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The effect of group substituent on the biological activity of antidiabetic Vanadium(IV) Complex (BMOV: bis (maltolato) oxovanadium)(Theoritical study)

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Abstract : Metals and metal complex have assumed key part in the advancement of present day chemotherapy. Metals can assume an essential part in adjusting the pharmacological properties of known medications after coordinating to a metal. Vanadium containing organic compounds have indicated extensive guarantee as available prodrugs that lighten the vast majority of the symptoms of diabetes. One of the biochemical mechanisms for insulin refinement by these compounds is that they hinder and inhibit PTPs "protein tyrosine phosphatases" that direct adversely on insulin receptor. In this work, we building and designing five derivative complexes in addition to standard (BMOV)and characterization the geometrical shape and crystal structure of a standard vanadium complex BMOV, [Bis(maltolato)oxovanadium(IV)]and it's derivative depending on the DFT "density functional theory" survey of the title complexes were performed using the Gaussian 03 program. Crystal structure information, Mulliken charges allocation, complex biological effectiveness, frontier molecular orbital energies (HOMO, LUMO) of the complexes, stability, and polarity were discussed.

Keywords : Diabetes mellitus (DM); protein tyrosine phosphatases (PTPs); organic vanadium complex; density functional theory (DFT); HOMO, LUMO energies.

Introduction

Metals and metal complex have assumed key part in the advancement of present day chemotherapy[1]. Metals can assume an essential part in adjusting the pharmacological properties of known medications after coordinating to a metal. The subsequent prodrugs have diverse physical and pharmacological properties, enabling the medication to be discharged in a controlled manner or at particular area. This approach may prompt the protect of medications that have fizzled on account of poor pharmacology or high lethality. For instance, complexation of nonsteroidal mitigating medications to copper conquers a portion of the gastric symptoms of these medications[2].Arrival of cytotoxins, for example; nitrogen mustards from redox-active metals such as cobalt in the hypoxic districts of strong tumors can possibly enhance tranquilize action and lessen toxicquality[3].The metal based medications are additionally being utilized for the treatment of an assortment of ailments; "cardiovascular illnesses", "rheumatoid arthritis", "diabetes", as well as "inflammatory and diagnosticagents"[4-6].

Diabetes mellitus (DM) is an extremely complex metabolic issue, and in spite of the fact that insulin can lighten a hefty portion of the manifestations in a discontinuous manner, there is no straightforward cure that reestablishes glucose homeostasis around the clock[7].

The requirement for medications for type 1 DM and new treatments for type 2 DM is convincing with the unstable increment in new cases of diabetes, particularly sort 2 DM. Secondary complications, the consequence of long-term excessive fluctuations in glucose and insulin levels, are a noteworthy reason for dreariness in diabetes.

Vanadium containing compounds have indicated extensive guarantee as available prodrugs that lighten the vast majority of the symptoms of diabetes: high glucose, elevated lipid levels, and gradually harming. Secondary complications, including renal dysfunction, heart disease, peripheral neuropathy, and cataracts[7].

The pivotal stride in developed of vanadium compounds for treatment of diabetes was the disclosure that adjustment of the vanadium center by chelation could enhance bio-dissemination and ability[8].Organovanadium compounds have been appeared to be human insulin sensitizers in vivo and in vitro. One of the biochemical mechanisms for insulin refinement by these compounds is that they inhibit and hinder protein tyrosine phosphatases (PTPs)that direct adversely on insulin receptor[9]. BMOV is the first (thus far unbeatable)of various compounds that exhibited better action over inorganic vanadium compounds (e.g. $VOSO_4$ or $NaVO_3$) through both in vivo as well as in vitro examines of bioactivities[10,11,12].

At recent days, various types of vanadium complexes crystal structures have been reported, which have shown promising anti-diabetic effectiveness and a good effectiveness in the protein tyrosine phosphatases (PTPs)inhibition and hinder[13,14].In this work, we characterization the building and designing geometrical shape and crystal structure of a standard vanadium complex BMOV, [Bis(maltolato)oxovanadium(IV)]and it's derivative depending on the density functional theory (DFT) survey of the title complexes were performed using the Gaussian 03 program. Crystal structure information, Mulliken charges allocation, complex biological effectiveness, frontier molecular orbital energies(HOMO, LUMO) of the complexes, stability, and polarity were discussed.

Aim of this work:

In the present work we are studying the biological effectiveness and stability of derivative complexes by chemical groups substitution on the known anti-diabetic drugs (BMOV).Different measurements will be used such as optimization, Molecular orbital energy measurement, complex stability, polarity, and frequency spectroscopy which are important tools for the diagnosis of inorganic complexes due to their simplicity and availability.

2.Calculation Method

The molecular designing was performed and accomplished using computations of Gaussian 03 (2003) program package. In the present work, the computations have been accomplished at "DFT/B3LYP" method with "3-21G(d,p)" basis set. Electron interconnection were included using "Becke3-Lee-Yang-Parr (B3LYP)"procedure[15]. This contains "Becke's gradient exchange corrections, Lee, Yang and Parr correlation functional and/or Vosko, Wilk and Nusair correlation functional"[16].

These study and investigation included calculated numerous physical and chemical properties of building complexes which represent an anti-diabetic drug. The Calculating of balance geometrical shape (Optimization) of molecules and the Electronic Density of the atoms in molecules (ligands and complexes), especially of metal ion and coordinated atoms of ligands, in addition HOMO"Highest occupied molecular orbital" and LUMO "lowest unoccupied molecular orbital" are the most critical to describe the biological activity of complexes, optical properties, and chemical reactivity.

3. Result and discussion:

The reason of increasing interest of trace element vanadium in the last years that the revelation of the insulin-like properties of vanadium element and its compounds which impelled research into the clinical utilization of vanadium. Some of naturally organic chelated vanadium complexes were discovered more strong and less poisonous than vanadium salts in vivo[17]. One organic vanadium complex, bis (maltolato) oxovanadium(IV) (BMOV)which have qualifying conditions as promising compounds were accessible to treat diabetes.

In the present work,a new derivative complexes of vanadium(IV) (five organic vanadylcomplexes) were performed and characterized using Gaussian 03 program for calculations. These complexes deferent about known drugs (C_1: BMOV) by group substituent instead of methyl group or hydrogen atom on the (maltolato) ligand, table (3-1) figure (3-1).

The complex C_2 is similar to C_1 except ethyl group instead of methyl, the complex C_3 is similar to C_1 except hydroxyl group substitution is found in two sides instead of hydrogen atom, the complex C_4 is similar to C_1 except nitro group substitution is found in two sides instead of hydrogen atom, C_5 complex is similar to C_1 except methyl group substitution is found in two sides instead of hydrogen atom, C_6 complex is similar to C_2 except methyl group substitution is found in two sides instead of hydrogen atom.

The survey focus in this review is on investigations of properties and crystal structures of organic vanadium compounds to see how basic differences in inhibitors for protein tyrosine phosphatases (PTPs) which mean functional differences in lightening the symptoms of diabetes. This includes thought of the coordination geometry of the vanadium complexes and relationship of the structure of the complexes to their biological impacts as they relate to diabetes.

Table (3-1): Symbol, chemical formula, and names of the calculated complexes (C_1-C_6).

Symbols	***Chemical formula***	***Name***
C_1	**$C_{12}H_{10}O_7V$(IV)**	bis(methyl maltolato)oxovanadium(IV)
C_2	**$C_{14}H_{14}O_7V$ (IV)**	bis(ethyl maltolato)oxovanadium(IV)
C_3	**$C_{12}H_{10}O_9V$ (IV)**	bis[hydroxy(methyl maltolato)]oxovanadium(IV)
C_4	**$C_{12}H_8N_2O_{11}V$(IV)**	bis[nitro (methyl maltolato)] oxovanadium(IV)
C_5	**$C_{14}H_{14}O_7V$(IV)**	bis(di-methyl maltolato)oxovanadium(IV)
C_6	**$C_{16}H_{18}O_7V$(IV)**	bis[ethyl (methyl maltolato)] oxovanadium(IV)

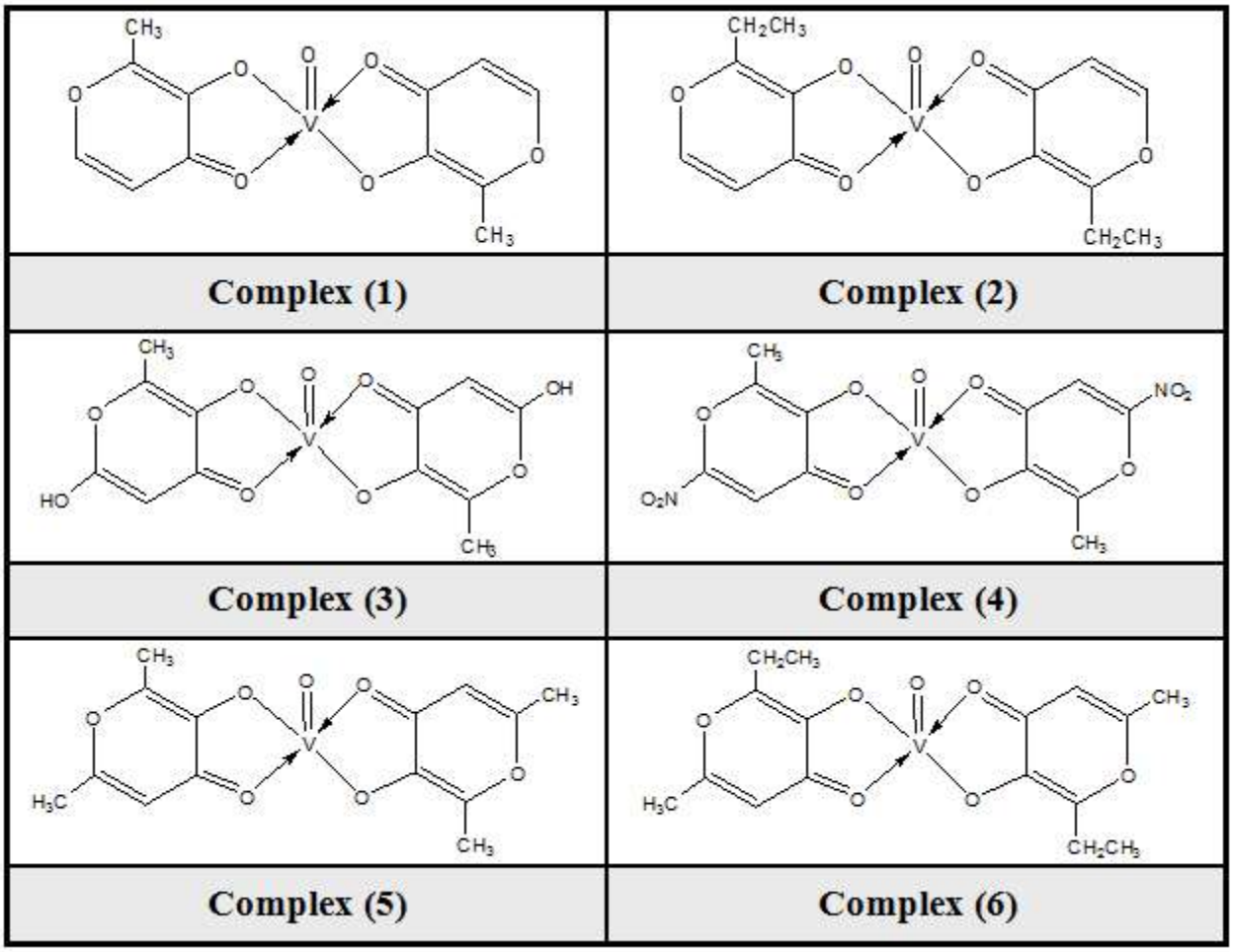


Figure (3-2): Vanadium (IV) ion and coordinated atoms of the ligand

The study of energy levels of each molecule and the ability of these to looses or acquirement electrons (oxidation-reduction process) in addition to electron distribution in molecular orbitals and the stability of geometric shape are very important to determine the biological activity of these molecules.

The stable geometrical shapes of ligands and their complexes and the spatial arrangement of atoms were studied by using "Gaussian 03, density functional theory (DFT) method, restricted B3LYP, and 6-31G basis set". The calculations proof that the geometric shapes of organic vanadium (IV) complexes are square pyramidal configuration and a few distorted toward trigonalbipyramidal, but when bond frequencies were calculated, negative value of frequencies for trigonalbipyramidal compounds and positive values of square pyramidal compounds were obtained, so the stable geometrical shapes are square pyramidal (according to bond frequencies). The following figure [(3-3) to (3-8)] show the geometric shapes of all compounds.

In trying to determine the symmetry of a molecule, we need to see whether it has any symmetry elements, which are geometrical entities (such as Identity: **E**, Proper rotation axis: $\mathbf{C_n}$, Symmetry plane: **σ**, Inversion center: **i**, and Improper rotation axis: $\mathbf{S_n}$), so the calculation of point group and determination of symmetry element for all compounds were to be complete in addition to vibrational, rotational, and translational energy calculation where to be restricted to "C_1" for each molecules (ligands and their complexes) because these molecules have not any symmetry element except the identity (E).

The conformations of the Vanadyl(IV) derivative complexes in addition to known promising prodrug(standard complex: BMOV) obtained from DFT calculation. The optimization process (the global minimum energy information of the compounds is achieved)was fully done to estimate the electronic density of atoms in all compounds, in these oxidation states the vanadiumcentre is predominantly pentacoordinate with

essentially squarepyramidal geometry, by coordinate the central vanadyl ion (IV) to five oxygen ion attack, table (3-2) figure [(3-2) to (3-8)].

Table (3-2): Electronic density of vanadium (IV) ion and coordinated atom of the ligands.

Complex	V (IV)	O_1	O_2	O_3	O_4	O_5
C_1	21.045349	8.094136	8.391205	8.304754	8.304750	8.391206
C_2	21.045867	8.094645	8.389890	8.305140	8.305123	8.390351
C_3	21.043457	8.095741	8.394413	8.311032	8.311032	8.394409
C_4	21.042503	8.070066	8.368872	8.300285	8.300290	8.368877
C_5	21.045306	8.098732	8.394596	8.311484	8.311482	8.394595
C_6	21.045845	8.099400	8.393520	8.311802	8.311382	8.393901

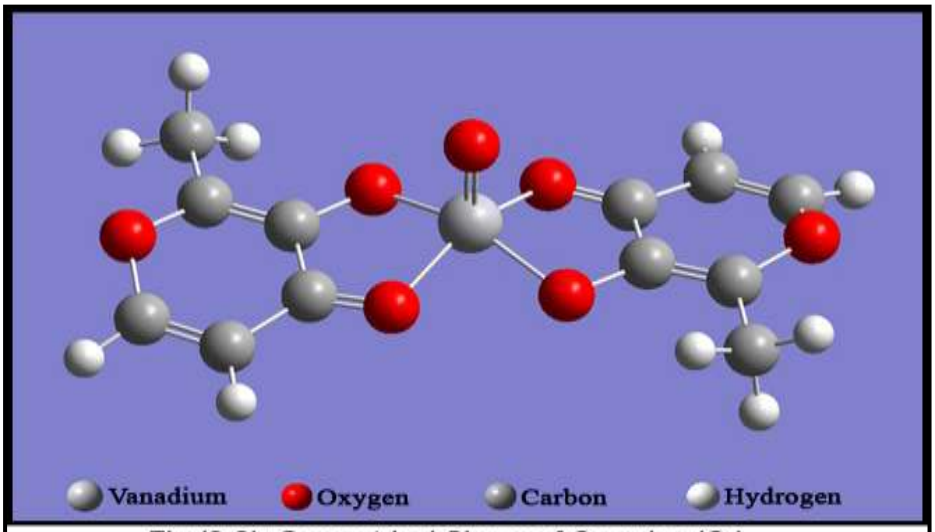


Fig (3-3): Geometrical Shape of Complex (C_1).

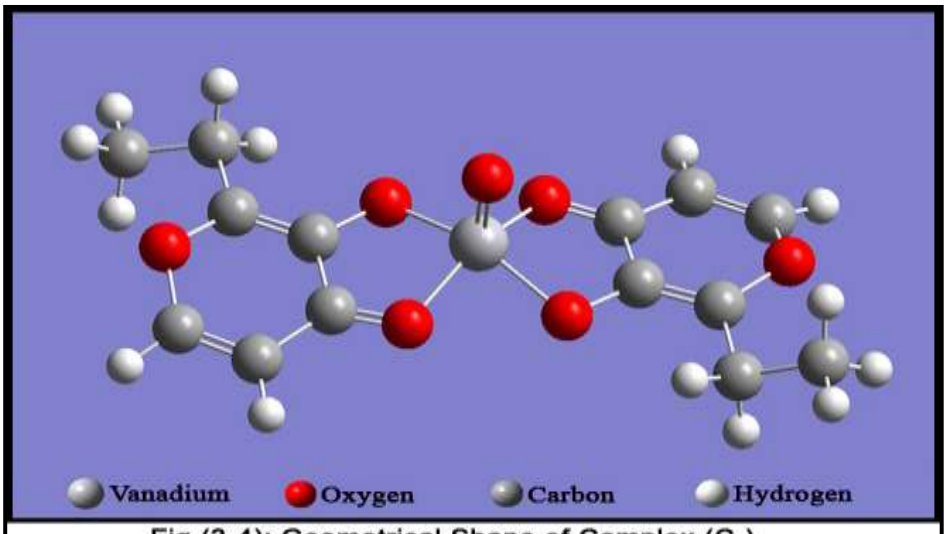


Fig (3-4): Geometrical Shape of Complex (C_2).

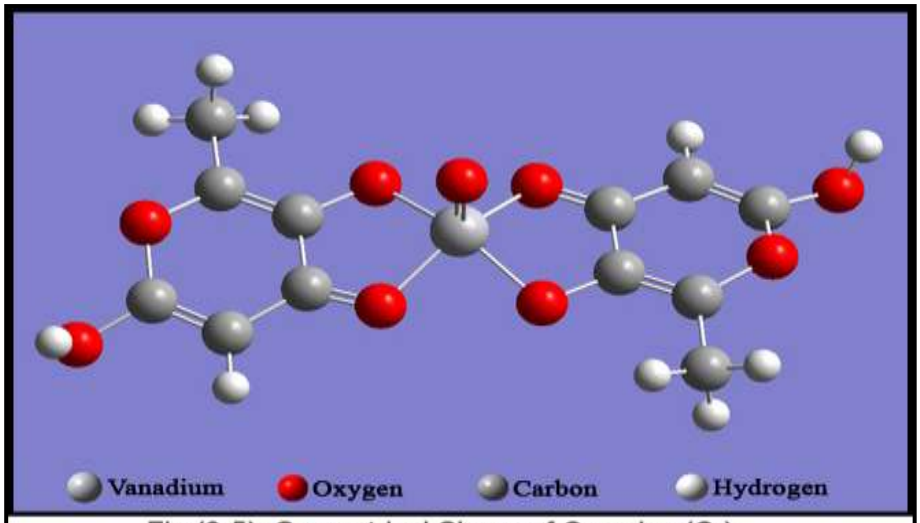


Fig (3-5): Geometrical Shape of Complex (C_3).

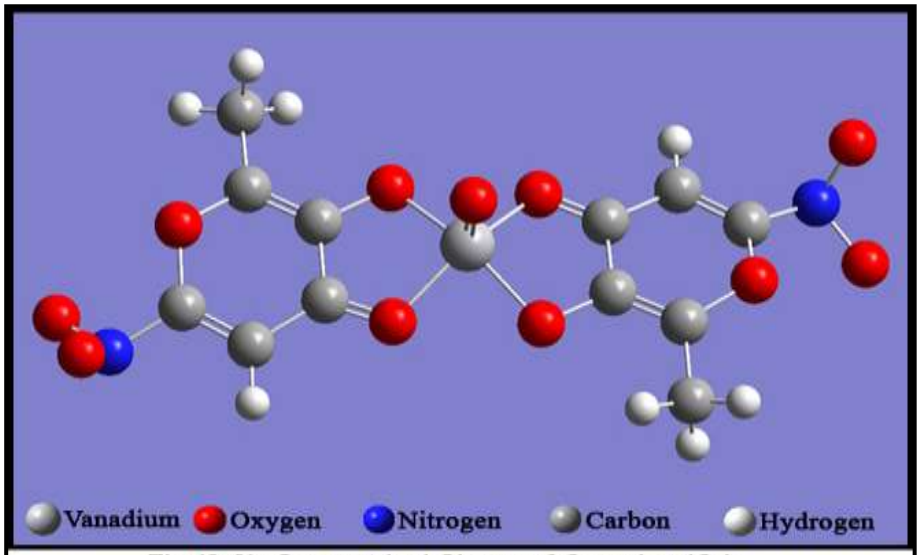


Fig (3-6): Geometrical Shape of Complex (C_4).

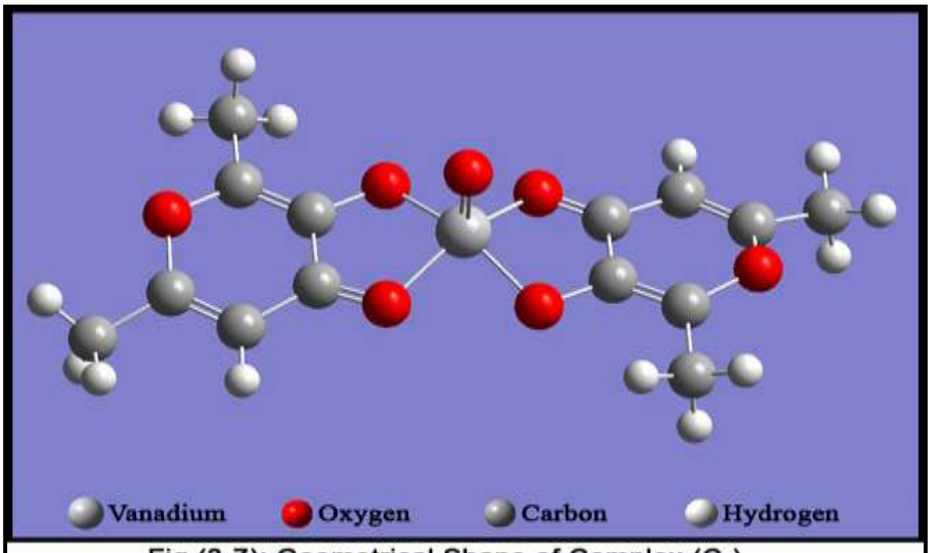


Fig (3-7): Geometrical Shape of Complex (C_5).

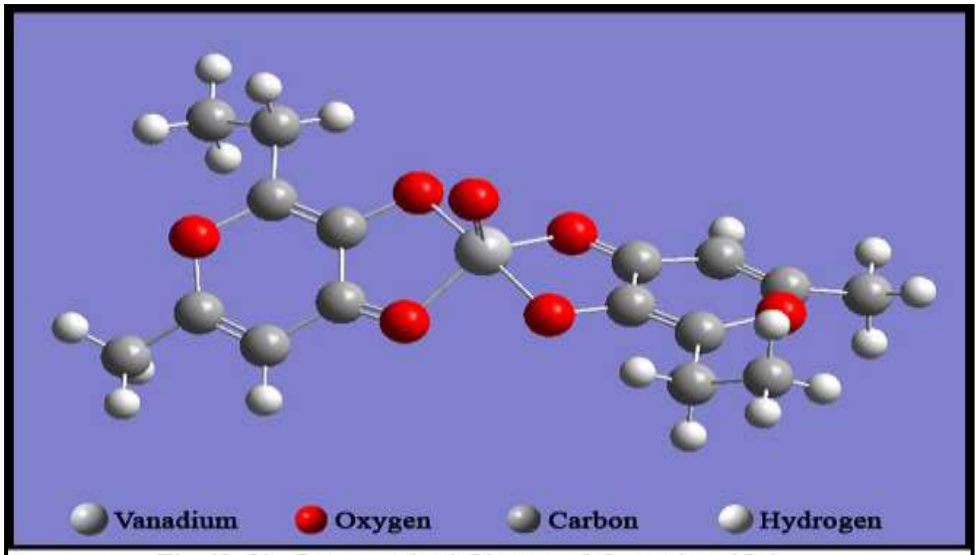


Fig (3-8): Geometrical Shape of Complex (C_6).

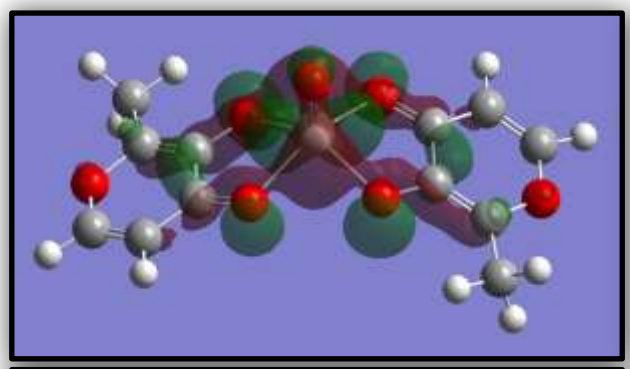
The exact mechanism to inhibition PTPs by the organic vanadium complexes in vivo is not yet fully understood. the acceptable mechanism is that vanadium readily associates and carried with proteins such as (transferrin, albumin and hemoglobin in addition to GSH) to the cell membrane, then organic vanadium complex can interconvert between two oxidation states V(IV) and V(V). V(V) can inhibit PTPs[18] while V(IV) can activate the recruitment glucose transporters to the cell membrane, thereby increasing glucose cell uptake and lowering blood glucose levels[19].

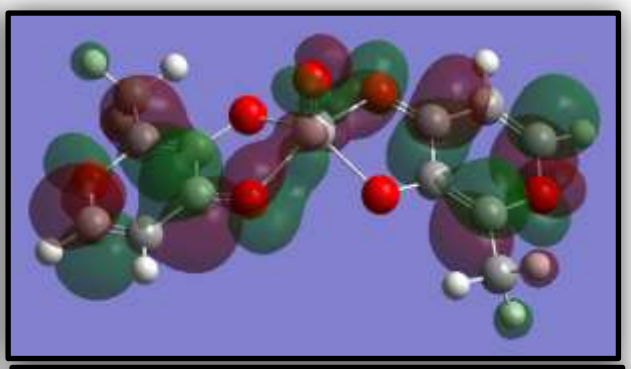
The most essential orbitals to describe the optical properties of the compound, and chemical and biological activity of the chemical species are the frontier highest occupied MO's and lowest unoccupied MO's(HOMO,LUMO). Higher value of HOMO of a molecule mean its act as a "Lewis Base"or it could be oxidation and has ability to donate electrons to convenient acceptor molecule with low energy(or empty molecular orbitals),while higher value of lowest unoccupied molecular orbital LUMO of a molecule mean its act as a "Lewis Acid"or it could be reduction and has a ability to accept electrons from convenient donor molecule.

In our work, the results show that inhibition and hinder protein tyrosine phosphatases (PTPs)activity of the building complexes (C_2, C_5, C_6) are higher when compared with that of C_1 complex (as a standard) according to highest occupied MO (HOMO) andΔE energy which indicate the ability to donate electrons and stability of building complexes respectively, while the other complexes gave lower than that of C_1 complex, table(3-3),figure [(3-9) to (3-20)].

Table (3-3): The energy of Highest Occupied Molecular Orbitals, Lowest Unoccupied Molecular Orbitals,ΔE.

Compound	E_{HOMO} (e.v.)	E_{LUMO} (e.v.)	ΔE (e.v.)
C_1	-0.21291	-0.07552	0.13739
C_2	-0.20103	-0.06481	0.13622
C_3	-0.21978	-0.07717	0.14261
C_4	-0.24730	-0.06266	0.18464
C_5	-0.20387	-0.06783	0.13604
C_6	-0.20208	-0.07251	0.12957





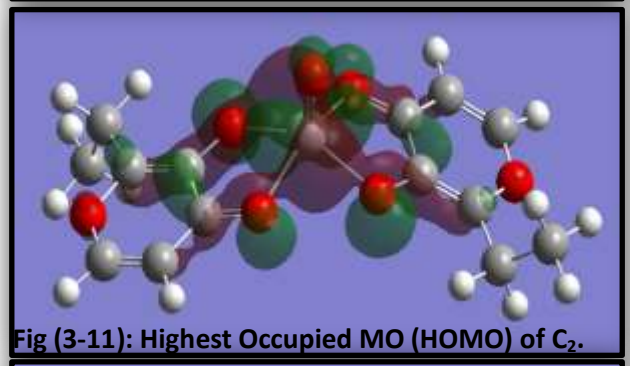


Fig (3-11): Highest Occupied MO (HOMO) of C_2.

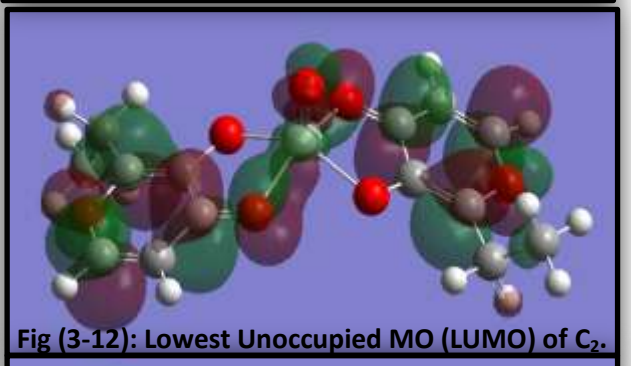


Fig (3-12): Lowest Unoccupied MO (LUMO) of C_2.

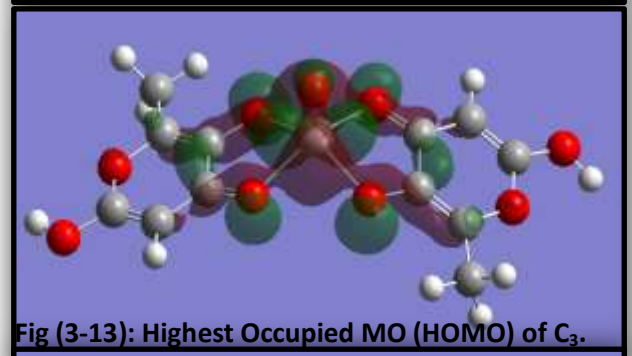


Fig (3-13): Highest Occupied MO (HOMO) of C_3.

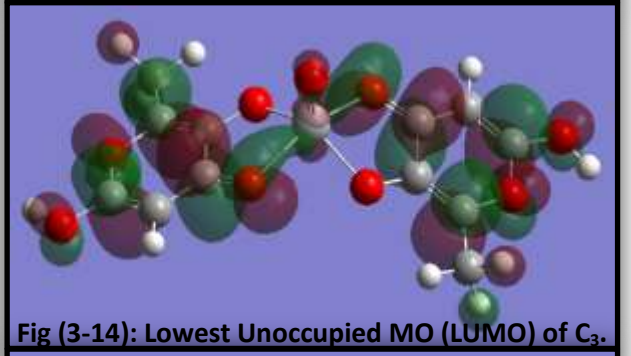


Fig (3-14): Lowest Unoccupied MO (LUMO) of C_3.

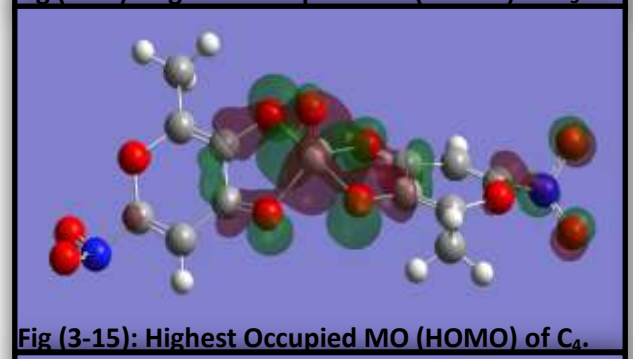


Fig (3-15): Highest Occupied MO (HOMO) of C_4.

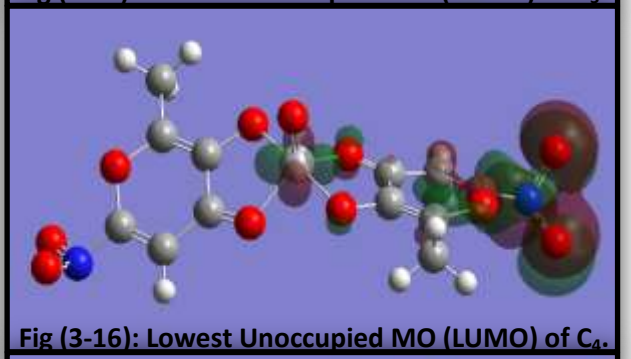


Fig (3-16): Lowest Unoccupied MO (LUMO) of C_4.

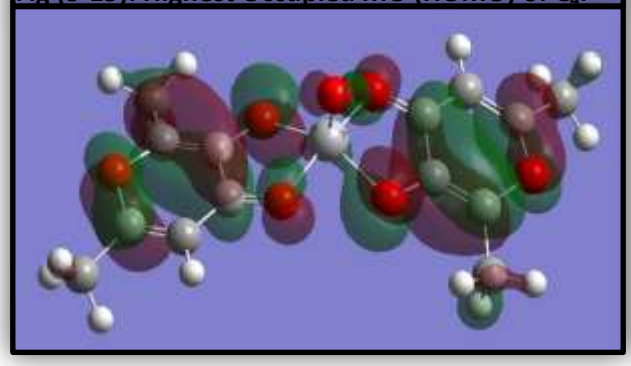


Fig (3-17): Highest Occupied MO (HOMO) of C_5.

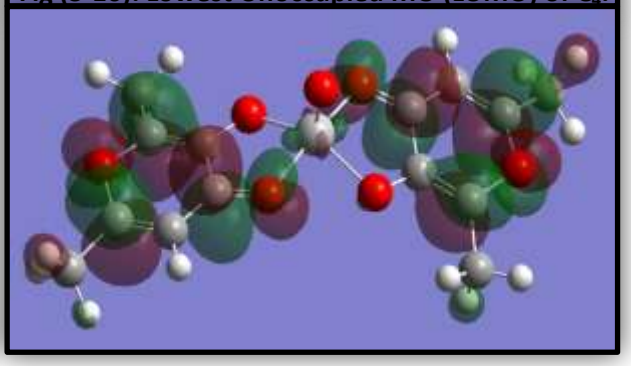


Fig (3-18): Lowest Unoccupied MO (LUMO) of C_5.

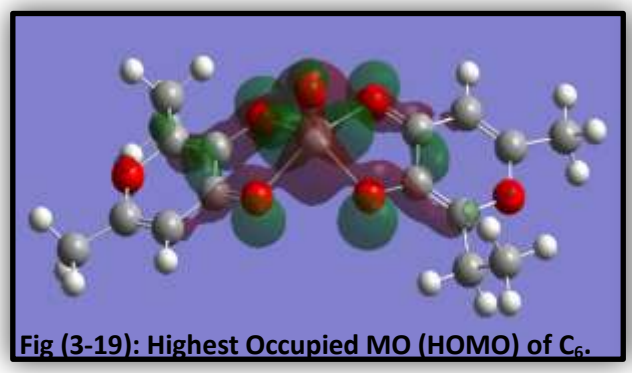


Fig (3-19): Highest Occupied MO (HOMO) of C_6.

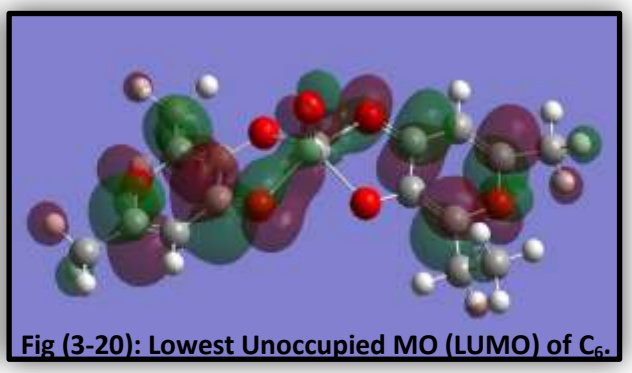


Fig (3-20): Lowest Unoccupied MO (LUMO) of C_6.

From Mulliken charge data [table (3-4)], the coordinated oxygen atoms of the ligand have negative charges while the carbon atoms of heterocyclic ligands which linking with coordinated oxygen atoms have positive charges in addition that the metal ion [V(IV)] have a positive charges. On the other hand, the metal ion charge is decreased from (IV) to ($2.19 < \mathbf{V} < 2.31$).These data show that part of the electronic density was transferred from the ligand to the central atom (vanadium) and thus the stable complexes formation.

Table (3-4): Mulliken atomic charges of Vanadium (IV) ion and coordinated atoms of the ligand, Polarity of the complexes.

complex	Mulliken atomic charge						Polarity (Debye)
	V	O_1	O_2	O_3	O_4	O_5	
C_1	2.192900	-0.764943	-0.972037	-1.014302	-1.014284	-0.972027	5.3641
C_2	2.205423	-0.763722	-0.984349	-1.023319	-1.016452	-0.980351	5.3649
C_3	2.310741	-0.781847	-1.025442	-1.042775	-1.042769	-1.025432	6.1763
C_4	2.256822	-0.741336	-0.970617	-1.112621	-1.112618	-0.970605	4.5144
C_5	2.265769	-0.780487	-1.014729	-1.052320	-1.052305	-1.014722	5.9268
C_6	2.278726	-0.778295	-1.026151	-1.061575	-1.055705	-1.021824	5.8558

The infrared spectrum technique of a molecule is represented to be a one of a important physical property and is described for the molecules. In that capacity, the (IR) spectrum can be utilized as a unique fingerprint for distinguishing and comparison between the derivative complexes and reference complex BMOV (standard complex).This first rules approach depends on the fact that structural properties of the complex, regardless of whether they are the spine of the complex or the functional groups attached to the complex ligands.

The following figures [(3-21) to (3-26)] show infrared vibration spectra of all building complexes.

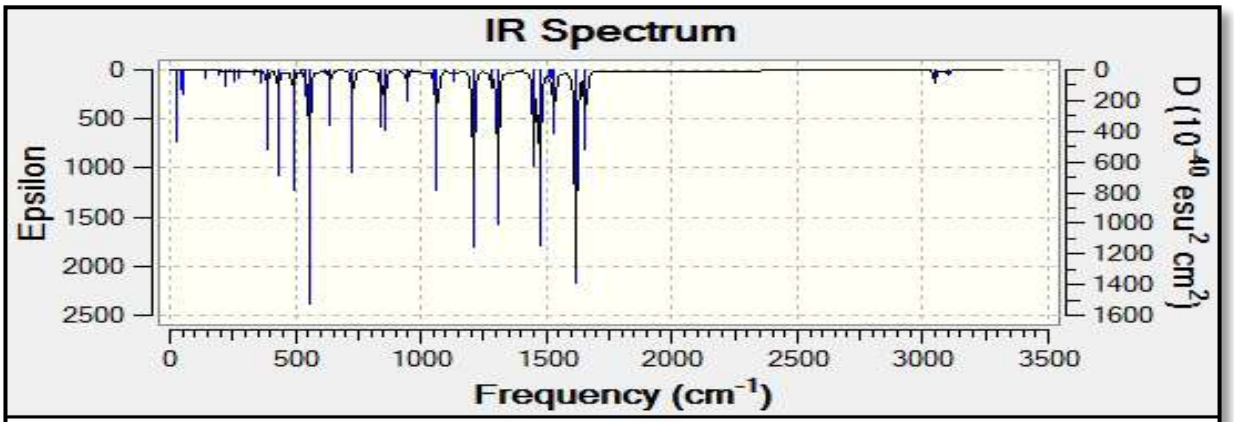


Fig (3-21): Infrared Spectrum of complex 1 (C_1).

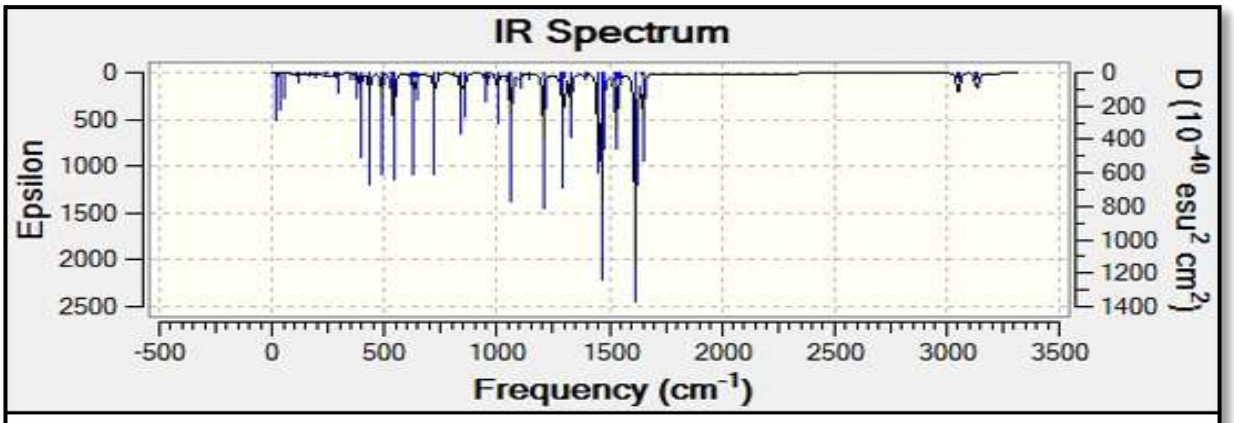


Fig (3-22): Infrared Spectrum of complex 2 (C_2).

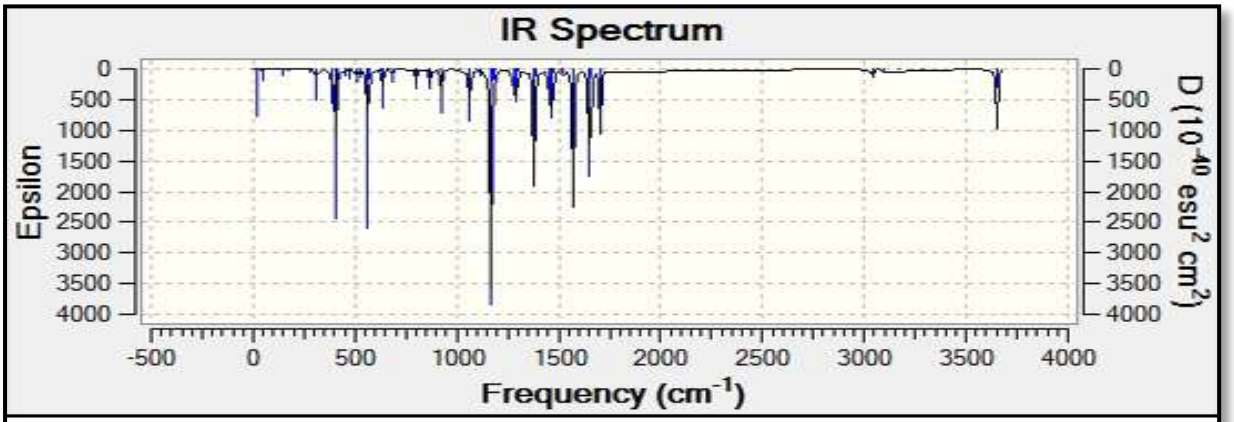


Fig (3-23): Infrared Spectrum of complex 3 (C_3).

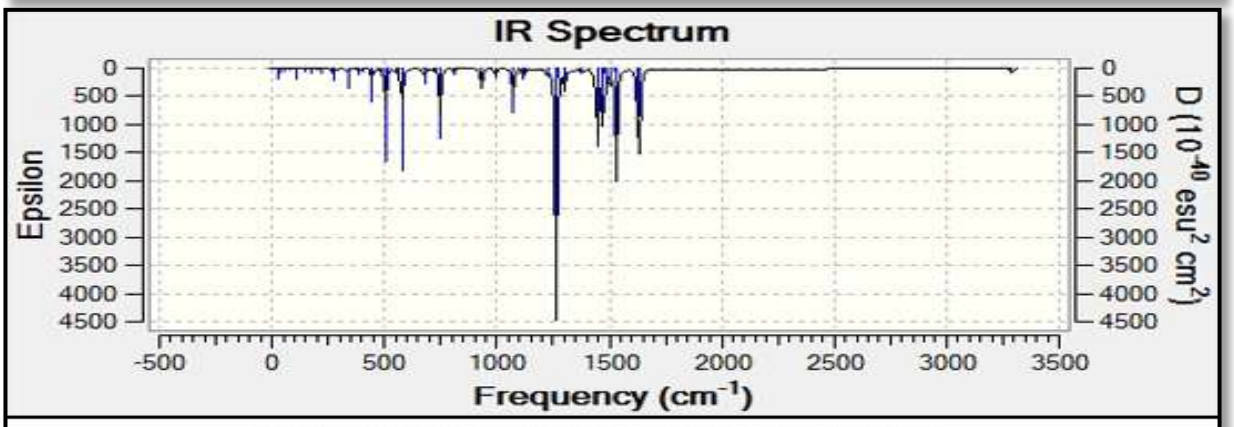


Fig (3-24): Infrared Spectrum of complex 4 (C_4).

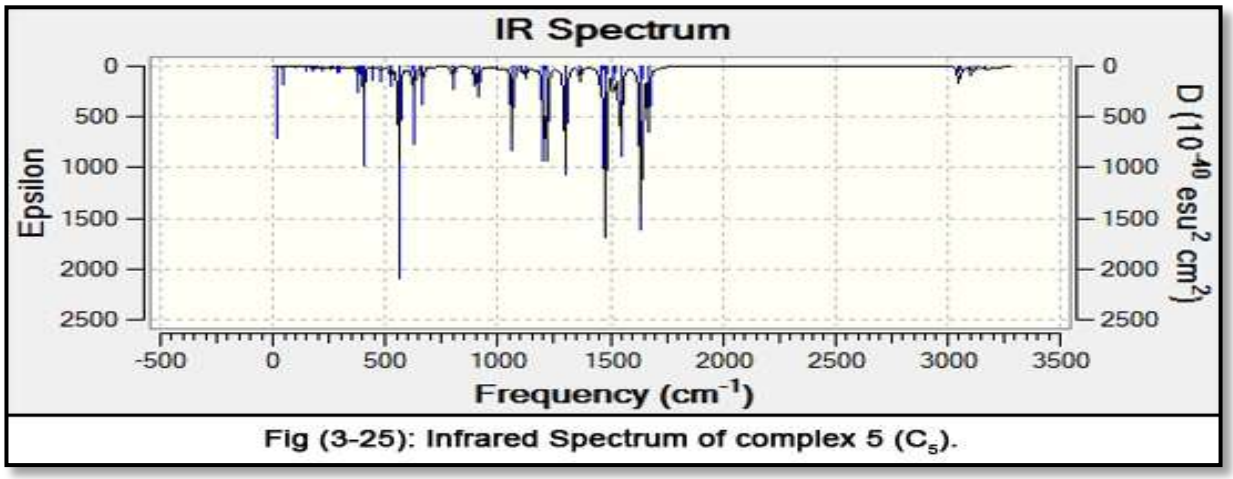


Fig (3-25): Infrared Spectrum of complex 5 (C_5).

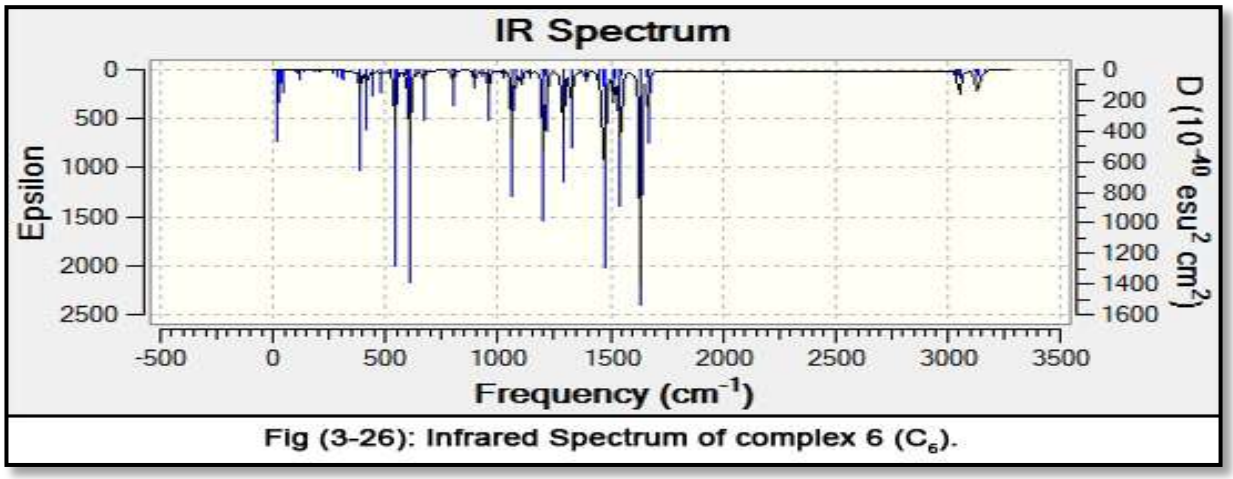


Fig (3-26): Infrared Spectrum of complex 6 (C_6).

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