

ADDIS ABABA UNIVERSITY
SCHOOL OF GRADUATE STUDIES



STUDIES ON METAL COMPLEXES
DERIVED FROM
PHYSIOLOGICALLY ACTIVE
QUINOXALINE DERIVATIVES

GRADUATE PROJECT CHEM. 774

BY
GOJJE GAMO

JULY 2006

STUDIES ON METAL COMPLEXES DERIVED FROM
PHYSIOLOGICALLY ACTIVE QUINOXALINE DERIVATIVES

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By

Gojje Gamo

July 2006

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BY
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DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE

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DECLARATION

I hereby declare that this project is my original work and has not been presented for a degree in any other university. I have cited and referenced all materials and results that are not original to this work. All materials and sources used for this project have been dully acknowledged.

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July 2006

This project has been submitted for examination with our approval as university advisors.

Prof. V.J.T. Raju_____

Dr. Yonas Chebude_____

TO MY WIFE, CHILDREN
AND
OUR PARENTS

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LIST OF ABBREVIATIONS AND SYMBOLES

- AAS = Atomic Absorption Spectroscopy
- Alq3 = tris-(8-hydroxyquinolinato) aluminum(III)
- AMPA = 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid
- AP = N- (aminoformimidoyl)phenol
- BDPQ = [2,3-bis(2-pyridyl)benzo[g]quinoxaline]
- CAPQ = 6,7-dicyano-2,3-di-(4'-diphenylamino-biphenyl-4-yl)quinoxaline
- CNQX = 6-cyano-7-nitroquinoxaline-2,3-dione
- CT = charge transfer
- DEPT = Distortionless Enhancement by Polarization Transfer
- DMeDPQ = [6,7-dimethyl-2,3-bis(2-pyridyl)quinoxaline]
- DMF = dimethylformamide (Me₂NCH=O)
- DCQX = 2,3-dichloroquinoxaline
- DMSO = dimethylsulfoxide (Me₂S=O)
- DNA = Deoxyribonucleic acid

DNQX = 6,7-dinitroquinoxaline-2,3-dione
dpq = dipyrido[3,2-*d*:2,3-*f*]quinoxaline
dppz = dipyrido[3,2-*a*:2,3-*c*]phenazine
dsDNA = double-stranded DNA
EB = ethidium bromide
en = ethylenediamine
g = grams
GluR = glutamate receptor
h = hour(s)
Him = imidazole
HMPA = hexamethylphosphoramide
HOMO = highest occupied molecular orbital
I = light intensity
IR = Infrared
KA = kanic acid
LUMO = lowest unoccupied molecular orbital
M = molarity
mL = milliliter
MLCT = metal to ligand charge transfer
mmol = milimole(s)
Mp = melting point
NBQX = 6-nitro-7-sulamoylbenzo[*f*]quinoxaline-2,3-dione
NMDA = N-methyl-D-aspartic acid
NMR = Nuclear magnetic resonance
PDA = o-phenylenediamine
PDT = photodynamic therapy
phen = 1,10-phenanthroline
phi = 9,10-phenanthrenequinone diimine
bpy (bipy) = 2,2'-bipyridine
py = pyridine
QX = quinoxaline

QXAP = Quinoxaline-2,3-bis-N(Aminoformimidoyl)phenol
 QXD = 2,3-quinoxalinedione
 QXDO = 2,3-quinoxalinedioxime
 rt = room temperature
 spiro Qux = spiro-quinoxaline
 TGA = thermogravimetric analysis
 THF = tetrahydrofuran [2,3,4,5-tetrahydrofuran], (CH₂)₄O
 TNQX = 2,3,7-trichloro-5-nitroquinoxaline
 UV = ultra-violet
 Vis = visible
 Λ_M = molar conductance
 τ = life time

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STUDIES ON METAL COMPLEXES DERIVED FROM PHYSIOLOGICALLY ACTIVE QUINOXALINE DERIVATIVES

Abstract

Coordination compounds, with bonds between a central metal atom and surrounding ligands, play critical roles in biology, biochemistry and medicine, controlling the structure and function of many enzymes and their metabolism. They play similarly vital roles in many industrial processes and in the development of new materials with specifically designed properties. Thus synthesis and study of such complexes is very important.

In this lab work, equimolar quantities of o-phenyldiamine and oxalic acid dihydrate were condensed in 5N HCl under reflux to 2,3-quinoxalinedione. Refluxing of 2,3-quinoxalinedione with phosphorus (V) chloride as well as with thionylchloride gave 2,3 dichloroquinoxaline which was then treated first with hydroxylamine hydrochloride to afford a new ligand 2,3-quinoxalinedioxime (QXDO) and secondly with N-(aminoformimidoyl)phenol to give quinoxaline-2,3-bis-[N-(aminoformimidoyl)phenol] (QXAP) both of which contain nitrogen and oxygen donor atoms. However, the formation of QXAP was unsuccessful as it was confirmed by ¹H NMR. Thus QXDO was further complexed with divalent metal salts to give different complexes. New metal complexes of nickel and copper with quinoxalinedioxime (QXDO) were prepared. The complexes were characterized by elemental analysis, conductance measurements, atomic absorption, IR, NMR and UV spectroscopy and magnetic moments. QXDO behaves as a bidentate ligand.

Key terms: Quinoxaline, o-phenyldiamine, salicylaldehyde, hydrazine, 2,3-quinoxalinedione (QXD), 2,3-dichloroquinoxaline (DCQX), 2,3-quinoxalinedioxime (QXDO).

CHAPTER ONE: THEORETICAL BACKGROUND

1.1. INTRODUCTION

Like all sciences, chemistry involves two parallel processes, experimentation and explanation. Explanations are built on the results of experiments and then using those explanations additional experiments are designed to further test the explanation and also provide new information [1]. The synthetic chemist is not only concerned with the preparation of new compounds; he often seeks new and better methods for preparing compounds that have been known to many years. Usually the first method used for the preparation of a compound is inefficient or inconvenient. Thus the motive for seeking a better synthetic procedure is obvious. There are many inorganic compounds that might change from laboratory curiosities to commercially important chemicals if practical syntheses were found for them [2]. Thus good synthetic techniques require due attention to the purity of reagents and solvents. Since repeatability is an important part of experimental work, impurities that may affect the outcome of a reaction must be eliminated and when choosing a solvent, the air and moisture-sensitivity of reagents should be considered.

With the general objectives of how to handle chemicals properly, formulation to perform laboratory experiments and learn how to apply theory to practical needs, each experiment should be considered as an independent piece of research with its own objective, theoretical bases and experimental proof of the conjectured result. The experiments must lead the chemist from superficial acquaintance with substances to an understanding of their properties through knowledge of their structure and thermodynamics, and further to the carrying out of an oriented experiment. The details of each experiment should always be planned carefully and it often helps to sketch apparatus before assembling it. Since synthetic chemistry is an art and synthetic chemists are judged by their ability to choose appropriate reagents and reaction conditions for the preparation of new compounds, it would be a good practice to carry out the experiment mentally first, so that one can envisage each step and anticipate any potential problems with material transfer or manipulation [3].

I report herein the synthesis of nickel (II) and copper (II) complexes with the Schiff base QXDO and their characterization using various physicochemical techniques. In this

project work quinoxaline derivatives were synthesized and further coordinated with the divalent transition metal chlorides. $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ salts were used to prepare the complexes.

1.2. OBJECTIVES

For educational, economic, environmental and social reasons, the trend toward the design, synthesis, characterization and application of chemical compounds is undoubtedly increasing. Especially the synthesis of biologically active compounds such as pharmaceuticals, agrochemicals, flavors and fragrances as well as creation of advanced materials have got great attention. Chemists in their research or project work are thus, usually interested in synthesizing, isolating, identifying, studying properties and applications of chemical compounds.

1.2.1. GENERAL OBJECTIVES

The general objectives are the following.

- Develop the skill of independent laboratory work
- Develop experience of how to handle and use chemicals.
- Develop the skill of synthesis, separation (purification) of compounds and then further characterizing them using analytical and spectral methods.
- Acquire knowledge of how to deal with the research or project work

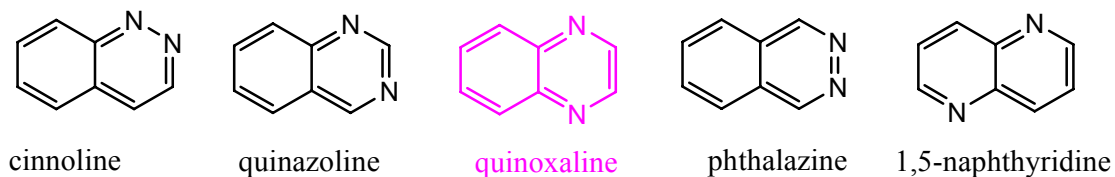
1.2.2. SPECIFIC OBJECTIVES

- Synthesis and isolation (purification) of quinoxaline derivatives- precursors- 2,3-quinoxalinedione and 2,3-dichloroquinoxaline; ligands- 2,3-quinoxalinedioxime and quinoxaline-2,3-bis-[(N-aminoformimidoyl)phenol]; and their Co, Ni, Cu and Zn complexes
- Characterization of these products (eg., melting point, thermal analysis, IR, NMR, etc.
- Interpretation of physical datas, like IR, NMR, magnetic susceptibility, etc.
- Explanation of their properties and applications.
- Elucidation of structural formula on the basis of interpretation of physiochemical data and theoretical explanations from the literature surveys.

1. 3. LITERATURE SURVEY

1. 3.1. QUINOXALINES

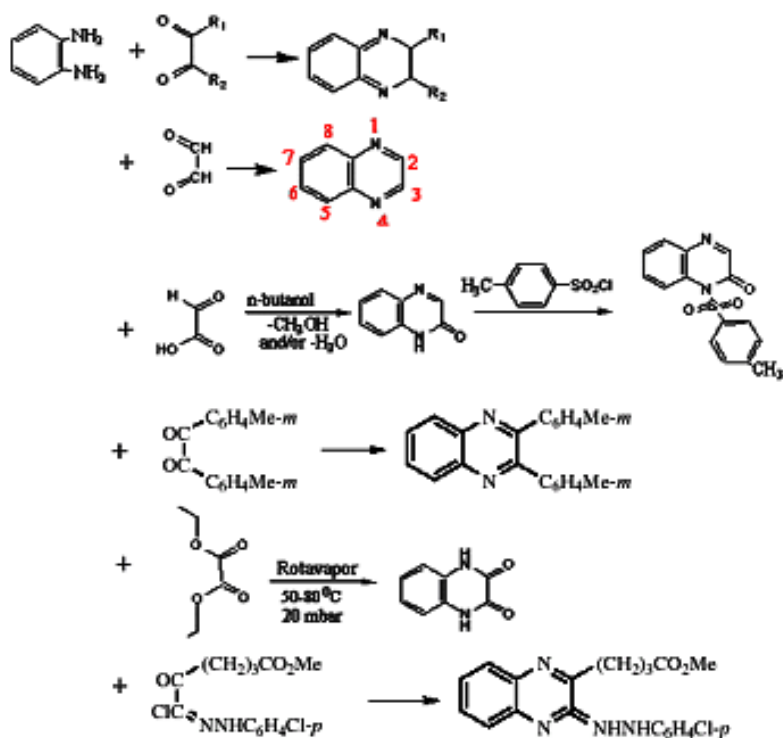
Quinoxalines, also called benzopyrazines, are heterocyclic compounds containing a fused ring made up of a benzene ring and a pyrazine ring, with the isomers cinnolines, phthalazines and quinazolines. All these belong to a class of heterocyclic compounds known as diazanaphthalenes, that may have the two heteroatoms in the same or different rings.



Scheme 1: The chemical structures of selected aromatic compounds (diazanaphthalenes).

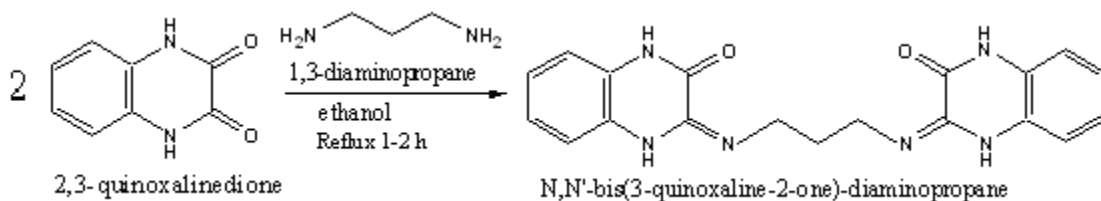
All these compounds have 10- π electrons that are located in five molecular orbitals that can be regarded as linear combination of 2p-atomic orbitals, one atomic orbital and one π -electron coming from each atom of the ring skeleton. There are also two non-bonding orbitals that lie in the molecular plane and largely are confined to the nitrogen atoms, each of these orbitals contains an electron pair and these electrons are responsible for the basic properties of the group of compounds [4, 5].

The primary synthesis of quinoxalines may be accomplished by cyclization of benzene substrates already bearing appropriate substituents; by cyclocondensation of benzene substrates with acyclic synthons to provide one or more of the ring atoms required to complete the pyrazine ring; by analogous processing of preformed pyrazine substrates; or by rearrangement, ring expansion/contraction, degradation, or modification of appropriate derivatives of other heterocyclic systems [6]. Quinoxalines are readily made from 1,2-dicarbonyl compounds and aromatic 1,2-diamines; i.e., a well-known route to quinoxalines is the reaction of o-phenylene diamine with a 1,2-dicarbonyl compound [7-14].



Scheme 2: Synthetic routes to quinoxaline and its derivatives

The condensation of ketone or aldehyde with a primary amine leads to the formation of an imine linkage with the liberation of water molecule. The N-atom carries a lone pair of electrons and can function as a Lewis base, forming complexes with transition metal ions [15]. For instance in the synthesis of *N,N'*-bis(3-quinoxaline-2-dione)diaminopropane, a mixture of quinoxaline-2,3-dione and 1,3-diaminopropane in ethanol was heated under reflux to give *N,N'*-bis(3-quinoxaline-2-one)-diaminopropane .



Scheme 3: Preparation of *N,N'*-bis(3-quinoxaline-2-one)-diaminopropane

N,N'-bis(3-quinoxaline-2-one)-diaminopropane is expected to display different tautomeric forms due to the mobility of the hydrogen between the ring exocyclic azomethine nitrogens and also the mobility of hydrogen atoms between the ring azomethine nitrogen and

hydroxyl group. This ligand can behave as bis-ON donor or bis-ONN donor system and lead to the formation of stable metal complexes [16].

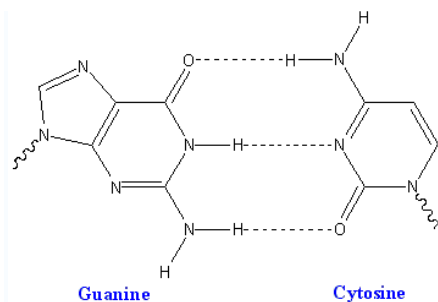
1.3.2. METAL COMPLEXES OF QUINOXALINE DERIVATIVES

1.3.2.1. The interaction of metal-quinoxaline complexes with DNA

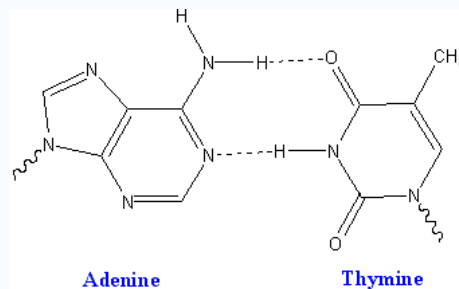
The investigation of interactions between double-stranded deoxyribonucleic acid (DNA) and DNA-binding agents is crucial to a deeper understanding of such important biochemical processes as replication, repair, recombination, and expression of genes. In principle, the possible binding mechanisms of ligands to double-stranded (ds) DNA can be divided into **sequence-specific binding**, and, on the other hand, binding modes that **lack sequence specificity**. Specific binding between ligand (protein) and receptor (dsDNA), often also termed “molecular recognition,” is the basis for the interaction of many transcription factors with DNA. Small agents that bind unspecifically or with lower sequence specificity to dsDNA are often capable of influencing or inhibiting these processes and intrinsically exhibit mutagenic properties. Consequently, these molecules find applications as pharmaceuticals, mainly in the treatment of cancer. Others are employed as DNA staining agents, for example in fluorescence assays [17].

Quinoxaline derivatives are capable of forming complexes with transition metals that interact with DNA. Thus nowadays the intercalation of quinoxaline based and other transition metal complexes with nucleic acids is a major area of research due to the utility of these complexes in the design and development of synthetic restriction enzymes, chemotherapeutic agents, footprinting agents, spectroscopic probes, site-specific cleavers and molecular photoswitches [18].

DNA structure consists of two strands that are paired or held together by hydrogen bonding between its bases. The base pairing of opposite strands is stereochemically selective, adenine always pairing with thymine, and guanine with cytosine. Two and three hydrogen bonds are formed in A-T and G-C base pairs, respectively as shown in the scheme 4.



A GC base pair demonstrating three intermolecular hydrogen bonds



An AT base pair demonstrating two intermolecular hydrogen bonds

Scheme 4: DNA: Hydrogen bonding and stability

DNA intercalation is a noncovalent interaction in which a molecule or a portion thereof, inserts between two adjacent DNA base pairs. Unless a covalent interaction subsequently occurs, the molecule is free to move on and off of the DNA in equilibrium controlled primarily by van der Waals forces coupled with electrostatic (e.g., hydrogen bonding) interactions. The number, strength, position, and absolute stereochemistry of electrostatic interactions largely control the extent of the non-bonded intercalation process. The biological consequences of intercalative interactions can include [frameshift mutagenesis and clastogenicity](#), but it is very clear that intercalation alone is not necessarily genotoxic [19]. Intercalation is thus used in host-guest chemistry for the reversible inclusion of a molecule (or group) between two other molecules (or groups). The host molecules usually comprise some form of periodic network. A large class of molecules intercalates into DNA. These molecules are mostly polycyclic, aromatic, and planar, and therefore often make good nucleic acid stains. Intensively studied DNA intercalators include ethidium, proflavin, daunomycin, doxorubicin, thalidomide and quinoxalines. [DNA intercalators are used in chemotherapeutic treatment of concern to inhibit DNA replication in rapidly growing cancer cells](#) [20].

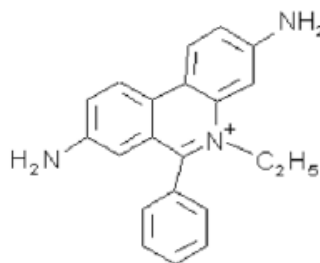
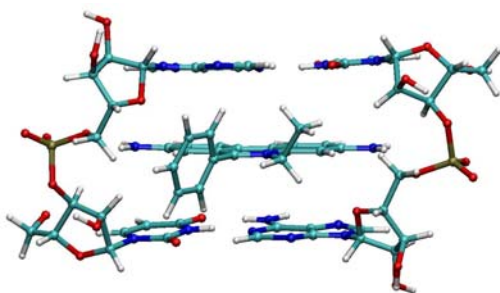


Fig 1: Intercalation mode showing ethidium intercalated between two adenine-uracil base pairs (left) and chemical structure of ethidium (right).

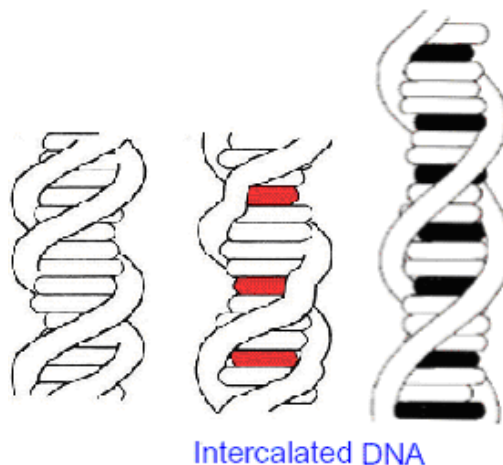


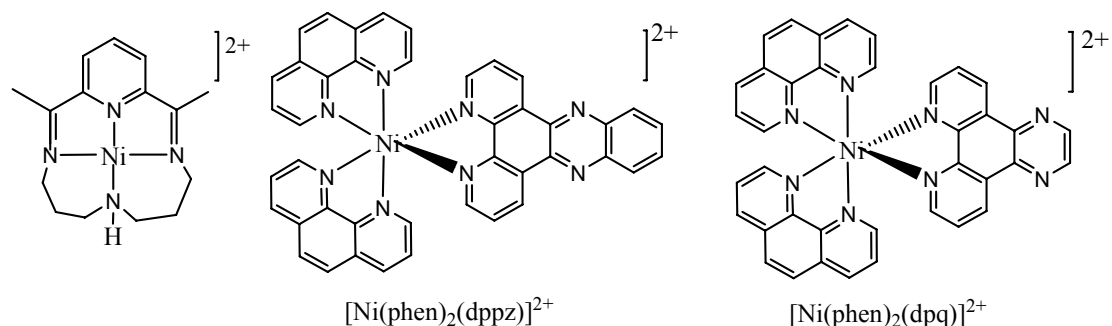
Fig 2: DNA structural distortions induced by intercalation. Insertion of flat, planar molecules between base pairs of dsDNA leads to length increase. Left: unchanged DNA strand. Middle and right: DNA strand intercalated at base pairing locations (shaded areas).

1.3.2.2. Nickel (II) complexes (Ni^{2+} , d^8)

The DNA binding ability of inert chiral transition metal complexes has attracted considerable interest. Recent studies have shown that a variety of transition metal complexes have significant potential as probes for sequence- and structure-specific DNA binding. Significant attention has centered upon metal complexes capable of binding DNA by intercalation, and, in particular, due to their luminescent properties and strong DNA binding affinity. Replacement of the hydrogen-bonded base pairing of natural DNA by alternative base pairing modes is expected to lead not only to expansion of the genetic alphabet but to novel DNA structures and [functions based on the controlled and periodic spacing of the building blocks along the helix axis](#).

In the majority of the complexes studied the metal ion serves as the oxidation agent while the ligand is responsible for DNA recognition. The modes of recognition are primarily based upon intercalation, groove-binding and hydrogen-bonding interactions. Site-specific DNA modification has also been observed for transition complexes that are covalently linked to DNA-binding proteins. In contrast, platinum chemotherapeutic agents such as cis- $\text{Pt}(\text{NH}_3)_2\text{Cl}_2$ (cis-platin) interact specifically with duplex DNA by forming covalent bonds between the platinum metal center and N7 of guanine. The mode of action of cis-platin is believed to involve the replacement of the two labile chloride ions with guanine resulting in

intrastrand cross-links. Nickel macrocyclic complexes that possess vacant or labile coordination sites may also ligate to DNA bases, and effect site-specific reactions with DNA.



Scheme 5: Nickel complexes

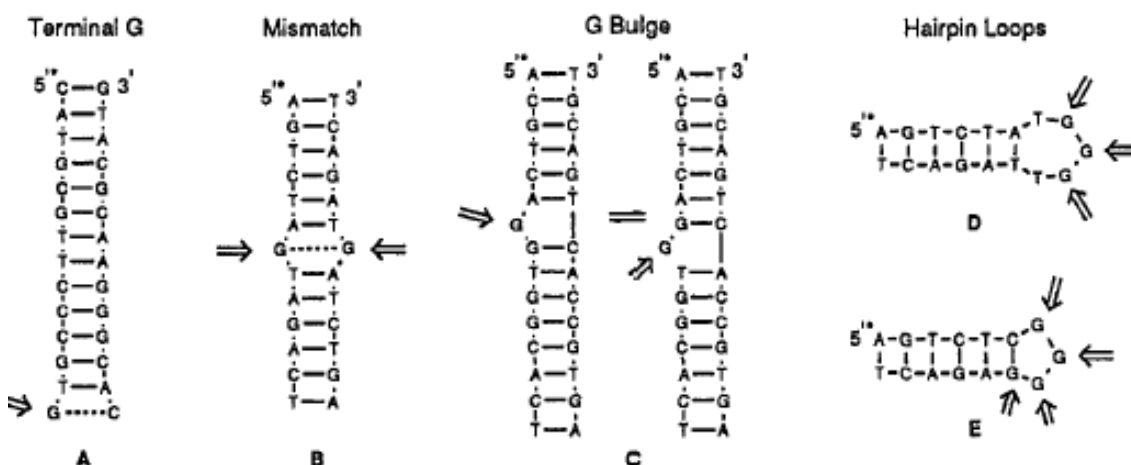


Fig. 3. DNA structures recognized by nickel complexes

Nickel complexes, those shown above have also proved useful in detecting highly accessible guanine sites such as those found in oligonucleotide bulges (**C**) and loops (**D** and **E**). The observed conformation specificity in oligonucleotides using the above complex is likely the result of steric requirements associated with the direct ligation of nickel to N7 of guanine, whereby the terminal, mismatched, bulged, or looped guanine residues provide an accessible coordination site for the nickel complex [21].

1.3.2.3. Copper (II) complexes (Cu^{2+} , d^9)

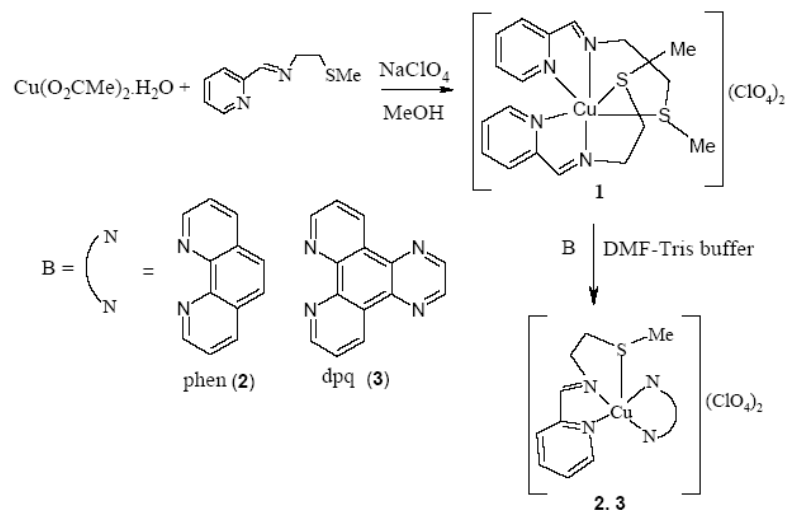
A new binary six-coordinate copper (II) complex containing tridentate Schiff-base ligand with CuN_4S_2 coordination is known and structurally characterized by X-ray crystallography. The complex shows cis disposition of two thiomethyl moieties having significantly long Cu–S distances. Complex 1 is found to be a poor binder and cleaver of DNA

in the absence of any planar ligand moiety needed for intercalative and/or groove binding of DNA. Using complex 1 as a precursor, two new ternary copper(II) complexes having the sulphur containing Schiff-base as photosensitizer and phen or dpq as DNA binder are generated under in situ reaction conditions.

Absorption and fluorescence spectral techniques have been used to determine the relative binding propensity of the complexes to CT DNA. The intrinsic binding constant values, obtained by absorption spectral method, vary as: $3 > 2 > 1$. The dpq complex with its extended aromatic quinoxaline ring shows efficient DNA-binding ability. The phen complex is relatively a poor binder to DNA. Earlier studies on *bis*-phen or *bis*-dpq copper complexes have shown that the complexes bind DNA in the minor groove.

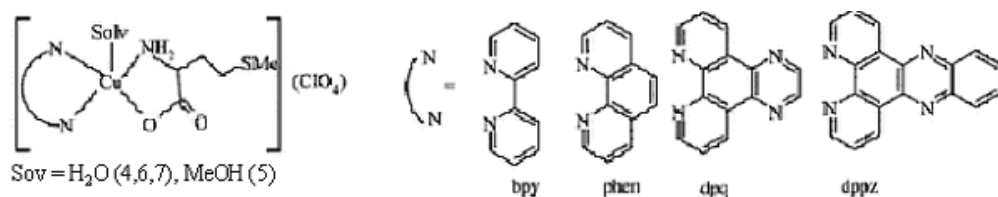
The oxidative DNA cleavage activity of the complexes was studied by gel electrophoresis using supercoiled (SC) DNA. The greater cleavage efficiency of the ternary complexes compared to that of the binary complex 1 is due to their efficient DNA-binding ability. Control experiments using Schiff base or the dpq ligand alone does not show any significant cleavage of (SC) DNA even on longer exposure time. The results indicate the important role of metal in these photo-induced DNA cleavage reactions

The ternary complexes display significantly enhanced DNA binding and photoinduced DNA cleavage activity in comparison to 1 owing to the formation of singlet oxygen as the reactive species in a type-II process. The steric constraints imposed by two five-membered chelate rings in the {CuL} moiety results in significant lengthening of the Cu–S bond. A weak Cu–S bond considerably reduces the photosensitizing effect of the Schiff-base ligand. The results show the importance of the Cu–S bond length on the photo-induced DNA cleavage activity and its significance in designing non-porphyrinic transition metal complexes for photodynamic therapy (PDT) applications. The *d–d* band being in the PDT window of 600–800 nm makes these complexes potential systems to explore the DNA cleavage activity on red-light irradiation. The complexes also exhibit charge transfer bands near 450 nm which could be assigned to the sulphur to copper(II) charge transfer LMCT band [22].



Scheme 6: The reaction pathways for the synthesis of the binary complex $[\text{CuL}_2](\text{ClO}_4)_2$ (**1**) and in situ generation of the ternary complexes $[\text{CuLB}](\text{ClO}_4)_2$ (B: phen, **2**; dpq, **3**).

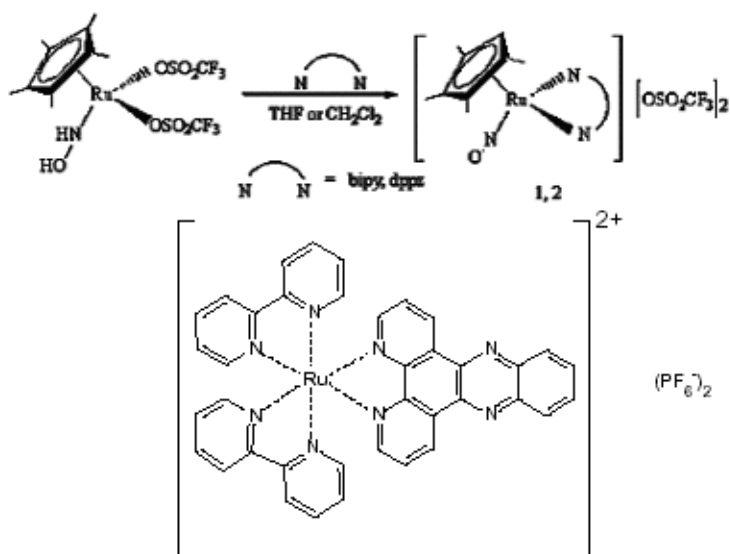
Below are considered some more pentacoordinated copper(II) complexes. These one electron paramagnetic complexes show a broad d-d band near 600nm in DMF. The complexes display a quasireversible cyclic voltammetric response which can be assigned to the Cu(II)/Cu(I) couple near -0.1 V in DMF-Tris buffer(1:4 v/v; pH 7.2). The high ΔE_p value suggests poor reversibility of the electron transfer process. The crystal structures of the complexes consist of a monomeric species with the metal ion in a square pyramidal (4+1) coordination geometry with a CuN_3O_2 core. The donor atoms in the basal plane are two nitrogen atoms of the heterocyclic base (B) and the N, O atoms of L-methionine. The axial site has a coordinated solvent molecule [23].



Scheme 7: pentacoordinated copper(II) complexes: Complexes **4-7** and the heterocyclic bases. 2,2'-bipyridine (bpy, **4**), 1,10-phenanthroline (phen, **5**), dipyrido[3,2-*d*:2,3-*f*] quinoxaline (dpq, **6**) and dipyrido[3,2-*a*:2,3-*c*] phenazine (dppz, **7**), and Solv is H_2O for **4,6,7** and MeOH for **5**.

1.3.2.4. Ruthenium (II) Complexes (Ru^{2+} , d^6)

The intercalation of metal complexes into DNA and direct binding of metals with DNA base pairs has been a major focus in the study of bioinorganic chemistry. The study of such interactions is important for the development of new pharmaceuticals, synthetic restriction enzymes, and luminescent reporters for DNA. The interaction of DNA with classical coordination compounds like $[\text{Ru}(\text{phen})_3]^{2+}$, cis-platinum complexes, and simple hydrated metal cations has been a principal focus of research. Ruthenium complexes containing dppz ligands exhibit enhanced photoluminescence and extended excited-state lifetimes when bound to DNA. Molecular orbital calculations suggest that the LUMO of $[\text{Ru}(\text{bipy})_2(\text{dppz})]^{2+}$ is localized on the phenazine region of the dppz ligand. Thus, the potential exists for photo-initiated electron transfer from the metal to a molecule of DNA as mediated through the phenazine region of dppz. Photo-induced DNA cleavage has been observed for a number of transition metal complexes, including $[\text{Rh}(\text{phen})_3]^{3+}$, $[\text{Co}(\text{NH}_3)_6]^{3+}$, and $[\text{Ru}(\text{bipy})_3]^{2+}$.



Scheme 8: Ruthenium (II) Complexes

The quantum yields of DNA cleavage for these complexes range from 10^{-7} to 10^{-4} per DNA plasmid. More recently, Shields and Barton reported sequence-specific DNA photocleavage by one of the enantiomers of $[\text{Rh}(\text{en})_2\text{phi}]^{3+}$, (en = ethylenediamine, phi = 9,10-phenanthrenequinone diimine). The efficiency of photocleavage processes is strongly affected by the absorption spectrum of the metal complex, as well as by the DNA binding affinity.

Studies performed with $[\text{Ru}(\text{bipy})_2(\text{dppz})]^{2+}$ indicate comparable binding to both AT- and GC-rich DNA with an equilibrium binding constant of $>10^6 \text{ M}^{-1}$ [24].

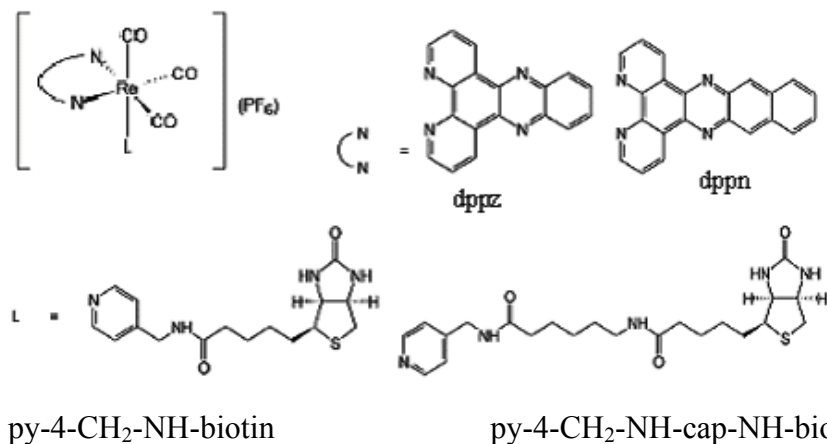
The dye most commonly used for the measurement of DNA rotational motions is ethidium bromide (EB). Apart from its very high toxicity this compound has the disadvantage of a short lifetime of 30 ns. Only short time motions of the DNA can be detected by anisotropy changes of bound EB. The slower bending motions of the double helix can be detected with an intercalating probe which offers a longer fluorescence lifetime. This enables to examine the slow motions of DNA by their influence on fluorescence polarization. The first metal-ligand complex based probe published previously contained a dipyrido-[3,2a:2',3'-c] phenazine (dppz) ligand (see Scheme 8). The principle of increased luminescence upon intercalation of the complex into the double strand is the same compared to EB. The increase is caused by a shielding of the nitrogen atoms of the dppz ligand from solvent molecules by the DNA bases [25].

1.3.2.5. Rhenium (I) Polypyridine Biotin Complexes (Re^+ , s^1d^5)

New rhenium(I) polypyridine biotin complexes have been prepared by making use of the extended planar diimine ligands dppz and dppn (scheme 9). These extended planar diimine ligands were expected to allow the complexes to intercalate into the base-pairs of dsDNA molecules, and the biotin moieties would enable the complexes to bind to avidin. Upon irradiation, the complexes exhibited intense and long-lived greenish-yellow to orange luminescence in solutions at room temperature and in low-temperature alcohol glass. In the presence of double-stranded calf thymus DNA, the low-energy absorption bands of all the complexes displayed pronounced hypochromism and a small bathochromic shift, and the emission of the complexes was substantially enhanced. These changes are attributable to the binding of the complexes to the DNA molecules by intercalation. The HABA assays showed that all the complexes bound to avidin with a stoichiometry of 4:1 (Re: avidin).

The emission intensities and lifetimes of the complexes also increased in the presence of avidin. The emission intensity enhancement factors varied from approximately 1.9 to 40. These complexes are the first luminescent probes that respond to both DNA molecules and avidin. It is believed that the avidin-induced emission enhancement is common to transition metal complexes that show environment sensitive emission with large Stokes shifts. From the results, it was found that more hydrophobic complexes can give rise to stronger binding to the

protein, but too high hydrophobicity will substantially lower the solubility of complexes in aqueous solution. Whilst a longer spacer-arm between the luminophore can enhance the binding affinity, it renders the probe more exposed to the bulk solution after the binding and thus lowers the enhancement factors of emission intensity (I/I_0) and lifetimes (τ/τ_0). These remarks will be taken into consideration in the design of related luminescent probes for avidin τ [26].



Scheme 9: Structures of rhenium(I)-biotin complexes containing extended planar diimine ligands.

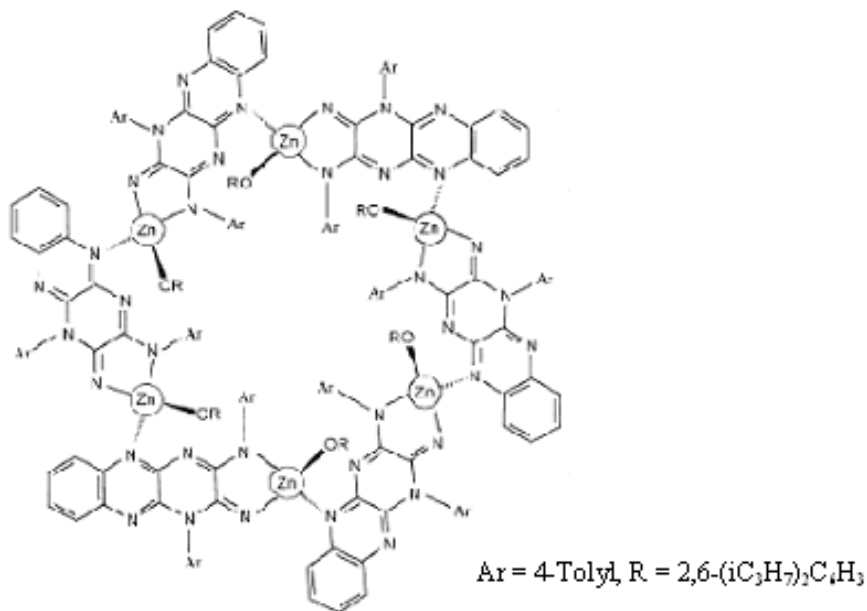
1.3.2.6. Zinc complexes (Zn^{2+} , d^{10})

Of the two functions of zinc in biology — structural and catalytic — the latter has found much more attention in the literature even though the structural function may be more important. It is essential for many enzymes, and the ubiquity of zinc finger motifs is underlined by the fact that about 1% of the human genome seems to encode zinc finger proteins [27]. Zinc can coordinate in mononuclear as well as polynuclear fashions.

In the past 20 years, a number of mononuclear zinc enzymes, such as phospholipase C, bovine lens leucine aminopeptidase, ATPases, carbonic anhydrases, and peptide deformylase, have been found and some of these have been determined by X-ray crystallography. They play a number of diverse and important roles in biological systems and have received considerable attention from inorganic chemists. Since mononuclear zinc complexes may serve as model compounds for these enzymes, a number of these complexes have been prepared in recent years for this purpose. 1,10-Phenanthroline (phen) and 2,2-bipyridine (bipy) have extended

planar systems and can be used in model compounds to mimic the noncovalent interactions in biological processes [28].

Polynuclear metal complexes can perform useful functions that mononuclear metal complexes cannot, such as multi-electron redox and light harvesting processes [29]. Experiments have shown that tricyclic derivatives which contain an additional quinoxaline ring could coordinate with the zinc ion.



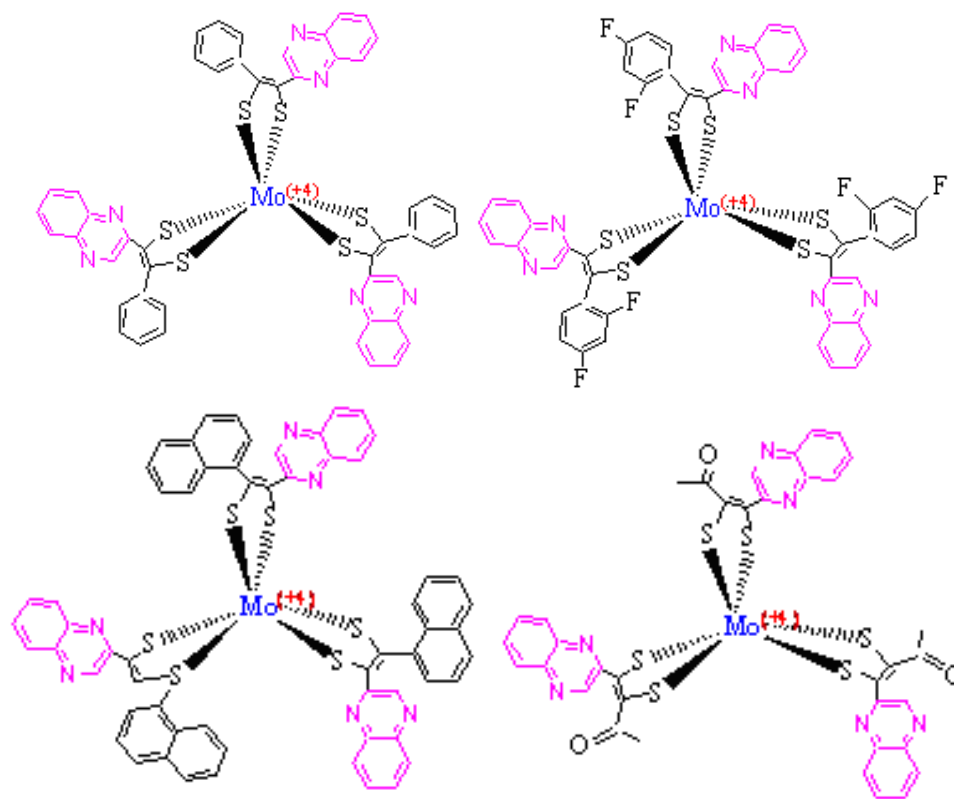
Scheme 10: Zinc-quinoxaline complex macrocyclic system

The ¹H NMR spectrum showed that only one phenolate group coordinates to the Zn atom, thus indicating that the quinoxaline acts as a monoanionic ligand. This was confirmed by X-ray crystallography. Rather surprisingly, the complex exhibits a 36-membered macrocyclic ring system composed of six monomeric units. All zinc ions are tetrahedrally coordinated with the quinoxaline ligand bridging two zinc cations. Both the imine nitrogen N2 and the amide nitrogen N1 in the quinoxaline bind to one zinc center to form a five-membered chelate ring. In addition, the amine nitrogen N5 acts as a bridging donor to connect two zinc centers. This results in the formation of an unusual macrocyclic system in which six zinc ions in a chair conformation are linked by six quinoxaline ligands. The orientation of the ligands relative to the central zinc atom alternates [30].

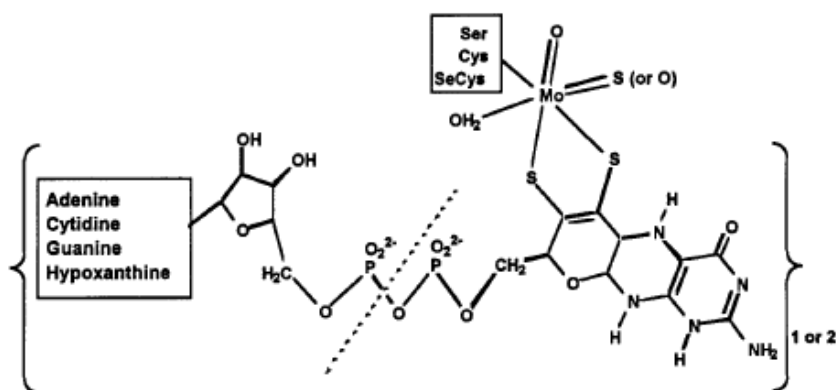
1.3.2.7. "Hyper-paramagnetic" Molybdenum tris-Dithiolene Complexes (Mo^{4+} , d^2)

Molybdenum is an essential trace element for all living systems. This metal acts as a vital component of the catalytic center of the nitrogenases and of the extensive family of enzymes, each of which transfers an oxygen atom to or from the substrate [31]. Molybdenum or tungsten is present at the active sites of over 30 distinct enzymes. The Mo enzyme nitrogenase, with its unique polynuclear metal sulfide clusters, falls in a class by itself. All other Mo and W enzymes are mononuclear, with pterin-ene-dithiolate coordination [32].

Molybdenum dithiolene compounds have been well studied because of their variable coordination geometries, unique properties and because a Mo-dithiolene group is present in the pterin-containing molybdenum enzymes. A class of molybdenum(+4) tris-dithiolenes have been discovered that exhibit unprecedented magnetic behavior. In contrast to most molybdenum(+4) tris-dithiolenes that are known to be diamagnetic, it is found that tris-dithiolenes bearing quinoxaline and aromatic substituents produce Mo(+4) complexes with "hyper-paramagnetic" behavior. Room temperature magnetic susceptibility measurements on these compounds have been observed as high as 8.0 BM, a value far in excess of that expected for a Mo(+4) d^2 center. The structural parameters that favor this unusual property are probed by synthesizing derivatives with variable aromatic substituents on the dithiolene ligands. Uv/Vis spectroscopy and cyclic voltammetry tools are used to probe the electronic structure in the new derivatives [33].



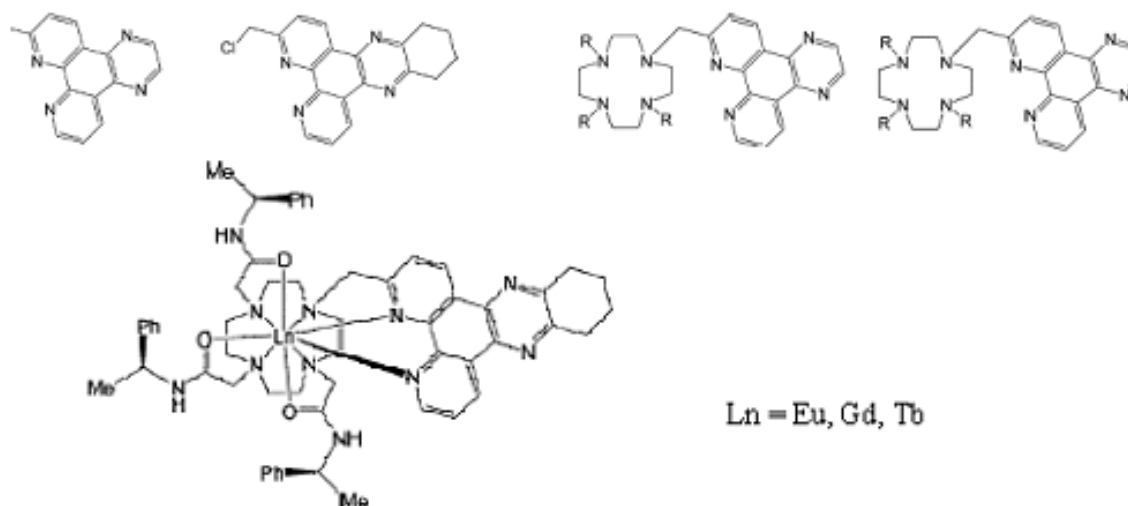
Scheme 11: Molybdenum Tris- Dithiolene Complexes



Scheme12: The pterin-ene-dithiolate complex of molybdenum which constitutes the molybdenum cofactor (Mom), or when tungsten substitutes for molybdenum, the tungsten cofactor (Wco). The cofactor may have one or two dithiolene ligands, zero, one, or two oxo ligands and, in certain cases, a sulfido, serine, cysteine, selenocysteine, or aquohydroxo ligand. In some cases, a dinucleotide form of the ligand is present as shown in the material to the left of the dotted line.

1.3.2.8. Lanthanide Complexes

The tetraazatriphenylene chromophore is an established sensitizer for lanthanide luminescence. It possesses a fast rate of **inter-system crossing**, so that the triplet-excited state may be populated efficiently in polar media. It has a triplet energy of the order of $24\,000\text{ cm}^{-1}$ (singlet energy *ca.* $29\,000\text{ cm}^{-1}$) and, being electron-poor, it is difficult to oxidize. It may serve as a bidentate ligand and several examples of ruthenium (and related d-block) complexes incorporating this ligand have been examined as luminescent probes for nucleic acids. Indeed, examples of enantiopure cationic complexes have been postulated to bind with some selectivity to DNA, with contributions from electrostatic attraction, groove and intercalative binding. Analogous complexes of the 'f'-block ions are virtually unexplored. The first examples were based on phenanthridinium conjugates but were of limited utility as the sensitizer singlet excited state was quenched by electron transfer, associated with intercalation with GC-rich DNA [34].



Scheme 13: Quinoxaline ligands and their lanthanide complexes

1.3.3. APPLICATIONS OF QUINOXALINES

So far we have considered different metal complexes bearing quinoxaline derivatives and their importance especially as DNA intercalators. In the foregoing discussion we shall focus on diverse applications of quinoxaline moieties and some more metal complexes of quinoxalines.

1.3.3.1. Quinoxalines for Chemotherapeutics

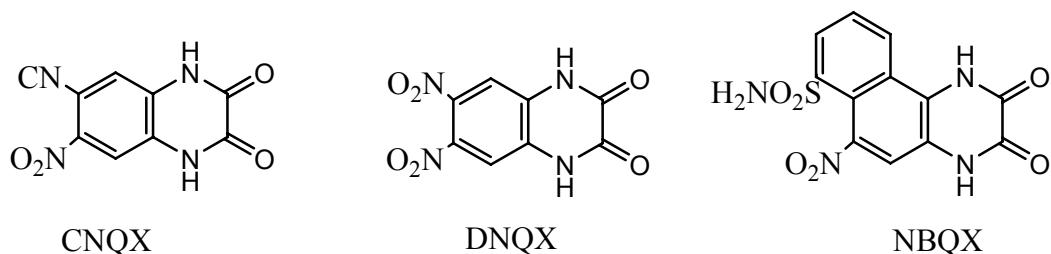
The aims of chemotherapy drugs are to either irreparably damage the DNA of cancer-affected cells, or to prevent the replication and synthesis of DNA. Both will prevent the affected cell from replicating and spreading the cancer. Due to the fact that they interact directly on DNA, most chemotherapy drugs are extremely potent. Although these drugs can be very sequence specific, so that they only interact with very specific sections of DNA, there is also a problem of side effects and toxicity associated with their use, due to their interaction with non-cancerous replicating DNA present in the body.

Much attention has been made for the synthesis of new heterocyclic compounds like triazole, 4,5-pyrazolinedione, quinoxaline, and isoxazoline derivatives in the quest for new chemotherapeutic drugs. Numerous quinoxaline derivatives are important as antibacterial, antifungal, anticancer, antidepressant and antiinflammatory agents [35]. Such compounds have the ability to bind and cleave double stranded DNA under physiological conditions and are of importance for their utility as diagnostic agents in medicinal applications and for genomic research [20]. For instance, coppers being a bio-essential element, its complexes, shown above, have found more applications in nucleic acid chemistry as compared to the heavier transition elements. Recently it has shown that non-porphyrinic binary and tertiary copper complexes are efficient photo cleavage of DNA on UV or visible light irradiation. The ligands or metal salts alone are found to be cleavage inactive. However when a photosensitizing ligand and a DNA binder are covalently bonded to a copper (II) center, the complex becomes cleavage active [19]. In addition to these as it is said above, in this section as illustrative examples, we shall have look at applications of different quinoxaline derivatives.

Current HIV treatments often consist of a combination of two or three drugs – often with different mechanisms of action. These are usually either protease inhibitors or reverse transcriptase inhibitors. Reverse transcriptase inhibitors fall into two classes: nucleoside

analogues, such as Epivir or Retrovir; and non-nucleosides – the [quinoxaline series of compounds are all non-nucleoside reverse transcriptase inhibitors \[36\]](#).

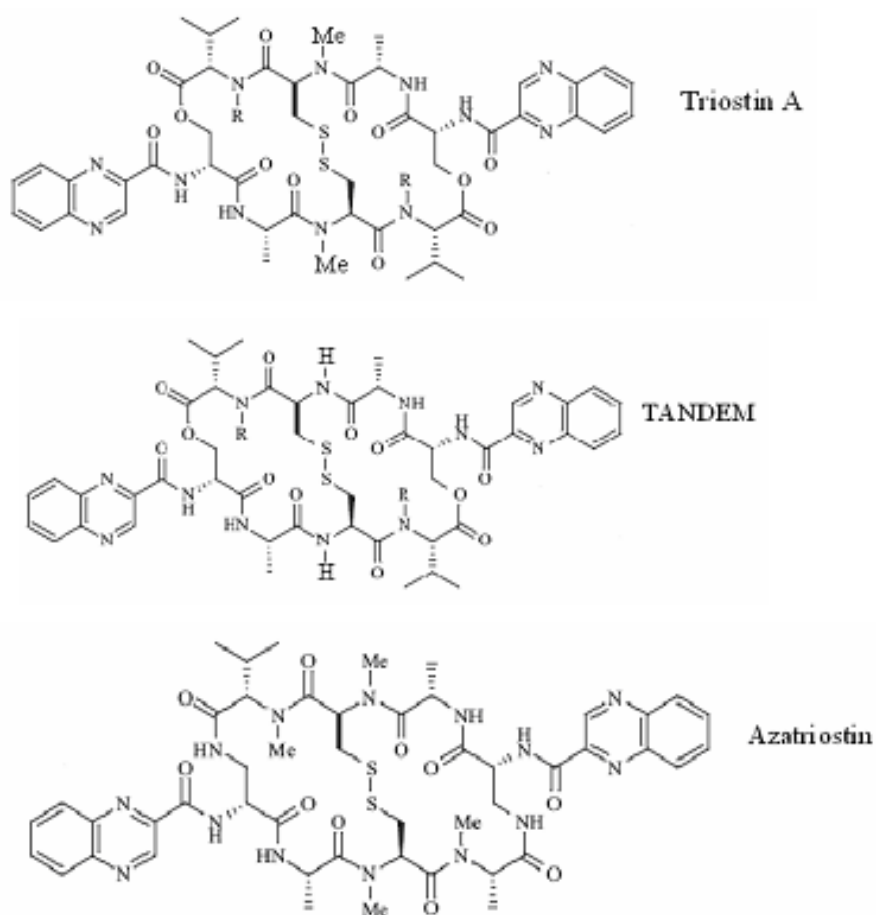
Glutamate neurotoxicity is thought to play a role in a number of pathophysiological conditions including ischemis, brain and spinal cord trauma, and a [variety of neurodegenerative disorders](#). Excitatory amino acid antagonists may have important therapeutic potential in the treatment of these disease states. Although molecular biologist's cloning efforts are in the process of further defining glutamate receptors (GluR), at least three ionotropic glutamate receptors have been identified by classical methodology. These ionotropic receptors are names for the agonists which activate them: N-methyl-D-aspartic acid (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) and kanic acid (KA). Several modulatory sites have been identified for the NMDA receptor-ion channel complex including a glutamate recognition site, a glycine recognition site, and an ion channel site to which compounds such as phencyclidine (PCP) and MK-801 (dizocilpine) bind. A number of quinoxalinediones, including 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), 6,7-dinitroquinoxaline-2,3-dione (DNQX), and 6-nitro-7-sulamoylbenzo[f] quinoxaline-2,3-dione (NBQX) are potent antagonists of the AMPA receptor. CNQX and DNQX were found to also have affinity for the glycine-binding site on the NMDA receptor [\[37\]](#).



Scheme 14: Quinoxalinediones, potent antagonists of the AMPA receptor

The potent *in vivo* activity of various quinoxaline-1,4-di-N-oxides (QdNO) against diverse bacteria, *Entamoeba histolytica*, and *Chlamydiae* of the psittacosis-lymphogranuloma venereum group has been known for more than two decades. Like many antibiotics (e.g., penicillin or tetracyclines) and chemotherapeutics (e.g., nitrofurans or sulfonamides), QdNO increases the live weight gain in young chickens, pigs, and calves when added to the diet. At present two QdNO, carbadox and olaquinox are on the market as growth promoters in various countries [\[38\]](#).

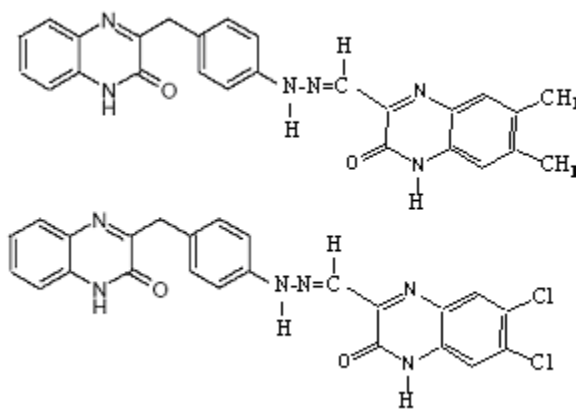
Triostin A is a member of the quinoxaline family of antitumor antibiotics that bind to DNA by bis-intercalation. Triostin A binding in the minor groove exhibits a sequence preference for GC. This GC selectivity is removed by replacement of the N-methyl amino acids with the natural unmethylated amino acids; the synthetic bis-intercalator TANDEM binds selectively to AT sequences. Azatriostin is derived from the natural antibiotic by replacing the D-serine amino acid with D- β -aminoalanine, affording an amide versus ester linkage in the cyclic peptide backbone [40].



Scheme 17: Quinoxaline families of antitumor antibiotics

Neurological diseases such as Creutzfeldt-Jacob disease, bovine spongiform encephalopathy and scrapie are caused by induced conformational changes of a normal host protein to an abnormally folded protein. Compounds which can affect the conformation of the protein chain could be helpful in treatment of such diseases. The newly discovered anti-prion compounds can be grouped into branched polyamines or rigid condensed heterocycles with tetrapyrrole or acridine skeletons. Some non-condensed polyatomic heterocyclic compounds in

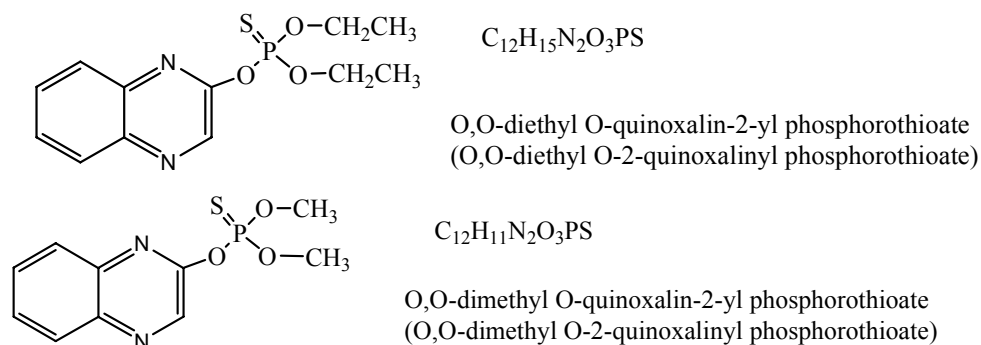
which free rotation of individual cycles can offer several conformations could be suitable in controlling conformations of the protein chain. Such molecules can adapt themselves to the spatial arrangement of a certain part of the protein chain but, at the same time, due to bonding and non-bonding interactions they can change the conformation of this chain [41].



Scheme 18: Quinoxaline compounds for the treatment of neurological diseases

1.3.3.2. Quinoxaline organothiophosphate insecticides

Different types of insecticides have been synthesized. One of these classes of insecticides is the organophosphorus insecticides. The following two are quinoxaline organothiophosphate insecticides synthesized and known so far [42].



Scheme 19: Quinoxaline organothiophosphate insecticides.

1.3.3.3. Quinoxalines for Wastewater Treatment

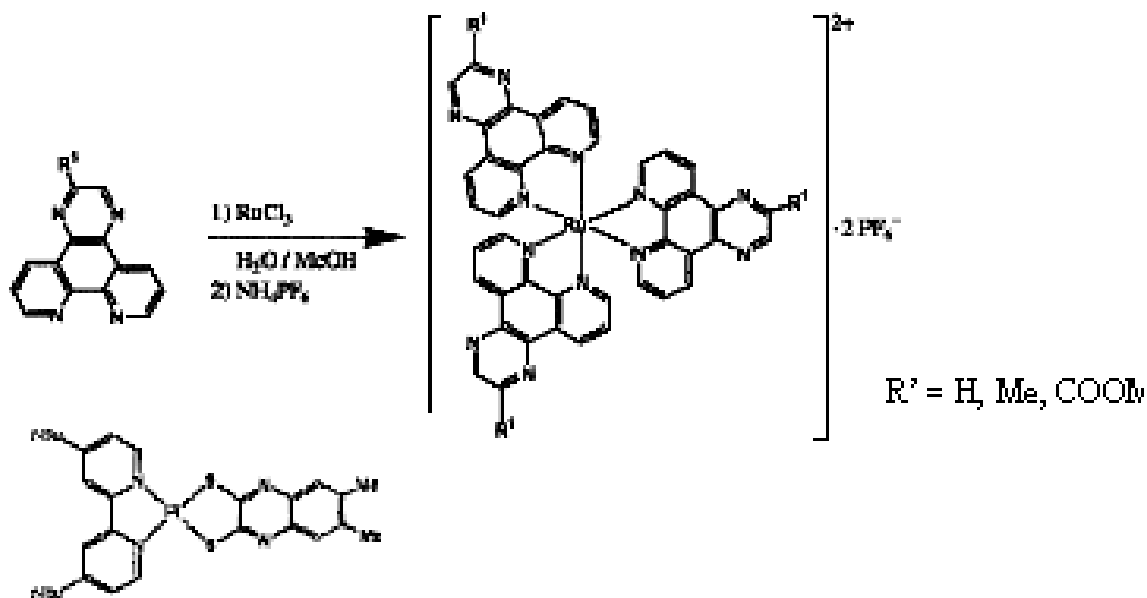
In modern times, the treatment of wastewater constitutes a crucial part of most industrial processes. Efficient separation of metal ions by solvent extraction either from industrial wastes or from raw materials is gaining importance as the most common technique used. The literature is well documented with the use of β -diketones and quinoxalines as

chelating ligands in solvent extraction. Previous studies focused on the extraction of lanthanoids by 1-phenyl-3-isoheptyl-1,3-propanedione and β -diketones, which have been extensively used as extractants in the separation of metal ions. Also, quinoxaline derivatives are currently being studied as chemical chelants and have been employed extensively as analytical reagents in the determination of metal ions by liquid-liquid extraction [13].

1.3.3.4. Quinoxalines for Organic Light Emitting Diodes (OLEDs)

Transition-metal complexes with polypyridines have been widely studied in the last decades mainly because of their special photophysical, photochemical, and electrochemical properties. These properties make them potential candidates to be used as dyes in artificial solar-energy-conversion devices, e.g., in photo-electrochemical solar cells. Specifically, (polypyridine) ruthenium(II) complexes have been anchored to semiconductor oxide electrodes, such as TiO_2 electrodes, and used to improve the light-to-electricity-conversion yield of the cell [43].

Research involving the excited-state processes of transition metal diimine complexes also has dominated the field of inorganic photochemistry for the past two decades. Growth in this area has been driven by rapid advances in the techniques of studying excited-state transient species and in the theory of photo-induced electron transfer. Further support has come from promising results concerning the use of metal diimine chromophores in applications such as solar energy conversion, supramolecular assemblies, photocatalysis, nonlinear optics, photonic molecular devices, and photoluminescent probes of biological systems. Research continues to focus on transition metal diimine complexes because they often possess long-lived excited states capable of bimolecular energy and electron transfer as well as efficient photoluminescence. Synthetic strategies are aimed at preparing complexes having a high degree of stability and having excited-state properties that can be controlled by systematic variation in molecular structure. These properties, which classical coordination compounds and organometallic complexes often lack, are crucial to most potential applications [44].

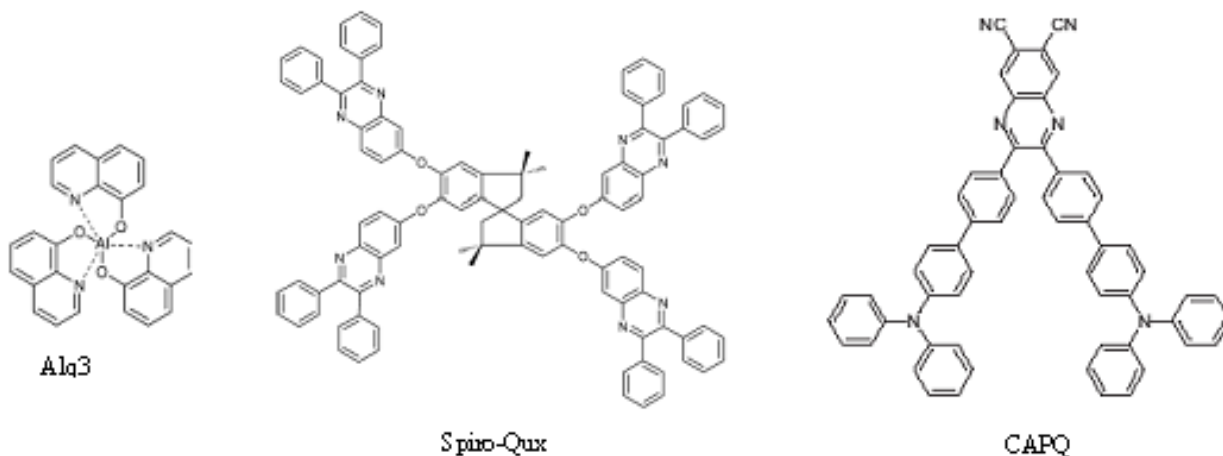


Scheme 20: (polypyridine) ruthenium(II) and platinum(II) diimine dithiolate complexes

Displays based on organic electroluminescence are one of the emerging flat panel display concepts for the next century [45]. An organic electroluminescence device which includes an anode, a cathode, a hole transport layer, an electron transport layer, and at least one organic luminescent medium doped with a pyrazolo[3,4b]quinoxaline derivative is disclosed. The present device provides improved efficiency, and the emission band associated there with is surprisingly narrow. The improved green emitting organic electroluminescence device exhibits high color purity [46].

Organic light-emitting devices (OLEDs) have received much attention since the pioneer work of Tang and Vanslyke owing to their application in the generation of low-cost, large area, and eventually flexible devices and in flat panel displays. Since the initial works on small-molecule and polymer OLEDs, much progress has been made to push the OLED devices for commercialization. However, much room still remains for improvement. Doping a suitable dye into a host layer has proven to be an efficient way for significant improvement of both the efficiency and the stability of devices. Apart from the efforts to modify the device structure, another effective approach to device improvement is to search for new materials for dopants. Thus, it becomes important to search for better doping dyes in respect of high emission quantum yield, high thermal and photochemical stability, and good colour purity etc. For example, doping highly fluorescent dyes, such as coumarin derivatives, quinacridone and its

derivatives, into a host, such as tris-(8-hydroxyquinolato) aluminum (Alq3), can remarkably improve the efficiency and hue of green-emitting devices [47-49].



Scheme 21: Structures of tris(8-hydroxyquinolato)aluminum(III) (Alq3), spiro-quinoxaline (spiro Qux) and 6,7-dicyano-2,3-di-(4'-diphenylamino-biphenyl-4-yl)quinoxaline (CAPQ).

1.4. THE SCOPE OF THE PRESENT WORK

Study of the transition metal complexes with quinoxaline derivatives has gained much attention because of their potential diverse applications for chemotherapy, insecticides, fungicides, organic light emitting diodes and so on. Thus in the recent years the discovery of such new compounds is on progress.

The present work involves synthesis of quinoxaline, new quinoxaline derivatives and their complexes and structural characterization on the basis of physiochemical methods.

CHAPTER TWO: MATERIALS AND METHODS

2.1. CHEMICALS

Ortho-phenylenediamine, prior to its use, was purified as follows. It was dissolved in Hot water containing some dithionite and a few grams of decolorizing carbon were added. The filtrate was then cooled in an ice-salt mixture. The colorless crystals were collected as pure o-phenylenediamine on a Buchner funnel, washed with ice water and dried in vacuo [50]. Ethanol and methanol were purified by distillation. The other reagents such as oxalic acid dihydrate, phosphorus (V) chloride, thionyl chloride, DMF, DMSO, petroleum ether, hydrazine hydrated, salicylaldehyde, chlorides of Co, Ni, Cu and Zn, etc were used as received. 5N HCl, 1N HCl, 0.05M and 0.005M of NaOH were prepared following the analytical procedures.

2.2. PHYSICAL MEASUREMENTS

The melting points were determined using electrothermal IA 9200 Digital Melting Point Apparatus. The IR spectra of successive products were taken in KBr discs with Perkin Spectrum BX FTIR Spectrometer in the range of 4000-400 cm^{-1} . The electronic (Uv-Vis) absorption spectra were measured on a Spectronic GENESY'S 2PC UV-Vis spectrophotometer in the 200-800 nm region in DMF and ethanol (2:1 v/v). ^1H - and ^{13}C - NMR were recorded on BRUKER Advance 400 MHz Spectrometer with TMS internal reference in CDCl_3 and DMSO-d_6 . Molar conductivities were measured with JENWAY 4330 Conducting and pH meter using 10^{-3} M solution of each complex in DMF at room temperature (21°C). The molar magnetic susceptibilities of powdered samples were measured using MSB-AUTO (Sherwood Scientific) at room temperature. Flame Atomic Absorption Spectrometer (BUCK MODEL SCIENTIFIC 210 VGB) was used to measure the amount of metals ($\mu\text{g/mL}$) in their prepared 5×10^{-4} M solutions. Elemental analysis was done using Exter Analytical CE 440 EA Elemental Analyser.

2.3. SYNTHESIS

Precursors, ligands and their complexes were synthesized following the procedures based on different literatures referred so far and through slight modifications. Quinoxaline-2,3-dione was synthesized from the condensation of 1,2-phenylenediamine with oxalic acid dihydrate. The prepared ligand was then converted to 2,3-dichloroquinoxaline by treating it

with phosphorus pentachloride, PCl_5 , as well as with the thionyl chloride, SOCl_2 . 2,3-dichloroquinoxaline was then converted into two ligands 2,3-quinoxalinedioxime and 2,3-quinoxaline-bis-[N-(aminoformimidoyl)phenol]. Formation of QXAP was not successful as NMR confirmed it so that only complexes of QXDO were prepared and analyzed. Divalent transition metal chlorides of nickel and copper were used for complexation.

2.3.1. PREPARATION OF LIGANDS

In recent years polyfunctional quinoxalines have been prepared and studied because of their interesting biological activities and DNA interactive behavior. Various derivatives of quinoxaline possess a wide spectrum of biological activity, including antimicrotubule, antitumor, anti-tubercular, antifungal, anticancer and antiviral activity, including AIDS [51]. Also some others are important as agrochemicals, herbicides, antimicrobial and amebicides and hence it is of immense importance to synthesize fused hetrocyclic rings with quinoxaline moiety [52]. Therefore, their synthesis from appropriate sources and study of the properties and applications is something attracting attention.

2.3.1.1. Preparation of 2,3-Quinoxalinedione (QxD)

The standard method of quinoxaline synthesis uses the interaction of o-phenylenediamine with an α -diketone; a 2,3-disubstituted quinoxaline is formed [5, 53]. In this experiment, the procedure for the synthesis of 2,3-quinoxalinedione was adapted from that of A.P. Komin and M. Carmack [54]. A solution of oxalic acid dihydrate (0.1mol, 12.6067 g) in 34 mL of water was heated to 95°C in a 500 mL Erlenmeyer flask. Concentrated hydrochloric acid, 37% HCl, (17 mL) was added followed by o-phenylenediamine (0.1mol, 11.0351g based on 98% Aldrich material). The mixture was refluxed for 15 minutes with continuous stirring. The mixture was cooled by the addition of ice (ca. 50g) and the silvery white solid was collected by filtration, washed with water, and dried at 50°C to give 11.87g (73.20%) of 2,3-quinoxalinedione. The product was then dissolved in 1N sodium hydroxide at room temperature. For complete dissolution stirring for about half an hour was required. The clear filtrate was acidified with 5N hydrochloric acid and the bulky white precipitate was filtered, washed well with water then methanol, and dried, and was found not to melt up to 350°C .

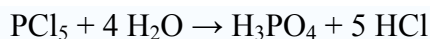
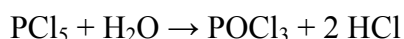
2.3.1.2. Preparation of 2,3-Dichloroquinoxaline

Method I

The replacement of halides with other ligands is a fundamental synthetic step so in many cases it will be necessary to prepare a suitable starting halide using a halogenating reagent. In this case imidoyl chlorides (PCl₅ method) [55] was employed. 2,3-quinoxalinedione (0.01mol, 1.6215g) and PCl₅ (0.02mol, 4.1653g) were refluxed in chloroform (30mL) at 90°C for 3h in a round-bottomed quickfit flask attached to a reflux condenser that was equipped with a drying tube filled with calcium chloride. Water bath and magnetic stirrer with hot plate were used for refluxing.

After the solution was cooled to room temperature, triethylamine, (C₂H₅)₃N, (0.02mol, 2.8 mL) was added carefully using a syringe and the mixture was stirred with a bar stirrer for 1 h. POCl₃ and the solvent (i.e., chloroform) were removed under vacuum using rotavapor and diethyl ether was added. After 3 h, solids were removed by filtration and the solution evaporated.

Caution: PCl₅ is highly air sensitive and it was carefully weighed under anhydrous condition. PCl₅ reacts with moisture (cold water) to give POCl₃ and in hot water, it is hydrolyzed all the way to ortho-phosphoric acid as follows.



Caution: Triethylamine is highly irritating. Exposure to it is believed to cause skin, eyes, nose, throat and respiratory tract irritation. Acute exposure to triethylamine vapors might cause corneal swelling on halo vision. Therefore about 1.1mL of triethylamine was taken using syringe from the bottle kept in hood and was transferred to the cold solution.

Method II

The procedure was adapted from that of A.P. Komin and M. Carmack [54] and literature [56]. To a solution of 2,3-quinoxalinedione (0.05mole, 8.1075g) in dioxane (20 mL) and catalytic amount of DMF (5 mL), thionyl chloride, SOCl₂, (25 mL) was added. The reaction mixture was refluxed with continuous stirring in a hood for 4h until the solid had

completely dissolved. Vacuum rotavapor was used to remove solvents under reduced pressure. The solid obtained was triturated with ice water, filtered, washed with water, and dried to afford yellowish green crystals of 2,3-dichloroquinoxaline in 76% yield. Mp 152-153°C.

2.3.1.3. Preparation of 2,3-Quinoxalinedioxime (L' = QXDO)

The two reactive chlorine atoms in 2,3-dichloroquinoxaline are prone to nucleophilic displacement reactions by a wide variety of nucleophiles [5, 57]; for example its reaction with amines leads to 2,3-disubstituted quinoxalines. Therefore 2,3-dichloroquinoxalines are suitable precursors for the generation of 2,3-quinoxalinedioximes.

For the preparation of a new ligand, 2,3-quinoxalinedioxime, the method was adapted from the literature [58]. To a solution of 2,3-dichloroquinoxaline (45 mmol, 8.96g) in a mixture of dimethyl sulfoxide (6mL) and ethanol (24 mL) were added hydroxylamine hydrochloride, $\text{NH}_2\text{OH} \cdot \text{HCl}$, (90mmol, slightly excess) and anhydrous sodium carbonate (12.5 mmol, 1.32g). The reaction mixture was stirred at room temperature for 36h and then heated under reflux for 1h. After allowing the reaction mixture to cool to room temperature, it was poured into cooled water (100 mL). The insoluble material was filtered off and washed with water. The product was recrystallized from ethanol. Yield 68%, doesn't melt up to 270 °C.

2.3.1.4. Preparation of N-(aminoforimidoyl)phenol (AP)

N-(aminoforimidoyl)phenol, was prepared by the reaction of salicylaldehyde with hydrazine 82%. The method was adapted from the literature [59]. An ethanolic solution of salicylaldehyde (0.1 mole, 10.5 mL) was added drop wise from a separatory funnel, at room temperature and with stirring over 1h to hydrazine hydrate, $\text{H}_2\text{NNH}_2 \cdot 2\frac{1}{2} \text{H}_2\text{O}$, (82%) (0.5mole, 25 mL) in a 250 mL Erlenmeyer flask. After the addition was complete, the mixture was stirred for 10min, and upon cooling in ice, a whitish solid appeared, which was collected by filtration, washed with diethyl ether and dried in vacuo. Yield 8.32g or 61% (79.8% reported). Mp 96-98°C.

2.3.1.5. Preparation of Quinoxaline-2,3-bis- N-(aminoformimidoyl) phenol (L" =QXAP)

To a suspension of 2,3-dichloroquinoxaline (25mmol, 4.9761g) in ethanol (25 mL) was added N-(aminoformimidoyl)phenol (50mmol, 6.80g) in ethanol(25 mL) portion wise over a period of 15min with constant stirring at about 60^oC [60]. After complete addition, the reaction mixture was further refluxed for 3h. After cooling, a red precipitate formed was separated by filtration, dried and recrystallized from ethyl ether to yield 8.27g (83%), MP. 129-132^oC.

2.3.2. PREPARATION OF COMPLEXES

Coordination compounds, with bonds between a central metal atom and surrounding ligands, play critical roles in biology, biochemistry and medicine, controlling the structure and function of many enzymes and their metabolism. They play similarly vital roles in many industrial processes and in the development of new materials with specifically designed properties. Different heterocyclic compounds including monocyclic and fused ring systems have been known, are being synthesized, complexed with metals and their applications are studied. Complexation with metals is mainly due to the presence of donor atoms [61-62].

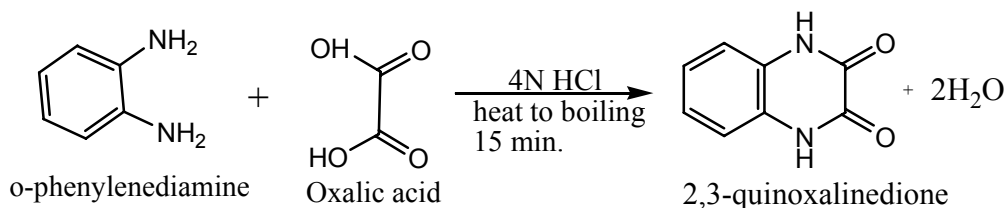
The preparation of QXDO complexes with Ni(II) and Cu(II), a typical procedure involved drop wise addition of an ethanolic solution of the ligand (8,5mmol, 1.634g, slightly greater) in 15mL of 95% ethanol with stirring to a hot solution of the metal chlorides (4.25mmol) in 25mL water. Heating was continued for about 8h. After cooling, the resulting solid product was filtered under suction, washed with aqueous ethanol (1:1, 20 mL), dried in air and stored in a desiccator [63].

CHAPTER THREE: RESULTS AND DISCUSSION

Synthesis, characterization, interpretation and structural elucidation are the core steps that enable a chemist to acquire adequate knowledge of chemistry laboratory practical work. Carrying out a reaction is often the easiest part of a synthetic work. Much more effort is usually involved in the work up, i.e. the separation and purification of various products and in the subsequent characterization of compounds obtained [64].

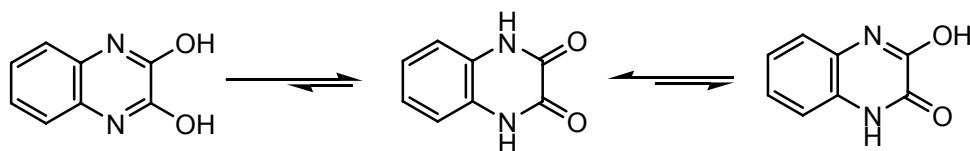
3.1. PREPARATION OF LIGANDS

Schiff bases of *o*-phenylenediamine and its complexes have a variety of applications including biological, clinical and analytical. Earlier work has shown that some drugs showed increased activity when administered as metal chelates rather than as organic compounds, and that the coordinating possibility of *o*-phenylenediamine has been improved by condensing with a variety of carbonyl compounds [65]. For example the equation for the reaction of *o*-phenylenediamine with oxalic acid dihydrate to form 2,3-quinoxalinedione, can be written as:



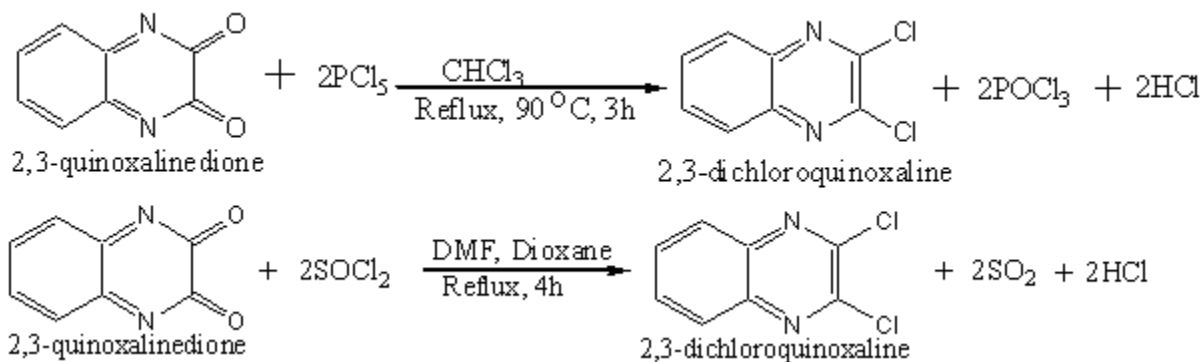
Scheme 22: Synthesis of 2,3-quinoxalinedione

The dione may exhibit tautomeric forms; physical measurements have confirmed the predominance of the cyclic amide over the hydroxy-tautomer [5].



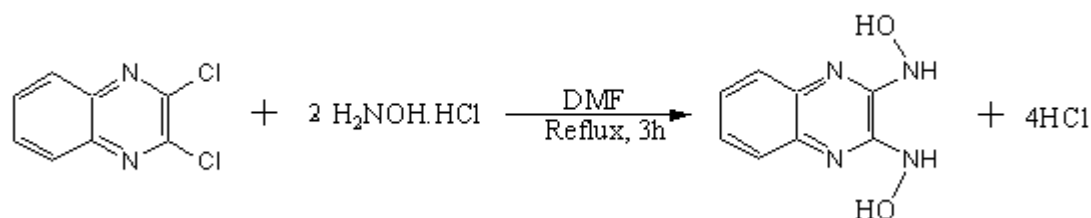
Scheme 23: Tautomeric forms QXD

The reactions for the conversion of dione in to dichloroquinoxaline were:



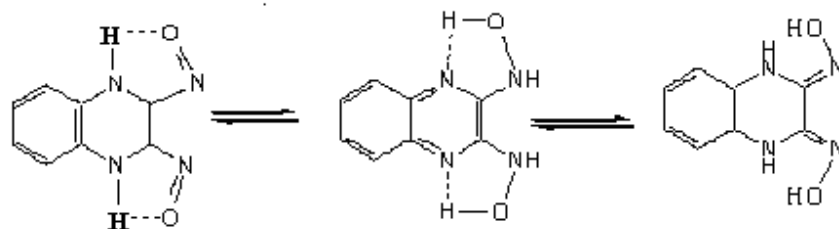
Scheme 24: Synthesis of 2,3-dichloroquinoxaline

Dichloroquinoxaline was converted into 2,3-quinoxalinedioxime by reacting with hydroxylamine hydrochloride as it is shown below.



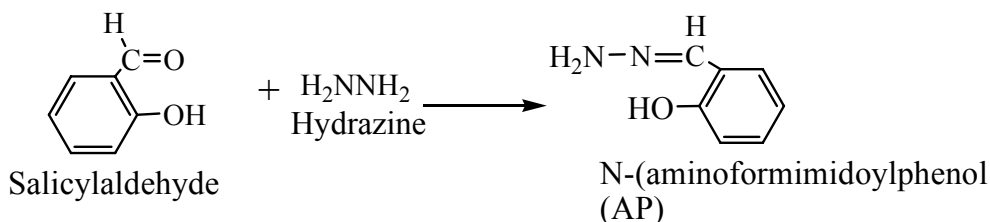
Scheme 25: Synthesis of 2,3-quinoxalinedioxime

2,3-quinoxalinedioxime may exhibit tautomeric forms:

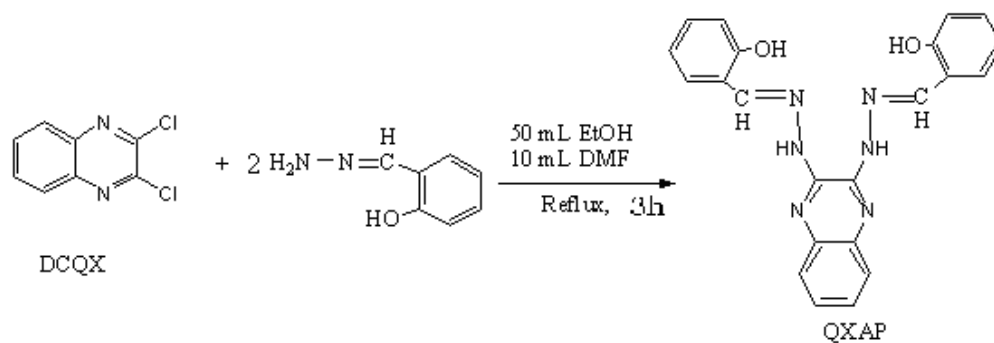


Scheme 26: Tautomeric forms of QXDO

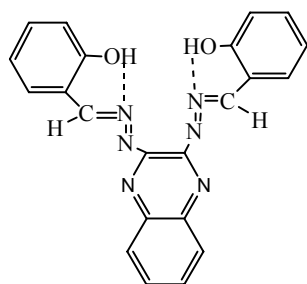
N-(aminoformimidoyl)phenol, was prepared by the reaction of salicylaldehyde with hydrazine and then converted into the second ligand, quinoxaline-2,3-bis-[N-(aminoformimidoyl) phenol], as it is already described in the experimental part.



Scheme 27: Synthesis of N-(aminoformimidoyl)phenol

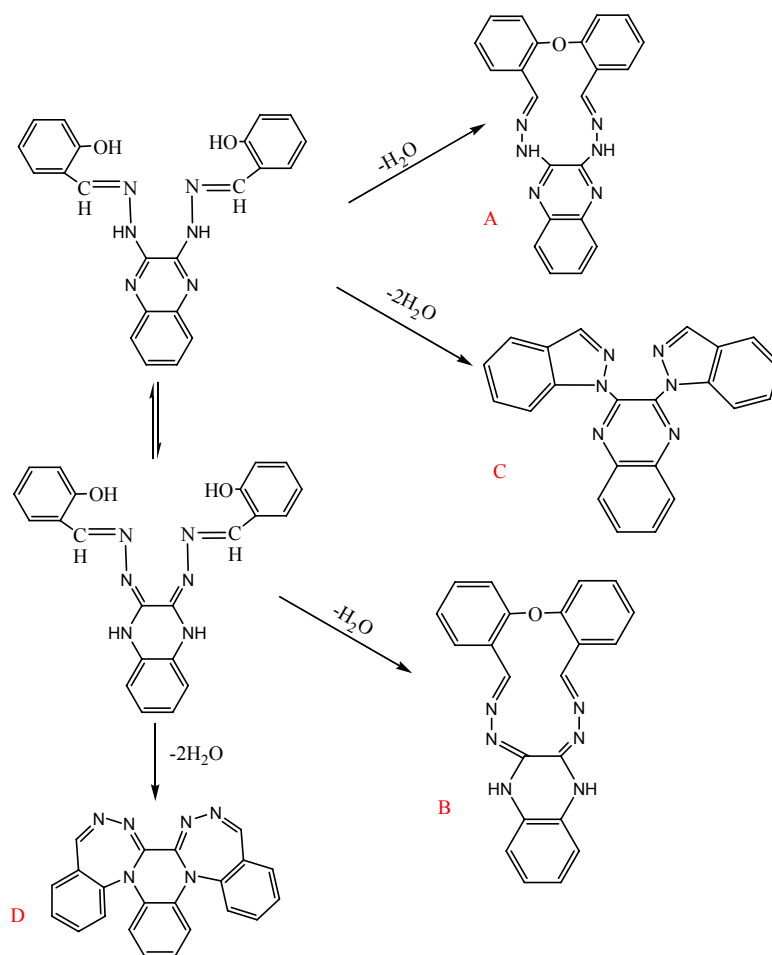


Scheme 28: Synthesis of quinoxaline-2,3-bis-[N-(aminoformimidoyl)phenol] (QXAP)



Scheme 29: Hydrogen bonding pattern in QXAP

It is better to elucidate structure of a new compound based on the experimental evidence or observation (eg IR, NMR etc) than predicting it based on the proposed reaction mechanism. The mechanism may or may not exact route or the predicted product may or may not be the only final product predicted. Some possibilities for the reaction between 2,3-dichloroquinoxaline and N- (aminoformimidoyl) phenol are shown below.



Scheme 30: Possible alternative products that may be formed during the synthesis of QXAP

3.2. SOLUBILITY OF LIGANDS AND COMPLEXES IN DIFFERENT SOLVENTS

The experimentally observed solubility results of different synthesized substances are summarized in table 1.

Table 1: Solubility of 2,3-quinoxalinedione (QXD), 2,3-dichloroquinoxaline (DCQX), 2,3-quinoxalinedioxime (QXDO), quinoxaline-2,3-bis-N-(aminoformimidoyl)phenol (QXAP) and metal complexes

Solvent	ϵ	QXD	DCQX	QXDO	QXAP	Ni(QXDO) ₂	Cu(QXDO) ₂
Water	80.4	Ins	Ins	Ins	Ins		
DMF	36.7	Ins	Sol	Sol	Sol	Sol	Sol
Acetonitrile	36.2	Sol	Sp	--	--	--	--
Nitrobenzene	34.8	Ins	Sol	--	--	--	--
Methanol	32.6	Sp	Sp	Ins	Sol	Ins	Ins
Ethanol	24.3	Sp	Sp	Ins	Sol	Ins	Ins
Acetone	20.7	Sp	Sp	--	--	--	--
<i>DMSO</i>	48	<i>V. Sol</i>	<i>V. Sol</i>	Sol	Sol	Sol	Sol
n-Hexane	2.0	Ins	Ins	--	--	--	--
Petroleum ether		Ins	Ins	--	--	--	--
1N NaOH		Sol	Ins	--	--	--	--
5N HCl		Ins	Ins	--	--	--	--
1,4-Dioxane	2.2	Sp	V. Sol				
Chloroform	4.8	Sp	Sol	Ins	Sol		
Carbon tetrachloride	2.2	Sp	Sol	--	--	--	--
Benzene	2.3	Sp	V. Sol	--	--	--	--

Key: ϵ = dielectric constant Sp = sparingly soluble Sol = Soluble Ins = Insoluble
 V. Sol = very soluble -- = not checked

3.3. CHLORIDE ESTIMATION IN THE COMPLEXES

Samples of the two complexes were well digested in concentrated nitric acid through refluxing. When 0.1M solution of silver nitrate was added to the cooled acid solutions and left for overnight, there was no formation of any precipitate in each solution. This suggests that chlorine is neither coordinated nor occur as counter anion in the complexes. This observation leads to the conclusion that the complexes do not contain any chlorine in their structures.

3.4. DETERMINATION OF MOLAR CONDUCTIVITY

The complexes were dissolved in DMF and the molar conductivities of 10^{-3} M of their solutions at 22 °C were measured. The values were in range 2-20 $\Omega^{-1}\text{cm}^2\text{mole}^{-1}$. These values are lower than those expected for an electrolyte. These observations indicate that the complexes are non-electrolytes in DMF (10^{-3}M) at room temperature [66-67]. The measured values are given in table 8.

*Note that the SI unit of resistance is the ohm (Ω). The SI unit of conductance is siemens (S) or Ω^{-1} and conductivity is the inverse of the resistivity. $\kappa = 1/\rho = L/RA$.

3.5. QUANTITATIVE DETERMINATION OF METAL CONTENT OF COMPLEXES BY ATOMIC ABSORPTION SPECTROSCOPY (AAS) AND GRAVIMETRIC METHODS

Atomic absorption spectrometry (AAS) is an analytical technique that measures the concentrations of elements. It is commonly used for determining the concentration of a particular metal element within a sample. AAS can be used to analyse the concentration of over 62 different metals in a solution [68]. AAS determines the presence of metals in liquid samples. Metals include Fe, Cu, Al, Pb, Ca, Zn, Cd and many more. Atomic absorption is so sensitive that it can measure down to parts per billion of a gram (g dm^{-3}) in a sample. Typical concentrations range in the low mg/L range.

In their elemental form, metals will absorb ultraviolet light when they are excited by heat. Each metal has a characteristic wavelength that will be absorbed. The AAS instrument looks for a particular metal by focusing a beam of UV light at a specific wavelength through a flame and into a detector. The sample of interest is aspirated into the flame. If that metal is present in the sample, it will absorb some of the light, thus reducing its intensity. The

instrument measures the change in intensity. A computer data system converts the change in intensity into an absorbance [69]. For instance, absorbances of cobalt and copper were analyzed at wavelengths 240.7nm and 324.7nm respectively. 25mL of 5×10^{-4} M solutions of copper and cobalt complexes were analyzed by AAS. In all cases standard concentration was 2ppm. Standard absorbances were for copper complex 0.092898 and for cobalt complex 0.049851. Masses of complexes taken to prepare 5×10^{-4} M of 25mL of solution were:

$$\text{Cu}(\text{QXDO})_2 \text{ 445.88): } 5 \times 10^{-4} \text{M} = (x/445.88 \text{g/mol})/0.025 \text{L}, x = 5.574 \times 10^{-3} \text{g}$$

$$\text{Element } (\mu\text{g/mL}) = \frac{(\text{Sample Absorbance})(\text{Standard concentration in } \mu\text{g/mL})}{\text{Standard absorbance}}$$

Copper in CuQXAP (447.9):

$$\text{Amount of copper, Cu}(\mu\text{g/mL}) = (1.9118 \times 2 \text{ppm})/0.092898 = 41.16$$

$$\text{Amount of copper in 1mL} = 41.16 \mu\text{g} = 4.116 \times 10^{-5} \text{g};$$

$$\text{then in 25mL} = 25 \times 4.116 \times 10^{-5} \text{g} = 1.029 \times 10^{-3} \text{g}$$

$$\text{Percent of copper is then } (1.029 \times 10^{-3} \text{g}/5.574 \times 10^{-3} \text{g}) \times 100 = 18.46\% \text{ (expected 14.25\%)}$$

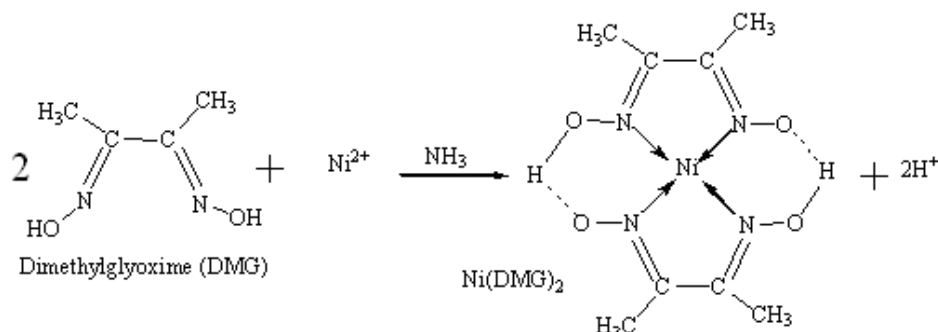
Table 2: AAS data of copper complex

Element	$\lambda_{\text{absorbance}}$ (nm)	Complex (MW, Estimated)	Concentration (M)	Sample Absorbance	Element ($\mu\text{g/mL}$)	%of metal
Copper	324.7nm	Cu(QXDO) ₂ , 459.95 CuC ₂₂ H ₁₆ N ₆ O ₂	5×10^{-4} M	1.9118	41.16	18.46 (14.25)

As it can be seen from the above table the experimental value deviates from the theoretical expectations. Different causes of errors could be personal error that may occur during weighing the sample, incomplete reaction, lack of exact preparation procedures, presence of impurity etc and the synthesis was not done repeatedly.

There was no nickel lamp for the analysis of nickel metal by AAS. Thus amount of nickel in the Ni(QXDO)₂ complex was determined by the gravimetric method following procedures adapted from [70] and [71].

- I). **Sample Dissolution:** To the weighed 0.60g of Ni(QXDO)₂ sample in a 250mL Erlenmeyer flask provided with condenser and stirring rod, 10mL conc. HNO₃ and 5 mL of HC were added. The sample was digested (heated) for an hour on a hot plate with constant stirring. The sample was then quantitatively transferred to 400mL beaker and diluted to 200mL with distilled water. 60 mL of 20% tartaric acid solution was added. Then the solution was heated to nearly boiling and ammonium hydroxide was slowly added until the solution became alkaline.
- II). **Precipitation:** 30mL of dimethylglyoxime in 2-propanol was added drop wise to the sample with constant stirring until precipitation took place. Red precipitate was settled out. The precipitate was filtered, washed with distilled water and dried at 50^oC. The precipitate was weighed to be 0.43g.
- III). **Discussion:** Addition of an alcoholic solution of dimethylglyoxime, C₄H₆(NOH)₂, to an ammoniacal solution of Ni(II) gave a rose-red precipitate, abbreviated Ni(DMG)₂. The formation of the red chelate occurred quantitatively in a solution in which the pH was made basic by the addition of ammonium hydroxide. The chelation reaction that occurs is illustrated below.



Scheme 31: The chelation reaction between Ni²⁺ and DMG to form zinc dimethylglyoximate

Although the loss of one proton occurs from one oxime group (NOH) on each of the two molecules of dimethylglyoxime, the chelation reaction occurs due to donation of the electron pairs on the four nitrogen atoms, not by electrons on the oxygen atoms.

Next let us calculate the percentage composition of nickel in the complex Ni(QXDO)₂.

Weight of sample = 0.60g, Weight of precipitate formed = 0.43g,

From the above balanced equation it is clear that one mole of Ni^{2+} combines with two moles of DMG to form one mole of $\text{Ni}(\text{DMG})_2$ (MW = 288.94). Thus on the basis of this formulation we can say that one mole of $\text{Ni}(\text{QXDO})_2$ (MW = 443.07) gives one mole of $\text{Ni}(\text{DMG})_2$. One mole of each contains one mole of nickel (At.wt = 58.71)

288.94g of $\text{Ni}(\text{DMG})_2$ contains 58.71g of nickel. Then

0.43g of $\text{Ni}(\text{DMG})_2$ contains $[(0.43 \times 58.71) / 288.94]$ g or 0.0874g of nickel.

Percentage of nickel in the complex is thus $(0.0874\text{g}/0.60\text{g}) \times 100 = 14.57\%$. This is experimental value. The theoretical value which closes to the true value can be calculated from the formula of the complex; i.e., $(58.71/443.07) \times 100 = 13.25\%$. The experimental value is higher than the theoretically expected one. The causes of error include lack of accuracy in weighing, presence of impurities and so on.

Table 3: Analytical and some physical properties of the ligands and complexes

Compound Formula, M.W.	mp ($^{\circ}\text{C}$) Yield (%)	Color & state	Calculated (found,%)					
			C	H	N	O	Cl	M
2,3-Quinoxalinedione $\text{C}_8\text{H}_6\text{N}_2\text{O}_2$, 162.1492	>370 $^{\circ}\text{C}$, 80	White solid	59.26	3.73	17.28	19.73	---	---
2,3-Dichloroquinoxaline $\text{C}_8\text{H}_4\text{N}_2\text{Cl}_2$, 199.0405	152-154 76	Yellowish green crystalline solid	48.28	2.03	14.07	---	35.62	---
2,3-Quinoxalinedioxime $\text{C}_8\text{H}_8\text{N}_4\text{O}_2$, 192.1786	>270 72	Orange yellow solid	50.00 (50.22)	4.20 (4.4)	29.15 (15.80)	16.65	---	---
N-(aminoformimidoyl) Phenol, $\text{C}_7\text{H}_8\text{N}_2\text{O}$, 136.1543	96-98 61	White fine powder	61.75	5.92	20.57	11.75	---	---
2,3-Quinoxalinebis-N- (aminoformimidoyl)phenol, $\text{C}_{22}\text{H}_{18}\text{N}_6\text{O}_2$, 398.4278	129-132 83	Orange red solid	66.32	4.55	21.09	8.03	---	---
$\text{Ni}(\text{QXDO})_2$, 441.05 $\text{Ni}(\text{C}_8\text{H}_7\text{N}_4\text{O}_2)_2$	>270 68	Yellow crystalline solid	43.57	3.20	25.40	14.51	---	13.31
$\text{Cu}(\text{QXDO})_2$, 445.88 $\text{Cu}(\text{C}_8\text{H}_7\text{N}_4\text{O}_2)_2$	71	Grey	43.10	3.16	25.13	14.35	---	14.25

3.6. MAGNETIC SUSCEPTIBILITY (χ_m)

When a substance is placed in an external magnetic field, the substance will produce its own magnetic field. If the substance is paramagnetic, this field adds to the applied field. If the substance is diamagnetic, this field subtracts from the main field. This contribution to the external magnetic field is known as the magnetic susceptibility (χ_m) of the substance. χ_m is positive for the paramagnetic material ($\chi_m > 0$), and the magnetic field is strengthened by the presence of the material and it is negative for the diamagnetic material ($\chi_m < 0$), and the magnetic field is weakened in the presence of the material. The magnetic susceptibilities of paramagnetic and diamagnetic materials are generally extremely small.

The experimentally obtained gram magnetic susceptibility (χ_g), calculated magnetic moment and nature of complexes are summarized in table 4.

Table 4: Magnetic moments of complexes

Complex	MW	χ_g $\times 10^{-6}$	$\chi_m = \chi_g M$	$\mu = 2.824[T \chi_m]^{1/2}$	Nature of the complex
Ni(QXDO) ₂	441.05	-0.437	-Ve	-----	Diamagnetic

A square planar geometry is particularly favorable for d^8 metals with π -acceptor ligands. In the case of Ni(QXDO)₂ complex, the experimentally measured gram magnetic susceptibility has a negative value indicating that the complex is diamagnetic and hence has a square planar geometry.

3.7. IR (FTIR) SPECTRA

Infrared (IR) radiation is electromagnetic radiation of a wavelength longer than that of visible light (400 to 800nm), but shorter than that of micro waves (longer than 1mm). The name means "below red" (from the latin *infra*, "below"), red being the color of visible light of longest wavelength. IR covers 12500 to 50 cm^{-1} in the electromagnetic spectrum. The IR region is divided in to three as near IR (12500-4000 cm^{-1}), middle IR (4000-400 cm^{-1}) and far IR (400- 50 cm^{-1}). Of these, middle IR is useful because almost all compounds having covalent

bonds whether organic or inorganic absorb various frequencies of electromagnetic radiation in the infrared region of electromagnetic spectrum and hence are studied in this region.

As with other types of energy absorption, molecules are excited to a higher energy state when they absorb IR radiation. A molecule absorbs only selected frequencies (energies) of infrared radiation. The absorption of IR corresponds to energy changes on the order of 8 to 40 kJ/mole. Radiation energies associated with this part are not large enough to excite electrons, but corresponds to the range encompassing the stretching and bending vibrational frequencies of the bonds in most covalent molecules.

As a general rule, the most important factors determining where a chemical bond will absorb are the bond order and the type of atoms joined by the bond. For the general trends in IR absorption, refer to appendix 3.

IR spectra may be obtained from samples in all phases (liquid, solid or gaseous). Liquids are usually examined as a thin film sandwiched between two polished salt plates (note that glass absorbs IR, whereas NaCl is transparent). If solvents are used to dissolve solids, care must be taken to avoid obscuring important spectral regions by solvent absorption. Perchlorated solvents such as carbon tetrachloride, chloroform, and tetrachloroethene are commonly used. Alternatively solids may be incorporated in a thin KBr disk, prepared under high pressure, or mixed with a little non-volatile liquid and ground to a paste (or a mull) that is smeared between salt plates.

The IR spectroscopy can provide valuable information as to whether or not reaction has occurred. The disappearance of certain absorption bands and the appearance of new bands seen in the spectra suggest that the product has been formed [72-74]. IR spectra of the starting material o-phenylenediamine shows strong bands at 3386 and 3364 cm^{-1} assigned to NH_2 asymmetric and symmetric stretching vibrations respectively. NH_2 bending vibrations occur at 1634 and 1592 cm^{-1} . 2,3-quinoxalinedione is the one prepared from o-phenylenediamine. Its IR spectra (fig 10) shows bands at 3448 (NH/OH), 3049 (aromatic sp^2 C-H stretch), 1682 (C=O stretch) and 1615 & 1458 cm^{-1} (aromatic C=C stretch). Note that 2,3-quinoxalinedione exhibits tautomeric forms (scheme 22) so that weak broad band at 3448 cm^{-1} is due to both N-H and O-H stretchings. The IR spectra of 2,3-dichloroquinoxaline (fig11) reveals the disappearance of C=O band (1682 cm^{-1}) which was initially observed in the parent compound. Besides several new bands in the 2,3-dichloroquinoxaline a band of weak intensity at 1654 cm^{-1}

¹ may be assigned to the $\nu(\text{C}=\text{N})$ vibration and appearance of the strong band at 768 cm^{-1} may be attributable to C-Cl stretching.

Table 5: Fundamental IR bands of the ligands and their complexes

Compound	$\nu(\text{OH})$	$\nu(\text{NH})$	$\nu(\text{NH}_2)$	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}=\text{C})$	$\nu(\text{C}-\text{Cl})$	$\nu(\text{N}-\text{O})$	$\nu(\text{M}-\text{O})$	$\nu(\text{M}-\text{N})$
PDA	----	-----	3364 3389	----	----	1636 1458	----	---	---	---
QXD	----	3448	----	1682	1615	----	---	---	---	---
DCQX	----	----	----	----	1654	----	768(s)	---	---	---
QXDO	3416	3416	----	----	1684(s)	----	---	1381	---	---
AP			3385(asy) 3290 (sy)							
QXAP	3446	3446	----	----	1623.95	1488	---	---	---	---
Ni(QXDO) ₂					1682	1473		1392	582	466
Cu (QXDO) ₂					1683				537(w)	504(w)

The ligand 2,3-quinoxalinedioxime was prepared from 2,3-dichloroquinoxaline. Strong new band appeared at 1684cm^{-1} is due to the C=N band as it can be referenced from simplified correlation IR chart given (appendix 3). The metal ligand bands are not seen for except Cu(QXDO)₂ at 537(w) and 504(w) which are attributable to Cu-O and Cu-N stretchings respectively. The reason may be that the bands may appear below 400cm^{-1} or overlap on bands of the ligands in the expected region.

3.8. NMR SPECTRA

Nuclear magnetic resonance (NMR) is an absorption spectroscopy involving the absorption of radio frequency EM waves. The energy associated with a photon in the radio frequencies is extremely small compared to IR frequencies. NMR involves changes in the *spin state* of the nucleus of an atom.

Not all nuclei display spin. In order to display spin, a nucleus must have an odd number of protons or neutrons. Hydrogen has one proton, so displays spin (¹H or proton NMR). Deuterium has one proton and one neutron and also displays spin. Other atoms that display spin are isotopes of common elements (deuterium is an isotope of hydrogen). The most common are ¹³C, ¹⁹F, ¹⁵N and ²⁹Si. An atom with spin has a non-zero *spin quantum number*, I.

For most nuclei of interest the spin quantum number is $\frac{1}{2}$. Deuterium and Nitrogen 15 have spin quantum numbers of 1. The number of spin states possible for a nucleus is given by $2I+1$.

The nucleus can be thought of as a magnet, and in the absence of a magnetic field these tiny magnets are randomly arranged in a sample with no preferred direction for the magnetic moment vectors. Application of a radiofrequency EM wave to such a sample has no effect, i.e. there is no absorption. There is not absorption because the system can no tell the difference between magnetic vectors pointing up or down or any other direction since these directions have not reference base. This is analogous to a guitar string which is not constrained or two atoms which are not bonded in IR. In the absence of constraints there is no perceptible absorption.

If a strong magnetic field is applied to the nuclei, they can tell the difference between alignment in the direction of the applied magnetic field and opposed to the applied magnetic field. In NMR the constraint which leads to quantized transitions is applied by the spectrometer. Because of this the frequency of absorption varies with the applied magnetic field and there is no absolute frequency or wavelength for a given absorption. NMR spectra are not plotted as absorption versus wave number as IR spectra are, they are plotted as absorption versus chemical shift, δ . The chemical shift for proton NMR is the difference between the frequency of absorption of the sample and a standard, tetramethylsilane (TMS) normalized by the frequency of absorption of TMS,

$$\delta = \frac{\nu_{Sample} - \nu_{TMS}}{\nu_{TMS}} \times 10^6$$

δ is expressed in parts per million (ppm) so the above equation is multiplied by 10^6 .

The strength of an IR absorption band depends on the change in dipole moment for the bond on vibration, i.e. how polar a bond is. The strength of a NMR absorption band depends on the magnitude of the magnetogyric ration, g , i.e. how large the magnetic dipole moment is. The absorption in IR is also proportional to the concentration of the absorbing bond. NMR depends on the presence of specific isotopes. In considering the strength of a NMR absorption band we consider the "natural abundance" of these isotopes. For example, 99.98 percent of hydrogen atoms are ^1H , and 0.0156 percent are deuterium, ^2H . The magnetogyric ratio for hydrogen is 26,700 while for deuterium is 4,100. This means that proton NMR (^1H)

results in 100 times the signal as deuterium if a sample contains natural abundance hydrogen. A similar comparison shows that proton NMR absorption is about 50 times stronger than ^{13}C NMR (natural abundance of ^{13}C is about 1%). An NMR absorption peak for a given nucleus is directly proportional to the number of these atoms in a sample.

In the ^1H NMR spectra the **number of signals** indicates the number of different types of protons and the **integration** specifies the ratios of number of protons. These can help in indicating molecular formula. **Chemical shifts** indicate the types of protons and functional groups present.

Numbers to know (All +1):	1ppm	Aliphatic protons
	2ppm	Alyllic protons
	3ppm	Aliphatic protons with one hetroatom attached protons
	6ppm	Alkene protons
	7ppm	Aromatic protons
	10ppm	Aldehyde protons
	12ppm	Acid

Most NMR spectra are recorded for compounds dissolved in a solvent. Therefore, signals will be observed for the solvent and this must be accounted for in solving spectral problems. *To avoid spectra dominated by the solvent signal, most ^1H NMR spectra are recorded in a deuterated solvent.* However, **deuteration is not 100%, so signals for the residual protons are observed.** In chloroform solvent (CDCl_3), this corresponds to CHCl_3 , so a singlet signal is observed at 7.26 ppm. For methanol solvent, this corresponds to CHD_2OD , so a 1:2:3:2:1 pentet signal is observed at 3.31 ppm. (Recall that deuterium has a spin quantum number (I) of 1, so n deuterium atoms will split a proton signal into $2In+1$ lines.) The same solvents are used for ^{13}C NMR spectra, so the same rules also apply here about splitting patterns.

It used to be common practice to add Me_4Si , or related compounds, as an internal reference standard for ^1H and ^{13}C NMR spectra with the proton signal occurring at 0.0 ppm and the carbon signal occurring at 0.0 ppm in the ^{13}C NMR spectrum. However, modern spectrometers can lock on solvent signals, so addition of internal reference standards is not usually required.

The chemical shifts of solvent signals observed for ^1H NMR and ^{13}C NMR spectra are listed in the following table. The multiplicity is shown in parentheses as 1 for singlet, 2 for doublet, 3 for triplet, etc.

Table 6: The chemical shifts of solvent signals observed for ^1H NMR and ^{13}C NMR spectra

Solvent	^1H NMR Chemical Shift	^{13}C NMR Chemical Shift
Acetic Acid	11.65 (1), 2.04 (5)	179.0 (1), 20.0 (7)
Acetone	2.05 (5)	206.7 (13), 29.9 (7)
Acetonitrile	1.94 (5)	118.7 (1), 1.39 (7)
Benzene	7.16 (1)	128.4 (3)
Chloroform	7.26 (1)	77.2 (3)
Dimethyl Sulfoxide	2.50 (5)	39.5 (7)
Methanol	4.87 (1), 3.31 (5)	49.1 (7)
Methylene Chloride	5.32 (3)	54.00 (5)
Pyridine	8.74 (1), 7.58 (1), 7.22 (1)	150.3 (1), 135.9 (3), 123.9 (5)
Water (D_2O)	4.8	

Where do the NMR water signals appear? Signals for water occur at different frequencies in ^1H NMR spectra depending on the solvent used. Listed below are the chemical shift positions of the water signal in several common solvents. Note that H_2O is seen in aprotic solvents, while HOD is seen in protic solvents due to exchange with the solvent deuteriums.

Table 7: Signals for water in ^1H NMR spectra depending on the solvent used

Solvent	Chemical Shift of H_2O (or HOD)
Acetone	2.8
Acetonitrile	2.1
Benzene	0.4
Chloroform	1.6
Dimethyl Sulfoxide	3.3
Methanol	4.8
Methylene Chloride	1.5
Pyridine	4.9
Water (D_2O)	4.8

^1H NMR spectra of the ligand QXAP sample was recorded in CDCl_3 . The ligand shows doublet of multiplet between 7-7.5 ppm that is due to aromatic protons. It shows a

singlet at about 7.25ppm assigned to $-\text{CH}$ group. ^1H NMR and ^{13}C NMR for QXDO were measured in DMSO. The multiplets in ^1H NMR seen at 7.062 -7.157 ppm are due to the four protons of the aromatic benzene ring. Singlet peak at about 11ppm is due the two protons bonded to oxygen atoms. Non-integrated peak at about 3.5ppm is due to the two protons of hydroxyl group. The singlet at about 2.5ppm is due to protons of the solvent DMSO.

When we come to ^{13}C NMR of QXDO, four types of carbons are being observed. Peak at 155ppm is due to the pyrazine carbons doubly bonded to the exocyclic nitrogen atoms. 126ppm peak is due the benzene ring carbons bonded to the cyclic nitrogen atoms. 123ppm is due to the middle carbons of the benzene ring while the last peak at about 115ppm is due to the ending carbons of the benzene ring. This is also confirmed by the DEPT spectra (fig. 24). The peak at 155 and 126ppm have disappeared because they were due to quaternary carbons. We see peaks at 132 and 115ppm of tertiary carbons.

3.9. UV-VIS (ELECTRONIC) ABSORPTION SPECTRA

The perception of color by the human eye results from the action of electromagnetic radiation with wavelengths occupying the range from about 400 to 780nm on the optical nerve. Simultaneous action of the wavelengths in the entire visible range causes the perception of white, while the narrow bands of radiation, or their combinations, which remain in the spectrum after extraction of some special bands, cause the perception of color. [3]. If a coordination compound absorbs light of one color, we see the complement of that color. For example, the deep blue color of aqueous solution of Cu(II) compound, containing the ion $[\text{Cu}(\text{H}_2\text{O})_6]^{2+}$ as the result of absorption of light 585 - 620 nm. Note that the color absorbed is orange and thus it is a complementary color of blue. In general for many coordination compounds, the electronic absorption spectrum provides a convenient method for determining the magnitude of the effect of ligands on the d-orbitals of the metal and it helps us to study this effect for coordination compounds of any geometry [75].

In the UV-Vis spectroscopy, the transitions that result in the absorption of electromagnetic radiation in this region of spectrum (190nm to 800nm) are **transitions between electronic energy levels**. As a molecule absorbs energy, an electron is promoted from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). The energy differences between electronic levels in most molecules vary from 125 to 650 kJ/mole. The wavelength, λ , is related to this energy difference, ΔE , by the equation:

$$\Delta E = h\nu = hc/\lambda$$

where $h = 6.63 \times 10^{-34} \text{Js}^{-1}$ is Planks constant and ν is the frequency of the light.

If the light of intensity I_0 at a given wavelength passes through a solution containing a species that absorbs light, the light emerges with intensity I ($I < I_0$), then the light absorbed may be described by the Beer-Lambert equation:

$$\text{Log}(I_0/I) = A = \epsilon lc,$$

where A = absorbance, ϵ = molar absorptivity l = path length through solution (cm).

The Uv-Vis spectrum is usually recorded as a plot of absorbance (A) versus wavelength (nm). It is then customary to replot the data with either ϵ or $\log \epsilon$ plotted on the ordinate and wavelength plotted on the abscissa. UV absorbances are generally broad because vibrational and rotational energy levels are superimposed on top of the electronic levels.

The choice of solvent to be used in the ultraviolet spectroscopy is quite important. The first criterion for a good solvent is that it should not absorb ultraviolet radiation in the same region as the substance whose spectrum is being determined. Usually solvents that do not contain conjugated systems are most suitable for this purpose, although they vary as to the shortest wavelength at which they remain transparent to ultraviolet radiation. Table below lists some common ultraviolet spectroscopy solvents and their cutoff points, or minimum regions of transparency. Refer to appendix 2.

A second criterion for a good solvent is its effect on the fine structure of an absorption band. A non-polar solvent is not hydrogen bonded with the solute and the spectrum of the solute closely approximates the spectrum that would be produced in the gaseous phase, where fine structure is often observed. In a polar solvent, the hydrogen bonding forms a solute-solvent complex, and the fine structure may disappear.

A third criterion for a good solvent is its ability to influence the wavelength of UV light that will be absorbed via stabilization of either the ground or the excited state. Polar solvents do not form hydrogen bonds as readily with the excited states of the polar molecules as with their ground states, and these polar solvents increase the energies of electronic transitions in the molecules. Polar solvents shift transitions of the $n \rightarrow \pi^*$ type to shorter wavelengths. On the other hand, in some cases the excited states may form stronger hydrogen bonds than the corresponding ground states. In such a case, a polar solvent shifts absorption to longer

wavelength, since the energy of the electronic transition is decreased. Polar solvents shift $\pi \rightarrow \pi^*$ type to longer wavelengths.

Although the absorption of UV radiation results from the excitation of electrons from ground to excited states, the nuclei that hold the electrons together in bonds play an important role in determining which wavelengths of radiation are absorbed. The nuclei determine the strength with which the electrons are bound and thus influence the energy spacing between ground and excited states. Hence the characteristic energy of a transition and the wavelength of radiation absorbed are properties of a group of atoms rather than of electrons themselves. The group of atoms producing such absorption is called a chromophore.

The spectral data of the compounds in DMF and EtOH (2:1 v/v) solution are presented in table 4. There are two absorption bands, assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, in the electronic spectrum of the ligands. These transitions are also found in the spectra of the complexes, but they are shifted towards lower and higher frequencies, confirming the coordination of the ligands to the metallic ions [76-77]. Charge transfer transitions are generally intense compared with ligand filled transitions, i.e., charge transfer gives rise to intense absorptions whereas 'd-d' bands are much weaker [78-79]. Since the zinc ion has d^{10} configuration, the absorptions at 295, 338, 356 nm could be assigned to a charge transfer transition. However, taking into account the spectrum and the configuration of the zinc(II) ion, a tetrahedral geometry could be assumed for its complex.

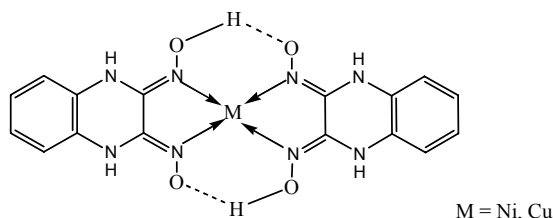
Table 8: Electronic spectral data and magnetic moments of the complexes recorded in DMF/EtOH (2:1 v/v) solution.

Compound	Absorption Bands (λ (nm))	Transition	Assigned coordination	magnetic moment(BM)	Conductivity $\text{Ohm}^{-1}\text{cm}^2\text{mol}^{-1}$
QXDO	294	$\pi \rightarrow \pi^*$	---	---	---
	356	$n \rightarrow \pi^*$			
QXAP	262	$\pi \rightarrow \pi^*$	---	---	---
	310	$n \rightarrow \pi^*$			
Ni(QXDO) ₂	294	LMCT	square planar	diamagnetic	2
Cu (QXDO) ₂	273-381	LMCT	square planar	paramagnetic	14
	480, 576	d-d			

3.10. STRUCTURES OF METAL COMPLEXES

Transition metal complexes of vicinal-dioximes are structurally well-known compounds, in which metal ions coordinate through nitrogen atoms. Generally coordination occurs through deprotonation of two ligands, to give neutral complexes. The most common example of dioxime complexes is the dimethylglyoxime-Ni(II) complex, which is also used for the analytical determination of Ni(II) ions [79-71, 80].

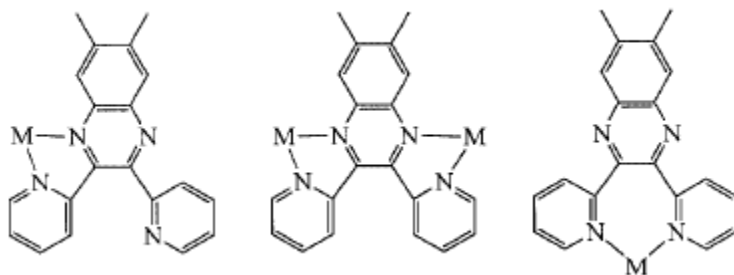
On the basis of the elemental analysis, molar conductivity measurements, magnetic susceptibility values, UV-Vis absorbances, IR spectra etc., it can be suggested that the most probable geometry is square planar for.



Scheme 32: Proposed Structures of metal complexes

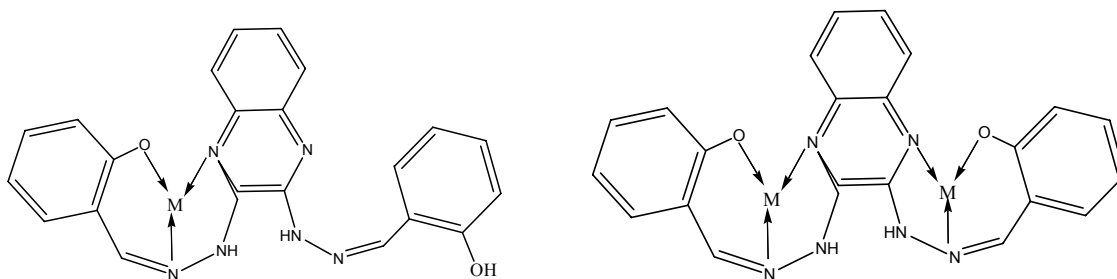
CONCLUSION AND FUTURE WORK

Coordination compounds play a crucial role in biological and other systems. Therefore, the synthesis, characterization and study of their properties is of great importance. In the preparation of complexes with QXAP ligand, 1:1 metal to ligand molar ratio was used. The preparation of the ligand was suffered from side reactions as it was revealed by NMR spectroscopy. It is referred from literatures that by altering molar ratios [81] complexes of different types can be obtained. Thus, for me, the work done in this case is not the final but the starting point of synthesis and analysis of the ligands and their transition metal complexes.



Scheme 33: Common coordination modes adopted by BDPQ and DMeDPQ

On the basis of this literature review the following coordination possibilities can be postulated.



Scheme 34: Alternative coordination modes by QXAP

In the recent years quinoxaline derivatives are getting promissive applications for the treatment of diseases like AIDS and in other areas like insecticides, purification of water, organic light emitting diodes and so on. Therefore, as far as the availability of starting materials and simplified synthetic methods are concerned, further studies and work are of immense importance for their synthesis and diverse applications.

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APPENDICES

Appendix 1: Expected molar conductance (Λ_M) ranges for 2, 3, 4, and 5 ion electrolytes

Expected molar conductance (Λ_M) ranges for 2, 3, 4, and 5 ion electrolytes

Solvent	Dielectric constant	1:1	2:1	3:1	4:1
Water	78.4	118-131	235-273	408-435	≈ 560
Nitromethane	35.9	75-95	150-180	220-260	290-330
Nitrobenzene	34.8	20-30	50-60	70-82	90-100
Acetone	20.7	100-140	160-200	----	----
Acetonitrile	36.2	120-160	220-300	340-420	----
N,N-dimethylformamide (DMF)	36.7	65-90	130-170	200-240	----
Methanol	32.6	80-115	160-220	----	----
Ethanol	24.3	35-40	70-90	----	----

Appendix 2: Solvent cutoffs

Acetonitrile	190 nm	n-hexane	201 nm
Chloroform	240	Methanol	205
Cyclohexane	195	Isooctane	195
1,4-Dioxane	215	Water	190
95% Ethanol	205		

Appendix 3: Simplified correlation IR chart

Types of vibration		Frequency (cm ⁻¹)	Intensity	
C-H	Alkanes (Stretch)	3000-2850	s	
	-CH ₃ (bend)	1450 and 1375	m	
	-CH ₂ (bend)	1465	m	
	Alkenes (stretch)		3100-3000	m
		(out-of-plane bend)	1000-650	s
	Aromatics (stretch)		3150-3050	s
		(out-of-plane bend)	900-690	s
	Alkyne (stretch)	ca. 3000	s	
	Aldehyde	2900-2800	w	
C-C	Alkane	Not interpretively useful		
C=C	Alkene	1680-1600	m-w	
	Aromatic	1600 and 1475	m-w	
C≡C	Alkyne	2250-2100	m-w	
C=O	Aldehyde	1740-1720	s	
	Ketone	1725-1705	s	
	Carboxylic acid	1725-1700	s	
	Ester	1750-1730	s	
	Amide	1680-1630	s	
	Anhydride	1810 and 1760	s	
	Acid chloride	1800	s	
C-O	Alcohols, ethers, esters, carboxylic acids, anhydrides	1300-1000	s	
O-H	Alcohols, phenols			
	Free	3650-3600	m	
	H-bonded	3400-3200	m	
	Carboxylic acids	3400-2400	m	
N-H	primary and secondary amines and amides			
	(stretch)	3500-3100	m	
	(bend)	1640-1550	m-s	
C-N	Amines	1350-1000	m-s	
C=N	Imines and oximes	1690- 1640	w-s	
C≡N	Nitriles	2260-2240	m	
X=C=Y	Alkenes, ketones, isocyanates, isothiocyanates	2270-1940	m-s	
N=O	Nitro (R-NO ₂)	1550 and 1350	s	
S-H	Mercaptans	550	w	
S=O	Sulfoxides	1050	s	
	Sulfones, sulfonyl chlorides, sulphates, sulfonamides	1375-1300 and 1350-1140	s	
C-X	Fluoride	1400-1000	s	
	Chloride	785-540	s	
	Bromide, iodide	<667	s	

Key: s = strong, m = medium, w = weak

Appendix 4: Electronic absorption spectrum of ligands and complexes

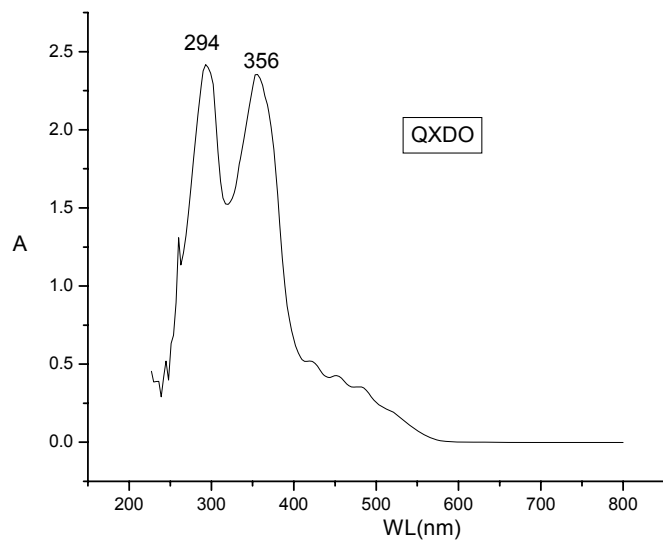


Fig 4: Electronic absorption spectrum of 2,3-quinoxalinedioxime in DMF and EtOH (2:1 v/v) solution.

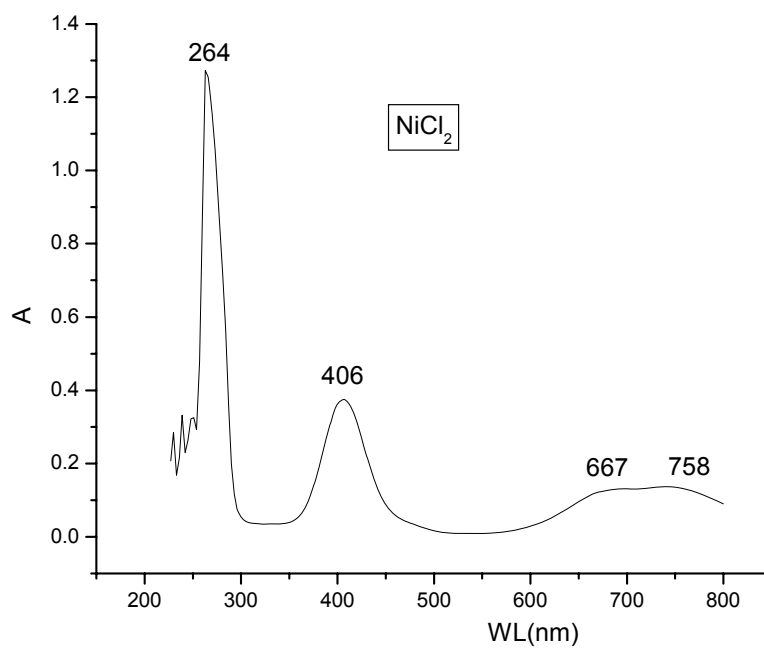


Fig 5: Electronic absorption spectrum of NiCl₂ in DMF and EtOH (2:1 v/v) solution

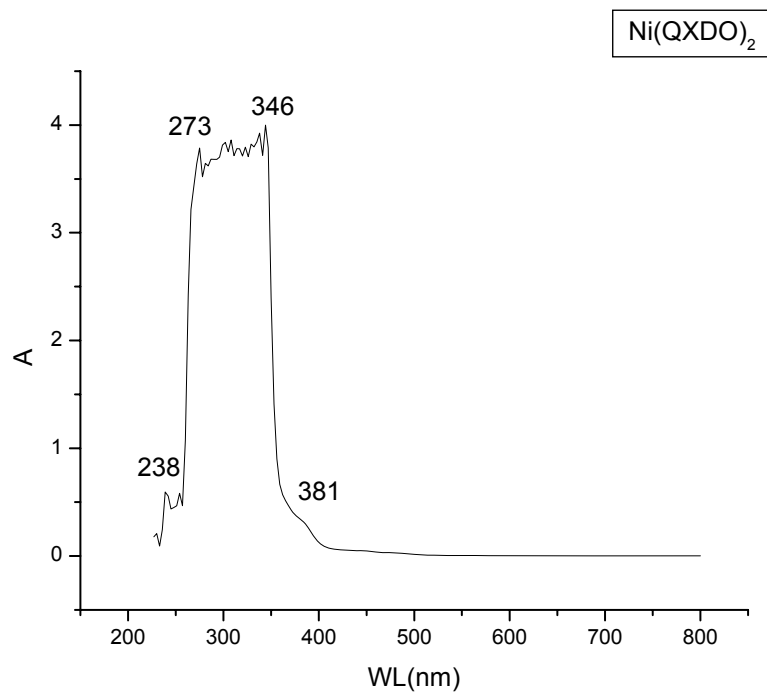


Fig 6: Electronic absorption spectrum of Ni(QXDO)₂ in DMF and EtOH (2:1 v/v) Solution.

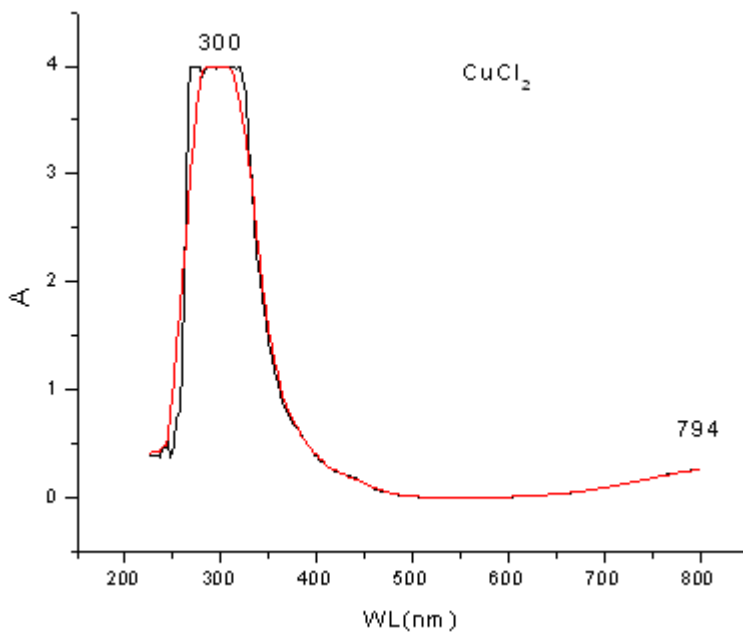


Fig 7: Electronic absorption spectrum of CuCl₂ in DMF and EtOH (2:1 v/v) solution

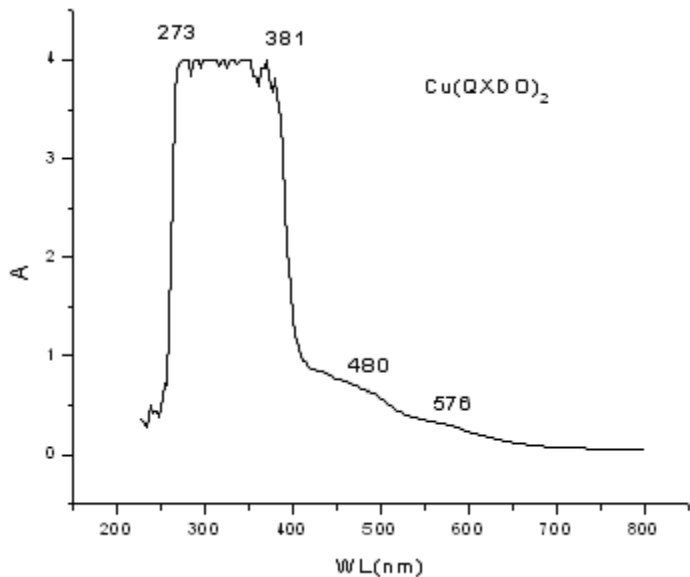


Fig 8: Electronic absorption spectrum of $\text{Cu}(\text{QXDO})_2$ in DMF and EtOH (2:1 v/v) Solution.

IR Spectra of ligands and complexes

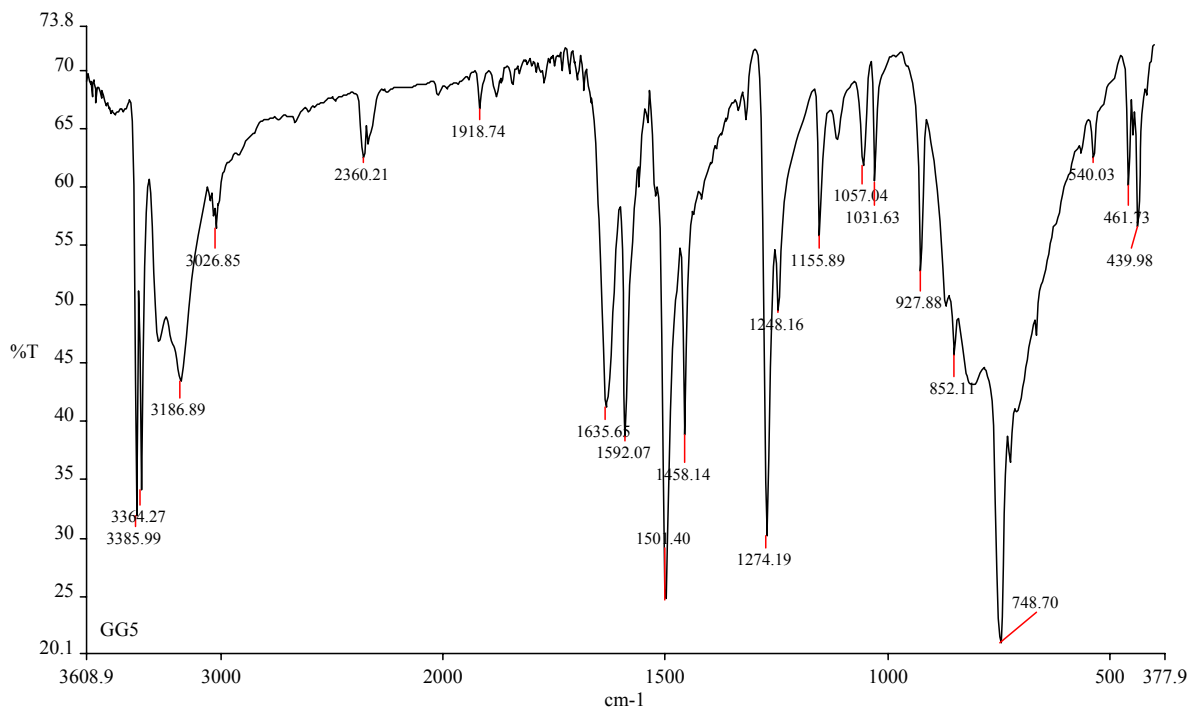


Fig 9: IR spectra of phenylenediamine

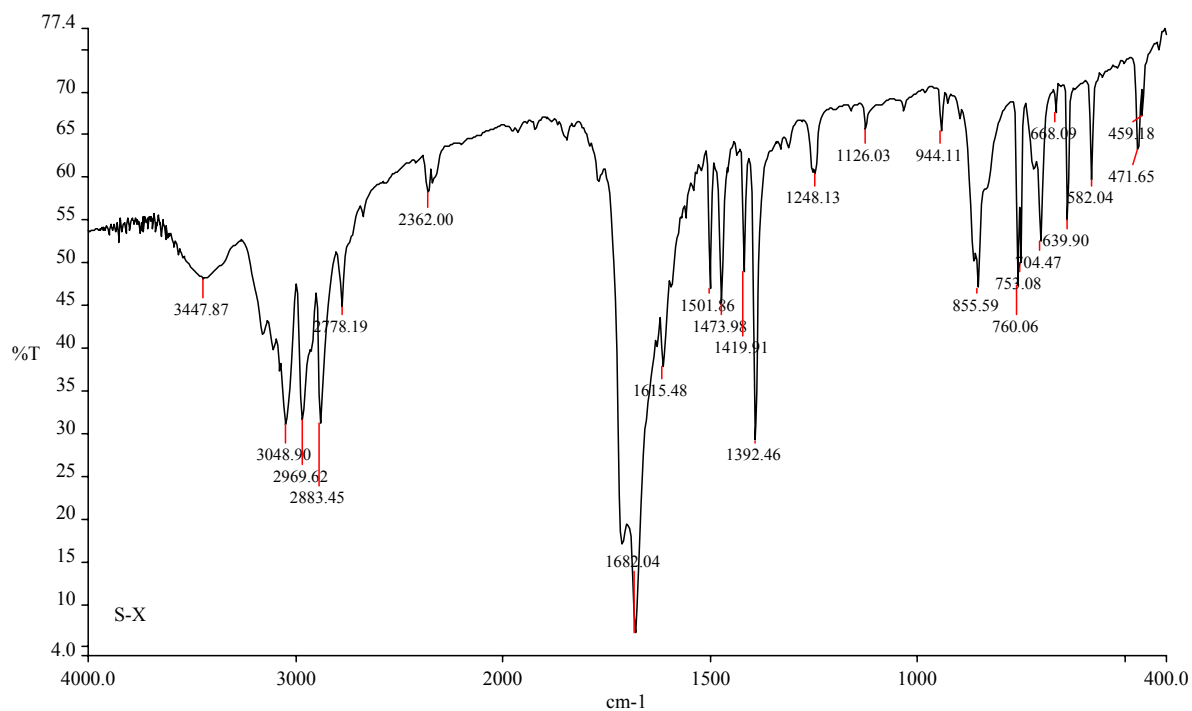


Fig 10: IR spectra of 2,3-Quinoxalinedione

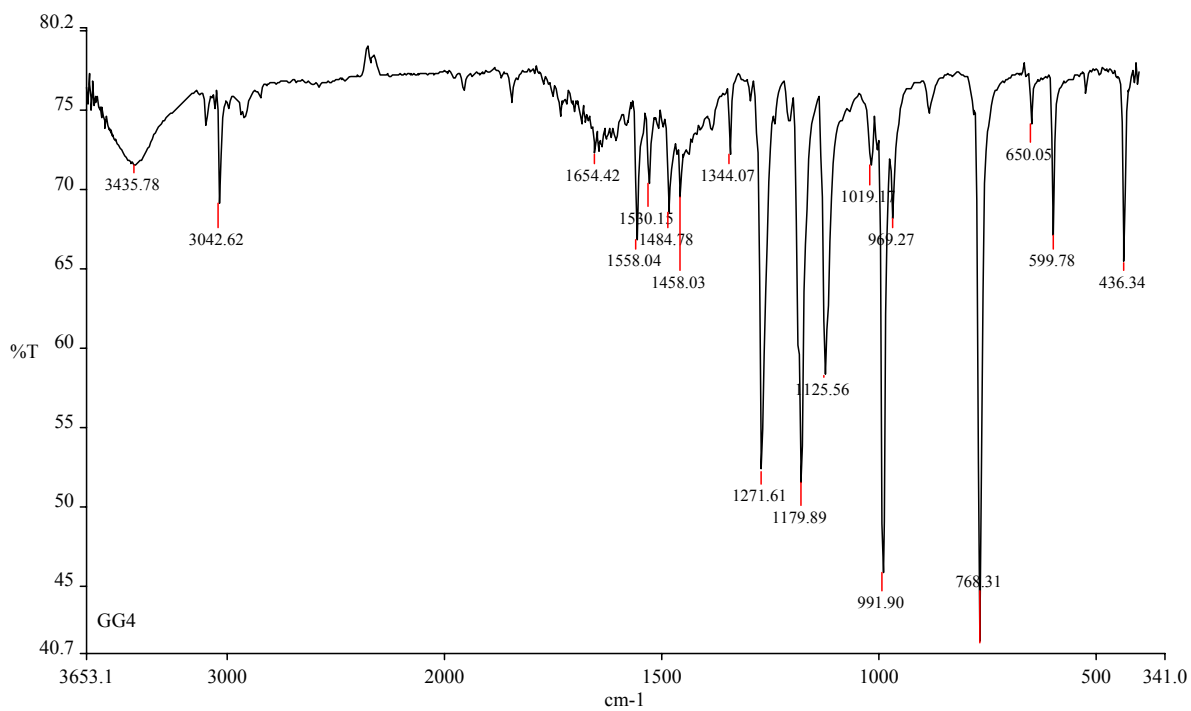


Fig 11: IR spectra of 2,3-Dichloroquinoxaline

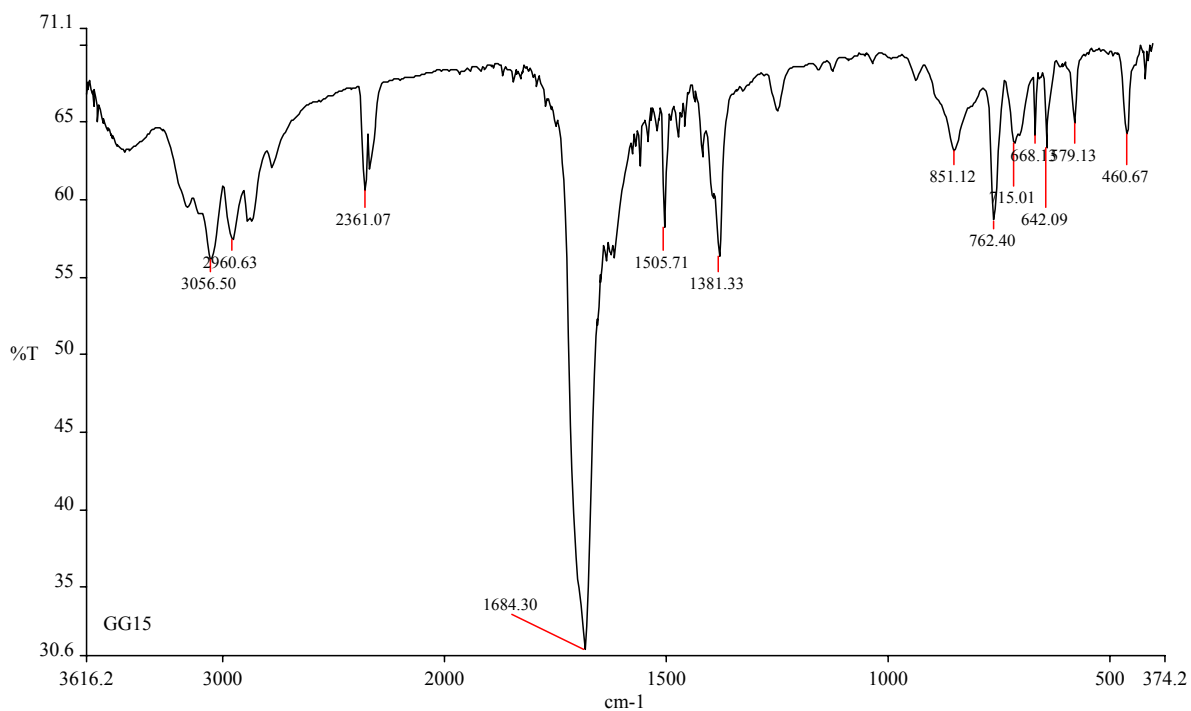


Fig 12: IR spectra of Quinoxalinedioxime

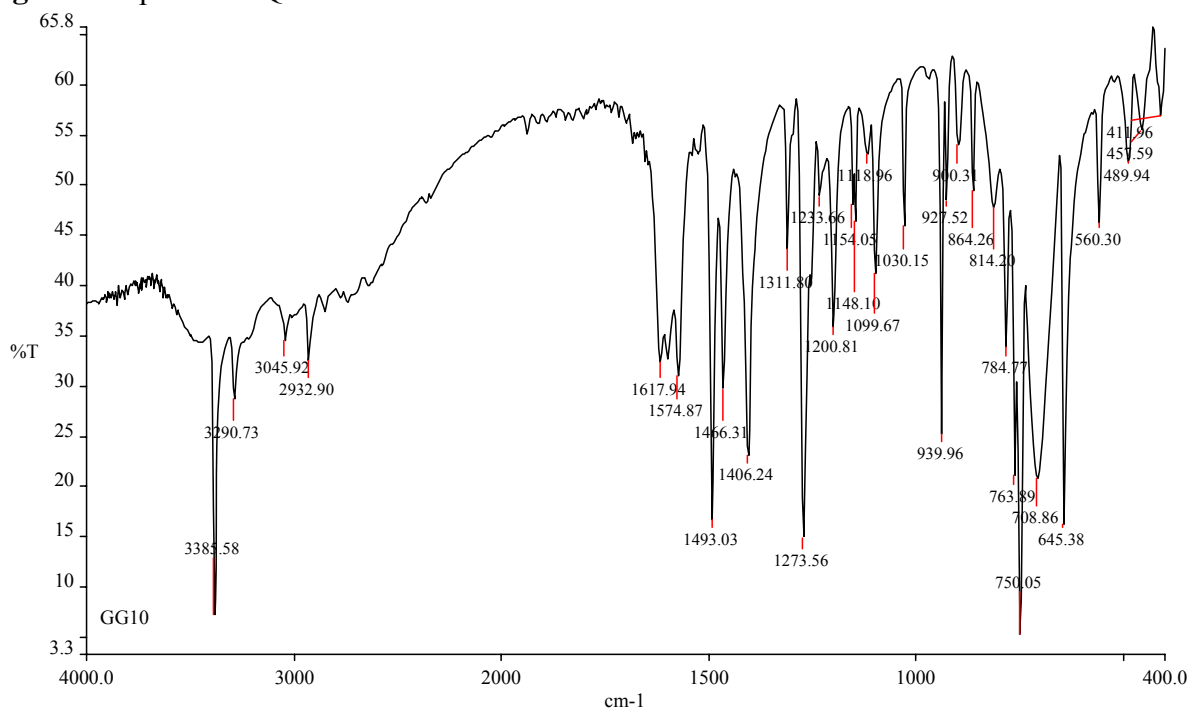


Fig 13: IR spectra of N-(Aminoformimidoyl)phenol (AP)

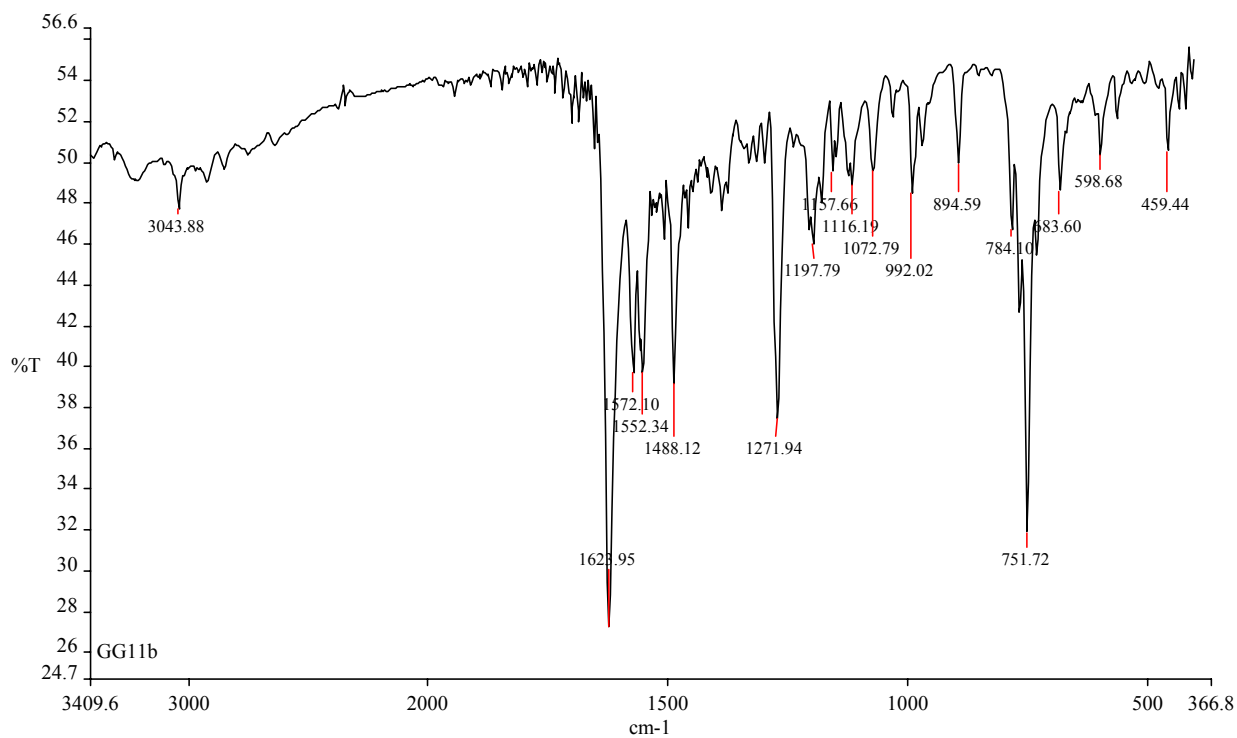


Fig 14: IR spectra of quinoxaline-2,3-bis-[N-(aminoformimidoyl)phenol] (QXAP)

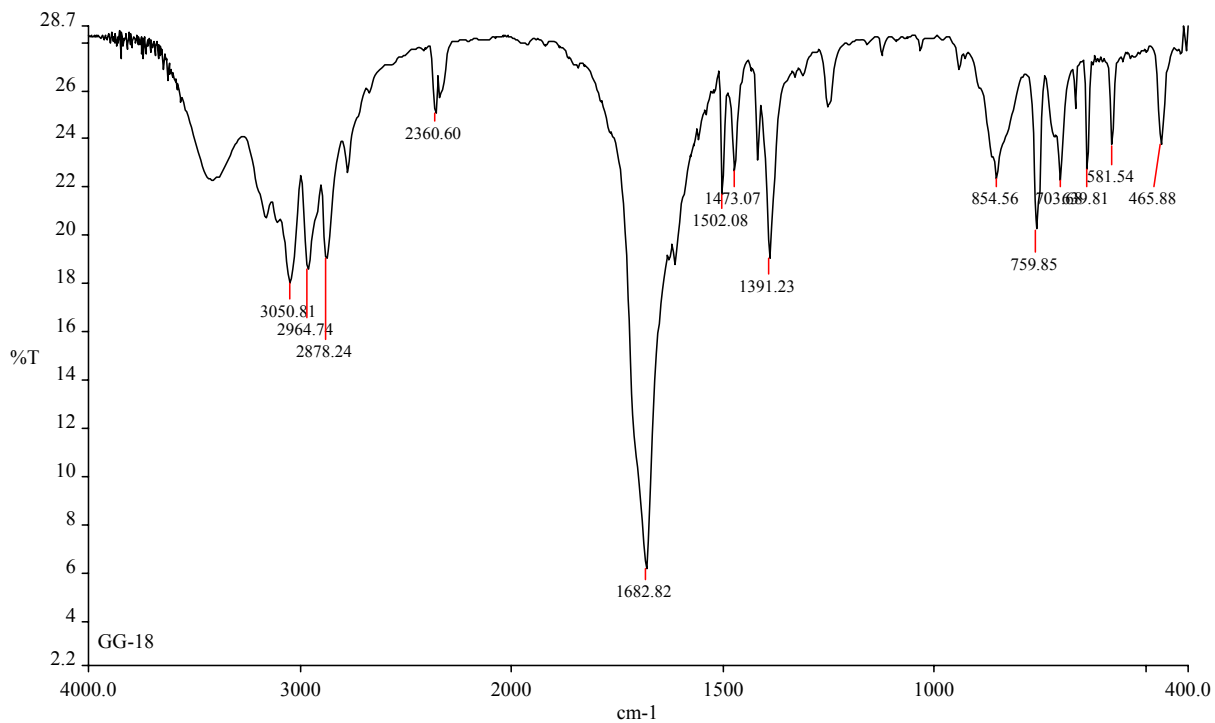


Fig 15: IR spectra of Ni(QXDO)₂

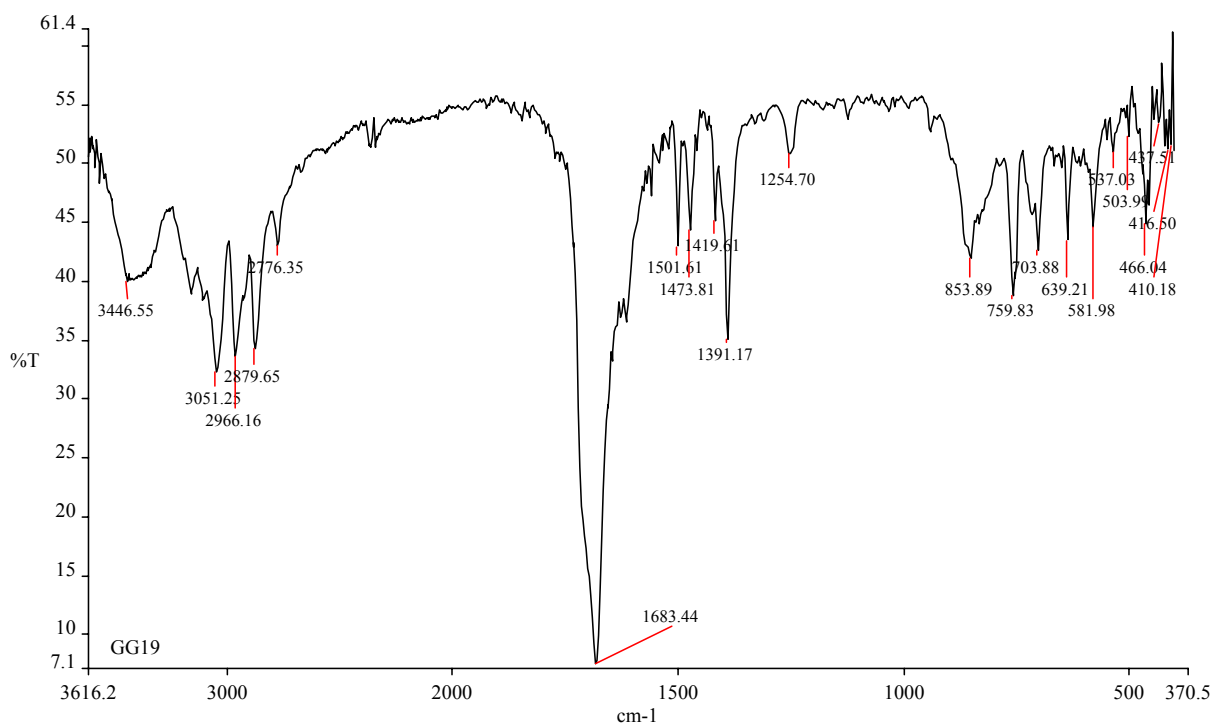


Fig 16: IR spectra of Cu(QXDO)₂