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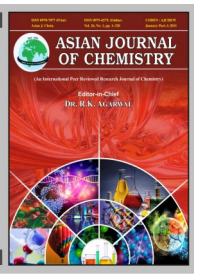

Synthesis and Antibacterial Activity of Copper(I) Complexes with Bisbenzoylthiourea

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Two copper(I) complexes, $[Cu(L)]ClO_4$ (**1**) and $[Cu(L)Cl]\cdot C_2H_5OH$ (**2**), have been synthesized by the reaction of copper(II) perchlorate hexahydrate and copper(II) chloride dihydrate with N,N'-(1,2-dimethylene)bisbenzoylthiourea (L), respectively and characterized by elemental analyses as well as IR spectra and TG-DTA analyses. Antibacterial activity assays exhibit MIC_{50} values of the two copper(I) complexes comparable to standard drugs for both Gram-positive and Gram-negative bacteria, both of them show stronger antibacterial activity.

Keywords: Bisbenzoylthiourea, Complex, Synthesis, Antibacterial activity.

INTRODUCTION

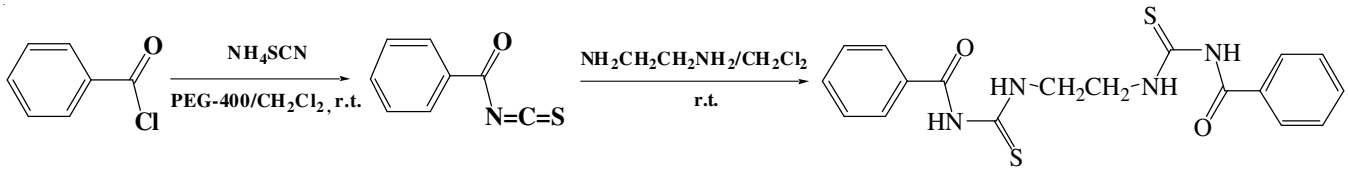
Benzoylthiourea and its derivatives are particular interest because of their versatility towards different metal ions either as a neutral ligand or as a deprotonated ligand through the N,S atoms[1-3]. Furthermore, benzoylthioureas and their complexes have demonstrated significant biological activity and new examples are being tested for their antitumor, antimicrobial and antiviral activities of the metal complexes differ from those of either the ligand or the metal ion itself and increased and/or decreased biological activities are reported for several transition metal complexes such as copper(II) and nickel(II)[4-13]. In many cases concerning synthesis of copper(I) complexes, the irreversible Cu(II)/Cu(I) redox system was observed[14-16]. In this paper, two copper(I) complexes with N, N'-(1,2-dimethylene)-bisbenzoylthiourea (L) have been synthesized and characterized by elemental analyses, IR spectra and TG-DTA analyses. The interactions of the two copper(I) complexes and antimicrobial activities were studied.

EXPERIMENTAL

Benzoyl chloride, ethanediamine and polyethylene glycol-400 were purchased and used without further purification. The other reagents and solvents were analytical grade reagents from Tianjin Chemical Reagent Factory. Elemental analyses for Cu was detected by an IRIS ER/S·WP-1 ICP atomic emission spectrometer. C, H and N analyses were carried out with a GmbH VariuoEL V3.00 automatic elemental analyzer. IR spectra in the range 4000-400 cm^{-1} were recorded on a VERTEX70 FT-IR spectrophotometer using KBr pellets. TG-DTA analyses were carried out at a heating rate of 5 °C/min on a ZRY-1P thermoanalyzer. The ^1H NMR spectra were recorded on a Mercury-400BB spectrometer at room temperature using DMSO-d_6 as solvent. Melting points was measured by the use of a microscopic melting point apparatus made in Beijing Taike Instrument Limited Company and the thermometer was uncorrected. The microbiology stains were obtained from China Center of Industrial Culture Collection, including 4 species of Gram-nzegative bacteria (*Salmonella typhimurium* CCTCCM91098, *Escherichia coli* ACCC11864, *Pseudomonas aeruginosa* NKCCMRNK10.PAO1ΔrhlI and *Shigella flexneri* CICC21534) and two Gram-positive bacteria (*Staphylococcus aureus* ACCC01331 and *Mycobacterium tuberculosis* CVCC343), Streptomycin and Ampicillin were served as standard antibacterial agents, respectively. The absorbance was measured using Synergy HT BioTekR USA microplate reader.

General procedure: Benzoyl chloride was treated with ammonium thiocyanate under the condition of solid-liquid phase transfer catalysis using PEG-400 as the catalyst to give the benzoyl isothiocyanate, without isolation, the obtained benzoyl isothiocyanate was treated with ethanediamine to afford the ligand (L) in good yield1[7,18]. Synthetic route to N, N'-(1,2-dimethylene)bisbenzoylthiourea is shown in **Scheme-I**. Two synthesized copper(I) complexes have been characterized by elemental analyses as well as IR spectroscopy and TG-DTA analyses (Tables-1 and 2)[19,20].

Synthesis of N,N'-(1,2-dimethylene)bisbenzoylthiourea (L): 1.41 g (0.01 mol) of benzoyl chloride was reacted with



Scheme-I: Synthetic route to N,N'-(1, 2-dimethylene)bisbenzoylthiourea (L)

1.15 g (0.015 mol) of ammonium thiocyanate in 25 mL of CH_2Cl_2 under solid-liquid phase transfer catalysis conditions, using 0.18 g of 3 % polyethylene glycol-400 as the catalyst, to give the benzoyl isothiocyanate after stirring for 1 h at the room temperature, a white pricipatate was formed and the white solution turned to yellow, filtered and washed with CH_2Cl_2, which was reacted with a CH_2Cl_2 (15 mL) solution of 0.27 g (0.0045 mol) of ethanediamine at the room temperature, after stirring for 2.5 h. The solid isolated was separated from the liquid phase by filtration, washed successively with CH_2Cl_2 and H_2O, respectively, the product was dried under reduced pressure and purified with recrystallization from DMF to obtain the title compound. The product was dried under reduced pressure and purified with recrystallization from DMF to yield 318.95 mg of colourless crystalline solid. Yield 82.3 %. m.p. 487-488 K. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) 3.98 (t, 4H, CH_2); 7.36-7.98 (m, 10H, C_6H_5); 10.95 (s, 2H, NH); 11.31 (s, 2H, NH).

Synthesis of copper(I) complex (1): To an DMF solution (5 mL) of the ligand (L) (193.2 mg, 0.50 mmol) was added an DMF solution (5 mL) of $Cu(ClO_4)_2{\cdot}6H_2O$ (203.8 mg, 0.55 mol). After the solution had been refluxed for 1 h, the mixture was fltered, washed successively with DMF and diethyl ether respectively, the product was dried under reduced pressure to obtain 92.5 mg of grass green crystalline solid. Yield: 28.5 %.

Synthesis of copper(I) complex 2: A solution of $CuCl_2{\cdot}2H_2O$ (22.2 mg, 0.13 mmol) in DMF/ethanol (1:1) (10 mL) was added dropwise to a solution of the ligand (L) (96.8 mg, 0.25 mmol) in DMF (3 mL) at room temperature. a yellow pricipatate was formed immediately. After stirring for 1 h, the mixture was fltered, washed with DMF and diethyl ether, respectively. The product was dried in vacuo and obtained 23.7 mg of yellow solid. Yield: 33.5 %.

Antimicrobial activities: Antibacterial activities were performed in sterile 96-wells microplates under aseptic environments[21]. The method is based on the principle that microbial cell number increases as the microbial growth proceeds in the log phase of growth which results in increased absorbance of broth medium. The organisms were maintained on stock culture agar. The test samples with suitable solvent and dilution were pipetted into wells (20 µg/well). Overnight maintained fresh bacterial cultures after suitable dilution with fresh nutrient broth were poured into wells (180 µL). The initial absorbance of the culture was strictly maintained between 0.12-0.19 at 540 nm. The total volume in each well was kept to 200 µL. The incubation was done at 37 °C for 16-24 h with lid on the microplate. The absorbance was measured at 540 nm, before and after incubation and the difference was noted as an index of bacterial growth. The percent inhibition was calculated using the formula:

$$\text{Inhibition (\%)} = 100 \times (X\text{-}Y)/X$$

where X is absorbance in control with bacterial culture and Y is absorbance in test sample. Results are mean of triplicate (n = 3, mean ± sem). Streptomycin and Ampicilin were taken as standard drugs. Minimum inhibitory concentration (MIC) was measured with suitable dilutions and results were calculated using EZF it 5 Perrella Scientific Inc. Amherst USA software and data expressed as MIC_{50}.

RESULTS AND DISCUSSION

The colour, yields and elemental analytical results of the synthesized bisbenzoyl-thiourea L and its copper(I) complexes are presented in Table-1. The copper(I) complexes **1** and **2** are yellow and green solid, respectively, stable in air and soluble in chloroform, DMF and DMSO, insoluble in methanol, ethanol, dichloromethane, ether, acetone, acetonitrile, benzene and *n*-hexane. The analytical results of the copper(I) complexes **1** and **2** are given in Table-1. Their compositions agree with the formula $[Cu(L)](ClO_4)_2$ for the complex **1** and $[Cu(L)Cl]{\cdot}C_2H_5OH$ for the complex **2**.

The molar conductance of the complex **1** at 20 °C in 10^{-3} mol/L DMF solution is 80.4 S cm^2 mol^{-1}, indicating that the complex **1** is 1:1 electrolyte and the molar conductance of the complex **2** at 20 °C in 10^{-3} mol/L DMF solution is 13.7 S cm^2 mol^{-1}, indicating that the complex **2** is non-electrolyte[22].

IR spectra: The important FT-IR spectra data for L and its corresponding copper(I) complexes are given in Table-2. The IR spectra of the copper(I) complexes show two bands at 3215 and 3431 cm^{-1}, due to NH stretchings. Because C=O groups are locked into the hydrogen bonds, the carbonyl stretching bands appears at 1676 cm^{-1}. A strong band at 1172 cm^{-1} is assigned as the thionyl group, which has a shift of 4 cm^{-1} to high wavenumber compared with 1168 cm^{-1} in free ligand L. This indicates coordination of the thionyl group with Cu(I) ion. In the range below 1000 cm^{-1}, two bands at 590 and 406 cm^{-1} are attributed to Cu-S and Cu-Cl vibrations, respectively[16,23].

TABLE-1
COLOUR, YIELDS AND ANALYTICALDATA OF L AND ITS COPPER(I) COMPLEXES

Comp.	Colour	Yield (%)	m.f. (m.w.)	Elemental analysis (%): Found (calcd.)			
				C	H	N	Cu
L	Colourless	82.3	$C_{18}H_{18}N_4O_2S_2$ (386.5)	55.90 (55.94)	4.59 (4.69)	14.28 (14.50)	–
$[Cu(L)]ClO_4$	Yellow	28.5	$C_{18}H_{18}ClCuN_4O_6S_2$ (549.5)	39.61 (39.34)	3.25 (3.30)	10.13 (10.20)	11.79 (11.56)
$[Cu(L)Cl]{\cdot}C_2H_5OH$	Green	33.5	$C_{20}H_{24}ClCuN_4O_3S_2$ (531.6)	45.36 (45.19)	4.37 (4.55)	10.28 (10.54)	12.21 (11.95)

TABLE-2
IR SPECTRAL DATA AND TG-DTA DATA OF L AND ITS COPPER(I) COMPLEXES

Comp.	IR (ν_{max}, cm^{-1})	Endothermic peak (°C)	Exothermic peak (°C)	Final product
L	3422, 3234 (NH); 1668 (C=O); 1158 (C=S)	215	289	
$[Cu(L)]ClO_4$	3429, 3275 (NH); 1674 (C=O); 1170 (C=S); 591 (Cu–S)	158	302, 346	CuO, CuS
$[Cu(L)Cl]\cdot C_2H_5OH$	3431, 3215 (NH); 1676 (C=O); 1172 (C=S); 590 (Cu–S); 406 (Cu–Cl)	75	262, 282	CuO, CuS

TABLE-3
ANTIBACTERIAL ACTIVITIES OF THE COMPLEXS **1** AND **2** (MEAN ± SEM, n = 3)

Comp.	Antibacterial activity MIC_{50} (µg/mL)					
	S. typhi	*E. coli*	*P. aeruginosa*	*S. flexneri*	*M. tuberculosis*	*S. aureus*
$[Cu(L)]ClO_4$	10.7 ± 0.21	10.1 ± 0.27	10.61 ± 0.17	11.8 ± 0.4	9.95 ± 0.23	10.55 ± 0.21
$[Cu(L)Cl]\cdot C_2H_5OH$	12.15 ± 0.07	11.45 ± 0.3	11.45 ± 0.15	No activity	12.8 ± 0.26	11.95 ± 0.31
Ampicillin	9.31 ± 036	9.28 ± 0.25	10.17 ± 0.2	10.55 ± 0.35	11.12 ± 0.33	11.41 ± 0.42
Streptomycin	11.18 ± 0.32	9.43 ± 0.27	10.26 ± 0.4	9.7 ± 0.25	7.93 ± 0.24	9.79 ± 0.31

Antimicrobial activities: In the antibacterial experiment, the statistic indicated lowest the MIC_{50} value, highest is the antibacterial activity. These compounds were active againest both Gram-positive and Gram-negative bacterial because of their strong oxidizing property. Compared the two compounds, $[Cu(L)]ClO_4$ possessed the lower MIC_{50} value, so it has the higher antibacterial activity. Both two compounds possessed MIC_{50} value close to the standard drugs streptomycin and ampicillin (Table-3). The concern is compound $[Cu(L)]ClO_4$ has the antitubercular activity close to streptomycin. The results of this study indicated that these two compounds synthesized above showed their biological importance and could be applied in biological medicine industry, especially in the aspect of antitubercular.

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