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Electronic Structure And Vibrational Analysis Of Norclozapine (8-Chloro-11-Piperazine-1-Yl-5H-Dibenzo[B,E] [1,4]Diazepine)

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Abstract

Introduction: N-desmethyl clozapine or norclozapine is a benzodiazepine substituted with chloro and piperazino groups which is a major metabolite of clozapine; a potent and selective 5-HT2C serotonin receptor antagonist. It has a role as a metabolite, a delta-opioid receptor agonist, and a serotonergic antagonist. It is a dibenzodiazepine, a member of piperazines, and an organochlorine compound.
Methods: The structure and the ground state energy of the molecules under investigation have been analyzed employing the DFT / B3LYP level. The optimized geometry and their properties such as equilibrium energy, frontier orbital energy, dipole moment, and vibrational frequencies have been used to understand the activity of Norclozapine.
Results: The calculated highest occupied molecule orbital or HOMO and the lowest unoccupied molecular orbital or LUMO energies show that charge transfer within the molecule. The vibrational spectra of IR and Raman have been interpreted with the help of the B3LYP level of theory with the 6-31G basis set from the Density function theory.
Conclusions: The optimized structural parameters such as bond lengths, and bond angle were determined at B3LYP level theory with a 6-31G basis set. Simulation work of Norclozapine is in process. Simulation report of Norclozapine we will report very soon.

Keywords: **Vibrational spectra, DFT, HOMO, LUMO, antipsychotic**

1. Introduction

N-Desmethylclozapine (NDMC), or norclozapine, is a major active metabolite of the atypical antipsychotic drug clozapine [1]. Unlike clozapine, it possesses intrinsic activity at the D_2/D_3 receptors and acts as a weak partial agonist at these sites similar to aripiprazole and bifeprunox [2]. Notably, NDMC has also been shown to act as a potent and efficacious agonist at the M_1 and δ-opioid receptors, unlike clozapine as well.

It was hypothesized that on account of these unique actions, NDMC might underlie the clinical superiority of clozapine over other antipsychotics [3-5]. However, clinical trials found NMDC itself ineffective in the treatment of schizophrenia. This may be because it possesses relatively low D_2/D_3 occupancy compared to 5-HT_2 (<15% versus 64-79% at a dose of 10–60 mg/kg s.c. in animal studies) [2].
In any case, though not useful in the treatment of positive symptoms on its own, it cannot be ruled out that NDMC may contribute to the efficacy of clozapine on cognitive and/or negative symptoms [4].

2. Objectives

The development of simple to use and cost-effective spectroscopy methods have led to an exponential growth of research and literature in the area of pharmaceutical science [6].These methods are based on the study of changes in the molecular vibrational state caused by the energy transferred by incident photons after the interaction of molecules with electromagnetic radiation [7-9]. In this paper vibrational analysis of N-Desmethylclozapine, or Norclozapine, which is a major active metabolite of the atypical antipsychotic drug clozapine will be carried out to find its Electronic Properties (HOMO and LUMO energy) andoptimized geometrical structural parameterssuch as bond lengths, bond angle using B3LYP level theory with 6-31G basis set [8, 10-12].

3. Materials & Methods

3.1 Materials & Technique

DFT is a computational quantum mechanical modeling method in physics, chemistry, and material sciences [4]. In the present contribution, the properties can be calculated with DFT, such as geometries, energies, and spectroscopic properties [7]. Density functional theory (DFT) calculations have been performed to predict the IR and Raman spectra for the molecule [11]. Fourier transform infrared (FTIR) and Raman spectra of the compound have been obtained experimentally. All FTIR and Raman bands of the compound obtained experimentally were assigned based on the modeling results obtained at the B3LYP/6-31G level. Calculations were performed using the Gaussian 09 [12]. Gaussian is a general-purpose computational chemistry software package. A basis set in theoretical and computational chemistry is a set of functions (called basis functions) that is used to represent the electronic wave function in the density-functional theory. DFT methods with 6-31G basis set calculations were made first to optimize the structures [5, 9]. The vibrational frequencies and non-linear optical properties were calculated using DFT methods at the corresponding optimized geometries. All the calculations converged to an optimized geometry which corresponds to a true energy minimum as revealed by the lack of imaginary values in the calculated vibration frequencies. Vibration frequencies are calculated using B3LYP/6-31G [11-14].

3.2 Optimized geometrical structure of Norclozapine

The optimized geometrical structure of Norclozapine is shown in figure1.

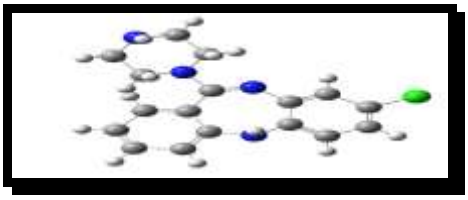

Figure 1 Structure of a Norclozapine Molecule

3.3 IR and Raman Frequency

Infrared spectroscopy involves the interaction of infrared radiation with matter [8]. It covers a range of techniques, mostly based on absorption spectroscopy. An IR spectrum can be visualized in a graph of infrared light absorbance (or transmittance) on the vertical axis vs. frequency or wavelength on the horizontal axis [15].

4. Results

Raman Spectra

RAMAN spectrum is a plot of the intensity of RAMAN scattered radiation as a function of its frequency difference from the incident radiation (usually in units of wavenumbers, cm^{-1}) [4]. This difference is called

the RAMAN shift because it is a difference value, the Raman shift is independent of the frequency of the incident radiation.Figures 2 and 3 show the calculated IR and Raman of Norclozapine [4].

Depolarization Spectra

The depolarization ratio is the intensity ratio between the perpendicular component and the parallel component of the Raman scattered light. Two polarization occur i.e. p- polarization and u- polarization [4,10]. The optimized spectra of p-depolarization and u-depolarization are shown in fig-4 and fig-5 [17]. Theoretically computed ground state optimized parameters-

Table 1. Ground State Optimized Parameters of Norclozapine

Parameters	Norclozapine (B3LYP/6-31G)
Energy	-1337.0100936a.u.
Dipole moment (in Debye)	5.4362Debye

The HOMO and LUMO energy calculated by B3LYP /6-31G method –

Table 2. HOMO and LUMO Energy of Norclozapine

HOMO Energy	-0. 20006a.u.
LUMO Energy	-0.05907a.u.
Energy gap	0.14090 a.u.

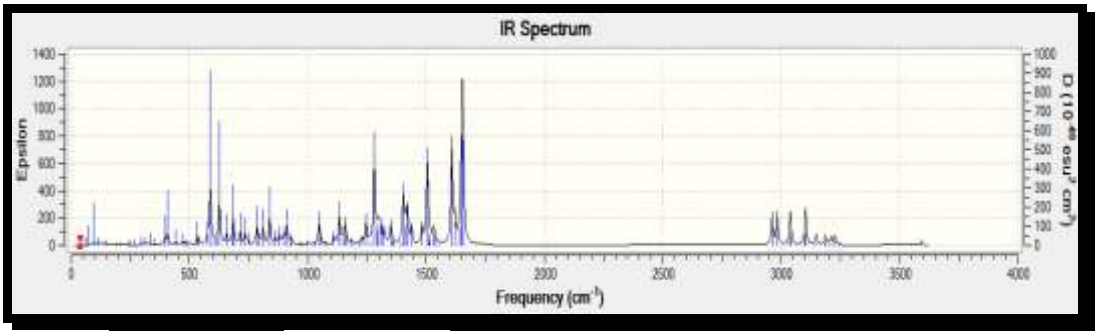

Figure 2.IR Spectra of Norclozapine

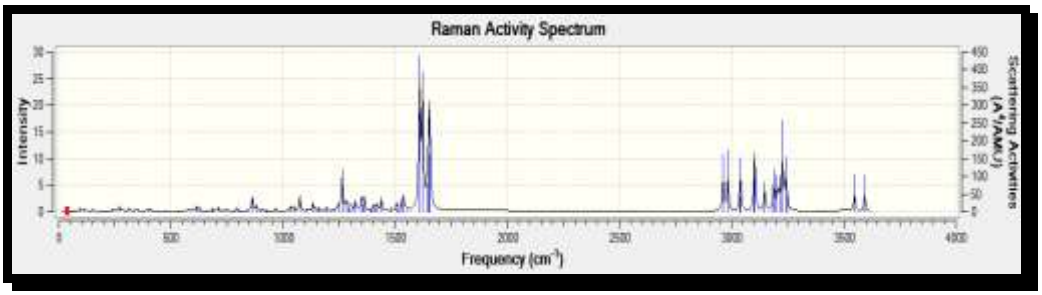

Figure 3.Raman Spectra of Norclozapine

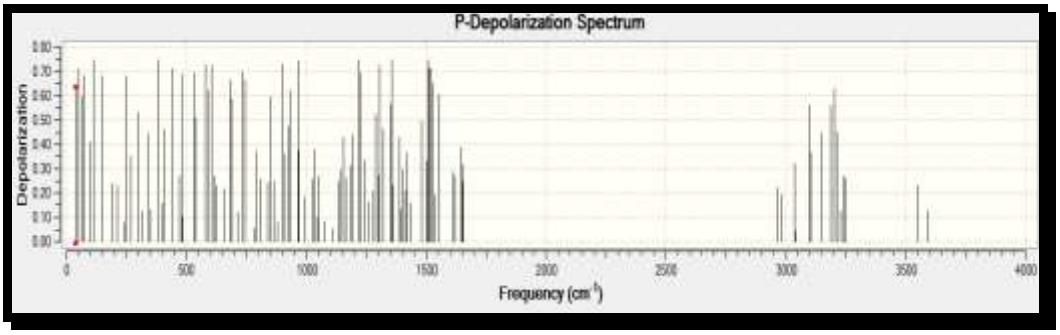

Figure 4.P-Depolarization Spectra of Norclozapine

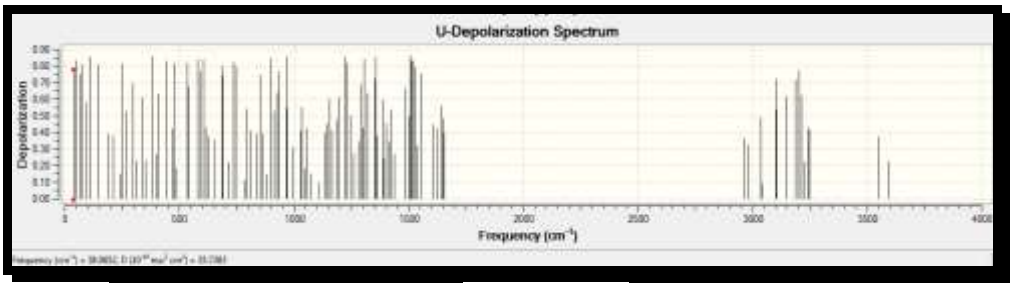

Figure 5.u-Depolarization Spectra of Norclozapine

Electronic Properties

The most important orbitals in a molecule are the frontier molecular orbitals, called the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) [11, 14]. These orbitals determine the way the molecule interacts with other species. HOMO-LUMO orbitals are also called frontier orbitals as they lie at the outermost boundaries of the electrons of the molecules [9].

The frontier orbital gap helps the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is generally associated with a high chemical reactivity, and low kinetic stability and is also termed a soft molecule. The difference in energy between these two frontier orbitals can be used to predict the strength and stability of transition metal complexes, as well as the colors they produce in solution [15].

The 3D plots of the frontier orbitals HOMO, and LUMO are shown in Figures 6 and 7 [18].

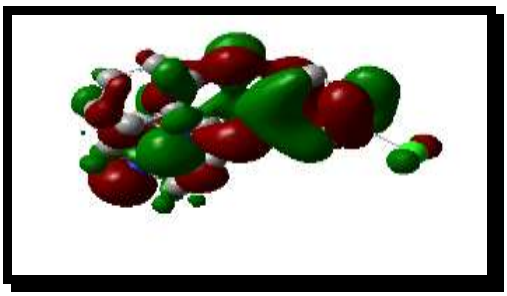

Figure 6.3D plots of the frontier orbitals HOMO

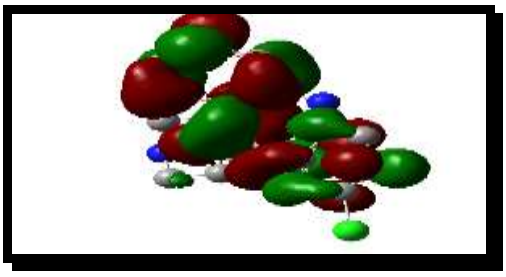

Figure 7.3D plots of the frontier orbitals LUMO

The optimized structural parameters such as bond lengths, and bond angle were determined at B3LYP level theory with a 6-31G basis set and are presented in Table 3 [13].

Table 3. Bond lengths in Norclozapine

Atom	Bond Length
C(5)-N(21)	1.30314
C(1)-N(22)	1.41813
C(2)-N(22)	1.426
C(5)-N(30)	1.39618
N(30)-C(25)	1.47794
N(30)-C(29)	1.48391
C(8)-Cl(24)	1.83167
N(27)-C(26)	1.4722

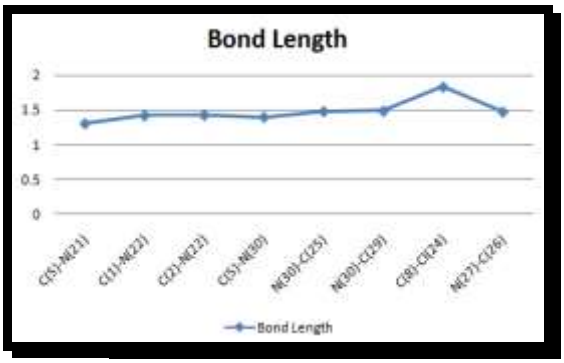

Figure 8. The plot of Bond Lengths in Norclozapine

Table 4. Bond angle in Norclozapine

Atom	Bond angle
C(2)-N(22)-C(1)	120.187
C(4)-N(21)-C(5)	126.744
C(25)-N(30)-C(29)	112.884
C(28)-N(27)-C(26)	112.952
Cl(24)-C(8)-C(7)	119.024

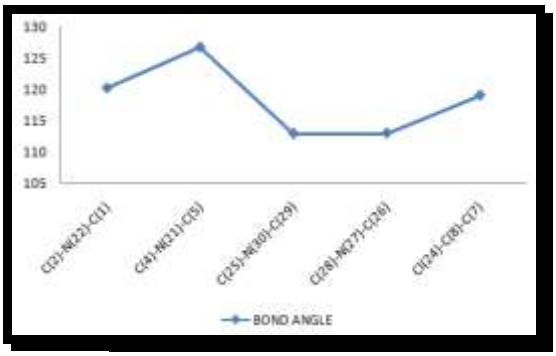

Figure 9. The plot of Bond Angle in Norclozapine

5. Discussion

In the present work, we have successfully performed an accurate analysis of essential information about the pharmaceutical drug under investigation with IR and Raman spectroscopy [2, 7]. Electronic Properties (HOMO and LUMO energy) andoptimized geometrical structural parameterssuch as bond lengths, and bond angle of N-Desmethylclozapine, or norclozapinehave been determined using DFT methods [13].
A molecule with a small frontier orbital gap is generally associated with a high chemical reactivity and low kinetic stability. The difference in energy between these two frontier orbitals can be used to predict the strength and stability of transition metal complexes [8].

Author Contributions: Conceptualization, A.P., and A.K.; methodology, A.P., and A.K.; software, A.P., and D.B.S.; validation, A.P, A.K., AND D.B.S.; formal analysis, A.P, A.K., AND D.B.S.; investigation, A.P, A.K., AND D.B.S.; resources, A.K., S.P.S., AND D.B.S.; data curation, A.P, A.K., AND D.B.S.; writing—original draft preparation, A.P.; writing—review and editing, A.P, A.K., S.P.S. AND D.B.S.; visualization, A.P., A.K., AND D.B.S.; supervision, A.K., AND D.B.S..; funding acquisition, A.P. All authors have read and agreed to the published version of the manuscript.

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