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Synthesis of Gd(III) Complex with Heptyl Methyl Dithiocarbamate and 2,9-Dimethyl Phenanthroline as an Antituberculosis

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Abstract. *Mycobacterium tuberculosis* is a bacterium that causes tuberculosis infection disease. This study aimed to produce complex compounds that can to damage the cell wall of *Mycobacterium tuberculosis*. Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline complex was synthesized and characterized by reacting N-heptyl methylamine, carbon disulfide, 2,9-dimethyl phenanthroline and lanthanide group metal ion (Gadolinium) using in situ method. Characterization was carried out using electrothermal melting point, conductometer, UV-Vis spectrophotometer, and FT-IR spectrophotometer. The resulting Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline complex was white in colour as much as 7.01%, conductivity 20 Ω^{-1} and melting point 208-210 °C. Testing of complex compounds gave effective results as antibacterial *Mycobacterium tuberculosis*.

Introduction

Tuberculosis is one of the biggest causes of death in the world. In 2019, the Global Report TB reported that the number of people with tuberculosis in 2018 reached 10 million and the number of deaths reached around 1.5 million. Eight countries accounted for two-thirds of the global total: India (26%), Indonesia (8.5%), China (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%) (WHO, 2020). *Mycobacterium tuberculosis* is a rod-shaped, aerobic bacterium that does not form spores. These bacteria are intracellular bacteria that grow slowly and have pathogenic properties that can survive in host macrophages *Mycobacterium tuberculosis* has a cell wall composed of mycolic acid. This specific component of the cell wall accounts for as much as 50% of the dry weight of the bacteria (Aini, et.al., 2017).

Efforts that can be made in inhibiting and stopping the growth of *Mycobacterium tuberculosis* is by damaging the active side of the cell wall, namely mycolic acid. The synthesis of complex compounds has been widely carried out and one of them is a complex compound using dithiocarbamate ligands. Dithiocarbamate ligands have wide applications. Based on several research, it is found that complex compounds with dithiocarbamate ligands have activity as antibacterial and also do not cause cytotoxicity to liver cells (Iv et al., 2015), as antifungal (Anggraini, et al., 2020), potential as breast anticancer (Prihantono, et al., 2020) and many more.

Complex compounds can occur by reacting a metal as the central atom with a ligand. Gadolinium as a lanthanide metal becomes the central atom in this complex compound. Gadolinium in its pure form has high economic value and is widely used for industrial, medical, chemical and metallurgical purposes. Gadolinium has relatively the same physical and chemical properties as other rare earth elements (Effendy et al., 2018). Metal lanthanide complex compounds are known to be utilized as supramolecular devices, fluorescent chemo sensors, or luminescent probes in the fields of biology and medicine, or as electroluminescent components for light-emitting diodes (LEDs) (Suarsa, 2017).

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Metal complexing with dithiocarbamate ligands is also inseparable from the HSAB (Hard Soft Acid Base) principle. Pearson (1963) explained that the lanthanide metal gadolinium (Gd) belongs to the hard acid group, while the dithiocarbamate ligand is classified as a soft base, so it will be difficult to form complex compounds if reacted. Therefore, nitrogen ligands (phenanthroline) are used to reduce the hardness of the lanthanide metal so that it can react and form complexes with dithiocarbamate ligands (Saito, 1996).

Experimental

Material and Methods

The materials used in this study were carbon disulfide CS2 99.5% (Ajax Chemical Ltd), $GdCl_3.6H_2O$, 2,9-dimethyl phenanthroline, N-heptyl methylamine, methanol (95%), DMSO (Dimethyl Sulfoxide), *Mycobacterium tuberculosis* bacteria, and Whatman 41 filter paper.

Procedures

Synthesis of Complex Compounds

The A total of 0.7435 g (2 mmol) of $GdCl_3.6H_2O$, was put into a 50 mL beaker, dissolved with 10 mL of methanol (95%) then added 0.4204 g (2 mmol) of 2,9-dimethyl phenanthroline. A total of 0.9047 g (7 mmol) of N-heptyl methylamine was put into a 100 mL beaker and then dissolved with 10 mL of methanol (95%). The amine solution was added with 0.42 mL of CS_2 solution (7 mmol in 10 mL of 95% methanol) slowly at 15 °C and then stirred for 15 minutes. After that, the ligand solution formed was then added to the metal solution and stirred with a magnetic stirrer for 30 minutes. The mixture was then allowed to stand until a precipitate formed. The precipitate formed was then filtered and put in a desiccator to dry and then crystalized with the appropriate solvent until pure crystals formed, analyzed and characterised.

Conductivity Analysis

The synthesized complex compound was dissolved into DMSO, then the electrical conductivity of the complex solution and its solvent were measured for using a conductometer.

Refractive Determination of Melting Point

The compounds produced in this study had their melting points determined using an electrothermal IA 9100 melting point device.

Characterization

Characterization of complex Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline was by a Jenwey UV-Vis spectrophotometer at 200-800 nm region and using an FTIR SHIMADZU spectrophotometer, to determine the typical functional groups of the complex measured at wavelengths between 4000-340 cm^{-1} .

Testing the Inhibition of Complex Compounds Against the Growth of *Mycobacterium tuberculosis* Bacteria

Testing the inhibitory power of the synthesized complex compound against the development and growth of *Mycobacterium tuberculosis* bacteria was carried out by diffusion method using a scrub bottle. Three sterile scrub bottles were prepared and then Lowenstein Jensen (LJ) medium was added. Furthermore, each bottle was filled with the complex compound solution, negative control (DMSO) and positive control (rifampicin). The scrub bottles were labeled to distinguish the samples tested. Next, colonies of *Mycobacterium tuberculosis* bacteria were injected and incubated for six weeks at 37 °C and then observed for bacterial growth.

Result and Discussion

Table 1 gives the results of the synthesis of complex compounds, melting point testing, and conductivity measurements.

Table 1. Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline.

Characterization	Result
Weight (g)	0.1825
Rendering (%)	7.01
Colour	White
Melting Point (°C)	208-210
Conductivity $(\Omega)^{-1}$	20
Characteristic	Nonelectrolyte

The synthesis of complex compound Gd (III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline was successfully synthesized and obtained a weight of 0.1825 g with a yield of 7.01%. The results show that the hard acidic property of gadolinium metal successfully reduced by recombining it with borderline base of phenanthroline so that gadolinium metal can react with heptyl methyl dithiocarbamate ligands which are soft bases. This finding is consistent with the concept of HSAB, where hard/borderline acids react well with soft/borderline bases.

The melting point measurement is one of the analyses for determining the purity of a compound. Pure substances melt at a sharp, highly-defined temperature: small temperature range, i.e <2 °C (Firdaus, 2011). The melting point measurement can give information of the strength of interaction between molecules. The higher the melting point, the stronger the interaction occurs between molecules. The result obtained a complex compound having a melting point of 208-210 °C. The difference obtained is 2 °C. This finding proves that this complex compound has good purity. In addition, the high melting point also indicates that this complex compound has a strong molecular attraction force between the metal center and its ligand.

The conductivity value of the complex compound is obtained at 20 Ω^{-1} while of the solvent used (DMSO) is 12 Ω^{-1}. Consequently, it can be said that the complex compound produced is neutral because the difference in conductivity value between the solvent and the complex compound is 8 Ω^{-1}. The difference in conductivity value between the solvent and the complex compound exceeds 65 Ω^{-1}, then the complex compound is charged while if less than 65 Ω^{-1} then the complex compound is neutral.

UV-Vis Characterization

The UV-Vis spectroscopy results of the complex compound using acetone solvent can be seen in Figure 1. The results of the UV-Vis spectrum analysis of the Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline complex compound showed maximum absorption peaks at 278 nm and 306 nm.

The absorption peak that appears indicates the occurrence of electron transitions in the molecule. Compounds containing C=S groups show strong bands in the 250-300 nm region. The electron transition that occurs is the intraligand $\pi \rightarrow \pi^*$ transition of the CS_2 compound which is influenced by the hyperconjugation effect of the R group, namely heptyl methyl to the nitrogen atom which is in the 278 nm absorption area (Prihantono et al., 2020). Absorption in the 306 nm region shows the electron transition from the $n \rightarrow \pi^*$ orbital in the N=C=S group (Rizal et al., 2022). This indicates that the reaction between the CS_2 compound and the N-heptyl methylamine ligand was successfully synthesized.

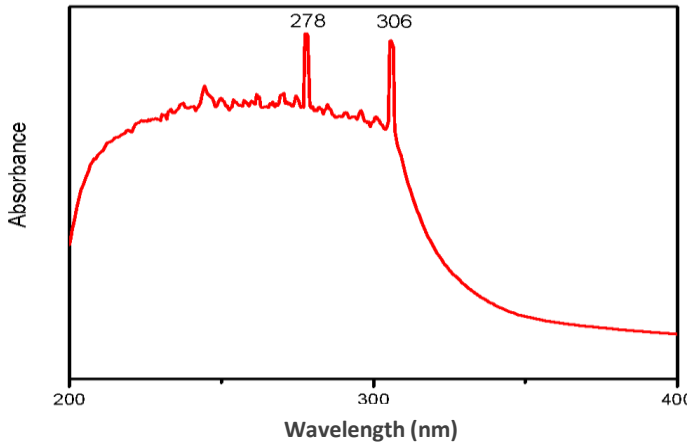

Figure 1. UV-Vis spectrum of Gd(III)heptylmethyldithiocarbamate 2,9-dimethyl phenanthroline.

IR Characterization

Infrared absorption peaks indicating the presence of dithiocarbamate compounds are characterized by the presence of absorption peaks at wave numbers 1450-1550 cm^{-1} and 950-1050 cm^{-1} for v(C=N) and v(C=S) stretching vibrations respectively (Adeyemi et. al., 2021). Table 2 shows the wave numbers of peaks obtained in the spectrum of the complex compound Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline. The absorption peak at 1050 cm^{-1} belongs to the absorption of the C=S bond and the one at 1550 cm^{-1} is for the absorption of the C=N bond. Furthermore, the absorption peak at 2926 cm^{-1} indicates the presence of aliphatic C-H groups (Raya et. al., 2021). The absorption peak of 375 cm^{-1} relates to the metal-sulfur (M-S) bond corresponding to stretching vibration of the M-S bond in the complex compound originating from the central atom and CS_2 on the ligand (Kumar and Nath, 2018). In this case, there has been a reaction between Gd metal as the central atom of the complex compound with the heptyl methyl dithocarbamate ligand.

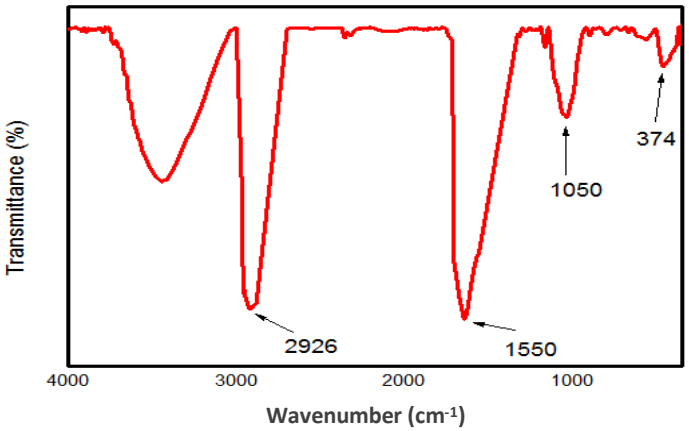

Figure 2. IR spectrum of Gd(III)heptylmethyldithiocarbamate 2,9-dimethyl phenanthroline.

Table 2. IR Data of Gd(III)heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline.

Compound	Wavenumber $(cm)^{-1}$
v(C-H)	2926 s
v(C=N)	1550 s
v(C=S)	1050 m
v(M-S)	374 w

Activity Test as Anti Tuberculosis

Tuberculosis testing complex compounds were dissolved with DMSO (Dimethyl Sulfoxide) as a solvent (negative control) so that *Mycobacterium tuberculosis* colonies can grow properly. The drug rifampicin with a concentration of 4000 ppm was used as a positive control for comparison to the complex compound in inhibiting the growth of *Mycobacterium tuberculosis*.

(a) (b) (c)

Figure 1. (a) Rifampicin; (b) Complex; (c) DMSO.

The method used is the diffusion method using solid media, namely Lowenstein Jensen (LJ) medium. Lowenstein-Jensen (LJ) is a selective medium used for culture and isolation of *Mycobacterium*. This media is a synthetic medium that contains eggs and is enriched with glycerol and asparagine which can fertilize the growth of *Mycobacterium tuberculosis* (Daulay et al., 2015). In addition, LJ media is considered a superior diagnostic tool in developing countries (Shoukrie et al., 2018) and based on research conducted by Pestariati and Meilinda (2021), showed that LJ solid media has good performance in growing *Mycobacterium tuberculosis* bacteria in BTA positive microscopic samples.

The results of the tuberculosis test showed at figure 3. The rifampicin, which is a tuberculosis drug, was unable to inhibit the growth of *Mycobacterium tuberculosis*, this is because rifampicin has drug resistance. DMSO as a negative control also allows the bacteria to grow on LJ media. As for the complex compound Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline showed positive results marked by the non-growth of *Mycobacterium tuberculosis*. This is because the central atom of Gd(III) will react with the active side of mycolic acid. The metal can enter the cell wall of *Mycobacterium tuberculosis* due to the presence of heptyl methyl dithiocarbamate ligand as a mobiliser which is nonpolar and will react with mycolic acid which is also nonpolar. Based on the HSAB theory, the central atom of Gd(III) is a hard acid that will react with OH and O groups that are hard bases in the mycolic acid structure. In addition, the existence of free electrons from the O atom

can cause coordination bonding and will form a chelate. When a reaction like this occurs, the active side of mycolic acid becomes damaged so that the complex compound Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline is able to inhibit the growth of *Mycobacterium tuberculosis.*

Conclusion

The complex compound Gd(III) heptyl methyl dithiocarbamate 2,9-dimethyl phenanthroline gives good results in terms of its characterization using UV-Vis and FTIR. The complex compound was successfully synthesized with a weight of 0.1825 g and a yield of 7.01%. Tuberculosis testing showed positive results and was able to inhibit the growth of *Mycobacterium tuberculosis* bacteria.

Conflict of Interest

The authors declare that there is no conflict of interest.

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