Spectroscopic characterization and electronic structure analysis of Linagliptin by DFT method

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The spectroscopic and electronic characterization of the molecule Linagliptin (LGP), one of the most important type-2 diabetes drugs, has been studied by the quantum mechanical method. The optimized molecular structure, electronic properties, dipole moment, rotational constants and important thermodynamic parameters of LGP molecule have been computed using HF (Hartree-Fock) and DFT (density functional theory) methods with 6-311++G (d,p) basis set. Spectroscopic properties such as FT-IR, Raman and absorption spectra are calculated in different solvents by the TD-DFT method and compared with the experimental data. The various types of intra-molecular interactions such as conjugative, hyper conjugative and other structural effects are analyzed from natural bonds orbitals of LGP. The relationship between linear polarizability and refractive index is used to describe the polarization behaviour of LGP in different solvents. The electronic charge density at different positions and reactivity descriptors of LGP are used in identifying the site of drug interaction. The various intra-molecular interactions are explained in terms of HOMO and LUMO energies. Mulliken charges and thermodynamic properties of LGP are also discussed.

Keywords: Linagliptin, Electronic structure, Spectroscopic properties, DFT

Linagliptin (LGP) or (8-(3-(R)-Aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazoline-2-ylmethyl)-3,7 dihydropyridine-2,6-dione $(C_{25}H_{28}N_8O_2)$ is one of the most important drugs used for treatment of diabetes mellitus type-II. The inhibitor dipeptidyl peptidase-4 (DPP-4) represents a new therapeutic approach to the treatment of type-II diabetes. LGP represent the most recently approved anti-diabetic drugs by both U.S. Food and Drug Administration (FDA) and Europe on 2 May 2011[1]. LGP is a DPP-4 inhibitor with a xanthine-based structure. The similar nature of other drugs of the same class (saxagliptin, sitagliptin, vildagliptin, with the exception of alogliptin) that all are peptidomimetic molecules. LGP was tightly bonded to the core of the DPP-4 enzyme forming three hydrogen bonds between the amino function on the piperidine ring and acceptor groups[2]. LGP is effective in modifying all parameters of hyperglycemia either in monotherapy or as add-on therapy, together with metformin or a sulfonylurea. It also exhibits a good tolerability profile with few side effects, absence (when used in monotherapy), or low risk (when in combination with a sulfonylurea) of hypoglycemia. More importantly, it has a weight neutral effect.

Understanding the versatility behaviour of the compound, the knowledge of its spectral, electronic and optical properties through both experimental and theoretical studies is required. Such study concerning a detailed characterization of LGP is barely available in the literature. In this regard, we performed a detailed experimental and theoretical spectral analysis of LGP. The refractive index, non-linear optical (NLO) parameters, and band gap energy were also computed using the Gaussian 09W program. Geometrical parameters are reported for the ground state of the molecule. The distribution of electron density (ED) in various bonding and anti-bonding orbitals and the energies are studied by NBO analysis to understand the nature of the bond orbital and charge transfer interactions in the drug molecule. HOMO-LUMO analysis has been used to establish charge transfer within the molecule. Mulliken population analysis of LGP is also carried out.

Materials and Methods

The drug Linagliptin (99.5% pure) was purchased from Sigma Aldrich Co. (India). FT-IR spectrum was recorded in a Perkin Elmer spectrophotometer equipped with mercury, cadmium and tellurium detector by incorporating the sample in a KBr pellet. The frequency range is 4000–400 cm^{-1} and resolution is 1.0 cm^{-1}. The FT-Raman spectrum was in region 4000–100 cm^{-1} using a Brucker RFS27 spectrophotometer equipped with Raman module accessory operating at 1.5 W powers with Nd:YAG laser and the excitation wavelength of 1064 nm. Both FT-IR and FT-Raman spectra were recorded in the Regional Sophisticated Centre, Indian Institute of Technology Madras, India. UV-visible spectra were recorded on a Shimadzu UV–1650 model spectrophotometer in the wavelength region 200 – 800 nm at a scanning rate of 0.2 nm/s and a slit width of 1 cm. Further, the baseline correction was done with the solvents (water, methanol, and ethanol) while recording UV spectra.

Computational details

The optimization of molecular geometry and vibrational frequency calculations of LGP were carried with GAUSSIAN 09W software package[3]. Hartree-Fock (HF) method[4] and density functional theory (DFT) method - B3LYP[5] method combined with 6-311++G (d,p) basis set was used. Gauss View interface program was used to get molecular vibrations and their displacement vectors[6]. The prediction of Raman intensities was carried out by the following procedure. The Raman activities (S-Ra) calculated by Gaussian 09 program were converted to relative Raman intensities (I-Ra) using the equation derived from the intensity theory of Raman scattering[7,8]. Scaled IR and Raman frequencies are reported for the investigated molecules[9]. By consideration of the optimized LGP structures, the electronic absorption wavelengths and oscillator strengths of LGP were obtained using the time-dependent DFT (TD−B3LYP level) method and 6-311++G(d,p) basis set.

The electronic transitions, vertical excitation energies, absorbance and oscillator strengths of LGP molecule were computed using TD-DFT/6-311++G(d,p) method. NBO and HOMO–LUMO analyses were performed on the molecule by both HF and DFT methods. These results obtained have been used to calculate thermodynamic properties such as heat capacity, entropy, and enthalpy. Mulliken

charges and molecular properties of LGP (dipole moment, mean polarizability and first static hyperpolarizability) are calculated using the finite field approach.

Results and Discussion

Optimized geometry and bond parameters of LGP

The Fig. 1 shows the most stable optimized structure of LGP obtained through a conformational analysis at HF/6-311++G(d,p) and B3LYP/6-311++G(d,p) level. Table S1 in Supplementary Data shows the optimized parameters of bond length and bond angles of LGP and the values are comparable by both HF and B3LYP methods. The C-O and N-C bond lengths obtained by DFT method are slightly greater than that obtained by the HF method. This comparison was also identified in aliphatic ketones which are present in this molecule[10]. The obtained bond lengths of N5-H45 and N5-H46 are close to 1 Å which is the general bond characteristics of the amino group present in this molecule. The aromatic carbon-carbon bond distances of the piperidine, dihydro purine and quinaldine ring, namely, C11-C12, C13-C14, C14-C15, C17-C18, C19-C24, and C37-C32 bond lengths are almost the same suggesting that the presence of oxygen and other substituent does not influence these bond lengths. The computed bond
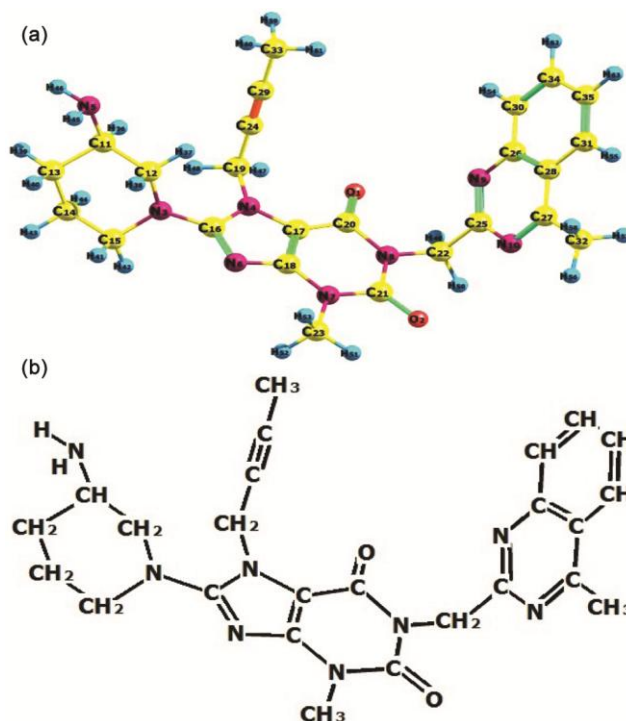

Fig. 1 — (a) Optimized and (b) normal molecular structure of LGP

angles N6–C18–N7 of approximately 127° is most distortion point of diazole ring, and C16–N6–C18 bond angle of 105° is the shortest angle in this molecule. The highest and lowest bond angles present in the diazole is the most important property of this molecule. Combination of C-C with nitrogen and oxygen bond angles are almost 120° and C-C-C bond angle is less than 120°, and it executes no more distortion of piperidine and quinaldine of hexagonal ring structure.

Vibrational assignments

The molecule LGP contains 63 atoms, and it has 182 normal modes of vibration. All the 182 fundamental vibrations are IR active. The harmonic-vibrational frequencies calculated for LGP and experimental frequencies (FTIR and FT-Raman) have been compared in Table S2, in Supplementary Data. Vibrational assignments are calculated using Gauss view and assignments reported in the literature.

The other important double bond stretching vibration corresponding to the C=O, C=C, and C=N bonds are generally considered in the 1650–1750 cm^{-1} region[11]. The C=O, C=C, and C=N stretching vibration are obtained at 1721(152 modes), 1678(150 modes), 1657(148 modes) cm^{-1} by the B3LYP method. Another important mode is C≡C stretching of LGP molecule obtained at 2763 and 2552 cm^{-1} in FT-IR and FT Raman spectrum. It shows better agreement with theoretically calculated value of 2456 cm^{-1} obtained by B3LYP/6-311++G(d,p) method.

The possible modes for amide (NH_2) group are symmetric, asymmetric, asymmetric non-planar deformation or wagging and twisting vibrations. The N-H symmetric stretching vibrations are expected in the region 3500-3300 cm^{-1}. The asymmetric -NH_2 stretching vibration is in the range 3500-3420 cm^{-1} [(Ref. 12)]. In the present study, symmetric NH_2 stretching is at 3222 cm^{-1} in the recorded spectra of LGP. Computed values for the two modes are 3220, 3470, 3555 cm^{-1} (B3LYP) and 3268, 3509, 3580 cm^{-1}(HF). There are differences between computed and experimental values and it may be due to intermolecular interactions in the solid state. The NH_2 wagging mode is different from the other two stretching modes. The NH_2 wagging vibration is similar to the inversion mode of ammonia and it is so strongly harmonic that it cannot be reproduced by harmonic treatment[13,14]. In the present study, the wagging mode of LGP molecule is obtained at 843 cm^{-1} in the FT-IR spectrum. It

shows better agreement with theoretically calculated value 844 cm^{-1} obtained by B3LYP/6-311++G(d,p) method as can be seen in Table S2. The NH_2 rocking, NH_2 scissoring, NH_2 wagging and NH_2 twisting mode are obtained at a different range of 100-800 cm^{-1}. The NH_2 rocking is assigned at 120 cm^{-1} for FT-Raman. This band may be too weak to be observed experimentally. The twisting and rocking vibrations for both the functional groups are present which are mixed with other vibrations.

In LGP, a very important vibration corresponds to the modes involving the vibrations of the ring atoms are observed. For the purpose of easing the analysis, we have classified the structure of LGP into four rings R1, R2, R3, and R4 as shown in Fig. 2. The ring stretching vibrations are complicated combinations of stretching of C–N, C=C, and C–C bonds. The C–C bond obtained from the FT-IR is at 1597 cm^{-1}. The most important ring stretching vibration is the ring
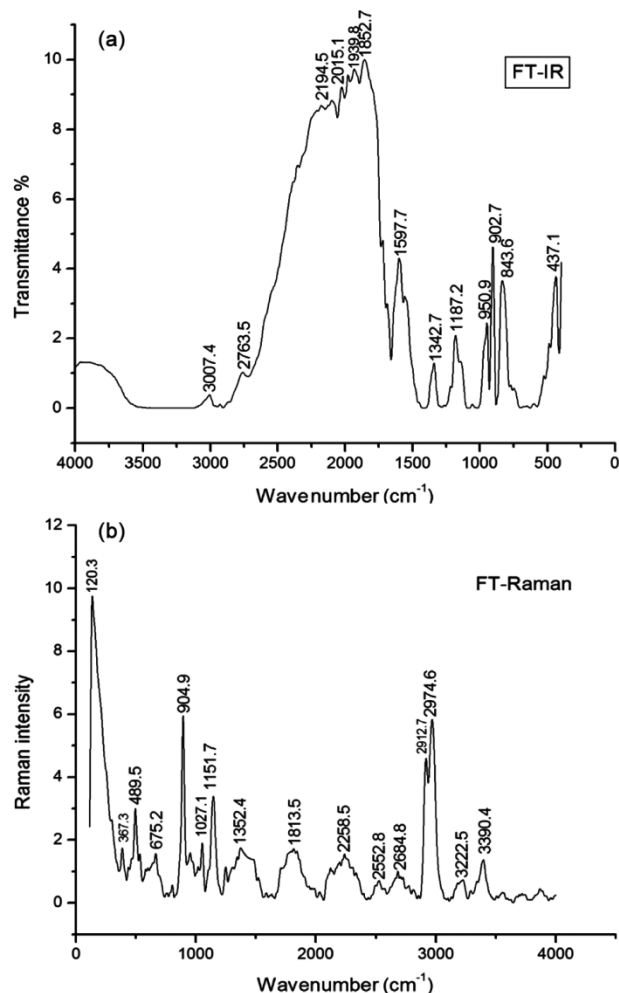

Fig. 2 — (a) FT-IR and (b) FT-Raman spectra of LGP

breathing vibration at mode 55. In this mode, all bonds of the rings appear to stretch and contract in-phase with each other. In the experimental Raman spectrum of LGP, this mode appears at 675 cm^{-1} and other ring vibration modes are present in a mixed profile. The other important functional group in LGP is the methyl (–CH$_3$) group. It produces nine modes of the vibrational methyl group. It shows a number of vibrations and these are distributed throughout the spectrum.

Natural bond orbital analysis

The NBO analysis of electronic charge transfer and intramolecular interaction within the LGP molecule[15] can be clearly understood by the DFT method and predicts satisfactorily the extent of delocalization in organic molecules[16]. The various interactions in LGP molecule from filled orbital of one atom to vacant orbital of another are investigated by NBO analysis. Larger the E(2) value, the more intensive is the interaction between electron donors from electron acceptors. Consequently, larger is the extent of conjugation in the entire molecular system. Delocalization of electrons present in occupied Lewis type (bonding or non-bonding) orbitals and unoccupied (antibonding) non-Lewis type orbitals shows significant donor-acceptor interaction. The interaction energy is obtained from the second-order perturbation theory[17]. The six interactions of the two lone-pairs LP(1) and LP(2) of oxygen, 26 interactions of the lone-pairs LP(1) of nitrogen, 4 interactions involving LP(1) of carbon are assessed using NBO analysis and the results are presented as Supplementary Data in Table S3. Out of the twenty-six interactions involving LP of nitrogen, three are significant. They are n1 N4/σ* N6-C16, n1 N7/σ*C17-C16 and n1 N8/σ*O7-C20. Thus the LP on nitrogen and oxygen atom interacts with the adjacent phenyl carbon atom. Of the four interactions of LP of C26 and C28, four are important and the most important is n1 C28/ σ* N10-C27.

NLO properties

The nonlinear optics (NLO) parameters for molecular systems is most important for electronic communication between electron accepting and donating groups, identifying the intramolecular charge and also to determine the relation between polarizability ($α_o$) which shows the polarization of the compounds through the electromagnetic field of light. It provides the value of susceptibility, $χ(n)$ which is inversely proportional to the value of applied electric field strength(s) and the path length needed to achieve the given nonlinear optical effect[18-20]. By Buckingham's definition, the value of molecular dipole moment, $α_o$, the anisotropy of polarizability and molecular first hyperpolarizability of LGP molecule are calculated by both HF and B3LYP methods and presented in Table 1. The ellipsoids flattered along this plane, contains XXX and XXY having a major part of the first hyperpolarizability. This means that this molecule is optically reactive in the X direction. The highest value of first hyperpolarizability (237.07 e.s.u.) is obtained by B3LYP method (1 a.u. = 8.3693 $×10^{-33}$ e.s.u.). It is interesting to note that first hyperpolarizability of LGP is more than twenty-eight times greater than that of urea, which is one of the prototypical molecules used in the study of the NLO properties. On the basis of high values of dipole moment and first hyperpolarizability, it may be concluded that LGP can possess significant NLO properties.

Electronic charge distribution in LGP

The electronic charge distribution at various positions in the molecule is related to intra-molecular

Table 1 — Component dipole moment, net dipole moment $μ_{tot}$ (D), component polarizability, mean polarizability ($α_o$ /10^{-22} esu), anisotropy polarizability ($Δα$ /10^{-25} esu) and component and total first hyperpolarizability ($β_{tot}$ /10^{-31} esu) values for LGP

Parameters	HF/6-311++G (d,p)	B3LYP/6-311++G(d,p)	Parameters	HF/6-311++G(d,p)	B3LYP/6-311++G(d,p)
$μ_x$	3.77	5.01	$β_{xxx}$	135.56	95.00
$μ_y$	3.05	3.11	$β_{xxy}$	94.55	107.77
$μ_z$	-2.22	-3.68	$β_{xxz}$	-86.60	-72.64
$μ_{tot}$	5.54	6.96	$β_{yyy}$	81.30	51.91
$α_{xx}$	-155.95	-149.21	$β_{yyz}$	-3.06	-19.90
$α_{yy}$	-202.15	-198.10	$β_{xyy}$	3.82	62.52
$α_{zz}$	-204.49	-199.23	$β_{xzz}$	10.05	13.77
$α_{xz}$	13.77	7.73	$β_{zzz}$	-15.69	-26.11
$α_o$	-187.53	-182.18	$β_{yzz}$	-25.68	-2.16
$Δ_α$	-796.3	-747.7	$β_{tot}$	237.07	159.13

interactions of LGP molecule which is computed by Mulliken method[21]. The results obtained at HF and B3LYP methods are presented in Table S4. In the ground state, LGP molecule is neutral and hence total electronic charge on the molecule is zero. It can be seen from the data that the negative charge is delocalized on all the nitrogen and oxygen atoms, but on specific carbon atoms. All the six fluorine atoms are negatively charged. It is seen that the eight nitrogen atoms contain almost the same electronic distribution. Two oxygen atoms are negatively charged as it is part of the dihydro purine group. It is also possible that there may be conjugative electronic interaction involving LP of N7 and N8 atom. Among the eight nitrogen atoms, N5 is found to be electron rich as the negative charge on this atom is high and N4 possess less negative charge. It is due to the fact that this is amino nitrogen and there is no conjugative influence with neighboring groups. The positive charge on C16, C20, and C21 is very high due to the presence of the electronegative three nitrogen and two oxygen atoms. The other five nitrogen atoms are directly attached to C25, C26, and C27 carbon atoms and hence they are also positively charged. The mesomeric interactions exist among the aromatic carbon atoms due to the less positive charge on these three carbon atoms. The other aromatic carbon atoms C30-C35 are negatively charged because they contain hydrogen atoms.

HOMO–LUMO energy

Energies of highest occupy molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very important parameters in quantum chemistry. The frontier molecular orbitals (FMOs) play important role in the optical and electronic properties as well as in UV–visible spectra of organic molecules[22]. The LGT molecule containing conjugated π electrons are characterized by hyperpolarizabilities and analyzed by means of vibrational spectroscopy[23,24]. In most cases, the strongest bands in the Raman spectrum are weak in the IR spectrum and vice versa even in absence of inversion symmetry. But the intramolecular charge transfer from the donor to acceptor group through conjugated single and double carbon-carbon bonds can induce large variation in both the molecular dipole moment and molecular polarizability, making IR and Raman bands relatively strong. At the same time the experimental spectroscopic behaviour

described above is well accounted for by HF calculations in π conjugated systems that predict exceptionally large Raman and Infrared intensities for the same normal modes. It is also observed that in our title molecule the bands in the FT-IR spectrum have their counterparts in Raman. The relative intensities in IR and Raman spectra are resulting from the electron cloud moment through π conjugated framework from the electron donor to electron acceptor groups. The interaction between HOMO and LUMO orbital, with transition of $\pi–\pi^*$ type is observed with regard to the molecular orbital theory[25]. Therefore, while the energy of the HOMO is directly related to the ionization potential, LUMO energy is directly related to the electron affinity. The energy difference between HOMO and LUMO orbital is called an energy gap that is important for the stability of structure[26]. The atomic orbital compositions of the frontier molecular orbital are sketched in Fig. 3 and their values are listed in Table 2.

Global and local reactivity descriptors

The electronic transport properties of this molecule are identified based on energy gap between HOMO and LUMO. This HOMO and LUMO energy values are related with global chemical reactivity descriptors of organic molecules such as hardness, chemical potential, softness, electronegativity, and electrophilicity index as well as local reactivity can be calculated[27-30]. Pauling introduced the concept of electronegativity as the power of an atom in a molecule to attract electrons to it. Hardness (η), chemical potential (μ) and electronegativity (χ) and softness is defined as follows:

$$\eta = \frac{1}{2}\left(\frac{\partial_2 E}{\partial N_2}\right) V(r) = \frac{1}{2}\left(\frac{\partial_\mu}{\partial N}\right) V(r)$$

$$\mu = \left(\frac{\partial E}{\partial N}\right) V(r)$$

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right) V(r)$$

In the above equations, E and V(r) is electronic energy and external potential of an N-electron system, respectively. Softness (σ) is a property of a molecule that measures the extent of chemical reactivity. It is the reciprocal of hardness. Using Koopman's theorem for closed-shell molecules, η, μ and χ are related to ionization potential (I) and electron affinity (A) of the molecule as

LUMO = − 0.815 eV

HOMO = −0.238 eV
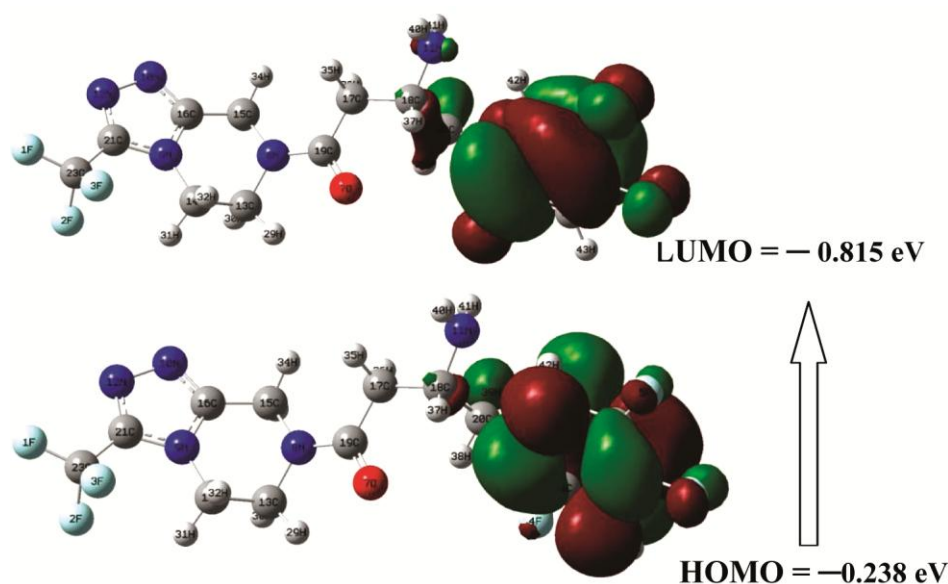
Fig. 3 — HOMO – LUMO energy diagram of LGP; Energy gap ΔE = 0.577 eV

Table 2 — HOMO, LUMO energy values, chemical hardness (η), electronegativity (χ), chemical potential (μ), electrophilicity index (ω) and softness (σ) of LGP in gas phase

Parameters	HF/6-311++G (d,p)	B3LYP/6-311++G(d,p)
E_{total} (kJ/ mol^{-1})	-5.48 x 10^5	-6.47 x10^5
E_{HOMO} (eV)	0.284	-0.238
E_{LUMO} (eV)	-1.230	-0.815
$\Delta E_{HOMO-LUMO}$ (eV)	1.514	0.577
η	0.181	0.069
χ	−0.112	−0.126
μ (eV)	0.112	0.126
ω	0.034	0.115
σ	5.51	14.45

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

$$\mu = \frac{-(I + A)}{2}$$

$$\chi = \frac{(I + A)}{2}$$

The ionization energy and electron affinity can be computed from HOMO and LUMO orbital energies. The ionization potential calculated by HF and B3LYP methods for LGP is 1.514 eV and 0.577 eV, respectively. With regard to chemical hardness, large HOMO–LUMO gap means a hard molecule and small HOMO– LUMO gap means a soft molecule. The stability of a molecule and its reactivity can be related to hardness. Generally, a molecule with least HOMO–LUMO gap (the soft molecule) is more reactive. Parr *et al.*[30] have proposed electrophilicity index (ω) as a

measure of energy lowering due to maximal electron flow between donor and acceptor.

$$\omega = \frac{\mu^2}{2\eta}$$

Using the above equation, the chemical potential, hardness, and electrophilicity index have been calculated for LGP and these values are shown in Table 2. The usefulness of this new reactivity quantity has been recently demonstrated in understanding the toxicity of various pollutants in terms of their reactivity and site selectivity[31,32]. The electrophilicity index has been used as a structural depicter for the analysis of the chemical reactivity of organic molecules[33,34]. Domingo *et al.*[35] proposed that high nucleophilic and electrophilic heterocycles corresponds to opposite extremes of the scale of global reactivity indexes. A good, more reactive nucleophile is characterized by a lower value of μ, and vice versa. A good electrophile is characterized by a high value of μ, ω. The electronegativity and hardness are used extensively to predict the chemical behaviour and to explain aromatic behaviour in organic compounds[36]. A hard molecule has a large HOMO–LUMO gap and a soft molecule has a small HOMO–LUMO gap. HOMO- LUMO energy, η, χ, μ, ω and σ values and dipole moment computed for LGP molecule in the gas phase are listed in Table 2. In the present computational study, HF method gave higher values of HOMO-LUMO energy gap and chemical hardness than B3LYP method. Similar values of other

molecular properties are obtained in both the methods. LGP molecule has very low values of μ, ω indicating that LGP acts more as a nucleophile than an electrophile. Relatively high values of HOMO-LUMO energy gap and chemical hardness indicate the significant aromatic character of LGP. This is probably due to the presence of two benzene rings and one pyrazole ring in the LGP molecule.

Analysis of UV-visible spectra

Electronic spectra of LGP in three different solvents are recorded and analyzed. Experimental electronic spectra of the compound observed in water, ethanol, and methanol solutions are presented in Fig. 4. Three bands are expected in the electronic spectra of LGP in the three solvents used in the present investigation (Table 3). These absorptions are
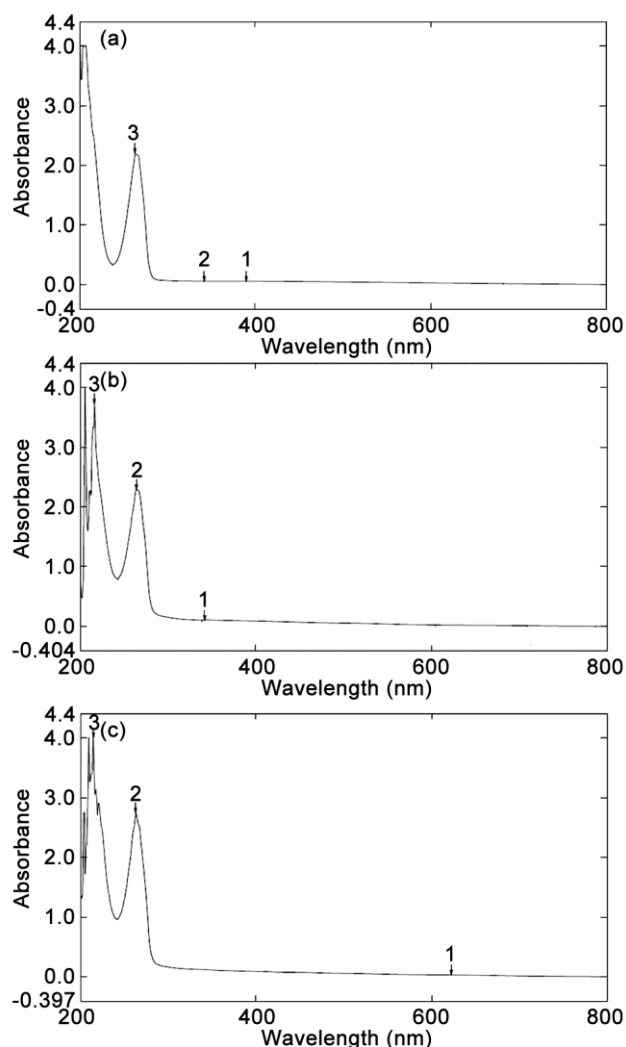

Fig. 4 — Experimental UV spectra of LGP in (a) water (b) ethanol and (c) methanol

due to π-π* and n-π* transitions. The λ_{max} at short wavelengths are due to π-π* transition and those at longer wavelengths are due to n-π*. It can be seen from the data in Table 3 that as the polarity of the solvent is increased, there is a bathochromic shift in both the computed and experimental absorptions, on going from less polar to more polar molecule[37]. The observed λ_{max} values are greater than the computed values in three solvents. This may be due to intermolecular hydrogen bond interaction between solvent molecules and LGP molecule. Molecular orbital coefficients based on the optimized geometry indicate that electronic transitions corresponding to above electronic spectra are mainly LUMO and HOMO-LUMO for the title compound. Fig. 4 shows the surfaces of HOMO and LUMO in LGP molecule[38].

Thermodynamic properties

The standard thermodynamic properties, zero-point vibrational energy (kJ mol^{-1}), thermal energy, molar heat capacity, standard molar entropy, standard Gibbs free energy and standard enthalpy are computed for LGP molecule at 298 K by both HF and B3LYP methods. These calculated values are shown in Table 4. The computed data indicate that total energy value calculated at B3LYP method gave higher values than that obtained at HF method. In the case of other thermodynamic functions, the values obtained in the HF method are greater than those obtained in the DFT method. The value of ZPVE (1458.16 kJ mol^{-1}) for LGP obtained in HF/6-311++G (d,p) method is higher than the value obtained in the B3LYP method. These standard thermodynamic parameters functions for the title molecule were calculated at 298 K by employing Perl script THERMO. PL[39]. The molar heat capacity is high which may be due to the high vibrational

Table 3 — Experimental (Obs. λ_{max}) and Computed electronic spectral data of LGP (wavelength of maximum absorption, λ_{max}, excitation energies E and oscillator strengths (f) using TD-DFT/B3LYP/6-311++G (d,p) method along with experimental λ_{max} values in different solvents

Solvent	Obs. λ_{max} (nm)	λ (nm)	ΔE (eV)	f (a.u.)
Water		371.98	3.33	0.0006
		334.79	3.70	0.0041
	305.50	322.60	3.84	0.0003
Ethanol		367.27	3.57	0.0007
		337.18	3.67	0.0044
	296.50	321.98	3.80	0.0003
Methanol	359.50	371.88	3.33	0.0006
	294.50	335.60	3.69	0.0041
	221.50	322.32	3.84	0.0003

Table 4 — Computed total energy, zero-point vibrational energy, thermal energy, molar heat capacity, standard molar entropy, standard Gibbs free energy, and standard enthalpy of LGP

Parameters	HF/6-311++G (d,p)	B3LYP/6-311++G(d,p)
SCF energy (a.u.)	-1547.64	-1557.48
Zero-Point vibrational energy (kJ mol^{-1})	1458.16	1366.46
Thermal Energy (kJ mol^{-1})	1583.10	1481.71
Molar capacity at constant volume (J K^{-1} mol^{-1}),	443.50	438.25
Entropy (J K^{-1} mol^{-1})	736.50	675.92
Gibbs free energy (kJ mol^{-1})	499.11	468.79
Enthalpy (kJ mol^{-1})	582.75	545.55

contribution of LGP at 298 K obtained in the HF method (443 J K^{-1} mol^{-1}). Comparable values are obtained for Gibb's free energy, enthalpy and entropy of LGP by HF method and B3LYP methods. The mechanism of drug action involving LGP can be analyzed form the thermodynamic functions of LGP reported in the present work. These values can be used to compute the changes in thermodynamic functions and predict the feasibility of chemical reactions involving the drug using the second law of thermodynamics[40,41]. In this regard, it is to be pointed out that all thermodynamic parameters of LGP were computed in the gas phase and when the investigation is done in a solvent, suitable solvation correction is to be incorporated.

Conclusions

In the present work, we have calculated the geometric parameters, vibrational frequencies, frontier molecular orbitals, electronic parameter and the nonlinear optical properties of Linagliptin using HF and DFT/B3LYP methods. Optimized geometry clearly shows that the structure of the title molecule is non-planar. The higher frontier orbital gap of 1.514 eV shows that Linagliptin has high kinetic stability and can be termed as a hard molecule. However, the higher value of dipole moment shows that the molecule is highly polar. The nonlinear optical behaviour of title molecule was investigated by the determination of the dipole moment, the polarizability, and the first static hyperpolarizability using density functional B3LYP method. In general, good agreement between experimental and calculated normal mode of vibrations have been observed. The present quantum chemical study may further play an important role in understanding the structure, activity, and dynamics of Linagliptin molecules.

Supplementary Data

Supplementary data associated with this article are available in the electronic form at http://nopr.niscair.res.in/jinfo/ijca/IJCA_60A(09)1172-1180_SupplData.pdf.

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