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SOLVENT-FREE PREPARATION AND ANTIMICROBIAL STUDIES OF METAL (II) COMPLEXES DERIVED FROM CLOXACILLIN

S. Jibril [1], B. A. Saje [1], I. Musa [1], M. A. Inusa [1], D. Dahuwa [2] and H. U. Maigari [3]

1 Department of Chemistry, Aminu Saleh College of Education, Azare, Bauchi State, Nigeria
2 Department of Physics, Faculty of Basic Sciences, Federal University of Health Sciences Azare, Bauchi State, Nigeria
3 Sani Abacha Estate Primary School Azare, Bauchi State, Nigeria

Correspondence author Email: shehuusmanjibril@yahoo.com. **Phone number**: 08038053855

ABSTRACT

The authors use an environmental friendly, solvent-free method to prepare metal (II) complexes of cloxacillin and to determine the activity of the complexes. The complexes are more active against the bacteria isolates than the free cloxacillin. The spectral studies showed the cloxacillin (ligand) as monobasic bidentate material that form a complex with metal ion through the carbonyl of amide and carboxylate groups of carboxylic acid, microanalysis results prove that the ligand to metal ratio is 2:1. The researchers recommend the use of solvent-free drugs in the manufacture of metal (II) complexes of active pharmaceutical ingredients to avoid the excessive use of solvents that cause global problems.

Key Words: Solvent-free, Cloxacillin, Complexes, Transition metals

INTRODUCTION

Historically, most chemical reactions have been carried out in solutions which are generally organic solvents to dissolve reactants in a reaction vessel. Overuse of solvents has a major impact on our environment, so researchers used solvent-free methods instead of traditional solvents to minimize the environmental damage. Mechanochemical as one of the solvent-free method offer advantages that avoid using excessive solvent and provides short reaction time and high efficiency [1]. Mechanochemistry refers to the reaction that is induced by the input of mechanical energy promoted by either mechanical milling or manual grinding [2]. Recently, researches such as; Braga and colleagues reported the mechanochemically grounded drug containing coordination and hydrogen bonding networks using antibiotic 4-aminosalicyclic acid and nootropic drug piracetam with silver and nickel cations [3], Jibril et al also reported the comparison synthesis of solvent-free and solution-based synthesis of aspirin with metal (II) ions and compared the obtained results in which the solvent-free synthetic results is the same with solution-based [4].

The aim of this research paper is to highlight the fact that; solvent-free synthesis offers an opportunity to reduce the overuse of solvents for both reactions media and purification.

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MATERIALS AND METHODS

Materials

The reagents used were of analytical grade and used without further purification. All metals and active ingredients of cloxacillin were purchased from sigma Aldrich. All glassware used was washed thoroughly with distilled water before and after each reaction. All weighings were performed using a Mettler Toledo Model B15 balance, molar conductivity was performed using a DDS-307 conductivity meter and melting/temperature decomposition were recorded using Stuart SMP 10 melting point apparatus, both at Bauchi State University Gadau chemical laboratory. Parking palmer Lambda 35 spectrometer in the 200-700 nm range, Agilent Technology FTIR spectrometer in the 400-4000 cm^{-1} range and antimicrobial activity test both at Bayero University Kano.

Methods

Synthesis of the Complexes

2g (10mmol) of M (M = $MnCl_2.4H_2O$ or $NiCl_2.4H_2O$) and 4g (20mmol) of Cloxacillin were ground in a glass mortar in molar ratios of 1:2 for 10-15minutes. The White deep or greenish product obtained was dried in desiccator [5].

$$M + 2Clox \rightarrow [M(clox)_2 Cl_2]$$

Where M = $MnCl_2.4H_2O$ or $NiCl_2.4H_2O$

Method for Antimicrobial Activity

Sensitivity discs were punched from whatman no. 1 filter paper, sterilized in bijou bottles by autoclaving at 121^{o}C for 15 minutes. Sensitivity discs were prepared by weighing 0.008mg of the extract or fraction and serial doubling dilution in DMSO followed by placing the improvised paper discs in the solution such that each disc took up 0.01ml to make the disc potency of 500ug, 1000ug, 2000ug and 4000ug. Standardized inoculate of each isolate were swabbed onto the surface of Mueller Hinton Agar in separate Petri dishes and discs of the extracts and standard antibiotic (cloxacillin 30ug) placed. The plates were inverted and allowed to stand for 30minutes for the extract to diffuse into the agar after which the plates were incubated aerobically at 35^{o}C for 18 hours. This was followed by measurement of zone inhibition formed by the test organisms around each of the extract and standard antibiotic discs [6].

RESULTS AND DISCUSSION

The solvent-free product was obtained within short period of time and without waste, therefore no further purification is needed.

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Table 1: ***The physical properties of cloxacillin and its metal (II) complexes***

Ligand/ Compound	Colour	Melting Temperature (ºC)	Decomposition Temperature (ºC)	Conductance ($\Omega^{-1}cm^2mol^{-1}$)	Magnetic moment (BM)
Cloxacillin	White	150	-	-	-
[Mn $(clox)_2 Cl_2$]	Yellow	-	245	9.6	4.59
[Ni $(clox)_2 Cl_2$]	Green	-	270	13.8	3.54

Reactions of the free ligand (cloxacillin) with metal ions of Mn (II) and Ni (II) gave colour yellow and green complexes as shown in Table 1. The ligand melted at 150ºC and its complexes temperature decomposed at 245 ºC and 270 ºC. These higher values provide the evidence of coordination between the ligand and metal ions as reported by [7]. Conductivity measurement as shown in Table 1 and performed in $1x10^{-3}$ml in DMSO solvent in the range of non-electrolyte based on the mobility of ions of the complexes and the results also used to deduce the structures of the complexes [8]. The magnetic properties as shown in Table 1 also suggest the likely octahedral geometry of the complexes due to the presence of unpaired electrons around the central metal ions, with values of 4.59BM of Mn (II) and 3.54BM of Ni (II) complexes falls within the expected range of high spin octahedral geometry [9].

Elemental analysis data of both the complexes are consistent with the proposed structure of [M $(clox)_2 Cl_2$], in which the percentage of C, H, N and metal ion of Mn (II) and Ni (II) matched. Similar results were reported by [10].

Table 2: ***Elemental analysis data of the complexes***

Compounds	Molecular formula (Molar Mass)	*Elemental analysis*: found (calculated) %			
		C	H	N	M
[Mn $(clox)_2 Cl_2$]	$C_{19}H_{18}Cl_3N_3O_5SMn$ (561.5)	40.52 (42.39)	3.2 (3.55)	2.48 (2.11)	9.77 (10.46)
[Ni $(clox)_2 Cl_2$]	$C_{19}H_{18}Cl_3N_3O_5SNi$ (565.2)	40.52 (41.66)	3.2 (4.00)	2.48 (1.98)	9.77 (9.64)

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Table 3: ***Electronic spectra in DMF solvent for complexes with their suggested geometry***

Ligand/ Complexes	Electronic spectra Wavelength (nm)	Energy (cm^{-1})	Transition	Suggested geometry
Cloxacillin	207	48309	n- π^*	-
	208	4955	π- π^*	
	238	4274	C T	
[Mn (clox)$_2$ Cl$_2$]	215	46511	n- π^*	Octahedral
	223	44843	π- π^*	(oh)
	238	42016	$^5T_{2g}$- $^5T_{2g}$	
	243	41152	$^5T_{2g}$-^5E_g	
[Ni (clox)$_2$ Cl$_2$]	223	44843	$^3A_{2g}$ -$^3T_{2g}$	Octahedral
	233	42918	$^3A_{2g}$ -$^3T_{1g}$	(oh)

The electronic spectra data is shown in Table 4 in which the ligand present three distinct absorption bands at 207nm, 208nm and 238nm attributed to n- π^*, π- π^* and C T which was assigned to the metal-ligand charge transfer [11]. These bands shifted to lower values in the complexes demonstrating the evidence of coordination between ligand and metal ion, as in the case of Mn (II) complexes at 215nm, 223nm, 238nm and 243nm which has been assigned to n- π^*, π- π^*, $^5T_{2g}$-$^5T_{2g}$ and $^5T_{2g}$-^5E_g respectively, while Ni (II) complex exhibits two prominent band at 223nm and 233nm assigned to $^3A_{2g}$-$^3T_{2g}$ and $^3A_{2g}$-$^3T_{1g}$ which account for octahedral geometry [12].

TABLE: ***The IR Spectra Data of Cloxacillin and its Metal (II) complexes***

Compounds	ν(N-H) cm^{-1}	ν(O-H) cm^{-1}	ν(C=O) cm^{-1} β-lactam	ν(C=O) cm^{-1} of (CO_2^-)	ν(C=N) cm^{-1}	M-O	M-Cl
Cloxacillin	3514.85	3677.85	1771.53	1689.66	1603	-	-
Mn(clox)$_2$Cl$_2$	3342.79	-	1767	1499	1603	441	772.72
Ni(clox)$_2$Cl$_2$	3361.63	-	1771.73	1659.59	1603	463.83	772.55

Keys: υ=Wave number, M = Metal, clox = cloxacillin

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The results of IR spectra of the free ligand and its complexes shown in Table 4 showed that the ligand appears to be a monobasic bidentate one, coordinating to the metal ion through its carbonyl groups of amide and carboxylate of the carboxylic acid at the values of 1771.53cm^{-1} and 1689.66cm^{-1} which translate to lower values of Mn (II) complexes at 1767.91 cm^{-1} and 1499.68 cm^{-1} and Ni (II) complex at 1771.73 cm^{-1} and 1659.59 cm^{-1} shifted indicating continuous complexation that occurs through both the carbonyl groups. These values agreed with the results of [13]. The new bands in the complexes which are absent in the spectrum of the ligand at 441.00 cm^{-1}, 772.72 cm^{-1} in the Mn (II) and 463.83 cm^{-1}, 772.55 cm^{-1} in the Ni (II) assigned to M-O and M-Cl respectively, which support the involvement of C=O of amide and carboxylate groups in the complexation with metal salts [14].

Table 4.1.6: ***Antibacterial activity test of cloxacillin and its metal (II) complexes.***

Compounds	Concentration(μg)	S. Aureus (nm)	E. coli (nm)
Cloxacillin	4000	17	14
	2000	15	11
	1000	12	8
	500	10	7
$[Mn(Clox)_2Cl_2]$	4000	12	14
	2000	8	11
	1000	7	8
	500	-	7
$[Ni(Clox)_2Cl_2]$	4000	14	12
	2000	12	9
	1000	8	7
	500	-	-
Control: Ciprofloxacin	500	35	30

Anti-bacterial activity test shown that the ligand and the complexes are active against all the bacteria isolates with the exception of $[Mn(Clox)_2Cl_2]$, which is inactive at lower concentration of 500μg in S. Aureus and $[Ni(Clox)_2Cl_2]$ in S. Aureus and E. Coli is inactive both at lower concentration of 500μg. All complexes show an increase in activity compared to the parent ligand at higher concentration. This finding is consistent with the findings of [15].

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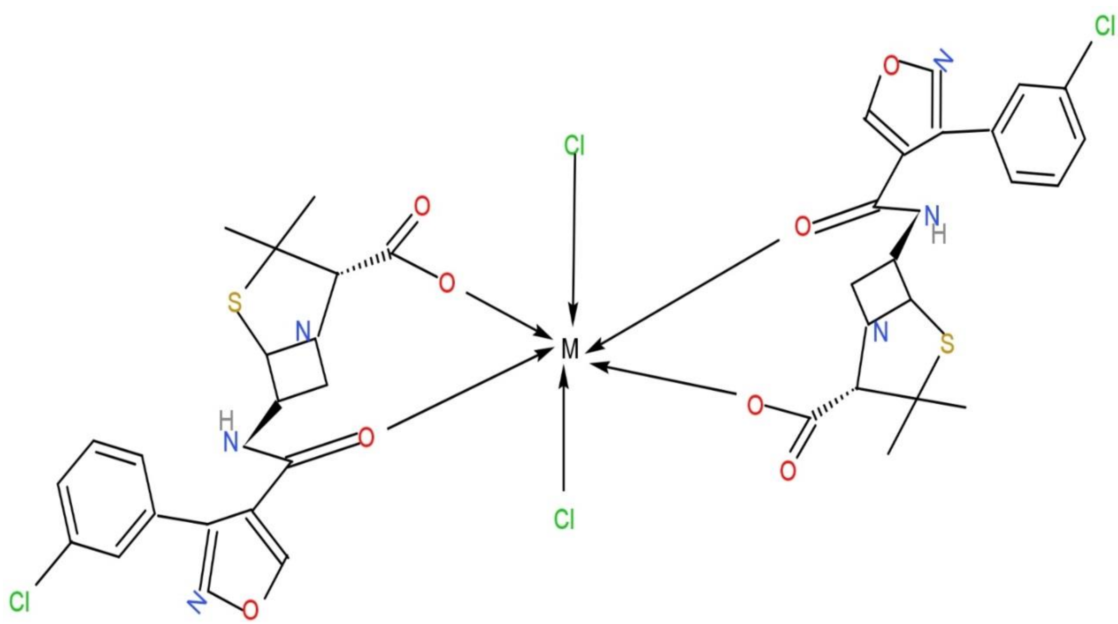
CONCLUSSION

From the spectral studies of IR and UV/Vis, conductivity measurement, magnetic moment, it was found that the cloxacillin behaves as monobasic bidentate ligand which coordinated through carbonyls of amide and carboxylate groups. Solubility, conductivity and melting point/temperature decomposition also rendered both complexes to be non-electrolyte in nature.

It was concluded that the solvent-Free preparation of metal (II) complexes using API could be adopted by drugs as all the values obtained are consistent with the findings of Eze and Coworkers (2014) using solution based synthesis [16].

From the analytical studies obtained using spectral, elemental analysis, conductivity measurement and effective magnetic moment, the preliminary proposed structure of the complexes are: -



Proposed Structure of Cloxacillin Complexes

(M = Mn^{2+} and Ni^{2+})

RECOMMENDATION

The authors recommend the use of solvent-free active ingredients for the manufacture of pharmaceuticals.

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