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Physicochemical Characterization and Antimicrobial Activity of Mechanochemically and Solvent-based Synthesized Mn(II) Complexes of Cefixime and Cefuroxime

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ABSTRACT

Mechanochemical and solvent-based complexes of Mn(II) with cefixime and cefuroxime were synthesized and characterized by melting point and conductivity measurements, elemental analysis, FTIR spectral studies, and electronic spectral analysis. The Mn(II) complexes with cefixime and cefuroxime synthesized mechanochemically were both ash colored, while Mn(II) cefixime and cefuroxime complexes synthesized through solvent-based method were milky and ash respectively. The molar conductivity values (14.9 – 16.6 Scm^2mol^{-1}) indicate non-electrolytic nature of the complexes. The FTIR revealed that the ligands were coordinated to the Mn(II) ion through the carboxylate ions (C=O). A six coordinate octahedral geometry has been proposed for the complexes. The result of the antibacterial assay of the synthesized complexes of Mn(II) with cefuroxime generally showed better activity against *Staphylococcus aureus, Streptococcus pyogenes* and *Methicillin-resistant Staphylococcus aureus (MRSA)* than the free ligand cefuroxime. Similarly, the Mn(II) complex of cefuroxime synthesized by mechanochemical method shows higher activity against the aforementioned organisms as compared to the solution-based complex which might be as a result of solvent effect.

1. Introduction

Mechanochemical reactions utilize mechanical force to accomplish chemical transformation and can be carried out in a number of ways. It can be both solvent free and less energy consuming than standard solution reaction. Mechanochemical transformations are rapidly becoming popular as a suitable alternative to conventional solution-based [1]. Mechanochemical synthesis can provide compounds phases and microstructures that are essentially different from the products of ordinary reactions [2]. Many mechanochemical reactions of organic compounds take place at low milling energy that is not sufficient to break primary bonds, but the gentle mechanical grinding can influence the relative position of macromolecules, leading to the formation of unique co-crystals and compounds [2].

Cephalosporin antibiotics are wontedly indicated for the treatment of infection which is due to particular bacterium that is resistant to the antibiotic needed for its treatment. Most of the initial cephalosporins are effective against Gram-positive bacteria while other types proved to be active against Gram–negative bacteria. Although, the use of broad spectrum cephalosporin has increased, resistance cephalosporin still exists [3]. The cephalosporins antibiotics are semisynthetic antibacterial derived from cephalosporin C, a natural antibiotic produced by the mould, *Cephalosporin acremonium* [4]. The antibiotics are very closely related to penicillin. Its mechanism of action, mechanism of resistance and some other properties are identical [5]. Both cephalosporins and penicillins belong to the β-lactam antibiotics [6]. Cephalosporins are classified into four generations according to their spectrum of activity [4]. The first generation cephalosporins are very active against Gram-positive *cocci*. They have limited activity against Gram-negative bacteria [7].

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Metal-drug complex compounds are more popular nowadays due to their greater biological activity than uncomplexed ligands of some drugs [8]. In most cases, the efficacy of the drugs is enhanced by the metal ions upon complexation [9]. Metal ions play important roles in different biological processes and they may be specific in action. Biological activity of metal ions depends on their concentration; they may either promote the health of the organism or cause toxicity [10]. Reports have shown that metal chelates possess several biological activities *viz.*, antibacterial, anti-fungal and anticancer activities [11]. In many cases, it was reported that the metal-drug complexes possess more antimicrobial activity than the uncomplexed ligand themselves [12].

Antimicrobial resistance is fast becoming a global concern with rapid increase in multidrug resistant bacteria. Some previously treatable pathogens are now becoming untreatable. To overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel active compounds against new targets is a matter of urgency [13].

Among these, novel metal complexes derivatives which show considerable biological activity represent an interesting approach for designing new antibacterial drugs. This may be due to the dual possibility of both ligands plus metal ion interacting with different steps of the pathogen life cycle [14].

The aim of the present study is to synthesize Mn(II) complexes of cefixime and cefuroxime with a view to finding compounds of enhanced antimicrobial activities.

2. Results and Discussion

2.1.1. Physical Properties of the Ligands and their Metal Complexes

The physical properties of the ligands and elemental data of the Mn(II) complexes of cefuroxime and cefixime for mechanochemical and the solution-based complexes are shown in Tables 1 and 2 respectively. Results for solubility test as well as relevant Infrared frequency (cm^{-1}) for the ligands and the complexes for both mechanochemical and solution-based methods are presented in Tables 3 and 4 respectively. Their structures have been proposed on the basis of FT-IR, electronic spectra data and conductivity values. The molar conductance values range from 14.9–16.6 $Scm^2\ mol^{-1}$, which indicates that the complexes are non-electrolytic in nature [15,16].

Table 1. Physical properties of the ligand and the mechanochemically synthesized Mn(II) complexes

Compounds	Molecular Formula (Molar mass)	Colour	Yield (g) (%)	Decomposition temperature (^{0}C)	Conductivity (Scm^2mol^{-1})	% metal found (cald)
Cefixime	$[C_{16}H_{15}N_5O_7S_2]$ (453.451)	White	------	218-225	------	------
Cefuroxime	$[C_{20}H_{22}N_4O_{10}S]$ (510.476)	White	------	135	------	------
$[Mn(CFU)Cl_2]$	$[Mn(C_{20}H_{22}N_4O_{10}S]$ (565.414)	Ash	5.256 (92.9)	187	16.6	6.27 (7.77)
$[Mn(CFE)Cl_2]$	$[MnC_{16}H_{15}N_5O_7S_2]$ (508.378)	Ash	4.691 (92.2)	295	16.2	7.76 (8.48)

CFU= Cefuroxime, CFE= Cefixime

Table 2. Physical properties of the Mn(II) complexes synthesised by solution-based method

Compounds	Molecular Formula (Molar mass)	Colour	Yield (g) (%)	Decomposition temperature (^{0}C)	Conductivity (Scm^2mol^{-1})	% metal found (cald)
$[Mn(CFU)Cl_2]$	$[Mn(C_{20}H_{22}N_4O_{10}]$ (565.414)	Ash	2.783 (49.2)	192	16.5	6.66 (7.77)
$[Mn(CFE)Cl_2]$	$[MnC_{16}H_{15}N_5O_7S_2]$ (508.378)	Milk	3.61 (71.0)	327	14.9	8.10 (8.43)

CFU= Cefuroxime, CFE= Cefixime

Table 3. Solubility of the ligands and their Mn(II) Complexes (Mechanochemical)

	Distilled water		**Methanol**		**Ethanol**		**Acetone**		***n*-hexane**		**Chloroform**		**DMSO**	
Compounds	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**
Cefixime	SS	S	SS	S	SS	SS	SS	SS	IS	IS	IS	SS	S	S
Cefuroxime	SS	S	SS	S	SS	S	IS	IS	IS	S	SS	SS	S	S
$[Mn(CFU)Cl_2]$	IS	SS	IS	SS	IS	SS	IS	IS	IS	IS	IS	IS	S	S
$[Mn(CFE)Cl_2]$	S	S	S	S	S	S	SS	S	IS	IS	SS	SS	S	S

C=Cold, H=Hot, S=Soluble, IS=Insoluble, SS=Sparingly Soluble, DMSO=Dimethylsulfuroxide

Table 4. Solubility of the $Mn(CFU)Cl_2$ and $Mn(CFE)Cl_2$ Solution-based Complexes

	Distilled water		**Methanol**		**Ethanol**		**Acetone**		**n-hexane**		**Chloroform**		**DMSO**	
Compounds	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**	**C**	**H**
$[Mn(CFU)Cl_2]$	IS	SS	S	S	IS	SS	IS	IS	IS	IS	IS	IS	S	S
$[Mn(CFE)Cl_2]$	S	S	S	S	S	S	SS	S	IS	IS	SS	SS	S	S

2.1.2 FT-IR Studies and Electronic Spectra

FTIR spectra for Mn(II) cefixime and cefuroxime complexes are presented in figures 1 – 4 and the relevant bands are summarized in Tables 5 and 6. The complexes display bands due to υ(C=N) stretching in the regions 1388-1419 cm^{-1} in the mechanochemically synthesized complexes and at 1643 cm^{-1} for solvent-based. The medium band at 1766 and 1743 cm^{-1} in the spectra of the ligands are characteristics of *ν*(C=O). The significant shift in the frequency to form sharp and medium bands at 1643 cm^{-1} in all the complexes indicates the coordination of metal ion to the ligands through the carboxylate anion [17]. The new bands appeared in the complexes at (570-609) cm^{-1} is typical for υ(M-O) modes, and literature revealed a υ(M-O) appearance at 543-690 cm^{-1} [17].

The electronic spectra of the complexes were recorded and are presented (Table 7 and 8; figure 5 and 6). The spectra show bands at 34129 cm^{-1} for both complexes formed through mechanochemical synthesis whereas the complexes formed through solution-based show band at 34482 and 33898 cm^{-1} for $[Mn(CFU)Cl_2]$ and $[Mn(CFE)Cl_2]$ respectively. These bands are slightly above those of free ligands which indicate coordination of the metal ions to the ligands around octahedral geometry. Similar bands at 347, 355, 353 and 354 nm for octahedral geometry were reported [18]. The proposed structures of the complexes are shown in Fig. 7.

Table 5. Relevant Infrared Frequency (cm^{-1}) for the Ligands and their Mn(II) Complexes (Mechanochemical)

Compounds	**ν(O─H) (cm^{-1})**	**ν(N─H_2) (cm^{-1})**	**ν(C═N) (cm^{-1})**	**ν(C─N) (cm^{-1})**	**ν(C═O) (cm^{-1})**	**ν(M─O) (cm^{-1})**
Cefixime	3402_b	2924_w	1543_w	1126_m	1766_m	-----
Cefuroxime	3402_b	2916_w	1527_w	1134_m	1743_m	-----
$[Mn(CFU)Cl_2]$	3394_b	2924_w	1419_w	1057_m	1643s	609_w
$[Mn(CFE)Cl_2]$	3402_b	2831_w	1388_w	1126_m	1643s	570_w

s=strong, b=broad, m=medium, w=weak sh=sharp

Table 6. Relevant Infrared Frequency (cm^{-1}) for the Mn(II) CFU and CFE Complexes (Solution-based)

Compounds	**ν(O─H) (cm^{-1})**	**ν(N─H_2) (cm^{-1})**	**ν(C═N) (cm^{-1})**	**ν(C─N) (cm^{-1})**	**ν(C═O) (cm^{-1})**	**ν(M─O) (cm^{-1})**
$[Mn(CFU)Cl_2]$	3402_b	2931_w	1643_m	1141_m	1643_m	609_w
$[Mn(CFE)Cl_2]$	3402_b	2924_w	1643_m	1141_m	1643_m	586_w

s=strong, b=broad, m=medium, w=weak sh=sharp

Table 7. UV-Visible Spectral Data of the Ligands and their Mn(II) Complexes (Mechanochemical)

Compounds	**λ_{max}(nm)**	**λ_{max} (cm^{-1})**	**Assignment**	**Proposed Geometry**
CEF	297	33670	π-π^*	-------
CFU	301	33222	π-π^*	-------

$[Mn(CFU)Cl_2]$	293	34129	π-π^*	Octahedral
$[Mn(CFE)Cl_2]$	293	34129	π-π^*	Octahedral

Table 8. UV-Visible Spectral Data of the Mn(II) Complexes (Solution-based)

Compounds	λ_{max}(nm)	λ_{max} (cm^{-1})	Assignment	Proposed Geometry
$[Mn(CFU)Cl_2]$	290	34482	π-π^*	Octahedral
$[Mn(CEF)Cl_2]$	295	33898	π-π*	Octahedral

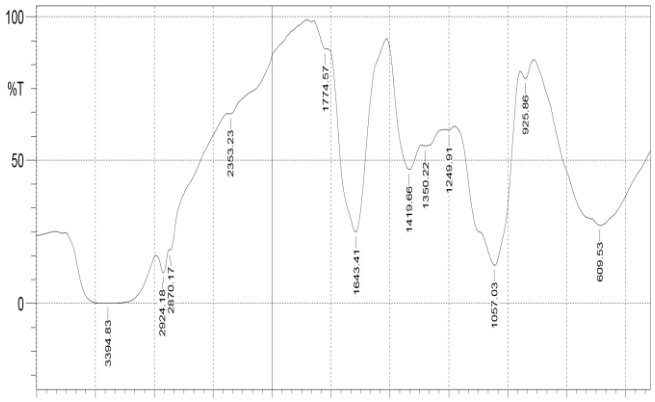


Fig. 1. IR Spectrum of $[Mn(CFU)Cl_2]$-Complex (Mechanochemical)

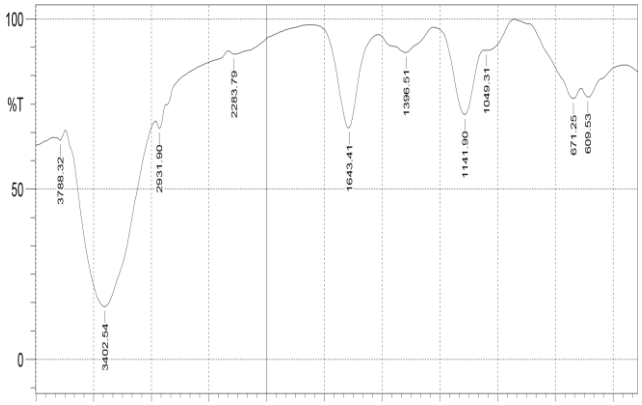


Fig. 2. IR Spectrum of $[Mn(CFU)Cl_2]$-Complex (Solution Based)

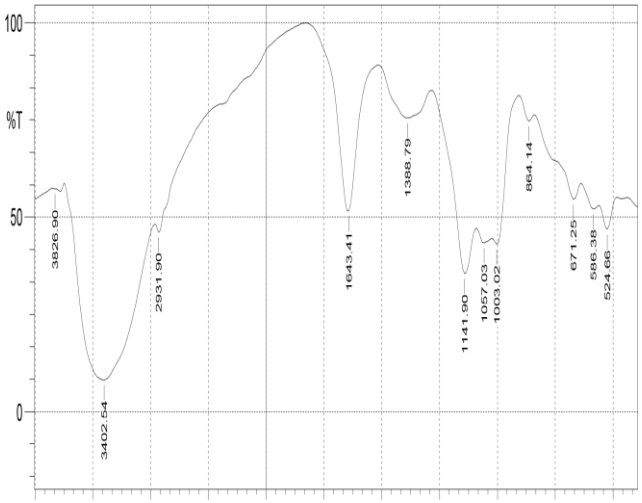


Fig. 3. IR Spectrum of $[Mn(CFE)Cl_2]$-Complex (Mechanochemical)

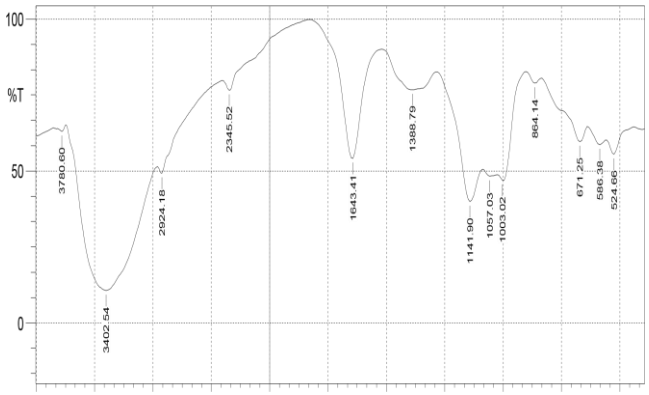


Fig. 4. IR Spectrum of $[Mn(CFE)Cl_2]$-Complex (Solution based)

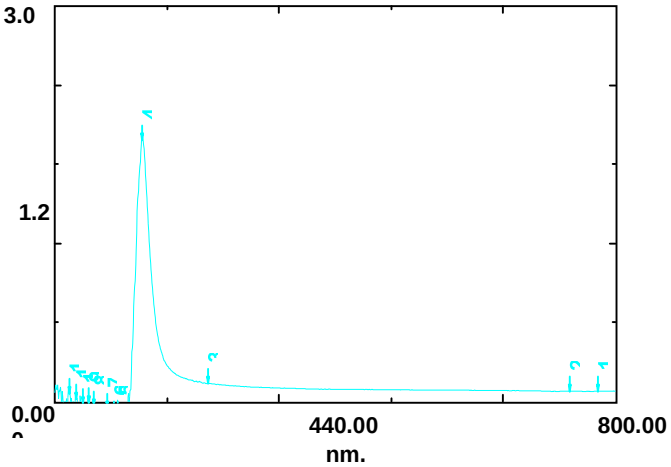


Fig. 5. Electronic spectrum for $[Mn(CFU)Cl_2]$-Complex (Mechanochemical)

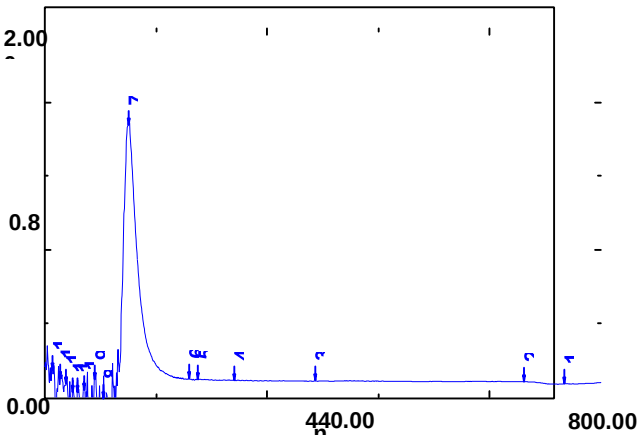
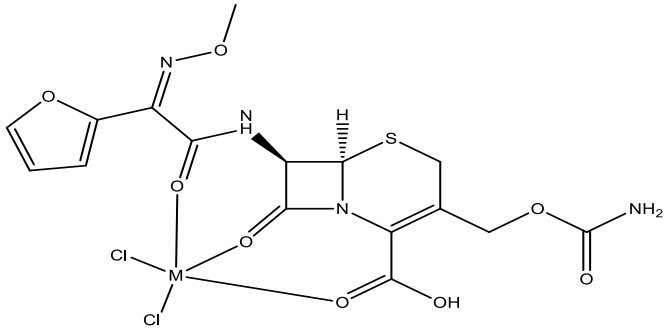
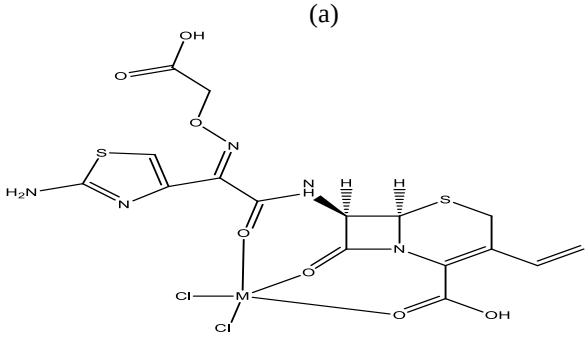


Fig. 6. Electronic spectrum for $[Mn(CFU)Cl_2]$-Complex (solution based)



(a)



(b)

Where M= Mn(II)

Fig. 7. Proposed Structure of Mn(II) Complexes with (a) Cefuroxime (b) Cefixime

2.1.3 Antibacterial Activities

The ligands and the synthesized compounds were tested against nine different microorganisms which comprises of Gram-positive and Gram-negative bacteria at the concentration of 10, 20 and 30 mg/ml. The antimicrobial activities are presented in Tables 9 and 10. Mn(II) complexes of cefuroxime synthesized both mechanochemically and solution-based showed higher activities against *S. aureus, S. pyogen, and MRSA* than the free ligands. [Mn(CFU)Cl_2] shows significant activities against *S. pyogen* and *P. aeruginasa* at 10, 20 and 30 mg/ml. At the same concentration tested, [Mn(CFU)Cl_2] complex synthesized by mechanochemical method shows higher activity against *S. aureus, S. pyogen, and MRSA* than the solution-based complex which might be as a result of solvent effect. Similar result was recorded with cefixime complexes which showed significantly enhanced antimicrobial and antifungal activities against microbial strains in comparison with free ligands [19].

Table 9. Antimicrobial Activities of the Ligands and Mn(II) CFU and CFE Complexes (Mechanochemical)

Compounds	Conc mg/ml	*S.aureus*	*S.pyogene*	*MRSA*	*K.pnemoniae*	*B.subtilis*	*E.coli*	*S.typhi*	*C.albicans*
CFE	10	10.3±04	20.0±0.0	13.3±04	18.7±0.4	24.7±0.4	9.7±.04	16.0±00	0.0±0.0
	20	15.7±04	25.0±0.0	18.3±04	24.3±0.4	30.0±0.0	20.3±04	21.7±04	8.0±0.0
	30	21.0±00	30.3±0.4	24.0±00	28.0±0.0	34.7±0.4	20.0±00	27.0±00	13.0±0.0
CFU	10	0.0±0.0	0.0±0.0	0.0±0.0	13.0±0.0	15.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
	20	8.0±0.0	0.0±0.0	7.0±0.0	19.7±0.0	20.0±0.0	8.0±0.0	10.0±00	7.0±0.0
	30	13.0±00	0.0±0.0	12.7±04	24.3±0.0	25.0±0.0	12.0±0.	15.0±00	11.0±0.0
[Mn(CFU)Cl_2]	10	9.0±0.0	9.0±0.0	8.7±0.4	11.3±0.0	0.0±0.0	0.0±0.0	7.0±0.0	0.0±0.0
	20	13.7±00	14.0±0.0	13.7±04	15.7±0.0	9.3±0.0	7.0±0.0	9.0±0.0	0.0±0.0
	30	18.7±00	19.0±0.0	19.7±04	20.3±0.0	14.7±0.4	13.0±00	13.0±00	0.0±0.0
[Mn(CFE)Cl_2]	10	7.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	9.0±0.0	0.0±0.0	12.6±00	0.0±0.0
	20	10.3±00	9.0±0.0	0.0±0.0	0.0±0.0	14.7±0.4	0.0±0.0	18.0±00	0.0±0.0
	30	15.0±00	14.0±0.0	10.7±00	8.7±0.0	20.0±0.0	10.0±00	23.3±04	0.0±0.0

S. aureu=Staphylococcus aureus, S. pyogene= Streptococcus pyogene, B. subtilis=Bacillus subtilis, E. coli=Escherichia coli, S. typhi=Salmonella typhi, K. pneumonia=Klesiella pneumonia, MRSA=Methicillin-resistant Staphylococcus aureus, C. albicans= Candida albicans

Table 10. Antimicrobial Activities of the Mn(ll) CFU and CFE Complexes (Solution-based)

Compounds	Conc. mg/ml	*S.aureus*	*S.pyogen*	*MRSA*	*K.pnemoniae*	*B.subtilis*	*E.coli*	*S.typhi*	*C.albicans*
[Mn(CFU)Cl_2]	10	7.0±0.0	8.3±0.4	7.0±0.0	7.3±0.0	7.7±0.4	0.0±0.0	7.0±0.0	0.0±0.0
	20	8.7±0.4	12.3±0.4	11.7±0.4	10.7±0.4	10.7±0.4	0.0±0.0	10.7±0.4	0.0±0.0
	30	11.7±0.4	17.3±0.4	16.0±0.0	14.3±0.4	15.3±0.4	0.0±0.0	14.7±0.4	0.0±0.0
[Mn(CFE)Cl_2]	10	7.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	8.0±0.0	11.3±0.4	13.3±0.4	0.0±0.0
	20	10.70.4	8.30.0	0.0±0.0	8.7±0.0	13.3±0.4	17.7±0.4	18.0±0.0	0.0±0.0
	30	15.3±0.0	11.7±0.0	8.7±0.0	13.7±0.4	18.0±0.0	23.3±0.4	24.3±0.4	0.0±0.0

3. Experimental

3.1. General

The chemicals used in this work were of analytical grade and used without additional purification. The Mn(II) salts used was $MnCl_2.4H_2O$. The ligands are cefuroxime (CFU) and cefixime (CFE). Infrared spectral analysis of the complexes was carried out in the range of 500-4000 cm^{-1} on SHIMADZU corporation FTIR-8400S spectrophotometer at National Research Institute for Chemical Technology (NARICT), Zaria, Nigeria. The metal estimation analyses were carried out using Atomic Absorption Spectroscopy (AAS) on AAS Buck Sci 210VGP at Yobe State University, Damaturu, Nigeria. The UV/visible spectra of the complexes and the ligands were also carried out using UV-2550 SHIMADZU Spectrophotometer in the wavelength range of 200-800 nm at NARICT, Zaria.

3.2. Synthesis of the Complexes

The complexes were synthesized by both mechanochemical and solution-based methods.

3.2.1. Mechanochemical Synthesis of the Complexes

Cefixime (10 mmol, 4.53 g) and $MnCl_2.4H_2O$ (10 mmol, 1.98 g) in the ratio of 1:1 (M:L) were carefully weighed and transferred into a mortar. The metal salt and the ligand (cefixime) were crushed (ground) for 20 minutes to obtain a homogenous powder. The homogenous mixture (powder) were then transferred to a beaker and stored in a desiccator. Same procedure was used for cefuroxime (10 mmol, 5.10 g) and the Mn(II) salts respectively [20].

3.2.2. Solution-based Synthesis of the Complexes

The complexes were synthesized using the literature procedure [21]. This was achieved by dissolving each of cefixime (10 mmol, 4.53 g) in 10 ml hot methanol and $MnCl_2.4H_2O$ (10 mmol, 1.98 g). The two solutions were mixed and refluxed for 2 hours with constant stirring. The mixture was carefully poured into a beaker and cooled to room temperature before filtration. The precipitate was washed three times with 5 ml portion each of methanol and distilled water, then dried in a desiccator over anhydrous calcium chloride for three days.

4. Conclusion

Complexes of Mn(II) with cefixime and cefuroxime were synthesized and characterized by both mechanochemical and solution-based techniques. The complexes were ash and milky in colour and are characterized by high decomposition temperature. The ratio of metal to ligand in the complexes is 1:1. The complexes are all air stable and generally soluble in DMSO and insoluble in *n*-hexane which indicates that the complexes are probably polar. The antimicrobial screening of the complexes revealed that Mn(II) cefuroxime complexes showed considerable antibacterial activities against the micro-organisms tested within 10-30 μg/ml. The UV-Vis spectra of the complexes synthesized *via* the two methods suggest that both methods produced similar products, and it has been observed from the results of infrared study, that coordination occurred through carboxylate oxygen.

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