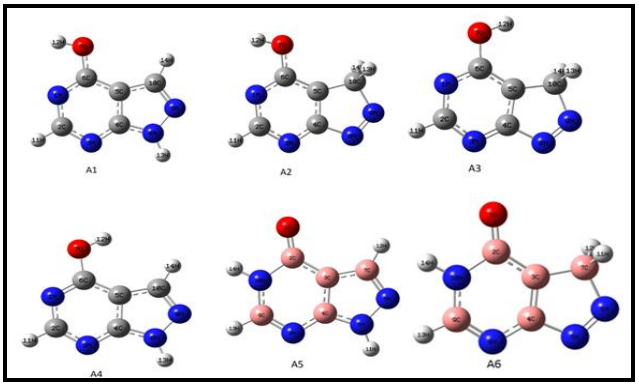

Figure 1: Optimized structure of Allopurinol isomers in the gas phase with DFT/(B3LYP) of 6-311++G (*d*,*p*) level

Table 1: The energies of isomers (k cal/mol), enthalpies (k cal/mol), free energies (k cal/mol), entropies (cal/mol) dipole moments (debye) at DFT/6-311++G(d,p) level in gas phase

Isomer	Energy (kcal/mol)	Enthalpy(kcal/mol)	Free Energy	Entropy	Dipole
A1	-305722.2181 (5.97)	-305717.3731	-305741.9314	85.052	0.7439
A2	-305696.7299 (31.46	-305691.8071	-305716.553	82.999	4.2869
A3	-305690.7956 (37.40)	-305685.7799	-305710.6958	83.570	4.1699
A4	-305716.6164 (11.58)	-305711.6848	-305736.4043	82.910	2.2143
A5	-305728.1914 (0.00)	-305723.3307	-305747.9693	82.638	3.8137
A6	-305700.3237 (27.86)	-305700.3237	-305720.2176	83.302	3.6835

Electronic Properties

The most important orbitals in a molecules are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). These orbitals determine the way the molecule interacts with other species. The frontier orbital energy gap helps characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule[28].

The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor. Table 2 summarizes the highest occupied molecular (HOMO), the lowest unoccupied molecular orbital (LUMO) and HOMO and LUMO energy gaps (ΔE_g) for studied molecules calculated at DFT level in the 6-311++G(d,p) basis set. The 3D plots of the frontier orbitals HOMO and LUMO figures for all isomers are shown in Fig. 2. From the resulting data shown in Table 2, based on the frontier orbital energy gap, the reactivity order of the isomers are A1 > A4 > A5> A3> A2> A6 respectively.

Table 2: The HOMO and LUMO energies and the energy gap between HOMO and LUMO (ΔE_g)), ionization potential (I), electron affinity (A) in eV units at DFT/6-311++G(d,p) level in gas phase

Isomer	HOMO(ev)	LUMO(ev)	(ΔE_g)	I	A
A1	-7.176892	-1.67653132	-5.500361	7.176892	1.676531
A2	-7.386153	-2.78052216	-4.605631	7.386153	2.780522
A3	-7.540989	-2.88773744	-4.653252	7.540989	2.887737
A4	-7.260161	-1.77367816	-5.486483	7.260161	1.773678
A5	-6.971986	-1.5823778	-5.389608	6.971986	1.582377
A6	-7.355540	-2.8999812	-4.455424	7.355540	2.899981

Global Descriptors

Global Hardness

The global descriptors, chemical potential, chemical, hardness and chemical softness for all studied isomers are given in Table 3. Ionisation potential (I) and electron affinity (A) values were calculated by the application of Koopmans' theorem[14]. This theorem establishes a relationship between HOMO and LUMO with the ionisation potential and the electron affinity, respectively. Although there is not a formal proof of this theorem within DFT, its validity is generally accepted. The obtained values of I and A were considered for the calculation of the electronegativity (χ) and global hardness (η) in each of the molecules. The dipole moment (μ in Debye) is another important electronic parameter which provides the information on the polarity and the reactivity indicator of the molecule.

Table.2. summarized the important global chemical parameters. Ionization energy is a fundamental descriptor of the chemical reactivity of atoms and molecules. High ionization energy indicates high stability and chemical inertness and small ionization energy indicates high reactivity of the atoms and molecules[29]. The low ionization energy 6.9719 (eV) of A5 isomer indicates that the isomer is less stable.

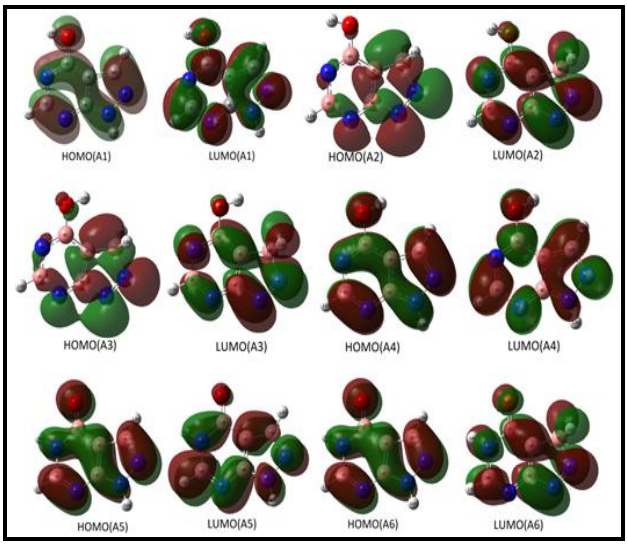

Figure 2: The HOMO and LUMO frontier molecular orbitals of studied molecules at at DFT/6-311++G (d,p) level in gas phase

Absolute hardness and softness are important properties to measure the molecular stability and reactivity. It is apparent that the chemical hardness fundamentally signifies the resistance towards the deformation or polarization of the electron cloud of the atoms, ions or molecules under small perturbation of chemical reaction. A hard molecule has a large energy gap and a soft molecule has a small energy gap[30]. In our present study A6 isomer have with low hardness values 2.2277 (eV) compared with other isomers respectively. Therefore, A6 isomer is stable and less reactivity.

Table 3: Calculated Global Quantities Chemical potential (μ), Electronegativity (χ), Hardness (η), Softness (s), and Electrophilicity (ω) of different isomers

Isomer	μ	χ	H	s	ω	ΔE_n	ΔE_e	ΔN_{max}
A1	4.4267121	-4.426712	2.7501807	0.1393360	3.5626348	-3.35306264	5.500361	-1.609607
A2	5.0833376	-5.083337	2.3028155	0.1353884	5.6105931	-5.56104432	4.605631	-2.207444
A3	5.2143634	-5.214363	2.326626	0.1326085	5.8431363	-5.77547488	4.653252	-2.241169
A4	4.5169198	-4.516919	2.7432417	0.1377379	3.7186962	-3.54735632	5.4864834	-1.646562
A5	4.2771821	-4.277182	2.6948043	0.1434311	3.3943627	-3.1647556	5.3896087	-1.587195
A6	5.1277602	-5127760	2.227780	0.4488771	5.9013731	-5.79996	4.4555604	-3.141053

Table 4: Fukui indices for nucleophilic and electrophilic attacks on atoms calculated from Natural population analysis at DFT/6-311++G (d,p) level in gas phase; maxima in bold

Isomer A1				Isomer A2				Isomer A3			
Atom	**f^+**	**f^-**	**f^0**	**Atom**	**f^+**	**f^-**	**f^0**	**Atom**			
N1	0.08059	0.02925	0.05492	N1	0.08025	0.12678	0.10351	N1	0.09989	0.12393	0.11191
C2	0.07013	**0.16155**	0.11584	C2	0.0293	0.04552	0.03741	C2	0.02577	0.04021	0.03299
N3	**0.1452**	0.13067	0.13793	N3	0.15426	0.05867	0.10646	N3	0.1782	0.06215	0.12017
C4	0.01409	-0.00222	0.00593	C4	-0.02138	0.0601	0.01936	C4	-0.01867	0.05139	0.01636
C5	0.01312	0.02667	0.01989	C5	0.05732	0.06455	0.06093	C5	0.05914	0.07378	0.06646
C6	0.05807	0.15909	0.10858	C6	0.02251	0.0438	0.03315	C6	0.02205	0.03516	0.02860
O7	0.10328	0.06283	0.08305	O7	0.04454	0.04088	0.04271	O7	0.062	0.04933	0.05566
N8	0.09318	0.03918	0.06618	N8	**0.23207**	0.16043	0.19625	N8	**0.2093**	0.16717	0.18823
N9	0.14101	0.1603	**0.15065**	N9	0.20396	**0.22314**	**0.21355**	N9	0.18425	**0.22176**	**0.20300**
C10	0.13157	0.10167	0.11662	C10	0.02845	-0.02463	0.00191	C10	0.02605	-0.01453	0.00576
H11	0.04318	0.04095	0.04206	H11	0.04209	0.03947	0.04078	H11	0.04281	0.03943	0.04112
H12	0.02803	0.02341	0.02572	H12	0.02435	0.02431	0.02433	H12	0.01264	0.00989	0.01126
H13	0.03902	0.03255	0.03578	H13	0.05116	0.0685	0.05983	H13	0.04828	0.07015	0.05921
H14	0.03951	0.03412	0.03681	H14	0.05113	0.06847	0.0598	H14	0.04828	0.0702	0.05924
Isomer A4				**Isomer A5**				**Isomer A6**			
Atom	**f^+**	**f^-**	**f^0**	**Atom**	**f^+**	**f^-**	**f^0**	**Atom**	**f^+**	**f^-**	**f^0**
N1	0.08472	0.03399	0.059355	O1	**0.20278**	0.09502	0.1489	O1	0.13915	0.10873	0.12394
C2	0.06264	0.14083	0.101735	C2	-0.02106	0.00785	-0.006605	C2	-0.0028	0.01671	0.006955
N3	**0.15876**	0.12613	0.142445	C3	0.10128	0.07476	0.08802	C3	0.06275	0.12816	0.095455
C4	0.0046	0.00083	0.002715	C4	0.06722	0.02415	0.045685	C4	-0.00491	0.06858	0.031835
C5	0.01585	0.02617	0.02101	N5	0.01434	0.06267	0.038505	N5	**0.25479**	0.12271	0.18875
C6	0.0616	0.15832	0.10996	N6	0.19089	0.12823	0.15956	N6	0.21101	**0.19223**	**0.20162**
O7	0.11333	0.06704	0.090185	C7	0.03832	0.03907	0.038695	C7	0.02289	-0.03716	-0.007135
N8	0.09792	0.04219	0.070055	N8	0.11591	0.09726	0.106585	N8	0.07393	0.01654	0.045235
N9	0.13075	**0.16677**	**0.14876**	C9	0.06941	**0.30341**	**0.18641**	C9	0.03931	0.09934	0.069325
C10	0.12799	0.11359	0.12079	N10	0.06501	0.03131	0.04816	N10	0.02889	0.0562	0.042545
H11	0.04358	0.04175	0.042665	H11	0.03637	0.03098	0.033675	H11	0.05346	0.07558	0.06452
H12	0.02042	0.01584	0.01813	H12	0.0396	0.03327	0.036435	H12	0.05346	0.07549	0.064475
H13	0.03875	0.03294	0.035845	H13	0.04474	0.0399	0.04232	H13	0.0384	0.04018	0.03929
H14	0.03907	0.03361	0.03634	H14	0.03516	0.03213	0.033645	H14	0.02967	0.03671	0.03319

Fukui Indices

Local reactivity was analyzed by means of the Fukui indices, since they indicated the reactive regions, as well as the nucleophilic and electrophilic behavior of each molecule. This was done to obtain broader knowledge of the reactive site responsible for the activity and to show which atom is responsible for bond formation. The analysis of the Fukui indices along with the charge distribution and the global hardness provides a complete scheme of the reactivity of a molecule[31]. The calculated Fukui functions for the isomers of allopurinol are presented in Tables 4.

From the Table 4, the preferred site for nucleophilic attack in all isomers are N3, N8, N8, N3, O1 and N5 for the isomers A1, A2, A3, A4, A5 and A6 respectively and the highest value of nucleophilic attack (f^+) in A6 isomer at N5 atom. In case of electrophilic attack in all isomers are C2, N9, N9, N9, C9 and N6 for the isomers A1, A2, A3, A4, A5 and A6 respectively and the A5 isomer have highest value of electrophilic attack (f^-) at C9 atom. The radical attack is interesting to observed in all isomers are same at atom N9 expect the A5 and A6 isomers are at C9 and N6 respectively. These results agree well with the analysis of the LUMO densities which also predicted these sites as the most electron deficient center.

CONCLUSION

The structure, energetics, and vibrational analyses of six gas phase isomers have been calculated within the DFT (B3LYP)/6-311++G(d,p) computational modeling frame. Global and local parameters are found to be very powerful indices for study of reactivity of species. Local reactivity indices, Fukui function, and local softness of particular atoms predict well, the reactive sites of molecules, which are important parameters for describing the reaction mechanism of a complex reaction system. In our present study A6 isomer have with low hardness values 2.2277 (eV) compared with other isomers respectively. Therefore, A6 isomer is stable and less reactivity. The radical attack is interesting to observed in all isomers are same at atom N9 expect the A5 and A6 isomers are at C9 and N6 respectively. These results agree well with the analysis of the LUMO densities which also predicted these sites as the most electron deficient center.

REFERENCES

1. Mikuls, T. R., MacLean, C. H., Olivieri, J., Patino, F., Allison, J. J., Farrar, J. T., Bilker, W. B., & Saag, K. G. (2004). *Quality of care indicators for gout management. Arthritis Rheum*, 50, 937.
2. Braden, G. L., Warzynski, M. J., Golighthy, M., & Ballow, M. (1994). *Immunol. Immunopathol*, 70, 145.
3. Hamanaka, H., Mizutani,H., Nouchi,N; Shimizu,Y., & Shimizu, M. (1998). Allopurinol hypersensitivity syndrome: hypersensitivity to oxypurinol but not allopurinol. *Clin. Exp. Dermatol*, 23, 32.
4. Ishibuchi, S., Morimoto, H., Oe, T., Ikebe, T., Inoue, H., Fukunari, A., Kamezawa, M., Yamada, I., & Naka, Y. (2001). Bioorg. Synthesis and structure – activity relationship of 1- phenylpyrazoles as xanthine oxidase inhibitors. *Med. Chem. Lett* 11, 879.
5. Becke, A. D. (1993). Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* 98, 5648.
6. Lee, C., Yang, W., & Parr, R.G. (1988). Development of the colle-salvetti conelation energy formula into a functional of the electron density. *Phys. Rev* B, 37,785.
7. Miehlich, B., Savin, A., Stoll,H., & Preuss, H. (1989). Results obtained with the correlation energy density functional of Becke and Lee, yang and Parr. *Chem. Phys. Lett* 157, 200.
8. Kohn, W., & Sham, L. J. (1965). Self-consistent equations including exchange and correlation effects. *Phys. Rev* 140, A1133.
9. Frisch, M. J., Trucks, G. W., & Schlegel, H.B.*et al*., Gaussian 09, Rev. A.1 (Gaussian, Inc., Wallingford CT, 2009).

10. Frisch, A., Hratchian, H. P., Dennington R. D. II, *et al.*, Gaussview, Ver. 5.0 (Gaussian, Inc., Wallingford CT, 2009).

11. Chermette H. (1997). Chemical reactivity indexes in density functional theory. *J. Comput Chem* 20, 129.

12. Parr, R.G., Donnelly, R.A., Levy, M., & Palke W.E. (1978). Electronegativity- the density functional view point, *J. Chem. Phys*. 68.3801.

13. Parr, R. G., Pearson, R. G. (1983). Absolute hardness: comparrion parameter to absolute electronegativity, *J. Am. Chem. Soc*. 105, 7512.

14. Koopmans, T. (1993). Ordering of wave functions and eigenergies to the individual electrons of an atom. *Physica*. 1, 104.

15. Pearson, R. G. (1963). Hard and soft acids and bases, *J.Am.Chem.Soc*. 85(22), 3533.

16. Lesar, A., & Milosev, I. (2009). Density functional study of the corrosion inhabitation properties of 1,2,4- triazole and its amino derivatives. *Chem. Phys. Lett. 483(4-6)***,** 198.

17. Parr, R. G., Szentpaly, L., & Liu, S. (1999). Electrophilicity index. *J. Am. Chem. Soc*. 121, 1922.

18. Ayers,P. W., Anderson, J. S. M.,& Bartolotti, L. J. (2005). Perturbative perspectives on the chemical reaction prediction problem, *Int. J. Quantum Chem* 101, 520.

19. Roos, G., Loverix, S., Brosens,E., Van Belle, K., Wyns,L., Geerlings,P., & Messens, J. (2006). The activation of electrphile, nuclephile and leaving group during the reaction catalysis by P1258 arsenate reductase, *ChemBioChem.* 7, 981.

20. Ayers, P.W., & Levy, M. (2000). Perspective on density functional approach to the frontier-electron theory of chemical reactivity, *Theor. Chem. Acc.*103. 353.

21. Parr, R. G., & Yang, W. (1984). Density functional approach to the frotier electron-density of chemical reactivity, *J Am Chem Soc*. 106, 4049.

22. Yang, W., & Parr, R. G. (1985). Hardness, softness, and the Fukui function in the electronic theory of metals and catalysis, *Proc Nati Acad Sci USA* 82, 6723.

23. Parr, R. G., & Yang, W. (1989). Density Functional Theory of Atoms and Molecules, *Oxford: Oxford University Press*.

24. Cavalli, A., Carloni, P., & Recanatini, M. (2006). Target-related applications of first principles quantum chemical methods in drug design, *Chem Rev*. 106, 3498.

25. Faver, J., & Merz, K. M. (2010). Utility of the hard/soft acid-base principle via the Fukui function in biological systems, *J Chem Theory Comput* 6, 548.

26. Melin, J., Aparicio, F., Subramanian, Galvan, M., & Chattaraj, P.K. (2004). Is the Fukui function a right descriptor of hard-hard interactions, *J Phys Chem A. 108,* 2487.

27. Yang, W., & Mortier, W. J. (1986). The use of global and local molecular parameters for theanalysis of the Gas – phase basicity of atoms, *J. Am. Chem. Soc. 108, 5708.*

28. Fleming, I.(1979). Frontier Orbitals and Organic Chemical Reactions, *John Wiley & Sons, New York.*

29. Chakraborty, T., & Ghosh, D, C. (2010). Computation on the atomic radil through the conjoint action of the effective nuclear change and the ionization energy, *Mol. Phys 108, (16),* 2081.

30. Obi-Egbedi, N.O., Obot, I.B., El-Khaiary, M.I., Umoren, S.A., & Ebenso, E.E. (2011). Computational simulation and statistical analysis on the relationship between corrosion inhabitation efficiency and molecular structure of some phenanthroline derivatives on mid steel surface, *Int. J. Electrochem. Sci*. 6, 5649.

31. Cruz, J., Martınez-Aguilera, L.M.R., Salcedo, R., & Castro, M. (2001). Reactivity Properties of derivatives of 2- imidazoline: An ab initio DFT study. *Int J Quantum Chem*. 85, 546.

