

Synthesis, Characterization and *In-Vitro* Antimicrobial Studies of M^{2+} Complexes of *p*-Chlorophenyl-, *p*-Bromophenyl-Dithiocarbamates

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Abstract

This study reports the synthesis of metal complexes of mixed ligands *p*-Chlorophenyl-, *p*-Bromophenyl-dithiocarbamates. The spectral properties of the metal complexes [Zn(II), Cd(II), Hg(II), Cu(II), Co(II) and Ni(II)] were obtained using the FTIR and UV/Vis spectroscopic techniques. Their antibacterial studies revealed that these complexes as well as the ligands could serve as possible antibacterial agents against pathogens. Melting point and solubility measurements were also carried out. It was observed that these complexes were non-toxic, non-electrolytic and stable solids.

Keywords

Metal Complexes, *p*-Chlorophenyl, *p*-Bromophenyl, Dithiocarbamates, Antibacterial Studies

1. Introduction

Dithiocarbamate is a group of organic compound, an analogue of carbamates in which both oxygen atoms are replaced by sulphur atoms [1]. The transition metal complexes (TMCs) of dithiocarbamates have been reported and applied in different areas of material science [2] [3] [4]. This is due to their stability in different oxidation states [5]. Metal complexes of dithiocarbamates have been studied extensively due to their biological, agricultural, chemical, medicinal, pharmaceutical and industrial applications [3] [6]. The presence of the dithiocarbamate moiety in some biologically active molecules has generated interest in their potentials for medical application [7] [8] [9] [10] [11]. Development of metal

based pharmaceuticals has received tremendous attention due to increased resistance to current generation of antibiotics by pathogens [12] [13] [14]. The TMCs of mixed ligands have been used in past and recent times for optimal applications especially in the area of medicine [5] [15]. This work was therefore designed to synthesize, characterize and evaluate the antimicrobial activities of mixed ligands *p*-Chlorophenyl- and *p*-Bromophenyl-dithiocarbamates metal complexes.

Thiocarbamate itself has been synthesized and characterized and reported for its potency against bacteria such as *Escherchia coli*, *Staphylococcus aureus*, *Bacillus subtilis* etc. and fungi such as *Aspergillus niger*, *Monilia americana*, *Candida albicans* etc. [5] [15] [16]. Also, a lot of metals have been reported for their medicinal and pharmaceutical applications. Bringing them together with ligands like the thiocarbamates creates synergistic effects for improved efficiency [5] [15] [16].

2. Materials and Methods

All chemicals and reagents used are analytical grade with no further purification needed. They include methanol, carbon disulphide, ammonium solution, toluene, ethanol, phosphorus pentoxide, sodium carbonate, chloroacetic acid, *p*-chlorophenyl amine, *p*-bromophenyl amine. The Gallen Kamp melting point apparatus was used to determine the melting points of the synthesized metal complexes. The Uv-vis measurements of the metal complexes were recorded in DMSO using Perkin Elmer Lambda 25 spectrophotometer from 800 - 200 cm^{-1} , while the FTIR data were obtained by using KBr discs on a Perkin Elmer 2000 FT-IR spectrophotometer in the range 4000 - 370 cm^{-1} .

2.1. Synthesis of the Ligands

2.1.1. Synthesis of Ammonium *p*-Chlorophenyl Dithiocarbamate Ligand, L1

9.6 g of *p*-chloroaniline, 6 ml of carbon disulphide and 11 ml of ammonium hydroxide were added into a 250 ml round bottom flask fitted to a reflux condenser, magnetic stirrer and thermometer. The mixture was stirred vigorously, the reaction was maintained at 30°C - 35°C by external cooling, a heavy yellow precipitate of ammonium *p*-chlorophenyl dithiocarbamate was separated out. The mixture was filtered and residue washed off with 30 ml portion of a 3% aqueous solution of ammonium chloride and with two 15 ml portions of 96% ethanol, dried in a desiccator (sodium hydroxide and phosphorus pentoxide as desiccant) (Figure 1).

2.1.2. Synthesis of Ammonium *p*-Bromophenyl Dithiocarbamate Ligand, L2

9.92 g of *p*-bromoaniline, 15 ml of carbon disulphide and 15 ml of ammonium hydroxide were added into a 250 ml round bottom flask fitted to a reflux condenser, magnetic stirrer and thermometer. The mixture was stirred vigorously, the reaction was maintained at 30°C - 35°C by external cooling, initially, the mixture turned milky and suddenly, a deep red was obtained. At the end of the

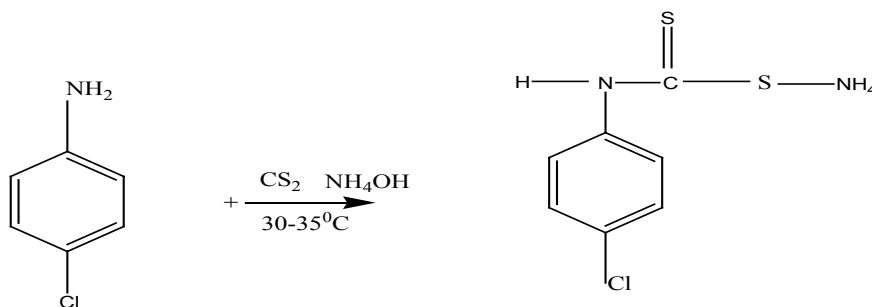


Figure 1. Synthesis of ammonium *p*-chlorophenyl dithiocarbamate ligand.

reaction, a foamy heavy orange precipitate of a heavy yellow precipitate of ammonium *p*-bromophenyl dithiocarbamate was separated out. The mixture was filtered and residue washed off with 30 ml portion of a 3% aqueous solution of ammonium chloride and with two 15 ml portions of 96% ethanol, dried in a desiccator (sodium hydroxide and phosphorus pentoxide as desiccant) (**Figure 2**).

2.1.3. Synthesis of M^{2+} Complexes of *p*-Chlorophenyl Dithiocarbamate and *p*-Bromophenyl Dithiocarbamate Ligand

0.2017 g of Zinc (II) sulphate, 0.5202 g of cadmium (II) chloride, 0.214 g of mercury (II) chloride, 0.1995 g of Copper (II) sulphate, 0.297 g of cobalt (II) chloride and 0.3285 g of nickel (II) chloride were weighed and transferred into a 250 ml beaker each. 50ml of distilled water was added into each beaker with a magnetic bar for effective stirring. Also, 0.276 g of *p*-chlorophenyl dithiocarbamate and 0.331 g of *p*-bromophenyl dithiocarbamate were out into 100 ml beakers each. 50 ml distilled water was added and each solution stirred on a magnetic stirrer after which the two ligands were poured into each salt solution simultaneously and step-wisely. The ligand/metal solution mixtures were then stirred vigorously for 3 hours each. A whitish precipitate was obtained for zinc (II) complex, yellowish precipitate for cadmium (II) complex, black precipitate for mercury (II) complex, a dark brown precipitate for copper (II) complex, purple precipitate for cobalt (II) complex and greenish yellow precipitate for nickel (II) complex. Individual products were suctioned and dried in a desiccator (using the mixture of sodium hydroxide and phosphorus pentoxide as desiccant) and weighed (**Figure 3**).

2.2. Biological Activities

Antibacterial Assay (*In Vitro*)

The ligands and their metal complexes were screened *in vitro* for their antibacterial potencies against gram positive and gram negative bacteria (*Escherichia coli*, *Serratia mercersens*, *Salmonella tyhi*, *Shigella flexneri* and *Staphylococcus aureus*) and fungi (*Trichoderma viride*, *Monilia albicans*, *Saccharomyces ludwigii*, *Rhizopus stolon* and *Mucor mucedo*). These compounds were dissolved in DMSO. Two-eight hour old bacterial inoculums containing approximately 10^4 - 10^6 colony forming units (CFU/ml) were used. Wells of 0.8 mm in diameter

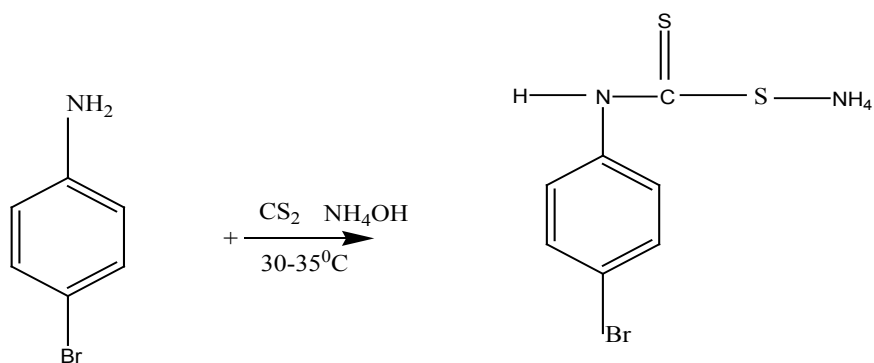


Figure 2. Synthesis of ammonium *p*-bromophenyl dithiocarbamate ligand.

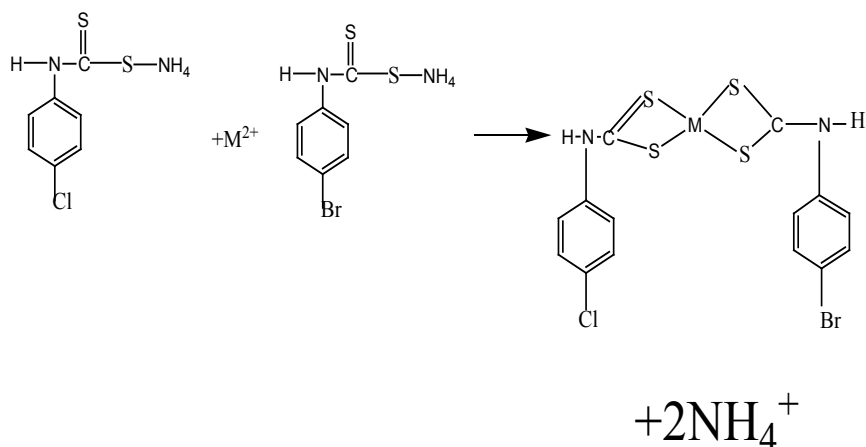


Figure 3. Synthesis of the TMCs: $M^{2+} = Zn^{2+}, Cd^{2+}, Hg^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}$.

were dug in the media with the aid of a sterile metallic cork borer. The test organisms were inoculated into disposable plates, each well bored at four equidistant peripheral points and inoculation was repeated three times. The wells were filled with 1 mg/ml and 10 μ g/ml for bacteria and fungi respectively of the complex solutions. DMSO and reference antibacterial and antifungal drugs (tetracycline and amphotericin respectively) were used as standard drugs. The organisms were grown on Mueller Hinton and potato dextrose (Agar) for bacteria and fungi respectively at 37°C for 48 hours (bacteria) and at 30°C for seven days (fungi).

3. Results and Discussion

3.1. Physical Parameters

Electro Thermal Digital melting point apparatus was used to obtain the melting points of the ligands and TMCs. The percentage yields values of the ligands and TMCs were relatively high (76% - 92%). The melting points showed that the compounds are stable in solid states (**Table 1**). The ligands were soluble in water, polar organic solvents and sparingly soluble in non-polar organic solvents. The TMCs were insoluble in water, but soluble in most organic solvents (**Table 2**). The solubility test suggests that the synthesized compounds are non-polar.

Table 1. Melting point measurements/yield percentage for both the ligands and their respective metal complexes.

Ligands/metal complexes	Melting points (°C)	Yield percentage (%)
<i>p</i> -chlorophenyl dithiocarbamate	122	92
<i>p</i> -bromophenyl dithiocarbamate	156	85
Zn ²⁺ complex	182	78
Cd ²⁺ complex	268	79
Hg ²⁺ complex	134	76
Cu ²⁺ complex	184	67
Co ²⁺ complex	220	71
Ni ²⁺ complex	266	72

Table 2. The solubility tests for the synthesized ligands and their metal complexes.

Solvents	Ligands		Metal complexes					
	<i>p</i> -bromophenyl DTC	<i>p</i> -chlorophenyl DTC	Zn(II)	Cd(II)	Hg(II)	Cu(II)	Co(II)	Ni(II)
Toluene	Soluble	Sparingly soluble	Insoluble	Sparingly soluble	Insoluble	Soluble	Sparingly soluble	Insoluble
Methanol	Soluble	Soluble	Insoluble	Insoluble	Insoluble	Sparingly soluble	Soluble	Partially soluble
Ethanol	Sparingly soluble	Soluble	Soluble	Sparingly soluble	Partially soluble	Partially soluble	Soluble	Insoluble
Chloroform	Sparingly soluble	Sparingly soluble	Insoluble	Insoluble	Insoluble	Partially soluble	Partially soluble	Sparingly soluble
Xylene	Insoluble	Sparingly soluble	Partially soluble	Partially soluble	Insoluble	Partially soluble	Insoluble	Insoluble
Ethyl acetate	Sparingly soluble	Soluble	Soluble	Insoluble	Insoluble	Partially soluble	Soluble	Soluble
Acetone	Insoluble	Sparingly soluble	Soluble	Insoluble	Insoluble	Soluble	Sparingly soluble	Sparingly soluble
Propan-2-ol	Insoluble	Soluble	Soluble	Insoluble	Insoluble	Soluble	Insoluble	Insoluble
DMSO	Soluble	Soluble	Soluble	Soluble	Soluble	Sparingly soluble	Soluble	Soluble
Water	Soluble	Soluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble

3.2. Spectroscopic Studies

The results of the FTIR spectroscopy (**Table 3**) showed absorption peaks for the ligands and the TMCs for $\nu(\text{C-N})$ at range 1488 - 1489 cm^{-1} . $\nu(\text{C-S})$ at range 931 - 997 cm^{-1} , the single band at this region is related to the bidentate coordination as revealed by previous researchers (Mcelwa, 2013), $\nu(\text{N-H})$ at range 3143 - 3440 cm^{-1} . The most important absorption at 600 - 900 cm^{-1} as observed in related works (Sunitha *et al.*, 2011) is the most important one resulting from the out of plane bending vibration. 720 cm^{-1} was observed for $\nu(\text{=C-H})$ bending modes of the aromatic ring (*p*-chlorophenyl dithiocarbamate) while 820 cm^{-1} was ob-

served for that of (*p*-bromophenyl dithiocarbamate).

The electronic spectra of the ligands and TMCs were recorded in DMSO using a Lamda Perkin Spectrometer. Zn (II) absorbed at around (244, 299 and 340 nm), Cd (II) at (268 and 328 nm), Hg (II) at (243 and 320 nm), Cu (II) at [261, 320, both due to intra ligand charge transfer and 402 (d-d transition) nm], Co (II) at [245, 323, both due to intra ligand charge transfer, 388 (metal to ligand charge transfer), 620 (d-d transition) nm] and Ni (II) at [(254 and 326), due to intraligand charge transfer, (386 and 435, medium bands due to metal to ligand charge transfer), (490 and 640, weak bands due to d-d transition) nm]. The transitions in Zn (II), Cd (II), Hg (II) are due to intraligand charge transfer and metal to ligand charge transfer.

3.3. Antimicrobial Assay

The antimicrobial activity of the ligands and TMCs were investigated *in vitro* against some selected bacteria such as *Escherichia coli*, *Serratia mercescens* and *Staphylococcus aureus*. From **Table 4** and **Table 5**, they showed good activity against the bacterial infections, with Cd (II), Hg (II), Co (II) and Cu (II) showing better activities than the ligands and standard drug. The TMCs were poor against the fungal infections.

Table 3. FTIR results of the ligands and TMCs in cm^{-1} .

Ligands/Metal complexes	V(C-N)	V(C-S)	V(N-H)
L1	1489	994	3428
L2	1485	994	3440
Zn(II)	1490	997	3274
Cd(II)	1488	991	3240
Hg(II)	1498	931	3143
Cu(II)	1490	976	3264
Co(II)	1496	1005	3445
Ni(II)	1528	996	3205

Table 4. The zones of inhibition of the ligands and their metal complexes.

Pathogens	Ligands		Metal complexes						Standard drug (+ve control)	
	L1	L2	Zn(II)	Cd(II)	Hg(II)	Cu(II)	Co(II)	Ni(II)		
Bacteria	<i>E. coli</i>	3.9	4.0	1.4	1.1	1.1	2.9	3.0	none	2.8
	<i>S. mercescens</i>	1.7	2.0	2.7	1.2	1.9	1.5	1.4	none	2.7
	<i>S. aureus</i>	3.2	4.0	4.0	3.0	1.9	1.9	2.0	1.5	3.2
Fungi	<i>T. viride</i>	2.5	none	none	none	none	3.1	none	none	2.4
	<i>M. albicans</i>	3.0	none	none	none	none	none	none	none	2.5

Table 5. The minimum inhibitory concentrations of the ligands and their metal complexes.

	Pathogens	Ligands		Metal complexes					
		L1	L2	Zn(II)	Cd(II)	Hg(II)	Cu(II)	Co(II)	Ni(II)
Bacteria	<i>E. coli</i>	0.25	0.25	0.75	0.5	1.0	0.25	0.25	none
	<i>S. mercerscens</i>	0.5	0.5	0.75	0.75	0.5	1.0	1.0	none
	<i>S. aureus</i>	0.25	0.25	0.75	0.25	0.75	0.5	0.25	0.5
Fungi	<i>T. viride</i>	2.5	none	none	none	none	2.5	none	none
	<i>M. albicans</i>	2.5	none	none	none	none	none	none	none

NB: MIC of standard antibacterial drug (tetracycline) = 0.25 mg/ml while antifungal drug (amphotericin B) is 2.5 µg/ml.

4. Conclusion

This study showed that some ligands and metal complexes synthesized could be used as potent drugs against the tested bacterial infections. Further studies however, are needed to ascertain their toxicity status and compatibility with human physiology.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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