Synthesis, characterization and biological evaluation of xanthate metal complexes

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CERTIFICATION

This is to certify that this thesis is a record of original research carried out by Casa Sandisiwe under my supervision at the Department of the Chemistry, Faculty of Science and Agriculture, University of Fort Hare, South Africa in fulfillment of the requirement for the award of Masters of Science degree in Chemistry.

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DEDICATION

To the memory of my late mother, Lizeka Lobishe

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My sincere appreciation goes to Almighty God who is the author and finisher of my faith. I am who I am and the King of glory. He ordered my steps because he knows the best for me and I will forever be grateful. My deepest gratitude goes to my supervisor, Prof Peter A. Ajibade for this opportunity given to me to study for this degree and his approach to hard work. I pray that God will bless him beyond his imaginations. I am indebted to some of my colleagues in the laboratory.

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List of Figures

Chapter One

Chapter Three

Chapter Four

List of scheme

Chapter Two

Chapter Three

List of table

Chapter Three

Chapter Four

List of abbreviation

Ag - silver

B. C - before Christ

CdS – cadium sulfide

Cu - copper

Cu–Ad - $Cu_2(adenine)_4Cl_4 \cdot 2EtOH$

CYT C- cytochrome c

DMSO - dimethyl sulfoxide

Dmtu - N,N-dimethylthiourea

H_2biim- 2,2-biimidazole

HIV - human immune virus

Metu - methylthiourea

Mpm - 2-mercaptopyrimidine

Mpy - 2-mercaptopyridine

N - nitrogen

P – phosphorus

Phendione - 1,10-phenanthroline-5,6-dione

Pt - platinum

Sac - saccharinate

SOD - superoxide dismutase

Tmtu - tetramethylthiourea

Tu - thiourea

Tna - thionicotinamide

UBI - ubiquitin

ZnS – zinc sulfide

4-MecdoaH_2 - 4-methylcoumarin-6,7-dioxyacyeic acid

Abstract

Ni(II), Ag(I), Cu(II), Pd(II) and Pt(II) complexes of xanthate were synthesized and characterized by elemental analysis, UV− Vis, FTIR, conductivity measurements, decomposition temperatures, and Pd(II), Pt(II) complexes and the xanthate ligands were further characterized by ^{1}H-NMR spectroscopy. Conductivity measurements displayed that the complexes are non− electrolytes in solution with conductivity values in the range 0.05 − 18.30 µS. Generally all the xanthate ligands are soluble in water and the complexes are insoluble both in non-polar solvents except polar coordinating solvents such as DMSO and DMF. The xanthate complexes are formulated as four coordinate (tetrahedral or square planar), and six coordinate (octahedral) compounds. However, in each of the complexes xanthate acted as bidentate ligand through the two sulfur atoms. The geometries around the metal ions are completed by triphenylphosphine. The ligands and complexes were screened against two bacterial isolates to determine their antibacterial activities. Antibacterial activity of the synthesized metal complexes shows a generally increased activity in comparison with that of their respective free ligands. At a lower concentration some of the complexes did not show any activity, a good number of complexes however showed activity at a higher concentration of 40 mg/ml. The degree of activity varies with metals. Silver complex have been observed to show the highest activity of MIC value of 1.25 mg/mL with regards to antibacterial strength, although it varies with different ligands.

TABLE OF CONTENT

Chapter One

Chapter Two

Chapter Three

Chapter Four

Chapter Five

Chapter one

Introduction and literature review

1.0 Introduction

Cancer is the type of disease that is characterized by cell growth that is out of control. There are different types of cancers, where each is categorized by the type of cell or organ that is originally affected. Damaged cells divide uncontrollably to form lumps or masses of tissue called tumours; lead cancer harms the body tissues, without leukemia case where cancer forbids normal blood function by abnormal cell separation in the blood stream. These damages done by the tumours can cultivate and interfere with a body system like digestive, nervous, and circulatory systems and they can discharge hormones that change body function [1]. When these two things occur: (a) A cancerous cell manages to move throughout the body using the blood or lymph systems, destroying healthy tissues in a process called invasion and (b) Cell manages to divide and grow, making new blood vessels to feed itself in a process called angiogenesis [1].

The tumours that stay in one spot and demonstrate limited growth are generally considered to be more dangerous or malignant. Those tumours that successfully spread to other parts of the body attacking and abolishing other healthy tissues. The route itself is called metastasis and it results in a serious illness that is very difficult to treat known as cancer. Cancer initiates in body genes. These genes assist and control our bodies constantly make new cells to allow us to grow, to replace dead cells, or heal damaged cells after an injury [2].

1.1 Causes of cancer

Cells that are uncontrollable in growing and do not die resulting in cancer. The body normal cells undergo an arranged path of death, growth, and division. Apoptosis is the program of cell death, and when this route is interrupted, cancer begins to form. Cancer cells do not experience programmatic death and instead continue to grow and divide into distinct regular cells. The destruction of genes causes all types of cancers. The destruction typically happens through our lifetime, while a slight number of people get a damaged gene from their parents. Cells usually grow and multiply in an orderly way. Though, spoiled genes can cause them to behave abnormally. The cells might grow into a lump called a tumour. Some causes of many cancers are not yet known. Other cancers are associated with our lifestyle habits and recreation, or materials in our environment that affect our bodies [3].

Doctors frequently cannot clarify why one person develops cancer and another does not. There are certain things that increase the risk of cancer and include:

- Asbestos
- Chemicals
- Diet
- Sun exposure
- Smoking

Cancer is not infectious. However, people with a family background of some cancers, such as bowel and breast cancer, might have a higher risk of developing the same cancer. Change in the gene that controls cell growth in a very few number of families is passed on from one generation to the next but not all family members get this change. Cancer cells grow because of damage to DNA of the normal body cells. DNA is the brain in every cell and it directs all

its actions. When the DNA gets damaged the cell either repairs the damage [4]. Whereas, in cancer cells this damage of the DNA does not repair. Instead, the cell division occurs and new cells are formed. New cells that are formed, can also be damaged DNA as the first cell does. The damage on the DNA; nevertheless most DNA damage is caused by faults that happen while the normal cell is reproducing or by something in our environment. Occasionally the cause of the DNA damage is something understandable, like cigarette smoking, whereas there is no clear cause that is found [5].

1.2 Spreading of cancer

In order for cancer to grow larger than the head of a pin, it must grow its own blood vessels. The growth is called angiogenesis. Occasionally cells move away from the primary cancer, by the local tissue fluid channels called lymphatic or through the bloodstream, and attack other organs. When they spread to a new site, they may continue to grow and form another tumour at that new site. This process is called a secondary cancer or metastasis. No matter how cancer spreads from its original place to another part of the body, the new tumour has the same kind of abnormal cells. For instance, if cancer of the uterus spreads to the lungs, the cancer cells in the lungs are really uterine cancer cells. The disease remains metastatic uterine cancer, not lung cancer, and its treatment is as uterine cancer treatment, not lung cancer. Surgeons occasionally call the new tumour “distant” disease. Cancer cells frequently travel to other body parts, where they begin to grow and form new tumours to replace normal tissue. The process itself is called metastasis. It happens when the cancer cells get transported by the bloodstream or lymph vessels of the body. It does not matter where a cancer may relocate; it is always named for the place where it started, e.g. lung cancer that has relocated to the liver is still called lung cancer, not liver cancer [6].

1.3 History of cancer

Cancer is being said to be the second foremost cause of death in the world after cardiovascular diseases. Fifty percent men and forty five percents of women in the United States have possibilities of developing cancer during their lifetimes. Nowadays, most of cancer people extend their life due to early identification and treatment. Cancer is not a novel disease and has afflicted people throughout the world. Cancer name came from a Greek word "karkinos" that describe carcinoma tumours by a physician Hippocrates (460-370 B.C), but he was not the first to discover this disease. The first evidence of human bone cancer was found in mummies in ancient Egypt and in ancient manuscripts dates about 1600 B.C. The oldest world's recorded case of breast cancer storms from ancient Egypt in 1500 B.C. and it was documented that there was no treatment for the cancer, only palliative treatment. According to the writings, surface tumours were surgically removed in a similar manner as they are removed nowadays [7].

1.4 Types of cancers

1.4.1 Lung cancer

Lung cancer is the foremost cause of cancer deaths in men around the globe and the second principal cause of cancer deaths in women, with an estimated 1. 1 million deaths globally in the year 2000 [8]. Lung cancer is the abnormal cell division occurring in the lung cells, this type of cancer has two major types such as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)**.**

Small-cell lung cancer, or oat-cell carcinoma is a highly malignant cancer type that commonly arises most within the lung, while it can irregularly arise in other body sites, such

as the cervix, prostate [9] and gastrointestinal tract. There is about 10-15% of all lung cancers are the small cell type. This type of cancer regularly starts in the bronchi near the center of the chest. Although the cancer cells are small, they can split quickly and form large tumors, and spread to lymph nodes and other organs throughout the body [10].

The non-small cell lung cancer is about 70-80% in diagnoses [11] and the disease is generally diagnosed at the advanced stage. The lifelong survival of non-small cell lung cancer patients that are in advanced stage is poorer, naturally less than 5% at 5 years, though additional treatment options continue to be explored [12]. Non-small cell lung cancer is about 75-80% of lung cancer cases. Nevertheless, even in patients with early stage non-small lung cancer is undetectable, metastasis at surgery has been reported [13,14]. Five-year survival rate was only 60-70% for non-small lung cancer patients that completely resected stage I cancer [15].

1.4.2 Breast cancer

Breast cancer is one of the foremost cancers in women [16]. Recent studies have revealed that black South African women have shown a lower incidence of breast cancer. Other factors recognized to be important in the epidemiology of breast cancer that are unique to this population include a slightly later menarche (14.7 years in rural black and 13.9 in urban black *vs* 12.6 in white women) [17], comparatively early age at birth of first child, high equivalence, and lactation (nearly universal and usually prolonged for several months). The South African demographic survey, 17.8% of black females aged 15 to 19 years have stated being ever pregnant versus 2.2% of white females [18].

1.4.3 Testicular cancer

Cancers of testes are fairly rare but highly treatable, and it occurs mainly in young and middle aged males, mutual age is between 15 to 35 years old. This type of cancer arises typically (98,9%) in the germ cells of the testes in adults. Non-germ cell testicular cancer is rare and encompasses a heterogeneous group. The main cause of cancer of the testes is unidentified. It is though; know that there are several risk factors related to testicular cancer. However, different types of cancers have different risk factors. Whereas, some risk factors, such as smoking, can be controlled. Other than those like a person's age or race cannot be altered. But having a risk factor and even several risk factors does not mean that a person will get the disease. Males who have had *cryptorchidism* are numerous times more likely to get testicular cancer than those who did not have the problem. *Cryptorchidism* is the term for undescended testes. Amongst males with a history of this problem, most cancers start in the testicle that has not moved down (National Cancer Institute) [19].

1.4.4 Pancreatic cancer

Cancer of the pancreas most affects the normal functioning of the pancreas, which includes the way the exocrine or endocrine glands work. This type of cancer frequently arises in the head of the pancreas where it can block the bile duct, causing a build-up of bile in the blood (jaundice). It can also spread to nearby lymph nodes such as the parts of the immune system as well as nerves, which causes pain. The two parts such as exocrine cells and endocrine cells of the pancreas forms totally different types of tumours. Exocrine cancers are by far the greatest common type of pancreatic cancer. Kind (non-cancerous) lumps and benign cancer called *cystadenomas* can occur, but most pancreatic exocrine cancers are malignant. Adenocarcinoma is a cancer that arises in gland cells. About 95% of cancers of the exocrine

pancreas are adenocarcinomas. These types of cancers regularly initiate in the ducts of the pancreas, but they occasionally develop from the cells that make the pancreatic enzymes [20].

1.5 Common forms of cancer treatment

1.5.1 Hormonal therapy

In 1878 Thomas Beatson discovered that the breasts of rabbits stopped producing milk after he removed ovaries. Advanced scientists recognized that dramatic regression of metastatic prostate cancer succeeding removal of the testes. Novel classes of drugs (aromatase inhibitors) are being used to treat prostate and breast cancers. How hormones influence growth of cancer has guided progress as well as reducing the risk of breast and prostate cancers [21].

1.5.2 Surgery

Surgery is the treatment that deals with cutting out the cancer. In best case situations this may be the only form of treatment that is used and has not yet spread. Surgeries like those for breast cancer, or prostatectomy for prostate cancer are quite common in this treatment. Because cancer often travels however, surgery will usually be combined with one or more of the other types of treatments [22].

1.5.3 Radiation Therapy

Radiation therapy uses radiation to kill cancer cells and shrink tumours by X-ray radiation. It can be administered either as externally or internally. The treatment is restricted and specific to the area being treated. This radiation abolishes cancer cells by damaging their genetic material. The entirely cells in the treated area are damaged, but normal cells usually recover,

however, radiation therapy is usually broken up in several treatments to let the healthy cells have a chance to heal [23].

X-ray was discovered in 1896 by Roentgen and 3 years later radiation was used for cancer diagnosis and in cancer treatment. In the early 20th century, researchers exposed that radiation could cause cancer as well as cure it. Nowadays several radiation therapies are being used, e.g. Conformal proton beam therapy (proton beam will be used for killing tumour cells instead of X-rays); stereotactic surgery and stereotactic therapy (gamma knife can be used to deliver and treat common brain tumours); and intra-operative radiation therapy (cancer has been removed surgically followed by radiation to the adjacent tissues) [24]

1.5.4 Targeted therapy

Targeted therapy is a quite a new cancer treatment which started to be used in the late 1990s. This form of therapy places an emphasis on attacking the proteins of cancer cells. These drugs work in a number of ways. Some act as protein inhibitors in the cancer cells. Some specifically bind to the protein of cancer cells. Others involve using small peptides that bind to cell receptors [25].

1.5.5 Natural Therapy

Natural therapy involves the use of natural treatments used by different cultures around the world throughout history. Forms of natural therapy include specific diets, minerals, vitamins, and alternative treatments like acupuncture and magnetic therapy. Natural therapy may be used on its own, or combined with other treatments to help with pain relief [26].

1.5.6 Chemotherapy

A cancer treatment that uses cytotoxic or anticancer drugs is called chemotherapy. The chemotherapy drugs are exactly designed to target rapidly dividing cells like cancer cells, although other rapidly dividing cells may also be targeted. Since the drugs also give dividing cells DNA damage, the cancer cells typically cannot repair this damage while normal cells can. Certain drugs work better when they are combined with similar drugs, so two or more drugs may be used at the same time in combination chemotherapy [27].

1.6 Transitional metal complexes in cancer treatment

1.6.1 Platinum coordination complexes

Transition metals have played important roles in the development of metal based pharmaceuticals. Recently there is some currently growing interest of dithiocarbamate complexes of dithiolates role in bio-inorganic chemistry as pharmaceuticals. These complexes of transition metal complexes are usually cationic, neutral or anionic species [28].

The important role played by metal ions in biology has led to a vast number of metal complex developments that has diverse therapeutic activity. Metal complexes such as *cisplatin*, carboplatin and oxaliplatin (Figure 1) are famous metal-based drugs widely used in cancer treatment. There are other metal complexes that have shown useful results in the treatment of diseases like diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases [29]. The platinum complexes in cancer treatment are very vital. *cisplatin* and carboplatin are broadly used as anticancer drugs and there are numerous other platinum compounds in clinical trials, including an orally active compound.

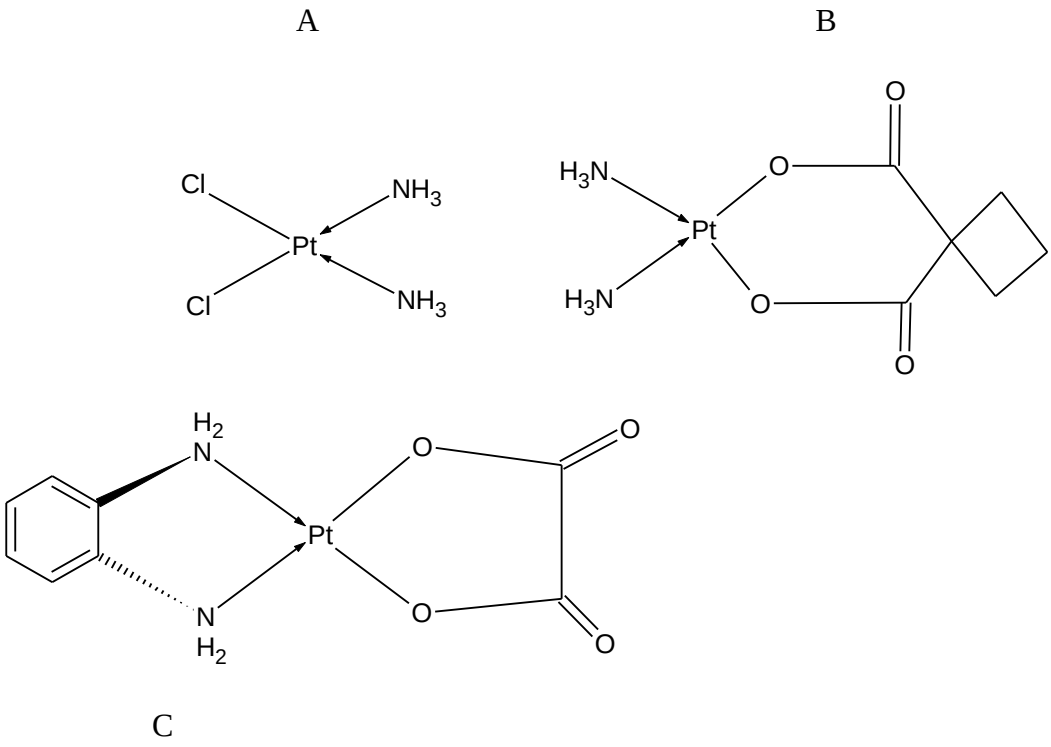

Figure 1: Structures of *Cisplatin*(A), carboplatin(B) and oxaliplatin(C).

Their activities as transition metals in bio-inorganic chemistry has started the development of metal based drugs with promising pharmacological applications and may offer unique therapeutic opportunities [30]. Metals are expected to be highly toxic and unstable in aqueous media which have led to the medical use of transition metals to be mutually exclusive. However, the unexpected discovery of the anti-cancer effects of *cis*-diaminedichloro platinum(II) (*cisplatin*) in 1965 by Rosenberg and co-workers led to the field of research of medicinal application of metal ions complexes [31,32].

A positively charge transition metal ion is favoured to bind to a number of negatively charged organic compounds and biomolecules that includes proteins and nucleic acids to form metal complexes. The use of these biomolecules as ligands in medicinal use in forming metal complexes has excellent potential in a bio-inorganic chemistry. That makes a wide range of medicinal uses of metal complexes to be investigated [33].

Ever since, the transition metal complex application as radiation therapeutic, diagnostic and imaging agent, and as small molecule drugs, platinum-based and ruthenium-based metal complexes bind DNA and allow the design of cancer therapeutics. *Cisplatin* complex forms intra-strand crosslinks with DNA that results in cell death and is used as an anticancer compound [34] as shown in Figure 2.

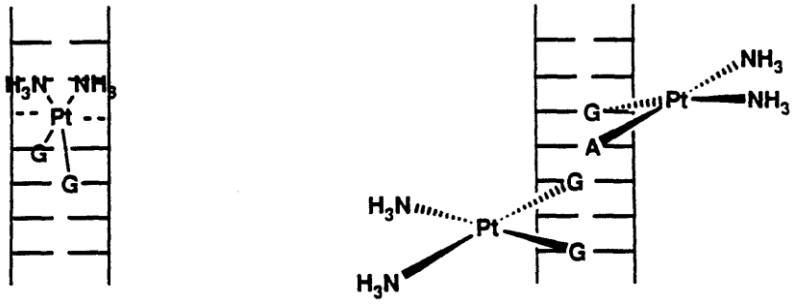

Figure 2: *Cisplatin* anticancer agent crosslinking to the DNA

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However, this being used by 50-70% of cancer patients, *cis-platin* and its derivatives do have disadvantages that include toxicity, development of drug resistance, and unsuccessfulness against some type of cancers like prostate, colorectal and breast cancer [35]. Transition metal complexes can intermingle in the body in many ways like binding to DNA, disturbing cellular equilibrium and prevent protein function. But their application is still limited by observed toxicities related to off-target effects and unselective activity with biological nucleophiles. These findings led to more work to be done and to discover compounds which can be more selective in interacting with therapeutic targets. These transition metal complexes have a great diversity in their application that make them to not be only used as anti-cancers but have also been used as anti-inflammatory, anti-infective and anti-diabetic compounds [35].

Transition metal complex development as drugs is not an easy assignment. More effort is required to get a compound of interest that could reduce limitations and side effects associated with *cisplatin*. Transition metal complexes that are most widely used as chemotherapeutic agents have and make a large contribution to medicinal application [36]. Whereas the side effect of some platinum complexes leads to dose-limiting, the toxicity as well as resistance to some of these platinum compounds is still a main problem that has prompted researchers to come with alternative ways to modify these platinum complexes to make them suitable inhibitors [37].

Proteins or other sulfur-containing ligands could be responsible for deactivation of the platinum agent *in vivo*. The understanding of the metabolite form is to improve the experiments with a view to prevent the metal complex from being deactivated [38]. For example, the reaction kinetics of *cisplatin* (*cis*-[diamminedichloroplatinum(II)]) with transferrin, myoglobin, ubiquitin, and metallothionein were investigated and the reaction products were suspected [39].

[(OC-6-43)-bis(acetato)(1-adamantylamine)amminedichloroplatinum(IV)], is an octahedral platinum(IV) complex containing a large number of hydrophobic ligand – adamantylamine. The use of hydrophobic amines as non-leaving ligands could increase the uptake of the compound by the cancer cells. Effects of [(OC-6-43)-bis(acetato)(1-adamantylamine)amminedichloroplatinum(IV)] on *cisplatin* resistant ovarian cancer cell lines were investigated and they were compared to those of *cisplatin* [40]. [Meso- and rac-1,2-bis (4-fluorophenyl)ethylenediamine] chloro [sulfinylbis(methane)-S] platinum(II) chlorides (meso- and rac-4F-PtCl(DMSO)) was synthesized and described as a good breast cancer

inhibitor and its properties as anti-cancer were studied. Rac-4F-PtCl(DMSO) overcome the usual carboplatin in its effect on the human MCF-7 breast cancer cell line and is more resistant than its dichloroplatinum(II) analogue rac-4F-$PtCl_2$ against attack of nucleophiles, a requirement for adequate stability in physiological environments and as a result for distinct anti-tumour activity *in vivo*. The complex of Rac-4F-PtCl (DMSO) is as shown [41]

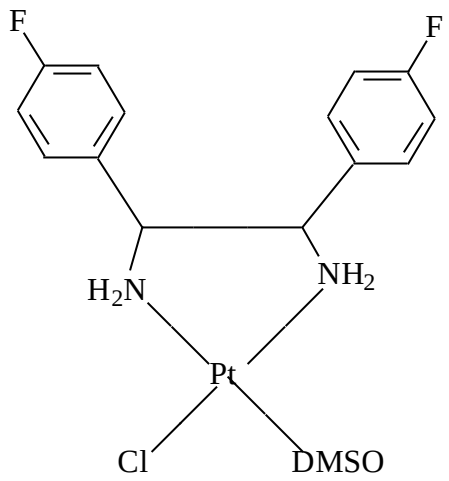


Figure 3: Structure of Rac-4F-PtCl (DMSO) complex

The platinum dicarboxylate complex anti-proliferative effect is very similar in their chemical, structural and kinetic properties to carboplatin. The anti-proliferative effect of the compound mainly depends on the kind of amine ligand. Primary amine (ethylenediamine) complexes are more effective than tertiary amine (1-alkylimidazole) complexes. The ethylenediaminemalatoplatinum(II) complexes show a differential *in vitro* anti-proliferative activity, though they may be projected that they inflict DNA lesions that are repaired by the nucleotide excision system [42]. But their cytotoxicity is directly interrelated in reactivity with glutathione. Whereas tertiary amine complexes toxicity is low and fairly low reactivity

with glutathione, comparable to the primary complexes, their cytotoxicity is inversely interrelated with reactivity with glutathione. These tertiary complexes, bis(1-ethylimidazole)(L-malato)platinum(II) and bis (1-propylimidazole (L-malta)) platinum(II), demonstrate a significant ability to arrest cells in G2 phase. The properties of these tertiary amine platinum complexes may be exploited in the joint platinum complex treatment and irradiation [42].

There are developments of the relationships between the structure of platinum based anti-cancer drugs and their biological activities that are reviewed [42]. The understanding of the mechanism or activity of this class of drugs leads to the formation of compounds that have anti-cancer activity and they fit in structure-activity rules. Whereas, they can also contribute to the focus on a group of compounds that has yet to create a key advance over *cisplatin* or carboplatin. The growth of new highly active platinum based drugs that do not fit the structure-activity rules were reviewed do not follow the path of structure-activity rule [43].

New structure-activity relationships are budding but there is a conclusion that in general it is doubtful that widely applicable rules will be continuously used. The results of recent work aimed at rationally probing the relationships between structure and activity was revealed. The studies aimed at determining why *cisplatin* does not bind to GpA sequences of duplex DNA and the determination of whether the GG interstrund adduct contributes to anti-cancer activity were described. However, chiral probes of Pt/DNA interactions, cytotoxicity and other toxicities are also studied. The stereoselective interactions of Pt complexes and DNA were reviewed as well as the factors contributing to the stercoselectivity [43].

In vitro investigation of compounds *cis*-[$Pt(NH_3)_2$(N1′-HMEL)$_2$] and *cis*-[$Pt(NH_3)_2$(N1′-HISO)$_2$], have revealed strong anti-proliferative effects on CH1 cells (ovarian carcinoma, human) compared to *cis*-diamminodichloridoplatinum(II), *cisplatin*. There is a clear indication that both HMEL-complex and HISO-complex form adducts with the three model protein ubiquitin (UBI), cytochrome c (CYT C) and superoxide dismutase (SOD), the $HISO^-$complex being significantly more effective than the $HMEL^-$ one [44]. However, *trans*-isomer does not reduce the enzyme activity. Instead, the compound retarded the enzyme in its ability to expand the primer strand of DNA. The studies showed two other possible mechanisms of inhibition when *trans*-diaminedichloroplatinum(II) can covalently bond to the polymers and to the template DNA. The platinum drug with the polymerase and DNA showed that the inhibition is principally due to covalent binding to the enzyme [45].

The intercalation DNA with bipyridyl complexes of platinum(II) containing thiourea moiety, with different substituents on thiourea moiety have been tested against a *cisplatin* (cDDP)-sensitive human ovarian carcinoma cell line (2008) and its resistant variant had been designed. It had been shown that the anti-proliferative efficacy of these drugs was dependent on molecular structure, since it increases with ancillary ligand bulkiness and hydrophobicity of substituents on thiourea moiety. However the presence of two phenyl groups on thiourea moiety confers an exceptional cytotoxicity [46].

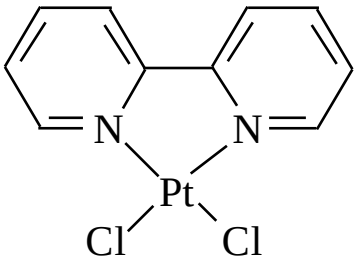


Figure 4: Structure of the Platinum(II) bipyridyl complex.

Complexes containing 1,1-dithiolato ligands have been used as fungicides, pesticides, vulcanization accelerators, flotation agents, lubricant additives and in deposition of ZnS or CdS thin films by metal organic chemical vapour deposition and also the xanthate family of dithiocarbonate is widely used in water purification in the mining industry [47]. The 1, 1-dithiolate ligands have recently attracted much attention mainly because of the ligand atoms. Indeed, the increasing renewed attention paid nowadays to these species arises from their high stability, solvatochromic behaviour, room temperature luminescence in solution [48] and their status as excellent candidates for applications such as photo catalysis. A lot of work is currently taking place to find how the excited state properties can be altered in a predictable manner through systematic ligand modification. In addition the variable coordination modes of 1,1-dithiolate ligands to metals make the structural studies more interesting. The 1,1-dithiolate ligands have also been used to stabilize unusually high oxidation states or to facilitate the syntheses of clusters [49] and to the syntheses of inorganic-organic hybrid materials, which have a potential in various applications such as electrical conductivity, magnetism, ion exchange, separation and catalysis [50].

These complexes can then react with DNA and adducts have been noticed. Sulfur compound methionine in these systems is also important. Methionine can bind to *cisplatin* via the sulfur atom, increasing its rate of reaction with DNA, and enhancing ammonia release due to the

high non effect of the sulfur. Methionine can also activate carboplatin, it opens chelate rings to form surprisingly stable adducts. The Pt(II) amine compounds can have anti-tumour activity they usually not be orally administered. In contrast, Pt(IV) pro-drugs they are inherently less reactive and can be effective if given by mouth, as the active Pt(II) compound forms prior to interaction with DNA [51].

1.7 Non-platinum metal complexes in cancer therapy

1.7.1 Ruthenium complexes

Based on tumour resistance of some platinum based anti-tumour agents, new ruthenium complexes, *trans*, *cis*, *cis*-[$RuCl_2$(DMS))$_2$(H_2biim)] and *mer*-[$RuCl_3$(DMSO)(H_2biim)] where [DMSO=dimethyl sulfoxide and H_2biim=2,20-biimidazole], have been synthesized and studied as anti-tumour agents. The *mer*-[$RuCl_3$(DMSO)(H_2biim)] complex [52] is less stable and is more cytotoxic against the four human cancer cell lines tested than *trains*, *cis*, *cis*-[$RuCl_2$(DMSO)$_2$(H_2biim)]. The studies further showed that *mer*-[$RuCl_3$(DMSO) (H_2biim)] and *trans*, *cis*, *cis*-[$RuCl_2$(DMSO)$_2$(H_2biim)] exhibit cell growth inhibition by triggering G0/G1 cell cycle capture and mitochondria-mediated apoptosis.The studies also showed that mer-[$RuCl_3$(DMSO)(H_2biim)] complex exerts strong inhibitory effects on the adhesion and it relocate in human cancer cells, whereas the target validation study of these complexes shows that cyclin-dependent kinases other than DNA are likely be targeted by these complexes [53]. Other complexes of ruthenium(II) such as [$RuCl_2$(*p*-cymene)]$_2$(μ-BESE), [$RuCl_2$(*p*-cymene)]$_2$(μ-BESP), and the mononuclear salt [RuCl(*p*-cymene)(BESE)]PF_6, containing the disulfoxides BESE and BESP were synthesized and they were studied and they showed an anti-cancer activity against mammary cell line of human *in vitro* [52].

The neutral or cationic arene ruthenium complexes can provide both hydrophilic as well as hydrophobic characteristics due to the robustness of the ruthenium–arene unit. However, mononuclear arene ruthenium complexes containing P- or N-donor ligands or N,N-, N,O- or O,O-chelating ligands, and tetranuclear arene ruthenium porphyrin derivatives that are photoactive as well as hexanuclear ruthenium cages that have either empty or filled with other molecules have shown to be active against a variety of cancer cells [54]. The role of autophagy in cancer development and response to cancer therapy also has been a subject of debate. Whereas the series of ruthenium(II) complexes containing a β-carboline alkaloid as ligand demonstrated the simultaneously induction of and apoptosis in tumour cells. These type of Ru(II) complexes are nuclear permeable and highly active in contradiction of a panel of human cancer cell lines, rather than those of cisplatin. The further studies display that suppression of autophagy using pharmacological inhibitors (3-methyladenine and chloroquine) enhances apoptotic cell death [55]. Some studies shown no doubt about the success of precious metals in the clinic; for example, platinum compounds being broadly used in the treatment of cancer, silver compounds have been useful antimicrobial agents and gold compounds used normally in the treatment of rheumatoid arthritis. The medicinal properties of other platinum group metals are recognised and of these a ruthenium anticancer agent has recently come into the clinic, displaying promising activity on otherwise resistant tumours. Similar to all other metal drugs like ruthenium compounds depends on both the oxidation state and the ligands. Through manipulating the features rutheniurn-centred antimalarial, antibiotic and immunosuppressive drugs have been made. Ruthenium has unique properties which make it particularly suitable in drug design [56].

The studies have revealed that ruthenium compounds evaluated for anticancer activity are coordination compounds with the ruthenium in the +3 oxidation state. However, it has been

wished oxidation state ruthenium is less active and is reduced *in vivo* to more active ruthenium(II) complexes, a route favoured in the hypoxic environment of a tumour [57]. It should be renowned that ruthenium(II) compounds also exhibit a low general toxicity and since cancer cells can also become oxidized at certain stages of their growth cycle oxidation of the ruthenium cannot be excluded. Meanwhile p-coordinated arenes are recognized to stabilize ruthenium in its +2 oxidation state, the likely of arene ruthenium(II) complexes as anticancer agents, and their associated aqueous chemistry, is being increasingly investigated [58].

1.7.2 Palladium complexes

Palladium(II) complexes with triphenylphosphine (PPh_3) and thioamides of the general formulae, $[Pd(L)_2(PPh_3)_2]Cl_2$ and $[Pd(L)_2(PPh_3)_2]$ have been prepared and studied (where L = thiourea (Tu), methylthiourea (Metu), N,N-dimethylthiourea (Dmtu), tetramethylthiourea (Tmtu), 2-mercaptopyridine(Mpy), 2-mercaptopyrimidine (Mpm) and thionicotinamide (Tna)). The coordination environment was studied around palladium(II) in *trans*-$[Pd(PPh_3)_2(Mpy)_2]$ and it showed to be nearly regular square-planar. The biological screening of these complexes showed that they are active. However, they show no cytotoxic and antitumour activity against prostate cancer cells (PC3) [59].

Anticancer effects were tested against human breast cancer cell lines, MCF-7 and MDA-MB-231 by the studies of palladium(II) complex, $[Pd(sac)(terpy)](sac).4H_2O$, where sac is saccharinate, and terpy = 2,2':6',2''-terpyridine. This Pd complex showed a strong anti-growth effect in a dose and time dependent manner *in vitro* representing a potentially active novel drug for the breast cancer treatment [60]. The results of some studies designate that [$PdCl_2$

(L)] is a strong chemotherapeutic agent for *cisplatin* resistance of gastric cancer and may have clinical applications [61]. The abilities of *trans*-palladium(II) complex that have diethyl (pyridin-2-ylmethyl)phosphates as non-leaving ligands (*trans*-[$PdCl_2$(2-pmOpe $_2$)]) to induce apoptosis and necrosis in ordinary lymphocytes, A549 cells and HT29 cell lines, were achieved by use of fluorochrome staining. Results exposed that the novel *trans*-palladium(II) complex was more cytotoxic against A549 and HT29 tumour cells than on the ordinary lymphocytes *in vitro*. This novel complex prompts apoptosis in all tested cells, nevertheless in lymphocytes to a slighter degree. That novel *trans*-palladium(II) complex successfully inhibited cancer cells growth [62]. Ever since the introduction of *cisplatin* to oncology in 1978, Pt(II) and Pd(II) compounds have been widely studied with a view to develop an enhanced anticancer agents. Polynuclear polyamine compounds, especially, have fascinated special attention, since they were found to yield DNA adducts not available to straight drugs (through long-distance intra- and interstrand cross-links) and to avoid acquired *cisplatin* resistance. Its study gave a modern overview of the anticancer chemistry of palladium compounds with an importance on the new strategies used in the development of new palladium anticancer agents [63].

Other palladium complexes were synthesised through the reaction of pyridyl triazole ligands with [Pd(COD)Cl_2] in dichloromethane. However, the ligands and complexes were tested for their cytotoxic activity on different cell lines like A549 (human alveolar adenocarcinoma cells), Neuro2a (mouse neuroblastoma cells), HeLa (cervical carcinoma cancer cells), MDA-MB-231 (human breast adenocarcinoma cells) and MCF7 (human breast adenocarcinoma cells). The complexes showed considerable cytotoxicity while the ligands were non-toxic on the tested cell lines [64].

Analysis of cancer cell viability showed that palladium(II) and platinum(II) complexes were cytotoxic on human colon cancer cells in dose-dependent manner. The cytotoxic activity of all palladium(II) and platinum(II) complexes towards selected cancer cells was meaningfully higher in comparison to *cisplatin*. Amongst the tested platinum(II) and palladium(II) complexes the lowest activity was detected for the compounds with the shortest ester chain and the highest activity was distinguished for palladium(II) complex with the n-Pr group in ester chain and for platinum(II) complex with the n-Bu group in ester chain [65]. However the search for a new compound has been going on, what is currently identified that some palladium-based anticancer compounds appear to have influential apoptosis-inducing effects in cancer cells. On these findings, a palladium(II)-saccharinate complex containing terpyridine which was investigated in terms of its anticancer effects against mouse embryonic fibroblast NIH/3T3 (normal cell line) and rat embryonic fibroblast 5RP7 (H-ras transformed cell line) *in vitro*. Its cytotoxic action was confirmed by real time cytotoxicity analysis system [66].

1.7.3 Silver complexes

Anticancer potential for 1,10-phenanthroline-5,6-dione (phendione), $[Cu(phendione)_3](ClO_4)_2 \cdot 4H_2O$ and $[Ag(phendione)_2]ClO_4$ were studied using four human cell lines to check anti-tumour activities of these complexes. The phendione derivatives induced a concentration-dependent decrease in the viability of the four examined cell lines and the results also showed that $[Cu(phendione)_3](ClO_4)_2 \cdot 4H_2O$ displayed the greatest activity. The mechanistic studies showed that phendione and its metal complexes inhibited DNA synthesis which did not appear to be mediated through intercalation. It was concluded from the results of this study that phendione and its Cu(II) and Ag(I) complexes may be

capable of acting as highly successful anti-cancer agents which with careful administration could supply very potent and effective alternatives to *cisplatin* [67].

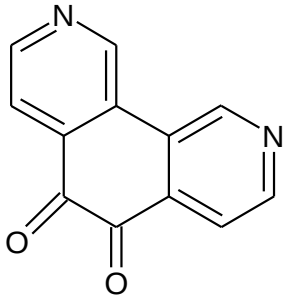


Figure 5: Chemical structure of phendione compound.

In vitro studies were done to examine anti-proliferative effect of 4-hydroxy-3-Nitro-coumarin (hncH), and the mixed-ligand silver(I) complex of 4-Oxy-3-nitro-coumarin-bis (phenanthroline), [Ag(hnc)$(phen)_2$], using four human-derived model cell lines. Whereas [Ag(hnc)$(phen)_2$] was shown to be almost four times more potent than *cisplatin* as anti-tumour agents against HepG2 cells and the experiential anti-proliferative effect shown to be both dose- and time-dependent and also decreased DNA synthesis, but did not intercalate with it. It was concluded that [Ag(hnc)$(phen)_2$] is a more potent anti-proliferative agent than *cisplatin*, capable of changing key biochemical events leading to cell death [68]. Silver nanoparticles lipoic acid complex was characterized using SEM and showed DPPH radical scavenging activity *in vitro* and anti-inflammatory activity against severe and chronic paw models of edema in mice. However, they also protected mice from entire body gamma radiation induced body weight losses and mortality revealing its radioprotecting capacity. Since, their administration to tumour budding mice prior to whole body gamma radiation exposure, aided in improved tumour growth delay [69]. Recently nanoscience is still showing regarding oligodynamic metals. Nanoscientists seem to be positioned to do more to advance some of the most complex strategies for treating cancer [70].

1.7.4 Copper complexes as anti-cancer

Adenine–copper complexes with various ligands [Cl^-, SCN^-, BF_4^- and acac (acetylacetonate ion)] was synthesized and studied, whereas, within these six copper complexes only $Cu_2(adenine)_4Cl_4{\cdot}2EtOH$ (abbreviated as Cu–Ad), showed some toxic effect on different cell lines. However, *in vitro* studies of the biological effect of Cu–Ad complex showed that it binds genomic DNA and decreases significantly. It was shown that $Cu_2(adenine)_4Cl_4{\cdot}2EtOH$(Cu–Ad), has many biochemical sites and with potential anti-cancer activity [71].

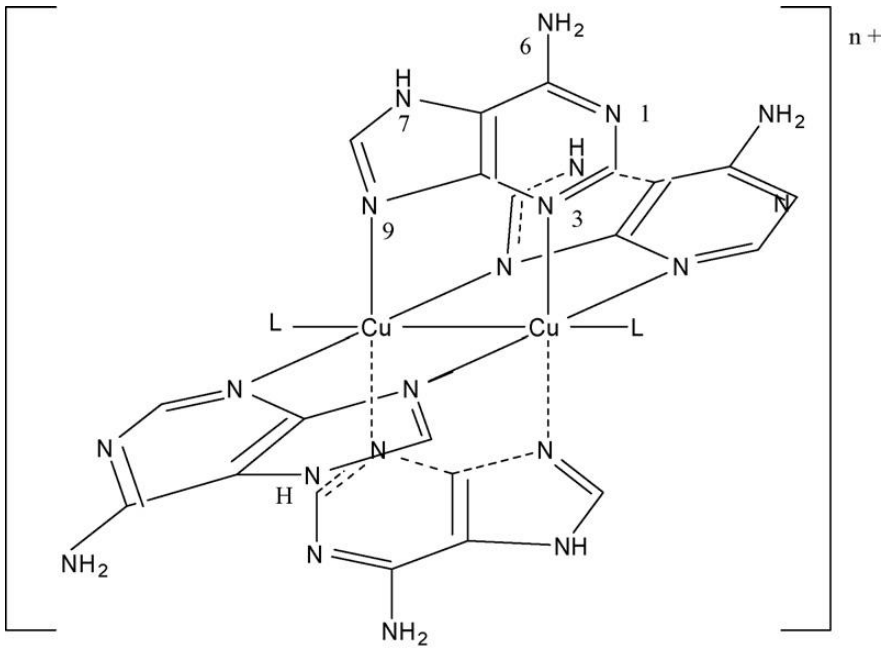


Figure 6: Structure of $Cu_2(adenine)_4Cl_4{\cdot}2EtOH$ [71]

The study of some copper complexes to examine the possibile *in vitro* anti proliferative result of the parent ligand, 4-methylcoumarin-6,7-dioxyacyeic acid (4-MecdoaH_2), and its copper(II) complex, *bis*(phenanthroline4-methylcoumarin-6,7-dioxacetatocopper(II) ([Cu(4-Mecdoa)$(phen)_2$]) using human model cell lines. The studies show that the complex could alter proliferation of both human neoplastic renal (A-498) and hepatic (HepG2) cells. The observed anti-proliferative effect appeared to be dose and time-dependent, and could be

attributed to the complex, rather than any of the free components that is the 1,10-phenanthroline or coumarin ligand, or the simple metal salt. But, this complex shown to decrease the DNA synthesis, but did not intercalate with it [72].

Whereas, [Cu(4-Mecdoa)$(phen)_2$] was shown to be almost 12 times more potent than *cisplatin*. There is no proof that p-glycoprotein-mediated multi-drug resistance is likely to decrease anti-proliferative activity. Finally, flow cytometric analysis showed that the complex functioned through an alteration in cell cycle progression. This copper complex, [Cu(4-Mecdoa)$(phen)_2$] has been shown to be a more potent anti-proliferative agent than either the ligand or *cisplatin,* and is capable of altering key biochemical events leading to the execution of apoptotic and/or necrotic cell death [72]. The bio-inorganic chemistry offers further opportunities for the design of therapeutic agents not available to organic compounds. Three recently synthesized copper complexes with pyridoxal semicarbazone as a ligand, after being exposed to biological tests, showed anticancer activity. As ligand pyridoxal semicarbazone is biologically active, results of biological activity are as expected. Definitely, an activity was demonstrated in breast cancer cells (MCF7 and MDA MB 231) and to proliferative cells (MCF7) [73]. However, anticancer activities of range of simple copper compounds including different types of nitrogen donor ligands such as purine, thiosemicarbazone, imidazole, benzohydroxamic acid and amino acid ligands have been studied [74]. So certain mixed chelate copper-based drugs have displayed better antineoplastic potency than *cisplatin in vitro* and *in vivo* studies [75]. Copper complexes seem to have a mechanism of achievement meaningfully different to that of the clinically used drug *cisplatin*. However the anti-cancer activity of TBZH is enhanced greatly when it is bound to a copper centre [76].

1.7.5 Gold complexes as anti-cancer

Gold complexes have been used to treat a wide range of ailments for many years. The use of gold(III) complexes as an alternative to *cisplatin* treatment was proposed due to the similarities of gold and platinum. Whereas the studies showed that gold(III) complexes might have the same molecular aim as *cisplatin*, many results indicated that proteins, rather than DNA, are targeted by gold complexes. The researcher evaluated cytotoxic and anti-cancer effects of a number of gold(III) dithiocarbamates against human breast cancer cells *in vitro* and *in vivo*. The identification the tumour proteasome as an important target for gold(III) complexes and have shown that proteasome inhibition by gold(III) complexes is linked with apoptosis induction in breast cancer cells. In addition, treatment of human breast tumour-bearing nude mice with a gold(III) dithiocarbamate complex was linked to tumour growth inhibition, supporting the significance of its potential development for breast cancer treatment [77]. Gold(III)-dithiocarbamato complexes have in recent times showed increasing attention as potential anticancer agents since of their strong tumour cell growth–inhibitory effects, commonly achieved by exploiting non-*cisplatin*-like mechanisms of action. Researchers work is to combine the anticancer properties of the gold(III) metal center with the potential chemoprotective purpose of coordinated dithiocarbamates in order to decrease toxic side effects (in particular nephrotoxicity) induced by clinically established platinum-based drugs [78]. The medical and therapeutic value of gold has been documented thousands of years ago, nonetheless its rational use in medicine has not begun until the early 1920s. However, gold(III) is isoelectronic with platinum(II) and the tetra-coordinate gold(III) complexes show the same square-planar geometries as *cisplatin*, that lead to the studies of anticancer activity of gold(III) compounds [79]. In view of structural similarity, square-planar gold(III) compounds were believed to interact with DNA and some other biomolecules in a way like to that of the platinum(II)-based drugs. The gold(III) ion can covalently bind to methionine,

ribonuclease A, and disulfides, and tempt DNA strand breaks under physiologically related conditions. That makes gold compounds to increasingly attracte researchers' consideration as a source of new cytotoxic substances, of potential use in cancer treatment. Several gold(III) compounds, with greatly different molecular structures, have been designed, synthesized and tested as antiproliferative agents during the last decade [80].

1.7.6 Vanadium complexes as anti-cancer

The studies on binuclear vanadium–catecholate complexes $[Et_3NH]_2$ $[V^VO_2$ (l-cat)$]_2$ and $[Et_3NH]_2$ $[V^VO_2$ (l-N-2, 3-D)$]_2$ (cat = catechol, N-2, 3-D = naphthalene-2,3-diol) have been done and the electrochemical behaviour of these two complexes was studied in comparison to that of the free ligands and the two complexes display different redox potentials. The results of the study lead to pharmaceutical screenings of the complexes that have been made against two representative cancer cell-lines A-549 (lung cancer) and Bel-7402 (liver cancer) by MTT assay. $[Et_3NH]_2$ $[V^VO_2$ (l-chat)$]_2$ exhibits well inhibition ratio against both two cell-lines (76.28% and 75.94%), while $[Et_3NH]_2[V^VO_2$(l-N-2, 3-D)$]_2$ displays good and bad effect (65.36% and -68.82%) respectively [81].

The protein tyrosine phosphatase inhibitor potassium bisperoxo (1,10-phenanthroline) oxo-vanadate (V) [bpV (phen)] to the culture medium of human ovarian cancer cells (OVCAR-3) resulted in a dose-dependent reduction in the formation of tumours. The assessment of the potency of bpV(phen) *in vivo* showed the anti-tumour activity. The study of the mechanism of action showed a decrease in Cdk2 kinase activity, an eminent level of Cdk2/$p27^{kip1}$, and the appearance of Cdk2/SHP-1 complexes. Therefore, a cytostatic dose of the protein tyrosine

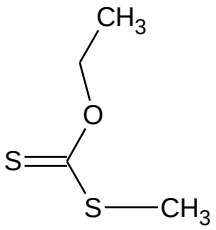
phosphatase inhibitor elevates the intracellular levels of Cdk2/p27 ^{kip} and Cdk2/SHP-1 complexes that show the presence of additional mechanisms underlying the anti-tumour activity [82].

A dual-function anti-cancer agent with anti-angiogenic and anti-mitotic properties structure of $[V(\acute{\eta} -C_5H_5)_2(CH_3C(O)CHC(O)CH_3)](O_3SCF_3)$, $(=[VCp_2(acac)](O_3SCF_3))$ have been studied and its properties of biological functions. The complex geometry is well described as a pseudo-tetrahedral like structure with the centroids of the cyclopentadienyl rings and the two oxygen atoms of the acetylacetonate ring in the ancillary positions of the central vanadium (IV) atom [83].

1.8 Dithiocarbamates and dithiocarbanates ligands

Dithiocarbamate ligands and dithiocarbanate ligands (S, O) show a rich and wide-ranging coordination chemistry with most of the transition metal ions and they are mainly known for their chelating effect [84]. The dithiocarbanate (dithiolate) and dithiocarbamate ligands (Figure 8) are the group of ligands with pronounced binding or chelating potential for transition metals and they are widely used in coordination chemistry cause of their properties [85]. The synthesis of these ligands is relatively simple with the most common method of preparation involving the reaction of carbon disulfide in the presence of a base such as sodium or potassium hydroxide, with any one of a large range of primary and secondary amines or alcohols. Xanthate typically denotes the compound with the formula $ROCS_2$-M+ (R = alkyl; M+ = Na+, K+) and the name xanthate was derived from the Greek word, with a meaning “yellowish, golden”, and indeed most xanthate salts are yellow [86]. Xanthates are

organosulfur compounds that are most important in these two areas, production of cellophane and in mining for the extraction of certain metal ores. They are useful intermediates in organic synthesis. Their name is also referred to esters of xanthic acid which have the structure ROC(=S)SR' as the structure shown below[87].



O-ethyl *S*-methyl carbonodithioate

Figure 7: chemical structure of some xanthate compounds

$ROH + CS_2 + KOH \rightarrow ROCS_2K + H_2O$

Scheme 1: Synthetic route of xanthate family

This reaction includes the attack of the alkoxide salt. Sodium ethoxide gives sodium ethyl xanthate. The purity grade xanthate salts are usually about 90–95% purity. The impurities that include alkali-metal sulfide, sulfate, trithiocarbonates, thiosulfate, sulfite, or carbonate as well as residual raw material such as alcohol and alkali hydroxide.

Some commonly important xanthate salts include:

- Sodium ethyl xanthate (SEX), $CH_3CH_2OCS_2Na$,
- Potassium ethyl xanthate, $CH_3CH_2OCS_2K$,
- Sodium isopropyl xanthate (SIPX)
- Sodium isobutyl xanthate (SIBX)
- Potassium amyl xanthate (PAX)

The metal complexes of these ligands present outstanding structural features and have varied applications, these involve high pressure lubricants in industry, fungicides and pesticides, also as accelerators in vulcanization [88]. Dithiocarbamate compounds have also found application in medicine as anti-malaria, anti-bacterial, anti-alcoholic drug, anticancer, and recently as co-adjuvant in AIDS treatment. However, dithiocarbanate compounds have a major role in flotation of many transition metals [89].

Xanthate compounds fall under the dithiocarbanate family. There are reports that reveal that there has been an increasing of interest in the coordination chemistry of xanthate ligands during the last few years**.** Some reports have approved the coordination chemistry of the xanthate ligands with transition metal and their chelating abilities as they are used in mining industry [90].

In present, days the xanthates (dithiocarbonates) have widespread used in organic syntheses of complex structures and in living radical polymerization chemistry, mainly exploiting the efficiency of these compounds in the production of alkyl free radicals [91] and they are also used in bioinorganic chemistry, in a wide range of chemotherapic applications.

1.8.1 Dithiolate based metal complexes

The studies of molecular structures of [CpCo(tdt)] and [CpCo(Cl_3bdt)] were examined and they revealed that [CpCo(tdt)] is monomeric and coordinatively unsaturated with 16-electrons with two legged piano-stool geometry. Whereas [CpCo(Cl_3bdt)] is dimeric, coordinatively saturated with 18-electrons with three-legged piano-stool geometry. Several intermolecular

Co…S interactions are also observable in the molecules of [CpCo(tdt)]. These dithiolene ligands are abbreviated as follows: tdt = toluene-3,4-dithiolate, Cl_2bdt =3,6-dichlorobenzene-1,2-dithiolate, Cl_3bdt = 3,4,6-trichlorobenzene-1,2-dithiolate, and Cl_4bdt = tetrachlorobenzene-1,2-dithiolate [92].

It have been revealed both dimeric and monomeric structures of [CpCo(dithiolene)] complexes with substituted benzene-1,2-dithiolate ligand and their reversible dimer–monomer structural changes by electrochemical redox reactions. However, the results showed that the [CpCo(tdt)] complex is much less prone to dimerize than the chlorinated complexes, and the fact is related to the electron withdrawing nature of the Cl atom which further decreases the electron density at the Co atom and hence favour the dimerization [92].

The N_2S_2 mixed ligand transition metal complexes, where N_2 stand for phenanthroline and S_2 = 1,2- dithiooxalate (dto) or 1,2-dithiosquarate (dtsq), were studied. Two series of diimine/dithiolate mixed ligand complexes, 1, 2- dithiooxalato-1,10-phenanthrolinemetal(II) and 1,2-dithiosquarato-1,10-phenanthrolinemetal(II) and they are synthetically obtainable for a variety of transition metal ions (M^{2+} = Ni, Cu, Zn, Pd, Pt) [93].

Cu(II) dithiocarbamates, [Cu{$S_2CNR(CH_2CH_2OH)\}_2$], R = Me (1), Et (2), Pr (3) and CH_2CH_2OH (4), have been prepared from $HNR(CH_2CH_2OH)$ (R = Me, Et, Pr and CH_2CH_2OH), CS_2 and $Cu(OAc)_2$ were studied against several colonies microbs *in vitro* studies. Though, they have shown a minimal inhibitory concentration values against *C. albicans* close to those found for Fluconazole. And also they are inert towards Gram-negative

or Gram-positive bacteria, *S. aureus* and *P. auruginosa* and they have good qualities to be an anti - fungal agent of certain microbs [94].

There were studies on several transition metal complexes of benzene-1,2-dithiolate in the various charges and spin states using theoretical approach and compared the calculated results with experimental data. Usually, the stability studies for the complexes showed a decrease with their negative charge and the most stable ones are square-planar $[Cu(bdt)_2]^-$, $[Ni(bdt)_2]^-$ and $[Co(bdt)_2]^-$. However, the complex strength depends on the central metal atom and on the spin state of the system and the changes are related mainly to sulfur atoms, although the influence is evident at the aromatic rings as well (including spin density distribution) [95].

Another series of mixed-ligand neutral copper(II) complexes of the general type [Cu(amine)(i-MNT)] and [Cu(tz)(i-MNT)] have been synthesized and studied for their anti-tumour activity. Though, the sensitive toxicity of the cytogenetic and the *in vivo* studies for anti-tumour activity of these mixed ligands complexes are related to their chemical and physicochemical properties. The aim of the study was to propose and synthesise Cu(II) mixed-ligands complexes with a diversity of controlled lipophilicity values. The remarkable biological results obtained for the compounds have encouraged the researchers to continue work on this study [96].

There were studies on tetraethyl-thiuram disulfide (TETDS) as a transporter of silver ion across a polymeric inclusion membrane; however, the compound is also used as an ionophore

in coated-wire ion-selective electrode for silver ion determination. Primary parameters as ion carrier concentration in the membrane phase and thiosulfate concentration in strip phase have been studied to observe their effect on the transport of silver ions. The silver transport efficiency in the presence of various interfering ions was examined. Their ion-selective electrode show high selectivity towards various alkali, alkaline earth and transition metal ions. Its electrode was used as an indicator electrode in titrations of I^-, Br^- and Cl^- with Ag^+ ion. The study of this compound shows an efficient and selective means for the transport of Ag^+ ion through a PIMs membrane and their performance as an ion-selective electrode containing thiuram sulfide as a transporter [97].

The biomimetic models of diiron dithiolate complexes containing rigid and conjugated bridges, [μ-SC_6H_4-2-(CO)S-μ]$Fe_2(CO)_6$, [2-μ-SC_5H_3N-3-(CO)-S-μ]$Fe_2(CO)_6$, and the PPh_3-monosubstituted complex [μ-SC_6H_4-2-(CO)S-μ]$Fe_2(CO)_5(PPh_3)$ (1-P), were prepared for the [FeFe]-hydrogenase active site. The outcome signify that the S-to-S bridge can apparently influence the redox characters of the diiron dithiolate model complexes, if another approach, besides CO-displacement, to tune the reduction potentials of candidate catalysts for electro- and photo-chemical proton reduction of molecular hydrogen [98].

The study of the synthesis of triorganotin(IV)-, chlorodiorganotin(IV)- and diorganotin(IV) 4-ethoxycarbonylpiperazine-1-carbodithioates with general R_3SnL {where R = CH_3 (1), n-C_4H_9 and C_6H_5}, R_2SnClL {where R = CH_3, n-C_4H_9 and C_6H_5} and R_2SnL_2 {where R = CH_3, n-C_4H_9 and C_6H_5}, correspondingly. However, the compounds of distinct antimicrobial (antibacterial and antifungal) potency and reasonable insecticidal activity and they also inhibit successfully the activity of urease enzyme. The organotin(IV) complexes derivatives

of 4-ethoxycarbonylpiperazine-1-carbodithioate ligand has been synthesized and results show the diverse structural motifs for these compounds (tetrahedral, square-pyramidal, trigonal-bipyramidal and octahedral geometries) depending upon the mode of coordination of ligand as well as the presence or absence of intermolecular S….Sn interactions (in case of five-coordinated Sn). Vital antimicrobial, insecticidal and anti-urease activity of these compounds can be credited to their simplicity of diffusion and the ability to find secondary interactions with the cell constituents [99].

The complexes [Pt(pq)Cl_2] (1) and [Pt(pq)(bdt)] (2) (where pq = 2-(20pyridyl)quinoxaline and bdt = benzene-1,2-dithiolate) have been synthesized and the photo cleavage of DNA by [Pt(pq)(bdt)] has been studied. Under these experimental conditions, it was indistinct that [Pt(pq)(bdt)] complex can photocleave DNA, also the ability of Pt(pq)(bdt) to inhibit proliferation of human tumour cell lines was tested and the results show a few cytoxytic effect on the SF-286 cells. In addition, the photo cleavage reaction on calf thymus and ds-DNA has been studied by CD and agarose gel electrophoresis. [Pt(pq)(bdt)] and [Pt(pq)Cl_2] emerge to be able to open the helix and change the base stacking, but the mechanism must be different due to the existence of the bdt ligand in [Pt(pq)(bdt)]. In conclusion these complexes may be helpful by probing DNA and further studies will be needed to understand the [Pt(pq)Cl_2] or [Pt(pq)(bdt)] interactions [100].

The study of the synthesis, classification, and structural computation of small molecular potassium-encapsulated arsenic-dithiolato compounds provide a basic understanding about arsenic metabolism behaviours in biological systems. The novel air stable potassium-encapsulated arsenic-dithiolato compounds, [$K_2As_2(L_1)_3$](BF_4) (1) and [$K_2As_2(L_2)_3$](BF_4) (2),

were prepared using deprotonated 2,6-bis(mercaptomethyl)pyridine (L_1H_2) and 1,3-dimercapto-m-xylene (L_2H_2) to react with $AsCl_3$ in the presence of potassium cation. The theory of density functional calculation as well chains for the formation and binding properties of the potassium-encapsulated arsenic-dithiolato compounds [101].

Exploitation of the oxo-rhenium core '3+1' chemistry has allowed preparation and characterization of a series of thiol based fatty acid metal complexes. The Group VII rhenium-oxo chemistry was converted to the gamma-emitting 99mTc isotope, however the synthesis of $[TcO\{\acute{\eta}^3\text{-}(SCH_2CH_2)_2N(CH_2)_{15}CO_2H)\}\{\acute{\eta}^1\text{-}(C_6H_5CH_2S)\}]$ that was HPLC purified, and injected into rats. In addition, the analogous rhenium complex was used to verify the synthesis of $[TcO\{\acute{\eta}^3\text{-}(SCH_2CH_2)_2N(CH_2)_{15}CO_2H)\}(\acute{\eta}^1\text{-}(C_6H_5CH_2S)]$ using HPLC. The outcome show myocardial uptake greater than 0.2% DPG at all-time points by high myocardial clearance rates [102].

The synthesis of an immobilized oxorhenium(V) dithiolate catalyst, (SiO_2-RTA)Re(O)(Me)(PPh_3), that oxidizes a sulfide and dibenzothiophenes has been studied and catalyst activity and selectivity mirror those exhibited by its solution analogue, [Re(O)(pdt)(Me)(PPh_3)]. Also a supported catalyst is recyclable and show a longer lifetime for DBT oxidation at 100°C than the homogeneous analogue [Re(O)(pdt)(Me)(PPh_3)]. In conclusion, the catalyst easily alter the refractory sulfur compounds DBT and 4,6-Me_2DBT in simulated petroleum feed stocks to their sulfoxides or sulfones [103].

1.9.1 Metal ion complexes as antimicrobial

The chemistry of transition metal complexes has received much attention in recent years on account of their rational design and synthesis in coordination chemistry, also because of their potential applications as functional materials, enzymatic reaction mechanism and in bioinorganic chemistry. The transition metal complexes with nitrogen donors are applied in various activities such as anticancer, antitubercular, antibiotic, antimicrobial and antifungal agent [104]. The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents[105]. Bacteria can grown in different materials that are in close contact with humans, foods, for example it is very important to control this matter in order to prevent risk of infections. Many biologically active compounds used as drugs possess modified pharmacological and toxicological potentials when administered in the form of metal based compounds. Various metal ions potentially and commonly used are cobalt, copper, nickel and zinc because of forming low molecular weight complexes and therefore, prove to be more beneficial against several disease [106]. Silver and its compounds have long been used as antimicrobial agents in medicine. Silver is active at low concentrations and has a low toxicity. Silver sulfadiazine is a widely used broad-spectrum antibiotic ointment, effective against a broad range of bacteria and some yeasts. It is used to prevent and treat skin infections on the areas of burnt skin.

Co-ordination compounds exhibit different characteristic properties which depend on the metal ion to which they are bound [107]. On the basis of nature of the metal as well as the type of ligand, these metal complexes have extensive applications in various fields of human interest. Chelation or complexation observes more potent antibacterial effect against some microorganisms than the respective drug. Synthesis of Co(II), Ni(II) and Zn(II) complexes with thiazole ring containing Schiff base ligands and their antimicrobial activities were tested against eight different microorganisms [108].

1.9.2 Metal xanthate complexes as antimicrobial

Alkyldithiocarbonates, more commonly referred to as xanthates, were first prepared by Zeise. Their applications as vulcanizers, fungicides and flotation agents in metallurg [109]. Cobalt xanthates are similar to hybrid materials,because they have an organic sulfide part and inorganic metal part as iron xanthate. These organometallic compounds have wide ranging properties such as optical, electrical, and magnetic characteristics. It has been shown that these cobalt xanthates thin films show different properties such as an antibacterial agent, magnetic and semiconductor material, which allowed them to be used for data storage, solar cell production, and water purification [110,111].

1.10 Hypothesis

This study involved the synthesis of the metal dithicarbonate (xanthate family) complexes and to study their biological application as antibacterial or anticancer agents. The focus is on the sulfur atoms of the xanthate family as there are many studies that have shown that they are applied as insecticides, and they can play a good role as anti-fungal agents and many

more. There is also a main challenge of synthesis of novel complexes that can replace the well-known *cisplatin* that have side effects as anticancer.

1.11 Aim of the study

- To synthesize dithiocarbonate/xanthate ligands
- To characterize the ligands with elemental analysis and spectroscopic techniques
- Synthesize metal dithiocarbonate complexes
- Characterize metal dithiocarbonate complexes
- Explore the biological application of the metal complexes as antibacterial and anticancer agents.

1.12 References

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Chapter Two

2.0 Experimental

2.1 Chemicals and solvents

Absolute ethanol, methanol, propanol, butanol, phenol, potassium hydroxide, carbon disulfide. nickel chloride hexa-hydrate, nickel bromide bis-triphosphine, silver nitrate, copper chloride di-hydrate, palladium di-acetonitrile chloride, and platinum 1, 5 hexa- octadiene

chloride. Ethanol, methanol, water, dichloromethane, chloroform, toluene, acetonitrile, diethyl ether.

2.2.0 Physical measurements

Melting point, solubility test, conductivity measurement, elemental analysis as well as spectroscopic techniques; infrared, UV− visible and NMR spectroscopy, has been used for the characterization of the complexes. The choice of characterization techniques was carefully selected to obtain information relating to the various aspects that constitute the nature of the synthesized complexes. Stuart melting point apparatus model SMP 11 was used for melting point determination, conductivity measurement was determined using CRISON EC-Meter BASIC 30+ conductivity/TDS Meter. FTIR as well as UV− Vis spectra was obtained on a Perkin− Elmer Model System 2000 FTIR spectrophotometer in the range 4000 − 400 cm^{-1} and Perkin− Elmer Lambda 25 UV− VIS spectrophotometer respectively. And NMR results were obtained on a Varian− NMR− vnmr s600 MHz spectrometer at 25 ^{o}C.

2.2.1 Melting point

Samples of complexes in capillary tubes were introduced into a Stuart melting point apparatus model SMP 11 to determine its melting point.

2.2.2 Solubility

Solvents of different dielectric constant and polarities at hot and cold temperatures, ranging from Ethanol, methanol, water, dichloromethane, chloroform, toluene, acetonitrile, diethyl ether etc., by way of shaking a little amount of complexes with them in test tubes were used to determine the solubility of complexes.

2.2.3 Conductivity measurement

CRISON EC-Meter BASIC 30+ conductivity/TDS Meter was used to determine the conductivity of ligands water as dissolving solvent and for complexes in solution in 10^{-3} chloroform, toluene and dichloromethane as dissolving solvent.

2.2.4 Elemental analysis

Elemental analyses for C, H, N and S were carried out on a Fison elemental analyzer.

2.2.5 Infrared spectroscopy

Infrared spectra of the complexes were recorded as KBr pellets on a Perkin− Elmer Model System 2000 FT− IR spectrophotometer in the range 4000 − 370 cm^{-1}, ensuring that the pellets are moisture free. Important IR bands, such as *ν*(C-S), *ν*(C-O-C), *ν*(C=S) and *ν*(M-S) symmetric and asymmetric stretching frequencies were studied to determine the mode of coordination between the metal ions and ligands.

2.2.6 UV− Visible spectroscopy

The UV− Vis (electronic) spectra were recorded on a Perkin− Elmer Lambda 25 UV− VIS spectrophotometer with quartz cells (1 cm path length) using water, chloroform, toluene and dichloromethane as solvents. Observed spectroscopic data, spectral components were obtained from the Gaussian curve analysis.

2.2.7 NMR spectroscopy

The ^{1}H-NMR spectra in CDC_3 and D_2O were performed and recorded on a Varian− NMR− vnmr s600 MHz spectrometer at 25 ºC, using high− power proton decoupling, and pulse sequence: s2pul. Proton chemical shifts in deuterated DMSO-d_6 and deuterated water D_2O were referenced to DMSO-d_6 (^{1}H NMR, δ(DMSO-d_6) = 2.49 ppm) and D_2O (^{1}H NMR, $\delta(D_2O)$ = 1.86 ppm). Chemical shifts for proton resonances are reported relative to tetramethylsilane.

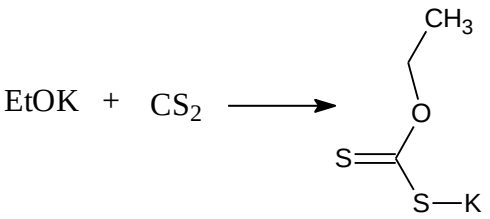
2.3.0 Synthesis of the ligands

2.3.1 Synthesis of potassium O-ethyl xanthate

Potassium hydroxide pellets (21 g, 0.75 mol) were placed in 250 mL round bottom flask that was fitted with refluxing condenser and 76 mL of absolute ethanol was added to the flask. The mixture was heated under reflux for 1 h. The refluxed mixture was allowed to cool and the liquid was decanted from the residual solid into dry 250 mL conical flask in an ice bath after which carbon disulfide (22.5 mL, 0.75 mol) was slowly added with constant stirring. The resultant solid was filtered on a sintered glass funnel under the pump and washed with diethyl ether (3 x 25 mL) to obtain yellowish gold solid. The solid was dried in desiccators over silica gel.

Yield: 11.7209 g (86.5 %). IR (cm^{-1}); *ν*(C-S) 621.97, *ν*(C-O-C) 1187.48, *ν*(C=S) 1049.81. M. p. = 195 ^{o}C

The other ligands were prepared using the same procedure described in KOEtdtc.

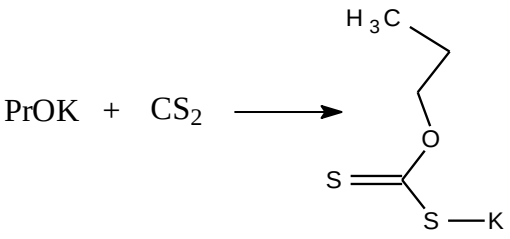


Scheme 2.1: Synthesis of potassium O-ethyl xanthate

2.3.2 Synthesis of potassium O-propyl xanthate

Potassium hydroxide pellets (21 g, 0.75 mol), absolute propanol (76 mL) and of carbon disulfide (22.5 mL, 0.75 mol) were used as staring materials. A pale yellow solid was obtained.

Yield: 13.8463 g (93.8 %). IR(cm^{-1}), *v*(C-S) 621.72, *v*(C-O-C) 1154.31, *v*(C=S) 1235.07. M. p. = 160 ^{o}C.

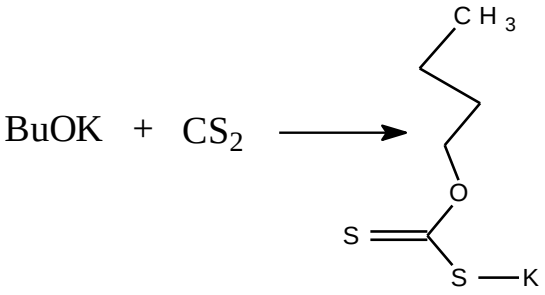


Scheme 2.2: Synthesis of potassium O-propyl xanthate

2.3.3 Synthesis of potassium O-butyl xanthate

Potassium hydroxide pellets (21 g, 0.75 mol) absolute butanol (76 mL) and carbon disulfide (22.5 mL, 0.75 mol) were used as starting materials. A yellowish brown solid was obtained.

Yield: 10.5361 g (95.4 %). IR(cm^{-1}), *v*(C-S) = 615.06, *v*(C-O-C) 1161.66, *v*(C=S) 184.98. M. p. = 189 ^{o}C.



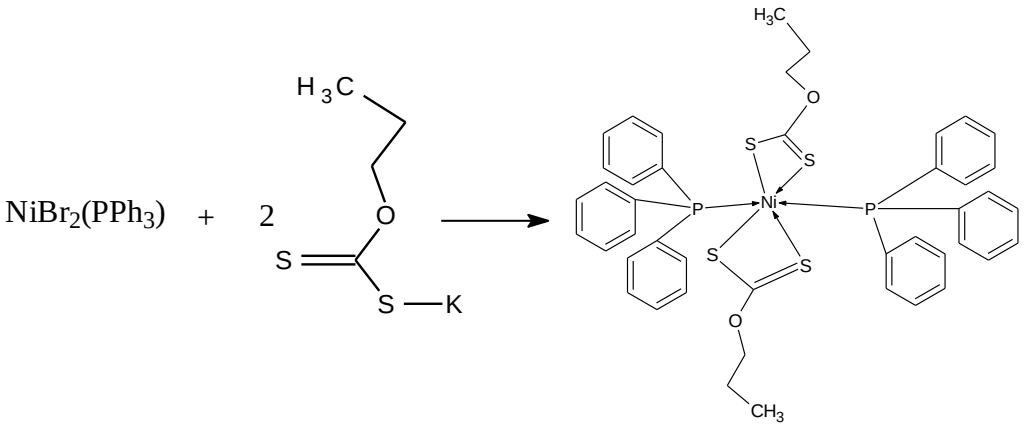
Scheme 2.3: Synthesis of potassium O-butyl xanthate

2.4.0 Synthesis of the complexes

2.4.1 Synthesis of $[Ni(PPh_3)_2(OPrdtc)_2]$

A concentrated solution of KOPrdtc (0.4358 g, 2.50 mmol) was dissolved in absolute ethanol (40 mL) follow by the addition of a solution of $NiBr_2{\cdot}(PPh_3)_2$ (0.9288 g, 1.25 mmol) in absolute ethanol (20 mL). The reaction was stirred at room temperature for 1h. A dark brown solid was obtained. The solid was filtered on a sintered glass funnel and washed with diethyl ether (3 x 25 mL) .

Yield: 1.0664 g (87.8 %). IR(cm^{-1}), *v*(C-S) 694.71, *v*(C-O-C) 1143.02, *v*(C=S) 1179.97 and *v*(M-S) = 357.90. Elemental analysis (Cal.) Found: C = (61.96) 61.91, H = (5.20) 4.88. M. p. = 260 ^{o}C. UV-vis (nm), (LLCT) 421, (MLCT) 483.

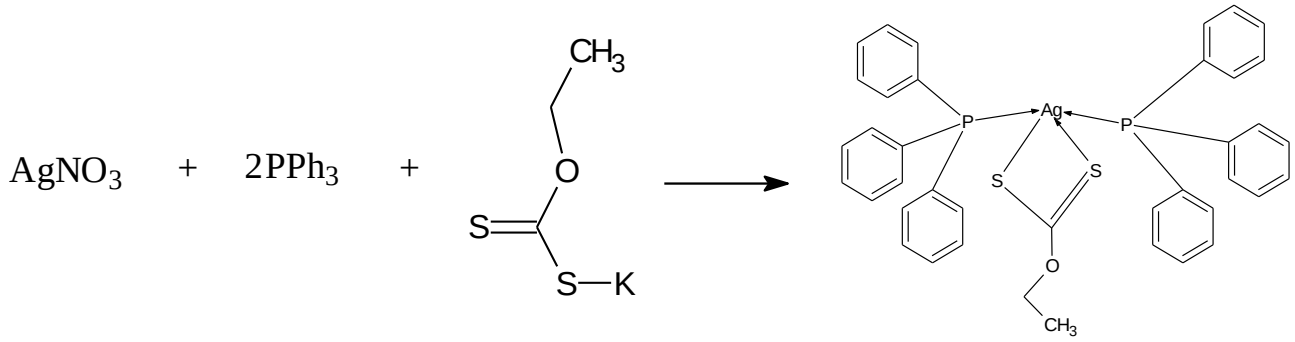


Scheme 2.4: Synthesis of $[Ni(PPh_3)_2(OPrdtc)_2]$

2.4.2 Synthesis of $[Ag(PPh_3)_2(OEtdtc)]$

A solution of ($AgNO_3$) (0.3397 g, 2 mmol) in water-acetoitrile mixture (1:4) was added to a solution of PPh_3 (1.0492 g, 4 mmol) in methanol (30 mL). The mixture was refluxed for 1 h and allowed to cool, after which an aqueous solution of KOEtdtc (0.3206 g, 2 mmol) was added. The mixture was stirred for 1 hr resulting in pale brown solid. The precipitate filtered and washed with diethyl ether (3 x 25 mL).

Yield: 0.8968 g (71.3 %). IR (cm^{-1}), *v*(C-S) 690.93, *v*(C-O-C) 1035.63, *v*(C=S) 1138.07 and *v*(M-S) 374.64. Elemental analysis (Cal.) Found : C =(62.23) 61.81, H = (4.69) 4.62. M. p. = 131 ^{o}C.



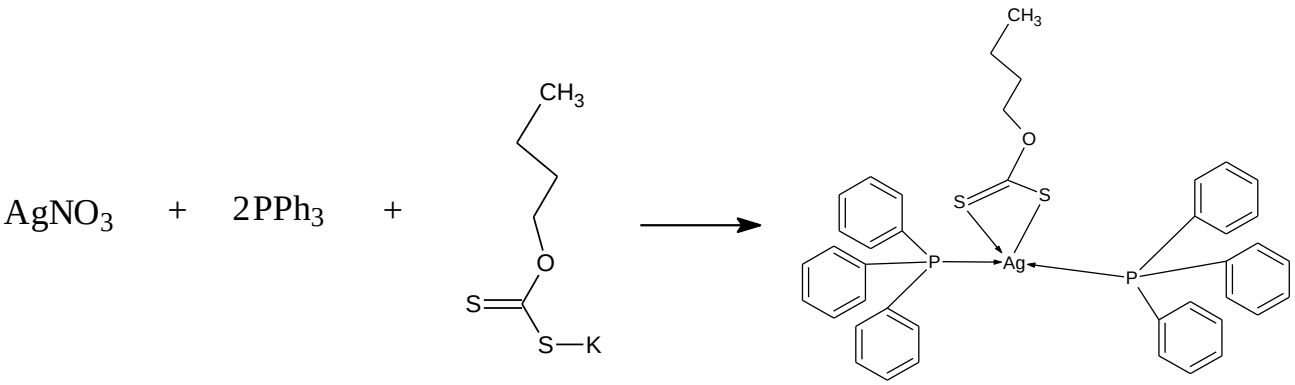
Scheme 2.5: Synthesis of $[Ag(PPh_3)_2(OEtdtc)]$

The other silver and copper complexes were prepared using the procedure for the synthesis for $[Ag(PPh_3)_2(OEtdtc)]$ in section 2.4.2.

2.4.3 Synthesis of $[Ag(PPh_3)_2(OBudtc)]$

$AgNO_3$ (0.3397 g, 2 mmol), PPh_3 (1.0492 g, 4 mmol) and KOBudtc (0.3767 g, 2 mmol) were used as starting materials. A pale solid was obtained.

Yield: 1.2726 g (66.7 %). IR(cm^{-1}), *v*(C-S) 693.45, *v*(C-O-C) 1130.66, *v*(C=S) 1046.61 and *v*(M-S) 355.98. Elemental analysis (Cal.) Found: C = (63.07) 62.67, H = (5.04) 4.82. M. p. = 119 ^{o}C.

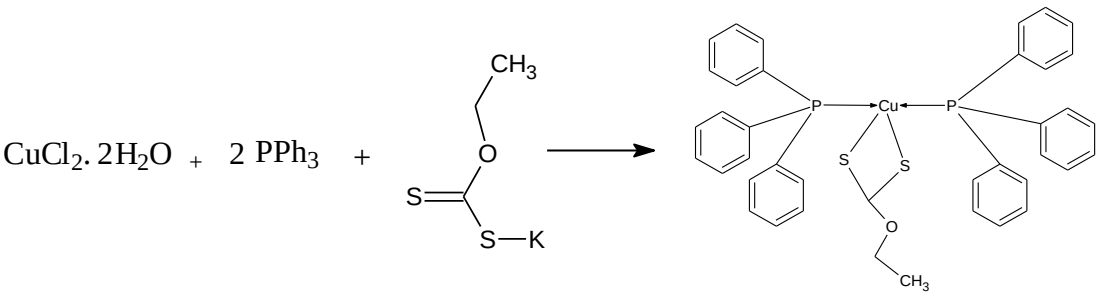


Scheme 2.6: Synthesis of $[Ag(PPh_3)_2(OBudtc)]$

2.4.4 Synthesis of $[Cu(PPh_3)_2(OEtdtc)]$

$CuCl_2.2H_2O$ (0.3410 g, 2 mmol), PPh_3 (1.0492 g, 4 mmol) and KOEtdtc (0.3206 g, 2 mmol) were used as staring materials. A brick red solid was obtained.

Yield: 1.0665 g (77.3 %). IR(cm^{-1}), *v*(C-S) 618.51, *v*(C-O-C) 1142.62, *v*(C=S) 1042.81 and *v*(M-S) = 370.03. Elemental analysis (Cal.) Found: C = (66.09) 66.16, H = (4.98) 4.66. M. p. = 288 ^{o}C. UV-vis (nm), (LLCT) 318, (MLCT) 340.

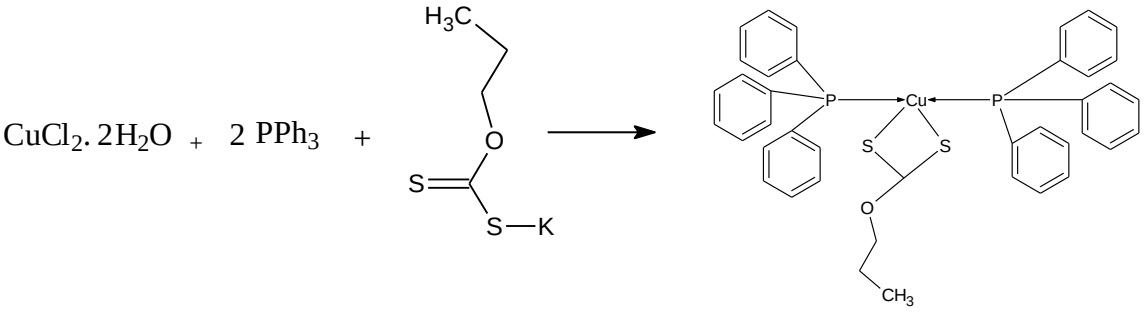


Scheme 2.7: Synthesis of $[Cu(PPh_3)_2(OEtdtc)]$

2.4.5 Synthesis of $[Cu(PPh_3)_2(OPrdtc)]$

$CuCl_2.2H_2O$ (0.3410 g, 2 mmol), PPh_3 (1.0492 g, 4 mmol) and KOPrdtc (0.3486 g, 2 mmol) were used as starting materials. A yellow solid was obtained.

Yield: 0.9915 g (65.1 %). IR(cm^{-1}), *v*(C-S) 692.12, *v*(C-O-C) 1168.57, *v*(C=S) 1026.93 and *v*(M-S) 382.75. Elemental analysis (Cal) Found: C = (66.47) 66.35, H = (5.16) 4.71. M. p. = 280 ^oC. UV-vis (nm), (LLCT) 321, (MLCT) 342.

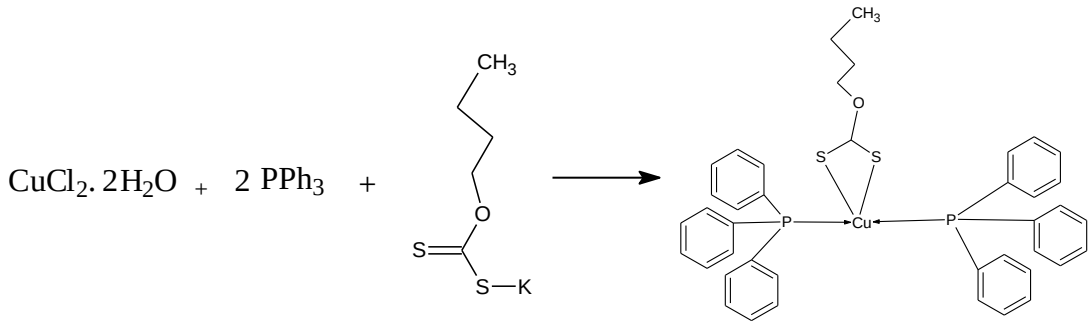


Scheme 2.8: Synthesis of $[Cu(PPh_3)_2(OPrdtc)]$

2.4.6 Synthesis of $[Cu(PPh_3)_2(OBudtc)]$

$CuCl_2.2H_2O$ (0.3410 g, 2 mmol), PPh_3 (1.0492 g, 4 mmol) and KOBudtc (0.3767 g, 2 mmol) were used as starting materials. A yellow solid was obtained.

Yield: 0.9947 g (78.4 %). IR(cm^{-1}), *v*(C-S) 618.41, *v*(C-O-C) 1157.73, *v*(C=S) 1026.44 and *v*(M-S) 374.03. Elemental analysis (Cal.) Found: C = (66.84) 66.72, H = (5.34) 5.52. M. p. = 277 ^oC. UV-vis (nm), (LLCT) 320, (MLCT) 344.

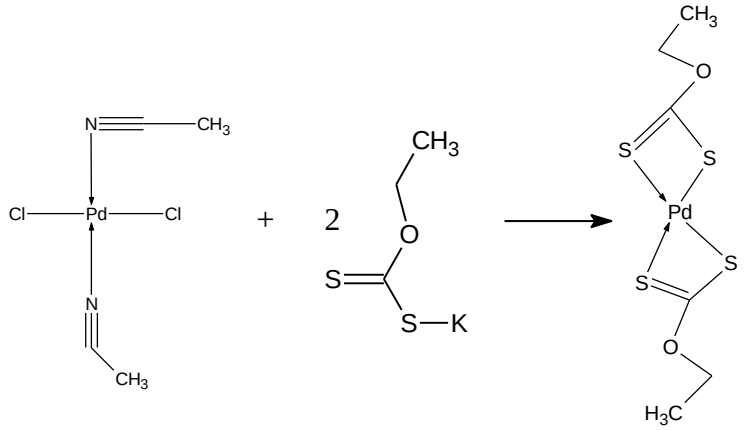


Scheme 2.9: Synthesis of $[Cu(PPh_3)_2(OBudtc)]$

2.4.7 Synthesis of $[Pd(OEtdtc)_2]$

A solution of $[Pd(CNCH_3)_2Cl_2]$ (0.2594 g, 1 mmol) dissolved in DCM (15 mL) was added to a solution of KOEtdtc (0.2424 g, 2 mmol) in methanol (15 mL). The reaction was refluxed for 4 h and allowed to cool, after which the the dark brown solid was filtered and washed with methanol followed by diether ether.

Yield: 0.2031 g (74 %). IR(cm^{-1}), *ν*(C-S) 619.57, *ν*(C-O-C) 1144.03, *ν*(C=S) 1009.97 and *ν*(M-S) 401.35. Elemental analysis (Cal.) Found: C = (27.87) 28.02, H = (3.74) 3.50. M. p. = 145 ^{o}C. UV-vis (nm), (LLCT) 361, (MLCT) 460.



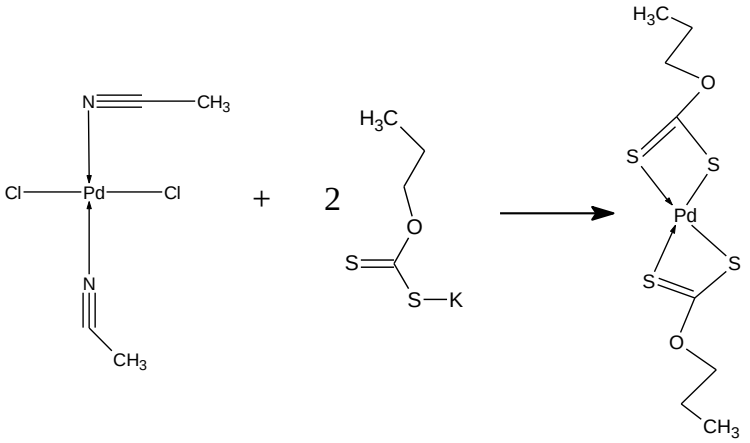
Scheme 2.10: Synthesis of $[Pd(OEtdtc)_2]$

The other palladium and platinum complexes were prepared using the procedure in the synthesis for $[Pd(OEtdtc)_2(CNCH_3)_2]$ in section 2.4.7

2.4.8 Synthesis of $[Pd(OPrdtc)_2]$

$[Pd(CNCH_3)_2Cl_2]$ (0.2594 g, 1 mmol) and KOPrdtc (0.2704 g, 2 mmol) were used as starting materials. A dark brown solid was obtained.

Yield: 0.3073 g (85 %). IR(cm^{-1}), *v*(C-S) 621.56, *v*(C-O-C) 1136.57, *v*(C=S) 1027.19 and *v*(M-S) 405.64. Elemental analysis (Cal.) Found: C = (31.40) 31.32, H = (4.39) 4.01. M. p. = 143 ^{o}C. UV-vis (nm), (LLCT) 362, (MLCT) 459.

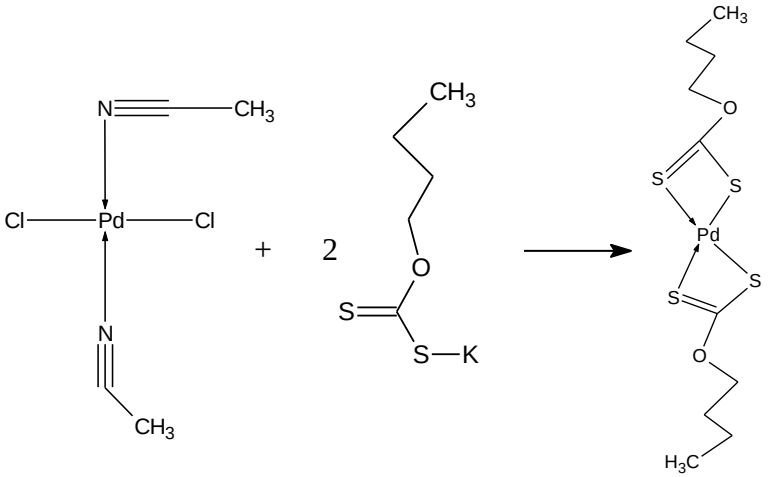


Scheme 2.11: Synthesis of $[Pd(OPrdtc)_2]$

2.4.9 Synthesis of $[Pd(OBudtc)_2]$

$[Pd(CNCH_3)_2Cl_2]$ (0.2594 g, 1 mmol) and KOBudtc (0.2985 g, 2 mmol) were used as starting materials. A dark brown solid was obtained.

Yield: 0.3545 g (92 %). IR(cm^{-1}), *v*(C-S) 619.99, *v*(C-O-C) 1141.92, *v*(C=S) 1025.60 and *v*(M-S) 388.50. Elemental analysis (Cal.) Found: C = (34.53) 34.23, H = (4.97) 4.74. M. p. = 150 ^{o}C. UV-vis (nm), (LLCT) 359, (MLCT) 461.

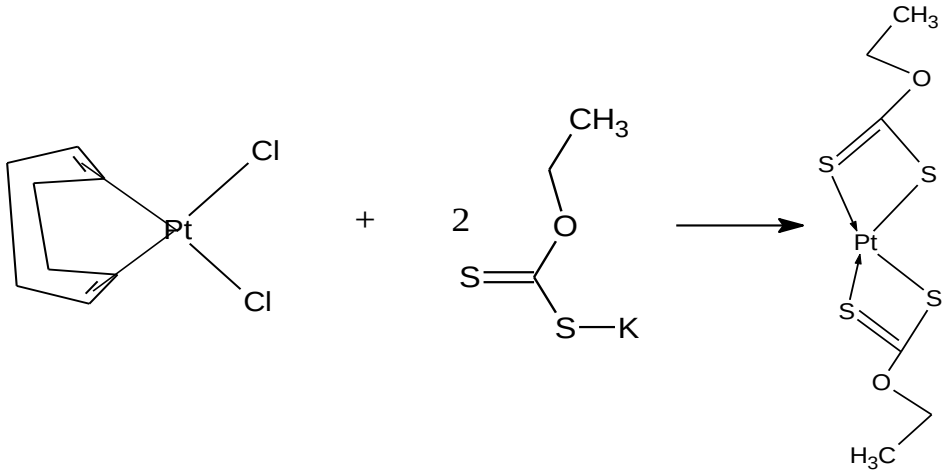


Scheme 2.12: Synthesis of [Pd(OBudtc)$_2$]

2.4.10 Synthesis of [Pt(OEtdtc)$_2$]

[Pt(COD)Cl$_2$] (0.3742 g, 1 mmol) and KOEtdtc (0.2424 g, 2 mmol) were used as starting materials. A brick red solid was obtained.

Yield: 0.2965 g (88 %). IR(cm^{-1}), *v*(C-S) 624.75, *v*(C-O-C) 1115.39, *v*(C=S) 1018.45 and *v*(M-S) 390.80. Elemental analysis (Cal.) Found: C = (30.82) 30.56, H = (4.06) 3.99. M. p. = 165 ^{o}C. UV-vis (nm), (LLCT) 362, (MLCT) 457.

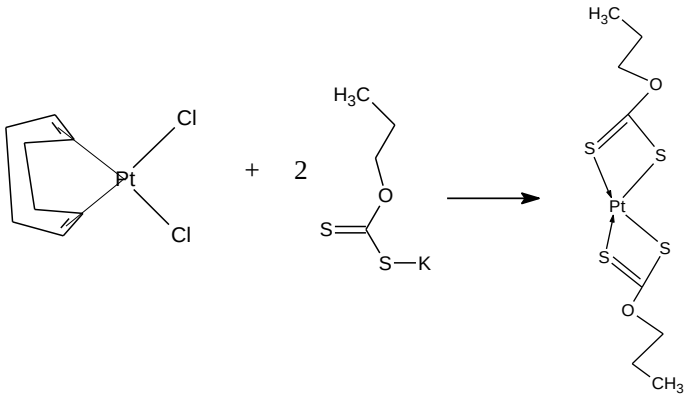


Scheme 2.13: Synthesis of [Pt(OEtdtc)$_2$]

2.4.11 Synthesis of [Pt(OPrdtc)$_2$]

[Pt(COD)Cl$_2$] (0.3742 g, 1 mmol) and KOPrdtc (0.2704 g, 2 mmol) were used as starting materials. A brick red solid was obtained.

Yield: 0.3823 g (70 %). IR(cm^{-1}), *v*(C-S) 623.06, *v*(C-O-C) 1168.08, *v*(C=S) 1024.08 and *v*(M-S) 387.46. Elemental analysis (Cal.) Found: C = (33.50) 33.40, H = (4.57) 4.20. M. p. = 160 ^{o}C. UV-vis (nm), (LLCT) 362, (MLCT) 463.

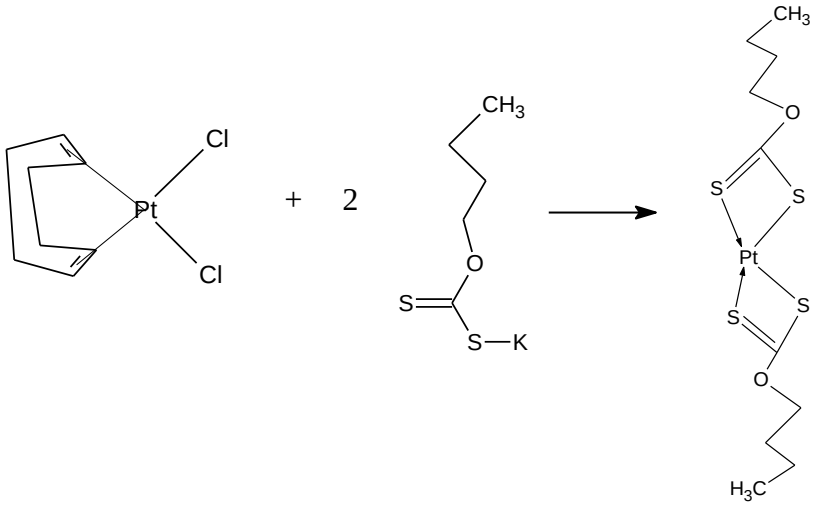


Scheme 2.14: Synthesis of [Pt(OPrdtc)$_2$]

2.4.12 Synthesis of [Pt(OBudtc)$_2$]

[Pt(COD)Cl$_2$] (0.3742 g, 1 mmol) and KOBudtc (0.2985 g, 2 mmol) were used as starting materials. A brick red solid was obtained.

Yield: 0.2111 g (87%). IR(cm^{-1}), *v*(C-S) 622.00, *v*(C-O-C) 1150.79, *v*(C=S) 1095.72 and *v*(M-S) 402.27. Elemental analysis (Cal.) Found: C = (35.93) 35.95, H = (5.03) 4.97. M. p. = 164 ^{o}C. UV-vis (nm), (LLCT) 361, (MLCT) 463.



Scheme 2.15: Synthesis of [Pt(OBudtc)$_2$]

Chapter Three

3.0 Results and discussion

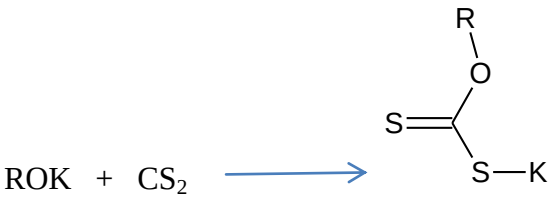
3.1 Introduction

Xanthate ligands and their corresponding Ni(II), Ag(I), Cu(II), Pd(II) and Pt(II) complexes were synthesized as presented in Chapter Two. All the compounds were characterized by FTIR, conductivity, elemental analysis, UV− Vis and melting point. The Pd(II) and Pt(II) complexes and xanthate ligands were further characterized by ^{1}H-NMR spectroscopy. Attempts to grow single crystals of the compounds were unsuccessful.

Dithiocarbamates and dithiocarbanate are multipurpose ligands which bind to transition metal ions to form stable complexes in a wide range of oxidation states. Dithiocarbanate and dithiocarbamate complexes are use in many areas like materials science, medicine, mining industry and agriculture. Their adaptability, distinct manner and the metal-centered electrochemistry is astonishing but the complexes are least explored in the growing field of supra-molecular chemistry [1]. Dithiocarbamates compounds have also found in medicine as anti-malaria, anti-bacterial, anti-alcohol drug, anticancer, and recently as co-adjuvant in AIDS treatment [2, 3].

3.2 Synthesis of xanthate ligands

Ligands **L1, L2** and **L3** were prepared by reacting potassium hydroxide with carbon disulfide and obtained in good yield. A general structure of the ligands is given in Figure 3.1. Characterization and spectroscopic data of the ligands are summarized in Table 3.1 and 3.2. Representative IR and UV-vis of the ligands are shown in Figure 3.2 and 3.3 respectively.



R = Et, Pro and Bu.

Scheme 3.1: General synthesis for the xanthate ligand.

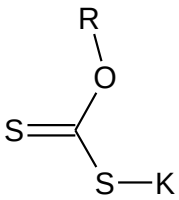


Figure 3.1: Proposed general structure of xanthates compounds

Table 3.1 Analytical data for the ligands

Compound	Molecular Formulae	Molar Mass g/mol	Colour	Analytical Data (%) C Found (calc.)	Analytical Data (%) H Found (calc.)	Yield (%)	M.P (ºC)	Cond. µS mS/cm
KOEtdtc	$KS_2OC_3H_5$	160.3	Yellowish gold	(22.48) 22.60	(3.14) 3.22	86.5	195	12.13
KOPrdtc	$KS_2OC_4H_7$	174.32	Pale yellow	(27.56) 27.62	(4.05) 3.90	93.8	160	4.53
KOBudtc	$KS_2OC_5H_9$	188.35	Yellowish brown	(31.89) 32.02	(4.82) 4.41	95.4	189	9.46

3.2.1 Infrared spectra of xanthate compound

Table 3.2: The FTIR data for the xhanthate compounds.

Compounds	ν(C-S) (cm^{-1})	ν_s(C-O-C) (cm^{-1})	ν_{as}(C=S) (cm^{-1})
(KOEdtc)	621.97	1049.81	1187.48
(KOPrdtc)	621.72	1235.07	1154.31
(KOBudtc)	615.06	1184.98	1161.66

Infrared spectra in xanthates and dixanthogens have been reported [5-7] and an understanding of the vibration frequencies of C=S and C-O groups for these compounds can be used as to determine their coordination modes. Assignment of these frequencies is slightly challenging since both of them lie in the same region 1000 to 1275 cm^{-1} [8]. In addition, the absorption bands of both these groups are intense and very vulnerable to the environmental changes in the molecules. It has been shown that the location of the C=S absorption frequency is a matter of some difficulty in organic thio compounds [4, 9]. While Bak et *al.* [10] have assigned the band close to 1200 cm^{-1} to the C=S stretching mode of vibration in dithioesters, Bellamy and Rogasch [11] have allocated the frequencies between 1000 and 1200 cm^{-1} for different types of thio compounds. These illustrations show that the C-O and C=S group frequencies fall in the same region. However, the C-O symmetrical stretching vibration takes place around 1030 cm^{-1} in compounds like alkyl esters, alcohols, and silicon ethers and around 1200 cm^{-1} in aryl esters [12]. In the current study, the higher frequency around 1200

cm^{-1} is due to the C=S group, while the lower one around 1030 cm^{-1} is due to the C-O group [8].

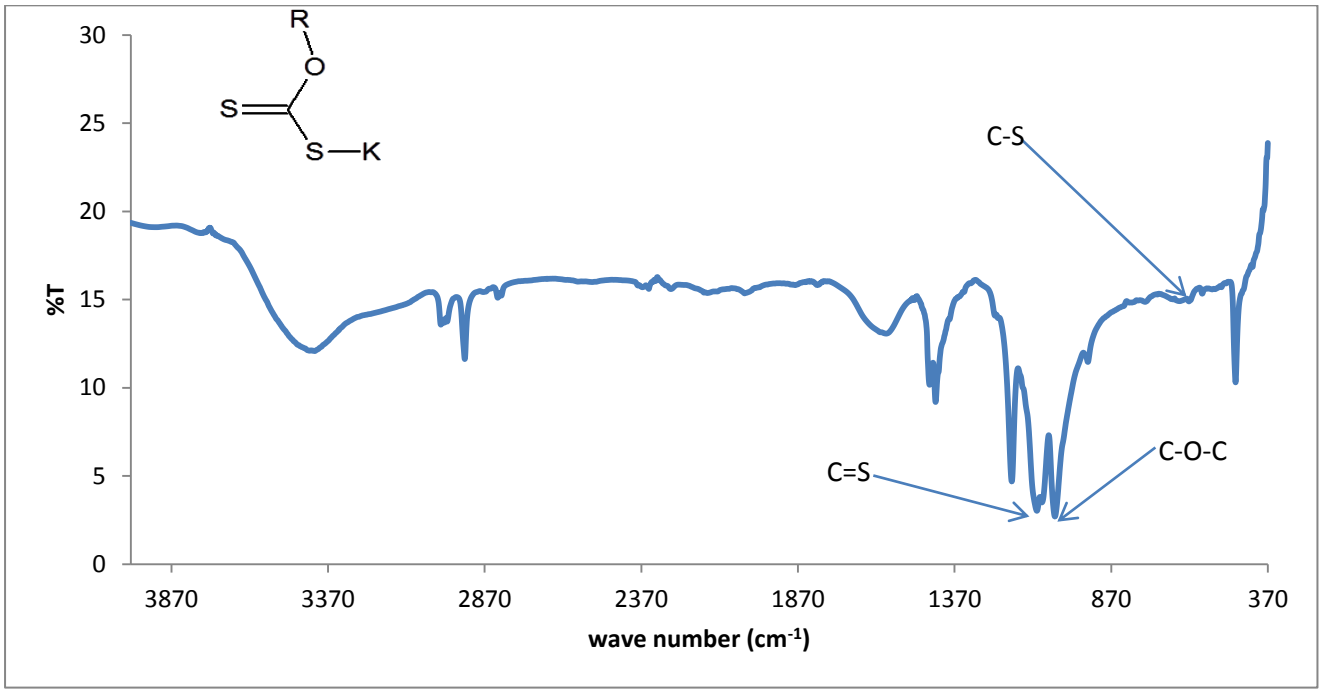


Figure 3.2: IR spectrum of Potassium O-ethyl xanthate compound

The infrared spectrum of synthesized ethyl xanthate in Figure 3.2 shows the appearance of absorption bands at 1154-1187 cm^{-1} and other bands at 1049-1235cm^{-1} respectively due to the vibrations of (C=S) and (O-C-S) [14]. There is also an appearance at 615-621cm^{-1} that is not clear for C-S stretching vibrations.

3.2.2 Electronic spectra of xanthate compounds

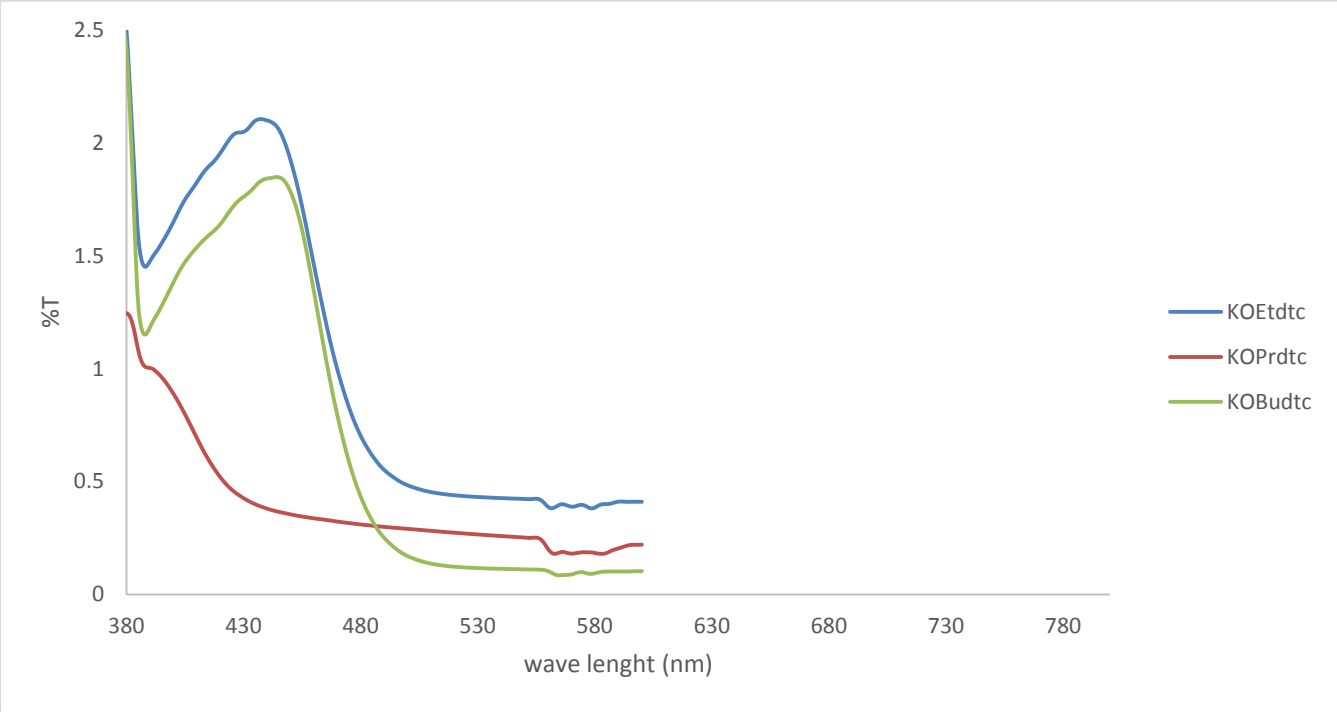


Figure 3.3 Electronic spectra of xanthate compounds

The electronic spectra display two π–π* transitions in acetone solution with λ_{max} between 602 and 639 nm and between 360 and 380 nm, which might be assigned to the $^3B_1(F) \rightarrow {}^3E(F)$ and $^3B_1(F) \rightarrow {}^3A_2, {}^3E(P)$ transitions, respectively [15, 16]. However, it should be noted that the initial xanthate concentration peak at 301 nm diminished with time, although at the same time, an absorption band at 347 nm appeared. Yamamoto *et. al* [14] proposed that an intermediate product of the xanthate decomposition, known as perxanthate, was formed [17]. Afer 15 minutes, xanthate was completely disintegrated and virtually no xanthate or perxanthate were noticed. The results from UV-visible spectroscopy further show the reduction in the recovery of pyrite. It has been established that sulphite decomposed the xanthate ions in solution, along with the presence of the pyrite surface. Perxanthate was formed at 350 nm during the xanthate decomposition [18].

$ROCSS^- + HSO_3^- + SO_3^{2-} + O_2 \rightarrow ROCSSO^- \rightarrow ROH + 2S_2O_3^{2-} + CO_2$

Scheme 3.2 Xanthate decomposition in solution via perxanthate formation

3.2.3 ^{1}H-NMR spectra of xanthate ligands

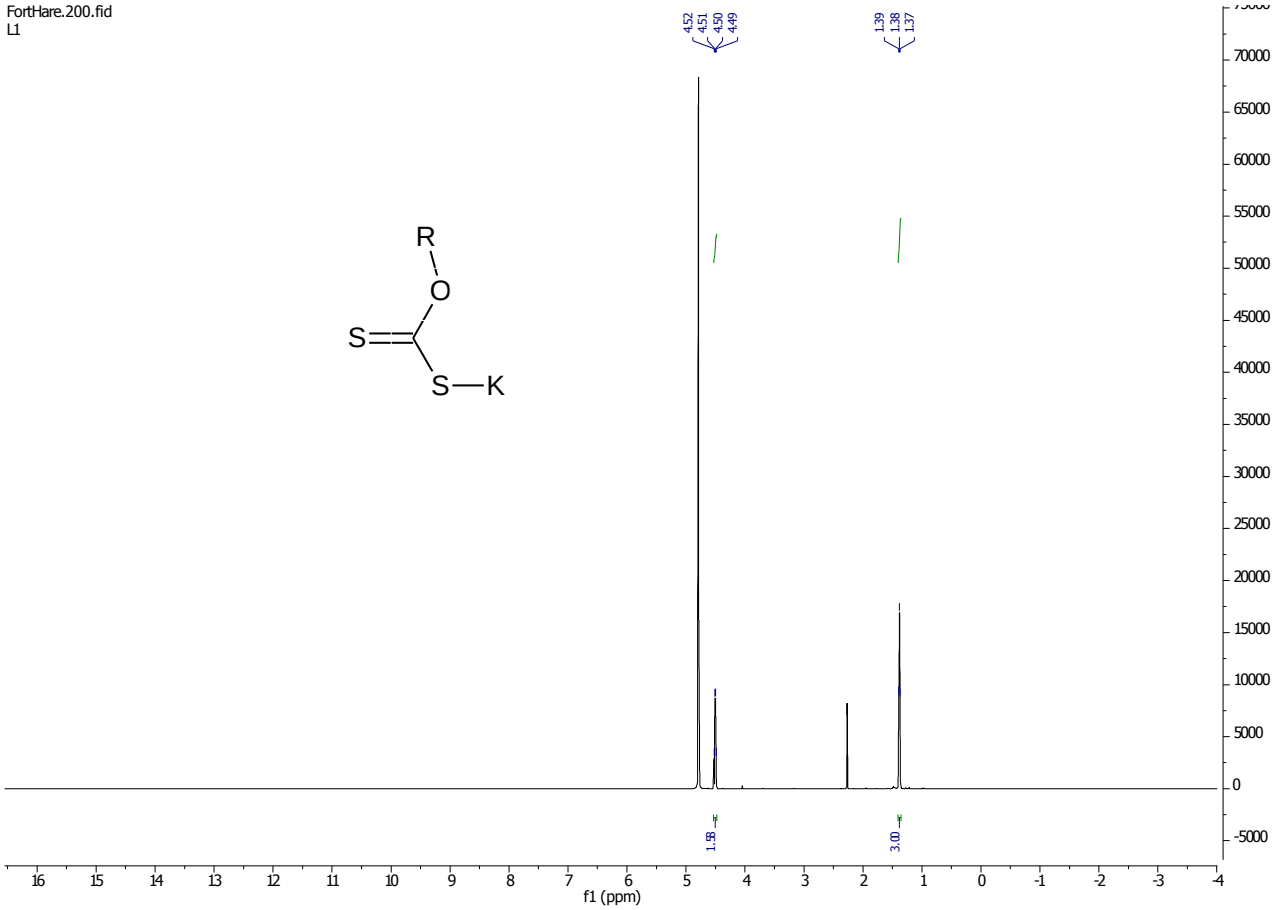


Figure 3.4: ^{1}H-NMR of Potassium O-ethyl xanthate ligand

^{1} H-NMR spectrum of KEX is characterized by the presence of the peaks at 1.37 ppm assigned to the methyl (-CH_3) and 4.45 ppm due to (-CH_2) [19]. Furthermore, as shown in Figure 3.4 methyl peaks shows triplets between 1.37- 1.39ppm and for (-CH_2) peaks are quintet that appears between 4.49-4.52ppm is caused by the electronegativity of the oxygen atom.

3.3 Nickel(II) complex of xanthates

Nickel(II) complex of xanthate formulated as $[Ni(SSOC_4H_7)_2(PPh_3)_2]$ has been synthesized as reported in Chapter 2. Six coordinated octahedral geometry is proposed for this complex. Each complex contains two molecule of xanthate acting as a bidentate ligand through the S atoms and two molecules of triphenylphosphine (PPh_3). The analytical data are presented in Table 3.3 and 3.4 and the proposed structure of the complex is shown in Figure 3.5 The compound was completely insoluble in water while soluble in non-coordinating solvents and soluble in polar solvents with strong donor strength like DMF and DMSO. The complex have a conductivity value range of 0.01-0.56 µS, this shows that it is a non-electrolytes in solution.

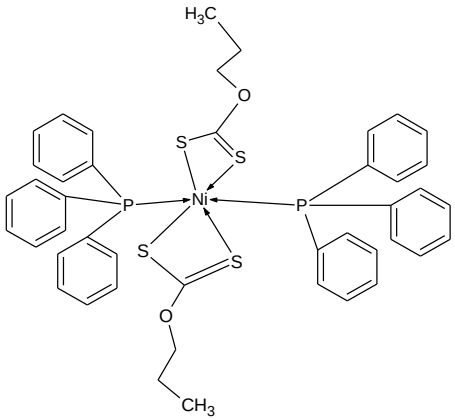


Figure 3.5: Proposed structure of nickel(II) complex of xanthate

Table 3.3 Analytical data and some physical properties of nickel complex

Complexes	Molecular Formulae	Molar mass g/mol	Colour	Analytical Data (%) C Found (calc.)	H Found (calc.)	Yield (%)	M.P (ºC)	Cond. µS
$[Ni(OPrdtc)_2(PPh_3)_2]$	$NiH_{44}C_{44}O_2S_4P_2$	853.737	dark brown	(61.96) 61.91	(5.20) 4.88	87.8	260	0.05

3.3.1 Infrared of Ni(II) xanthate complex

Table 3.4 Relevant infrared frequencies (cm^{-1}) for the nickel xhanthate complex.

Compunds	*ν*(M-S) (cm^{-1})	*ν*(C-S) (cm^{-1})	ν_s(C-O-C) (cm^{-1})	ν_{as}(C=S) (cm^{-1})	*ν*(ringC=C) (cm^{-1})	*ν*(ringC-H) (cm^{-1})
$[Ni(OPrdtc)_2(PPh_3)_2]$	357.90	694.71	1143.02	1179.97	1474.89	3436.24

In the nickel xanthate, the bands observed in the range 1143 and 1179 cm^{-1} are assigned to C-O-C and C=S respectively. IR spectrum of the xanthate ligand was closely compared with the complex spectrum to identify *υ*(C–O) and *υ*(C=S) stretching frequencies [20] as shown in Figure 3.6, the peaks were disappearing in the metal complex spectra because of the metal that is present. The IR spectrum of the nickel xanthate complex show stretching frequency at about 1010 cm^{-1}, this is assigned to the stretching vibration of C=S, demonstrating the bidentate nature of the xanthate anion in the complex [21, 22]. Moreover, the bands that appear in the region 3000–3100 cm^{-1} are very important because they correspond to the υ(C–H) stretching vibrations of the ethyl group of the xanthate compound.

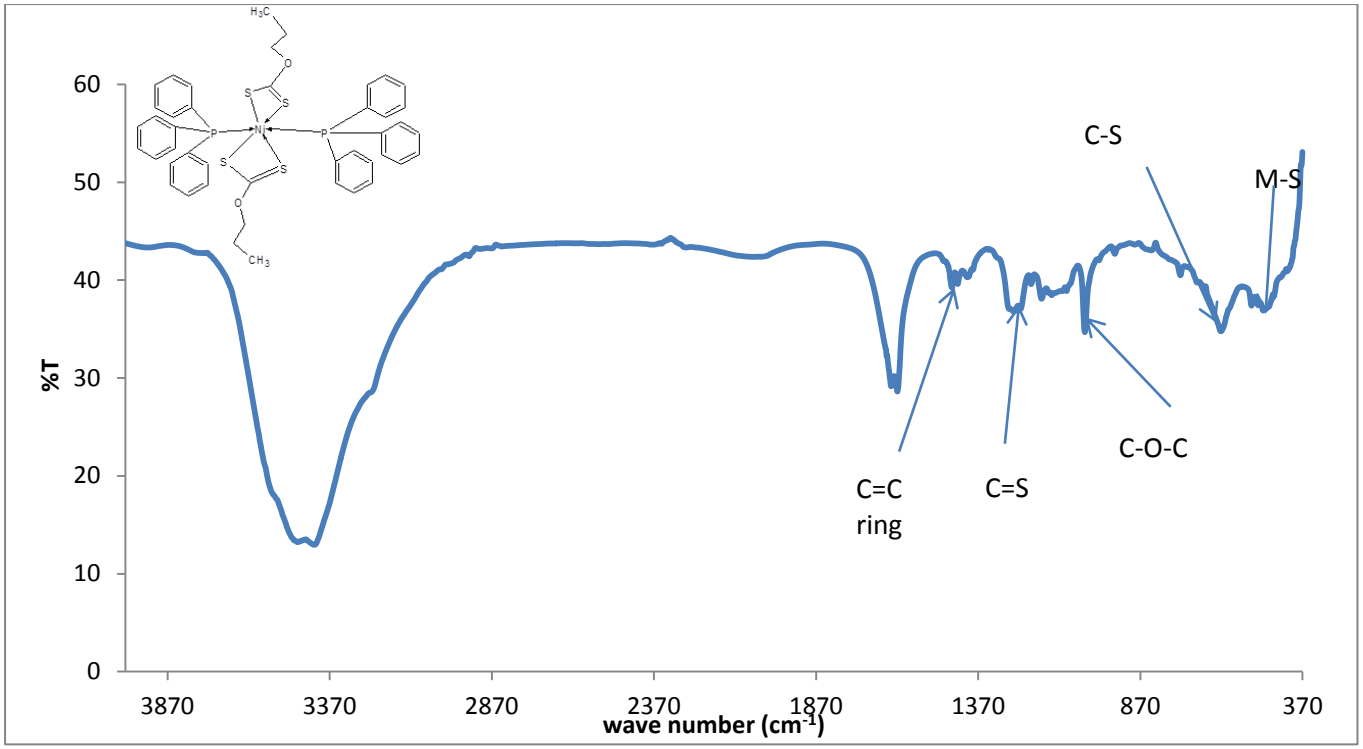


Figure3.6: Nickel(II) bis(O-propyl-xanthate) bis(triphosphen) complex spectrum

3.3.2 Nickel xanthate electronic spectrum

The electronic spectrum of nickel(II) have been recorded in DMF and displays three bands which are allocated to : $^3A_{2g} \rightarrow {}^3T_{2g}(F)(\nu 1)$, $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ ($\nu 2$) and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ ($\nu 3$) transitions respectively [23]. These three broad bands along with shoulders shows that there is a *trans* octahedral geometry around nickel(II) ion [24]. Four bands are to be expected for Ni(II) complexes with D_{2h} symmetry [25, 26]. According to results published [27], the low intensities of the first two bands at 640 and 490 nm show that these bands could be assigned to d-d, Laporte forbidden, spin-allowed transitions of the Ni(II) ion. The medium-intensity bands at 440 and 410 nm are those of metal-ligand charge transfer processes [28]. However, the last two bands at 320 and 230 nm are typically credited to transitions in the ligand. The likely local symmetry around the nickel(II) ion is not firmly D_{4h}, but D_{2h} symmetry, as the S–S distances between the two sulphur atoms belonging to the same dithiocarbamate ligand are

usually shorter than the distances between the two sulphur atoms in the *cis* locations belonging to two ligands [29].

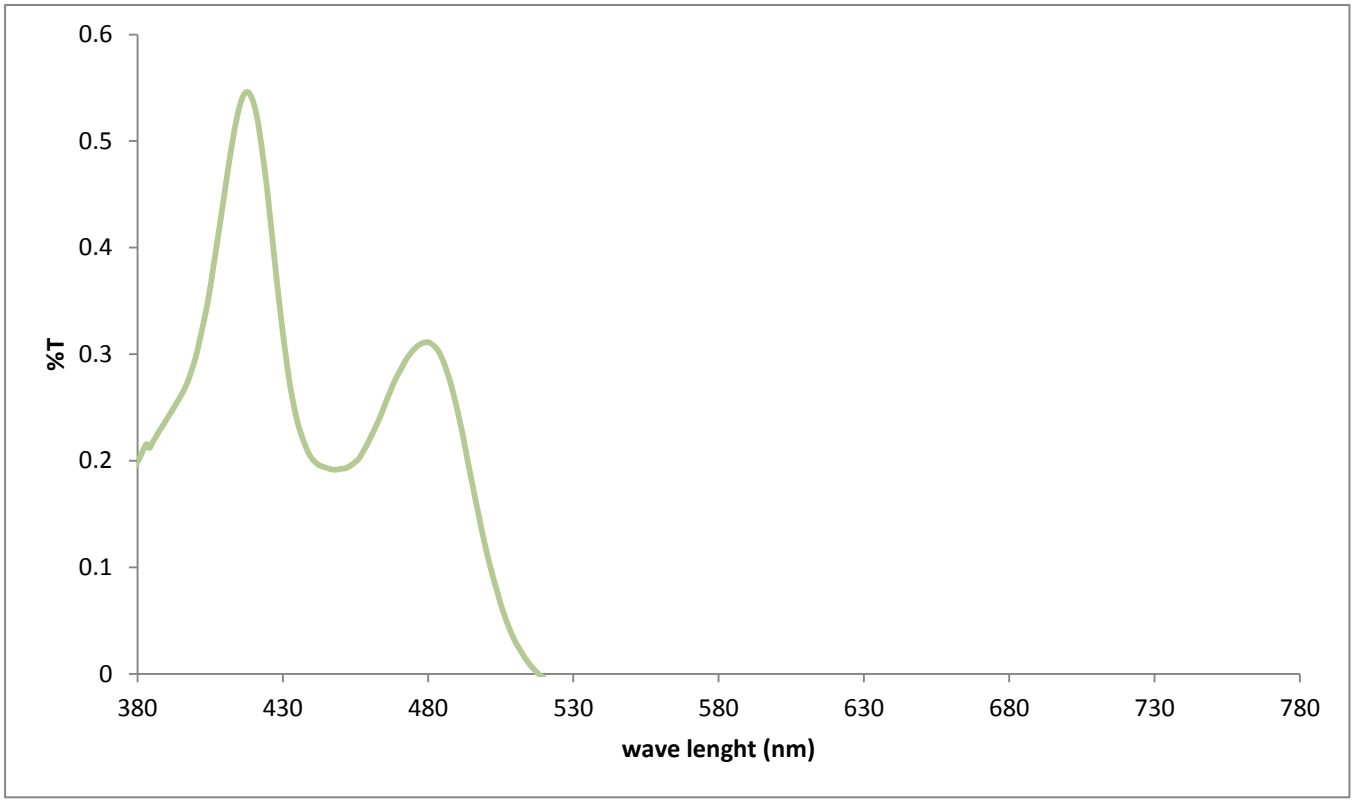


Figure 3.7: Electronic spectra of Nickel(II) bis(O-propyl-xanthate) bis(triphosphen) complex of xanthate

3.4 Silver(I) and copper(II) complexes of xanthate

Silver(I) and Copper(II) complexes of xanthate formulated as $[Ag(PPh_3)_2(OEtdtc)]$, $[Ag(PPh_3)_2(OBudtc)]$, $[Cu(PPh_3)_2(OEtdtc)]$, $[Cu(PPh_3)_2(OPrdtc)]$ and $[Cu(PPh_3)_2(OBudtc)]$ have been synthesized as reported in Chapter 2. Four coordinates geometriess are proposed for the complexes. Each complex contains one molecule of xanthate acting as bidentate ligand through the S atom and two molecules of triphenylphosphine (PPh_3). The analytical

data are presented in Table 3.5 and the proposed structures of the complexes are shown in Figure 3.8.

The complexes were completely insoluble in water and in non-coordinating solvents but soluble in polar solvents with strong donor strength like DMF and DMSO. The complexes were non− electrolytes in DMF with a conductivity value of 12.00 − 19.00 µS.

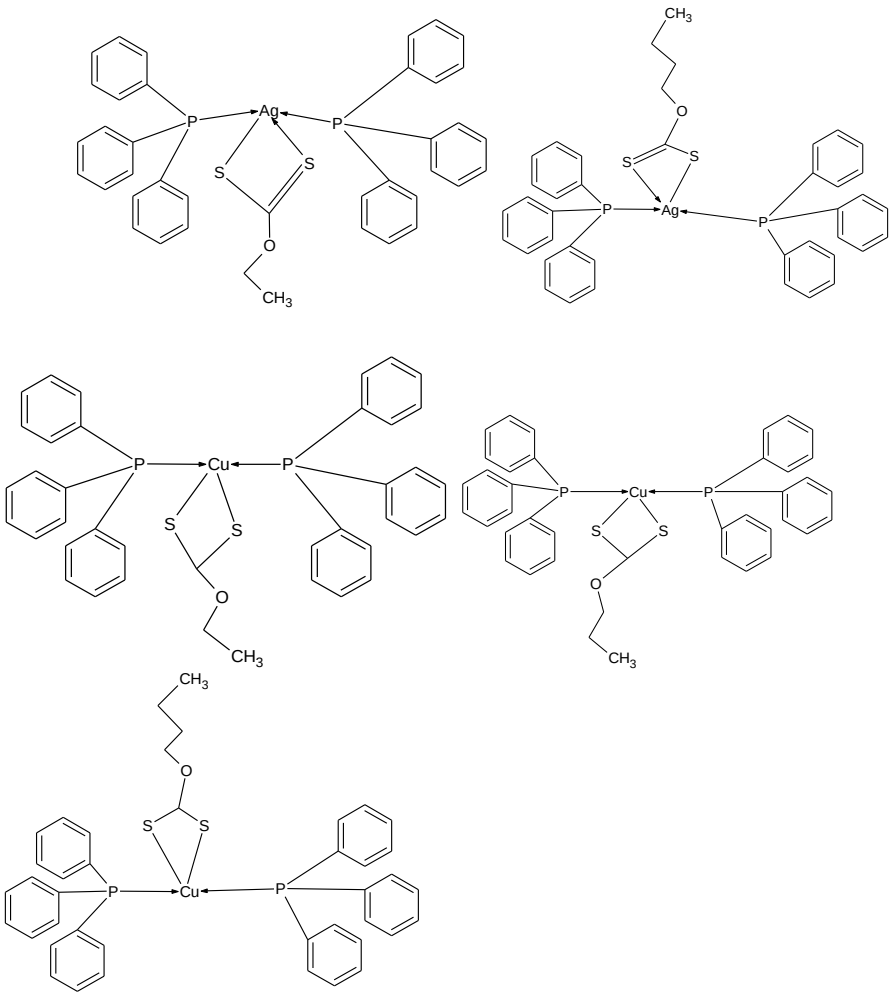


Figure 3.8: Proposed structure of silver and copper complexes of xanthate

Table 3.5 Analytical data and some physical properties of silver and copper complexes

Complexes	Molecular Formulae	Colour	Molar mass g/mol	Analytical Data (%) C Found (calc.)	Analytical Data (%) H Found (calc.)	Yield (%)	M.P (ºC)	Cond. µS
$[Ag(PPh_3)_2(OEtdtc)]$	$AgH_{35}C_{39}OS_2P_2$	Pale brown	752.07	(62.23) 61.81	(4.69) 4.62	71.3	131	12.10
$[Ag(PPh_3)_2(OBudtc)]$	$AgH_{39}C_{41}OS_2P_2$	Pale	780.10	(63.07) 62.67	(5.04) 4.82	66.7	119	12.31
$[Cu(PPh_3)_2(OEtdtc)]$	$CuH_{35}C_{39}OS_2P_2$	Brick red	708.09	(66.09) 66.16	(4.98) 4.66	77.3	288	18.30
$[Cu(PPh_3)_2(OPrdtc)]$	$CuH_{37}C_{40}OS_2P_2$	Yellow	722.11	(66.47) 66.35	(5.16) 4.71	65.1	280	18.08
$[Cu(PPh_3)_2(OBudtc)]$	$CuH_{39}C_{41}OS_2P_2$	Yellow	736.12	(66.84) 66.72	(5.34) 5.52	78.4	277	18.01

3.4.1 Infrared spectra of silver(I) and copper(II) complexes of xanthate

Table 3.6 Relevant infrared frequencies (cm^{-1}) for the ligand and silver and copper complexes.

Compounds	*v*(M-S) cm^{-1}	*v*(C-S) cm^{-1}	v_s(C-O-C) cm^{-1}	v_{as}(C=S) cm^{-1}	*v*(ringC=C) cm^{-1}	*v*(ringC-H) cm^{-1}
$[Ag(PPh_3)_2(OEtdtc)]$	374.64	690.93	1035.63	1138.07	1640.14	3069.27
$[Ag(PPh_3)_2(KOBudtc)]$	355.98	693.45	1130.66	1046.61	1583.76	3008.18
$[Cu(PPh_3)_2(OEtdtc)]$	370.03	618.51	1142.62	1042.81	1583.76	3015.94
$[Cu(PPh_3)_2(OPrdtc)]$	382.75	692.12	1168.57	1026.93	1583.92	2970.40
$[Cu(PPh_3)_2(OBudtc)]$	374.03	618.41	1157.73	1026.44	1584.29	3047.53

The IR spectrum of the xanthate ligand has been carefully compared with that of the complexes and absorption bands assigned accordingly. There is no interpretation of vibrational frequencies, however the work done so far on other metal xanthate compounds shows that there is coupling between the fundamental modes of vibration of alkyl xanthate ions. Nonetheless, many authors [30, 31] have assigned the band at about 1200 cm^{-1} (its precise location depends on the metal ion in the compound) to the stretching vibration of the C-O-C group of the xanthate ion. A contribution from stretching of the S-C-S group to the band around 1200 cm^{-1} has also been suggested in the case of CuEX [30]. Absorption bands of the ligands have (C-S) at 700-600 cm^{-1} range, (C-O-C) at 1170-1114 cm^{-1} range (C=S) at 1250-1020 cm^{-1} range, ring (C-H) at 3060-3030 cm^{-1} and ring (C=C) at 1600-1498 cm^{-1} in the symmetrical and asymmetrical stretching vibrations [31]. The metal sulfur (S-M) bond is observed at the 350-395 cm^{-1} range. These absorption bands shifted slightly in

[$Ag(PPh_3)_2(OEtdtc)$], [$Ag(PPh_3)_2(OBudtc)$], [$Cu(PPh_3)_2(OEtdtc)$], [$Cu(PPh_3)_2(OPrdtc)$] and [$Cu(PPh_3)_2(OBudtc)$]. The shift is probably due to due to the coordination of the metal with the ligand [32, 33].

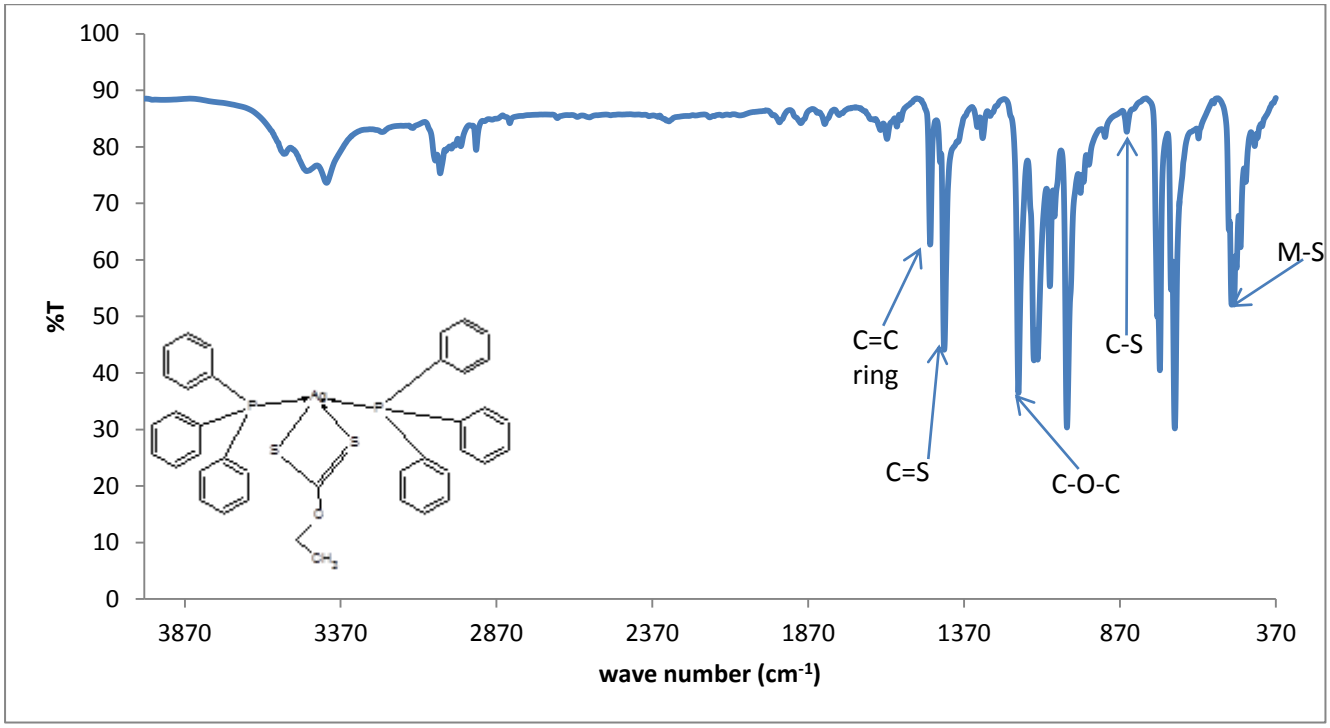


Figure 3.9: IR spectrum of Silver(I) O-ethyl-xanthate bis(triphosphen) complex

3.4.2 Electronic spectra of copper(II) complexes of xanthate

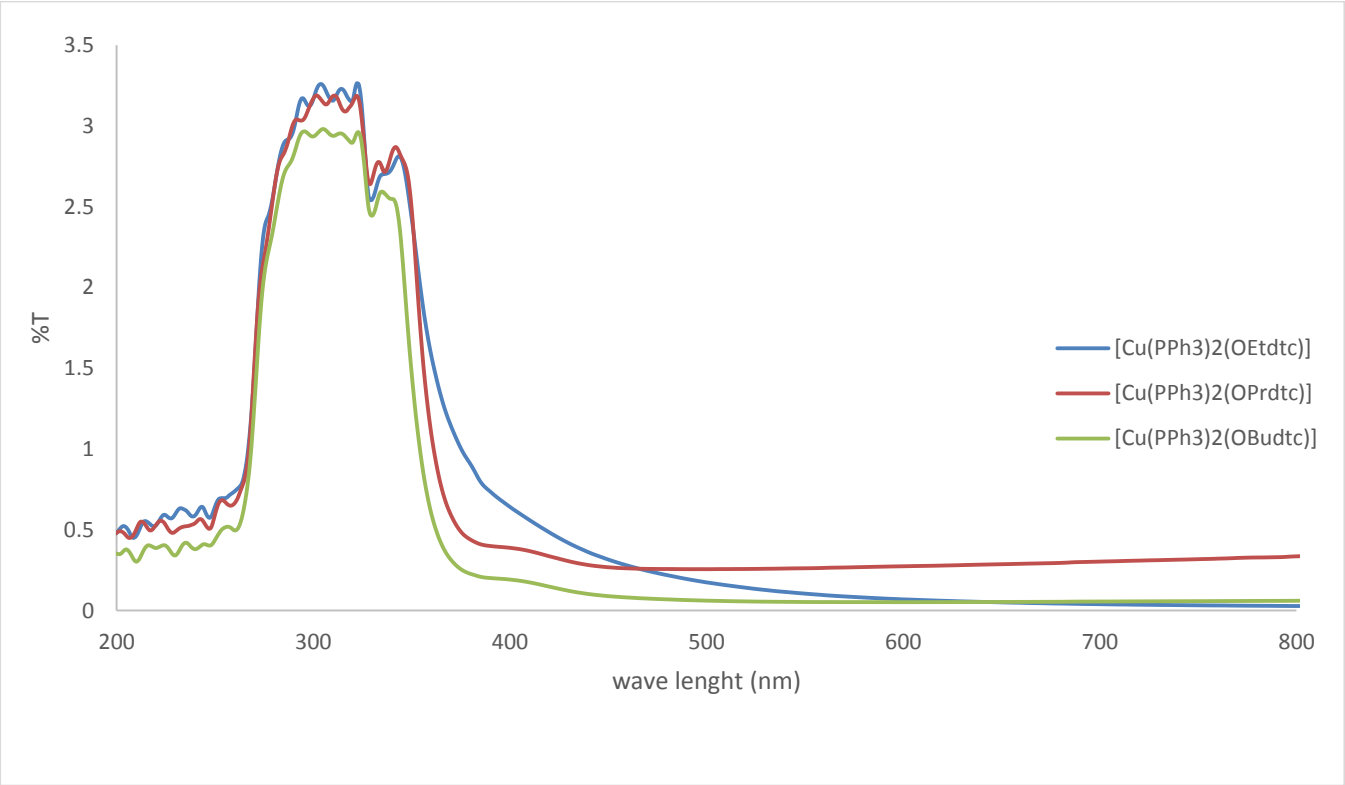


Figure 3.10: Electronic spectra of copper complexes of xanthate

The electronic spectra of all the complexes in this study show intense absorptions in the UV-region, which is assigned to charge transfer from π orbital of the donor ligand to the d orbitals of the metals, d→π* and interligand n→π* transitions [34, 35]. Moreover, the charge transfer transitions may interfere and prevent the observation of all the expected transitions in the spectra [36]. In copper(II) complexes a single band in the visible region corresponding to $t_{2g} \rightarrow e_g$ transition is expected [33]. But due to strong Jahn-Teller distortion, octahedral Cu(II) complexes often give a broad band resulting from several overlapping bands, or where the bands are resolved, up to three close bands [37]. The band broadness could be attributed to the overlapping of several bands as a result of strong Jahn–Teller distortion expected in a d^9 configuration [38, 39]. Another weak absorption band almost un-noticeable can also be seen at 580 nm and it is probably assigned to $^2B_{1g} \rightarrow {}^2E_g$ transition. However weak bands around

580 nm that can be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ d-d transitions in four coordinate square planar complexes [40]. According to other authors [41], two bands at 660 and 460 nm are to be likely for Cu(II) complexes with D_{2h} symmetry. These bands are due to $d_{xy} \rightarrow d_{z2}$ and $d_{xy} \rightarrow d_{xz}$ transitions. The isolated copper complex shows only one very broad and intense band at 438 nm with no indication of a resolution. This band could be ascribed to dxy→dxz transitions of the Cu(II) ion but the band originating from $d_{xy} \rightarrow d_{z2}$ transitions were not recorded because of its low intensity.

3.5 Palladium(II) and platinum(II) complexes of xanthate

Square planar four coordinate Pd(II) and Pt(II) complexes of xanthate have been proposed. The formations of palladium and platinum complexes are favoured by four coordinate square planar geometries [42]. All six complexes have two molecules of xanthate bonding to the metal ion. [Pd(xanthate)$_2$] and [Pt(xanthate)$_2$] is coordinated with two molecules of xanthate each to form the four coordinate square planar geometry. The elemental analysis data of the complexes which are consistent with the calculated results, conductivity values, as well as some physical properties of the complexes are presented in Table 3.7 and 3.8. Proposed structures of the complexes are shown in Figure 3.11. Conductivity measurement of the complexes ranges from 16.00-16.80 µS indicating that they are non-electrolytes in solution.

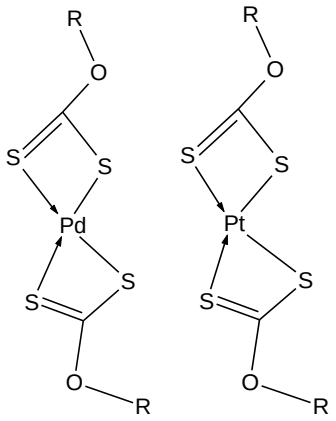


Figure 3.11: Proposed general structures of Pd(II) and Pt(II) complexes of xanthate.

Table 3.7: Analytical data and some physical properties of Pd(II) and Pt(II) xanthate complexes

Complexes	Molecular formula	Molar mass (g/mol)	Colour	Analytical Data (%) C Found (calc.)	H Found (calc.)	Yield (%)	M.P (ºC)	Cond. µS
$[Pd(OEtdtc)_2]$	$PdS_4O_2C_6H_{10}$	348.80	Dark brown	(27.87) 28.02	(3.74) 3.50	74	145	16.56
$[Pd(OPrdtc)_2]$	$PdS_4O_2C_8H_{14}$	376.86	Dark brown	(31.40) 31.32	(4.39) 4.01	85	143	16.23
$[Pd(OBudtc)_2]$	$PdS_4O_2C_{10}H_{18}$	404.91	Dark brown	(34.53) 34.23	(4.97) 4.74	92	150	16.70
$[Pt(OEtdtc)_2]$	$PtS_4O_2C_6H_{10}$	437.46	Brick red	(30.82) 30.56	(4.06) 3.99	88	165	16.11

$[Pt(OPrdtc)_2]$	$PtS_4O_2C_8H_{14}$	465.52	Brick red	(33.50) 33.40	(4.57) 4.20	70	160	16.03
$[Pt(OBudtc)_2]$	$PtS_4O_2C_{10}H_{18}$	493.57	Brick red	(35.93) 35.95	(5.03) 4.97	87	164	16.63

3.5.1 Infrared spectra of palladium(II) and platinum(II) complexes of xanthate

Table 3.8 Relevant infrared frequencies (cm^{-1}) for Pd(II) and Pt(II) complexes

Compounds	*v*(M-S) cm^{-1}	*v*(C-S) cm^{-1}	ν_s(C-O-C) cm^{-1}	ν_{as}(C=S) cm^{-1}	*v*(ringC=C) cm^{-1}	*v*(ringC-H) cm^{-1}
$[Pd(OEtdtc)_2]$	401.35	619.57	1144..03	1009.97	29.24	1621.33
$[Pd(OPrdtc)_2]$	405.64	621.56	1136.57	1027.19	2964.50	1456.51
$[Pd(OBudtc)_2]$	388.50	619.99	1141.92	1025.60	3028.15	3236.30
$[Pt(OEtdtc)_2]$	390.80	624.75	1115.39	1018.45	3237.56	1617.87
$[Pt(OPrdtc)_2]$	387.46	623.06	1168.08	1024.08	2960.71	1458.65
$[Pt(OBudtc)_2]$	402.27	622.00	1150.79	1095.72	2969.29	1452.46

The infra-red spectrum for ethyl xanthate show the appearance of absorption bands in the region 1144-1150 cm^{-1} while other bands in the region 1009-1095 cm^{-1} that are due to the vibrations of (C-O-C) and (C=S). Bozkurt *et al.* reported that the bands at 1242, 1267 and 1022 cm^{-1} are characteristic of dixanthogen [43]. However for dixanthogen the asymmetrical stretching shows a strong absorption peak at ~1265 cm^{-1} while the symmetrical stretching appears as a weak absorption peak at ~1150 cm^{-1}. Meanwhile, in the case of the xanthate both the asymmetrical and symmetrical C–O–C stretching absorption peaks have the same

intensities and the symmetrical C–O–C stretching for the xanthate is at ~1150 cm^{-1} (~1150 cm^{-1} for dixanthogen) and the asymmetrical stretching absorption is at ~1100 cm^{-1} (~1265 cm^{-1} for dixanthogen) [44, 45].

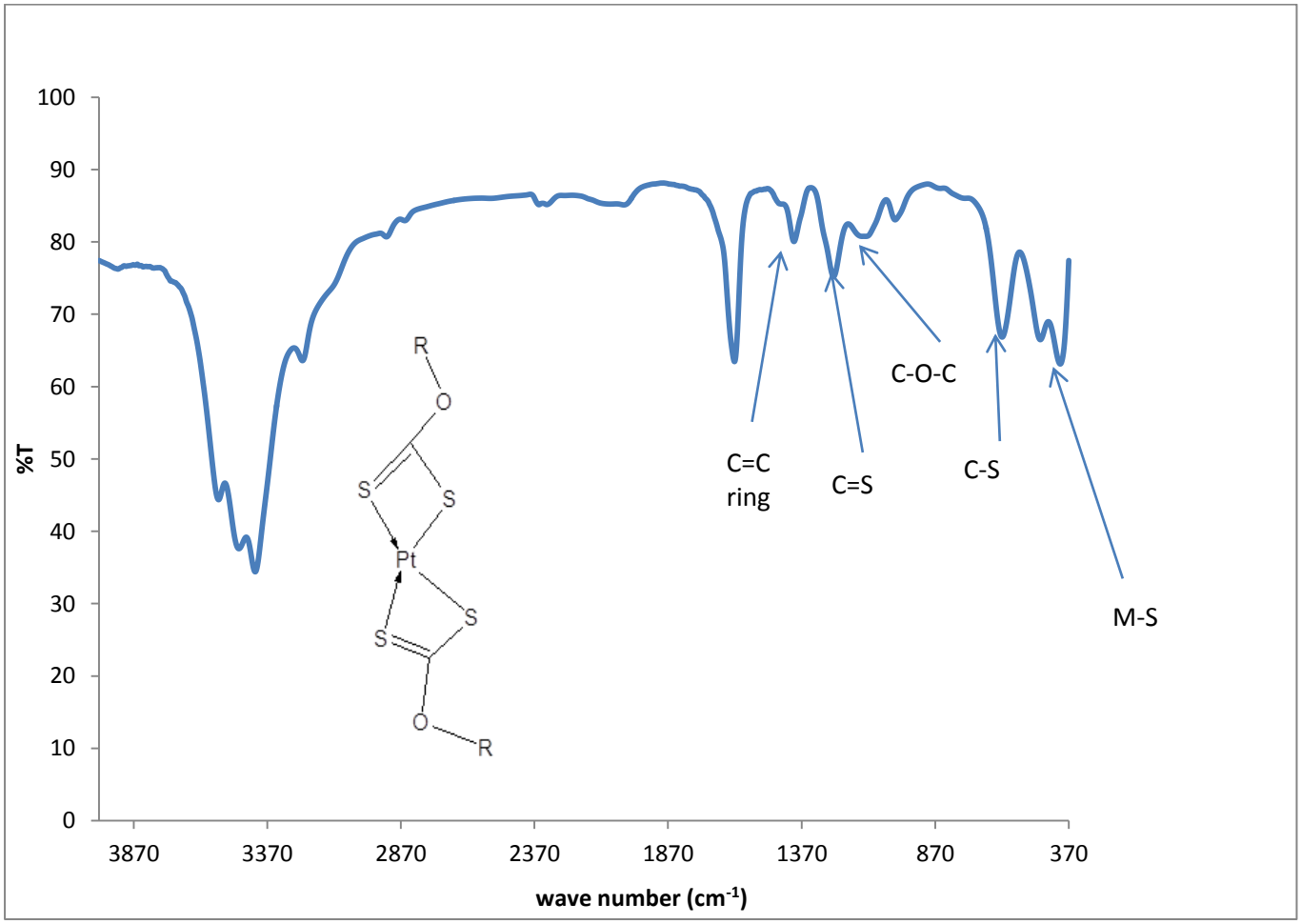


Figure 3.12: IR spectrum of Palladium(II) bis(O-ethyl xanthate) complex

3.5.2 Electronic spectra of Pd(II) and Pt(II) complexes of xanthates

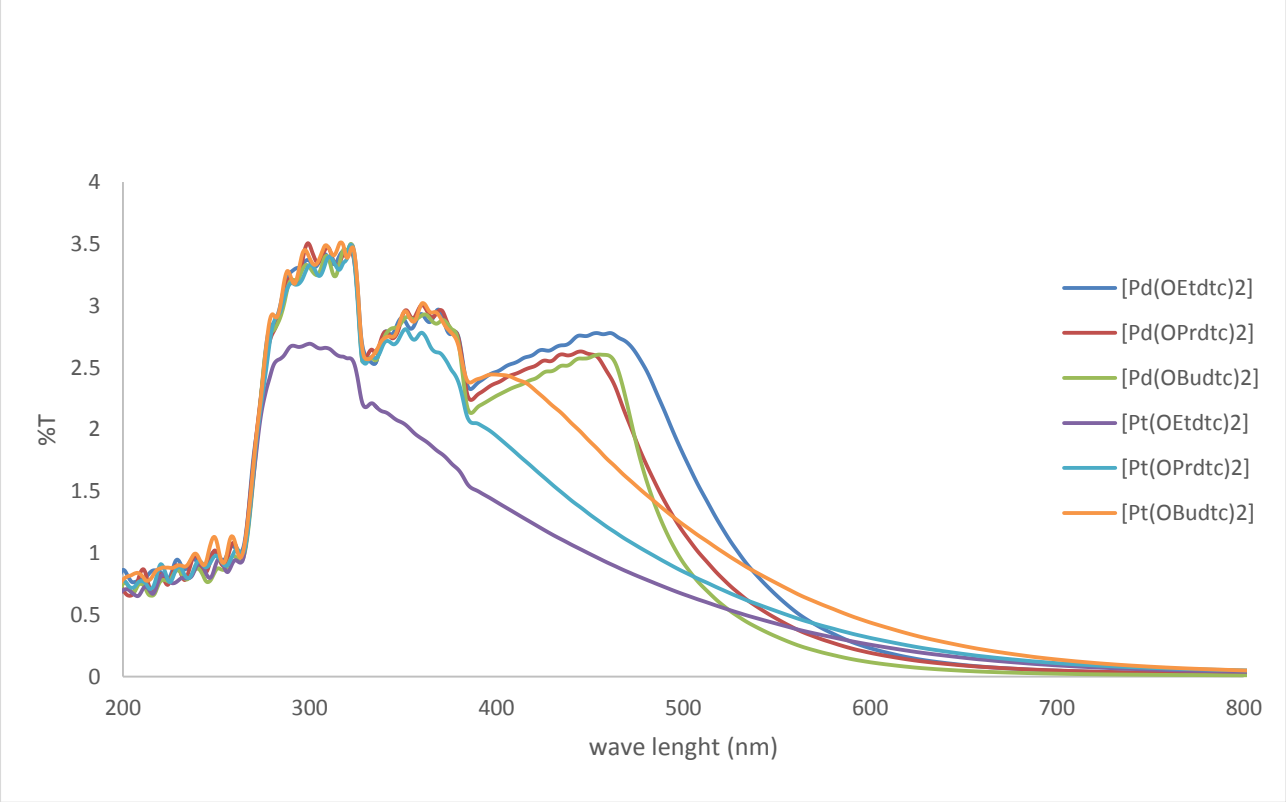


Figure 3.13: Electronic spectra of palladium(II) and Platinum(II) complexes of xanthate

The consequence of complexation on the splitting of the d orbital is more clear for Pd(II) and Pt(II), and therefore their complexes are diamagnetic and majority of them are planar. The electronic spectra of Pd(II) and Pt(II) complexes like any other square planar complexes can be assigned easily. Nevertheless, the situation is complicated in the Pt(II) series with the expectation that the d– d transitions will occur at comparable energies to LMCT transitions, and a clear distinction between these two types of transition may be difficult. The palladium complexes show absorption bands at around 450-480 nm in all the complexes corresponding to $^{1}B_{1g} \leftarrow {}^{1}A_{1g}$ and $^{1}A_{2g} \leftarrow {}^{1}A_{1g}$ for low spin allowed d-d transition [47]. The d-d transition in the platinum complexes is not seen, and this can be obvious from its brick red colour which makes it MLCT bands dominant, as compared to the dark brown colour of palladium [48]. All six complexes displays a high energy absorption band (intense absorption) around 300

nm and below (not shown in spectra) which corresponds to $^1A_{2u} \leftarrow {}^1A_{1g}$ and $^1E_u \leftarrow A_{1g}$ of charge transfer transition [47], and it's typical of square planar complexes with electronic spectra dominated by charge transfer bands [48]. These transitions reveal that the complexes possess D_{4h} symmetry.

3.5.3 ^{1}H-NMR spectra of Pd(II) and Pt(II) complexes of xanthate

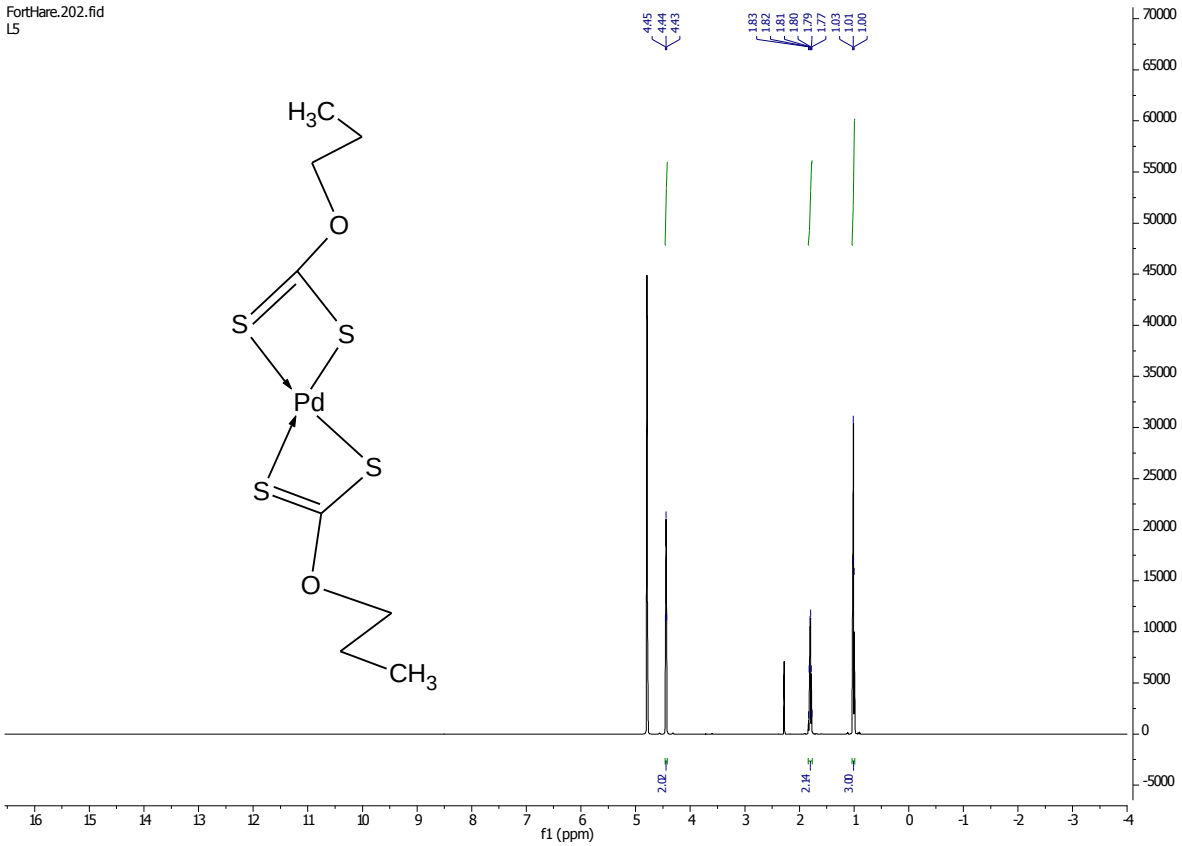


Figure 3.14: ^{1}H-NMR spectrum of Palladium(II) bis(O-propyl) xanthate complex

The metal complexes of xanthate are generally insoluble, and as a result the ^{1}H NMR of the palladium(II) and platinum(II) complexes of xanthate show poor resolution in DMSO-d_6 and CDC_3, and as such assignments of signals in their NMR spectra was only possible for the platinum complexes. There is a resonance between δ2.6 and 1.3 ppm that is assigned to methylene protons and at δ 0.9 ppm to methyl protons [46]. In Figure 3.14 triplets and sextets

are observed at 1.00-1.03 ppm and 1.79-1.83 ppm for (-CH_2) and (-CH_3) respectively and triplets at 4.43-4.45 ppm for (-CH_2) that is close oxygen. There is a singlet that is shown by the proton of the methyl group of the xanthate at 3.84 and 3.84 ppm for the xanthate ligand [48]. The ^{1}H-NMR spectra of the complexes are straight forward showing correct proton ratios and peak multiplicities for the xanthate ligands. In such complexes, singlet for each methyl group, *syn* and *anti*-protons are observed [47].

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CHAPTER FOUR

4.0 ANTIMICROBIAL STUDIES

4.1 Introduction

The treatment of transmissible diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of drug resistant microbial pathogens. That leads to large number of antibiotics and chemotherapeutics being produced for medical use, however at the same time the appearance of old and new antibiotic resistance created in the past years bare a substantial medical need for new classes of antimicrobial agents. There is apparent need for the discovery of new compounds that can show antimicrobial activity. Due to the outbreak of infectious diseases produced by different pathogenic bacteria and the growth of antibiotic resistance, researchers are searching for new antibacterial agents. The new antimicrobial agents and nanotechnological materials have to be synthesized for reduction of resistant bacterial diseases. After the discovery of cisplatin, metallo-drugs are becoming an interesting research area, eversince then, many complexes have been synthesized and tested on biologicaldifferent systems.

Copper complexes are recognized to have a wide spectrum of biological action, nevertheless its concentration as free metal ion inside cells should be lower than 10–15 M when calculated or 10–12 M when observed. If its concentration is higher than 10–9 M in the cytoplasm can be poisonous [1]. The transition metal complexes chemistry received much attention in

modern years on account of their rational design and synthesis and also because of their potential applications as functional materials [2], enzymatic reaction mechanism [3] and in bioinorganic chemistry [4]. Transition metal complexes with nitrogen donors are applied in several biological activities such as anticancer, antibiotic, antimicrobial and antifungal agents [5, 6, 7]. Antimicrobial study can be linked with the study of bacteria or the study of fungi because they are microorganism. The antimicrobial susceptibility test is used to evaluate the efficacy of potential antimicrobials against different microbial species [8]. Zone of inhibition measured by diffusion through agar in the agar well diffusion method on standard environments of growth of organisms, can be assess in a series of doubling dilution of antimicrobial in different concentrations on solid media [9].

4.2 Agar well diffusion method

After incubation in the case of the agar well diffusion method, the diameter of the growth− free area around the antimicrobial agent reservoir can be measured and taken as the antimicrobial ability of that product. When using the Agar well diffusion method, note should be taken to ensure that antimicrobial solutions are water soluble to allow for a proper diffusion into the solidified water− based agar in the plates. The method is not acceptable for testing samples that are not highly soluble in water, regardless of whether the substance is applied in a non-polar solvent or not. Diffusion methods are well suitable for the preliminary screening of pure substances, such as alkaloids, terpenoids and flavanoids. The methods however, cannot be used for samples that are difficult to diffuse in the media, as there is no direct correlation between diffusion power and antimicrobial activity. The solubility of the antimicrobial agent solution as well as its molecular size will determine the extent of the area of solution infiltration around the disc. Diffusion assays are therefore not appropriate for screening the properties of non− polar substances [10].

4.3.0 Dilution assay technique

The dilution methods are used to determine the minimum inhibitory concentrations (MICs) of antimicrobial agents and they are the reference methods for antimicrobial susceptibility testing against which other methods, such as disc diffussion, are calibrated. The MIC values are broadly used in the comparative testing of new agents. In clinical laboratories they are utillized to establish the susceptibility of organisms that give confusing results in disc tests, for tests on organisms where disc tests may be unreliable, and when a more accurate result is required for clinical management. In these dilution tests, microorganisms are tested for their capability to produce visible growth on a series of agar plates (agar dilution) or in microplate wells of broth (broth microdilution) that contain dilutions of the antimicrobial agent. So the lowest concentration of an antimicrobial agent that show inhibition on the visible growth of a microorganism is known as the MIC.

4.3.1 Agar and broth dilution assay

The agar dilution method is an antimicrobial susceptibility testing [11] and is recommended in many countries [12, 13]. Broth Dilution method is a simple process for testing a small number of isolates, even single isolate. It also has the added advantage that the same tubes can be taken for MBC tests.

4.4 The minimum bactericidal concentration (MBC) and Minimum inhibitory concentration (MIC)

The minimum bactericidal concentration (MBC) is used to describe the lowest concentration of antibiotics essential to completely kill the microorganism. The antimicrobials are commonly regarded as bactericidal if the MBC is no more than four times the MIC. Minimum Inhibitory Concentration (MIC) diffusion tests is broadly used to determine the susceptibility of microorganisms isolated from clinical samples that have their limitations when equivocal results are found. Also the terms 'susceptible' and 'resistant' can have a representative interpretation. However, when in doubt, the way to a precise assessment is to determine the MIC of the antibiotic to the microorganisms disturbed. These are two methods of testing for MIC broth dilution method and agar dilution method.

4.5.0 Antibacterial test

4.5.1 Materials

1) Nutrient broth
2) Mueller– Hinting Agar

The following typed cultures bacterial as obtained from the American Type Culture Collection (ATCC) were used:

Gram Positive bacterium

1) *Bacillus cereus (ATCC 10702)*

Gram Negative bacterium

1) *Proteus vulgaris (ATCC 6830)*

4.5.2 Preparation of nutrient broth

For every 500 mL of distilled water, 8 g of nutrient broth was dissolved and this is the standard method of preparation. The nutrient broth solution was then dispensed into test tubes and taken to the autoclave to sterilize.

4.5.3 Preparation of Mueller– Hinton Agar

Müeller-Hinton agar preparation includes the next steps. Müeller-Hinton agar should be prepared from a commercially accessible dehydrated base according to the manufacturer's instructions. Immediately after autoclaving, allow it to cool in a nearly 40°C so that it can not kill the microogarnisms. Pour the freshly prepared and cooled medium into glass or plastic, flat-bottomed petri dishes on a level, horizontal surface to give a uniform depth of approximately 4 mm. That corresponds to 60 to 70 ml of medium for plates with diameters of 150 mm and 25 to 30 ml for plates with a diameter of 100 mm. The agar medium should be allowed to cool to room temperature, unless the plate is used the same day, stored in a refrigerator (2 to 8°C). Plates must be used within seven days after preparation except adequate precautions, such as wrapping in plastic, have been taken to minimize drying of the agar. A representative sample of each batch of plates should be examined for sterility by incubating at 30 to 35°C for 24 hours or longer. The standard method for the preparation of Mueller− Hinton agar (a medium suitable for testing the sensitivity of clinically important pathogens towards antibiotics and suphonamides) is, dissolving 19 g of the solid Mueller− Hinton agar in every 500 mL of distilled water while stirring and boiling to dissolve completely. The Mueller–Hinton agar solution was dispensed into Mc Cartney bottles and kept for autoclaving.

4.5.4 Preparation of complexes for antibacterial test

Preparation of antibiotic stock solutions. It is suggested to use pure antibiotics from commercial sources, and not use injectable solutions. Powders must be accurately weighed

and dissolved in the appropriate diluents to produce the required concentration, using sterile glassware. 5 mg of each complex was dissolved in 0.5 mL of DMF each in a bujon bottle, to obtain a concentration of 1 mg/mL stock solution of complex. To the same amount of dissolving solvent 20 mg (0.02 g) of complexes each were dissolved to 2 mL DMF in a bujol bottles to obtain 40 mg/ml of complexes stock solution.

4.5.5 Preparation of microorganism (Subculture process)

The microorganisms (bacterial) used were each transferred, into prepared nutrient broth of a particular volume in different text tubes (Broth inoculation of organisms) with the use of an inoculating loop, and placed in an incubator with temperature of 37 ^{o}C for 18 hours. Sub cultured microorganisms were transferred from the sub-cultured media to another prepared broth solution in test tubes. This is done to ensure that the smallest amount of microorganism is in the nutrient broth solution.

4.5.6 Sensitivity test of complexes on bacteria isolates

The sensitivity testing of complexes was determine using agar well diffusion method as described by [14, 15] with little modifications. The inoculated organisms in nutrient broth media together with the prepared liquid Mueller– Hinton agar were poured into plates and allowed to solidify. Wells were bored into the solidified agar medium using a sterile 10 mm cork borer. The wells were then filled up with the solution of prepared complex ensuring that the complex solution does not spill to the surface of the medium. The plates were allowed to stand for between 1 – 3 hours for proper inflow of the complex solution into the medium before incubating at 37 ^{o}C in an incubator. The plates were observed for the zones of inhibition after 24 hours.

4.5.7 Minimum inhibitory concentration (MIC) of the complexes

Serial dilution of complexes stock solution, i.e. complex in the sterilized dissolving solvent (1:10 of DMF and distilled water respectively) was done by introducing an equal volume of complex stock solution into the same volume of sterilized distilled water, this was followed by taking the same volume of diluted stock solution into another distilled water of the same volume in a test tube to attain a second dilution concentration, this process continued to give final concentrations of 20.00, 10.00, 5.00, 2.50 and 1.25 mg/mL. This was done in duplicate. 2 mL of different concentration of the prepared complexes was introduced one after the other to 18 mL of pre sterilized molten nutrient agar at a temperature of 50 ^{o}C. The mixture was then poured into sterile plates and allowed to set. To the solidified nutrient agar mixture, bacterial isolates with standardized inoculums was streaked on it. The plates were incubated at 37 ^{o}C for 24 hours after which they were examined for the presence or the absence of growth. Macro− broth dilution technique [16,17] has been used, with few modifications accordingly. The MIC was taken as the lowest concentration of the tested antibiotics that shows no visible bacterial growth [18].

4.5.8 Minimum bacteria concentrations (MBC) of the complexes

Minimum bacteria concentrations of the complexes were determined with the method reported in [19], and the samples of organisms were taken from plates which were used for the MIC test that were with no visible growth and were sub− cultured on to freshly prepared

nutrient agar medium by streaking. These plates were incubated at 37 ^{o}C for 24 hours. MBC was taken as the lowest concentration of complexes at which all bacteria are killed.

4.6.0 Result and discussion

The antibacterial screening of the metal complexes alongside their ligands have been carried out in duplicate, depending on the concentration of the complexes, putting their control experiments in each case into consideration. 1 mg/mL was used for the screening of the first set of xanthate metal complexes, and they did not show activity at that concentration. The second set of complexes screening was carried out in a higher concentration of 40 mg/mL and the complexes showed activities against some of the selected bacterial isolates, using the method of agar well diffusion assay.

4.6.1 Antibacterial studies of metal complexes of xanthate

Zones of inhibition of the metal complexes and the solvent (DMF) used to dissolve them are presented in Table 4.1. It does show that the metal complexes as well as the free ligand did not show activity against the selected bacterial isolates, and because of their non− activity, the MIC and MBC analysis was not done on the metal complexes for 1 mg/mL concentration because they did not show any inhibition.

Table 4.1 Zone of inhibition exhibited by xanthate complexes at 1 mg/mL (mm)

Complexes	*B. pumilus*	*P. vulgaris*
DMF	NI	NI

O-ethyl xanthate	NI	NI
O-propyl xanthate	NI	NI
$[Ag(PPh3)_2(OEtdtc)]$	NI	NI
$[Cu(PPh3)_2(OEtdtc)]$	NI	NI
$[Pd(OPrdtc)_2]$	NI	NI
$[Pt(OEtdtc)_2]$	NI	NI

Key - NI = No inhibition

The antibacterial results of the remaining metal complexes with xanthate are presented below. The second set of screening was carried out using a concentration of 40 mg/mL of the metal complexes samples. Bacterial isolates used varied from a set of screening to the other as some of the bacterial microorganism experienced malfunctioned growth on culturing, thereby not meeting the standard for the screening process, and as such NA (not applicable) has been used to represent the situations when a particular isolate was not applicable.

All metal complexes as well as the xanthate ligand show a positive activity on the selected bacterial isolates as presented in Table 4.2. $[Ag(PPh_3)_2(OEtdtc)]$ as well as O-ethyl xanthate showed broad spectrum characteristics as they showed activity on all tested antimicrobial agents. Pd(II) and Pt(II) complexes also show inhibition on some of the bacterial isolate. $[Pd(OPrdtc)_2]$ show a zone of inhibition of 13 mm against *Bacillus cereus.* $[Cu(PPh_3)_2(OEtdtc)]$ was responsive against *Proteus vulgaris* only, with a zone of inhibition of 14 mm, which can be ascribed to its weak antimicrobial potential.

Table 4.2 Zone of inhibition exhibited by xanthate complexes at 40 mg/mL (mm)

Complexes	*B. cereus*	*P. vulgaris*
DMF	NI	NI

O-ethyl xanthate	15	9
O-propyl xanthate	11	10
$[Ag(PPh_3)_2(OEtdtc)]$	17	12
$[Cu(PPh_3)_2(OEtdtc)]$	14	NI
$[Pd(OPrdtc)_2]$	13	NI
$[Pt(OEtdtc)_2]$	NI	NI

The lowest MIC value of 1.25 mg/ml was observed in $[(PPh_3)_2Ag(OEtdtc)]$ against *Bacillus cereus* which revealed that the complex is the most active. The MIC results also show that the Pd(II) complexes is more active than the Pt(II), with Pd(II) showing the lowest MIC value of 2.5 mg/mL. O-ethyl xanthate has the highest MIC values showing that it is the least active (Table 4.3).

Table 4.3 MIC values (mg/mL) of xanthate complexes on selected Bacteria.

Complexes	*B. cereus*	*P. vulgaris*
O-ethyl xanthate	5.0	2.50
O-propyl xanthate	NI	NI
$[Ag(PPh_3)_2(OEtdtc)]$	1.25	5.0
$[Cu(PPh_3)_2(OEtdtc)]$	NI	NI
$[Pd(OPrdtc)_2]$	NI	NI
$[Pt(OEtdtc)_2]$	NI	NI

MBC result (Table 4.4), also shows that $[Ag(PPh_3)_2(OEtdtc)]$ has the highest activity with a low MBC value of 2.5 mg/mL, exhibited against a gram negative *Bacillus cereus.* The MBC result once again shows that the metal complexes are more active than the xanthate ligand.

Table 4.4 MBC values (mg/mL) of xanthate complexes on selected Bacteria.

Complexes	*B. cereus*	*P. vulgaris*
DMF	NI	NI
O-ethyl xanthate	NI	NI
O-propyl xanthate	NI	NI
$[Ag(PPh_3)_2(OEtdtc)]$	2.5	5.0
$[Cu(PPh_3)_2(OEtdtc)]$	NI	NI
$[Pd(OPrdtc)_2]$	NI	NI
$[Pt(OEtdtc)_2]$	NI	NI

Active antibiotics

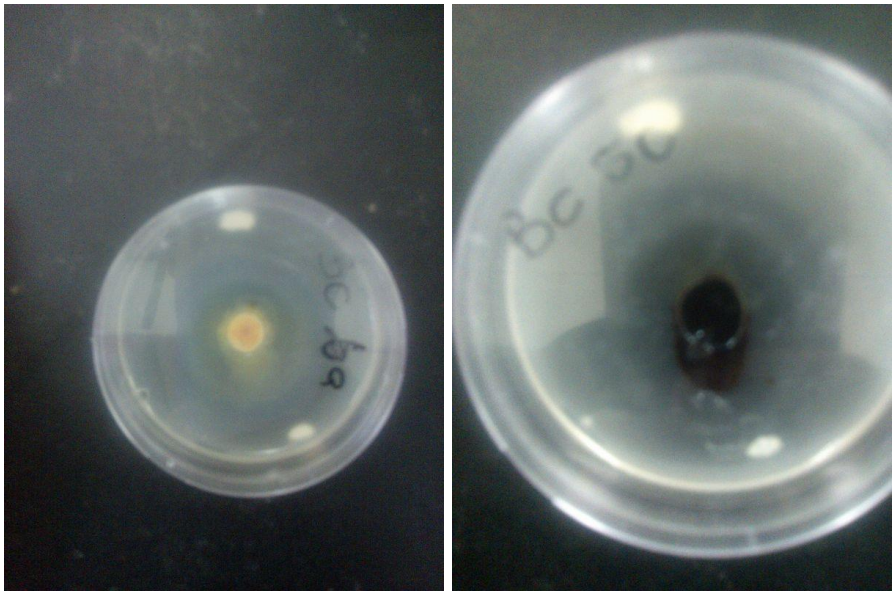

Figure 4.1 Non active Pt(II) and Pd(II) complexes

4.7 Reference

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Chapter Five

5.0 Conclusion

5.1 Summary of results

Ni(II), Ag(I), Cu(II), Pd(II) and Pt(II) complexes of xanthate have been synthesized and characterized by elemental analysis, UV− Vis, FTIR, conductivity measurements, M.pt / decomposition temperatures, and Pd(II), Pt(II) complexes and xanthate ligand by ^{1}H-NMR spectroscopy. Conductivity measurement on the complexes showed that they are non− electrolytes in solution with conductivity values in the range 0.05 − 18.30 µS. Generally all the xanthate ligands are soluble in water and the complexes are insoluble both in non-polar solvents except polar coordinating solvents such as DMSO and DMF.

The xanthate complexes formed four (tetrahedral / square planar), and six (octahedral) coordinate compounds. In each of the complexes xanthate acted as bidentate ligand through the two sulfur atoms. The geometries around the metal ions are completed by triphenylphosphine. ^{1}H-NMR spectroscopy of the ligands and the coupled diamagnetic platinum and palladium complexes revealed very useful information about some of the ligands and their complexes in spite of the limitations of poor solubility of most of the complexes which gave poor resolutions that cannot be properly assigned.

Antibacterial activity of the synthesized metal complexes shows a generally increased activity in comparison with that of their respective free ligands. At a lower concentration some of the complexes did not show any activity, a good number of complexes however showed activity at a higher concentration of 40 mg/ml. The degree of activity varies with

metals. Silver complex have been observed to show the highest activity of MIC value of 1.25 mg/mL with regards to antibacterial strength, although it varies with different ligands. And the least active are the copper complex. The trend in the activity of palladium and platinum complexes has the least activity. It was observed that palladium complex show more activity as compared to the platinum compare with xanthate ligand. The anticancer activity could not be reported because of computer glitches at the University of Western Cape Biotechnology department where the study was carried out.

5.2 Deductions from study

With regards to the results obtained and reported in this dissertation, we can conclusively say that we have been able to synthesize metal complexes of xanthate that can serve as alternative therapy for antibacterial, whilst I did not manage to discuss the anticancer side because I was still waiting for the results. Apart from the establishment of the structural formulations, based on available characterization techniques, of some metal complexes of xanthate, the antibacterial activity has confirmed that some of these metal complexes actually have more enhance antibacterial activity compared to their free ligands, which agrees to proposed objectives of study. This research study has also gives me a lead to subsequent research work towards development of alternative synthetic antimicrobial compounds, and in view of this the recommendations below have been proposed for possible further work and also to take care of the limitations that have been encountered in the course of this study.

5.3 Recommendations

The complexes need to be further derivatized to make them more water soluble because their poor solubility in water and other common solvents will ultimately limit their biological applications. Mass spectroscopy of all complexes is required as this will add to justify their proposed structure and stereochemistry. It is also necessary to grow single crystals suitable for X− ray analysis in order to confirm the propose formulations for some of the complexes. Apart from xanthate ligands that are synthesized from primary alcohol, I need to use secondary and tertiary alcohol for the future work so I can compare their activity as they are synthesized from different types of alcohols. In the area of application of metal complexes as antimicrobial agents, further specific studies like cytotoxicity of the synthesized antimicrobial agents can be looked at. This work studied the antibacterial activities of synthesized complexes; subsequent work can be, to look at the antimalarial. Initially, eight bacterial isolates were selected consisting of four grams positive and four grams negative but six of them did not grow properly. It is there necessary to rescreen the complexes in as many bacterial isolates as it is practically possible.