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HOMO –LUMO Analysis of Dasatinib

K. Rajalakshmi[a]and DurgeshKumar Nayak[b]

[a, b] Department of Physics,
Sri ChandrasekharendraSaraswathiViswaMahaVidhyalaya, Kanchipuram,

Corresponding author: k_rajalakshmi123@yahoo.com

Abstract

The molecular vibrations of Dasatinib, one in all the necessary cancer medication that slows the expansion and unfold of cancer cells within the body are investigated at room temperature by Fourier Transform Infrared (FTIR) and Fourier Transform Raman (FTR) qualitative analysis. The FTIR and FT-Raman spectra of the title compound are recorded within the region 4000-400 cm^{-1} and 4000-100cm^{-1} respectively. A satisfactory band assignment has been created on the basic modes of vibrations using the ab-initio Hatree-Fock (HF) and Density Functional Theory (DFT) by using B3LYP functional at 6-31G (d, p) levels. The theoretical vibrational frequencies and parameters like bond lengths and bond angles are calculated and compared with the experimental values .The highest occupied molecular orbital (HOMO) and lowest un-occupied molecular orbital (LUMO) energies are calculated with B3LYP/6-31G (d, p) level. These calculated energies show that charge transform takes place among the molecule. The other molecular properties like thermodynamic properties and Mulliken population analysis of title compound has been calculated. It has been found that each ways gave consistent knowledge for geometric parameters. However DFT yielded vibrational frequencies much closer to experimental values.

Keywords: Dasatinib, HF, DFT, FTIR, FT-RAMAN

INTRODUCTION

Dasatinib with the molecular formula $C_{22}H_{26}ClN_7O_2S$ is a cancer medicine that slows the growth and spread of cancer cells in the body. It is commonly called Sprycel. Its IUPAC name is N-(2 cloro-6- methylphenyl)-2-[[6-[4-(2 hydroxyethyl) piperazin -1-yl]-2-methylpyrimidin -4-yl]amino] -1, 3-thiazole-5-carboxamide. It is used to treat Chronic Myeloid Leukemia(CML) [1].And Acute Lymphoblastic Leukemia (ALL) [2]. When all other cancer treatments have not been effective. Sprycel can lower blood cells. That helps body fight infections and helps blood to clot. Blood will need to be tested often and cancer treatments may be delayed based on the results of these tests.

EXPERIMENTAL: STRUCTURE AND SPECTRA

The Spectroscopically pure grade sample of dasatinib was procured from a reputed pharmaceutical company, M/s. Sigma Aldrich Co., with a stated purity of 99% and was used as such without further purification. The Fourier transform infrared spectra are recorded using Perkin Elmer spectrometer in KBr dispersion in the range of 4000 to 400 cm^{-1}. The FT-Raman spectrum of dasatinib was recorded using the 1054 line of Nd: YAG Laser as excitation wavelength in the region 4000-100 cm^{-1}in the solid state at SAIF, IIT Madras, Chennai, India.

COMPUTATIONAL DETAILS

In the present work, the density functional method (DFT) has been employed using Beck's three parameter hybrid exchange functional with the Lee-Yang –Parr correlation[3] functional to optimize the structure of the molecule and also to calculate the electronic structure of the title molecule [4]. The entire calculations were performed at ab-initio Hartree Fock(HF) and DFT method using B3LYP levels at 6-31 G(d,p) basis sets on aPentium V/ 1.6 GHz personal computer using Gaussian 09W [5] program package and applying geometry optimization Initial geometry generated was minimized at the Hartree Fock level using
6-31 G (d,p) basis set.

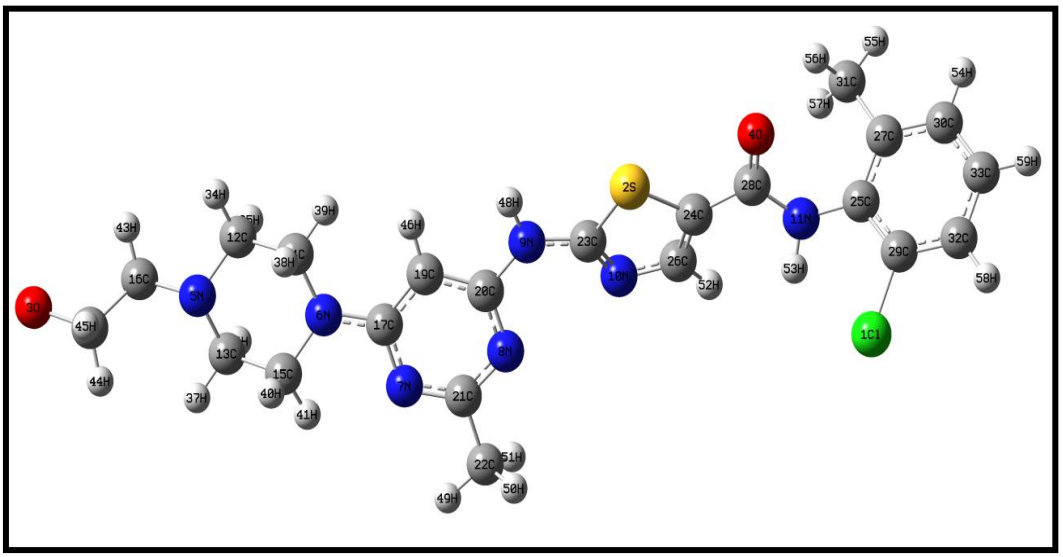

Fig:1 Geometry of Dasatinib Optimized at DFT/B3LYP/6-31 G (d, p) level

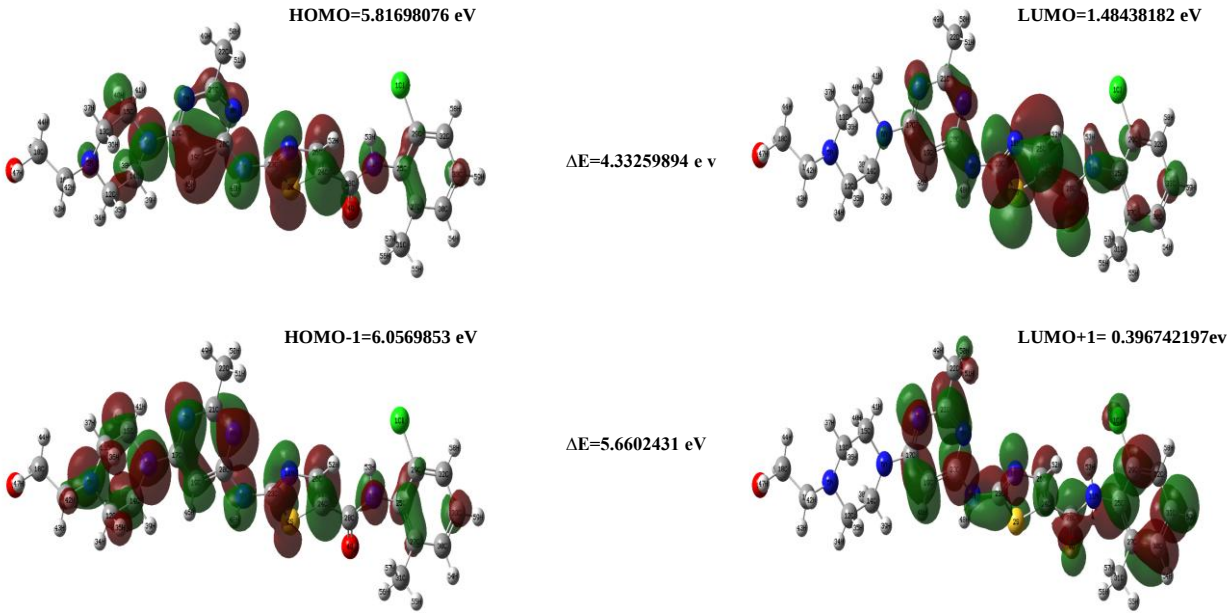

Fig: 2 Electron density plot for the frontiermolecular orbitals of Dasatinib

Table-1 Selected occupied and unoccupied molecular orbital energies and energy gap of Dasatinib

Molecular orbitals	**Energy**	**Energy Gap(ΔE)**	
		Orbitals	**Possible Molecular Orbital Energy Transition**
occupied HOMO	5.81698076 eV	HOMO-LUMO	4.33259894 eV
HOMO-1	6.0569853 eV	HOMO-1 & LUMO+1	5.6602431 eV
HOMO-2	6.26787365 eV		
HOMO-3	6.40692389 eV		
Unoccupied LUMO	1.48438182 eV	HOMO-2 & LUMO+2	6.03684887eV
LUMO+1	0.396742197ev		
LUMO+2	0.231024778ev	HOMO-3 & LUMO+3	6.20147783eV
LUMO+3	0.205446062eV		

FRONTIER MOLECULE ORBITALS

The highest occupied molecular orbital, HOMO, and the lowest unoccupied molecular orbital, LUMO, of a molecule are called the frontier orbitals. It was Fukui [6] who first noticed the prominent role played by HOMO and LUMO in governing chemical reactions. The positive phase is represented in red colour and the negative phase is represented in green colour. The energy gap of HOMO–LUMO explains the charge transfer interaction within the molecule.The HOMO–LUMO analysis for Dasatinib was conducted byB3LYP/6-31G (d, p) level of theory.

The gaps between Homo & Lumo of Dasatinib is 4.33259894eV.Similarly for HOMO-1 and LUMO+1 is 5.6602431 eV.This large gap indicates that charge transfer is taking place within the molecule. The energy gap measures the kinetic stability of the molecules.A large gap implies high stability and small gap implies low stability [7]. The high stability in turn indicateslow chemical reactivity and small gap indicates high chemical reactivity. A molecule having higher Soft value is more reactive than a molecule havingsmaller Soft value. In general, it can be said that the increase in softness increases chemical reactivity and increasein hardness decreases chemical reactivity.The energy gap between HOMO and LUMO has been used to prove the bioactivity of the molecule. More gaps also indicate that the molecule is less polarised and is known as hard molecule and it implies high stability being less chemical reactivity. The different value of Homo and Lumo has mentioned on the above Table 1.

OTHER MOLECULAR PROPERTIES

The thermodynamic properties and Mulliken population analysis calculated at HF and DFT/B3LYP/631 G (d,p) levels of the title compound are presented in Table 2 and Fig-3 respectively. According to HF and B3LYP calculations, the largest dipole moment were observed for HF and decrease in the energy were observed for DFT [8].

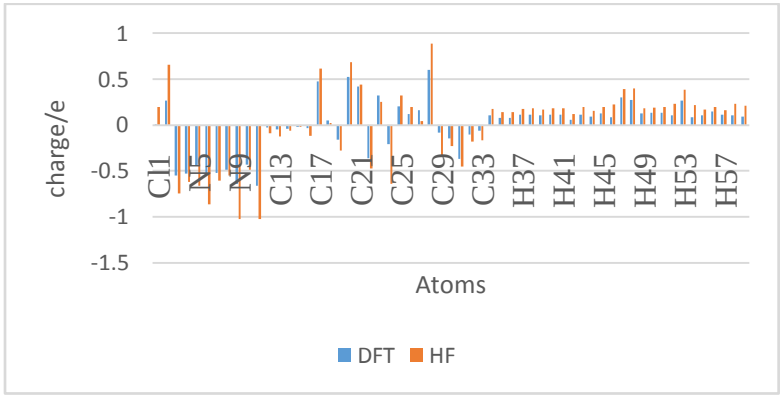

Fig-3: Mulliken draw for Dasatinib

Table 2: Thermodynamical properties of Dasatinib

Thermodynamic parameters	HF/ 6-31 G (d,p)	DFT/B3LYP/ 6-31 G (d,p)
SCF energy (a.u.)	-2235.433	-2246.110
Total energy (thermal) E_{total}(Kcal mol^{-1})	339.476	316.332
Vibrational energy, E_{vib}(Kcal mol^{-1})	337.698	314.554
Zero point vibrational energy (Kcal mol^{-1})	320.636	296.23519
Specific heat, C_v (cal $mol^{-1}K^{-1}$)	109.886	119.241
Entropy, S(cal $mol^{-1}K^{-1}$)	209.509	216.097
Rotational constants (GHz)		
X	0.420	0.398
Y	0.026	0.026
Z	0.025	0.026
Dipole moment μ(Debye)		
μ_x	-0.024	-2.323
μ_y	0.582	-0.956
μ_z	-3.281	1.839
Total	3.333	3.114

The mulliken population analysis of Dasatinib has been calculated by takeing atoms along x-axis and charge(e)along y-axis using DFT/B3LYP/6-31 G(d,p) being colour blue and HF/6-31 G(d,p) levels having colour orange.The Mulliken charge distribution is shown in figure-3.The charge distributionof the molecule in Fig -3 shows that the carbon atoms attached to oxygen atoms have positive charges. And some of the carbon atoms attached to nitrogen atom are negative. The oxygen atoms(O_3, O_4) have more negative charges and this result suggest that the atoms bonded oxygen atoms are electron acceptor.And more positive charge density has been found at C_{28} than that ofother ring carbon atoms and this is 0.600437e for DFT and 0.88956e for HF. The high positive charge at C_{28}inMulliken atomic charges are due to the effect of oxygen (O_4) atom attached with it[9]. Similarly N_{10} has the highest negative charge for DFT it is -0.429825e and for HF it is -0.486250e this happens due to the attach of two double bonded carbon atoms with this (c_{23},c_{26}).

CONCLUSIONS

The present investigation thoroughly analyzed the vibrational spectra, both infrared and Raman of Dasatinib,The optimized geometries, harmonic vibrational wavenumbers and intensities of vibrational bands of Dasatinibhave been carried out using the DFT/B3LYP method using the standard 6-31 G (d,p)basis set.

HOMO-LUMO analysis shows that charge transfer takes place within the molecule which supports the bioactive property of the molecule.For the molecule Dasatinib the energy gap is more. So it represents high stability and represents less chemical reactivity. It canbe said thatIncrease in softness Increase chemical reactivity .Thus it confirms the molecule having a higher hard value.

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