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College of Science
Department of Chemistry

Theoretical Studies for some Manganese (III) Complexes Containing Oxygen and Nitrogen Atoms

A Thesis

Submitted to the College of Science Al-Nahrain University in partial fulfillment of the requirements for the Degree of Master of Science in Chemistry

By

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(B.Sc 2005)

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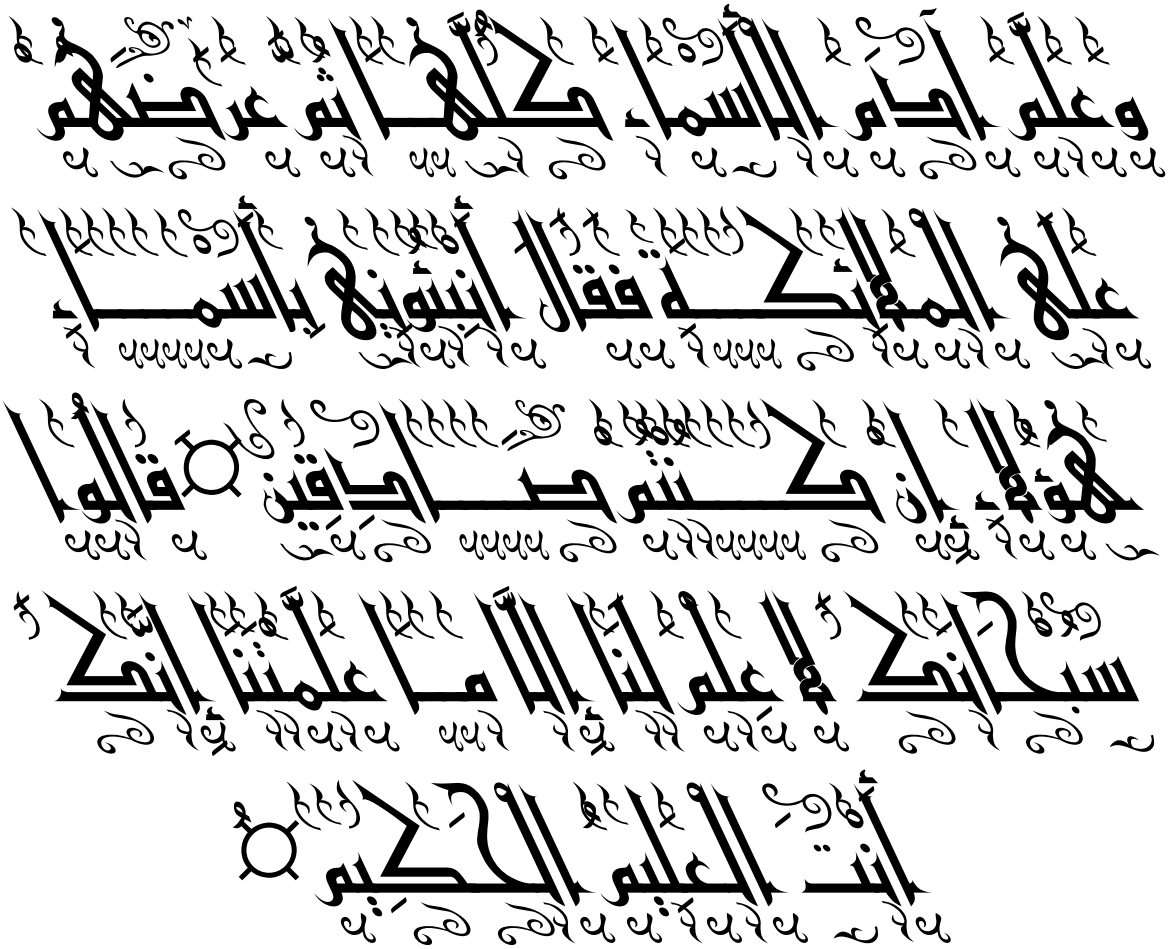
بسم الله الرحمن الرحيم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صدق الله العظيم

سورة البقرة: 31 ـ 32

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We, the Examining Committee, certify that we read this thesis and have examined the student *Ahmed Abd Al-Sattar Ali* in its contents and that, in our opinion; it is adequate as a thesis for the Degree of Master of Science, in Chemistry.

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الاهداء

الى وطني الحبيب مهد الحضارات الأنسانية وأول معلم للبشرية.....

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إلى من جعل الله الجنة تحت أقدامها وتأنس روحي بقربهـا ويـستنير دربي بدعائها وتغفوا أحزاني بأبتسامة عينيها.....

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الى محيط امالي وعنوان عزتي وسؤددي .....

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الى رفيقات حياتي وصديقات عمري وقدوة دربي .....

اخواتي

الى كل من له معزة في قلبي .....

اهدي ما وفقني اليه ربي ثمرة جهدي .....

احمد ?

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Abstract

Reactive oxygen species (ROS) are small, highly reactive, oxygen containing molecules that are naturally generated in small amounts during the body's metabolic reactions and can react with and damage complex cellular molecules such as fats, proteins, and DNA. Superoxide dismutase (SOD) represents an essential defense system against oxygen-derived free radicals, specifically superoxide ($O_2^{\bullet -}$). Superoxide can initiate a series of free radical reactions that yields other oxygen radicals, which together are thought to act as inflammatory mediators and induce cellular damage.

The presence of natural superoxide dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx) is to perform as defense systems against the cells damage which caused by superoxide compounds. These various enzymes allow to founding a widely area of treatment of many diseases.

In our thesis, a series of ten Schiff-bases manganese (III) complexes which is previously prepared have been designed and build as SOD and CAT mimetics. The complexes along with the known Mn-Salen [(C_1: a known drug used as standard against superoxide anion (O_2^-) (SOD-mimetic activity) and hydrogen peroxide (H_2O_2) (CAT-mimetic activity)], have been characterized using the Gaussian 03 program (2003). The results show the following:

1. The manganese (III) ion in these complexes is surrounded by two nitrogen atoms of the Schiff-base, and two oxygen atoms and metal ion above the basal plane toward the anion (Cl^-).
2. The behavior of building complexes is different in the oxidation-reduction reactions.
3. Some complexes which have mixed ligands (heteroligands), show to have better activities than that of the same ligands (homoligands).

4. Some complexes get high mimetic enzyme activity in one reaction (SOD-mimetic or CAT-mimetic activities), but low mimetic enzyme activity in the other reactions.
5. The activities of both C_2 and C_7 complexes are higher than that of C_1 complex in both reaction types (SOD-mimetic and CAT-mimetic activities).
6. The activities of (C_4, C_9, C_{10}) complexes are higher mimetic enzyme than that of C_1 complex as superoxide dismutase.
7. The activities of (C_3, C_5, C_6, C_8, C_{11}) complexes are higher mimetic enzyme than that of C_1 complex as Catalase.
8. The calculation of geometrical shapes of building complexes were achieved by calculate the bond frequencies and force constant, the results indicate that all the building complexes have square pyramidal shape.

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List of Abbreviations

Abbreviation	Means
UV	Ultra-Violet spectra.
IR	Infra-Red spectra.
ROS	Reactive Oxygen Species.
DNA	Deoxy ribonucleic acid.
NAD	Nicotine Amide Adenine Dinucliotide.
NADH	Nicotine Amide Adenine Dinucliotide Hydride reduced.
NADPH	Nicotine Amide Adenine Dinucliotide Phosphate Hydride reduced.
NADP	Nicotine Amide Adenine Dinucliotide Phosphate.
PD	Parkinson's disease.
SOD	Superoxide Dismutase.
CuZnSOD	Superoxide Dismutase containing Cu, Zn at active site.
ECSOD	Extra Cellular Superoxide Dismutase.
MnSOD	Superoxide Dismutase containing Mn at active site.
CAT	Catalase.
GPx	Glutathione peroxidases.
GSH	Glutathione in reduced form.
GSSG	Glutathione in oxidized form.
SB	Schiff Bases.
DFT	Density Functional Theory.
MM	Molecular Mechanics.
CNDO	Complete Neglect of Differential Overlap.
INDO	Intermediate Neglect of Differential Overlap.
MINDO	Modified Intermediate Neglect of Differential Overlap.
MNDO	Modified Neglected of Diatomic Differential Overlap.
AM1	Austin Model Version 1.
PM3	Parameterization Model, Version 3.
ZINDO	Zerner's Intermediate Neglect of Differential Overlap.

List of Abbreviations

Abbreviation	Means
CPU	Central Processing Unit.
RAM	Random Access Memory.
SCF	Self Consistent Field system.
NMR	Nuclear Magnetic Resonance spectra.
PDB	Protein Data Bank.
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
HF	Hartree-Fock
HSAB	Hard-Soft Acids Bases
r,θ,φ	Spherical coordinate
c	speed of light
h	Plank constant.
$\hat{h}$	Hamiltonian operator
ψ_i	Wave function

Chapter One

1

Introduction

Part-I

1.1 Inorganic biochemistry

Inorganic biochemistry can be defined most simply as the chemical reactivity of metal ions in biological systems. It is a widely and relatively young science that has attracted researchers from many different fields and apparently unrelated backgrounds [1]. The disciplined nature of this field may well be what differentiates it best from other areas of biochemical science such as synthetic chemistry, spectroscopy, electrochemistry, theoretical chemistry, biochemistry, and molecular biology meet at the frontiers of chemistry and biology. The apparent variety of the field, in fact does hide a simple truth: the rules governing the chemistry of biological molecules are the same as those that define the chemical and physical properties of typical organic and inorganic molecules and materials. For this reason, a thorough understanding of the fundamental kinetics, thermodynamic, and structural principles of organic and inorganic chemistry will prove very useful in occupying the reactivity of apparently complex biological systems [2].

The bulk and trace elements that form the core of inorganic biochemistry are noted in figure (1-1) and are the essential building blocks for all life forms [1]. Table (1-1) illustrates how each class of elements serves a distinctive biochemical role (structural, catalytic, regulatory). The field of inorganic biochemistry is directed toward understanding this chemistry. The biochemistry of carbon, hydrogen, nitrogen, oxygen, and phosphorus compounds which include the largest part of the material found in living organisms , will not be considered directly, although the chemistry of these main group elements forms a

structural core around which our considerations of the biochemistry of metal ions and their relationship with proteins, enzymes, nucleic acids, lipids, sugars, vitamins, and hormones will be formed [3] .

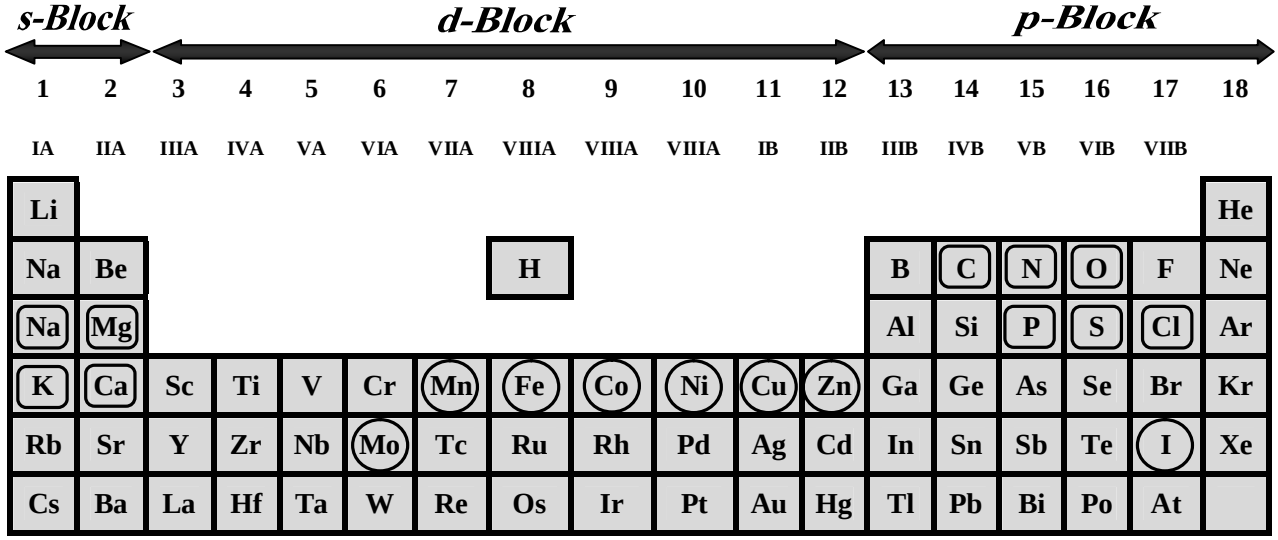


Figure (1-1): Elements known to be essential for life are highlighted (◯ : bulk elements, ▢ : trace elements).Labels 1-18 (new system) or IA-VIIB (old system) at the heads of columns represent groups of electronically and chemically related elements. The important valence electrons for each category of elements are noted in parentheses as follows:- group 1: Alkali elements (ns); group 2: Alkaline earth elements (ns); group 3-12: transition elements [(n-1)d]; groups 13-17,main group (np); group 18 noble gases [1].

Table (1-1): Overview of the biochemical roles of the elements [3].

Elements	Biochemical Roles
Alkali metals	Charge neutralization, voltage gating, structural stabilization.
Alkaline earths	Messengers, enzyme activators, structure regulation.
Transition metals	Electron transfer, redox catalysis.
Main group	Structural elements of biological materials, conformational triggering.

The alkali, alkaline earth, and main group elements tend to take an oxidation state that corresponds to stable noble gas configuration (figure 1-1), the noble elements (or inert elements) in group 18 which have filled outer valence orbital. Such electronic configurations are stable, and so these elements have little reason to distribute in further chemistry. Other elements also tend to react so that they lose electrons to form positively charged species (cations) or accept electrons to form negatively charged species (anions) in order to extend to such a configuration. The oxidation state of an ion is a extremely useful to keep on geometrical shape that helps in electron counting, although the effective charge at the atomic center may be different as a result of electron delocalization from neighboring atoms.

The transition elements display the most variable and interesting oxidation-reduction chemistry in the periodic table. Multiple oxidation states are common, explain the relative ease of removing d-electrons [1].

There are few d-electrons to be lost in the early part of first transition series, and so only lower oxidation states are available. At the other extreme it becomes gradually more difficult to remove electrons as we move across the series, since the d-orbitals are stabilized and their energies are lower. Also the electrons toward the right of the transition series have fewer unfilled d-orbitals to participate in bonding with electron donating ligands[2] .Table (1-2) lists the biologically important oxidation levels for the essential bulk and trace metals noted in figure (1-1) . Although several transition metals may form complexes with higher oxidation states, the ligand environments required to stabilize such valences, which explain the ability to complexes formation, are not commonly found in biology. For similar reasons, low oxidation states (M^{n+}: $n \leq 1$) are also uncommon. Other than organic frameworks of biological macromolecules , the

main group elements tend to be found as small anionic such as SO_4^{2-}, NO_3^-, HCO_3^-, Cl^- or gaseous species such as O_2 , N_2 , CO_2, and SO_2 [1] .

The aqueous solution chemistry of first-row transition metal ions is dominated by low or moderate oxidation states. Higher oxidation states tend to be the rule for second and third-row transition metals, which consequently require electronegative ligands for stability to avoid oxidation by the high valent metal center. For example, anionic oxo- and halo- ions are formed (ReO_4^-, $PtCl_4^{2-}$, $PtCl_6^{2-}$). Since oxo- and halo- ions do not result in biologically functional complexes of these metals, second and third-row transition metals are generally unsuitable for use in biological chemistry. A second, and in more practical reason for the use of first-row transition metals because the large abundance of these metals in nature. This provides a strong driving force in the world of natural selection [2].

Table (1-2): Oxidation states commonly available to essential bulk and trace elements [1].

Metals Name	Symbols	Available oxidation states [a]						
Sodium	**Na**	**1**						
Potassium	**K**	**1**						
Magnesium	**Mg**		**2**					
Calcium	**Ca**		**2**					
Vanadium	**V**		**2**	**(3)**	**(4)**	**(5)**		
Chromium	**Cr**		**2**	**(3)**	**(4)**	**(5)**	**(6)**	
Manganese	**Mn**		**2**	**(3)**	**(4)**	**(5)**	**(6)**	**(7)**
Iron	**Fe**		**2**	**3**	**(4)**	**(5)**		
Cobalt	**Co**	**1**	**2**	**3**				
Nickel	**Ni**	**1**	**2**	**3**				
Copper	**Cu**	**1**	**2**					
Zinc	**Zn**		**2**					
Molybdenum	**Mo**		**(2)**	**(3)**	**4**	**5**	**6**	

[a] Numerals indicate positive oxidation levels , those in parentheses are not generally found in biological molecules .

Coordination data for common biological ions are noted in table (1-3), and common coordination geometries are illustrated in figure (1-2). Note that the coordination numbers and geometries of the alkali and alkaline earth metals depend on the relative sizes of the cation (complexes) and anion (ligands). Coordination preferences for the transition metals again depend, in part, on the size and geometrical shape (explain the steric properties) of the ligands which that surrounding the metal ion. In the other hand small cations can be suitable for fewer ligands in their inner coordination spheres and tend to take place tetrahedral geometry that minimizes steric and electrostatic repulsion relative to square planar. Unlike the alkali and alkaline earth metals, where the bonding is predominantly electronic in origin, while the coordination complexes of transition metals contain a substantial degree of covalence. The energies of d-orbital are comparable with the ligands orbital energies and may interact favorable in a bonding fashion [3].

Table (1-3): Coordination numbers (C.N.) and preferred geometries for selected metal ions [3].

Cation	C.N.	Geometry	Biological ligands
Na^{+}	6	Octahedral	O, ether, hydroxyl, carboxylate
K^{+}	6-8	Flexible	O, ether, hydroxyl, carboxylate
Mg^{2+}	6	Octahedral	O, carboxylate, phosphate
Ca^{2+}	6-8	Flexible	O, carboxylate, carbonyl, phosphate
Mn^{2+} (d^5)	6	Octahedral	O, carboxylate, phosphate N, imidazol N
Mn^{3+} (d^4)	5	Square pyramidal	O, N, Salen
	6	Tetragonal	O, carboxylate, phosphate, hydroxyl
Fe^{2+} (d^6)	4	Tetrahedral	S, thioate
	6	Octahedral	O, carboxylate, alkoxide, oxide, phenolate N, imidazol N, porphyrin
Fe^{3+} (d^5)	4	Tetrahedral	S, thioate
	6	Octahedral	O, carboxylate, alkoxide, oxide, phenolate N, imidazol N, porphyrin
Co^{2+} (d^7)	4	Tetrahedral	S, thioate N, imidazol N
	6	Octahedral	O, carboxylate N, imidazol N, porphyrin
Ni^{2+} (d^8)	4	Square planer	S, thioate N, imidazol N, polypyrrole
	6	Octahedral	Uncommon
Cu^{+} (d^{10})	4	Tetrahedral	S, thioate, thioether N, imidazol N
Cu^{2+} (d^9)	4	Tetrahedral	S, thioate,thioether N, imidazol N
Cu^{2+} (d^9)	4	Square planer	O, carboxylate N, imidazol N
	6	Tetragonal	O, carboxylate N, imidazol N
Zn^{2+} (d^{10})	4	Tetrahedral	O, carboxylate,carbonyl S, thioate N, imidazol N
	5	Square pyramidal	O, carboxylate, carbonyl N, imidazol N

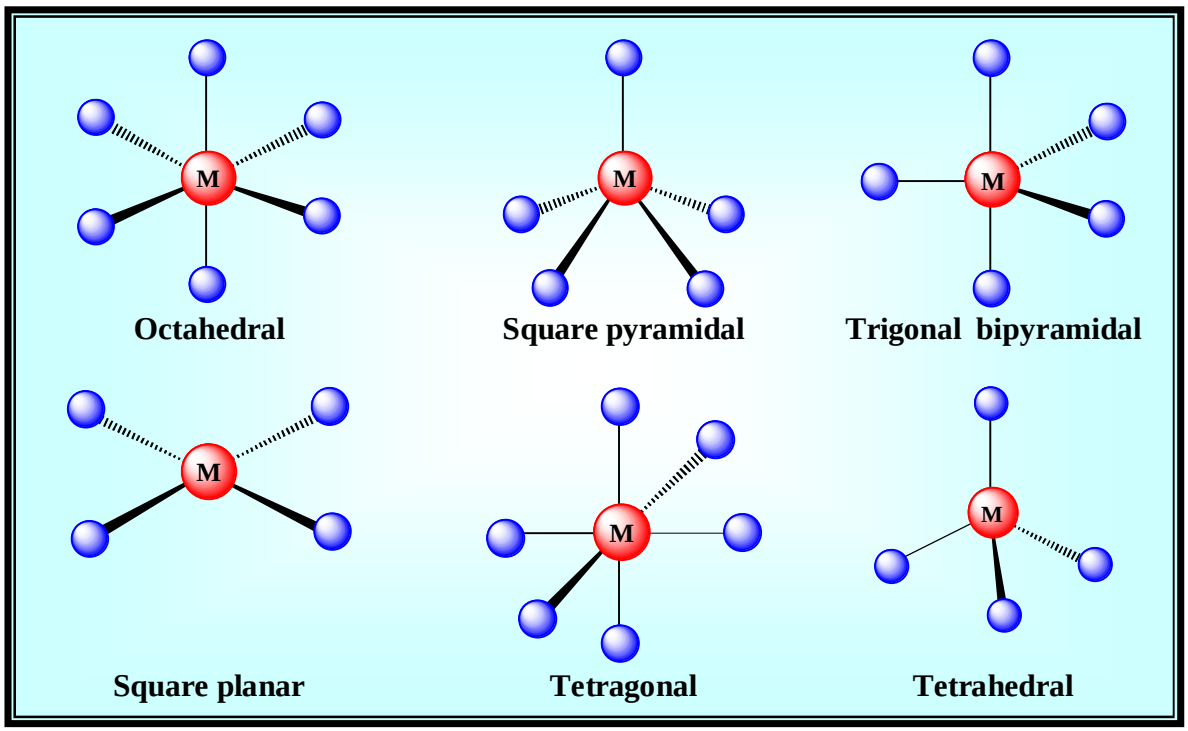


Figure (1-2): Common coordination geometries around a metal ion. In a biological macromolecular the ligand atoms (represented by ●) may each be distinict, and structural distortions from the regular geometries shown are common [3].

1.2 Free Radical

The free radical can be defined as a chemical species, an atom or molecule that has one or more unpaired electrons in valance shell and is capable of existing independently. The presence of an odd electron in the free radical makes it unstable, short lived and highly reactive; therefore it can react quickly with other compound, trying to capture the needed electron to increasing the stability. Generally, free radical attacks the nearest stable molecule, "stealing" its electron or react with itself. When the attacked molecule looses its electron, it becomes a free radical itself, beginning a chain reaction cascade resulting in destroying of a living cell. The radical natures of a species are conventionally indicated by writing it with a heavy superscript dot. e.g. $X^{\bullet}$ [4].

1.2.1 How Free Radical are Formed [4]

A) Covalent bond cleavage of normal molecule: Atoms are boanded together when they share or transfer electron to form molecule. A covalent bond is formed when a pair of electrons is shared. The bond breakage occurs in two ways "homolytic cleavage" in this type of cleavage both atoms retain one electron each due to symmetrical rupture of bond. Therefore two fragments formed will contain an unpaired electron. These are called as free radicals (e.g. A-B $\rightarrow$ $A^{\bullet}$ + $B^{\bullet}$). Such type of cleavage requires high energy input either in the form of high temperature, U.V light or ionizing radiation to cause homolysis of covalent bond. Whereas, in other type of cleavage i.e. "heterolytic cleavage" one of the atoms retains both the bonding electrons and another takes none. This results in forming of ionic species (e.g. A-B $\rightarrow$ A^{+} + B^{-}).

B) Electron transfer: Electron transfer is a far more common and important source of generation of free radicals in biological system.

i) Oxidation reaction: By loss of a single electron from a normal species.

ii) Reduction reaction: By addition of a single electron to a normal species.

1.2.2 Biosynthesis and Effects of Free Radicals

The most common cellular free radicals are hydroxyl radical ($OH^{\bullet}$), super oxide radical ($O_2^{\bullet}$), nitric dioxide ($NO_2^{\bullet}$) and nitric oxide ($NO^{\bullet}$).Other molecules, such as hydrogen peroxide (H_2O_2) and peroxynitrate ($ONOO^{\bullet}$), are not free radicals but can lead to the generation of free radicals through various chemical reactions, figure (1-3). Free radicals and related molecules (e.g., H_2O_2 and $ONOO^{\bullet}$) often are classified together as reactive oxygen species (ROS) to signify

their ability to lead to oxidative changes within the cell. Free radicals and other ROS are by-products of cellular metabolism, and cells normally have a number of mechanisms to defend against damage induced by free radicals. Problems occur, however, when the production of ROS exceeds the ability of cells to defend against these substances. This imbalance between cellular production of ROS and the ability of cells to defend against them is referred to as oxidative stress. Oxidative stress can cause cellular damage and subsequent cell death because the ROS oxidize critical cellular components, such as lipids, proteins, and DNA. It follows that cells would undergo degeneration and death if subjected to damage induced by free radicals [5].

1.3 Reactive Oxygen Species (ROS)

In biological systems the most important free radicals are radical derivatives of oxygen. Oxygen and ROS are among the major sources of primary catalysts that initiate oxidation ***in vivo*** and ***in vitro*** [6]. The electronic structure of oxygen has two unpaired electrons in its outermost energy level. The triplet state of oxygen can react with other molecules to yield ROS such as hydrogen peroxide (H_2O_2), superoxide ($O_2^{\bullet}$), and hydroxyl radical ($OH^{\bullet}$). Superoxide radical ($O_2^{\bullet}$) is generated by the four electron reduction of molecular oxygen into water [7].

Oxygen is required to transfer various substances for the release of the energy and detoxify xenobiotics. During these processes oxygen acts as terminal electron acceptor and is eventually converted to more stable compound, water. This reduction of one molecule of O_2 via the cytochrome oxidase system of respiratory chain requires 4 electrons. Such type of reduction is known as trans-valent reduction of oxygen to water [4].

$$O_2 \xrightarrow{4e^- + 4H^+} 2H_2O$$

Mitochondrial cytochrome oxidase system

However, certain reactions permit this reduction to take place by a series of incomplete univalent reductions each of which needs a single electron. Such type of reductions can produce a series of reactive radicals and non-radicals which are collectively known as reactive oxygen species (ROS) [8].

Thus, ROS includes free radical as well as other non-radical derivatives of oxygen e.g. H_2O_2 and Singlet Oxygen. These ROS can produce oxidative damage to the tissue and hence are known as oxidants in biological system [9].

1.3.1 Sources of Reactive Oxygen Species (ROS)

Numerous cellular systems can produce ROS. The major source of ROS production in the cell is the mitochondrial respiratory chain, which, as described earlier, utilizes approximately 80 to 90 percent of the O_2 a person consumes. Thus, even though only a small percentage of that oxygen is converted to ROS, figure (1-3), the mitochondrial respiratory chain in all cells generates most of the ROS produced in the body [6].

Another major source of ROS, especially in the liver, is a group of enzymes called the cytochrome P450 mixed-function oxidases. Many different variants of these iron-containing enzymes exist, some of which are responsible for removing or detoxifying a variety of compounds present in our environment and ingested (e.g., foods or drugs), including alcohol. Some cytochrome P450 enzymes also are important for metabolizing substances that naturally occur in the body, such as fatty acids, cholesterol, steroids, or bile acids. The biochemical

reactions spurred (i.e., catalyzed) by the cytochrome P450 molecules use molecular oxygen, and during these reactions small amounts of ROS are generated. The extent of ROS generation may vary considerably depending on the compound to be degraded and on the cytochrome P450 molecule involved. One type of cytochrome molecule that is especially active in producing ROS is known as CYP2E1. This enzyme is of particular interest when investigating alcohol-induced oxidative stress because its activity increases after heavy alcohol exposure and because CYP2E1 itself also metabolizes alcohol [10].

ROS also are produced by a variety of oxidative enzymes present in cells, such as the previously mentioned xanthine oxidase. Under normal physiological conditions, xanthine oxidase acts as a dehydrogenase that is, it removes hydrogen from xanthine or hypoxanthine and attaches it to NAD, thereby generating NADH. However, under certain conditions, such as the disruption of blood flow to a tissue, xanthine dehydrogenase is converted to a ROS-producing oxidase form. Alcohol consumption also may promote the conversion of xanthine dehydrogenase to xanthine oxidase which can generate ROS, thereby enhancing oxidative stress [11].

Other sources of ROS in the body are two types of immune cells called macrophages and neutrophils, which contain a group of enzymes, called the NADPH oxidase complex and when activated generate superoxide radicals and hydrogen peroxide. Hydrogen peroxide then interacts with chloride ions present in the cells to produce hypochlorite (the active ingredient in bleach), which in turn destroys the pathogen. The NADPH oxidase complex and the resulting ROS production are critical to the body's defense against all kinds of diseases, in which ROS production by the NADPH oxidase complex is drastically reduced.

Patients with this condition are highly sensitive to infections and usually die at an early age.

Besides the ROS generation that occurs naturally in the body, humans are constantly exposed to environmental free radicals, including ROS, in the form of radiation, UV light, tobacco smoke, and certain compounds referred to as redox cycling agents, which include some pesticides, but also certain medications used for cancer treatment. The toxicity of these medications against tumor cells (as well as normal body cells) results from the fact that the compounds are modified by cellular enzymes to an unstable intermediate, which then reacts with molecular oxygen to produce the original product plus a superoxide radical. Thus, a vicious cycle of chemical reactions involving these compounds continually produces ROS [12].

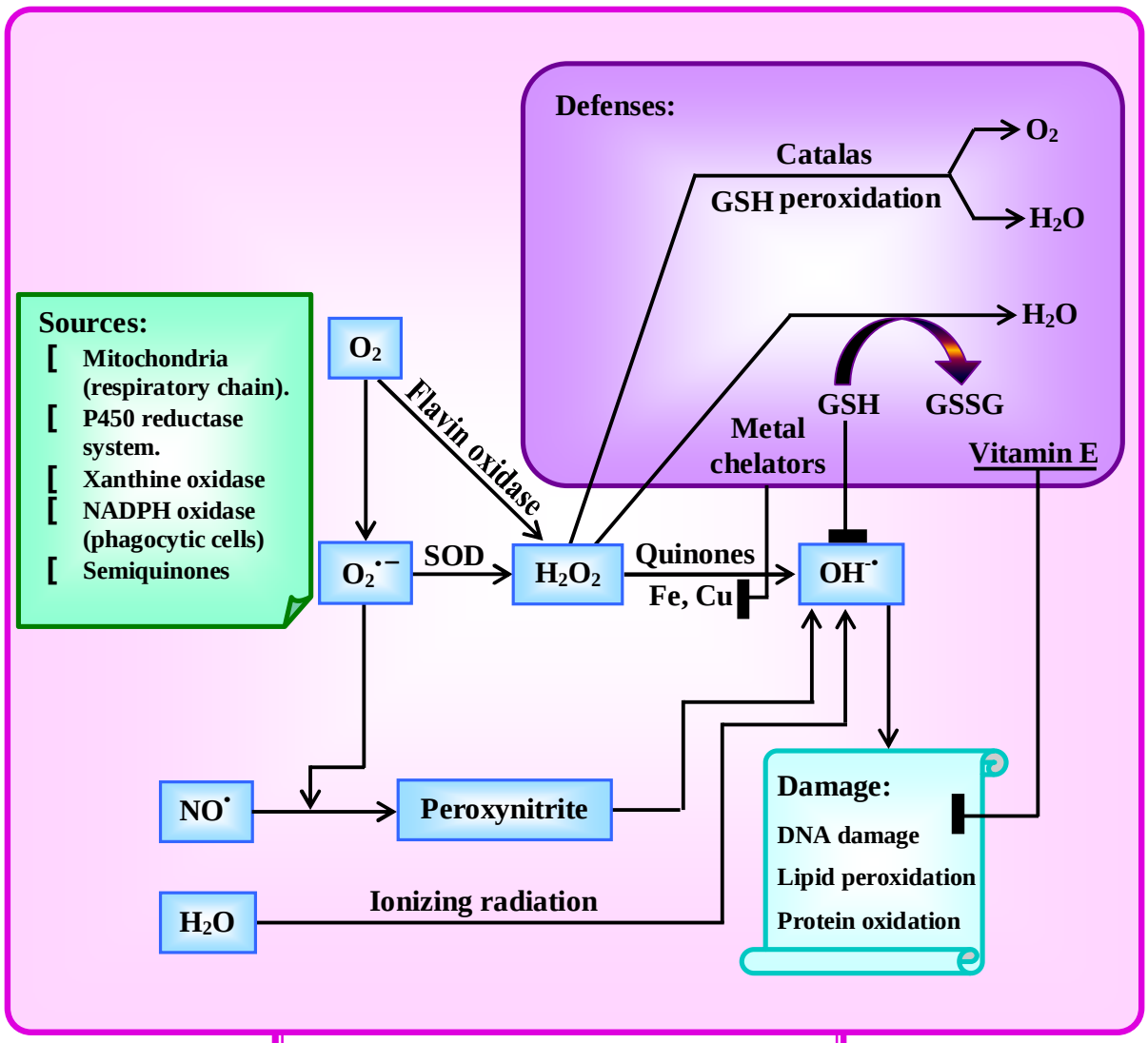


Fig (1-3): Sources of Reactive Oxygen Species (ROS) [12]

1.4 Neurological Diseases of Reactive Oxygen Species

1.4.1 Alzheimer's disease

Alzheimer's disease is a physical condition which attacks the brain resulting in impaired memory, thinking and behavior. It is named after Alois Alzheimer, the German physician who, in 1907, first described it.

As brain cells shrink or disappear abnormal material builds up as "tangles" in the centre of the brain cells, and "plaques" outside the brain cells. These disrupt messages within the brain, damaging connections between brain cells. The brain cells eventually die and this means that information cannot be recalled. As Alzheimer's disease affects each area of the brain, certain functions or abilities are lost. Memory of recent events is the first to be affected, but as the disease progresses, long-term memory is also lost. The disease also affects many of the brain's other functions and consequently many other aspects of behavior are affected. Once ability is lost it can be rarely regained or relearned. There are two different types of Alzheimer's disease: (i) Sporadic Alzheimer's disease (ii) Familial Alzheimer's disease [13].

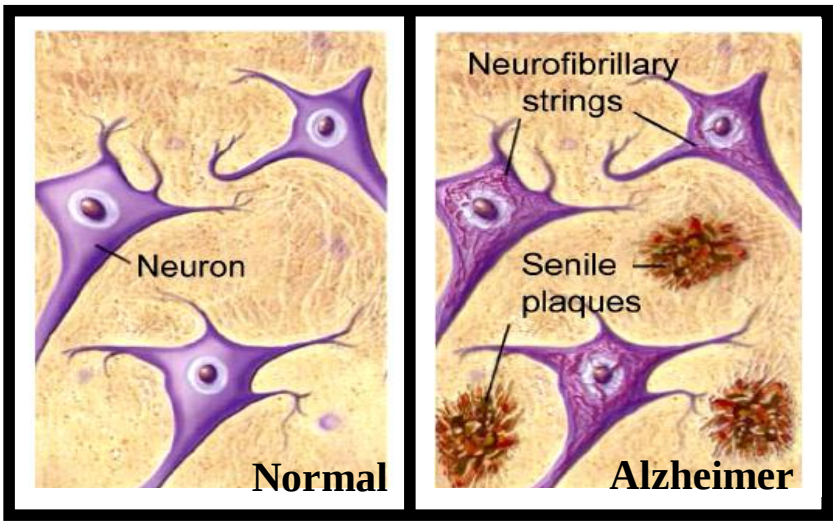


Fig (1-4): Lesions caused by AD. Neurofibrillar degeneration is characterized by "strings" of tau proteins inside the neurons, and the senile plaques by b-amyloid deposits which appear as flat "pastilles" situated in between the cells [14].

1.4.2 Parkinson's disease (PD)

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder (after Alzheimer's disease) [15]. The cause of PD remains unclear. Mutations occur in rare, familial cases of PD [16], but most cases of PD are sporadic. Researchers have identified several risk factors, including exposure to pesticides, head trauma, and aging [17] PD most commonly affects people during or after their sixth decade (only 15% of cases are diagnosed before age 50).

The four primary motor symptoms of PD are resting tremor, rigidity, bradykinesia, and postural instability. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. Nonmotor symptoms include urinary problems, constipation, skin problems, sleep disruptions, orthostatic hypotension, and depression and other emotional changes [18]. Individual variability in the occurrence of symptoms and in the disease progression and intensity is typical of PD.

1.4.3 Down's syndrome

Down's syndrome is a genetic birth defect that causes delays in physical and mental development. People with Down's syndrome have 47 chromosomes instead of the typical 46 that most people have. There are two copies of chromosome 21. Down's syndrome is caused by an error in cell division that occurs at conception. There is increased risk of giving birth to a child with Down's syndrome as the age of a mother increases. However, many children with Down's syndrome are born to younger mothers [19].

There are three types of Down's syndrome: (i) Trisomy 21 (ii) Translocation, and (iii) Mosaic [20]. Most children with Down's syndrome are

developmentally delayed. They complete most developmental tasks but do so at a later age than do children without Down's syndrome. For instance, most children learn to walk between 10 and 14 months of age. Children with Down's syndrome typically learn to walk between 18 and 24 months of age. Other characteristics include [19]: Upward slanting eyes, flat face, small ears, large tongue, short neck, small hands with short fingers, crease inside of palm, small head size, wide gap between first and second toes, speech and language delays, mild to moderate retardation (a few individuals may not be classified as mentally retarded), and average life span of 55 years.

1.5 Oxidative Stress

Oxidative stress can be defined as the disruption of the equilibrium between the factors that promote free-radical formation and anti–oxidant defense mechanisms. Being very reactive species, free radicals may cause damage in biologically critical molecules including DNA, cellular proteins and membrane lipids [21].

The increased oxidative stress may arise from a variety of factors such as (a) enhanced generation of free radicals, (b) reduced levels of antioxidants available, (c) enhanced consumption, leakage or destruction of antioxidants, (d) decreased protective capacity including antioxidant enzymes, (e) leakage of electrons from the disrupted mitochondrial electron transport chain, and (f) phagocyte recruitment and activation [22].

1.6 Antioxidant

From a biological point of view, antioxidants have been defined as substances that in concentrations lower compared to the substrate susceptible to oxidation are capable of delaying or inhibition oxidative processes, by inhibiting the initiation or propagation of oxidizing chain reactions, and is also involved in scavenging free radicals [23]. In this definition, "substrate" refers to any oxidizable molecule ***in vivo***: lipids, proteins, carbohydrates and DNA. As antioxidants react to protect biological targets from oxidation, they are themselves oxidized. The stability of an oxidized antioxidant molecule is essential, as to prevent oxidation from progressing; oxidized antioxidants must retain low reactivity towards bio-molecules [24]. Antioxidants physiologically act to prevent cellular component damage caused by free radicals. In the biological system of human body, many anti-oxidative systems are used. Generally, they can be divided into enzymatic and non-enzymatic systems. The exact activity of a given antioxidant depends on kind of the reactive species involved [25].

Also antioxidants can be divided into four categories, namely; (a) endogenous (NADPH, NADH, glutathione, uric acid, bilirubin, metallo-enzymes), (b) exogenous especially from diet (vitamin C, α-tocopherol, carotenoid), (c) metalbinding protein in the body such as albumin, transferrin, ferritin, and (d) antioxidant enzymes (superoxide dismutase, glutathione peroxidase, catalase) [26].

An antioxidant in the body may act in five different ways: (i) replacing damaged "target molecules", (ii) reducing formation of reactive species, (iii) repairing damaged "target molecules", (iv) binding metal ions required to the formation of highly reactive species (such as $OH^{\bullet}$), (v) scavenging reactive

species either by using enzymes or directly by reaction whereby the antioxidant itself would be used up [25].

1.7 Antioxidant Enzymes

1.7.1 Superoxide Dismutase (SOD).

Superoxide dismutase (SOD) is metallo-enzymes that catalytically scavenge the superoxide radical, figure (1-6). They are essential for the aerobic survival of all forms of life. SOD was subsequently found to be a universal enzyme, which exits in three different metalloforms where each form incorporates a transition metal ion at the active site. SOD is not known to react catalytically with any substrate other than the superoxide radical. It is now well appreciated that, under normal circumstances, in healthy individuals, superoxide dismutase (SOD) enzymes contain this radical burden [27].

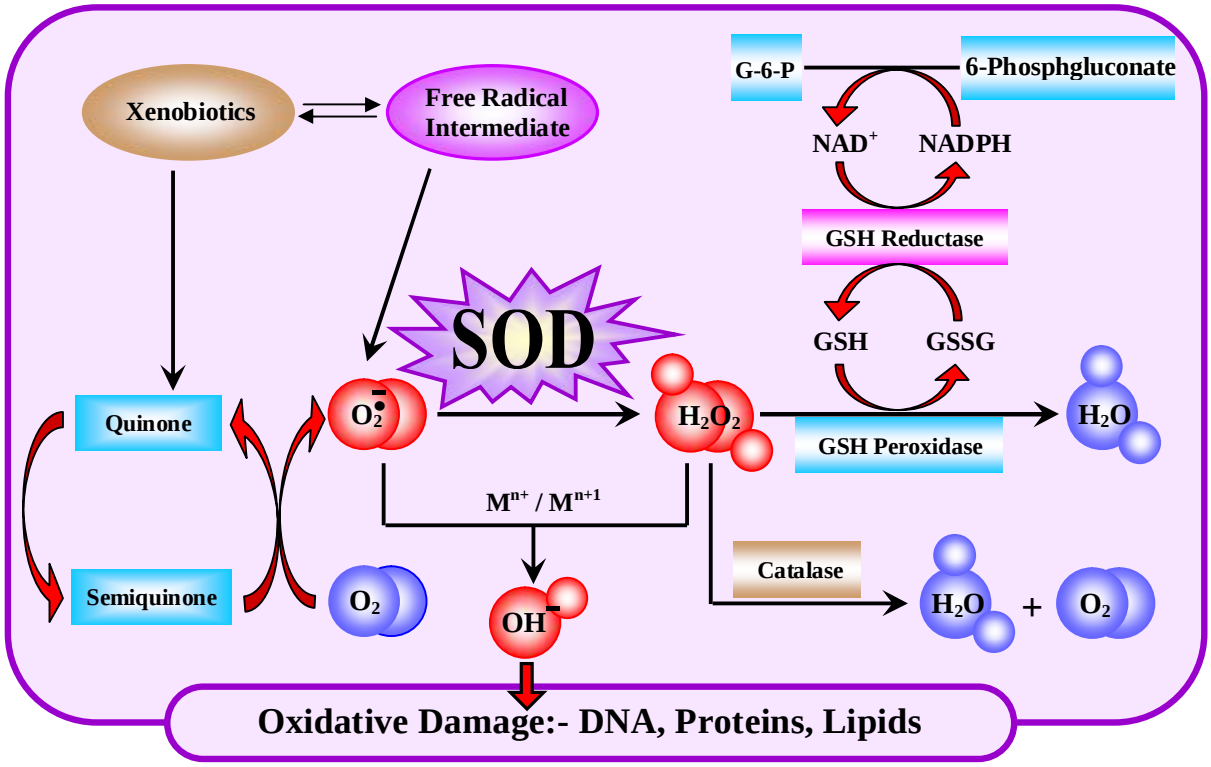


Fig (1-5): Mechanism of Antioxidant Enzymes to Conversion Free Radical to Molecular Oxygen and Water [27].

There are three types of SOD that can be isolated from eukaryotic cells. These enzymes are a class of oxidoreductase enzymes, which contain Cu\Zn, Mn or Fe at the active site (in mammalian SOD contain either Cu or Mn at the active site) and catalyze the dismutation of superoxide, the one-electron reduction product of molecular oxygen, SOD catalyzes the following reaction [28]:

$$O_2^- + M^{n+1} \longrightarrow O_2 + M^{n+}$$

$$O_2^- + M^{n+} + 2H^+ \longrightarrow H_2O_2 + M^{n+1}$$

The over all reaction

$$2O_2^- + 2H^+ \xrightarrow{\text{SOD}} H_2O_2 + O_2$$

Where M^{n+1} and M^{n+} are the metalloenzymes in the oxidized and reduced form respectively. This is believed to be an inner sphere mechanism with the superoxide radical directly binding to the metal during or before the electron transfer reaction. The reaction can proceed spontaneously at relatively rapid rate, but the enzyme increases this rate by more than 10000-fold [29]. Three different isoforms of SOD have been characterized in mammalians. The SOD enzymes have a distinct genomic structure and are well-compartmentalized [30].

SOD1 or CuZnSOD and SOD3 or ECSOD both have Cu in their catalytic centre, while SOD2 or MnSOD has Mn in the catalytic centre. SOD1 has been found in the cytoplasm, nuclear compartments and in the inter membrane space of the mitochondria. SOD2 is localized in the mitochondria matrix of the cells and SOD3 has been found in the extra-cellular compartments [31], figure (1-6), several compartments such as the plasma, lymph, cerebrospinal fluid and lung (this organ has the highest concentration of this enzyme) [32].

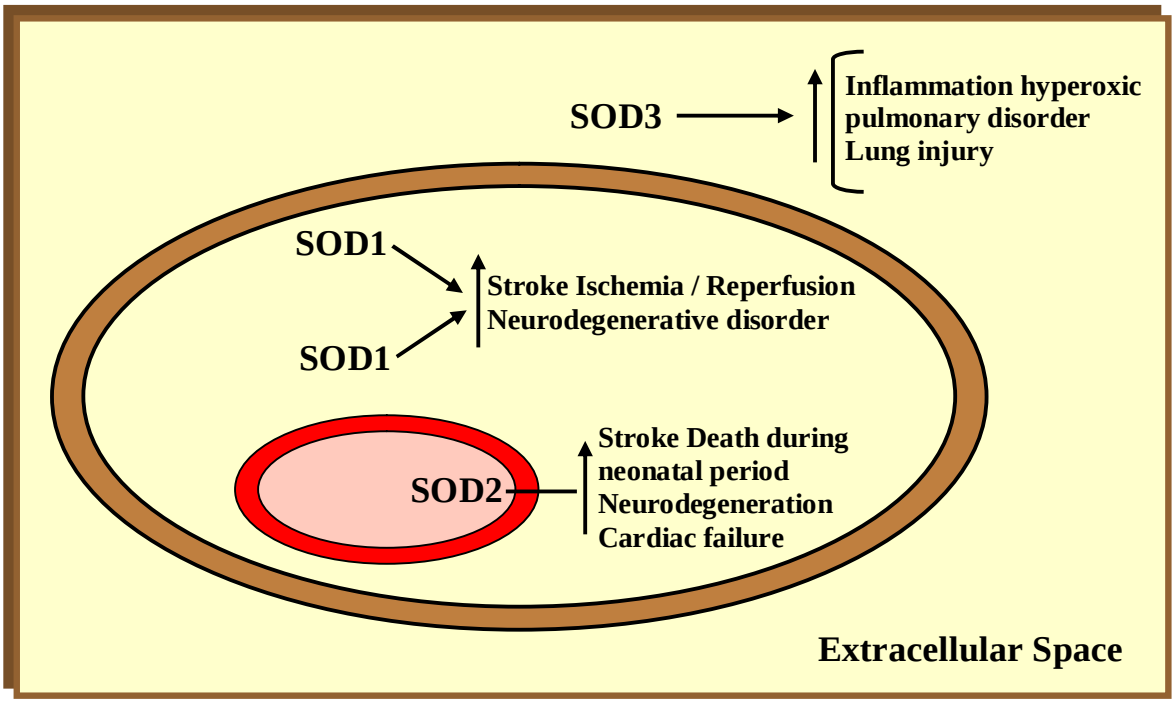


Figure (1-6): Relative roles of SOD isoforms in disease. SOD isoforms are well compartmentalized inside the cell (SOD1, cytoplasm; SOD2 in the mitochondria) and in the extracellular space (SOD3) [32].

The deficiency of SOD2 resulted in an increased production of superoxide, which in turn inhibits the respiratory chain by inactivating complex I (oxidized form of SOD2) and complex II (reduced form of SOD2) [33]. Loss or reduction of the SOD2 activity has been associated with mitochondrial vacuolization and lipid peroxidation, which in turn leads to neuro degeneration and heart failure [30].

1.7.2 Catalase (CAT).

Catalase represents one of the most active catalysts known. The reactions it catalyses are crucial to life. Catalase catalyses conversion of hydrogen peroxide, and another powerful and potentially harmful oxidizing agent to water and molecular oxygen. Catalase also uses hydrogen peroxide to oxidize phenols, formic acid, formaldehyde and alcohols. It is one of the first enzymes to be purified and crystallized and has accept a lot of attention in recent years because of its link to cancers disease, diabetes disease, and aging disease in humans and animals [34, 35].

1.7.3 Glutathione Peroxidase (GPx).

Glutathione peroxidases (GPx) are a family of enzymes that can be divided to two groups, selenium-independent and selenium-dependent enzymes. Glutathione, a tri-peptide consisting of glutamic acid - cysteine - glycine, is the substrate for glutathione peroxidase (GPx), which is an important enzymatic component of the intracellular antioxidant defenses [36]. Glutathione peroxidases reduce hydrogen peroxide and alkyl hydroperoxides to alcohols using reduced glutathione as effective reducer.

$$2H_2O_2 \xrightarrow{\textbf{GPx}} 2H_2O + O_2$$

$$ROOH + AH_2 \xrightarrow{\textbf{GPx}} ROH + H_2O + A$$

Where:- (AH_2) an acidic molecules, (A) conjugated base.

However, this does not mean that reduced glutathione is the sole thiol substrate of the enzymes. Glutathione disulfide, produced in the enzymatic reaction is recovered in the glutathione redox cycle [37], (see fig (1-7)).

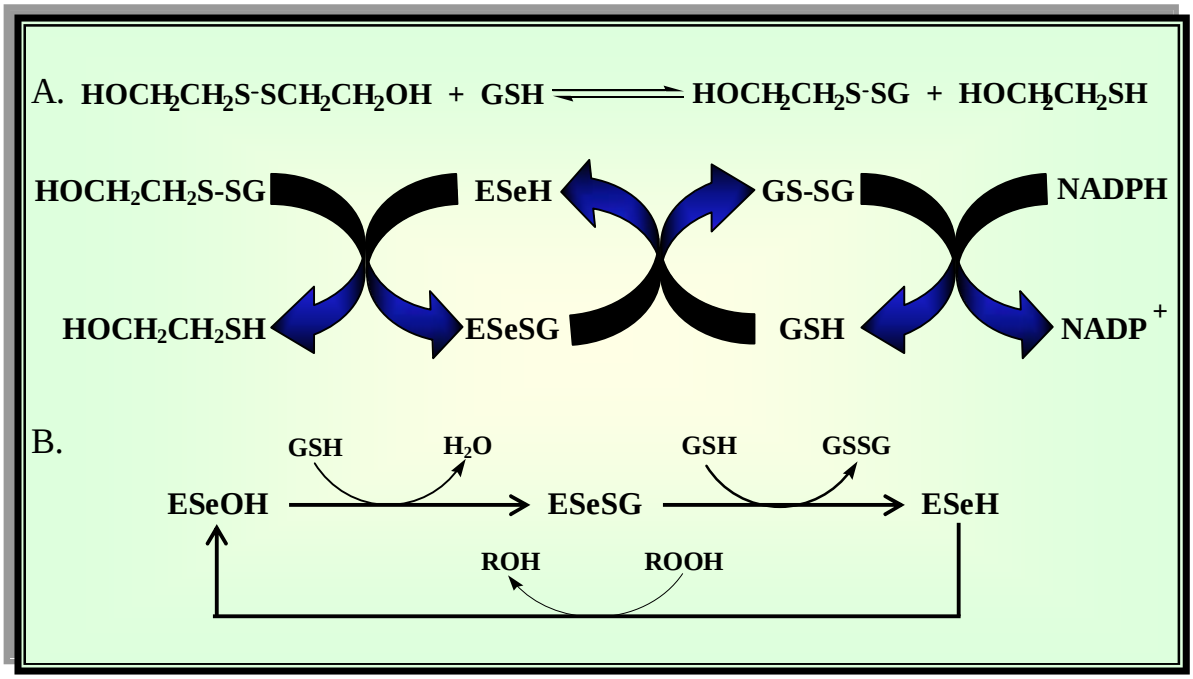
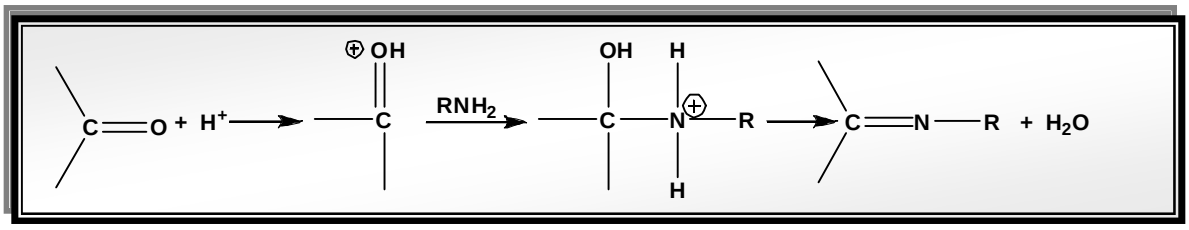


Fig (1-7): Glutathione Redox Cycle A) Disulfide exchange B) Postulated catalytic cycle of the GPx-catalyzed reduction of hydrogen peroxide by glutathione (GSH) [38].

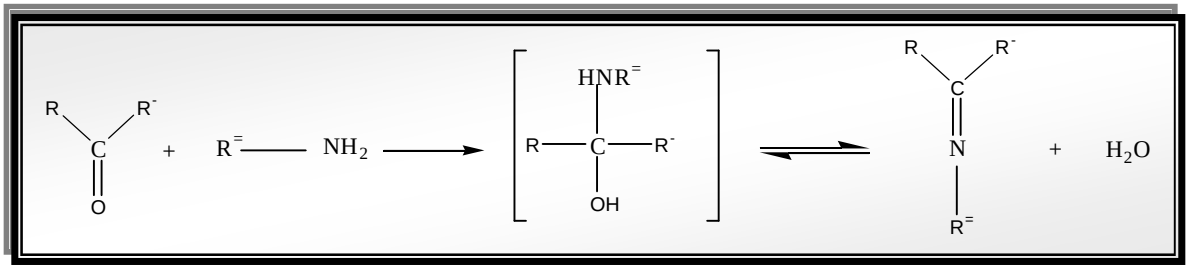
1.8 Schiff Bases (SB)

The term Schiff base is used to define those organic compounds which contain the functional group (-C=N-) and can be designated structurally as (R''R'C=NR). The nature of R group is limited to alkyl or aryl substituents or hydrogen at the point of attachment to the imino (C=N) carbon or nitrogen.

The Schiff bases were first prepared by (Schiff) in 1864 [39] from the condensation reaction of aldehydes or ketones with primary amines by refluxing the mixture in absolute ethanol, benzene, or any other suitable solvent for half or one hour some times, the reaction may be catalyzed by acid. The addition of proton to the carbonyl group yields the conjugated acid in which the carbon of the carbonyl group is more electrophilic, thus facilitating the attack of the amine on the carbonyl group. The added acid will enhance elimination of water molecule to give the final product (SB) [40].



The general mechanism of the Schiff base formation reaction can be depicted as follows:

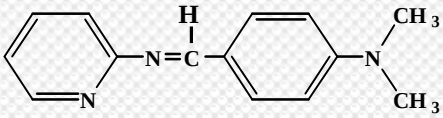
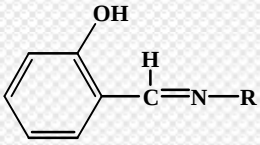
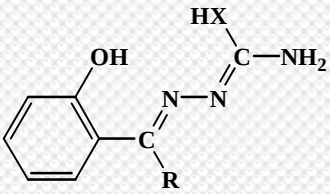
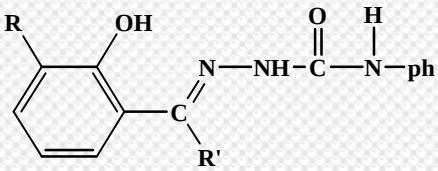
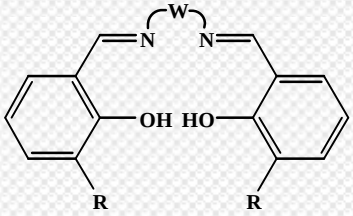


These bases can also be prepared by refluxing of equimolar quantities of aldehyde or ketone with amine without solvent or by slow melting for 10 minutes and then isolating and purifying the product by recrystallization or sublimation under reduced pressure [41].

Staab [42] prepared Schiff bases by removing water which is formed by condensation of aldehyde with the amine by refluxing in benzene, this done by mixing the amine and the aldehyde in benzene and then the residual solution is distilled under vacuum.

Imine (SB) and other C=N compound can be reduced by $LiAlH_4$, $NaBH_4$, Na-EtOH, hydrogen and catalyst, as well as with other reducing agents. Schiff bases can be classified according to the number of coordinating sites, type of bonding, type of donor atom (rather than azomethine nitrogen), number of donated electron and other method of ligand classification. Of these methods the one which depend on the coordination site is considered to be the most important. Table (1-4) shows examples of Schiff bases classified according to this method.

Table (1-4): Some types of Schiff-bases and their biological activities [43, 44].

No.	Structure of Schiff-Base	Donor Atoms	Donor Type	Biological Activity
1		N	**Monodentate**	**Antifungal**
2	 **R = ph, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$**		**Bidentate**	**Antifungal**
3	 **R = H, H, Me, Me** **X = S, O, S, O**	(ONS) Or (ONN)	**Tridentate**	**Antibacterial**
4	 **R = H, H, OCH$_3$** **R' = H, CH$_3$, H**	ONO	**Tridentate**	**Antibacterial**
5	 **R = H, OMe** **W = (CH$_2$)$_2$, (CHMeCH$_2$), (CH$_2$)$_4$**	ONNO	**Quadridentate**	**Antifungal**

Part-II

1.9 Computational Chemistry [45]

The term "theoretical chemistry" may be defined as the mathematical description of chemistry. Currently, there are two ways to approach chemistry problems: computational theoretical chemistry and non-computational theoretical chemistry.

Computational theoretical chemistry is primarily concerned with the numerical computation of molecular electronic structures and molecular interactions and non-computational quantum chemistry deals with the formulation of analytical expressions for the properties of molecules and their reactions.

The term "computational chemistry" is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer.

Computational chemistry is the application of chemical, mathematical and computing skills to the solution of interesting chemical problems. It uses computers to generate information such as properties of molecules or simulated experimental results. Very few aspects of chemistry can be computed exactly, but almost every aspect of chemistry has been described in a qualitative or approximate quantitative computational scheme. The biggest mistake that computational chemists can make is to assume that any computed number is exact. However, just as not all spectra are perfectly resolved, often a qualitative or approximate computation can give useful insight into chemistry if you understand what it tells you and what it doesn't.

Computational chemistry has become a useful way to investigate materials that are too difficult to find or too expensive to purchase. It also helps chemists make predictions before running the actual experiments so that they can be better prepared for making observations. The quantum and classical mechanics as well as statistical physics and thermodynamics are the foundation for most of the computational chemistry theory and computer programs. This is because they model the atoms and molecules with mathematics. Using computational chemistry software you can in particular perform:

- Electronic structure determinations,
- Geometry optimizations,
- Frequency calculations,
- Definition of transition structures and reaction paths,
- Protein calculations, i.e. docking,
- Electron and charge distributions calculations,
- Calculations of potential energy surfaces (PES),
- Calculations of rate constants for chemical reactions (kinetics)
- Thermodynamic calculations- heat of reactions, energy of activation, etc
- Calculation of many other molecular and balk physical and chemical properties.

The computational chemist must learn and apply a variety of methods to specific modeling situations. The focus will be on four general methods: (i) ***Density Functional Theory*** (DFT), (ii) ***ab-initio*** quantum chemical methods, (iii) ***semi-empirical*** quantum chemical methods, and (iv) ***Molecular Mechanics*** (MM) methods. Depending on how broadly one defines molecular modeling or computational chemistry, there are a number of other methods that can be considered [46].

1.9.1 Density Functional Methods

The density functional theory (DFT) become more popular in addition to the ab-initio and semi-empirical quantum mechanical calculations. These are a relatively new type of calculation that bears a very close resemblance to ab-initio calculations [47]. Density Functional Theory (DFT) has become the main workhorse of computational chemistry during the past decade. It combines an impressive accuracy with modest computational cost.

Density functional theory (DFT) is a quantum mechanical method used in physics and chemistry to investigate the electronic structure of many-body systems, in particular molecules and the condensed phases. DFT is among the most popular and multi utilization methods available in condensed matter physics (computational physics) and computational chemistry [48].

The basic idea behind DFT is to use the electron density rather than the quantum mechanical wave function to obtain information about atomic and molecular systems. While this idea came up in the very first years of quantum mechanics with the pioneering work of Thomas Fermi in 1927 and was continued with Slater in 1951[49], the Hohenberg-Kohn theorems from 1964 are regarded as the real beginning of DFT. Nevertheless, it took several decades before DFT became a valuable tool for chemists, although this method had already proved its usefulness in solid state physics. The turning point was the development of a new type of density functionals in the late 80s, making DFT applicable to real chemical problems. The gradient corrected and furthermore the hybrid functionals provided powerful tools which led to the current popularity of DFT [49].

Traditional methods in electronic structure theory, in particular Hartree-Fock theory and its descendants, are based on the complicated many-electron wave function. The main objective of density functional theory is to replace the many-body electronic wave function with the electronic density as the basic quantity. Whereas the many-body wave function is dependent on 3N variables, three spatial variables for each of the N electrons, the density is only a function of three variables and is a simpler quantity to deal with both conceptually and practically.

1.9.2 ab-initio Electronic Structure Methods:

The term "***ab-initio***" is Latin for "from the beginning". This name had given to computations, which derived directly from theoretical principles. Most of the time, this is referring to an approximate quantum mechanical calculation. The approximations made are usually mathematical approximations, such as using a simpler functional form for a function or getting an approximate solution to a differential equation.

The programs used in computational chemistry are based on many different quantum-chemical methods that solve the molecular Schrödinger equation associated with the molecular Hamiltonian. Figure (1-8) shows various ***ab-initio*** electronic structure methods in terms of energy [50]. Because of the large number of particles in molecules (benzene, for instance, has 12 nuclei and 42 electrons) computer programs are used to do the calculations necessary for the solution of Schrödinger equation. The calculation involving an enormous number of difficult integrals for large molecules. ab-initio computational methods solve all of these integrals without approximation.

ab-initio methods are the most reliable for small and medium-sized molecules, but are prohibitively time-consuming for large molecules (20 atoms or so for PCs, around 100 atoms if workstations are available) [51,52].

ab-initio Molecular Orbital methods are the most accurate and have consistent predictions with high accuracy (±20 kJ/mol) over a wide range of systems, because they provide the best mathematical approximation to the actual system.

ab-initio methods mainly use Hartree-Fock method as starting point, the wave function is used to describe electronic structure. [53,54]. ab-initio method based on the Laws of quantum mechanics, the masses and charges of electrons and the values of fundamental physical constants, such as the speed of light (c=2.98 x 10^8 m/s) or Plank constant $h = 6.626x10^{-34}$ J.s and contains no approximations [55]. ***ab-initio*** molecular orbital calculations are specified by (model chemistry). The chemistry model includes the choice of method and basis set, a sophisticated method and large basis set will provide more accurate results but will also require computer resources [55, 56].

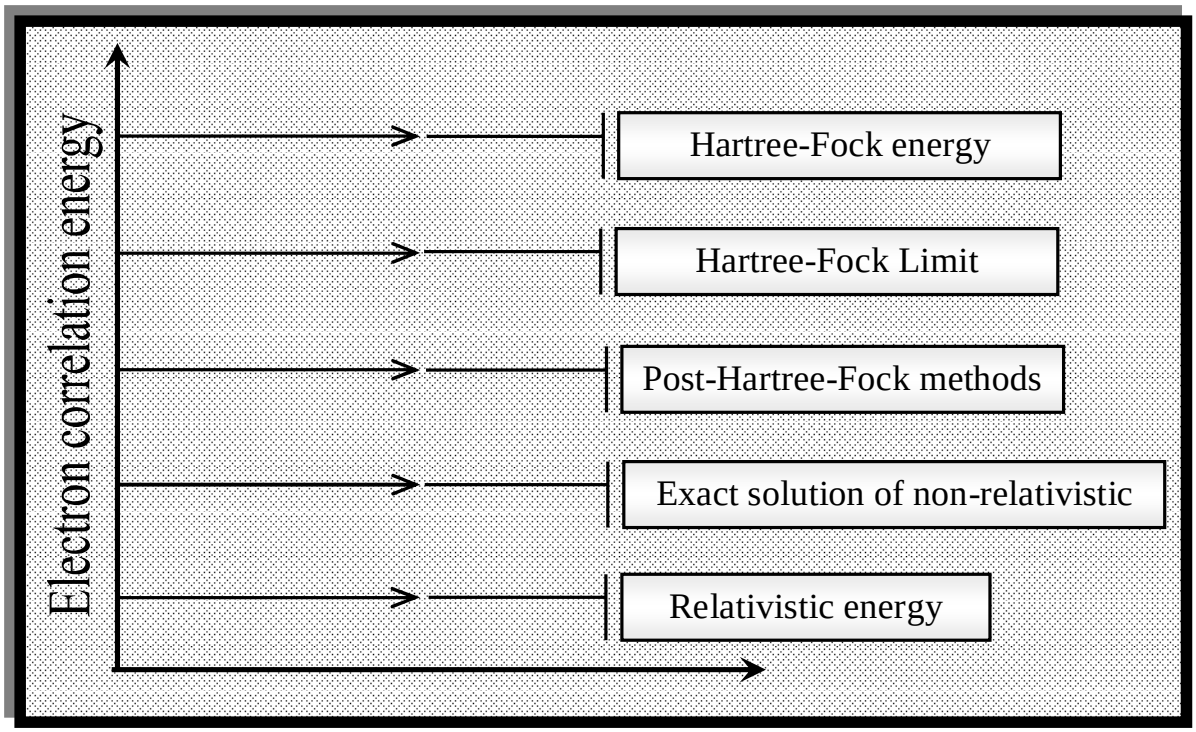


Figure (1-8): Various ab-initio electronic structure methods in terms of energy.

1.9.3 Semi-Empirical Methods

Semi-empirical molecular orbital theory method have been developed which ignore or approximate some of the integrals used in ab-initio of the Schrödinger equation [57]. To compensate for neglecting the integrals, the semi empirical methods introduce parameters based on molecular data.

In semi-empirical (and ab-initio) molecular orbital theory the energy is calculated by taking account the interactions of each electron with the average field of all the other electrons. For each electron i, the Schrödinger equation may be written as

$$\hat{H}\, y_i = E\, y_i \quad \text{..... (2.4)}$$

Where Ĥ is the Hamiltonian operator, E is the Eigen value, and y is the wave function.

One-electron Fock operator which includes kinetic and potential energy terms of one-electron is the average field of the others [58]. Many semi-empirical methods are available to computational chemistry which can be summarized into the following [59]:

1. Zeroth-order Methods
2. Hückel and the Extended-Hückel Methods
3. Complete Neglect of Differential Overlap (CNDO) method
4. Intermediate Neglect of Differential Overlap (INDO) method
5. Modified Intermediate Neglect of Differential Overlap (MINDO/3)
6. Modified Neglect of Diatomic Differential Overlap (MNDO)
7. Austin Model 1 (AM1): although more accurate than MNDO, AM1 does not handle phosphorus-oxygen bonds, nitro compounds and peroxide bonds [60].
8. PM3: Parameterization Model, Version3 MNDO. A second reparam-eterization of MNDO, functionally similar to AM1, but with some significant improvements. PM3 is a recently developed semi-empirical method that may contain as yet undiscovered defects [61].
9. Zerner's INDO method (ZINDO/1 and ZINDO/S)

1.9.4 Molecular Mechanics:

It is a classical mechanical method that represents a molecule as a group of atoms held together by elastic bonds. Molecular Mechanics methods give predictions of molecular geometries and the energy of internal coordinates $E(r,\theta,\varphi)$ [62].

It is a method which represents molecules as spheres connected by springs, observable data used to parameterize constants based on Hook's Law, allowing systems to be represented by classical physics and simple potential energy functions. This method ignores the explicit presence of electrons which enable larger systems to be calculated but the drawback of this method is that it is only useful for the description of molecular ground states, making it difficult to follow reaction paths . It is a relatively cheap calculation although the accuracy of the calculation is highly dependent on the system used to parameterize the constant and it is similarity to the system under study [63].

1.10 A comparison between the methods described [64]

1.10.1 Summary

Ab-initio method	*Semi-Empirical method*
< **Uses quantum physics.** < **Mathematically rigorous.** < **No empirical parameters.**	< **Uses quantum physics.** < **Uses experimental parameters.** < **Uses extensive approximations.**
Molecular Mechanics method	*DFT method*
< **Relies on force field with embedded empirical parameters**	< **Replace the many-body electronic wave function with the electronic density as the basic quantity.**

1.10.2 Advantages

Ab-initio method	*Semi-Empirical method*
< **Useful for a broad range of systems.** < **Does not depend on experiment-al data.** < **Calculates transition state and excited states.**	< **Less demanding computationally than ab-initio methods.** < **Calculates transition states and excited states.**
Molecular Mechanics method	*DFT method*
< **Computation is not expensive, fast and useful with limited computer resources.** < **Can be used for large molecules like enzymes.**	< **The many-body wave-function is dependent on 3*N* variables, three spatial variables for each of the *N* electrons; the density is only a function of three variables and is a simpler quantity to deal with both conceptually and practically.**

1.10.3 Disadvantages

Ab-initio method	*Semi-Empirical method*
< **Computationally expensive.**	< **Requires ab-initio or experimental data for parameter.** < **Less rigorous than ab-initio methods.**
Molecular Mechanics method	*DFT method*
< **Does not calculate electronic properties.** < **Requires ab-initio or experimental data for parameters.** < **Commercial software applicable to a limited number of molecules.**	< **DFT cannot properly describe intermolecular interactions or in calculations of the band gap in semiconductors.**

1.10.4 Best For

Ab-initio method	*Semi-Empirical method*
< **Small systems (tens of atoms).** < **Electronic transition.** < **Systems without experimental data.** < **Systems requiring high accuracy.**	< **Medium–sized systems.** < **Electronic transitions.**
Molecular Mechanics method	*DFT method*
< **Large systems (thousand of atoms).** < **Systems or processes that do not involve bond breaking.**	< **DFT has been very popular for calculations in solid state physics for its relatively low computational costs.**

Aim of this work

In the present work we are interested in studying the electronic and geometrical structure of some of manganese complexes with two Schiff bases ligands. These kinds of complexes were designed to be mimetic the SOD and CAT in their activities. Furthermore, the mimicity of these complexes to the SOD and CAT in their activities will be studied and their activities with the standard complex are compared.

Different measurements will be used such as optimization, HOMO and LUMO mesurement and frequency spectroscopy which are important tools for the diagnosis of inorganic complexes due to their simplicity and availability. In brief, the present work aims at the following:-

1. Building a number of manganese complexes which is previously prepared with two Schiff bases ligands.
2. Identification the resulted complexes using the available techniques by using Gaussian 03 (2003) programs.
3. Comparing the activities of these complexes with a standard manganese-salen complex (a known drug) against superoxide anion (O_2^-), (SOD-mimetic activity) and against hydrogen peroxide (H_2O_2), (CAT-mimetic activity).
4. Modeling the stability of these complexes using modern computer techniques of Gaussian 03 (2003) programs and using DFT (Density Functional Theory) method, B3LYP (B3: Becke Three-Parameter Hybrid, LYP: connected energy of Lee-Yang-Parr) method, and 6-31G basis set to founding the stability geometrical shape of prepared complexes.

Chapter Two

Calculation Method

2.1 Computers and Theoretical Calculations

The theoretical calculations are required to know the two different and twin areas at the same belonging computers because the time of complete calculations is inversely proportional with the increasing of computer options. The first one is a set of technical equipment such as capacity of CPU process and RAM which the speed of computer depend on it, storage, and technical feasibility of computer with each other. The other area is software where the time of complete the calculation depending on the types of programs that can be used such as MOPAC software Series, HyperChem software Series, Gaussian Series of Programs and the type of calculation such as energy, frequency, and heat of formation, ….etc.

The theoretical programs including mathematical, chemical, and quantum mechanical equations that are used to solve the problems of find physical and chemical properties for a variety of molecules that are going to be studied.

Most of the computer programs are similar in many options and can perform many calculations. These are different in the accuracy and the time of calculation which is directly proportional to the accuracy. Besides the number of equations which and used to solve the problem of job type, and preview of common programs can be given by the following.

2.2 Important programs of theoretical chemical calculations.

2.2.1 MOPAC software Series

MOPAC software is an important software that assist in the completion semi-empirical quantum mechanical calculations. Then characterized by speed and ease with the completion of the calculation [65].

Dewar and his group contributions to the development of semi-empirical methods have great role in the development of MOPAC [66] chain software which the results of that calculation using the methods **(MNDO, MINDO3, AM1, PM3**) for some molecules are very close to the empiricism values.

This software can help in completing many tasks such as calculating a balanced geometric shape for each system (optimization) which has the least energy, analysis of the elements for compounds, bond lengths, and bond order calculations. This software can help in completing heat of formation calculation (ΔH^{o}_{f}) as well, the overall energy and vibration analysis of Infra-Red radiation (IR) of Self-Consistent Field method (SCF), also helps in the formulation of the overhead surface curves of energy, and curves of electronic density distribution …. etc. A modern version of this software gives Nuclear Magnetic Resonance (NMR) spectrum of the molecules under study, which are often all that time is short and easy implementation [67].

2.2.2 HyperChem software Series

HyperChem software has been written by ***Norman Allinger*** assistance from University of Georgia [68]. The software provides support and assistance necessary to accomplish the semi-empirical and ab-initio quantum mechanical

calculations. Despite the multiple functions of the program, however, is limited circulation for reasons of complexity program work,

This software could help in drawing atoms and molecules in the three-dimensional model easily, also it provides a number of large organic molecules forms that an installed such as proteins and nucleic acids of the basic amino acids, which can be used particles of more than one source because it contains an example of protein databank files (PDB) and doing the chemical calculations using Molecular mechanical.

2.2.3 Gaussian Software Series

The Gaussian software series is a series of software produced by ***John Pople*** and his group [69], It represent a software for ab initio method and density functional theory method (DFT) [70, 71, 72], in addition to semi-empirical methods. The first issue of these programs has an GAUSSIAN 70 [73] and follow by GAUSSIAN 76 [74], GAUSSIAN 80 [75], leading to the latest version GAUSSIAN 03 which product in 2003.

Advantage of this program is highly accurate in completing the equilibrium geometry (optimization) plus the coordinates for it where can be converted internal coordinates that depend in the calculate to Cartesian coordinates or versa easily without complexity.

Energy calculation can be done (total energy, energy of formation…etc) using semi-empirical quantum mechanicals calculation method or ab initio calculation method or density functional (DFT) calculation method. Also the Gaussian software helps in solving closed orbits or open orbits regulations equations by self-consistent field system (SCF), Further; this software provides the possibility of calculating the vibration frequencies of infra-red (IR) and high

absorption and results analysis where results are given disaggregated tables or in the form of a chart. This software also can be used to analyze the electronic configuration of chemical compounds using different methods of the NMR spectrum. It also helps in calculating many physical attributes of different chemical compounds using the method of ab-initio calculation and in a short time when compared it to other software that provides this possibility.

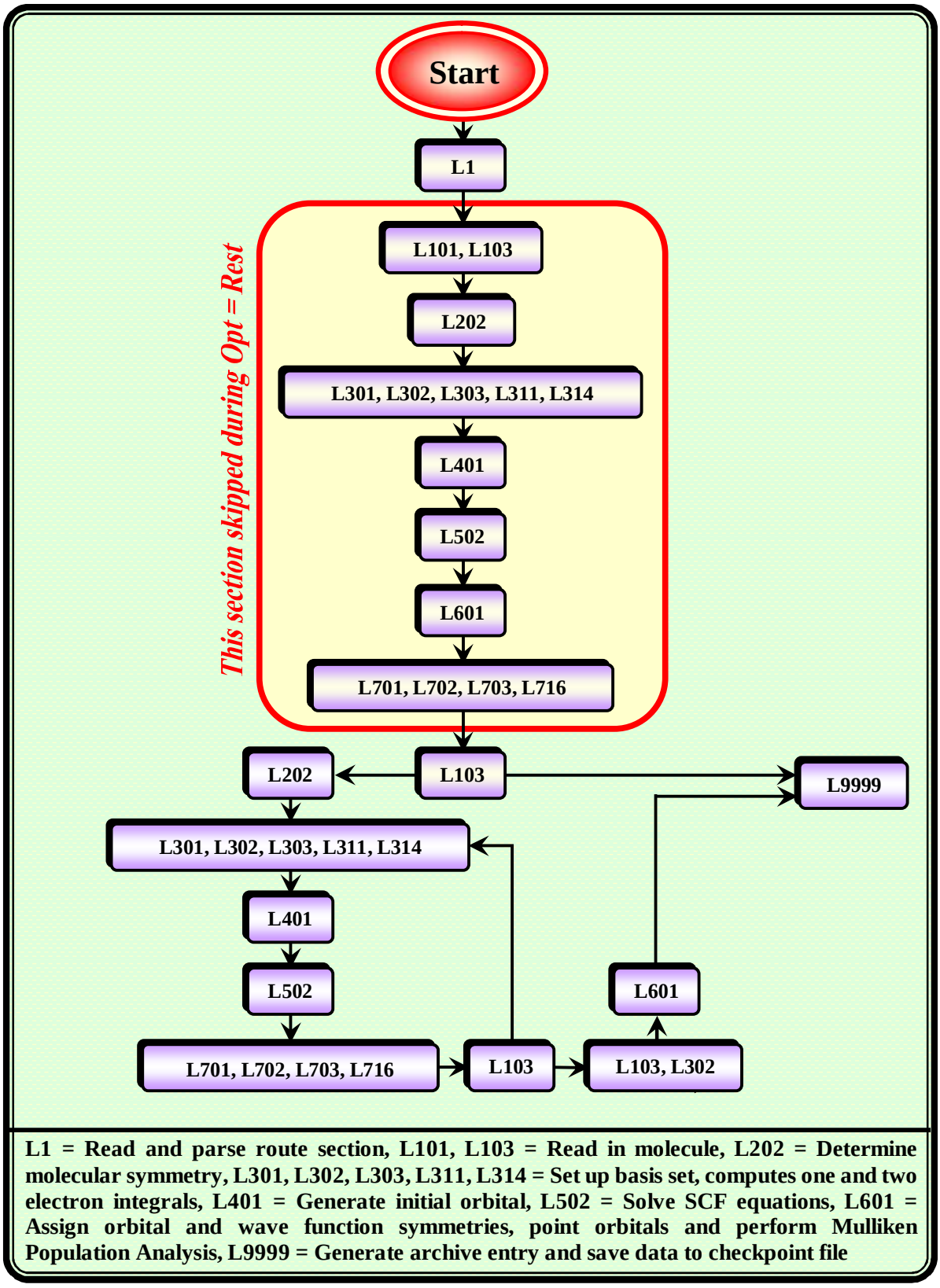


Fig (2-1): Flowchart for the Gaussian program

2.3 Calculation Method

For doing the density functional method of any molecule, can follow the following steps:

2.3.1 Building Molecule

The first stage of calculation of a molecule build to be calculated using the tools available in the Gaussian program, this operation done in two ways: (i) usual method, which includes the selection of atoms required through the periodic table available in the program and linked by different bonds to get the required molecule, and (ii) the second way, The selection of ready-made forms of chemical molecules available in the program such as (aromatic compounds, cyclic compounds, donating groups compounds, with drawing groups compounds, hydrocarbon chains group…etc.) to build the required Molecule.

2.3.2 The Job Type

By using Gaussian program (Gaussian 03) can be calculated many physical and chemical properties of drugs molecule (co-enzyme) which were under studying including a DFT method such as:

a)- Calculating the balance geometrical shape (Optimization) of molecules and finding bond angles, bond lengths, and molecular dimensions.

b)- Calculating the Electronic Density of each atom in molecules (ligands and complexes).

c)- Calculating Highest Occupied Molecular Orbital (HOMO) energy and Lowest Unoccupied Molecular Orbital (LUMO) energy.

d)- Finding point group of each compound (complex) which will enable us to find symmetry characteristics (symmetry elements) of each one.

e)- Study complexes which allow us to determine how the metal ion (Mn^{3+}) joins with different ligands.

f)- Study the impact of different ligand on electronic density of metal ion and that affected the effectiveness of the complex activity as Antioxidant.

g)- Determination the stability geometrical shape of each compound (Ligands and Complex) by studying the frequencies and types of it.

2.3.3 Calculation Method

Often used (B3LYP) method of calculation, which recalling the term (B3LYP) [76-79] to one hybrid calculation methods between the Hartree-Fock (HF) method of calculating and the density functions theory (DFT) method of calculating, which gives the best match between the calculated values and practical value [80]. The term (B3) represents triple hybrid exchange energy of Becke scientist [81-83] (Becke Three-Parameter Hybrid). The term (LYP) represents connected energy for each of scientists (Lee-Yang-Parr) [84].

2.3.4 Basis set

Used in calculating the basis set (6-31G) [85-89] and As well as set in the selection of one basis set is the degree of calculation accuracy associated with the number of functions, which is described by the wave function and the molecular form of this function if it was Polarization [90] or Diffuse [91], it is important to choose a great basis set enough to give a good description of the molecular wave function, and concentrated on the base functions of atoms; therefore sometimes called atomic functions. In this type of program functions you used to gauss functions to describe the basis functions [92], An idea of using gaussian functions in the calculation of quantum mechanics comeback to the Boys scientist [93] Year (1950), and the general formula of gaussian function can be written as following [94]:

$$g_{(x,y,z)} = x^{l} y^{m} z^{n} e^{-af^{2}r^{2}} \ldots\ldots\ldots\ldots\ldots (2\text{-}1)$$

where

(x, y, z) = Topical Cartesian coordinates of the atom center.

(n, l, m) = positive integer number.

(r) = radius from the atom Center.

(f) = Special measurement factor of basis function.

(α) = Quantity arise from power.

Chapter Three

Results & Discussion

3.1 Complexes Formation

Complexes formation can be defined as the chemical reactions of ligand with metal ion, whereas the cations (metal ions) represent an acidic part while the anions (ligands ion) represent a basic part (depending on Lewis rule). To form a stable complex between metal ions with ligands depend on many rules such as the hard, soft acids and bases (HSAB) rule for Pearson [95]. Which imply that metal ion tends to coordinate with certain functional groups of the ligand to form a stable complex.

On the other hand, the tendency of transition metal ion for special oxidation states is affected by the coordination to certain ligands. This phenomena is called (symbiosis) [96].

Increasing the positive charge on the central transition metal ions strengthens the metal-ligand bonds. The metal ion prefers to bind with atoms of high electron density such as N^{3-}, O^{2-}, P^{3-}, S^{2-} and C^{4-} [97]. The Irving Williams series of stability for a given ligand show a good criterion for the stability of complexes with di-positive metal ions which follows the order:

$$Ba^{2+} < Sr^{2+} < Ca^{2+} < Mg^{2+} < Mn^{2+} < Fe^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} > Zn^{2+}$$

A second observation is that certain ligands (such as: I^-, Br^-, ….) form their most stable complexes with metal ions such as Ag^+, Hg^{2+}, and Pt^{2+}, but other ligands show to prefer ions such as Al^{3+}, Ti^{4+}, and Co^{3+}. Ligands and metal ions were classified as belonging to type (a) or (b) according to be their preferential bonding. Class (a) metal ions include those of alkali metals, alkaline earth metals, and lighter transition metals in higher oxidation states such as Ti^{4+}, Cr^{3+}, Fe^{3+}, Co^{3+} and the hydrogen ion (H^+). Class (b) metal ions include those of the heavier transition metals, and those in lower oxidation states such as Cu^+,

Ag^{+}, Hg^{2+}, Pd^{2+}, and Pt^{2+}. According to their preferences toward either class (a) or class (b) metal ions, ligands may be classified as type (a) or (b), respectively. Stability of these complexes may be summarized as follows:

Tendency to complex with class (a) metal ions	Tendency to complex with class (b) metal ions
N >> p > As > Sb	N << P >> As > Sb
O >> S > Se > Te	O << S < Se ≅ Te
F > Cl > Br > I	F < Cl < Br < I

So the ligand should have certain characteristic properties to make it suitable to form a stable complex with transition metal ions .The size, geometrical shape , coordination number, and geometrical arrangement of ligand donor atoms play the important role in stability of the resultant complex .

Also the transition metal compounds have certain characteristic properties which make them suitable in many sides of life .Many biologically important reactions take place with the aid of proteins in which transition-metal atoms play important roles [98].

3.2 Metallo-enzymes

Biomedical inorganic chemistry "elemental medicine" is an important new area of chemistry. It offers the potential for the design of novel therapeutic and diagnostic agents and hence for the treatment and understanding of diseases which are currently intractable, figure (3-1) [99].

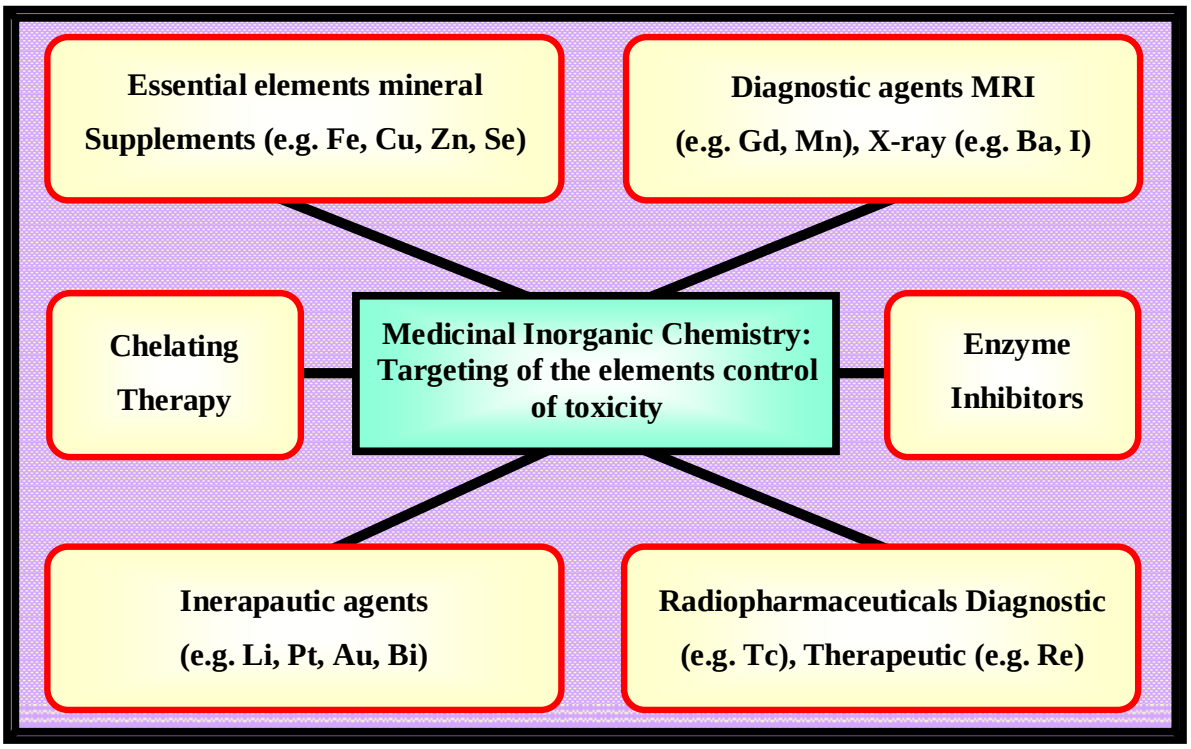


Fig (3-1): The major key areas of medical inorganic chemistry [99]

It is imperative for organisms to the ***steady states*** which are far from the equilibrium state by the continuous flow of food and energy in the changed environment in order to stay a live.

This flow is controlled by certain compounds and inorganic ions which create a dynamic flow system.

The processes of preserving a balanced live system is very complicated, hence the presence of cofactor is very important to keep a balanced live system. Cofactors are enzymes that are protein in nature and about (30%) of enzymes are metallic enzymes which contain a metal ion in the active site of the entire enzyme.

The metallo-enzymes controlling on many processes such as acid-catalyzed hydrolyses, oxidation-reduction, synthesis of isomerases of hydrocarbon compounds.

Superoxide dismutases, Catalase, and Glutathione Peroxides are metallo-enzymes that catalyze the dismutation of toxic superoxide radicals to oxygen and hydrogen peroxide and are considered as the first line of defense against the toxicity of oxygen-related radicals.

Manganese-salen complexes (Mn-Salen), including prepared complexes have been reported to possess combined superoxide dismutase (SOD) and catalase (CAT) mimetic functions. Because of this SOD/CAT mimicry, the prepared complexes have been investigated as possible therapeutic agents in neurological disorders resulting from oxidative stress. Including Alzheimer's disease, Parkinson's disease, stroke and multiple sclerosis. These actions have been explained by the ability of the Mn-Salen to remove deleterious superoxide (O_2) and (H_2O_2). However, in addition to oxidative stress, cells in models for neurodegenerative diseases may also be subjected to damage from reactive nitrogen oxides (nitrosative stress), resulting from elevated levels of NO and analogue compounds, including peroxynitrite (NO_3^-).

Many researchers have perform numerous experiments to prepare some of Mn-salen derivatives and determination of the biological activity of these compounds in addition to make some theoretical calculations like dipole

moment, bonds length, angles, balanced geometrical shapes, and some energies calculations such as ΔH^{o}_{f}, ΔH_{r} [100].

Several researches have provided that two different geometrical shapes of Mn-salen complexes. Some of them were classified as square pyramidal (dsp^3 hybridization) [101,102], where the metal ion (manganese ion) was connected to two oxygen atoms and two nitrogen atoms of the schiff base ligands. While the other classified Mn-salen complexes as octahedral (d^2sp^3 hybridization) [100] in which the metal ion was coordinate with ethanol solvent in sixth location to give octahedral geometrical shapes.

The Gaussian 03 program, Density Functional Theory (DFT) method and 6-31G basis set were employed to study the physical and chemical properties of salen Ligand and its complex (Mn-salen) in addition to the balanced geometrical shapes (minimizing the energy) of these compounds which is a known drug [101] used as antioxidant to dismutase free radicals and used as standard to compare it with another building derivative of salen ligand and Mn-salen complex.

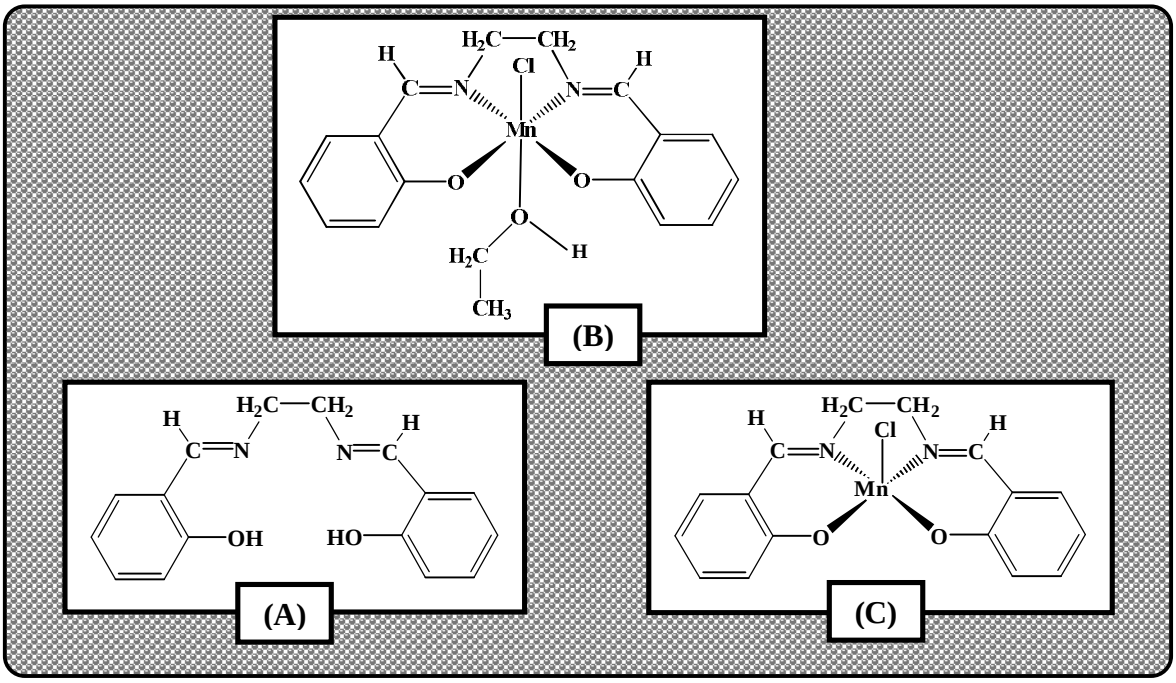


Fig (3-2): Chemical Structure of (A) Salen Ligand (B) Mn-Salen Complex as assumed [O.h.] [100], and (C) Mn-Salen Complex [sq.py.]: Complex (C_1) [101,102].

By using Gaussian 03 program, Density Functional Theory (DFT) method and 6-31G basis set, achieved building ten ligands and their complexes as salen ligands and Mn-salen complexes derivative.

The complex C_2 is similar to C_1 except naphthalene group is found on one side instead of benzene ring, the complex C_3 is similar to C_1 except naphthalene group is found in two sides instead of benzene ring, the complex C_4 is similar to C_2 except *p*-NO_2 group is found on the benzene ring, C_5 complex is similar to C_1 except *p*-NO2 groups are found on both benzene rings, C_6 complex is similar to C_2 except *m*-OH group is found on the benzene ring, C_7, C_9 complexes are similar to C_3, C_1 complexes respectively, except a bridge benzene ring is found, C_8, C_{11} complexes are similar to C_1 complex except *m*-OH group is found on one side of the benzene ring C_8, or on two sides C_{11}, and C_{10} complex is similar to C_1 except *p*-NO_2 groups are found on one side of the benzene rings, see figure (3-3), and table (3-1).

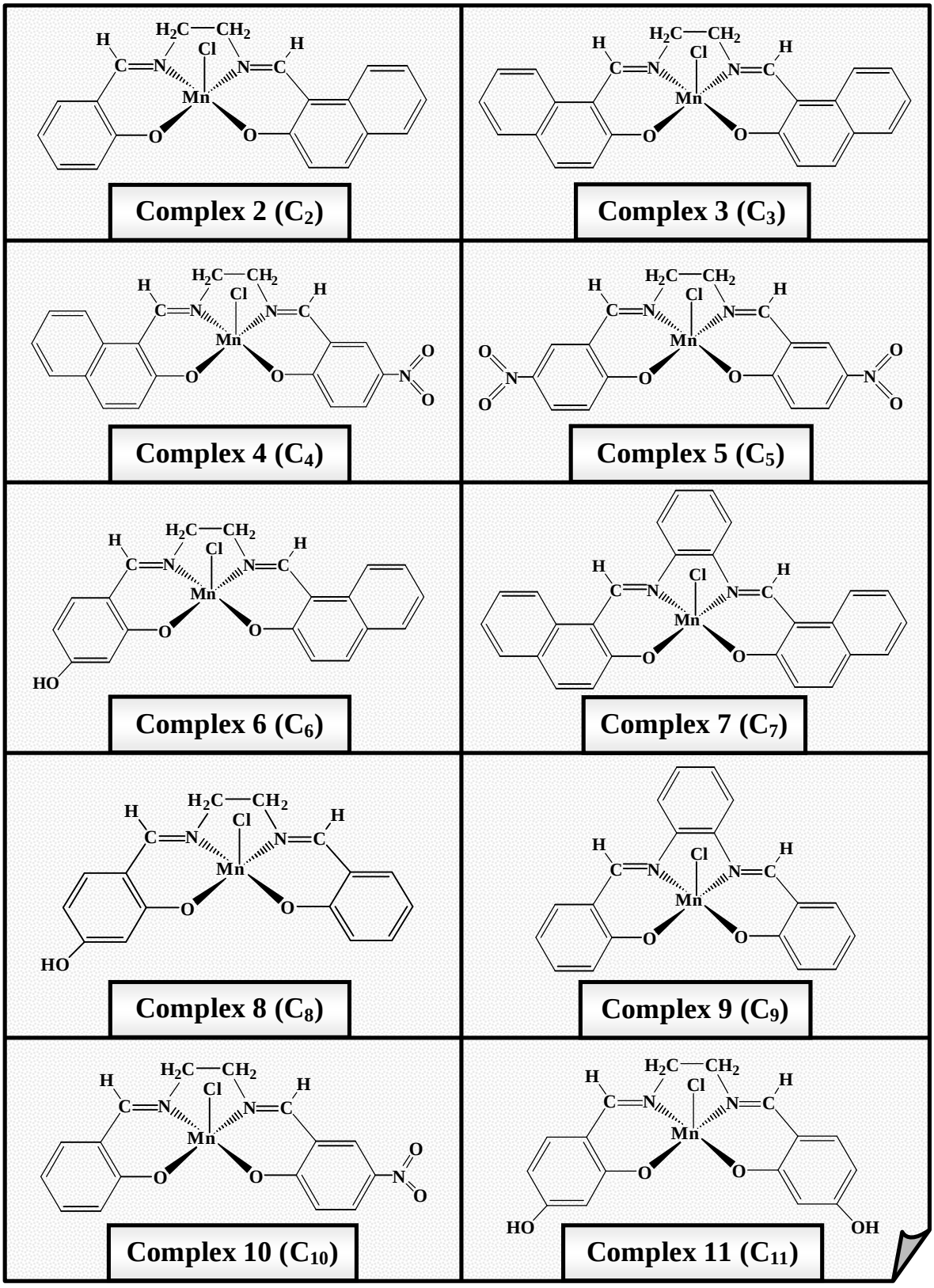


Fig (3-3): derivative complexes of Mn-Salen complex.

Table (3-1): Symbol, chemical formula and names of the calculated ligands (L_1-L_{11}) and their complexes (C_1-C_{11}).

Symbols	*Chemical formula*	*Name*
L_1	$C_{16}H_{16}N_2O_2$	N,N`- bis(salicylidene) ethylene diimine.
C_1	$C_{16}H_{14}N_2O_2MnCl$	chloro-[N,N`- bis(salicylidene) ethylene diimin] manganese (III) .
L_2	$C_{20}H_{18}N_2O_2$	N-(salicylidene),N-(2-hydroxy naphthalidene) ethylene diimine.
C_2	$C_{20}H_{16}N_2O_2MnCl$	chloro-[N-(salicylidene),N-(2-hydroxy naphthalidene) ethylene diimino] manganese (III)
L_3	$C_{24}H_{20}N_2O_2$	N, N`-bis (2-hydroxy naphthalidene) ethylene diimine.
C_3	$C_{24}H_{18}N_2O_2MnCl$	chloro-[N,N`-bis (2-hydroxy naphthalidene) ethylene diimino] manganese (III).
L_4	$C_{20}H_{17}N_3O_4$	N-(2-hydroxy naphthalidene), N`-(5-nitrosalicylidene) ethylene diimine.
C_4	$C_{20}H_{15}N_3O_4MnCl$	chloro-[N-(2-hydroxy naphthalidene), N`-(5-nitrosalicylidene) ethylene diimino] manganese (III).
L_5	$C_{16}H_{14}N_4O_6$	N,N`-bis(5-nitrosalicyldehyde) ethylene diimine.
C_5	$C_{16}H_{12}N_4O_6MnCl$	chloro-[N,N`-bis(5-nitrosalicyldidene) ethylene diimino] manganese (III).
L_6	$C_{20}H_{18}N_2O_3$	N-(5-hydroxy salicylidene),N`-(2-hydroxy naphthalidene) ethylene diimine.
C_6	$C_{20}H_{16}N_2O_3MnCl$	chloro-[N-(5-hydroxy salicylidene),N`-(2-hydroxy naphthalidene) ethylene diimino] manganese (III).
L_7	$C_{28}H_{20}N_2O_2$	N,N`-bis (2-hydroxy naphthalidene) ortho-phathalene diimine.
C_7	$C_{28}H_{18}N_2O_2MnCl$	chloro-[N,N`-bis (2-hydroxy naphthalidene) ortho-phathalene diimino] manganese (III).
L_8	$C_{16}H_{16}N_2O_3$	N-(5-hydroxy salicylidene) ,N`-(salicylidene) ethylene diimine.
C_8	$C_{16}H_{14}N_2O_3MnCl$	chloro-[N-(2-hydroxy naphthalidene) ,N`-(salicyldidene) ethylene diimino] manganese (III).
L_9	$C_{20}H_{16}N_2O_2$	N,N`-bis (salicylidene) ortho-phenylene diimine.
C_9	$C_{20}H_{14}N_2O_2MnCl$	chloro-[N,N`-bis (salicylidene) ortho-phenylene diimino] manganese (III).
L_{10}	$C_{16}H_{15}N_3O_4$	N-(salicylidene),N`-(5-nitro salicylidene) ethylene diimine.
C_{10}	$C_{16}H_{13}N_3O_4MnCl$	chloro-[N-(salicylidene),N`-(5-nitro salicylidene) ethylene diimino] manganese (III).
L_{11}	$C_{16}H_{16}N_2O_4$	N,N`-bis(5-hydroxy salicylidene) ethylene diimine.
C_{11}	$C_{16}H_{14}N_2O_4MnCl$	chloro-[N,N`-bis(5-hydroxy salicylidene) ethylene diimino] manganese (III) .

The study included the calculation of parameters that were optimized to give a suitable values agreement to the experiment [100] and may serve well for more arrangements of the compounds. The conformations of the ligands and their complexes obtained from DFT calculation were fully re-optimized to estimate the electronic density of atoms in all compounds (index A, B), implied in it the electronic density of metal ion [manganese (III)] and ligand atoms that are connected to the metal ion to form complexes which include nitrogen, oxygen, and chloride, table (3-2).

Table (3-2): Electronic density of manganese (III) ion and coordinated atoms of the ligand

	Mn	N_1	N_2	O_1	O_2	Cl
L_1	--------	**7.278**	**7.278**	**8.569**	**8.569**	--------
C_1	**23.897**	**7.537**	**7.610**	**8.668**	**8.645**	**17.429**
L_2	--------	**7.301**	**7.298**	**8.576**	**8.589**	--------
C_2	**23.896**	**7.549**	**7.610**	**8.664**	**8.648**	**17.423**
L_3	--------	**7.297**	**7.299**	**8.592**	**8.588**	--------
C_3	**23.895**	**7.546**	**7.623**	**8.669**	**8.640**	**17.424**
L_4	--------	**7.301**	**7.300**	**8.559**	**8.588**	--------
C_4	**23.896**	**7.554**	**7.611**	**8.662**	**8.637**	**17.404**
L_5	--------	**7.280**	**7.280**	**8.554**	**8.554**	--------
C_5	**23.894**	**7.542**	**7.613**	**8.661**	**8.637**	**17.392**
L_6	--------	**7.287**	**7.484**	**8.573**	**8.636**	--------
C_6	**23.896**	**7.548**	**7.617**	**8.666**	**8.653**	**17.425**
L_7	--------	**7.374**	**7.398**	**8.623**	**8.578**	--------
C_7	**23.877**	**7.641**	**7.751**	**8.669**	**8.635**	**17.409**
L_8	--------	**7.302**	**7.308**	**8.576**	**8.576**	--------
C_8	**23.895**	**7.542**	**7.609**	**8.672**	**8.645**	**17.431**
L_9	--------	**7.315**	**7.316**	**8.569**	**8.569**	--------
C_9	**23.879**	**7.630**	**7.736**	**8.670**	**8.640**	**17.412**
L_{10}	--------	**7.282**	**7.278**	**8.572**	**8.551**	--------
C_{10}	**23.895**	**7.537**	**7.612**	**8.662**	**8.646**	**17.411**
L_{11}	--------	**7.454**	**7.286**	**8.650**	**8.578**	--------
C_{11}	**23.896**	**7.542**	**7.613**	**8.671**	**8.650**	**17.432**

The biological activity of complexes as antioxidant depended on the electronic density distribution on the metal ion [manganese (III)] in addition to the energy of HOMO and LUMO of complexes, and the determination of the electronic density exchange of metal ion by ligands exchange.

Table (3-2) shows that the electron density of metal ion [manganese (III)] was changed by either addition of aryl group or the change it to the first complex (standard complex) as in the case of complexes (C_2, C_3, C_4, C_6 C_7, C_9).The electronic density of metal ion was decreased when the aryl group increased such as C_2 which contain naphthalene group on one side instead of benzene group. Also for C_3 which contain two naphthalene group instead of benzene group and so on for the other prepared complexes.

In the other hand, replacement of bridge group (ethylene) by aromatic ring (benzene) leads to decreasing in electronic density of metal ion such as (C_7, C_9).

Aromatic system is more stable than both non-aromatic and aliphatic system so additional process of aryl group to the ligands leads to a decrement in donation of the ligand and the electronic density of metal ion is inversely proportional to the additional aryl group size.

Also the addition of substituted benzene by (nitro group: -NO_2, hydroxyl group: -OH) to some prepared complexes was affected the electron density of metal ion. Nitro group represents an electron withdrawing group while the hydroxyl group represents an electron donating group, in addition the two groups have pairs of electrons on the nitrogen and oxygen atoms which contribute to the conjugated system of benzene ring.

The electron density of ligand atoms (nitrogen, oxygen) which is attached to metal ion to form a complex was increased if compared with ligands alone,

this occurs because these atoms attached to R-group which is an electron donating group in one side and metal ion which have a vacant orbital.

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 Mn-salen complexes a square pyramidal and not octahedral. When bond frequencies were calculated negative value of frequencies for octahedral compounds and positive values of square pyramidal compounds were obtained. The following figure [(3-4) to (3-25)] show the geometric shapes of all compounds.

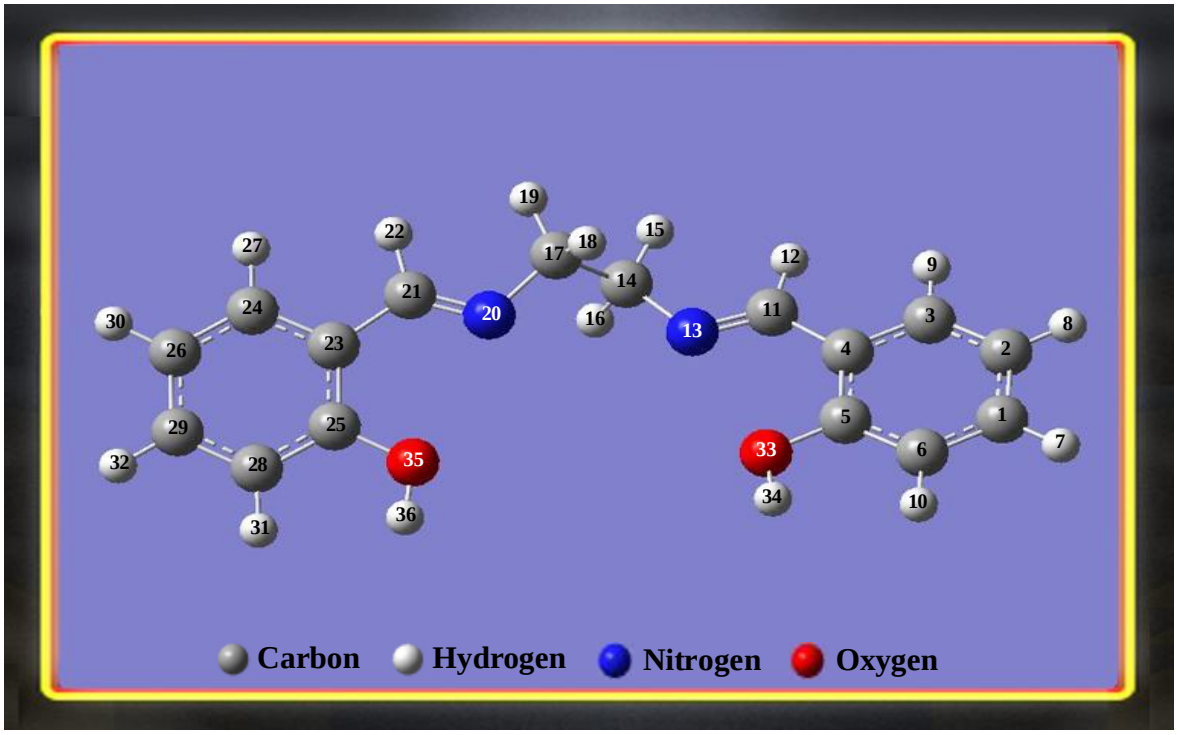


Fig (3-4):- Geometrical Shape of Ligand (L_1).

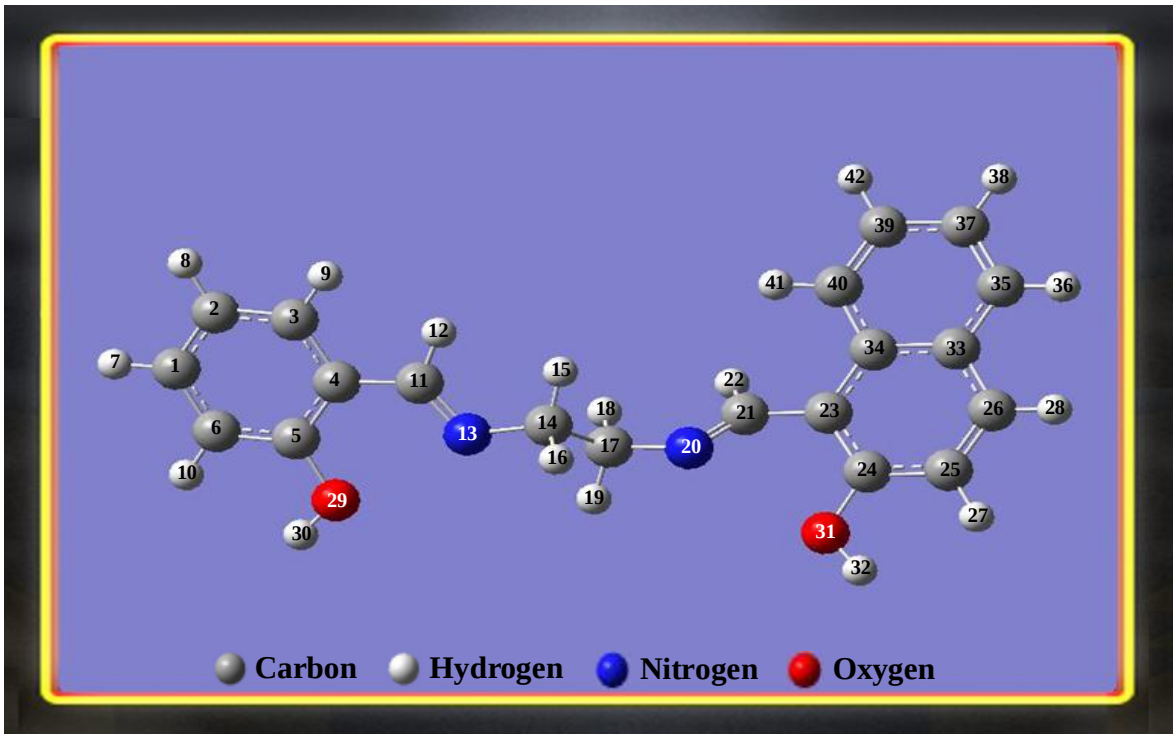


Fig (3-5):- Geometrical Shape of Ligand (L_2).

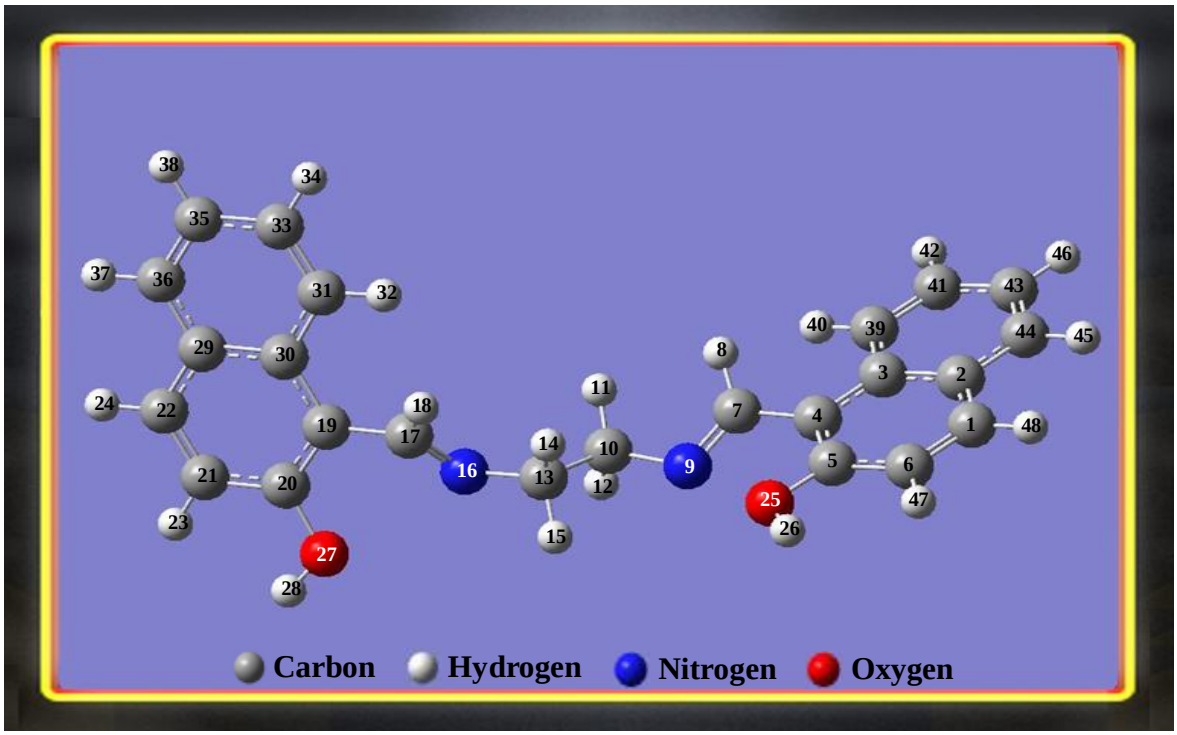


Fig (3-6):- Geometrical Shape of Ligand (L_3).

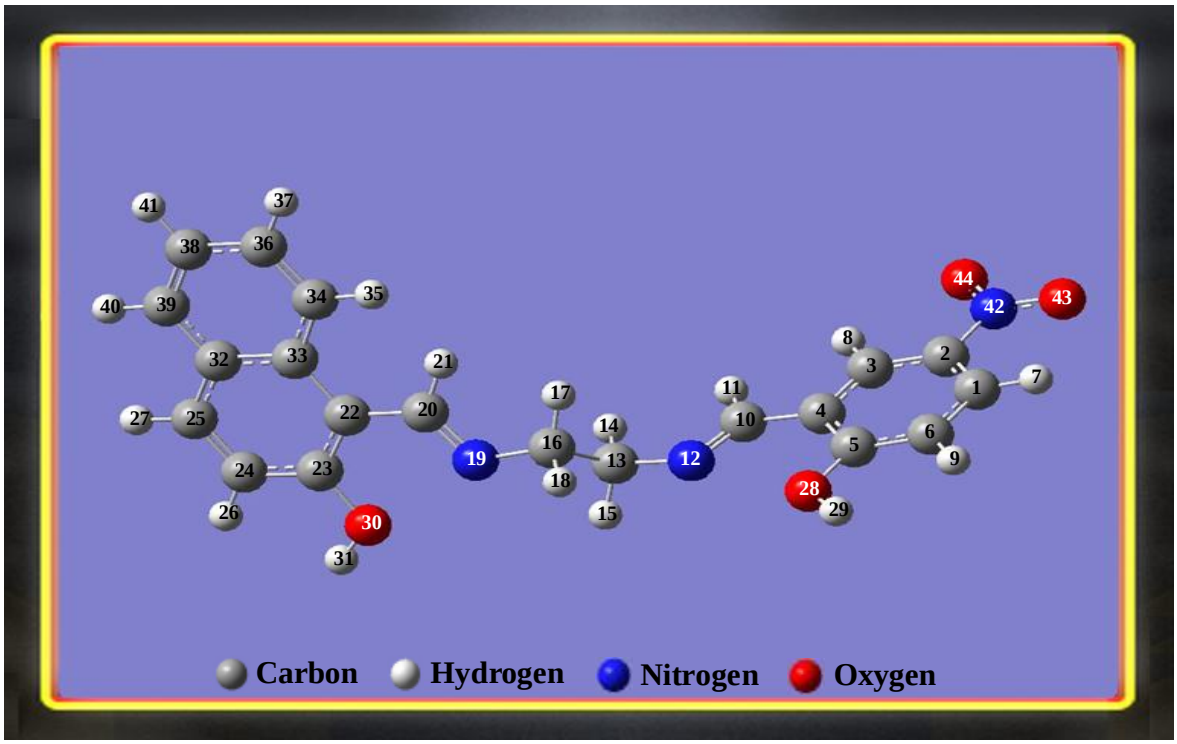


Fig (3-7):- Geometrical Shape of Ligand (L_4).

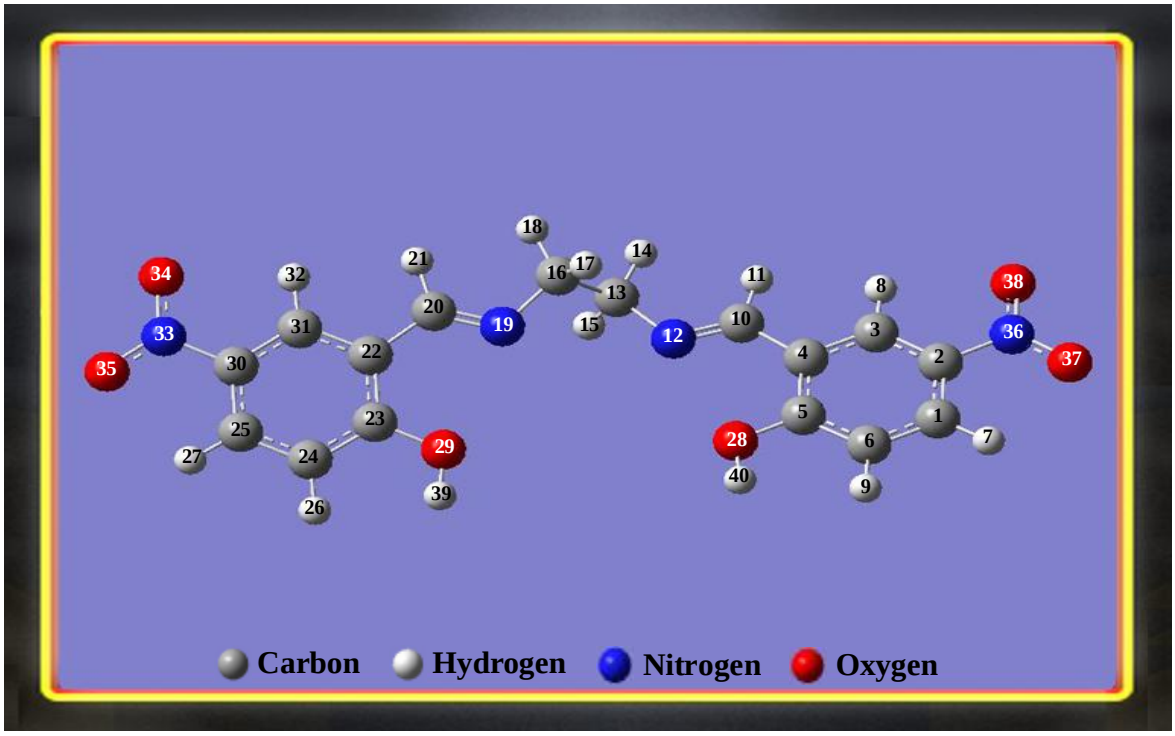


Fig (3-8):- Geometrical Shape of Ligand (L_5).

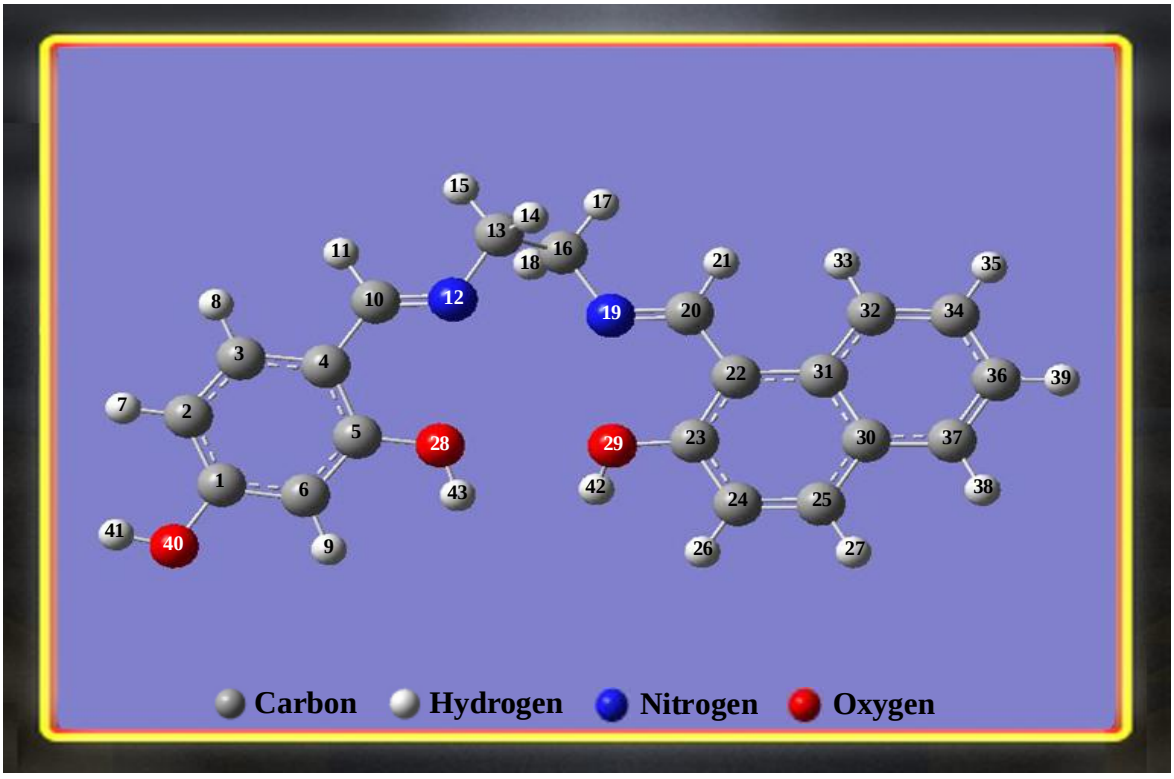


Fig (3-9):- Geometrical Shape of Ligand (L_6).

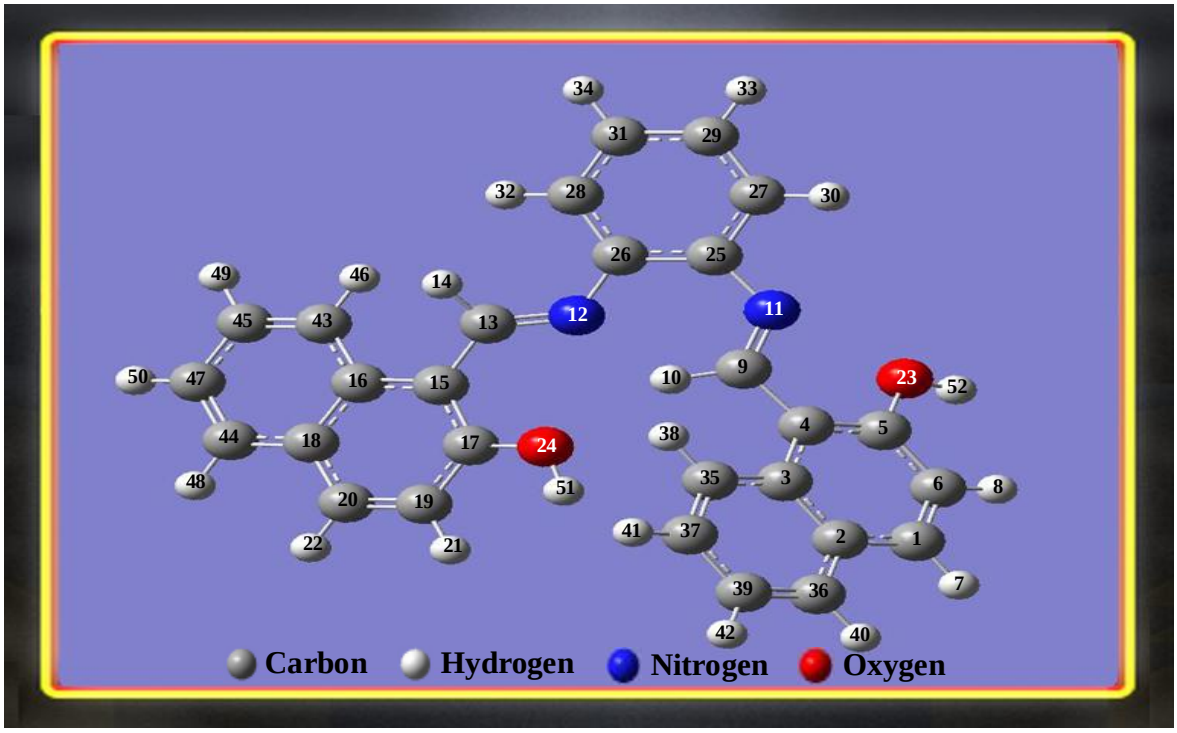


Fig (3-10):- Geometrical Shape of Ligand (L_7).

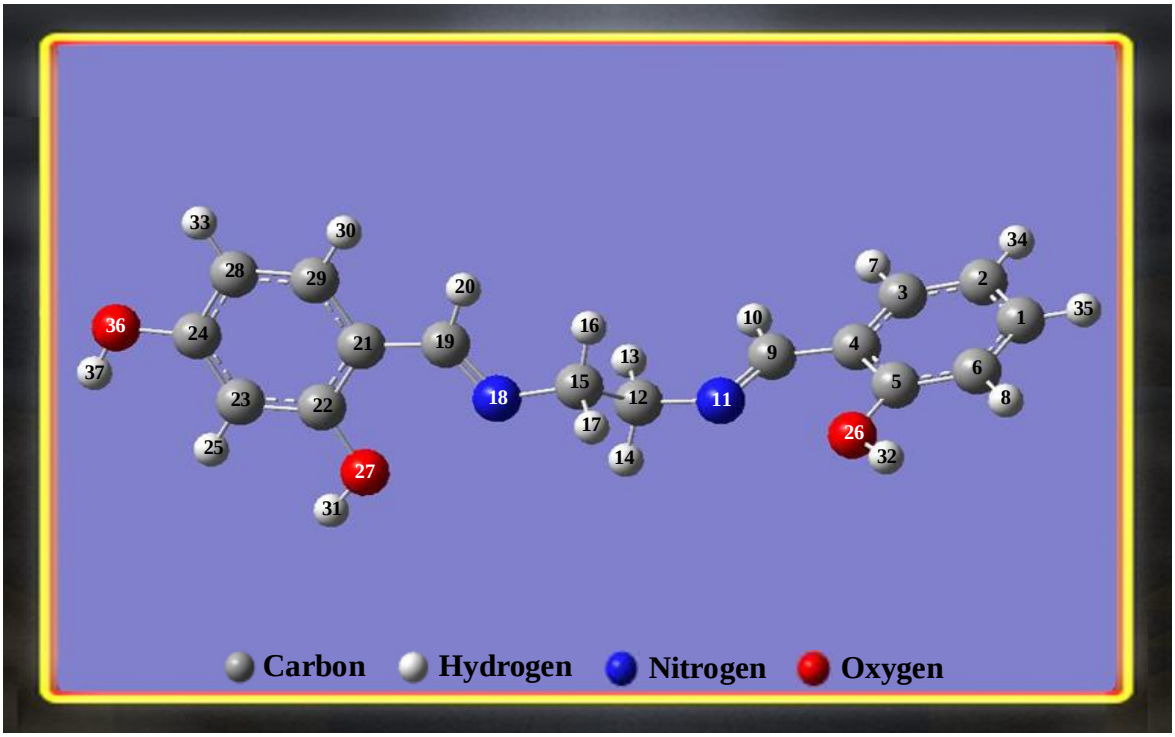


Fig (3-11):- Geometrical Shape of Ligand (L_8).

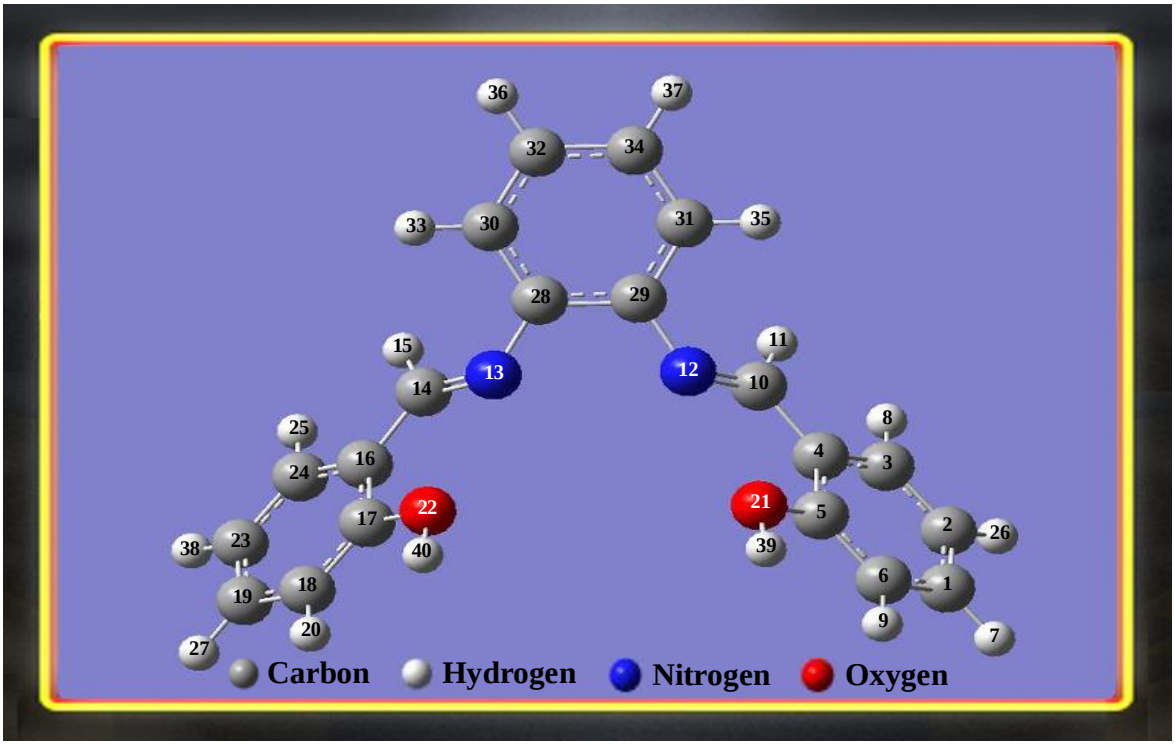


Fig (3-12):- Geometrical Shape of Ligand (L_9).

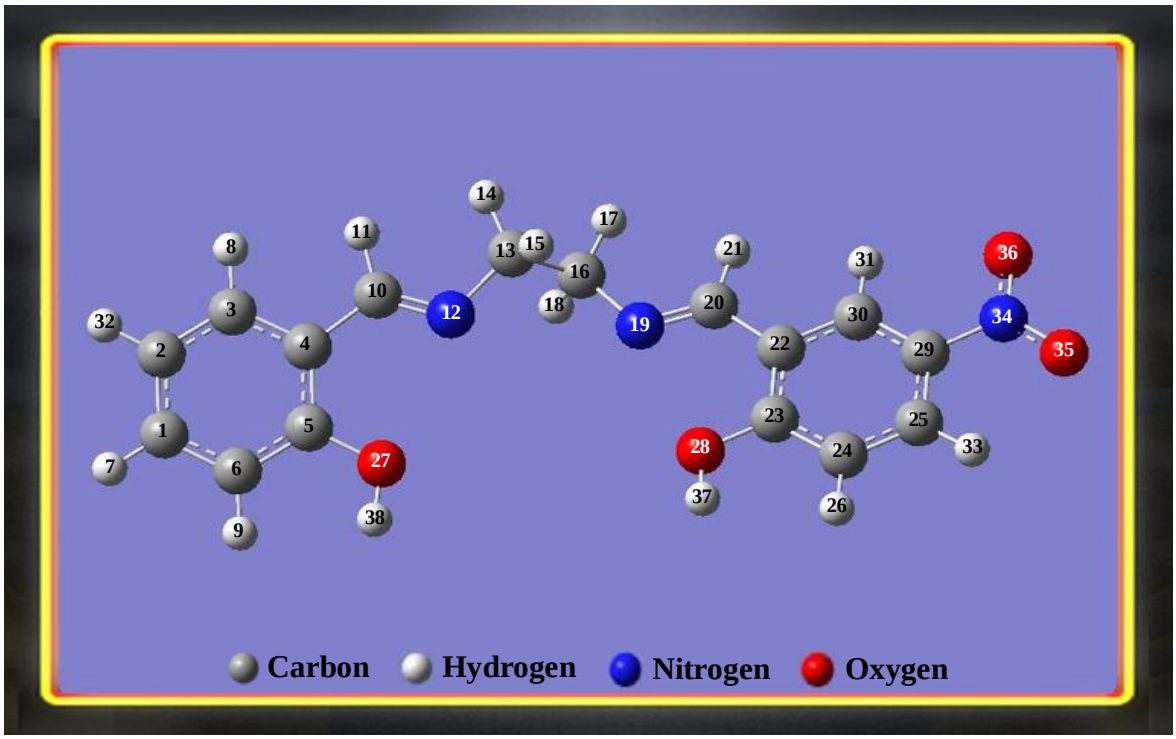


Fig (3-13):- Geometrical Shape of Ligand (L_{10}).

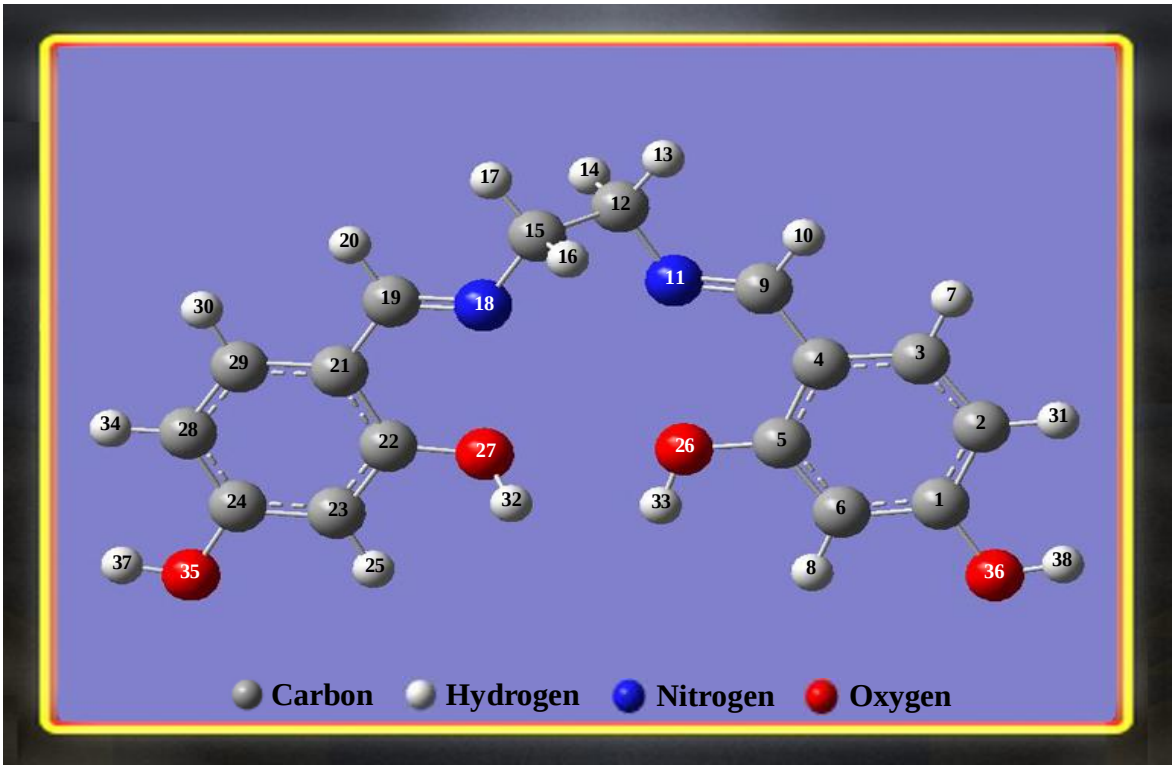


Fig (3-14):- Geometrical Shape of Ligand (L_{11}).

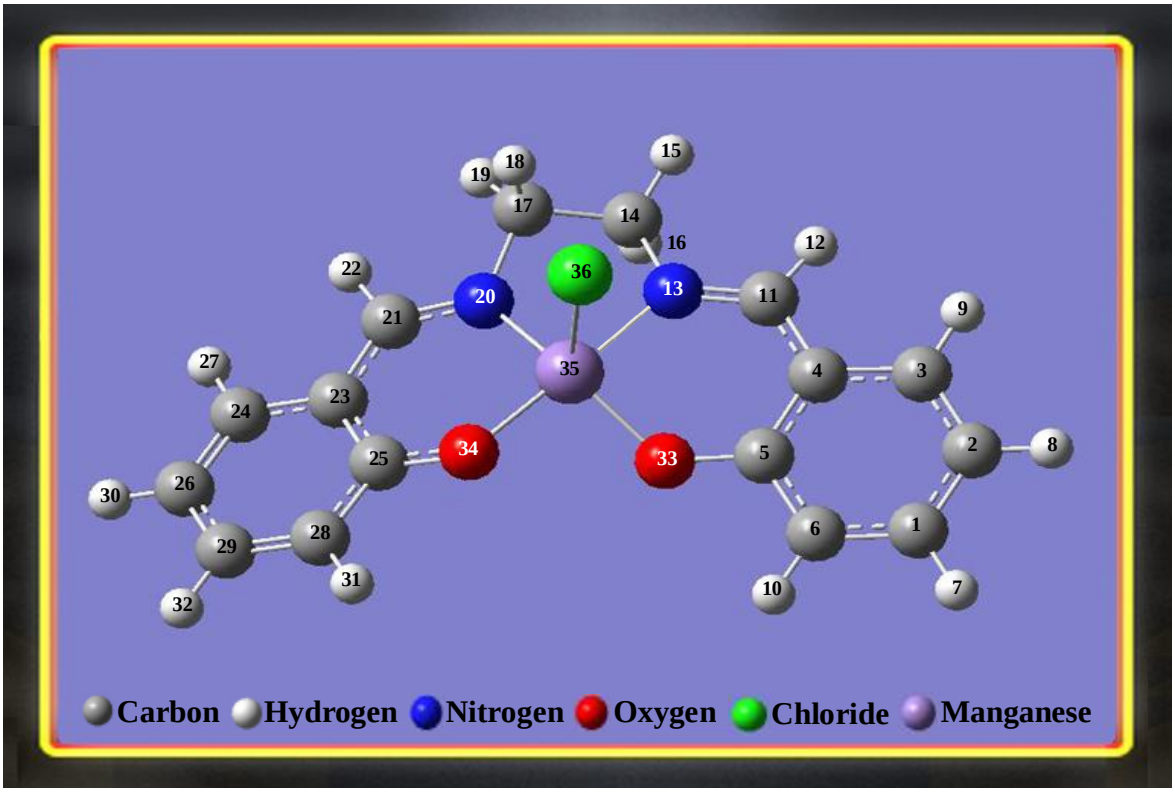


Fig (3-15):- Geometrical Shape of Complex (C_1).

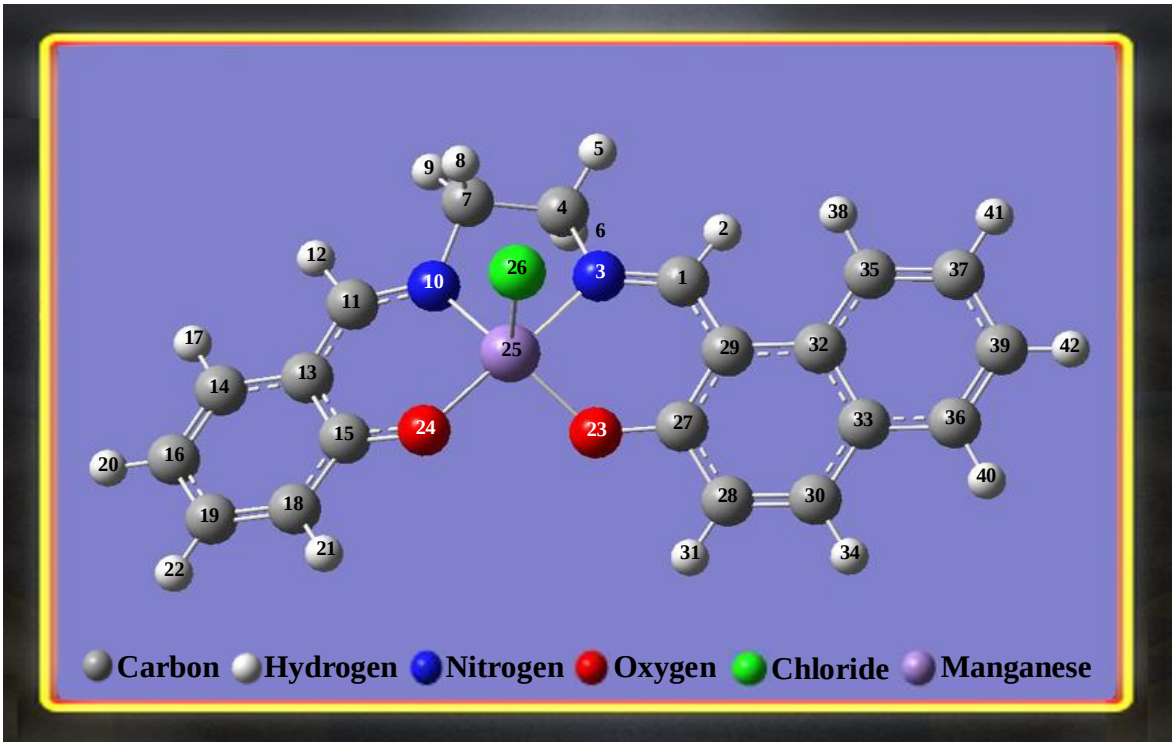


Fig (3-16):- Geometrical Shape of Complex (C_2).

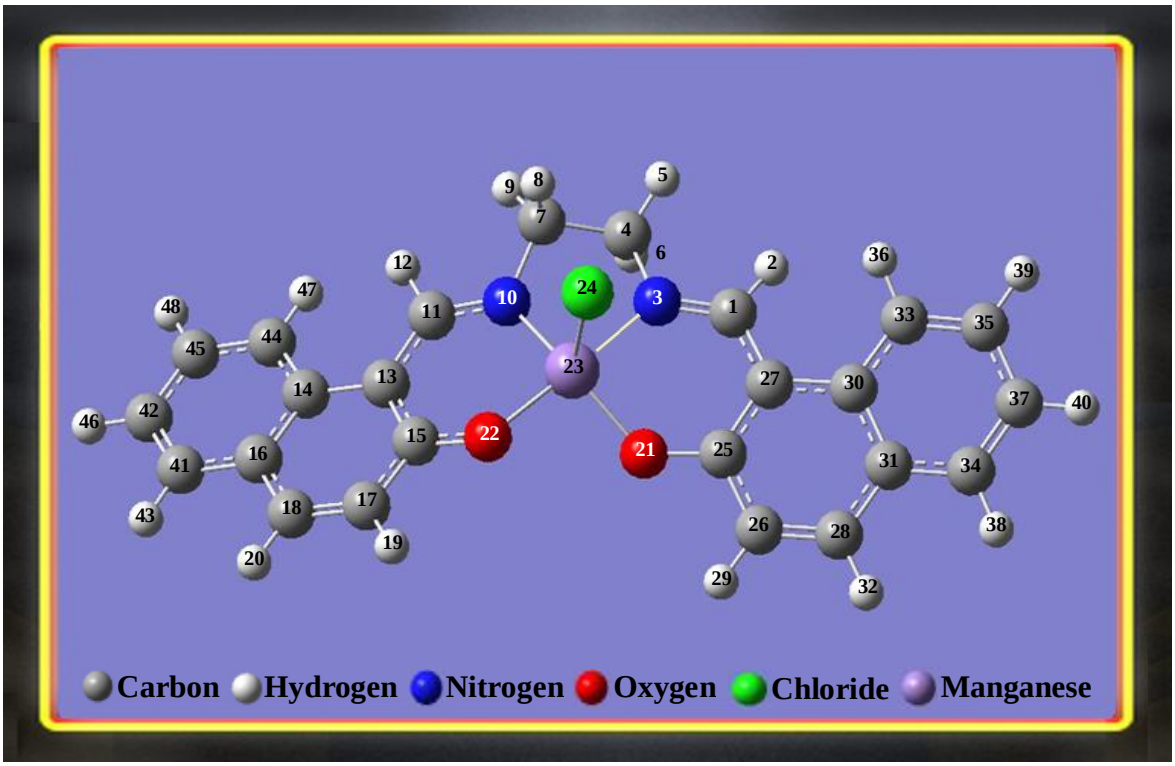


Fig (3-17):- Geometrical Shape of Complex (C_3).

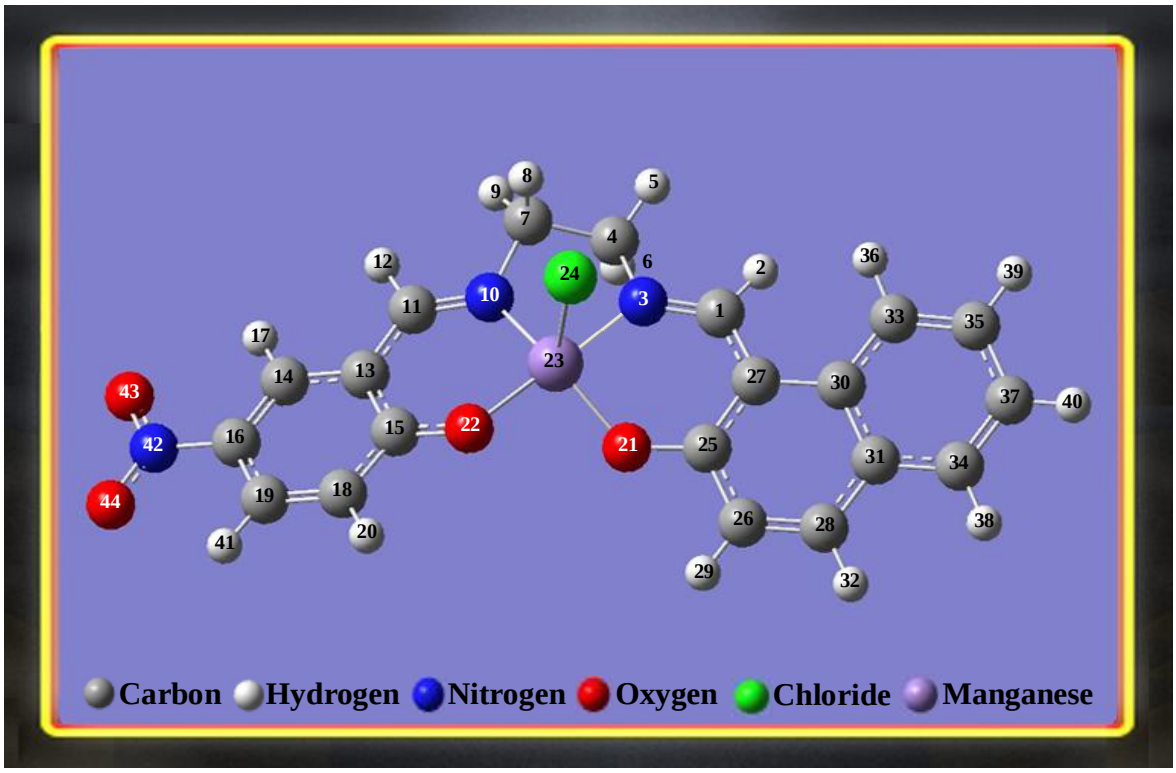


Fig (3-18):- Geometrical Shape of Complex (C_4).

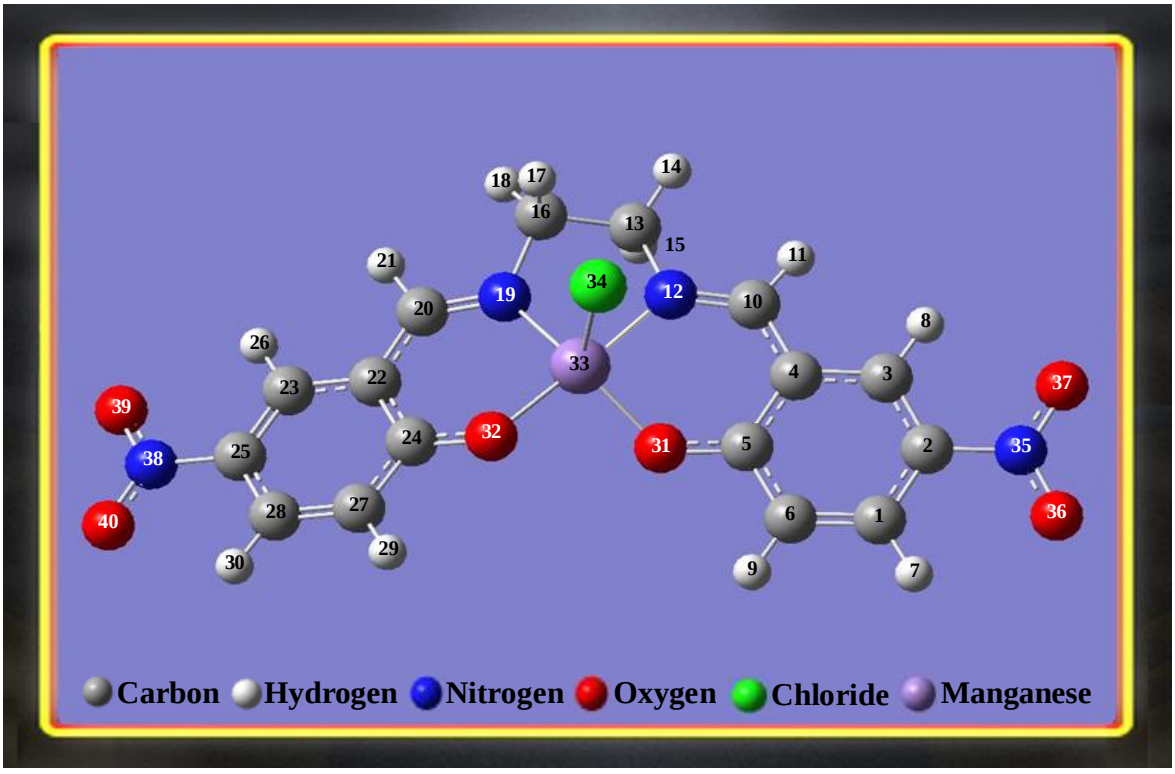


Fig (3-19):- Geometrical Shape of Complex (C_5).

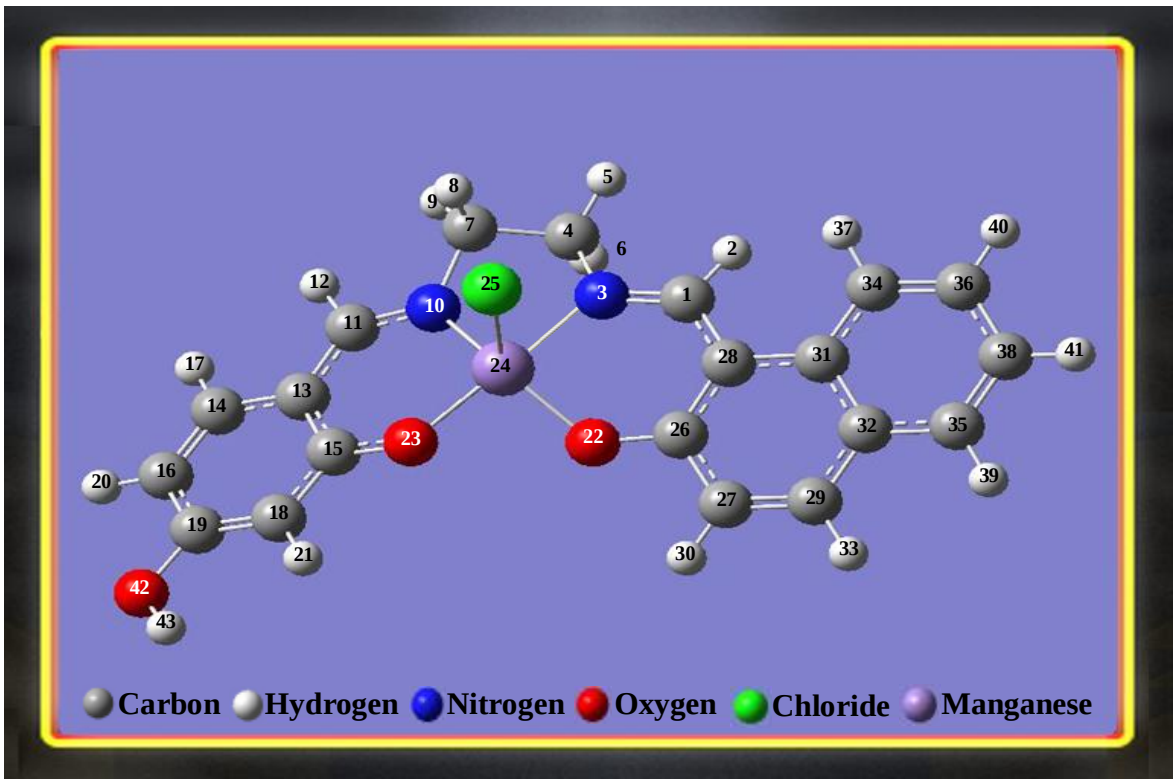


Fig (3-20):- Geometrical Shape of Complex (C_6).

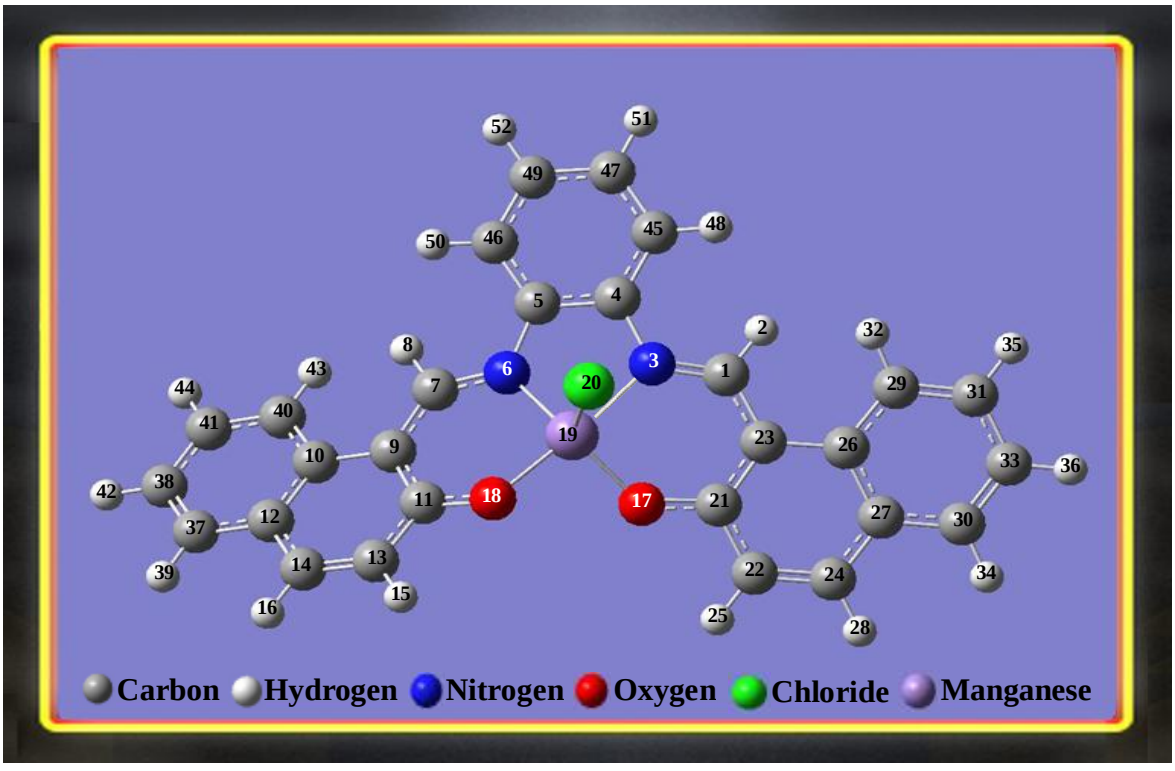


Fig (3-21):- Geometrical Shape of Complex (C_7).

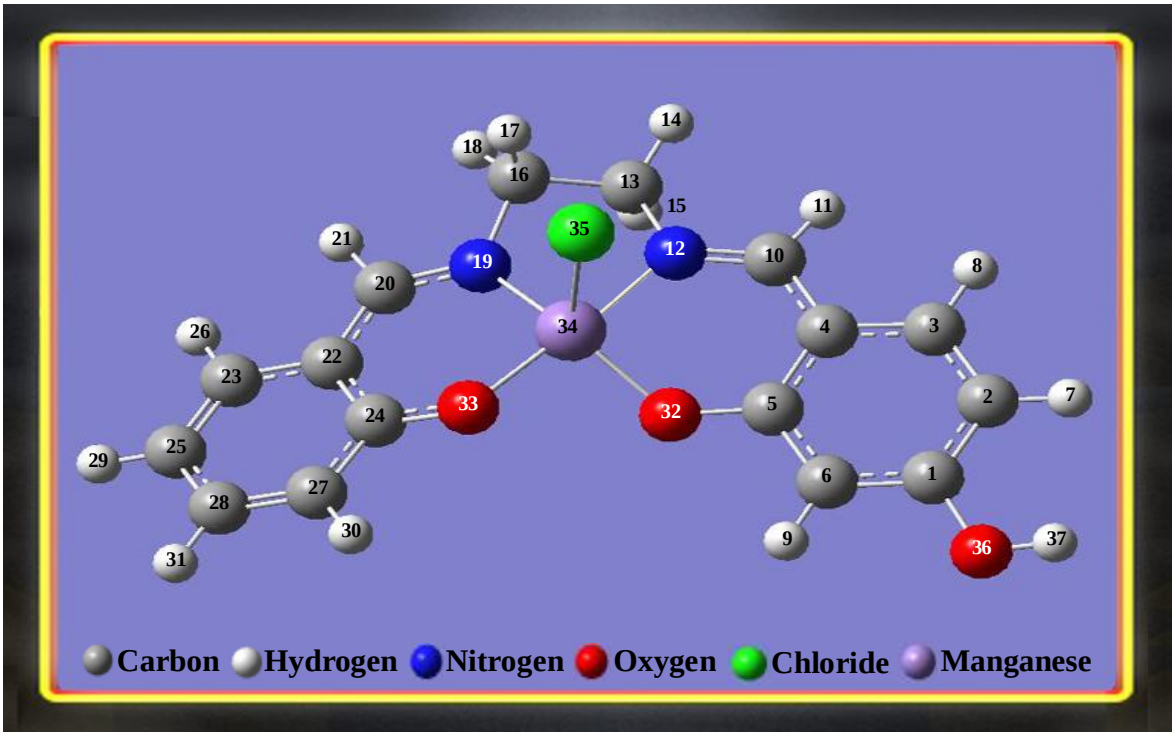


Fig (3-22):- Geometrical Shape of Complex (C_8).

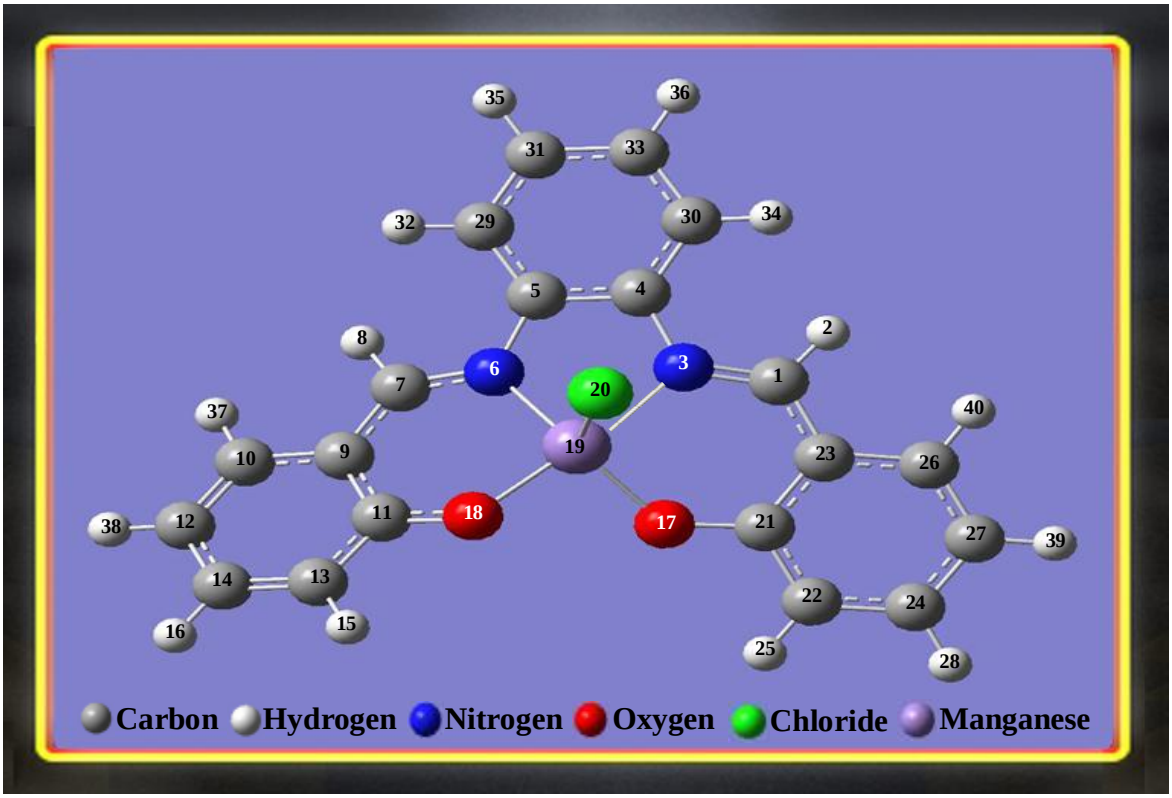


Fig (3-23):- Geometrical Shape of Complex (C_9).

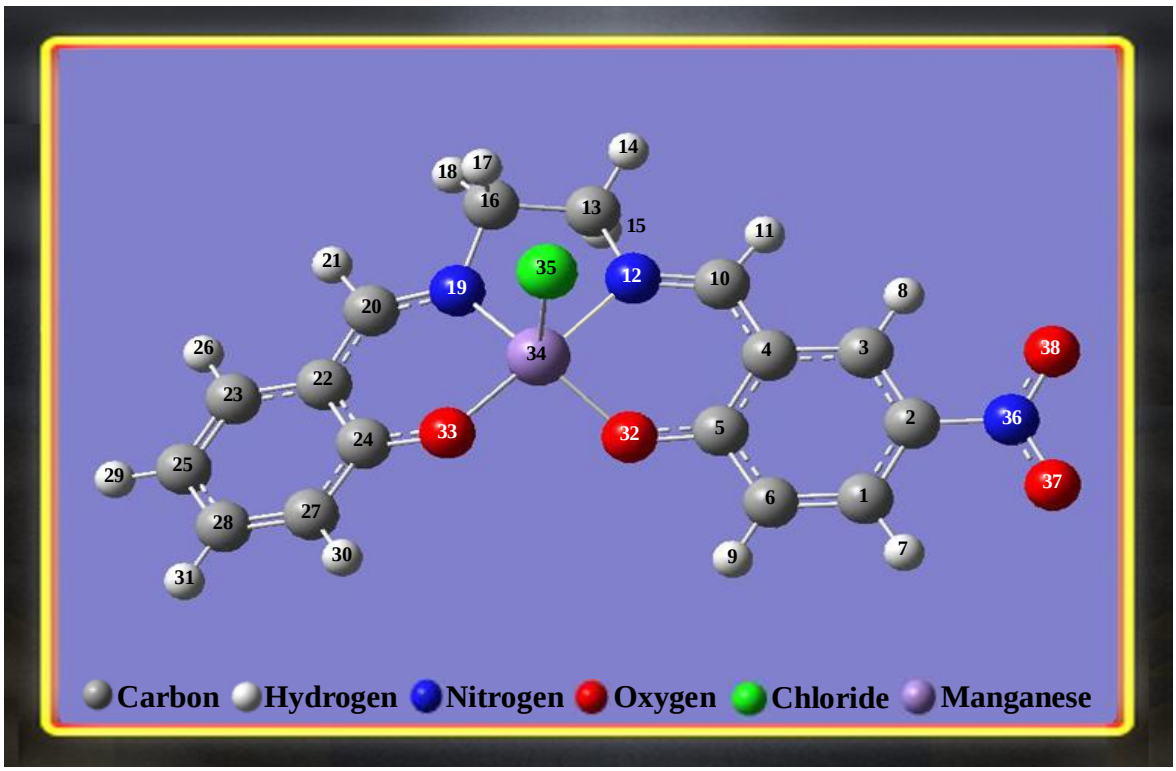


Fig (3-24):- Geometrical Shape of Complex (C_{10}).

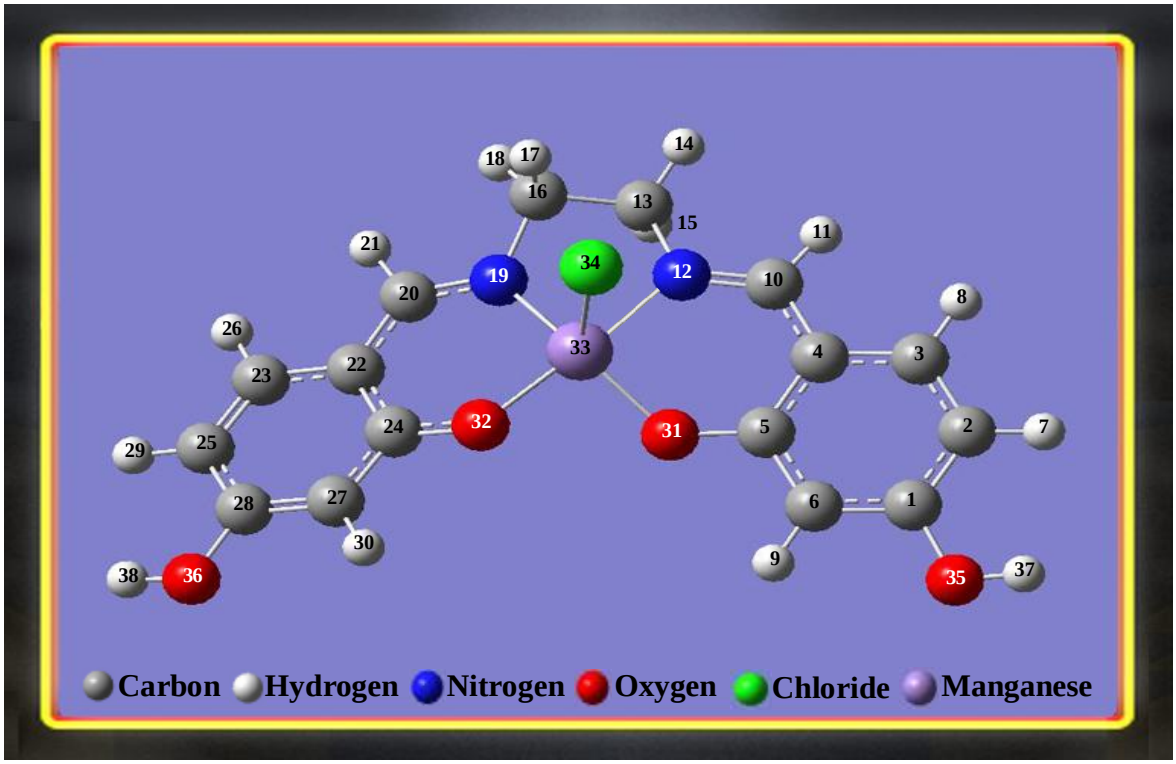


Fig (3-25):- Geometrical Shape of Complex (C_{11}).

The geometric shapes of prepared complexes show that the manganese (III) ion has five-coordinate geometry attached to the nitrogen and oxygen of tetra-dentate ligand (N_1, N_2, O_1, O_2) and chloride ion and the stereo composition of prepared complexes were square pyramidal. The following table (3-3) shows the bonds lengths of metal ion with the attached atom of the ligand in addition to metal ion chloride bond and figure (3-26) display the direction of attached atom to the manganese (III) ion.

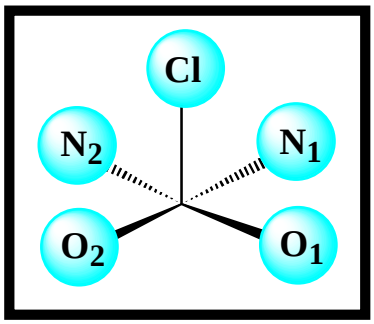


Fig (3-26):- manganese (III) ion and coordinated atoms of the ligand.

Table (3-3):- Bond length (angstroms) of manganese (III) ion to the coordinated atom of the ligand.

	Mn—N_1	Mn—N_2	Mn—O_1	Mn—O_2	Mn—Cl
C_1	2.035291	1.913540	1.828666	1.863826	2.287087
C_2	2.019998	1.909681	1.839201	1.863578	2.282810
C_3	2.019892	1.894828	1.836127	1.865729	2.282548
C_4	2.013616	1.917827	1.827668	1.878174	2.272322
C_5	2.036445	1.916193	1.835967	1.868709	2.267893
C_6	2.019115	1.909328	1.839255	1.870091	2.282617
C_7	2.018915	1.915328	1.838825	1.872711	2.279917
C_8	2.036782	1.913122	1.830462	1.863200	2.287389
C_9	2.062704	1.922160	1.823387	1.859235	2.268740
C_{10}	2.041715	1.907887	1.847689	1.854925	2.277707
C_{11}	2.035908	1.914574	1.830751	1.867502	2.288190

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 activity of these molecules.

Using Gaussian 03 program, Density Functional Theory (DFT) method and 6-31G basis set, calculation to be completed of highest occupied molecular orbital (HOMO) [which display the ability of molecules to donate the electrons and the donation of electron is directly proportional to the highest occupied molecular orbitals value increasing] and lowest unoccupied molecular orbital (LUMO) [which display the ability of molecules to accept the electrons and the acceptation of electron is inversely proportional to the lowest unoccupied molecular orbitals value increasing], where these results show that the SOD mimetic activity of the building complexes (C_2, C_4, C_5, C_7, C_9, C_{10}) are higher when compared with that of C_1 complex (as a standard), while the other complexes gave lower than that of C_1 complex, while the CAT mimetic activity of the (C_2, C_3, C_6, C_7, C_8, C_{11}) are higher when compared with that of C_1 complex (as a standard), while the other complexes gave lower than that of C_1 complex, table (3-4).

The stability of the building complexes can be determined by find the deference between HOMO and LUMO energy:

$$\mathrm{D}\mathbf{E} = \mathbf{E_{HOMO}} - \mathbf{E_{LUMO}} \quad \text{..... (3-1)}$$

So the prepared complexes were appeared (except C_8, C_{11}) that more reactive (less stable) than C_1 complex, while C_8, C_{11} were appeared to be more stable, figure (3-28). Table (3-4) shows the energy of HOMO, LUMO, and ΔE, figures [(3-29) to (3-72)] display the HOMO and LUMO distribution.

Table (3-4): The energy of Highest Occupied Molecular Orbitals, Lowest Unoccupied Molecular Orbitals, and DE.

Compound	E_{HOMO} (ev)	E_{LUMO} (ev)	DE (ev)
L_1	-5.4423	-0.9249	4.5174
C_1	-5.4007	-2.3726	3.0281
L_2	-5.5740	-1.3007	4.2733
C_2	-5.3424	-2.3742	2.9682
L_3	-5.5498	-1.3317	4.2180
C_3	-5.3300	-2.3127	3.0172
L_4	-5.7002	-2.7717	2.9285
C_4	-5.7930	-3.0158	2.7772
L_5	-6.5838	-2.8493	3.7345
C_5	-6.3955	-3.4417	2.9538
L_6	-5.3955	-1.3747	4.0207
C_6	-5.3261	-2.3331	2.9930
L_7	-5.1764	-1.6261	3.5508
C_7	-5.3277	-2.4196	2.9081
L_8	-5.7772	-0.9774	4.7998
C_8	-5.3653	-2.3353	3.0300
L_9	-5.1381	-1.3080	3.8300
C_9	-5.4314	-2.4692	2.9622
L_{10}	-6.0875	-2.7143	3.3731
C_{10}	-5.9155	-2.9048	3.0107
L_{11}	-5.6319	-1.0008	4.6311
C_{11}	-5.3111	-2.2800	3.0311

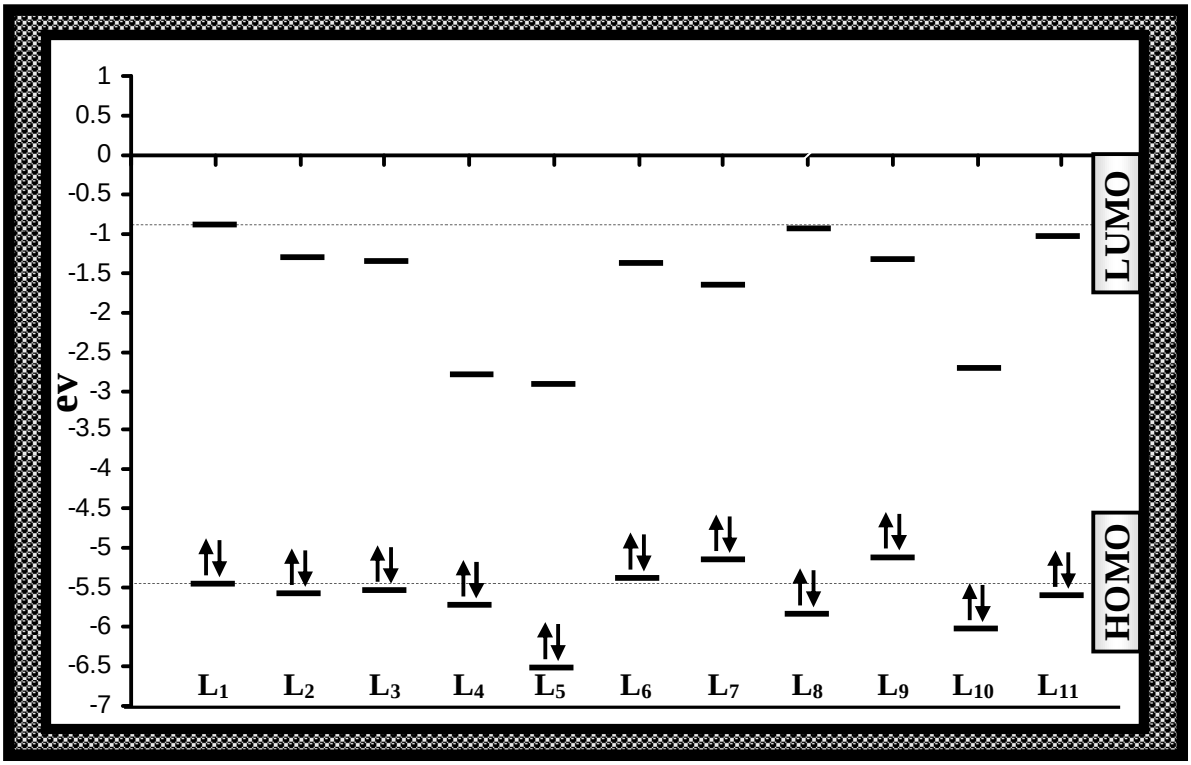


Fig (3-27): Highest Occupied Molecular Orbitals (HOMO) and Lowest Unoccupied Molecular Orbitals (LUMO) of building Ligands.

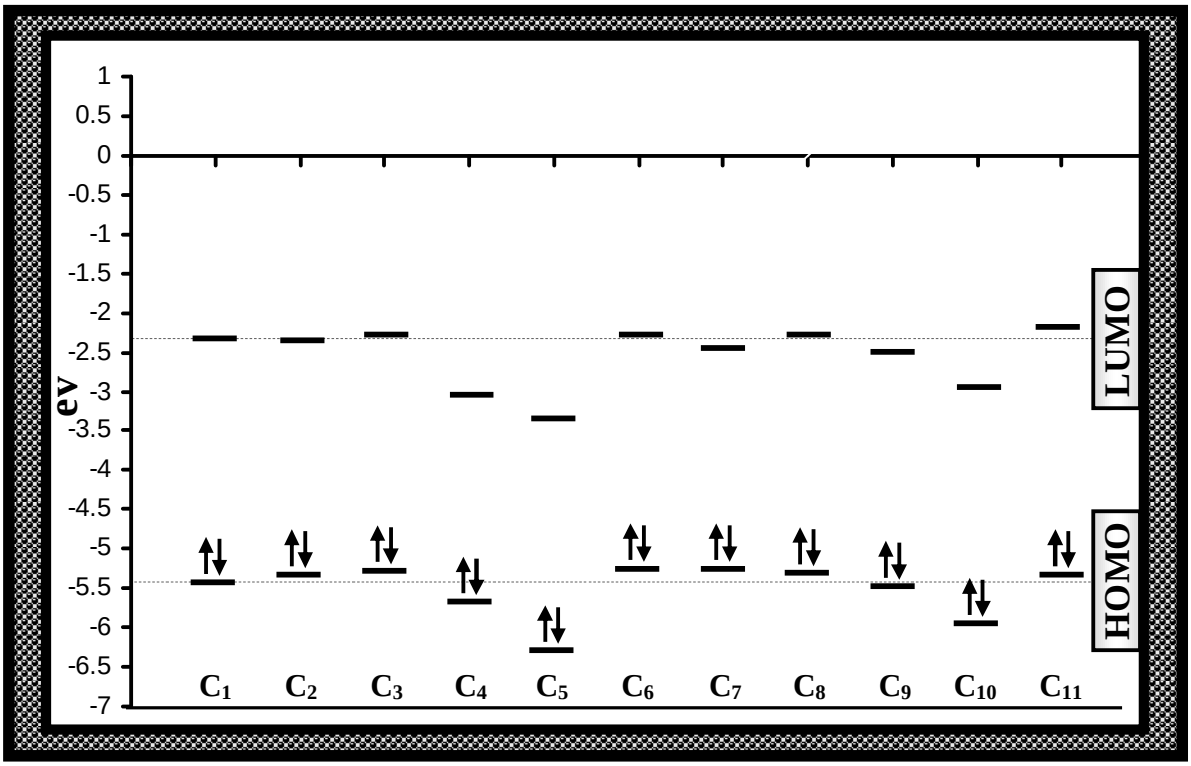


Fig (3-28): Highest Occupied Molecular Orbitals (HOMO) and Lowest Unoccupied Molecular Orbitals (LUMO) of building Complexes.

Fig (3-30): Lowest Unoccupied Molecular Orbital (LUMO) of L_1.

Fig (3-32): Lowest Unoccupied Molecular Orbital (LUMO) of L_2.

Fig (3-29): Highest Occupied Molecular Orbital (HOMO) of L_1.

Fig (3-31): Highest Occupied Molecular Orbital (HOMO) of L_2.

Fig (3-34): Lowest Unoccupied Molecular Orbital (LUMO) of L_3.

Fig (3-33): Highest Occupied Molecular Orbital (HOMO) of L_3.

Fig (3-36): Lowest Unoccupied Molecular Orbital (LUMO) of L_4.

Fig (3-35): Highest Occupied Molecular Orbital (HOMO) of L_4.

Fig (3-38): Lowest Unoccupied Molecular Orbital (LUMO) of L_5.

Fig (3-37): Highest Occupied Molecular Orbital (HOMO) of L_5.

Fig (3-40): Lowest Unoccupied Molecular Orbital (LUMO) of L_6.

Fig (3-39): Highest Occupied Molecular Orbital (HOMO) of L_6.

Fig (3-42): Lowest Unoccupied Molecular Orbital (LUMO) of L_7.

Fig (3-44): Lowest Unoccupied Molecular Orbital (LUMO) of L_8.

Fig (3-41): Highest Occupied Molecular Orbital (HOMO) of L_7.

Fig (3-43): Highest Occupied Molecular Orbital (HOMO) of L_8.

Fig (3-45): Highest Occupied Molecular Orbital (HOMO) of L_9.

Fig (3-46): Lowest Unoccupied Molecular Orbital (LUMO) of L_9.

Fig (3-47): Highest Occupied Molecular Orbital (HOMO) of L_{10}.

Fig (3-48): Lowest Unoccupied Molecular Orbital (LUMO) of L_{10}.

Fig (3-49): Highest Occupied Molecular Orbital (HOMO) of L_{11}.

Fig (3-50): Lowest Unoccupied Molecular Orbital (LUMO) of L_{11}.

Fig (3-51): Highest Occupied Molecular Orbital (HOMO) of C_1.

Fig (3-52): Lowest Unoccupied Molecular Orbital (LUMO) of C_1.

Fig (3-54): Lowest Unoccupied Molecular Orbital (LUMO) of C_2.

Fig (3-56): Lowest Unoccupied Molecular Orbital (LUMO) of C_3.

Fig (3-53): Highest Occupied Molecular Orbital (HOMO) of C_2.

Fig (3-55): Highest Occupied Molecular Orbital (HOMO) of C_3.

Fig (3-58): Lowest Unoccupied Molecular Orbital (LUMO) of C_4.

Fig (3-60): Lowest Unoccupied Molecular Orbital (LUMO) of C_5.

Fig (3-57): Highest Occupied Molecular Orbital (HOMO) of C_4.

Fig (3-59): Highest Occupied Molecular Orbital (HOMO) of C_5.

Fig (3-62): Lowest Unoccupied Molecular Orbital (LUMO) of C_6.

Fig (3-64): Lowest Unoccupied Molecular Orbital (LUMO) of C_7.

Fig (3-61): Highest Occupied Molecular Orbital (HOMO) of C_6.

Fig (3-63): Highest Occupied Molecular Orbital (HOMO) of C_7.

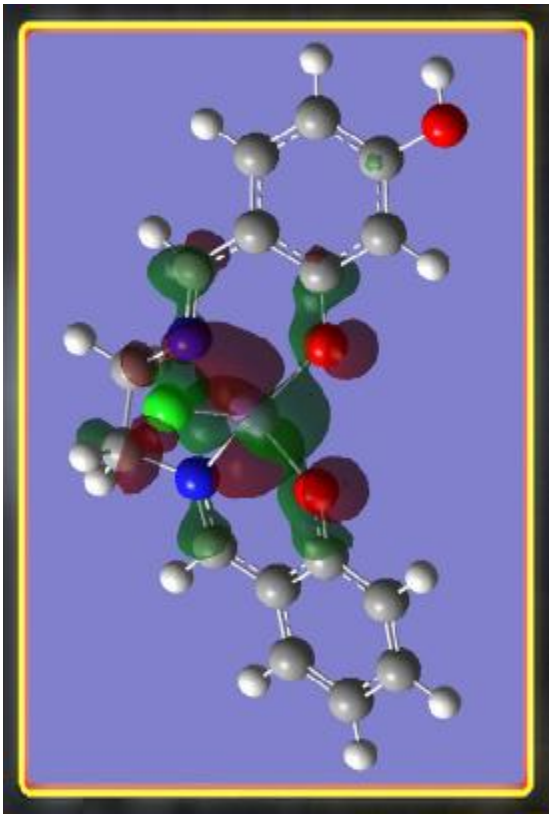


Fig (3-66): Lowest Unoccupied Molecular Orbital (LUMO) of C_8.

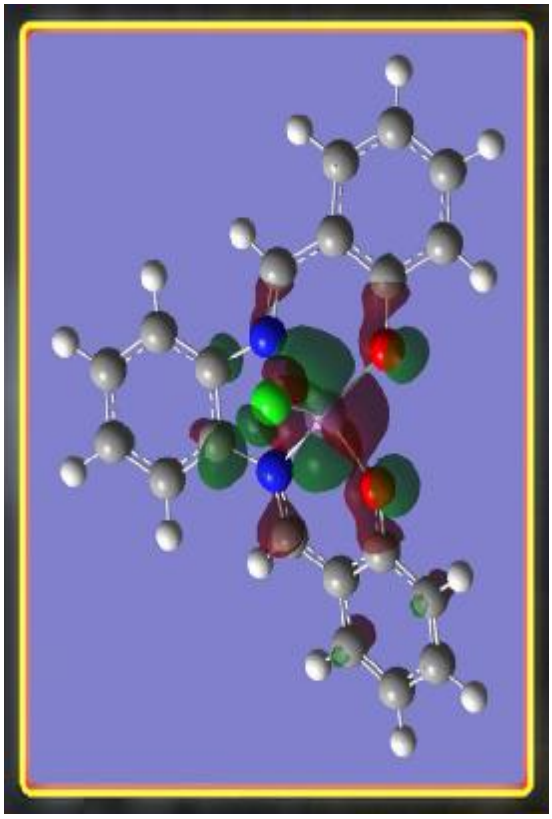


Fig (3-68): Lowest Unoccupied Molecular Orbital (LUMO) of C_9.

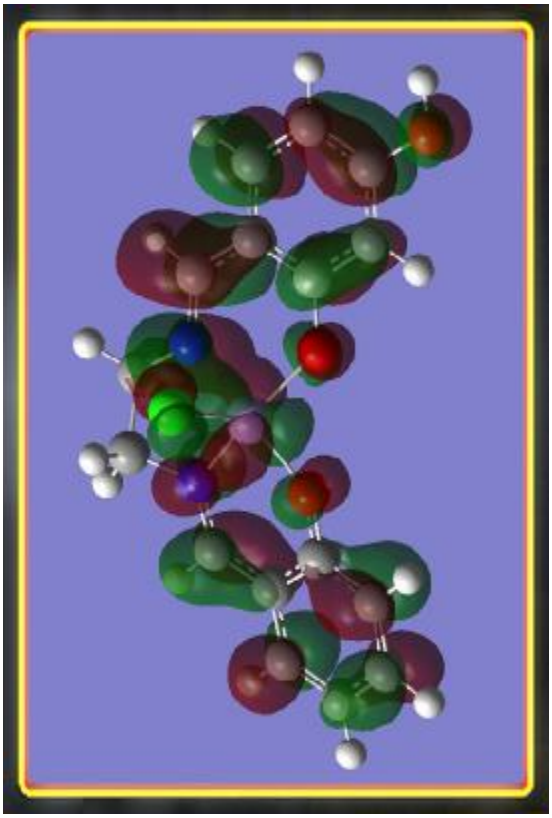


Fig (3-65): Highest Occupied Molecular Orbital (HOMO) of C_8.

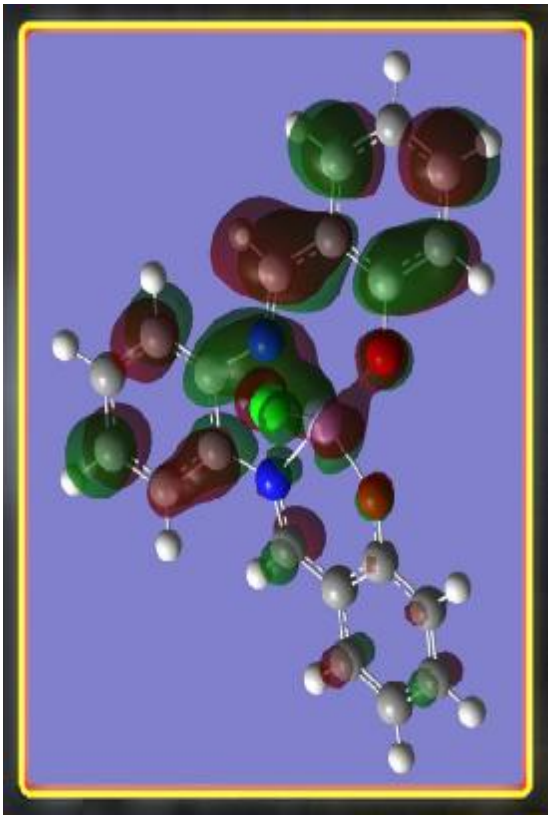


Fig (3-67): Highest Occupied Molecular Orbital (HOMO) of C_9.

Fig (3-69): Highest Occupied Molecular Orbital (HOMO) of C_{10}.

Fig (3-70): Lowest Unoccupied Molecular Orbital (LUMO) of C_{10}.

Fig (3-71): Highest Occupied Molecular Orbital (HOMO) of C_{11}.

Fig (3-72): Lowest Unoccupied Molecular Orbital (LUMO) of C_{11}.

3.3 Superoxide dismutase mimetic activity (SODm)

The mechanism for the dismutation of O_2^- involves the reduction of Mn (III) to Mn (II) by O_2^-, which is oxidized to O_2. This Mn (II) is subsequently oxidized back to Mn (III) by another molecule of O_2^-, yielding H_2O_2. This mechanism is very similar to that of native MnSOD enzyme [42].

$$Mn^{3+} + O_2^- \longrightarrow Mn^{2+} + O_2 \quad \text{..... (3-2)}$$

$$Mn^{2+} + O_2^- + 2H^+ \longrightarrow Mn^{3+} + H_2O_2 \quad \text{..... (3-3)}$$

3.4 Catalase mimetic activity

The mechanism for dismutation of H_2O_2 as a catalase mimetic involves the oxidation of Mn (III) to an oxo-manganese-complex [Mn (V)] by H_2O_2, releasing water. The oxo-manganese is then reduced by another molecule of H_2O_2 to regenerate the Mn (III) and generate water and O_2.

$$Mn^{3+} + H_2O_2 \longrightarrow Mn^{5+}\text{-}O^{2-} + H_2O \quad \text{..... (3-4)}$$

$$Mn^{5+}O^{2-} + H_2O_2 \longrightarrow Mn^{3+} + H_2O + O_2 \quad \text{..... (3-5)}$$

3.5 Symmetry and Structure of Build Complexes

In the study of the structure and properties of molecules and crystals, the concept of symmetry is of fundamental importance. Symmetry is an abstract concept associated with harmony and balance in nature or in social relationship. Yet in chemistry this ever-evolving concept does have a very practical role to play.

The main advantage of studying the symmetry characteristics of a chemical system is that we can apply symmetry arguments to solve physical problems of chemical interest. Specifically, we utilize a mathematical tool called group theory to simplify the physical problem and to yield solutions of chemical significance. The advantage of this method becomes more obvious when the symmetry of the chemical system increases.

Before applying group theory, we need to recognize the symmetry properties of a chemical system. For individual molecules, we only need to consider the symmetry of the species itself, but not the symmetry that may exist between the species and its neighbors. In trying to determine the symmetry of a molecule, we need to see whether it has any **symmetry elements**, which are defined as geometrical entities (such as Identity: E, Proper rotation axis: C_n, Symmetry plane: σ, Inversion center: i, and Improper rotation axis: S_n). A **symmetry operation** on a molecule may be defined as an exchange of atoms in the molecule about a symmetry element such that the molecule's outward appearance, including orientation and location, remains the same after the exchange.

Symmetry is a fundamental concept of paramount importance in art, mathematics, and all areas of natural science. In the context of chemistry, once

we know the symmetry characteristics (point group) of a molecule, it is often possible for us to draw qualitative inferences about its electronic structure, its vibrational spectra, as well as other properties such as dipole moment and optical activity.

To determine the symmetry of a molecule, we first need to identify the symmetry elements it may possess and the symmetry operations generated by these elements. The twin concepts of symmetry operation and symmetry element are intricately connected and it is easy to confuse one with the other. In the following discussion, we first give definitions and then use examples to illustrate their distinction.

A symmetry operation is an atom-exchange operation (or more precisely, a coordinate transformation) performed on a molecule such that, after the interchange, the equivalent molecular configuration is attained; in other words, the shape and orientation of the molecule are not altered, although the position of some or all of the atoms may be moved to their equivalent sites. On the other hand, a symmetry element is a geometrical entity such as a point, an axis, or a plane, with respect to which the symmetry operations can be carried out.

By using Gaussian 03 program, Density Functional Theory (DFT) method and 6-31G basis set 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 the point group 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).

Conclusions:

From the deferent results of the building complexes which appeared in calculations, we can to conclude that:

1. The electronic density of metal ion was decreased when the aryl group increased.
2. Replacement Bridge group (ethylene of standard complex) by aromatic ring (benzene) leads to decreasing in electronic density of metal ion.
3. Addition of substituted benzene by (nitro group: NO_2^-, hydroxyl group: OH^-) to some building complexes was affected the electron density of metal ion.
4. The electron density of ligand atoms (nitrogen, oxygen) which is coordinated to metal ion to form a complex was increased if compared with the ligands alone.
5. The geometric shapes of building complexes show that the manganese (III) ion has five-coordinate geometry through the nitrogen and oxygen of tetra-dentate ligand (N_1, N_2, O_1, O_2) and chloride ion, this shape appeared by calculation the frequencies and force constant of each complexes.
6. from the above calculations and measured the biological activity of building complexes, we conclude that two of the building complexes (C_2 and C_7) were of higher activity than the selected drug (C_1) toward both superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2). While other complexes showed to have a higher activity for either (O_2^-) or (H_2O_2) compared with C_1.
7. The gaps energy between HOMO and LUMO levels of prepared complexes were smallest than C_1 (as a standard) except C_8 and C_{11}.

Future work

In the light of the present study, the following suggestion can be made for future work:

1. Studying the activities of the new manganese complexes against nitric oxide ($NO^{\cdot}$) and its daughters.
2. Determining the other activities of the building complexes against diabetes.
3. Using metals other than manganese to form complexes with the selected ligands.
4. Preparing another set of ligands to react with manganese and in deferent oxidation state or other metals.

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Appendixes

Appendix A

The Electronic Density of All Atoms in All Ligands.

Appendix B

The Electronic Density of All Atoms in All Complexes.

Appendix C

Bond Length of Coordinated Atoms in Both Ligands and Complexes and Angles of Complexes Rule.

Appendix A

The Electronic Density of All Atoms in the Ligaands

Ligand (1):- 36 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	6.122	H_{19}	0.899
C_2	6.123	N_{20}	7.278
C_3	6.197	C_{21}	6.034
C_4	5.838	H_{22}	0.906
C_5	5.788	C_{23}	5.838
C_6	6.136	C_{24}	6.197
H_7	0.870	C_{25}	5.788
H_8	0.874	C_{26}	6.123
H_9	0.868	H_{27}	0.868
H_{10}	0.882	C_{28}	6.136
C_{11}	6.034	C_{29}	6.122
H_{12}	0.906	H_{30}	0.874
N_{13}	7.278	H_{31}	0.882
C_{14}	6.139	H_{32}	0.870
H_{15}	0.899	O_{33}	8.569
H_{16}	0.834	H_{34}	0.633
C_{17}	6.139	O_{35}	8.569
H_{18}	0.834	H_{36}	0.633

Ligand (2):- 42 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**6.122**	**H_{22}**	**0.885**
C_2	**6.123**	**C_{23}**	**5.914**
C_3	**6.196**	**C_{24}**	**5.792**
C_4	**5.841**	**C_{25}**	**6.136**
C_5	**5.786**	**C_{26}**	**6.155**
C_6	**6.137**	**H_{27}**	**0.878**
H_7	**0.868**	**H_{28}**	**0.863**
H_8	**0.872**	**O_{29}**	**8.576**
H_9	**0.867**	**H_{30}**	**0.633**
H_{10}	**0.881**	**O_{31}**	**8.589**
C_{11}	**6.027**	**H_{32}**	**0.630**
H_{12}	**0.900**	**C_{33}**	**5.940**
N_{13}	**7.301**	**C_{34}**	**5.981**
C_{14}	**6.146**	**C_{35}**	**6.153**
H_{15}	**0.893**	**H_{36}**	**0.869**
H_{16}	**0.826**	**C_{37}**	**6.127**
C_{17}	**6.141**	**H_{38}**	**0.874**
H_{18}	**0.821**	**C_{39}**	**6.130**
H_{19}	**0.892**	**C_{40}**	**6.155**
N_{20}	**7.298**	**H_{41}**	**5.871**
C_{21}	**6.017**	**H_{42}**	**0.874**

Ligand (3):- 48 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	6.155	O_{25}	8.592
C_2	5.940	H_{26}	0.630
C_3	5.980	O_{27}	8.588
C_4	5.915	H_{28}	0.631
C_5	5.791	C_{29}	5.940
C_6	6.136	C_{30}	5.982
C_7	6.016	C_{31}	6.153
H_8	0.885	H_{32}	0.868
N_9	7.297	C_{33}	6.127
C_{10}	6.146	H_{34}	0.874
H_{11}	0.893	C_{35}	6.130
H_{12}	0.829	C_{36}	6.155
C_{13}	6.139	H_{37}	0.871
H_{14}	0.822	H_{38}	0.874
H_{15}	0.888	C_{39}	6.153
N_{16}	7.299	H_{40}	0.867
C_{17}	6.017	C_{41}	6.127
H_{18}	0.885	H_{42}	0.874
C_{19}	5.912	C_{43}	6.130
C_{20}	5.792	C_{44}	6.155
C_{21}	6.136	H_{45}	0.871
C_{22}	6.155	H_{46}	0.874
H_{23}	0.878	H_{47}	0.878
H_{24}	0.863	H_{48}	0.863

Ligand (4):- 44 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**6.101**	**C_{23}**	**5.792**
C_2	**5.681**	**C_{24}**	**6.136**
C_3	**6.190**	**C_{25}**	**6.154**
C_4	**5.855**	**H_{26}**	**0.877**
C_5	**5.757**	**H_{27}**	**0.862**
C_6	**6.153**	**O_{28}**	**8.559**
H_7	**0.808**	**H_{29}**	**0.621**
H_8	**0.807**	**O_{30}**	**8.588**
H_9	**0.861**	**H_{31}**	**0.630**
C_{10}	**6.017**	**C_{32}**	**5.941**
H_{11}	**0.884**	**C_{33}**	**5.980**
N_{12}	**7.301**	**C_{34}**	**6.153**
C_{13}	**6.150**	**H_{35}**	**0.870**
H_{14}	**0.885**	**C_{36}**	**6.126**
H_{15}	**0.819**	**H_{37}**	**0.873**
C_{16}	**6.140**	**C_{38}**	**6.129**
H_{17}	**0.821**	**C_{39}**	**6.154**
H_{18}	**0.891**	**H_{40}**	**0.870**
N_{19}	**7.300**	**H_{41}**	**0.873**
C_{20}	**6.016**	**N_{42}**	**6.960**
H_{21}	**0.884**	**O_{43}**	**8.298**
C_{22}	**5.913**	**O_{44}**	**8.297**

Ligand (5):- 40 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**6.101**	**H_{21}**	**0.888**
C_2	**5.681**	**C_{22}**	**5.853**
C_3	**6.191**	**C_{23}**	**5.758**
C_4	**5.853**	**C_{24}**	**6.153**
C_5	**5.758**	**C_{25}**	**6.101**
C_6	**6.153**	**H_{26}**	**0.861**
H_7	**0.808**	**H_{27}**	**0.808**
H_8	**0.807**	**O_{28}**	**8.554**
H_9	**0.861**	**O_{29}**	**8.554**
C_{10}	**6.023**	**C_{30}**	**5.681**
H_{11}	**0.888**	**C_{31}**	**6.191**
N_{12}	**7.280**	**H_{32}**	**0.807**
C_{13}	**6.145**	**N_{33}**	**6.960**
H_{14}	**0.886**	**O_{34}**	**8.297**
H_{15}	**0.828**	**O_{35}**	**8.297**
C_{16}	**6.145**	**N_{36}**	**6.960**
H_{17}	**0.828**	**O_{37}**	**8.297**
H_{18}	**0.886**	**O_{38}**	**8.297**
N_{19}	**7.280**	**H_{39}**	**0.622**
C_{20}	**6.023**	**H_{40}**	**0.622**

Ligand (6):- 43 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.745	C_{23}	5.779
C_2	6.132	C_{24}	6.107
C_3	6.201	C_{25}	6.148
C_4	5.847	H_{26}	0.864
C_5	5.779	H_{27}	0.867
C_6	6.123	O_{28}	8.573
H_7	0.880	O_{29}	8.636
H_8	0.866	C_{30}	5.947
H_9	0.861	C_{31}	5.978
C_{10}	6.024	C_{32}	6.153
H_{11}	0.905	H_{33}	0.876
N_{12}	7.287	C_{34}	6.132
C_{13}	6.143	H_{35}	0.877
H_{14}	0.895	C_{36}	6.127
H_{15}	0.842	C_{37}	6.164
C_{16}	6.123	H_{38}	0.872
H_{17}	0.839	H_{39}	0.877
H_{18}	0.883	O_{40}	8.623
N_{19}	7.484	H_{41}	0.626
C_{20}	5.897	C_{42}	0.546
H_{21}	0.866	H_{43}	0.618
C_{22}	5.967		

Ligand (7):- 52 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**6.157**	**C_{27}**	**6.128**
C_2	**5.938**	**C_{28}**	**6.130**
C_3	**5.974**	**C_{29}**	**6.134**
C_4	**5.940**	**H_{30}**	**0.872**
C_5	**5.768**	**C_{31}**	**6.121**
C_6	**6.135**	**H_{32}**	**0.860**
H_7	**0.863**	**H_{33}**	**0.876**
H_8	**0.872**	**H_{34}**	**0.876**
C_9	**5.999**	**C_{35}**	**6.154**
H_{10}	**0.868**	**C_{36}**	**6.155**
N_{11}	**7.374**	**C_{37}**	**6.127**
N_{12}	**7.398**	**H_{38}**	**0.867**
C_{13}	**5.994**	**C_{39}**	**6.129**
H_{14}	**0.781**	**H_{40}**	**0.870**
C_{15}	**5.918**	**H_{41}**	**0.873**
C_{16}	**5.991**	**H_{42}**	**0.873**
C_{17}	**5.794**	**C_{43}**	**6.184**
C_{18}	**5.942**	**C_{44}**	**6.156**
C_{19}	**6.135**	**C_{45}**	**6.144**
C_{20}	**6.155**	**H_{46}**	**0.845**
H_{21}	**0.877**	**C_{47}**	**6.130**
H_{22}	**0.863**	**H_{48}**	**0.870**
O_{23}	**8.623**	**H_{49}**	**0.871**
O_{24}	**8.578**	**H_{50}**	**0.874**
C_{25}	**5.826**	**H_{51}**	**0.632**
C_{26}	**5.840**	**H_{52}**	**0.620**

Ligand (8):- 37 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**6.122**	**H_{20}**	**0.901**
C_2	**6.123**	**C_{21}**	**5.834**
C_3	**6.196**	**C_{22}**	**5.790**
C_4	**5.841**	**C_{23}**	**6.151**
C_5	**5.786**	**C_{24}**	**5.737**
C_6	**6.137**	**H_{25}**	**0.889**
H_7	**0.867**	**O_{26}**	**8.576**
H_8	**0.881**	**O_{27}**	**8.576**
C_9	**6.027**	**C_{28}**	**6.103**
H_{10}	**0.900**	**C_{29}**	**6.209**
N_{11}	**7.302**	**H_{30}**	**0.863**
C_{12}	**6.143**	**H_{31}**	**0.632**
H_{13}	**0.892**	**H_{32}**	**0.633**
H_{14}	**0.826**	**H_{33}**	**0.856**
C_{15}	**6.142**	**H_{34}**	**0.873**
H_{16}	**0.827**	**H_{35}**	**0.868**
H_{17}	**0.892**	**O_{36}**	**8.622**
N_{18}	**7.308**	**H_{37}**	**0.627**
C_{19}	**6.027**		

Ligand (9):- 40 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**6.121**	**O_{21}**	**8.569**
C_2	**6.125**	**O_{22}**	**8.569**
C_3	**6.190**	**C_{23}**	**6.125**
C_4	**5.850**	**C_{24}**	**6.190**
C_5	**5.781**	**H_{25}**	**0.866**
C_6	**6.136**	**H_{26}**	**0.872**
H_7	**0.868**	**H_{27}**	**0.868**
H_8	**0.866**	**C_{28}**	**5.868**
H_9	**0.882**	**C_{29}**	**5.868**
C_{10}	**6.023**	**C_{30}**	**6.123**
H_{11}	**0.887**	**C_{31}**	**6.123**
N_{12}	**7.315**	**C_{32}**	**6.131**
N_{13}	**7.316**	**H_{33}**	**0.870**
C_{14}	**6.023**	**C_{34}**	**6.131**
H_{15}	**0.887**	**H_{35}**	**0.870**
C_{16}	**5.850**	**H_{36}**	**0.879**
C_{17}	**5.781**	**H_{37}**	**0.879**
C_{18}	**6.136**	**H_{38}**	**0.872**
C_{19}	**6.121**	**H_{39}**	**0.633**
H_{20}	**0.882**	**H_{40}**	**0.633**

Ligand (10):- 38 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**6.122**	**C_{20}**	**6.024**
C_2	**6.123**	**H_{21}**	**0.891**
C_3	**6.196**	**C_{22}**	**5.852**
C_4	**5.839**	**C_{23}**	**5.759**
C_5	**5.787**	**C_{24}**	**6.152**
C_6	**6.136**	**C_{25}**	**6.102**
H_7	**0.867**	**H_{26}**	**0.862**
H_8	**0.866**	**O_{27}**	**8.572**
H_9	**0.881**	**O_{28}**	**8.551**
C_{10}	**6.033**	**C_{29}**	**5.681**
H_{11}	**0.903**	**C_{30}**	**6.191**
N_{12}	**7.282**	**H_{31}**	**0.808**
C_{13}	**6.140**	**H_{32}**	**0.871**
H_{14}	**0.893**	**H_{33}**	**0.809**
H_{15}	**0.834**	**N_{34}**	**6.961**
C_{16}	**6.144**	**O_{35}**	**8.299**
H_{17}	**0.827**	**O_{36}**	**8.298**
H_{18}	**0.891**	**H_{37}**	**0.621**
N_{19}	**7.278**	**H_{38}**	**0.633**

Ligand (11):- 38 atoms in its composition

No. of Atom	*Electronic Density*	*No. of Atom*	*Electronic Density*
C_1	**5.741**	**H_{20}**	**0.905**
C_2	**6.145**	**C_{21}**	**5.850**
C_3	**6.183**	**C_{22}**	**5.775**
C_4	**5.913**	**C_{23}**	**0.123**
C_5	**5.757**	**C_{24}**	**5.745**
C_6	**6.107**	**H_{25}**	**0.860**
H_7	**0.870**	**O_{26}**	**8.650**
H_8	**0.853**	**O_{27}**	**8.578**
C_9	**5.926**	**C_{28}**	**6.132**
H_{10}	**0.878**	**C_{29}**	**6.200**
N_{11}	**7.454**	**H_{30}**	**0.867**
C_{12}	**6.129**	**H_{31}**	**0.883**
H_{13}	**0.884**	**H_{32}**	**0.615**
H_{14}	**0.839**	**H_{33}**	**0.548**
C_{15}	**6.143**	**H_{34}**	**0.880**
H_{16}	**0.843**	**O_{35}**	**8.623**
H_{17}	**0.895**	**O_{36}**	**8.623**
N_{18}	**7.286**	**H_{37}**	**0.626**
C_{19}	**6.023**	**H_{38}**	**0.628**

Appendix B

The Electronic Density of All Atoms in the Complexes

Complex (1):- 36 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	6.115	H_{19}	0.856
C_2	6.135	N_{20}	7.610
C_3	6.157	C_{21}	5.921
C_4	5.906	H_{22}	0.845
C_5	5.677	C_{23}	5.910
C_6	6.125	C_{24}	6.154
H_7	0.864	C_{25}	5.678
H_8	0.870	C_{26}	6.139
H_9	0.867	H_{27}	0.869
H_{10}	0.845	C_{28}	6.123
C_{11}	5.908	C_{29}	6.114
H_{12}	0.851	H_{30}	0.870
N_{13}	7.537	H_{31}	0.843
C_{14}	6.121	H_{32}	0.863
H_{15}	0.836	O_{33}	8.668
H_{16}	0.821	O_{34}	8.645
C_{17}	6.133	Mn_{35}	23.897
H_{18}	0.779	Cl_{36}	17.429

Complex (2):- 42 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.897	H_{22}	0.863
H_2	0.850	O_{23}	8.664
N_3	7.549	O_{24}	8.648
C_4	6.120	Mn_{25}	23.896
H_5	0.839	Cl_{26}	17.423
H_6	0.822	C_{27}	5.695
C_7	6.131	C_{28}	6.122
H_8	0.781	C_{29}	5.947
H_9	0.856	C_{30}	6.139
N_{10}	7.610	H_{31}	0.842
C_{11}	5.921	C_{32}	5.970
H_{12}	0.845	C_{33}	5.945
C_{13}	5.909	H_{34}	0.859
C_{14}	4.155	C_{35}	6.147
C_{15}	5.678	C_{36}	6.163
C_{16}	6.139	C_{37}	6.131
H_{17}	0.869	H_{38}	0.872
C_{18}	6.123	C_{39}	6.124
C_{19}	6.115	H_{40}	0.866
H_{20}	0.870	H_{41}	0.872
H_{21}	0.844	H_{42}	0.871

Complex (3):- 48 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.897	C_{25}	5.695
H_2	0.850	C_{26}	6.122
N_3	7.546	C_{27}	5.946
C_4	6.118	C_{28}	6.139
H_5	0.839	H_{29}	0.843
H_6	0.823	C_{30}	5.970
C_7	6.129	C_{31}	5.945
H_8	0.782	H_{32}	0.859
H_9	0.858	C_{33}	6.146
N_{10}	7.623	C_{34}	6.163
C_{11}	5.912	C_{35}	6.131
H_{12}	0.845	H_{36}	0.872
C_{13}	5.937	C_{37}	6.124
C_{14}	5.969	H_{38}	0.866
C_{15}	5.696	H_{39}	0.872
C_{16}	5.955	H_{40}	0.872
C_{17}	6.120	C_{41}	6.166
C_{18}	6.134	C_{42}	6.123
H_{19}	0.839	H_{43}	0.865
H_{20}	0.857	C_{44}	6.151
O_{21}	8.669	C_{45}	6.129
O_{22}	8.640	H_{46}	0.870
Mn_{23}	23.895	H_{47}	0.876
Cl_{24}	17.424	H_{48}	0.872

Complex (4):- 44 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.894	Mn_{23}	23.896
H_2	0.845	Cl_{24}	17.404
N_3	7.554	C_{25}	5.696
C_4	6.121	C_{26}	6.120
H_5	0.834	C_{27}	5.946
H_6	0.817	C_{28}	6.138
C_7	6.134	H_{29}	0.839
H_8	0.775	C_{30}	5.969
H_9	0.848	C_{31}	5.944
N_{10}	7.611	C_{32}	0.854
C_{11}	5.904	C_{33}	6.146
H_{12}	0.830	C_{34}	6.162
C_{13}	5.931	C_{35}	6.130
C_{14}	6.154	H_{36}	0.871
C_{15}	5.648	C_{37}	6.123
C_{16}	5.699	H_{38}	0.862
H_{17}	0.809	H_{39}	0.868
C_{18}	6.142	H_{40}	0.867
C_{19}	6.092	H_{41}	0.809
H_{20}	0.829	N_{42}	6.960
O_{21}	8.662	O_{43}	8.305
O_{22}	8.637	O_{44}	8.296

Complex (5):- 40 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	6.093	H_{21}	0.825
C_2	5.697	C_{22}	5.933
C_3	6.145	C_{23}	6.150
C_4	5.930	C_{24}	5.647
C_5	5.645	C_{25}	5.699
C_6	6.142	H_{26}	0.806
H_7	0.804	C_{27}	6.140
H_8	0.806	C_{28}	6.090
H_9	0.827	H_{29}	0.825
C_{10}	5.894	H_{30}	0.804
H_{11}	0.832	O_{31}	8.661
N_{12}	7.542	O_{32}	8.637
C_{13}	6.127	Mn_{33}	23.894
H_{14}	0.822	Cl_{34}	17.392
H_{15}	0.810	N_{35}	6.957
C_{16}	6.139	O_{36}	8.292
H_{17}	0.771	O_{37}	8.298
H_{18}	0.842	N_{38}	6.958
N_{19}	7.613	O_{39}	8.300
C_{20}	5.901	O_{40}	8.290

Complex (6):- 43 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.897	O_{23}	8.653
C_2	0.850	Mn_{24}	23.896
N_3	7.548	Cl_{25}	17.425
C_4	6.119	C_{26}	5.695
H_5	0.840	C_{27}	6.122
H_6	0.822	C_{28}	5.947
C_7	6.129	C_{29}	6.139
H_8	0.782	H_{30}	0.844
H_9	0.857	C_{31}	5.970
N_{10}	7.617	C_{32}	5.945
C_{11}	5.923	H_{33}	0.859
H_{12}	0.846	C_{34}	6.147
C_{13}	5.902	C_{35}	6.163
C_{14}	6.165	C_{36}	6.131
C_{15}	5.680	H_{37}	0.872
C_{16}	6.116	C_{38}	6.124
H_{17}	0.864	H_{39}	0.866
C_{18}	6.145	H_{40}	0.872
C_{19}	5.727	H_{41}	0.871
H_{20}	0.851	O_{42}	8.617
H_{21}	0.852	H_{43}	0.620
O_{22}	8.666		

Complex (7):- 52 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.898	C_{27}	5.949
H_2	0.842	H_{28}	0.857
N_3	7.641	C_{29}	6.146
C_4	5.772	C_{30}	6.163
C_5	5.733	C_{31}	6.130
N_6	7.751	H_{32}	0.874
C_7	5.907	C_{33}	6.123
H_8	0.843	H_{34}	0.865
C_9	5.936	H_{35}	0.870
C_{10}	5.972	H_{36}	0.870
C_{11}	5.692	C_{37}	6.166
C_{12}	5.957	C_{38}	6.122
C_{13}	6.119	H_{39}	0.864
C_{14}	6.133	C_{40}	6.152
H_{15}	0.837	C_{41}	6.128
H_{16}	0.856	H_{42}	0.869
O_{17}	8.669	H_{43}	0.872
O_{18}	8.635	H_{44}	0.870
Mn_{19}	23.877	C_{45}	6.095
Cl_{20}	17.409	C_{46}	6.106
C_{21}	5.692	C_{47}	6.132
C_{22}	6.122	H_{48}	0.855
C_{23}	5.950	C_{49}	6.130
C_{24}	6.137	H_{50}	0.854
H_{25}	0.842	H_{51}	0.862
C_{26}	5.966	H_{52}	0.862

Complex (8):- 37 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.732	C_{20}	5.921
C_2	6.144	H_{21}	0.845
C_3	6.167	C_{22}	5.911
C_4	5.899	C_{23}	6.154
C_5	5.679	C_{24}	5.678
C_6	6.115	C_{25}	6.139
H_7	0.876	H_{26}	0.869
H_8	0.863	C_{27}	6.122
H_9	0.830	C_{28}	6.115
C_{10}	5.910	H_{29}	0.870
H_{11}	0.854	H_{30}	0.842
N_{12}	7.542	H_{31}	0.863
C_{13}	6.119	O_{32}	8.672
H_{14}	0.837	O_{33}	8.645
H_{15}	0.823	Mn_{34}	23.895
C_{16}	0.133	Cl_{35}	17.431
H_{17}	0.779	O_{36}	8.615
H_{18}	0.857	H_{37}	0.625
N_{19}	7.609		

Complex (9):- 40 atoms in its composition

No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.910	C_{21}	5.671
H_2	0.844	C_{22}	6.125
N_3	7.630	C_{23}	5.913
C_4	5.776	C_{24}	6.113
C_5	5.734	H_{25}	0.844
N_6	7.736	C_{26}	6.155
C_7	5.918	C_{27}	6.136
H_8	0.840	H_{28}	0.862
C_9	5.913	C_{29}	6.106
C_{10}	6.154	C_{30}	6.094
C_{11}	5.672	C_{31}	6.128
C_{12}	6.139	H_{32}	0.853
C_{13}	6.122	C_{33}	6.132
C_{14}	6.114	H_{34}	0.851
H_{15}	0.842	H_{35}	0.860
H_{16}	0.862	H_{36}	0.860
O_{17}	8.670	H_{37}	0.867
O_{18}	8.640	H_{38}	0.868
Mn_{19}	23.879	H_{39}	0.868
Cl_{20}	17.412	H_{40}	0.866

Complex (10):- 38 atoms in its composition

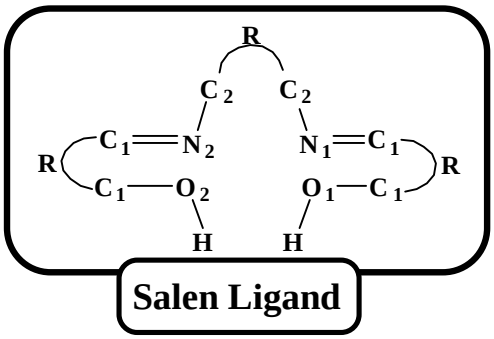
No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	6.094	C_{20}	5.918
C_2	5.697	H_{21}	0.839
C_3	6.147	C_{22}	5.910
C_4	5.929	C_{23}	6.152
C_5	5.644	C_{24}	5.676
C_6	6.144	C_{25}	6.137
H_7	0.808	H_{26}	0.864
H_8	0.809	C_{27}	6.121
H_9	0.831	C_{28}	6.113
C_{10}	5.897	H_{29}	0.864
H_{11}	0.837	H_{30}	0.839
N_{12}	7.537	H_{31}	0.858
C_{13}	6.125	O_{32}	8.662
H_{14}	0.827	O_{33}	8.646
H_{15}	0.814	Mn_{34}	23.895
C_{16}	6.135	Cl_{35}	17.411
H_{17}	0.776	N_{36}	6.960
H_{18}	0.849	O_{37}	8.297
N_{19}	7.612	O_{38}	8.303

Complex (11):- 38 atoms in its composition

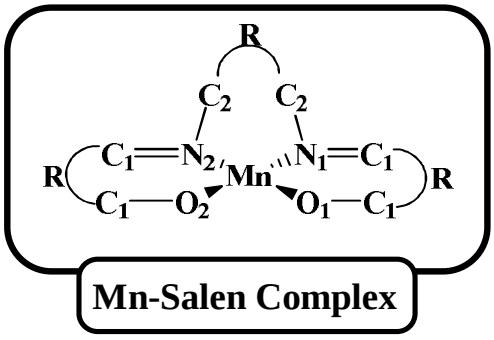
No. of Atom	Electronic Density	No. of Atom	Electronic Density
C_1	5.732	C_{20}	5.922
C_2	6.144	H_{21}	0.848
C_3	6.167	C_{22}	5.904
C_4	5.899	C_{23}	6.164
C_5	5.679	C_{24}	5.677
C_6	6.115	C_{25}	6.147
H_7	0.876	H_{26}	0.864
H_8	0.863	C_{27}	6.118
H_9	0.830	C_{28}	5.729
C_{10}	5.910	H_{29}	0.875
H_{11}	0.854	H_{30}	0.829
N_{12}	7.542	O_{31}	8.671
C_{13}	6.119	O_{32}	8.650
H_{14}	0.839	Mn_{33}	23.895
H_{15}	0.824	Cl_{34}	17.432
C_{16}	6.132	O_{35}	8.615
H_{17}	0.781	O_{36}	8.614
H_{18}	0.858	H_{37}	0.625
N_{19}	7.613	H_{38}	0.625

Appendix C

Bond Length of Coordinated Atoms in Both Ligands and Complexes and Angles of Complexes Rule



Salen Ligand



Mn-Salen Complex

Bond length (angstroms) of attached atom of the ligand before complex formations:

	N_1-C_1	N_1-C_2	N_2-C_1	N_2-C_2	O_1-C_1	O_1-H	O_2-C_1	O_2-H
L_1	1.284	1.466	1.284	1.466	1.380	0.977	1.380	0.977
L_2	1.284	1.464	1.284	1.465	1.382	0.978	1.385	0.976
L_3	1.284	1.465	1.284	1.465	1.386	0.976	1.385	0.976
L_4	1.282	1.465	1.284	1.465	1.371	0.978	1.385	0.976
L_5	1.283	1.466	1.283	1.466	1.370	0.978	1.370	0.978
L_6	1.283	1.455	1.298	1.459	1.373	0.976	1.355	1.036
L_7	1.287	1.406	1.287	1.406	1.383	0.976	1.383	0.976
L_8	1.284	1.464	1.285	1.464	1.382	0.978	1.381	0.977
L_9	1.289	1.405	1.289	1.405	1.380	0.977	1.380	0.977
L_{10}	1.285	1.466	1.282	1.466	1.381	0.977	1.369	0.978
L_{11}	1.294	1.459	1.283	1.455	1.360	1.021	1.372	0.976

Bond length (angstroms) of attached atom of the ligand and metal ion after complex formations:

	Mn-N_1	Mn-N_2	Mn-O_1	Mn-O_2	N_1-C_1	N_1-C_2	N_2-C_1	N_2-C_2	O_1-C_1	O_2-C_1
C_1	2.035	1.913	1.828	1.863	1.300	1.483	1.323	1.481	1.351	1.326
C_2	2.019	1.909	1.839	1.863	1.304	1.482	1.323	1.481	1.345	1.326
C_3	2.019	1.894	1.836	1.865	1.304	1.483	1.330	1.481	1.346	1.319
C_4	2.013	1.917	1.827	1.878	1.305	1.483	1.318	1.482	1.827	1.878
C_5	2.036	1.916	1.835	1.868	1.298	1.485	1.319	1.483	1.341	1.319
C_6	2.019	1.909	1.839	1.870	1.304	1.482	1.325	1.480	1.345	1.324
C_7	2.061	1.920	1.821	1.857	1.305	1.416	1.332	1.424	1.821	1.857
C_8	2.036	1.913	1.830	1.863	1.301	1.482	1.323	1.481	1.350	1.326
C_9	2.062	1.922	1.823	1.859	1.307	1.419	1.334	1.425	1.823	1.859
C_{10}	2.041	1.907	1.847	1.854	1.298	1.485	1.324	1.481	1.338	1.328
C_{11}	2.035	1.914	1.830	1.867	1.301	1.482	1.324	1.480	1.349	1.325

Angles of Metal ion with the attached atoms (Nitrogen and Oxygen) of the Ligands in all complexes.

	Angles			
C_1	N_1-Mn-O_2	169.673	N_2-Mn-O_1	145.874
C_2	N_1-Mn-O_2	169.720	N_2-Mn-O_1	145.645
C_3	N_1-Mn-O_2	170.039	N_2-Mn-O_1	144.210
C_4	N_1-Mn-O_2	169.510	N_2-Mn-O_1	145.737
C_5	N_1-Mn-O_2	169.534	N_2-Mn-O_1	145.548
C_6	N_1-Mn-O_2	169.448	N_2-Mn-O_1	145.155
C_7	N_1-Mn-O_2	169.547	N_2-Mn-O_1	145.876
C_8	N_1-Mn-O_2	169.666	N_2-Mn-O_1	145.238
C_9	N_1-Mn-O_2	172.394	N_2-Mn-O_1	135.959
C_{10}	N_1-Mn-O_2	169.379	N_2-Mn-O_1	144.965
C_{11}	N_1-Mn-O_2	169.549	N_2-Mn-O_1	145.556

الخلاصة

تتميز جذور الاوكسجين الحرة بصغرها، وفعاليتها، واحتوائها على ذرة الاوكسجين والتي تتكون بصورة طبيعيه بكميات صغيرة خلال عمليات الايض الخلوي والتي بامكانها الضرر باجزاء الخلايا المختلفة مثل الدهون، البروتينلت، و DNA. تمثل مركبات السوبر اوكساید دسميوتيز انظمة حماية ضرورية لمكونات جسم الكائن الحي ضد مشتقات الاوكسجين الضارة خاصة فوق الاوكسيد ($O_2^{\cdot-}$) حيث يدخل في سلسلة من التفاعلات لتكوين جذور الاوكسجين الاخرى لتعمل معاً على الاضرار بمحتويات الخلايا الحيه، حيث ان العديد من الامراض تتسبب بواسطة وجود فوق الاوكسيد.

ان وجود انزيمات فوق الاوكسيد دسميوتيز (SOD)، الكتليز (CAT)، الكلوتاثايون بيروكسديز(GPx) الطبيعيه يعمل كنظام حمايه ضد الضرر الذي تسببه مركبات فوق الاوكسيد. ان تنوع هذه الانزيمات يسمح بايجاد مساحة اوسع لعلاج الكثير من الامراض.

تم خلال البحث تحضير عشرة قواعد شف جديدة لمعقدات المنغنيز الثلاثي التكافو [Mn(III)] صممت وبنيت كمقلدات لإنزيمي فوق الاوكسيد دسميوتيز (SOD) وكتليز (CAT) .هذه المعقدات الجديدة اضافة إلى المعقد المعروف بمنغنيز- سالين (C_1:- وهو عقار معروف استخدم كمادة قياسية ضد ايون فوق الاوكسيد ($O_2^{\cdot-}$) (مقلد لفعالية إنزيم فوق الاوكسيد دسميوتيز) وبيروكسيد الهيدروجين (H_2O_2) (مقلد لفعالية إنزيم الكتليز) وقد تمت دراسة هذه المركبات وتشخيص النتائج باستخدام برنامج كاوسين (2003) [Gaussian 03] وقد اضهرت النتائج مايلي:-

1. يكون ايون المنغنيز في هذه المعقدات محاطا بذرتي نتروجين لقواعد شف وذرتي أوكسجين ويكون الايون الفلزي فوق مستوى القاعدة نحو الايون السالب (Cl^{1-}).
2. اختلاف سلوك المركبات المحضرة في تفاعلات الاكسدة والاختزال عن المركب الاول (C_1).
3. اضهرت بعض المعقدات المتكونة من مزيج من الليكندات (ليكندات غيرمتشابهة) فعاليات أفضل من تلك التي لها الليكندات نفسها (ليكندات متشابهة).
4. بعض المعقدات أعطت فعاليات إنزيمية مقلدة عالية لإحدى التفاعلين (كمقلد لإنزيم فوق الاوكسيد دسميوتيز أو كمقلد لإنزيم الكتليز) وواطئة للتفاعل الأخر.
5. فعالية كلا المعقدين (C_2, C_7) كانت أعلى من تلك التي للمعقد C_1 في كلا نوعي التفاعل .
6. تمتلك المعقدات (C_4, C_9, C_{10}) فعالية اعلى كمقلد لفوق الاوكسيد دسميوتيز من المعقد الاول (C_1).
7. تمتلك المعقدات (C_3, C_5, C_6, C_8, C_{11}) فعالية اعلى كمقلد للكتليز من المعقد الاول (C_1).

8. تم حساب الشكل الهندسي المتوازن من خلال حساب ترددات الاواصر وثابت القوة حيث اضهرت النتائج بان المعقدات المحضرة تمتلك الشكل هرم مربع القاعدة حيث تتكون القاعدة من ذرتي الاوكسجين وذرتي النيتروجين ويكون ايون المنغنيز فوق مستوى القاعدة بينما يشكل ايون الكلورايد راس الهرم.

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دراسة نظرية لبعض معقدات المنغنيز (III) الحاوية على ذرتي النيتروجين والاوكسجين

رسالة
مقدمة إلى كلية العلوم- جامعة النهرين
وهي جزء من متطلبات نيل درجة الماجستير في الكيمياء

من قبل

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