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CONFORMATIONAL, CHEMICAL REACTIVITY, THERMODYMANIC PROPERTIES AND THE SEM STUDY OF YOHIMBINE HYDROCHLORIDE

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ABSTRACT

We have presented a study on structural conformation of yohimbine hydrochloride using density functional theory (DFT) method. A short description about the surface morphology with scanning electron microscopy imaging has been included. Correlation between different thermodynamic properties with variation in the temperature has been given. The global and local chemical reactivity descriptors have been calculated, from which nucleophilicity and electrophilicity of the given atomic sites in the molecule can be known.

Keywords: YHCl, DFT, SEM, thermodynamic property, reactivity descriptor

INTRODUCTION

Natural products (including plants, animals and minerals) have been the basis of treatment of human diseases from the ancient time. Yohimbine, an indole alkaloid is either the active ingredient obtained from the bark of the tree *Pausinystalia* y*ohimbe*, tall evergreen tree indigenous to southern African countries or from the root of *Rauwolfia serpentina* which has been known as an aphrodisiac compound since before the last century [1-5]. Yohimbine hydrochloride (YHCl) is the standard product form. It was found (based on gel mobility shifts) to block cleavage of the internal loop RNA site by >50% and seemed to inhibit protein binding [6]. Besides its many applications, there are some noticeable side effects of YHCl [7-9].

In the present study, we have performed detailed conformational analysis of the title molecule employing quantum chemical methods. The thermodynamic properties were also calculated at different temperatures revealing the correlation between the standard heat capacities (C), entropies (S), enthalpy changes (H) and temperatures with density functional theory (DFT) [10-12] employing 6-311G(d,p) basis set. Surface morphology has been studied with scanning electron microscopy (SEM) method. We have proposed a multiphilic chemical reactivity descriptors calculated with the help of Fukui functions (FF) obtained from the DFT calculations employing 6-31G(d,p) basis set. It is defined as the difference between nucleophilic (ω_k^+) and electrophilic (ω_k^-) condensed philicity functions. This descriptor is capable of simultaneously explaining the nucleophilicity and electrophilicity of the given atomic sites in the molecule.

EXPERIMENTAL

The sample was grinded in a crucible and the thin film was made. For this, the gel of the material was spin coated on the alumina/glass substrate using photo resist spinner. The surface morphology in the form of thin film was investigated with a scanning electron microscope (SEM, LEO-0430 Cambridge) at room temperature.

COMPUTATIONAL DETAILS

The molecular structure, potential energy scan for conformational study and the thermodynamic parameters were computed by *ab initio* Hartree-Fock (HF) and DFT using Gaussian 09 [13] program package employing 6-311G(d,p) basis set based on Becke's three-parameter (local, non-local, HF) hybrid exchange functional with Lee-Yang-Parr correlation functional (B3LYP) [10-12]. Visualization and confirmation of calculated data were done by using the CHEMCRAFT program [14].

RESULTS AND DISCUSSION

Geometric structure/conformational study

Geometry optimization was performed as the first task, using X-ray diffraction parameters [1]. Using the optimized parameters, the potential energy scan has been performed around the bonds C6-C10-C19-O2 and C10-C19-O2-C26, respectively. Four conformers, two regarding to each rotation have been found as shown in the Fig. 1. The geometric parameters and molecular structure shows that the conformer I′ is a form of conformer I, hence the molecule possesses three conformers. Thus, excluding conformer I′ from the list of conformers, we have reported I, II and III as the possible molecular conformers of YHCl as shown in the Fig. 2. Among these three, conformer I is the most stable (having lowest energy), while conformer II is the least stable one. There seems a large drop while going from conformer II to conformer I (i.e., -180^o to 110^o) in the figure 1, which is due to the intra-molecular hydrogen bonding O1-H45…O3. Selected geometric parameters (bond length, bond angle and dihedral angle) of the reported conformers are listed in the Table 3.

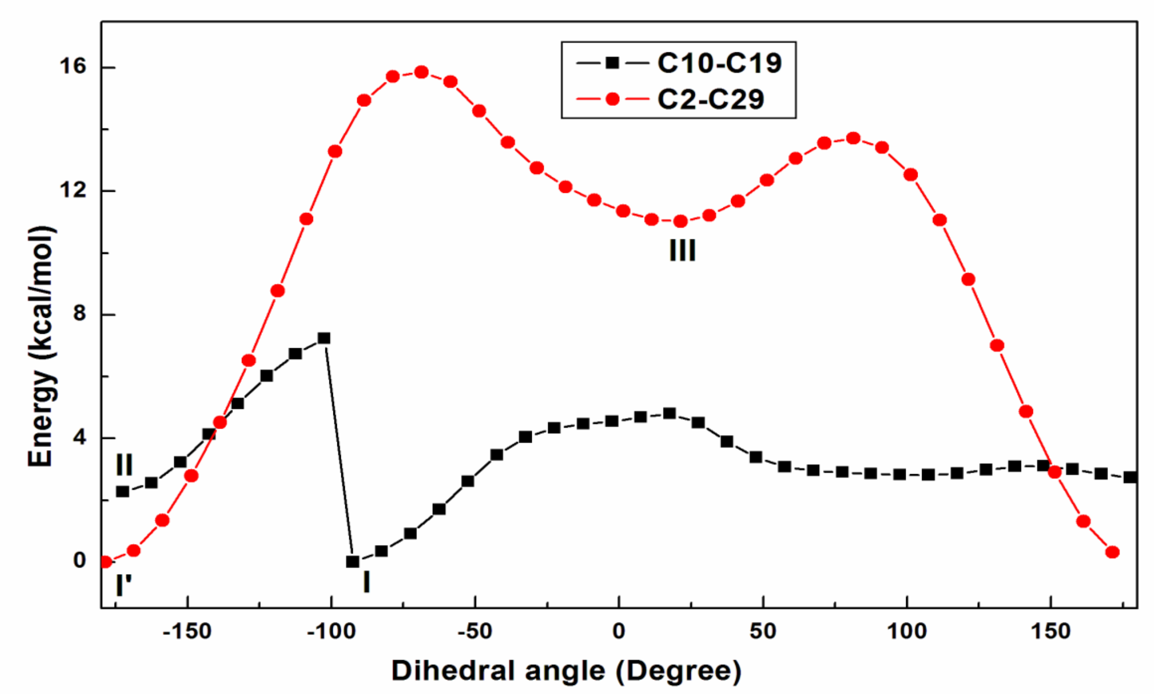

Fig. 1 Potential energy curves obtained on rotation about the dihedral angles C6-C10-C19-O2 (conformers I & II) and C10-C10-O2-C26 (conformers I′ & III).

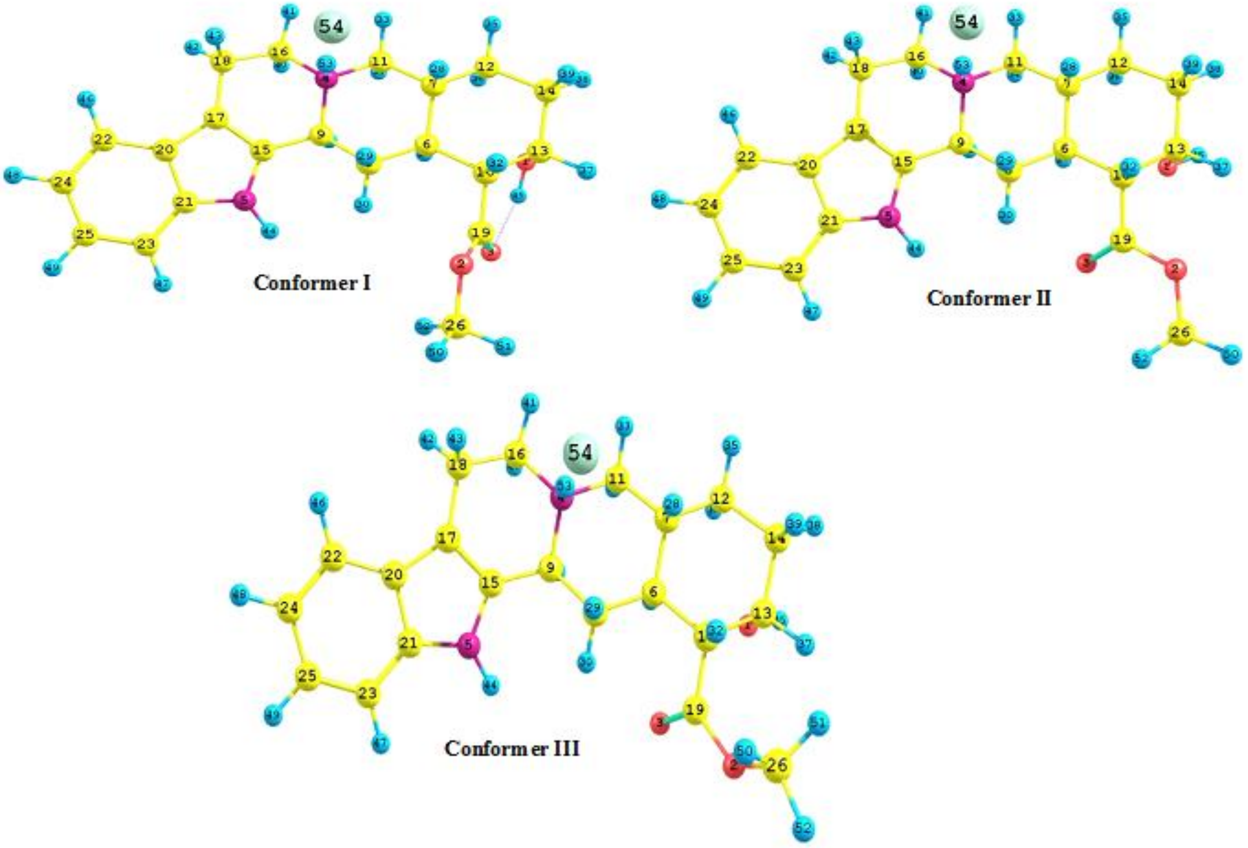

Fig. 2 Optimized structures of different conformers of YHCl.

Another potential energy curve obtained on rotation around the bond C19-O2-C26-H50 shows a uniform curve with equal minima due to tetrahedral structure of methyl group and shown in Fig. 3.

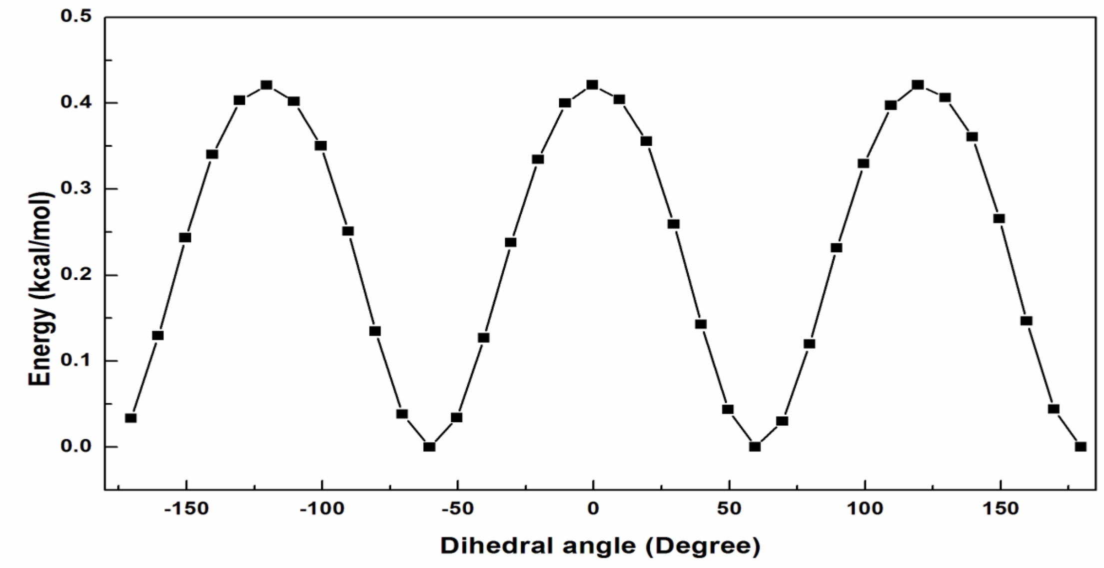

Fig. 3 Potential energy curve about the bond C19-O2-C26-H50.

Table 1. Selected bond lengths (in Å), bond angles (°) and dihedral angles (°) for different conformers of YHCl.

Parameters	CI	CII	CIII
O3-H45	1.970	4.232	4.031
C10-C19-O2	112.47	110.57	118.06
C10-C19-O3	124.95	126.31	124.19
C6-C10-C19-O2	-92.40	-172.45	-163.08
C19-O2-C26	115.89	115.48	130.02
C10-C19-O2-C26	-179.66	-178.71	21.35

SEM analysis

A scanning electron microscope (SEM) is a type of electron microscope that produces images of a sample by scanning it with a focused beam of electrons. A beam of electrons interact with electrons in the sample and produce images containing information about the sample's surface topography and composition. Fig. 4 shows the surface morphologies of YHCl at two different magnifications. These images show that the particles combine with each other to form crystallites, while some spaces between them are left and acts as pores.

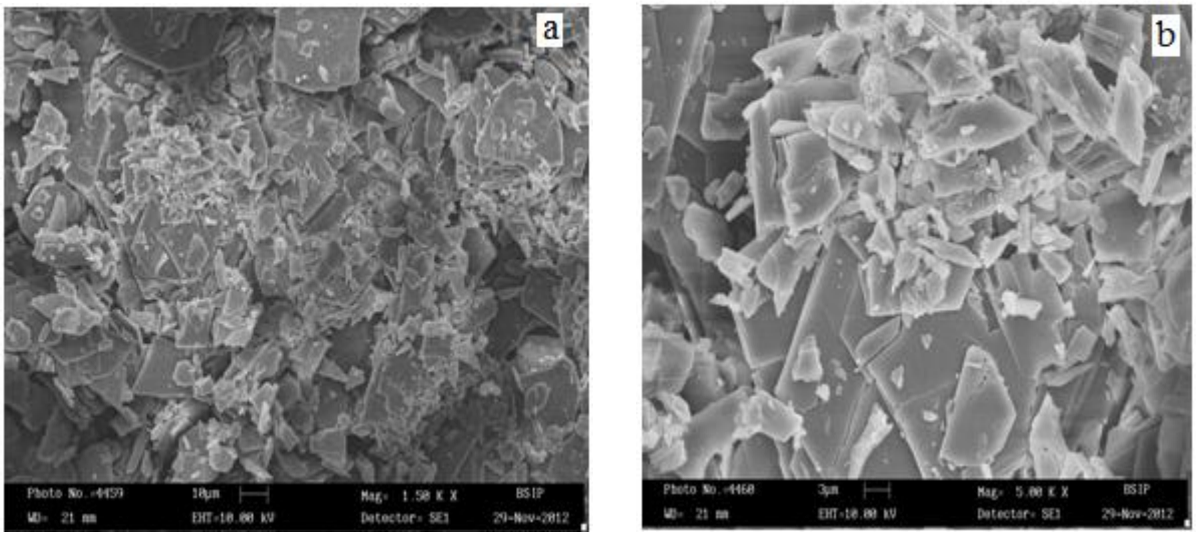

Fig. 4 SEM images of YHCl.

Thermodynamic Properties

Computation of molecular thermodynamic properties has importance in thermochemistry and chemical equilibrium. The relations derived from statistical thermodynamics with the two key ideas, the Boltzmann distribution and the partition function, are used for computing thermochemical data in Gaussian programs. The equations utilized in those programs are given in statistical mechanics texts [15,16]. The partition function is like a thermodynamic wave function, in the sense that it contains all thermodynamic information about the system, just as the quantum mechanical wave function contains all dynamic information [17]. The total energy, zero point energy, rotational constants, dipole moment, heat capacity ($C^{o}_{p,m}$), entropy (S^{o}_{m}) and enthalpy (H^{o}_{m}) of the YHCl were obtained from the output of Gaussian programs using B3LPY employing 6-311G(d,p) basis set and listed in the Tables 2 and 3. From the Table 2, it is observed that the parameters $C^{o}_{p,m}$, S^{o}_{m} and H^{o}_{m} increase with rise in temperature from 100 K to 700 K due to increase in molecular vibtational intensities.

Table 2. Thermodynamic parameters H^{o}_{m} (kJ/mol), $C^{o}_{p,m}$ (J/mol-K) and S^{o}_{m} (J/mol) at different temperature.

Temperature (K)	H^{o}_{m} KJ/mol	$C^{o}_{p,m}$ J/mol-K	S^{o}_{m} J/mol-K
100	1209.011	158.5098	417.9666
200	1230.801	276.7035	570.1144
300	1264.709	403.5456	709.229
400	1311.6	532.8789	845.6182
500	1370.781	647.5572	979.0396
600	1440.457	742.8153	1107.341
700	1518.77	820.906	1229.188

Table 3. Theoretically calculated thermodynamic properties at room temperature using 6-311G(d,p) basis set.

Thermodynamic properties	DFT (B3LYP)	HF
Total energy (eV)	-43870.32	-43653.1
Zero-point energy (kJ/mol)	1200.9942	1280.0266
Rotational constants (GHz)	0.27416 0.10786 0.08747	0.27416 0.10786 0.08747
Dipole moment (D)	6.8619	7.0284
Entropy (J/mol-K)	706.6875	626.7701
Enthalpy (kJ/mol)	1263.965	1334.511
Specific heat (J/mol-K)	401.1086	362.2346

Fig. 5 shows a correlation graph between the thermodynamic properties and the temperature. The correlation equations (1-3) are as follows:

$$H^{o}_{m} = 1196.78614 + 0.05633\ T + 5.78613 \times 10^{-4} T^{2}\ (R^{2} = 0.9991) \qquad \text{……….(1)}$$
$$S^{o}_{m} = 267.00903 + 1.55069T - 2.51792 \times 10^{-4} T^{2}\ (R^{2} = 0.99997) \qquad \text{……….(2)}$$
$$C^{o}_{p,m} = 4.53536 + 1.49908T - 4.61601 \times 10^{-4} T^{2}\ (R^{2} = 0.99889) \qquad \text{………(3)}$$

where R^2 indicates the coefficient of determination for the regression analysis.

These relations could be useful in predicting Gibbs free energy, direction of chemical reaction according to the second law of thermodynamics in the thermodynamic field.

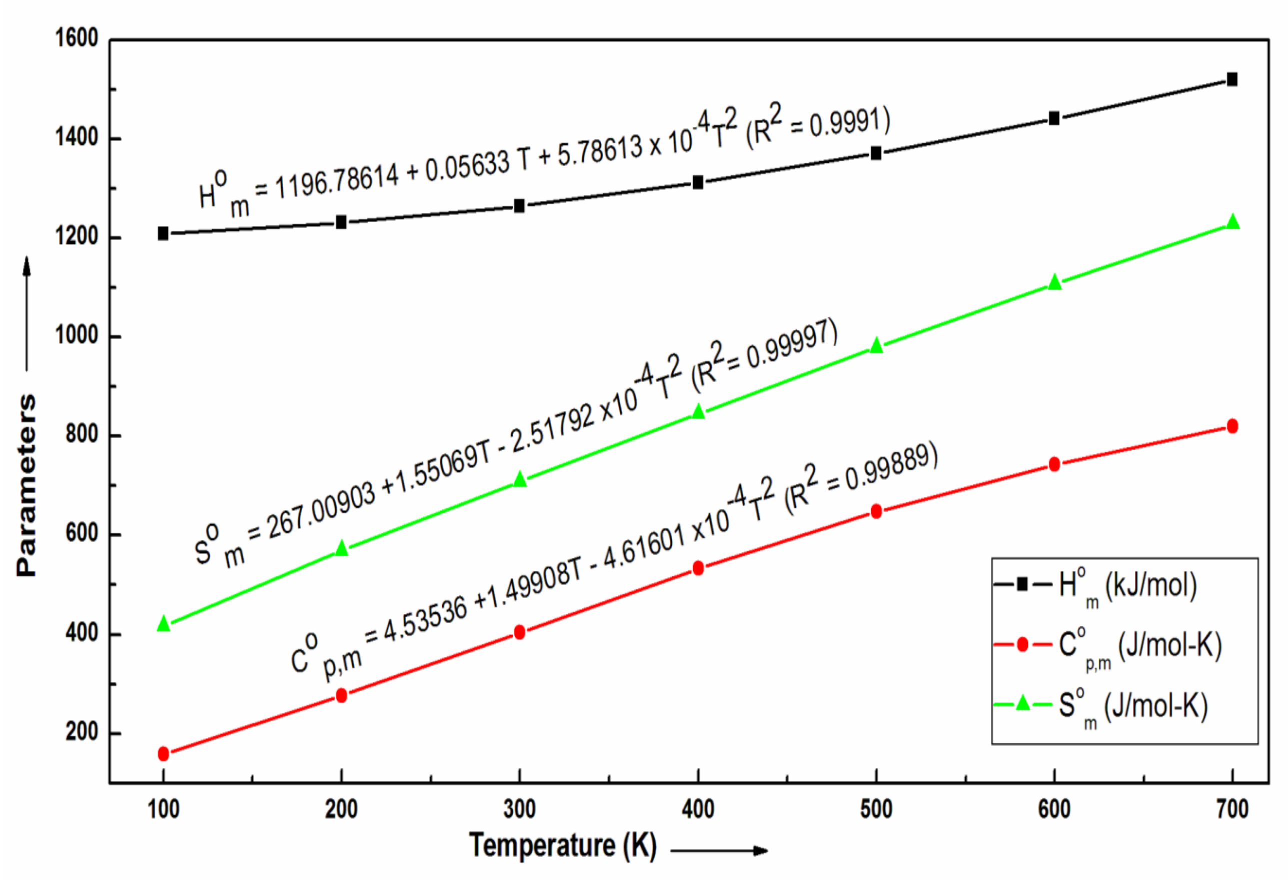

Fig. 5 Thermodynamic parameters (enthalpy, entropy and specific heat) vs temperature.

Global reactivity descriptors

Electronegativity and hardness are two important molecular properties, which are useful for interpreting and understanding the stability and reactivity of molecular systems [12]. According to the Hohenberg and Kohn (HK), theorems [18], the energy of the basic state of an electronic system is a functional of electron density. The process of minimization of these chemical reactivity descriptor functional through the method of Lagrange multipliers, with the restriction that the integral of electronic density over all the space is equal to the total number of electrons N of the molecule, leads directly to the Euler-Lagrange equation [12] of chemical electronic potential (μ). This measures the tendency of the system to attract and retain electrons and defined as the slope of the curve of energy against the number of electrons maintaining the external potential constant. This slope can be described in terms of the ionization potential (I), and the electronic affinity (A). Physically, μ describes the escaping tendency of electrons from an equilibrium system that can be associated with the negative of Mulliken’s electronegativity (χ) [19] as given in equation (4);

$$\mu = - (I+A)/2 = - \chi \qquad \text{…………(4)}$$

The chemical potential that depends upon both the number of electrons and the external potential leads to the definition of two other very important indicators of reactivity: the global hardness and the local indicator of reactivity called the Fukui function [20]. According to Parr and Pearson [21] the global hardness (η) may be defined as the resistance of the chemical potential to change due to variations in the number of electrons and expressed in terms of ionization potential as follows in relation (5);

$$\eta = (I\text{-}A)/2 \qquad \ldots\ldots\ldots\ldots(5)$$

Similarly, global softness (S) is defined as 0.5 times the inverse of global hardness [22]. Both the global hardness and softness are concepts that have been used to explain chemical reactivity. According to Koopman theorem the chemical potential, hardness and softness can be written in terms of the frontier orbital energies (E_{HOMO} and E_{LUMO}). The negative of these two values define the ionization potential and electronic affinity, respectively. The calculated values of the global reactivity descriptos are listed in the Table 4 below:

Table 4. Calculated E_{HOMO}, E_{LUMO}, energy band gap (ΔE), electronegativity (χ), chemical potential (μ), global hardness (η), global softness (s), global electrophilicity index (ω) and additional electronic charge (ΔN_{max}) (in eV) for YHCl, using B3LYP/6-31G.

E_{HOMO}	E_{LUMO}	ΔE	μ	η	S	ω	ΔN_{max}
-5.7218	-0.59206	5.12974	-3.15693	2.56487	0.19494	1.94281	1.23083

According to Parr et al., electrophilicity index (ω) is as a global reactivity index similar to the chemical hardness and chemical potential. This reactivity index measures the stabilization in energy when the system acquires an additional electronic charge (ΔN_{max}) from the environment. The electrophilicity index (ω) is positive, definite quantity and the direction of the charge transfer is completely determined by the electronic chemical potential (μ) of the molecule because an electrophile is a chemical species capable of accepting electrons from the environment and its energy must decrease upon accepting electronic charge. Therefore, its electronic chemical potential must be negative.

Local reactivity descriptors

Using Hirshfeld population analysis of neutral, cation and anion state of molecule, Fukui Functions are calculated using following relations (6-8):

$f_k^+ = [q(N+1) - q(N)]$ for nucleophilic attack ………(6)

$f_k^- = [q(N) - q(N-1)]$ for electrophilic attack ..……..(7)

$f_k^0 = ½[q(N+1) - q(N-1)]$ for radical attack ..…….(8)

where N, N-1 and N+1 are total electrons present in neutral, cation and anion state of molecule, respectively.

In addition to these functions, local softness (s_k^+, s_k^-, s_k^0) and local electrophilicity indices (ω_k^+, ω_k^-, ω_k^0) are also used to describe the reactivity of atoms in molecule. Values of Fukui function and local electrophilicity descriptor of the atoms are listed in the Table 5. These local reactivity descriptors associated with a site k in a molecule are defined with the help of the corresponding ‘condensed to atom’ variants of FF, using the following relations (9,10):

$s_k^+ = Sf_k^+$, $s_k^- = Sf_k^-$, $s_k^0 = Sf_k^0$ and ……….(9)

$\omega_k^+ = \omega f_k^+$, $\omega_k^- = \omega f_k^-$, $\omega_k^0 = \omega f_k^0$ ………(10)

where +, −, 0 signs show nucleophilic, electrophilic and radical attack, respectively.

In YHCl the relative high value of local reactivity descriptors (f_k^+, ω_k^+, s_k^+) at Cl54 and N5 indicate that these sites are more prone to nucleophilic attack whereas the relative values of local reactivity descriptors (f_k^-, ω_k^-, s_k^-) at C17 and O2 indicate that these site are more prone to electrophilic attack.

Table 5. Atomic charges (in esu), Fukui functions (f_k^+, f_k^-); Local softness (s_k^+, s_k^-); and local electrophilicity indices (ω_k^+, ω_k^-); in eV for atomic sites of YHCl, using Hirshfeld population analysis at B3LYP/6-31G(d,p) level.

Atom no.	Hirshfeld atomic charges			Fukui functions		Local softness		Local electrophilicity Indices	
	q_N	q_{N+1}	q_{N-1}	f_k^+	f_k^-	S_k^+	S_k^-	ω_k^+	ω_k^-
1 O	-0.108038	-0.096516	-0.126246	0.0115	0.0182	0.0022	0.0035	0.0223	0.0354
2 O	-0.135634	-0.135343	-0.169896	0.0029	0.0343	0.0006	0.0067	0.0056	0.0666
3 O	-0.266105	-0.257580	-0.338641	0.0085	0.0725	0.0017	0.0141	0.0165	0.1409
4 N	0.124946	0.126937	0.124785	0.0020	0.0002	0.0004	0.0001	0.0039	0.0003
5 N	0.064894	0.138572	0.034567	0.0737	0.0303	0.0144	0.0059	0.1432	0.0589
6 C	0.009378	0.016625	-0.003248	0.0072	0.0126	0.0014	0.0025	0.0140	0.0245
7 C	0.005933	0.005932	-0.001847	0.0000	0.0078	0.0000	0.0015	0.0000	0.0152
8 C	0.022047	0.033298	0.010366	0.0113	0.0117	0.0022	0.0023	0.0220	0.0227
9 C	0.082893	0.107564	0.047687	0.0247	0.0352	0.0048	0.0069	0.0480	0.0684
10 C	0.016522	0.018161	-0.003587	0.0016	0.0201	0.0003	0.0039	0.0031	0.0391
11 C	0.110655	0.131904	0.081775	0.0212	0.0289	0.0041	0.0056	0.0412	0.0561
12 C	0.020233	0.035406	-0.000661	0.0152	0.0209	0.0030	0.0041	0.0295	0.0406
13 C	0.085082	0.097693	0.066470	0.0126	0.0186	0.0025	0.0036	0.0245	0.0361
14 C	0.028928	0.045330	-0.000064	0.0164	0.0290	0.0032	0.0057	0.0319	0.0563
15 C	0.022031	0.079676	-0.025479	0.0576	0.0475	0.0112	0.0093	0.1119	0.0923
16 C	0.117290	0.149214	0.088351	0.0319	0.0289	0.0062	0.0056	0.0620	0.0561
17 C	0.048777	0.049805	-0.081087	0.0010	0.1299	0.0002	0.0253	0.0004	0.2524
18 C	0.041676	0.093197	0.009144	0.0515	0.0325	0.0100	0.0063	0.1001	0.0631
19 C	0.218247	0.226259	0.141770	0.0080	0.0765	0.0016	0.0149	0.0030	0.1486
20 C	-0.032202	-0.018170	-0.055717	0.0140	0.0235	0.0027	0.0046	0.0272	0.0457
21 C	0.038875	0.055632	0.025464	0.0168	0.0134	0.0033	0.0026	0.0326	0.0260
22 C	0.002561	0.088067	-0.090723	0.0855	0.0933	0.0167	0.0182	0.1661	0.1813
23 C	-0.021105	0.060786	-0.109539	0.0819	0.0884	0.0160	0.0172	0.1591	0.1717
24C	-0.013655	0.052748	-0.075615	0.0664	0.0620	0.0129	0.0121	0.1290	0.1205
25 C	-0.006637	0.086875	-0.093294	0.0935	0.0867	0.0182	0.0169	0.1817	0.1684
26 C	0.169287	0.181264	0.114144	0.0120	0.0551	0.0023	0.0107	0.0233	0.1070
54 Cl	-0.549787	-0.330788	-0.571345	0.2190	0.0216	0.0427	0.0042	0.4255	0.0420

CONCLUSION

The geometric structure study with the help of potential energy scan of the title molecule confirms that the three conformers may coexist at the room temperature, among them conformer I is the most stable. The surface morphology by SEM images showed that there are the small pores in between the particles. Therefore, YHCl may have optical properties. The total energy, zero point energy, rotational constants, dipole moment, heat capacity ($C^o_{p,m}$), entropy (S^o_m) and enthalpy (H^o_m) of the YHCl were obtained. The calculated chemical reactivity descriptors show the charge transfer property within the molecule active sites, which involve in biological activities.

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REFERENCES

[1] Ambady, G & Karth G, "Crystal structure and absolute configuration of yohimbine hydrochloride, C21H27ClN2O3", *J. Cryst. Mol. Struct*., 3 (1973)37.

[2] El Gindy A E, Farouk M, Abd El Aziz L, & Shokry E S, "tability Indicating Assay of Yohimbine Hydrochloride Using High Performance Liquid Chromatography", *J. Appl. Sci. Res*., 5 (7) (2009)693.

[3] Goldberg M R & Robertson D, "Yohimbine: a pharmacological probe for study of the α2-adrenoceptor", *Pharmcol. Rev*., 35 (1983)143.

[4] Eweka A O, Om'Iniabohs F A E & Momodu O, "The histological effects of mixed diet containing *Pausinystalia yohimbe* ground stem bark on the kidney of adult Wistar rats (*Rattus norvegicus*)", *Biol. Med*., 2 (1) (2010)30.

[5] Lal S, Thavundayil J X, Krishnan B, Nair N P V, Schwartz G & Guyda H, "The Effect of Yohimbine, an Alpha$_2$ Adrenergic Receptor Antagonist, on the Growth Hormone Response to Apomorphine in Normal Subjects", *J. Psychiat. Neurosci*., 21 (1996)96.

[6] Tibodeau J D, Fox P M, Ropp P A, Theil E C & Thorp H H, **"**The up-regulation of ferritin expression using a small-molecule ligand to the native mRNA PNAS", Proceedings of the National Academy of Sciences, 103(2) January 10 (2006)253.

[7] Andrade S F, Sakate M, Laposy C B & Sangiorgio F, "Yohimbine and Atipamezole on the Treatment of Experimentally Induced Amitraz Intoxication in Cat", *Intern. J. Appl. Res. Vet Med*., 4(3) (2006)200.

[8] Joshi B D, Srivastava A, Tandona P & Jain S,"Molecular structure, vibrational spectra and HOMO, LUMO analysis of yohimbine hydrochloride by density functional theory and *ab initio* Hartree–Fock calculations", *Spectrochim. Acta A*, 82 (2011)270.

[9] Quinton R M, "The increase in the toxicity of yohimbine induced by imipramine and other drugs in mice", *Brit. J. Pharmacol*., 21(1963)51.

[10] Lee C T, Yang W & Parr R G, "Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density" *Phys. Rev*., 37B, (1988)785.

[11] Becke A D, "Density-functional thermochemistry. III. The role of exact exchange", *Chem. Phys*., 98(1993)5648.

[12] Parr R G & Yang W, "Density Functional Theory of Atoms and Molecules", Oxford University Press, New York, 1989.

[13] Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Cheeseman J R*, et al*., Gaussian 09, Revision, Gaussian, Inc., Wallingford CT, 2009.

[14] Zhurko G A & Zhurko D A, Chemcraft (2005) <http://www.chemcraftprog.com>

[15] McQuarrie D A & Simon J D, "Molecular Thermodynamics", *University Science Books*, Sausalito, CA, 1999.

[16] Hehre W J, Radom L, Schleyer P V R, & Pople J A, "*Ab Initio* Molecular Orbital Theory", Wiley, New York, 1986.

[17] Li X W, Shibata E & Nakamura T, "Thermodynamic Properties of Polybrominated Dibenzo-*p*-dioxins and Dibenzofurans Calculated by Density Functional Theory", *Mater. Transact.*, 44(5) (2003)1004.

[18] Hohenberg P & Kohn W, "Inhomogeneous Electron Gas", *Phys. Rev*., (1964) 136B, 864-871.

[19] Parr R G, Donnelly R A, Levy M & Palke W E, "Electronegativity- the density functional viewpoint", *J. Chem. Phys*., 68 (1978)3801.

[20] Yang W & Parr R G, "Hardness, softness and the Fukui function in the electronic theory of metals and catalysis", *Proc. Natl. Acad. Sei*., USA 82 (1985)6723.

[21] Parr R G & Pearson R G, "Absolute hardness: comparison parameter to absolute electronegativity", *J. Am. Chem. Soc*., 105 (1983)7512.

[22] Lee C, Yang W & Parr R G, "Local softness and chemical reactivity in molecules CO, SCN and H2CO", *J. Mol. Struct*. (*THEOCHEM*)*,* 163 (1988)305.