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Synthesis, Characterization Antifungal and Antibacterial activity of Dithiocarbamate Metal Momplexes

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ABSTRACT

Au(III), Mn(II) and Ru(III) complexes of dithiocarbamate have been synthesized and characterized by elemental analysis and spectral studies (IR, 1H and 13C-NMR). The single crystal X-ray structure of the Au complex revealed that the complex contains a Au centre with a distorted tetrahedral coordination sphere in which the di nuclear Au complex resides on a crystallographic inversion centre and each Au atom is coordinated to four S atoms from the dithiocarbamate moiety. The course of the thermal degradation of the complexes has been investigated using thermo gravimetric and differential thermal analyses techniques. Thermogravimetric analysis of the complexes show a single weight loss to give MS (M = Au, Mn ,Ru) indicating that they might be useful as for biological activity.

Keywords: Distorted tetrahedral Au complex, Dithiocarbamate moiety, thermo gravimetric

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INTRODUCTION

Dithiocarbamates are versatile ligands capable of forming complexes with most of the elements and able to stabilize transition metals in a variety of oxidation states [1]. This property of stabilizing high oxidation states in metal complexes reflects strong o-bonding characteristic of these ligands. Although the sulphur atoms of dithiocarbamato ligands possess o-donor and n-back-donation characteristics of the same order of magnitude, these ligands have a special feature in that there is an additional n-electron flow from nitrogen to sulphur *via* a planar delocalized π-orbital system, as shown below: This effect results in strong electron donation and hence a high electron density on the metal leading to its next higher oxidation state [2]. While dithiocarbamate complexes have been known for over a century, with many thousands having been prepared, the vast majority of these contain only simple alkyl substituents such as methyl and ethyl. A developing interest in the area of dithiocarbamate chemistry is the functionalization of the backbone such that new applications and interactions can be developed. This area is still in its early stages but already interesting potential applications have been noted including the functionalization of gold complex, the stepwise build-up of multi metallic arrays, the synthesis of dithiocarbamate-containing supra molecular systems which can be used for anion binding, the development of technetium radiopharmaceuticals [1]. Dithiocarbamates are a class of metal-chelating, antioxidant compounds with various applications in medicine for the treatment of bacterial and fungal infections, and possible treatment of AIDS [3]. In this view, we synthesized Mn (II) complex with 2-hydroxy 3-methyle pyridine and a sulphur donor ligand such as hexadentate dithiocarbamate sodium salt.We have synthesized dithiocarbamate complexes and characterized by elemental analyses, IR, UV-Visible, 1H NMR and 13C NMR spectroscopic studies. The antibacterial activities of synthesized compounds were studied against two Gram-negative species, Escherichia coli, Klebsiella pneumoniae and two Gram-positive species, Staphylococcus aureus and Bacillus subtilis and, for in vitro antifungal activity against, Candida albicans, Aspergillus flavus, Aspergillus nigar.

MATERIALS AND METHODS

The reagents and solvents were of analytical grade. 2-hydroxy 3-methyle pyridine , carbondisulfide were purchased from Merck Company. 1H and 13C NMR measurements were recorded on a Bruker 300 spectrometer (300 and 75 MH, respectively) in CDCl3 using TMS as the internal reference. IR spectra of the compounds as KBr-disks were recorded in the range of 400 – 4000 cm−1 with a Mattson 1000 FT spectrometer. Melting points of sulfonamide derivatives were determined on a Gallenkamp melting point apparatus and are uncorrected Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu Kα radiation. The micro dilution both method was used to determine the antibacterial activity of compounds against the bacteria:

Synthesis of dithicarbomate ligond

The ligand was prepared by the addition of 12.1 mL (0.2 mol) of carbon disulphide (density 1.2) into an ice cold solution of sodium hydroxide (8 g, 0.2 mol) dissolved in 10 mL of distilled water. To the solution, 21.80 mL of 2-amino 3-hydroxy pyridine (density 0.985) was added and the mixture was stirred for about 2 h while ensuring the temperature was less than 4 °C. A yellowish-white solid product separated out which was filtered, washed with small portion of ether. Pure [Na $C_6H_6N_2OCS2$)] was obtained by recrystallization from acetone. Yield: 84%. Selected IR, (cm−1) **L**: 1444 υ(C=N), 1252 υ(C2—N), 941, 1007 υ(S=C=S), 3390 υ(O—H), 1612 σ(O—H).

2.2. Synthesis of Au complex

An H2O solution AuCl3.6H2O (1 mmol) and an H2O solution of the 2-Amino 3-hydroxy pyridine (1 mmol) were mixed with stirring. ligand was then added dropwise with vigorous shaking. Dark green complexes separated out, which were filtered, washed thoroughly with H2O recrystallized from CH3Cl and dried *in vacuo* over P2O5. Yield: 95%, m.p. 250 C°. Anal. Calc. for $C12H12AuN4S4O_2$(Mw = 569.70): C, 25.31; H, 2.12; N, 9.84; S, 22.52. Found C, 25.21; H, 2.11; N, 9.82; S, 22.50. IR (KBr) (cm-1):330, 2995.83, 2673.46, 1622.85, 1470.36, H^1 NMR (CDCl3, TMS, 60MHz): δ (ppm) 4.0,5.0.,6.47,7.07.7.87., C^{13} NMR (CDCl3, TMS, 75.45 MHz): 114.8,125.9,139.8,140,75,192.12Molar conductance measurement for the complex is 30.26 Ω−1mol−1cm2

Spectroscopic Analysis

The IR spectra of the complexes and the ligand were compared and assigned on careful comparison. Three main regions are of interest in dithiocarbamate compounds: the 1580–1450 cm−1 region primarily associated with the stretching of the C—N of NCS2−; the 1060–940 cm−1 region, associated with ν(—CSS); and the 420–250 cm−1 region which is associated with ν(M—S) [8]. The strong bands at about 1450 –1491 cm−1 in all the complexes are attributed to the ν(C—N) stretching vibration. This band is observed at a lower frequency in the free ligand (1430–1454 cm−1) and indicates an increase of the carbon-nitrogen double bond character, caused by electron delocalization toward the metal center upon coordination to the metal atoms [1]. It is found that the coordination mode of alkyl-aryl dithiocarbamate ligands with group 12 metals is bidentate by the sulfur atoms [2]. This is consistent with the crystal structure of the mercury complex. The ν(CS2)asym and ν(CS2)sym which appear at 1055 cm−1 and 961 cm−1 in the ligand [3] are replaced by strong singlet at about 1000 cm−1 in all the complexes indicating that the dithiocarbamate moiety is symmetrically coordinated to the metal ions [4]. It has been shown that the presence of only one band in the 1000 ± 70 cm−1 region is characteristic of a bidentate nature for the dithiocarbamate moiety, while the splitting of the same band within a difference of 20 cm−1 in the same region is due to the monodentate binding of dithiocarbamate ligand [5]. The ν(C—H) stretching for the methyl group is shown in the region 2925–2850 cm−1 while the C—H bending modes appeared as an intense band around 1356 cm−1 in all the compounds [6]. The ν(=C—H) stretching of the aromatic ring which occurs slightly above 3000 cm−1 [7] is observed between 3057 and 3080 cm−1 while σ(=C—H) bending modes of the aromatic ring occurred around 700 cm−1 [27,28]. The spectra of both the ligand and the complexes showed two bands in the region 1620–1550 cm−1 that may be assigned to ν (C=C) of the aromatic ring. The M—S vibration occurs at far infra red region.

The 1H NMR of the complexes contain a sharp singlet, corresponding to three protons, in the region 4.0–3.64 ppm, ascribed to hydrogen linked directly with N atoms contained in dithiocarbamate. A downfield by δ = 0.4–0.6 ppm as compared to the chemical shifts of dimethyl dithiocarbamate (observed in the range δ = 3.26–3.40) [7] is observed. The difference could be due to the effect of the electronegativity of nitrogen atom compared to alkyl carbon [10]. It is shown that the coordinated dithiocarbamate group is more electronegative than in the case where there is no coordination [11]. The multiple signals observed in the region δ = 7.87–6.40 ppm are attributed to the protons of phenyl rings. 13C NMR spectra of the complexes exhibit weak signals in the region 114–192.10 ppm assign to NCS2 carbon atoms of the dithiocarbamate moieties. Signals observed at 47.24, 45.40, and 48.78 ppm for the Au, Mn and Ru complexes respectively correspond to methyl carbon attached to the nitrogen atom. The signals due to the carbons of aryl groups were exhibited between 137.17–126.31, 128.55–126.44, and 139.65–125.38 ppm in the Au, Mn and Ru complexes respectively

Thermal Analyses of the Complexes

The thermal properties of the complexes were studied by TGA and DSC in the temperature ranging from 20 to 800 °C under nitrogen atmosphere. The content of a particular component in a complex changes with its composition and structure. These can be determined based on mass losses of these components in the thermogravimetric plots of the complex. The pertinent thermal decomposition data for the complexes are presented in their degradation pattern and the DSC curves of the complexes are presented in Figure 2. The compounds start decomposing above 210 °C and the thermogram for each complex exhibits two distinct decomposition steps at 219, 270, 168 and 450, 430, 361 °C for the Au, Mn and Au complexes respectively. The first decomposition step stretches beyond 50 °C and exhibits 65–70% weight loss. This corresponds to decomposition of the organic moiety [10] leaving behind metal sulfide as the end product. The slight weight loss (<2%) observed in the mercury complex around 185 °C could be ascribed to the presence of entrapped water or solvent molecule [11]. The absence of any thermal change before this temperature is reached indicates that samples restructuring did not take place before the degradation processes started [12], and also demonstrates their high thermal stability. The second decomposition temperature stretches to around 650 °C in Au and Mn complexes but less than 600 °C in Ru complex. The products correspond to the respective metal oxides except in the Hg complex where the thermogram indicates volatilization). The presence of oxygen and sulfur in the end product of the zinc and cadmium complexes at 800 °C, as shown by the EDX result (Figures 3 and 4), may indicate oxysulfate which probably have formed due to the oxidation of the sulfide. It is evident from the thermogram (Figure 1) that the Hg complex has the least thermal stability as previously observed [13].

Antifungal activity.

In the current study (Table 1) of some synthesized complexes were tested against pathogenic fungal strains such as Candida albicans, Aspergillus flavus and Aspergillus niger. Ketoconazole was used as reference drug for fungi. The minimum inhibitory concentrations (MICs) by microbroth dilution assays (MDA) are 180-297 µg/mL. The complexes had highest in vitro antifungal activity against pathogenic fungal strains. The reason for the highest activity might be related to the presence of dithiocarbamate group in the [Au (AHMP)2 complex.

Table 1. In vitro antifungal studies of the complexes

S.NO	Complex	*Candida albicans Mda*	*Aspergillus*	*Aspergillus niger*
01	AHPDTC	223	218	180
02	$Au(AHPDTC)_2$	250	206	271
03	$Mn(AHPDTC)_2$	226	274	200
04	$Ru(AHPDTC)_2$	228	296	297

Where, MDA: Micro-dilution activity

In vitro antibacterial study

In the antibacterial study (Table 2) of some synthesized complexes were tested against pathogenic bacterial strains such as Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus and Bacillus subtilis using the disc diffusion method. Gentamycin was used as reference drug for bacteria. In general, the compounds showed significant antibacterial activity and the bacterial strains with the zone of inhibition, 23 mm at minimum inhibitory concentration (MIC) of 30.0 µg/disc.

Table 2. In vitro antibacterial studies of the complexes

S.No	Complex	Zone Of Inhibition			
		Escherichia coli	*Klebsiella pneumonia*	*Staphylococcus aureus*	*Bacillus subtilis*
01	AHPDTC	14	15	17	13
02	$Au(AHPDTC)_2$	30	19	25	24
03	$Mn(AHPDTC)_2$	25	26	19	22
04	$Ru(AHPDTC)_2$	27	27	22	21

CONCLUSION

Au(II),Mn(II) and Ru(II) complexes of 2-amino 3-hydroxy pyridine have been synthesized and characterized by elemental analyses and spectroscopic techniques. Four coordinate geometries are proposed for the Au(III) and Mn(II) complexes. Single crystal X-ray structure of the Ru(III) complex revealed that the complex is dimeric and the coordination geometry around each Au atom is a distorted tetrahedral..

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