Synthesis and characterization of transition metal complexes with aspirin thiourea ligands

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DECLARATION

No portion of the work referred to in this dissertation has been submitted in support of an application for another degree of qualification of this or any other university or institution of higher learning.

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LIST OF ABBREVIATION

MIC – minimal inhibitory concentration

FTIR – Fourier-Transform Infrared Radiation

$^1$H NMR – Proton Nuclear Magnetic Resonances

LMCT – Ligand-metal charge transfer

s – singlet

d – doublet

t – triplet

m - multiplet
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ABSTRACT

The focus of this research is to react aspirin thiourea ligands with 3d transition metal (II) ion. There are two types of ligands that have been synthesized which are chloroaspirin with amine and chloroaspirin with amino acids. The ligands have been obtained by the condensation reaction between amine group and amino group. Then, transition metal complexes were synthesized by the direct reaction of 3d transition metal salts with aspirin thiourea ligands. Pure compounds of ligands and their metal complexes were characterized with FTIR, UV-Visible, $^1$H NMR and $^{13}$C spectroscopy, and molar conductivity. All FTIR spectra of the ligands and transition metal complexes shows $\nu$(N-H), $\nu$(C=O) (carbonyl), $\nu$(C=O) (carboxylic), $\nu$(C=S), and $\nu$(C-N) absorption bands. The important $^1$H NMR chemical shift that were observed are $\delta$(N$_1$-H), $\delta$(N$_2$-H), $\delta$(Ar-H), and $\delta$(OH) chemical shift. Aspirin thiourea complexes were screened for their antibacterial activity using E. coli. 120 ppm is minimum inhibition concentration (MIC) values of the compounds 12 toward the bacteria were determined.

Keywords: aspirin thiourea; synthesize; complexes; characterized; antibacterial activity.

ABSTRAK

Fokus kajian ini ialah untuk menindakbalas ligan aspirin tiourea dengan logam peralihan 3d. dua jenis ligan telah disintesis iaitu cloroaspirin dengan amine dan cloroaspirin dengan acid amino. Ligan tersebut diperolehi daripada process kondensasi antara kumpulan amine dan kumpulan amino. Seterusnya, kompleks logam peralihan disintesiskan secara terus melalui tindakbalas antara logam peralihan 3d dengan ligan aspirin tiourea. Sebatian ligan dan kompleks logam yang tulen dicirikan menggunakan spektroskopi inframerah (FTIR), ultralembayung-boleh Nampak (UV-Vis), resonans magnet nuklear $^1$H, dan konduktiviti molar. Semua spektra FTIR bagi ligan dan kompleks logam peralihan menunjukkan regangan pada $\nu$(N-H), $\nu$(C=O) (karbonil), $\nu$(C=O) (karbosilik), $\nu$(C=S), and $\nu$(C-N). Anjakan kimia NMR yang telah ditunjukkan ialah $\delta$(N$_1$-H), $\delta$(N$_2$-H), $\delta$(Ar-H), and $\delta$(OH). Kompleks aspirin tiourea juga diaji untuk aktiviti antibakteria menggunakan E. coli. 120 ppm ialah Nilai kepekatan rencatan minimum (MIC) bagi sebation 12 ke atas bakteria tersebut ditentukan.

Kata kunci: aspirin tiourea; sintesis; kompleks; gambaran sifat; aktiviti antibakteria.
1.0 INTRODUCTION

Thiourea is an organic compound of carbon, nitrogen, sulfur and hydrogen, with the formula CSN₂H₄ or (NH₂)₂CS. Thiourea is basically occurs in two tautomeric forms and has three functional groups which are very important for the structural modifications to synthesize new derivatives. Thiourea and its derivatives display a broad spectrum of applications in industries, chemistry, medicine and others (Khan et al., 2008). It is similar to urea, except that the oxygen atom is replaced by the sulfur atom. The properties of urea and thiourea differ significantly because of the difference in electronegativity between sulfur and oxygen. Thiourea is a versatile reagent in organic synthesis. Thiourea has mitogenic properties. The chemical did not induce gene mutations in bacteria. Inconsistent results, with the majority being negative, were obtained in assays in mammalian cells. Thiourea induced chromosomal recombination in yeast and Drosophila. It is not considered to be a genotoxic carcinogen. At high doses, thiourea can cause thyroid hyperplasia in mice and thyroid adenomas and carcinomas, hepatocellular adenomas, and tumours of the Zymbal or Meibomian gland in rats. However, none of the studies of carcinogenicity would meet present-day standards. Although no definite conclusion regarding the mechanism of carcinogenicity can be made, it is probable that thiourea acts via the known mechanism for non-genotoxic thyroid carcinogens (Zhong et al., 1982).

Thiourea-based C₂-symmetric ligand was synthesized, and its application in the palladium-catalyzed Heck and Suzuki coupling reactions of arenediazonium salts was evaluated. The reactions, which were performed at room temperature, without added base, and under aerobic conditions, produced product in 4 h with good yield. The corresponding arenediazonium salts were easily generated in one step from anilines (Mingji et al., 2004).
Thiourea is generally unidentate or bidentate ligand, so bis-thiourea ligand can form very stable complexes with transition metal. With those elements, bis-thiourea can form bis-thiourea complexes. They are very important and play vital roles at the molecular level in a living system. The self-assembly of transition metals with bridging ligands to produce metal–organic networks (MONs) is currently a very active area of study. Copper(I) centers are especially flexible with respect to coordination environment, ranging from 2- to 4-coordinate. However, also important in MON formation are the bonding capabilities of the ligands chosen. A recent review has divided MONs according to dimensionality produced through organic versus inorganic ligand bridging. Since the mid nineteenth century, metal complexes with bis-thiourea ligand have been discovered (Aslanidis et al., 2009).

Industrial production and the use of Fe, Co, Cu, Ni, Zn, Cd, and Pb elements can cause environmental pollution. On the other hand, some of these metals are present in trace amounts as essential elements for biological systems and these metal ions also play an important role in bioinorganic chemistry. In order to understand the role of these metal ions in biological systems, structural studies of the biological compounds and their metal complexes are extremely important (Arslan et al., 2009).

Compounds containing carbonyl and thiocarbonyl groups occupy an important position among organic reagents as potential donor ligands for transition metal ions. Among these thiourea derivatives are potentially very versatile ligands, able to coordinate to a range of metal centres as neutral ligands, monoanions or dianions (Mallick et al., 2010). The oxygen, nitrogen and sulfur donor atoms of thiourea derivatives provide a multitude of bonding possibilities. Both the ligands and their metal complexes display a wide range of biological activity including antibacterial, antifungal, antitubercular, antithroid, antihelmintic,
rodenticidal, insecticidal, herbicidal, and plant-growth regulator properties (Arslan et al., 2009).

Amidic and ureic compounds and their sulfur-containing analogs have a broad range of chemical activities, affect the environment as herbicides and pesticides and as mammalian metabolic waste product, solubilize hydrocarbons and other carcinogenic, can be used to tailor polymers and other materials for specific uses (Zhou et al., 2004). In this research, aspirin acts as starting material to produce aspirin thiourea ligands because aspirin are available in the laboratory. Besides that, aspirin are quite safe to use.

1.3 OBJECTIVES

The main objectives of this research project are:

a) To synthesize aspirin thiourea ligands
b) To synthesize transition metal complexes with aspirin thiourea ligands
c) To characterize the aspirin-thiourea ligands and their transition metal complexes by UV-Visible, FTIR, and $^1$H-NMR spectroscopy.
d) To determine the molar conductivity of the transition metal complexes.
e) To determine the antibacterial activity of the synthesis compound.
2.0 LITERATURE REVIEW

2.1 Aspirin

The chemical name of aspirin is acetylsalicylic (C₉H₈O₄) acid or 2(acetyloxy)benzoic acid. Aspirin have three functional groups which are aromatic ring, ester, and carboxylic acid. Aspirin is a white solid that is almost completely insoluble in water. Aspirin (acetylsalicylic acid) is a versatile drug. In medical application, at very lower doses, aspirin is used to treat and prevent heart attacks and blood clots (Martín et al., 2000).

At higher doses it is used as an analgesic to reduce pain and as an antipyretic to reduce fever. At very high doses, it is an effective anti-inflammatory agent used to treat rheumatic fever, gout and rheumatoid arthritis. It is also an anticoagulant, it dissolves corns and calluses, and it provokes loss of uric acid (a toxin) but promotes retention of fluids in the kidneys. It kills bacteria and induces peptic ulcers. The exact mechanisms of its pharmacological actions are still under study. In many plants, salicylates can induce flowering. Aspirin has been theorized to reduce cataract formation in diabetic patients, but one study showed it was ineffective for this purpose. The role of aspirin in reducing the incidence of many forms of cancer has also been widely studied. In several studies, aspirin use did not reduce the incidence of prostate cancer (Singh et al., 2008).
2.2 Synthesis of acetylsalicylic acid (aspirin)

The esterification reaction between salicylic acid and acetic anhydride can produce acetylsalicylic acid. The extraction of acetylsalicylic acid from commercial aspirin tablets using 95% ethanol was also successful according to this journal. The melting point of the synthesized aspirin was 128 - 130°C. The melting point of the acetylsalicylic acid that was isolated from commercial aspirin was 127 - 136°C. By comparing these observed melting points with the literature value of 128 - 137°C for acetylsalicylic acid, it was found that the values were relatively close, indicating that both products were acetylsalicylic acid. The acid from the commercial aspirin had a melting point that was a little lower and broader due to impurities in the product, which may have included some starch or ethanol that did not completely separate out or evaporate, respectively. It may also be the result of binding materials in the commercial aspirin. Overall, the melting point observations proved that the synthesized product and the product obtained from commercial aspirin were both acetylsalicylic acid (Jamie et al., 2003).

Aspirin can be synthesised through organic synthesis. Aspirin can be produced in a one step chemical process by reacting salicylic acid (C₇H₆O₃) with acetic anhydride, according to the reaction (scheme 1):

![Scheme 1: Synthesis of aspirin](image)
The -OH group of salicylic acid react with acetic anhydride to form an ester-like product. The carboxylic acid group of salicylic acid remains unchanged. Cerazy et al., (2004) state that phosphoric acid are used as a catalyst in the experiment. The main impurity in the crystallized aspirin will be salicylic acid, which will co-precipitate with the aspirin if the procedure is done too quickly (Cezary et al., 2004)

2.3 Synthesis of (2-chlorocarbonyl)phenyl acetate

In this synthesis, oxalyl chloride, tetrahydrofuran (THF), and dimethylformamide (DMF) are used as the reagent to form chloroaspirin from aspirin compound (Scheme 2).

![Scheme 2: Synthesis of (2-chlorocarbonyl)phenyl acetate](image)

It is mainly used in organic synthesis for the preparation of acid chlorides from the corresponding carboxylic acids. Like thionyl chloride, the reagent produces volatile side products in this application (Strazzolini, 1998).

The –OH functional group on the aspirin compound can be converted into the –Cl. Oxalyl chloride tends to be a milder, more selective reagent. A small amount of N,N-dimethylformamide (DMF) is usually added as a catalyst for the reaction. In this reaction,
the sulfur dioxide (SO₂) and hydrogen chloride (HCl) generated are both gases that can leave the reaction vessel, driving the reaction forward. Excess thionyl chloride (b.p. 79 °C) is easily evaporated as well. THF used as a solvent in the laboratory when a moderately higher-boiling ethereal solvent is required. The THF reagent may react with the oxygen in the atmosphere (Smith & David, 1999).

2.4 Thiourea

All the obtained thioureas in the synthesis were soluble in common organic solvents such as ethanol, methanol, toluene, benzene and DMF (Nguyen & Nguyen, 2009). Thiourea and its derivatives are versatile ligands in iron coordination chemistry, including bioinspired chemistry for modeling iron-sulfur proteins. In recent years, chelating scaffolds with three thiourea-like donor groups (Figure 1) have been developed, which serve as useful tripodal face-capping ligands for sulfur-ligated transition metal centers. An important property in this context is the resonance structure of the thiourea moiety, which imparts partial thiolate-like character to the sulfur (Steffen et al., 2010).

![Figure 1: Structure of bis(3-tert-butyl-2-thione-imidazoly)methane](image)

Damir et al.,( 2010) reported that the syntheses of two N-phosphorylated thioureas 2-PyNHC(S)NHP(O)(OiPr)₂ by addition of phosphorylisothiocyanate to the corresponding 2- or 3-aminopyridine. It was established that in CDCl₃ solution 2-PyNHC(S)NHP(O)(OiPr)₂ forms
an intramolecular hydrogen bond between the NHP hydrogen and 2-pyridyl nitrogen atoms, which leads to the formation of zwitterions. Single crystal X-ray diffraction studies showed the thiourea 2-PyNHC(S)NHP(O)(OiPr)$_2$ (Figure 2) to form both intra- and intermolecular hydrogen bonds which in turn lead to polymeric chain formation. Moreover, according to X-ray data 2-PyNHC(S)NHP(O)(OiPr)$_2$ forms π.....π stacking interactions between molecules of two neighboring chains.

![Figure 2: Structure of 2-aminopyridine with the isothiocyanate (iPrO)$_2$P(O)NCS](image)

In recent years, thiourea derivatives, especially acylthiourea derivatives (Figure 3), are of great interests for chemists because they are excellent H-bonds donors and acceptors, and have strong ability to coordinate with metal ions. The investigations of acylthiourea derivatives, especially molecular single crystal structures, are very helpful in assembling some supramolecular structures, synthesis of novel coordination compounds, anion recognition and the research of the applications of thiourea derivatives (Su, 2007).

![Figure 3: Structure of N-p-nitrobenzoyl-N'-p-chlorophenylthiourea](image)
Emmanuel et al., (1998) reported on the coordination of copper, nickel and cobalt with unsymmetrical bidentate ligands (Figure 4). The bis (N,N-diethyl,N’-benzoylthiourea) copper (II) can crystallize in three monoclinic forms. The crystal structure of one of these forms indicates that the S and O atoms are arranged in cis position in a slightly tetrahedrally distorted square geometry. The presence of S, N and O electron donors, the versatility and interesting behaviour of acylthioureas as building blocks in polydentate ligands for metal ions have become a topic of interest in the last few years. The substituted acylthiourea ligands might act as monodentate sulfur donors, bidentate oxygen and sulfur or oxygen and nitrogen donors. They could also coordinate through the keto- or enol-thione form, depending of the ligands themselves, and the metal ions and counter-anions used (Yuan et al., 2001).

![Figure 4: Example of S, O ethoxyl ligands](image)

Thiourea leaching is a relatively nontoxic process, posses a rapid dissolution rate for gold and silver, slow dissolution rate of impurities and high selectivity (Aguayo & Encinas, 1998).

For the past few decades, thiourea derivatives have attracted great attention as versatile ligands in numerous applications. This is due to its unique properties which enable to
coordinate with various transition metal ions as monodentate or bidentate ligands. Thiourea derivatives for instance derived as substituted benzoylthiourea or phenylthiourea derivatives (Figure 5) are attractive model compounds for the studies in solid-state chemistry due to their tendency for the formation of intra- and intermolecular hydrogen bonds of the NAH proton-donor groups to sulphur and carbonyl oxygen atoms. Thiourea derivatives are widely used in numerous applications such as in pharmaceutical industry for potential therapeutic agents as antibacterial, anti-HIV, anticancer drugs, antidepressants and antihyperlipidemic, antiallergic, antiparasitic, platelet antiaggregating, antiproliferative activities (Sukeri et al., 2010).

Figure 5: Structure of N-(3,4-dichlorophenyl)-N’-(2, 3 and 4-methylbenzoyl)thiourea
2.5 Synthesis and application of thiourea

The derivatives of thiourea have been widely used due to their antibacterial activity, including Gram-positive cocci, Gram-negative rods, and antifungal activity. Thiourea derivatives are associated with a broad spectrum of biological activities including antibacterial, antifungal, tuberculostatic, antitumor, anticonvulsant and antiviral properties (Struga et al., 2010). They also reported the synthesis and antimicrobial activity of compounds containing the thiourea system attached to polycyclic imide.

Other industrial use of thiourea includes the production of flame retardant resins and vulcanization accelerators. Thiourea is used as an auxiliary agent in diazo paper (light-sensitive photocopy paper) and almost all other types of copy paper. The liquid silver cleaning product TarnX is essentially a solution of thiourea. A leaching agent for gold leaching and silver leaching can be created by selectively oxidizing thiourea, bypassing the steps of cyanide use and smelting (Athey, 1979).

The structural flexibility and efficacy of thiourea–amine catalysts for the supramolecular activation and ring-opening polymerization (ROP) of lactide are described. The nature of the hydrogen bonding group and its strength as well as the steric congestion have been altered, leading to shorter polymerization times, better control, and pathways to influence the stereochemistry of the resulting polymer. The tolerance to functionality and the mild conditions of the ROP mechanism allow for block copolymer synthesis by combination of nitroxide-mediated polymerization as well as reversible addition fragmentation and chain transfer polymerization using dual-headed initiators. Tandem hydrogen bond activation to organocatalyze ROP of lactide is an effective, versatile means to generate polymers with
predictable molecular weights, narrow polydispersities, control of microstructure and a variety of complex architectures and block copolymers (Russell et al., 2006).

Thiourea leaching has been used to treat an antimony-rich concentrate in New South Wales (Australia) and has been investigated as a process option for the treatment of several other ores, but no large scale commercial process has been developed (Aguayo & Encinas, 1998).

In the USA, thiourea is used in animal hide glue, which contains thiourea at a concentration of 10–20% as a liquefying agent. Reports indicate its use in the production of flame retardant resins and as a vulcanization accelerator. In Germany, thiourea is not used in the leaching of ore mines and not processed to thiourea dioxide. Instead, the following use pattern is reported, auxiliary agent in diazo paper (light-sensitive photocopy paper) and almost all other types of copy paper (19%), metal cleaning, including silver polish (4%), precipitation of heavy metals (3%), additive in slurry explosives (3%), electroplating/electroforming (1%), corrosion inhibitor (1%), processing to organic intermediates (41%), mercaptosilanes (6.5%), vulcanization accelerators (0.5%), resin modification (4.5%), and chemicals industry and miscellaneous (16.5%). In Japan, thiourea is added to fertilizers to inhibit the nitrification process. Data on the quantities used are not available (Kubota & Asami, 1985).

Thiourea is emitted by manufacturers of electronic components and accessories and manufacturers of aircraft and aircraft parts. Organic thiourea derivatives are used as vulcanization accelerators, pharmaceuticals (antiseptic, thyrotherapeutic, narcotic, and tuberculostatic agents), and plant protection agents and pesticides (e.g., chloromethiuron, diafenthiuron, thiophanate, and thiophanate-methyl) (Mertschenk et al., 1995).
Besides that, thiourea is used in dyeing and finishing processes in the textile industry. Finishing involves the application of thiourea as a fire retardant to the cloth, which will typically contain ≤0.02% thiourea after this stage. An investigation at a textile factory on the prevalence of hypothyroidism gave typical concentrations of 5 µg thiourea/m³ at an inlet of the local exhaust ventilation of the finishing machines. No thiourea was found in the atmosphere of the process area (Roberts et al., 1990).

2.6 Complexation of thiourea

Thiourea has a long history as a ligand in co-ordination chemistry being able to coordinate to a metal via either sulphur or nitrogen. Andrew et al., (1999) stated that, original interest in thioureas and the related thiosemicarbazides arose as these ligands allow the retention of a hydrogen-bonding surface within a complex following co-ordination. The reactions of thiourea with gold(III) and iron(III) are of special interest. The redox reaction with gold(III) is rapid in acidic solutions, and the reduction to gold(I) is quantitative. This reaction has been recommended for the analytical determination of gold(III). Only one ion of gold(I)-thiourea is known, namely [Au(CS(NH₂H)₂)]⁺. The reaction between iron(III) and thiourea is slow because of the formation of very stable metal-ligand co-ordination bonds. The complex [Fe(III)SO₄(CS(NH₂)₂)]⁺ (stability constant log β=6.64) was identified in a mixed sulphatethiourea medium, and, upon completion of the reduction process, the complex [Fe(II) (CS(NH₂)₂)]SO₄ was identified.

Previous journal reported that the use of the two parallel N–H hydrogen bond donor groups present in co-ordinated thiosemicarbazides together with the two parallel hydrogen bond acceptors in equivacarboxylates (Figure 6) as part of crystal engineering studies of nickel and zinc complexes. Similar hydrogen bonds have been exploited as the basis of
carboxylate receptors and for the effect they have on C–N bond rotation (Andrew et al., 1999).

Figure 6: Interconversion of platinum complexes of NHMeC(S)NHNMe.

Complex formation of thiourea with copper takes place as an intermediate step in the preparation of copper sulfide thin films by spray pyrolysis starting from aqueous solutions of copper(II) chloride and thiourea (Figure 7). The stoichiometry of the complex and that of the resulting thin film primarily depends on the molecular ratio of the starting materials. In addition syntheses, structural (single crystal XRD also at low temperature 193 K) and spectroscopic studies (FTIR and Raman) of six copper–thiourea complexes are now reported. The copper to thiourea stoichiometric ratio is 1:3 in four of these complexes, but their structures are basically different as dimerization or polymer formation takes place depending on whether the water of crystallisation is present or absent (Petra et al., 2004).