ELECTRONIC STRUCTURE AND VIBRATIONAL ANALYSIS OF ZUCLOPENTHIXOL (2-[4-[(3Z)-3-(2-chlorothioxanthen-9-ylidene)propyl]piperazin-1-yl]ethanol)

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Abstract

Zuclopenthixol is a thioxanthene with therapeutic actions similar to the phenothiazine antipsychotics. It is an antagonist at D1 and D2 dopamine receptors.Zuclopenthixol is a typical antipsychotic neuroleptic drug of the thioxanthene class. It mainly acts by antagonism of D1 and D2 dopamine receptors. Zuclopenthixol also has high affinity for alpha1-adrenergic and 5-HT2 receptors. It has weaker histamine H1 receptor blocking activity, and even lower affinity for muscarinic cholinergic and alpha2-adrenergic receptors. The ground state and the excited state properties of the title molecule have been calculated employing DFT/ B3LYP level of theory. As vibrational and electronic spectroscopic study provides very useful information about the structure and conformation of the molecules if used in synergy with quantum chemical calculations, therefore in order to obtain a complete description of molecular dynamics, vibrational wave number calculation along with the normal mode analysis has been carried out at the DFT level of theories. The comprehensive investigation of geometrical and electronic structure in ground and the first excited electronic states, dipole moment, along with the molecular electrostatic potential surface and contour map may lead to better understanding of the structural, spectral characteristics of the compound under study.

Keywords: *schizophrenia, antipsychotic agent Vibrational spectra, DFT, Antiviral, HOMO, LUMO*

INTRODUCTION

Zuclopenthixol, also known as Zuclopentixol or Zuclopenthixolum, is an antipsychotic agent. Zuclopenthixol is a thioxanthene-based neuroleptic with therapeutic actions similar to the phenothiazine antipsychotics. It is an antagonist at D1 and D2 dopamine receptors. Major brands of zuclopenthixol are Cisordinol, Acuphase, and Clopixol. This drug is a liquid. This compound belongs to the thioxanthenes. These are organic polycyclic compounds containing a thioxanthene moiety, which is an aromatic tricycle derived from xanthene by replacing the oxygen atom with a sulfur atom.

Zuclopenthixol is a D_1 and D_2 antagonist, α_1-adrenergic and 5-HT_2 antagonist. While it is approved for use in Australia, Canada, Ireland, India, New Zealand, Singapore, South Africa and the UK it is not approved for use in the United States.

Zuclopenthixol is available in three major preparations:

- As zuclopenthixol decanoate (Clopixol Depot, Cisordinol Depot), it is a long-acting intramuscular injection. Its main use is as a long-acting injection given every two or three weeks to people with schizophrenia who have a poor compliance with medication and suffer frequent relapses of illness. There is some evidence it may be more helpful in managing aggressive behaviour.
- As zuclopenthixol acetate (Clopixol-Acuphase, Cisordinol-Acutard), it is a shorter-acting intramuscular injection used in the acute sedation of psychotic inpatients. The effect peaks at 48–72 hours providing 2–3 days of sedation.
- As zuclopenthixol dihydrochloride (Clopixol, Cisordinol), it is a tablet used in the treatment of schizophrenia in those who are compliant with oral medication.

It is also used in the treatment of acute bipolar mania.

The present chapter deals with investigation of molecular structural properties, vibrational and energetic data of zuclopenthixol. The calculated highest occupied molecule orbital or HOMO and the lowest un-occupied molecular orbital or LUMO energies shows that charge transfer within the molecule. The vibrational spectra of IR and Raman have been interpreted with the help of B3LYP level of theory with the 6-31G basis set from the Density function theory.

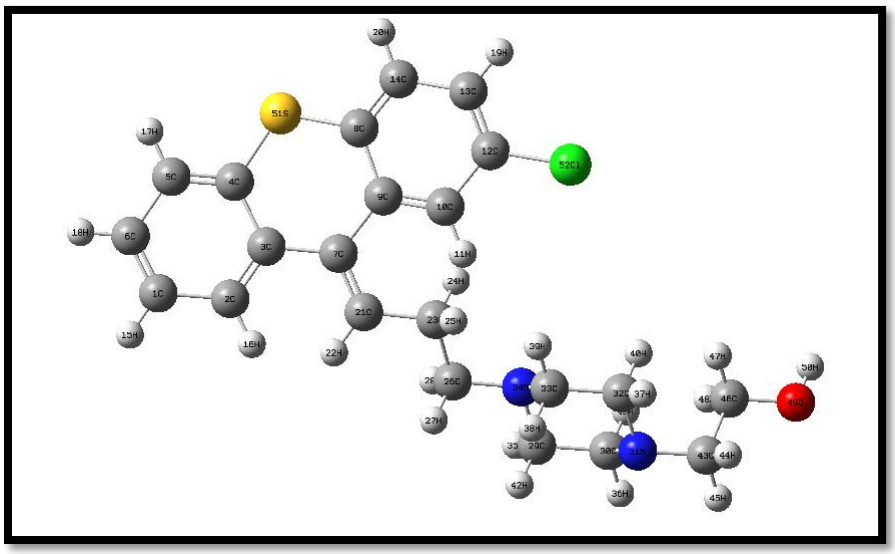
METHOD ,MATERIAL AND THEORY

Density functional theory (DFT) has become very popular in recent years. This is justified based on the pragmatic observation that it is less computationally intensive than other methods with similar accuracy. The premise behind DFT is that the energy of a molecule can be determined from the electron density instead of a wave function.

In general, ab initio calculations give very good qualitative results and can yield increasingly accurate quantitative results as the molecules in question become smaller. The advantage of ab initio methods is that they eventually converge to the exact solution once all the approximations are made sufficiently small in magnitude.

The geometries of molecule were optimized using the Gaussian 09 suite of programs. The ground state geometry of zuclopenthixol were optimized using DFT. The basis set used for all atoms was 6-31G.

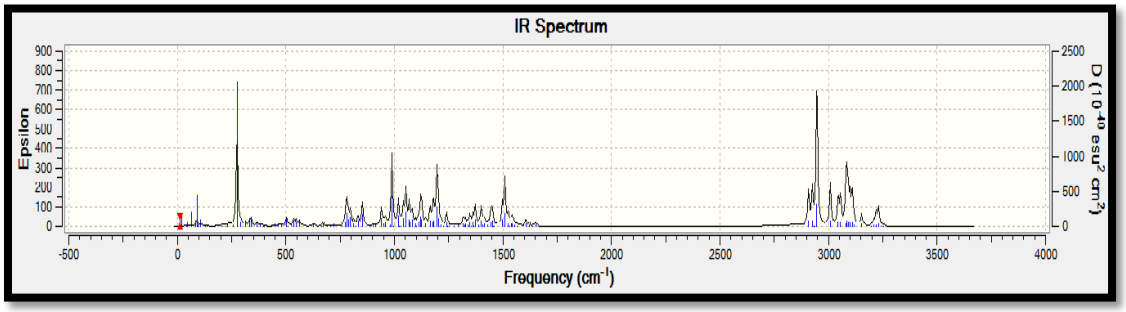
Optimized geometrical structure of zuclopenthixol is shown in fig 1.

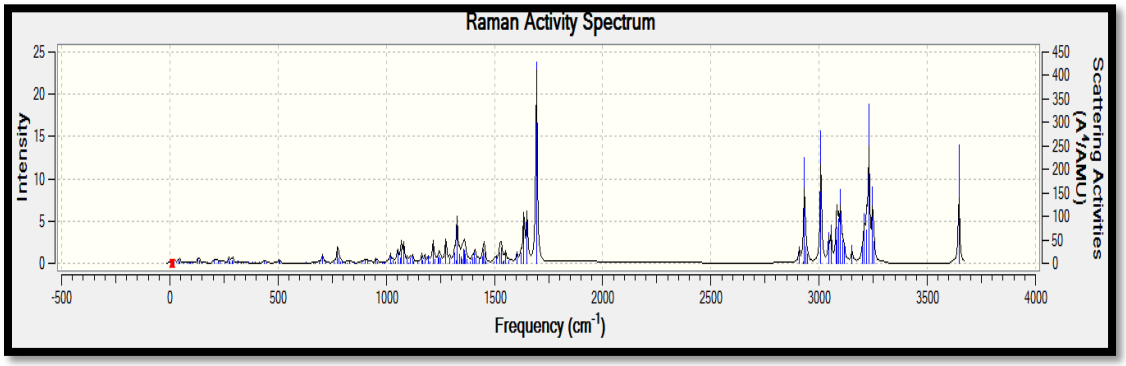


IR AND RAMAN FREQUENCY

IR SPECTRA-Infrared spectroscopy involves the interaction of infrared radiation with matter. 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.

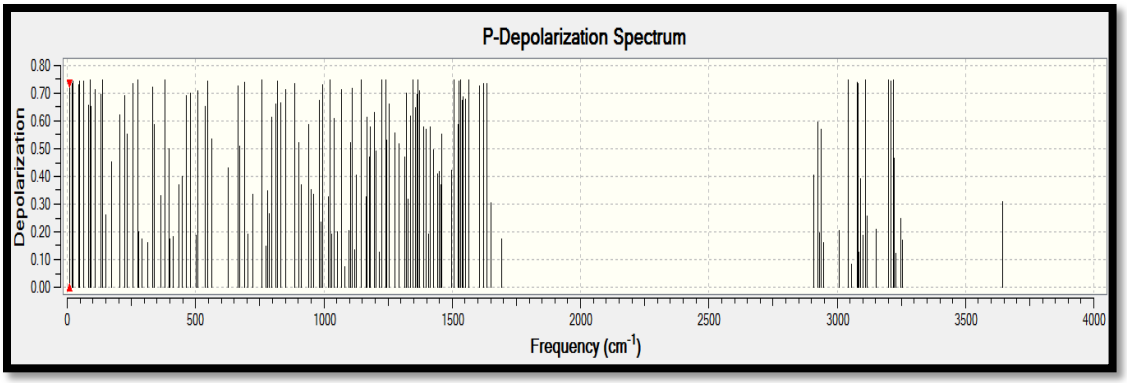
RAMAN SPECTRA- RAMAN spectrum is a plot of the intensity of RAMAN scattered radiation as a function of its frequency difference from the incident radiation (usually in units of wavenumbers, cm^{-1}). This difference is called the *RAMAN shift*, because it is a difference value, the Raman shift is independent of the frequency of the incident radiation. Figure 2 and 3 show the calculated IR and Raman of zuclopenthixol.

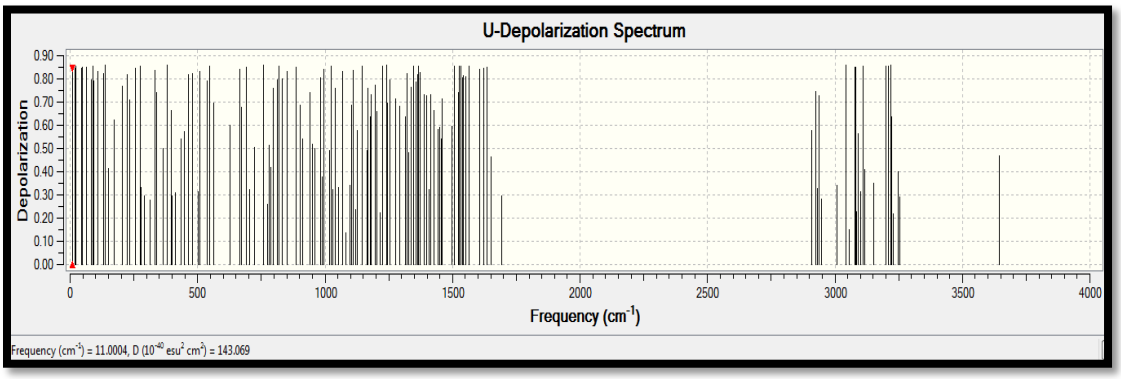




DEPOLARIZATION SPECTRA

In Raman spectroscopy, the **depolarization ratio** is the intensity ratio between the perpendicular component and the parallel component of Raman scattered light. The Raman scattered light is emitted by the stimulation of the electric field of the incident light. Therefore, the direction of the vibration of the electric field, or polarization direction, of the scattered light might be expected to be the same as that of the incident light. The optimised spectra of p-depolarization and u-depolarization is shown in the fig-4 and fig-5





Theoretically computed ground state optimized parameters

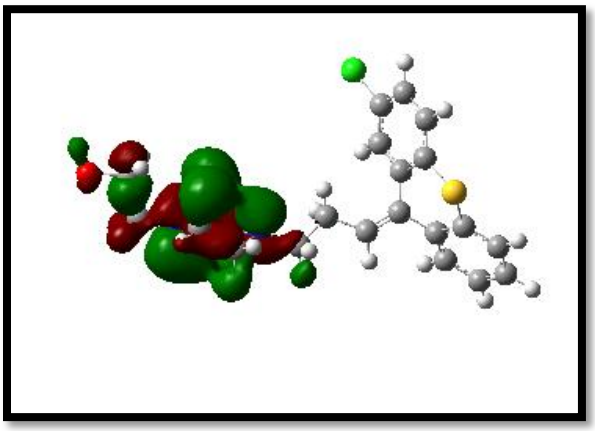
Parameters	Zuclopenthixol (B3LYP/6-31G)
Energy	-1896.14487859a.u.
Dipole moment (in Debye)	1.4647 Debye

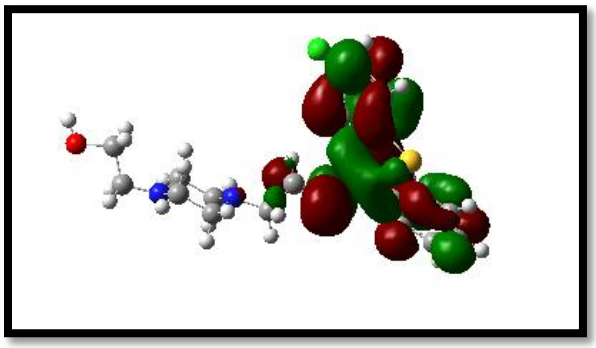
ELECTRONIC PROPERTIES

HOMO and LUMO are acronyms used in orbital interaction theory of organic chemistry. HOMO stands for highest occupied molecular orbital and LUMO for lowest unoccupied molecular orbital, respectively. The energy difference between the HOMO and LUMO is termed the HOMO–LUMO gap. HOMO and LUMO are sometimes referred to as frontier orbitals.Through qualitative molecular orbital analysis through a molecular orbital diagram, the chemist is able to display the resulting molecular orbitals stemming from atomic interaction based on their relative energies and assign bonding, nonbonding and/or antibonding character to each molecular orbital. After these assignments are made, the chemist is able to identify the Highest Occupied Molecular Orbital (HOMO) that contains electrons and the Lowest Unoccupied Molecular Orbital (LUMO) that does not contain electrons. 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 .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.

HOMO Energy	-0.19587a.u.
LUMO Energy	-0.04515 a.u.
ENERGY GAP	0.15072 a.u.

The density plot of the HOMO and LUMO of zuclopenthixol is calculated at B3LYP/6-31G level of theory and are shown in Figure 6 and 7.

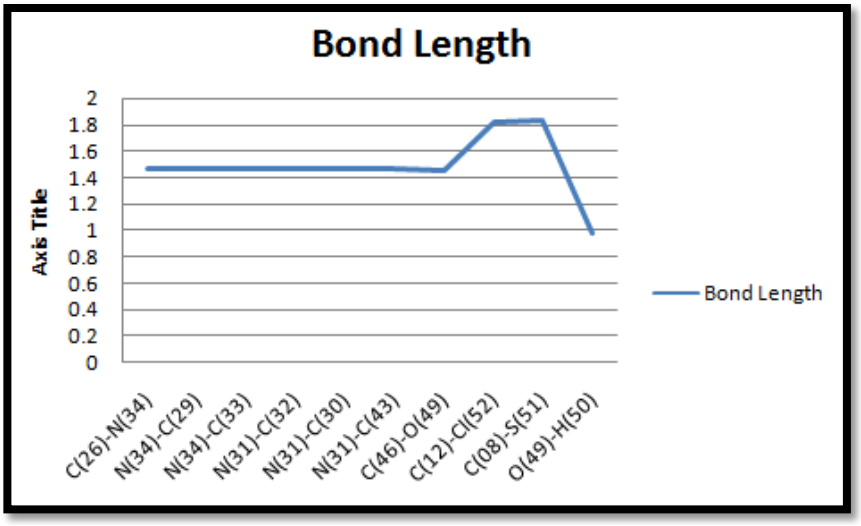




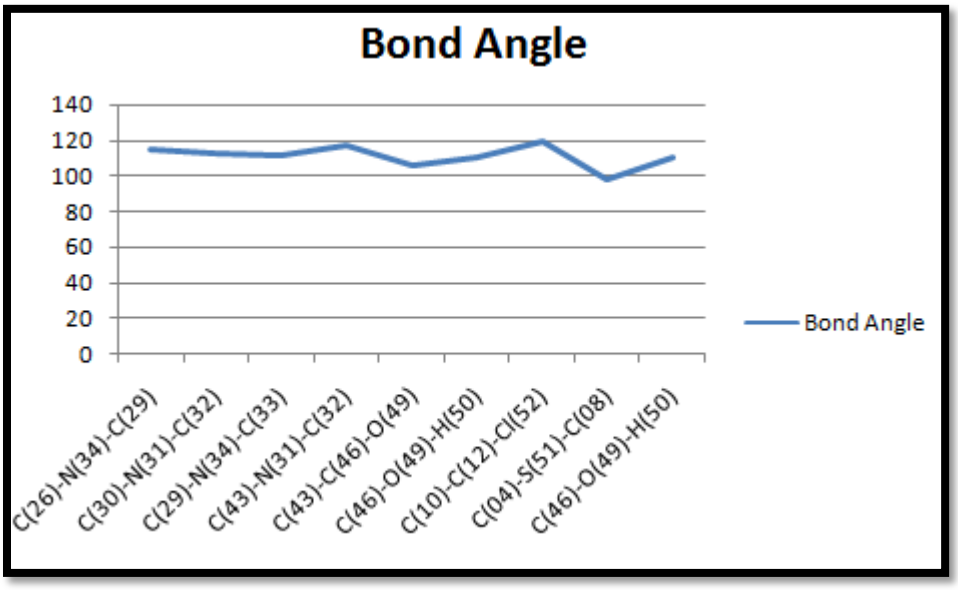
BOND LENGTH AND BOND ANGLE

In molecular geometry, bond length or bond distance is the average distance between nuclei of two bonded atoms in a molecule. It is a transferable property of a bond between atoms of fixed types, relatively independent of the rest of the molecule. Molecular geometries can be specified in terms of bond lengths and bond angles. The bond length is defined to be the average distance between the nuclei of two atoms bonded together in any given molecule. A bond angle is the angle formed between three atoms across at least two bonds. Such as bond lengths and bond angle are the optimized structural parameters, so these parameters were determined at B3LYP level theory with 6-31G basis set and they are presented in a table. Bond length and Bond angle table of zuclopenthixol given below

Atom	Bond Length
C(26)-N(34)	1.46942
N(34)-C(29)	1.47525
N(34)-C(33)	1.4748
N(31)-C(32)	1.46849
N(31)-C(30)	1.46884
N(31)-C(43)	1.46428
C(46)-O(49)	1.4568
C(12)-Cl(52)	1.82866
C(08)-S(51)	1.83879
O(49)-H(50)	0.97722



Atom	Bond Angle
C(26)-N(34)-C(29)	114.301
C(30)-N(31)-C(32)	112.85
C(29)-N(34)-C(33)	111.168
C(43)-N(31)-C(32)	116.814
C(43)-C(46)-O(49)	105.642
C(46)-O(49)-H(50)	110.605
C(10)-C(12)-Cl(52)	118.807
C(04)-S(51)-C(08)	98.496
C(46)-O(49)-H(50)	110.605



CONCLUSION

Simulation work of zuclopenthixol is in the process. Simulation report of zuclopenthixol we will reported very soon.

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