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Improved Synthesis of Copper (Ii) And Silver (I) Complexes with Cefuroxime: Mechanochemical Study On Cephalosporin-Resistant Bacteria

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ABSTRACT

Complexation is a pivotal technique in drug development, offering significant modifications to the pharmacological, toxicological, and physico-chemical properties of drugs. This study focuses on the mechanochemical synthesis of Copper (II) and Silver (I) complexes with cefuroxime, utilizing a solvent-free approach. The synthesized complexes were characterized using various physico-chemical methods, including infrared spectroscopy (IR), UV/Visible spectroscopy, elemental analysis, melting point determination, solubility tests, and conductivity measurements. The proposed molecular formulas for the synthesized complexes are $[Cu(CFU)_2H_2O]$ and $[Ag(CFU)NO_3]$, where CFU denotes cefuroxime. The characterization results indicate that these complexes exhibit enhanced antimicrobial activity compared to the free ligand. The IR spectral data reveal coordination of cefuroxime to the metal ions through the carboxyl group (v(COO)), carbonyl group (v(C=O)), and the oxygen atom of a water molecule. Notably, the melting points, color, and electronic spectra of the complexes differ from those of the free ligand, confirming the formation of new coordination compounds. The study highlights the potential of these metal complexes as effective agents against cephalosporin-resistant bacterial strains, underscoring the advantages of mechanochemical synthesis in pharmaceutical applications.

Keywords: Antibiotic resistance, Cephalosporin, Silver, Copper, Mechanochemical synthesis

1. Introduction

The treatment of infectious diseases presents an ongoing and complex challenge due to factors such as emerging pathogens and the rising prevalence of multi-drug resistant microbial strains. Despite the extensive arsenal of antibiotics and chemotherapeutics

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available, the last few decades have witnessed a troubling increase in antibiotic resistance. This phenomenon underscores the urgent need for novel antimicrobial agents with mechanisms of action distinct from those of existing drugs, especially against pathogens that have developed resistance to current treatments [1].

Antibiotic resistance arises when bacteria undergo genetic changes that reduce or eliminate the effectiveness of drugs designed to combat infections. This resistance enables bacteria to survive and proliferate despite treatment efforts. Resistance mechanisms can include the production of enzymes that neutralize the antibiotic, the active expulsion of the drug from bacterial cells, or alterations in the drug's target sites [2]. As a result, resistant microbes become increasingly difficult to treat, necessitating the development of alternative therapeutic strategies or higher drug doses. Unfortunately, the pace of new drug development has slowed significantly, prompting a renewed focus on finding effective treatments [3].

Cephalosporins, a class of β-lactam antibiotics, share a mechanism of action with other β-lactams such as penicillins by inhibiting the synthesis of the bacterial cell wall's peptidoglycan layer. This layer is crucial for maintaining cell wall integrity, and its disruption leads to bacterial cell death. The final step in peptidoglycan synthesis, transpeptidation, is mediated by penicillin-binding proteins (PBPs) [4]. Resistance to cephalosporins can occur through decreased affinity of PBPs or the acquisition of β-lactam-insensitive PBPs. Strains of Citrobacter freundii, Enterobacter cloacae, Neisseria gonorrhoeae, and Escherichia coli, among others, have shown varying degrees of cephalosporin resistance [5].

Silver and copper have long been recognized for their antimicrobial properties. Silver sulfadiazine is a well-established broad-spectrum antibiotic ointment used effectively against a variety of bacteria and some yeasts [1]. Copper, known for its natural antimicrobial properties, was utilized by ancient civilizations long before the microbiological understanding of pathogens emerged [6].

Mechanochemistry, which involves reactions induced by mechanical energy (such as grinding in ball mills), is increasingly studied for its potential in promoting reactions between solids efficiently, often without solvents or with minimal solvent use. This approach, while traditionally a secondary method compared to solution-based techniques, is gaining attention for its ability to facilitate rapid and quantitative reactions [7].

Building on previous research into antibiotic resistance [8], this study investigates the efficacy of mechanochemically synthesized Copper (II) and Silver (I) complexes with cefuroxime against cephalosporin-resistant bacteria. This research aims to explore alternative approaches to combat bacterial resistance and contribute to the development of new therapeutic strategies.

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1. Materials and Methods

Chemicals and Reagents: All chemicals used in this study were of analytical grade and obtained from Bristol Scientific Company Limited. These chemicals were used without further purification. The ligand used for complexation was cefuroxime (CFU), while the metal salts used were copper chloride dihydrate [$CuCl_2 \cdot 2H_2O$] and silver nitrate [$AgNO_3$].

Characterization Techniques:

- **Infrared Spectroscopy (IR):** The IR spectra of the complexes and the ligand were recorded using a FTIR spectrometer in the range of 4000-400 cm^{-1}. The samples were prepared as KBr pellets.
- **Atomic Absorption Spectroscopy (AAS):** Metal content analysis of the complexes was performed using a Perkin-Elmer Spectrometer, Model 3110.
- **Ultraviolet-Visible Spectroscopy (UV-Vis):** The UV-Vis spectra were obtained with a UV-2550 Shimadzu Spectrophotometer, covering the wavelength range of 200-800 nm.

Synthesis of the Complexes: The synthesis of the metal complexes was performed using a mechanochemical method with modifications to the literature procedure [9]. Cefuroxime (10 mmol, 4.25 g) and copper chloride dihydrate (10 mmol, 1.705 g) were weighed accurately and transferred into a mortar. The reactants were ground together for 20 minutes to achieve a homogeneous powder. The resulting powder was stored in a desiccator. Similarly, silver nitrate (10 mmol, 1.699 g) and cefuroxime (10 mmol, 4.25 g) were mixed and ground under the same conditions.

Chemical Reactions:

For Copper Complex: $CuCl_2 \cdot 2H_2O + CFU \rightarrow [Cu(CFU)_2H_2O] + Cl_2$

For Silver Complex: $AgNO_3 + CFU \rightarrow [Ag(CFU)NO_3]$

Antimicrobial Screening: The antimicrobial activities of the cefuroxime and its metal complexes were evaluated using the disc diffusion method. The microorganisms tested included *Streptococcus pneumoniae*, *Bacillus subtilis*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Escherichia coli*, *Methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. A suspension of each microorganism was spread onto sterile nutrient agar plates. Discs containing different concentrations (30, 20, and 10 mg/mL) of the antibiotics and their metal complexes in methanol were placed on the agar. The plates were incubated at 37°C for 24 hours. The zones of inhibition were measured in millimeters. Compounds showing inhibition zones of 10 mm or more were further evaluated for minimum inhibitory concentration (MIC) and minimum bactericidal

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concentration (MBC) using concentrations of 6, 4, and 2 mg/mL in methanol, tested in peptone water [10].

Infrared Spectroscopy: The IR spectra of the complexes and the free ligand are summarized in Table 2. The band assignments are based on comparisons with literature on mixed ligand complexes and metal-drug complexes [11]. The vibration centered around 3190 cm^{-1} in the free ligand corresponds to the O-H stretching frequency, which shifts upon complexation. The band at 3560 cm^{-1} in the free ligand is attributed to N-H_2 vibrations of the amine group, and the band at 1550 cm^{-1} is assigned to C=N vibrations. The free ligand also displays a strong band at 1720 cm^{-1}, assigned to C=O stretching. The complexes show bands at 620 and 630 cm^{-1}, attributable to M-O stretching, indicating the formation of coordination compounds.

Electronic Spectroscopy: The electronic spectral data for cefuroxime and its metal complexes are presented in Table 3. The $\pi \rightarrow \pi^*$ transition in cefuroxime occurs around 349 nm. The $[Cu(CFU)_2H_2O]$ complex displays a low-intensity band at 340 nm, attributed to metal-to-ligand charge transfer (MLCT). The $[Ag(CFU)NO_3]$ complex shows absorption bands at 287, 301, and 313 nm, indicating a bathochromic shift relative to the free ligand and suggesting a weak MLCT interaction between the ligand and the silver ion [16, 17].

Microanalysis

The microanalysis of the metal complexes is presented in Table 4. The results revealed that the percentages of Carbon (C), Hydrogen (H), and Nitrogen (N) are in good agreement with the proposed structures. The complexes analyzed appear to be [Cu(L)2H2O][\text{Cu(L)}_2\text{H}_2\text{O}][Cu(L)2H2O] and [Ag(L)NO3][\text{Ag(L)NO}_3][Ag(L)NO3], where L = CFU.

Antimicrobial Studies

Transition metal complexes play a vital role in biological studies, with some being widely studied for their antimicrobial and anticancer properties [15]. Extensive investigations in the field of metal complexes have been reported [18]. A novel Cu(I) and Ag(I) complex has also been studied for its antimicrobial activities [16]. In continuation of this discovery, the present study synthesized new Cu(II) and Ag(I) complexes with cefuroxime using a mechanochemical method, and the antimicrobial effects were evaluated to determine whether the compounds exhibit any activity.

Both the ligand and the complexes were tested against both gram-positive and gram-negative bacteria, including *Streptococcus pneumoniae*, *Bacillus subtilis*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Escherichia coli*, Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The results showed that the complexes were more effective against the microorganisms than the ligand. Specifically,

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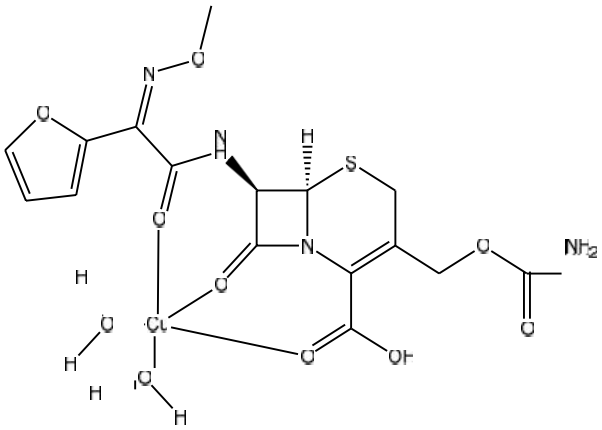
Bacillus subtilis was inhibited to the greatest degree by the prepared complexes, followed by *Staphylococcus aureus*. However, *Escherichia coli* and *Pseudomonas aeruginosa* were not inhibited by either the ligand or the complexes at any concentration (Table 5). The complexes also inhibited *Klebsiella pneumoniae* at concentrations of 20 and 30 mg/mL, whereas the ligand showed less activity at the same concentrations.

Structure of the Complexes

The analytical data revealed that cefuroxime coordinates to the metal ions through the oxygen atom of the carboxylate anion, the oxygen atom of the water molecule, and the oxygen atom of the carbonyl group, resulting in a coordination number of five for both complexes (Fig 1 and 2). This is consistent with our previous report [8].

Figure 1: Copper complex of cefuroxime



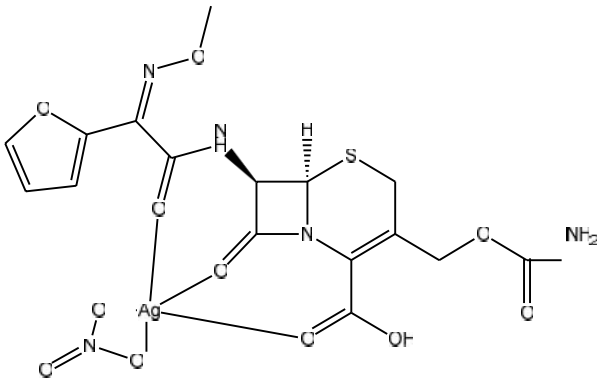


Figure 2: Silver complex of cefuroxime

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Table 1: Analytical data of cefuroxime and its complexes

Compounds	Molecular formula (Molar mass)	Color	Yield (g) (%)	M.pt (^{0}C)	Conductivity (Scm^2/mol)	TLC (RF Values)
CFU	$C_{16}H_{16}N_4O_8S$ (424.39)	White	-	218	-	0.4
[Cu(CFU)2H_2O]	[$Cu(C_{16}H_{20}N_4O_{10}S$] (523.89)	Light green	5.61 (94.0)	120	4.5	0.8
[Ag(CFU)NO_3]	[$Cu(C_{16}H_{16}N_5O_{11}S$] (594.76)	White	5.82 (98.0)	110	3.6	0.6

CFU= Cefuroxime

Table 2: Infrared spectral data of cefuroxime and its metal complexes

Compounds	v(O-H) (cm^{-1})	v(N-H) (cm^{-1})	v(C=O) (cm^{-1})	v(NH_2) (cm^{-1})	v(C=N) (cm^{-1})	v(C-S) (cm^{-1})	v(C=C) (cm^{-1})	v(M-O) (cm^{-1})
CFU	3190	1872	1720	3560	1550	2050	1235	-
[Cu(CFU)2H_2O]	3235	1890	1700	3451	1500	2030	1245	620
[Ag(CFU)NO_3]	3120	1865	1680	3473	1570	2040	1250	630

Table 3: UV-Vis spectra of cefuroxime and its metal complexes

Ligand/Complexes	Formula	Wavelength (nm)	Energies (cm^1)	Assignment
CFU	$C_{16}H_{16}N_4O_8S$	349	2865	$\pi\rightarrow\pi^*$
[Cu(CFU)2H_2O]	[$Cu(C_{16}H_{20}N_4O_{10}S$]	340	2941	MLCT
[Ag(CFU)NO_3]	[$Cu(C_{16}H_{16}N_5O_{11}S$]	287 301 313	3484 3322 3195	$n\rightarrow\pi^*$ MLCT MLCT

Table 4: Microanalysis of Cu(II) and Ag (I) complexes

Compounds	Molecular formula (Molar mass)	Microanalysis: found (calculated)%			
		C	H	N	M
[Cu(CFU)2H_2O]	[$CuC_{16}H_{20}N_4O_{10}S$] (523.89)	36.62 (36.65)	3.80 (3.82)	10.62 (10.69)	12.15 (12.12)
[Ag(CFU)NO_3]	[$AgC_{16}H_{16}N_5O_{11}S$] (594.76)	32.01 (32.28)	2.50 (2.69)	11.75 (11.77)	18.17 (18.14)

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Table 5: Antimicrobial activities of cefuroxime and its metal complexes

Compounds	Conc. mg/mL	*MRSA*	*S.aureus*	*S.pneumoniae*	*B.subtilis*	*E.coli*	*S.typhi*	K.*pneumoniae*	*p.aeruginosa*
CFU	10	7.0±0.8	10±0.5	0.0±0.0	12±0.5	0.0±0.0	10±0.4	0.0±0.0	0.0±0.0
	20	11±0.2	11±0.6	0.0±0.0	14±0.3	0.0±0.0	13±0.6	0.0±0.0	0.0±0.0
	30	14±0.5	13±0.4	0.0±0.0	18±0.6	0.0±0.0	16±1.0	0.0±0.0	0.0±0.0
[Cu(CFU)2 H_2O]	10	9.0±0.8	11±0.3	0.0±0.0	13±0.4	0.0±0.0	11±0.5	0.0±0.0	0.0±0.0
	20	11±0.7	14±0.8	0.0±0.0	16±0.3	0.0±0.8	16±0.4	8.0±0.0	0.0±0.0
	30	15±0.4	17±0.8	0.0±0.0	23±1.0	0.0±0.9	22±0.3	11±0.0	0.0±0.0
[Ag (CFU)NO_3]	10	9.0±0.1	11±0.2	0.0±0.0	13±0.0	0.0±0.0	8.0±0.3	0.0±0.0	0.0±0.0

MRSA= Methicillin -resistance *staphylococcus aureus, s.aureus = staphylococcus aureus, s.pneumoniae = Strepto coccuspneumonia, B.subtilis=Bacillus subtilis, E.coli= Escherichia coli, S.typhi= Salmonella typhi, K.pneumoniae=Klebsiellapneumonia and P.aruginosa= Psuedomonas aeruginosa.*

Table 6: Minimum inhibitory concentration (MIC) of cefuroxime and its metal complexes

Compounds	Conc. mg/mL	*MRSA*	*S.aureus*	*B.subtilis*	*S.typhi*	K.*pneumoniae*	*p.aeruginosa*	*E.coli*	*S.pneumoniae*
CFU	1	R	R	R	R	NA	NA	NA	NA
	2	R	R	R	R	NA	NA	NA	NA
	4	R	R	R	R	NA	NA	NA	NA
	6	R	S	S	S	NA	NA	NA	NA
	8	S	S	S	S	NA	NA	NA	NA
	10	S	S	S	S	NA	NA	NA	NA
[Cu(CFU)2H2O]	1	R	R	R	R	NA	NA	NA	NA
	2	R	R	R	R	NA	NA	NA	NA
	4	R	R	R	R	NA	NA	NA	NA
	6	R	S	S	R	NA	NA	NA	NA
	8	S	S	S	S	NA	NA	NA	NA
	10	S	S	S	S	NA	NA	NA	NA
[Ag(CFU)NO3]	1	R	R	R	R	NA	R	R	R
	2	R	S	R	R	NA	R	R	R
	4	R	S	S	R	NA	R	R	S
	6	R	S	S	S	NA	S	S	S
	8	R	S	S	S	NA	S	S	S
	10	S	S	S	S	NA	S	S	S

R= resistant, S= susceptible and NA= not applicable

From the result of minimum inhibitory concentration (MIC), it appears that both the ligand and the complexes have MIC of 6 and 8 mg/mL on *MRSA*, *s. aureus*, *B. subtilis* and *S. typhi*. However, [Ag(CFU)NO_3] has MIC of 4mg/mL on *S. pneumoniae* and 6 mg/mL on both *E.coli and P.aeruginosa* (Table 6).

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Table 7: Minimum Bactericidal concentration (MBC) of efuroxime and its metal plexes

Compounds	Conc. mg/mL	*MRSA*	*S.aureus*	*B.subtilis*	*S.typhi*	K.*pneumoniae*	*p.aeruginosa*	*E.coli*	*S.pneumoniae*
CFU	2	R	R	R	R	NA	NA	NA	NA
	4	R	R	R	R	NA	NA	NA	NA
	6	R	S	S	S	NA	NA	NA	NA
	8	S	S	S	S	NA	NA	NA	NA
	10	S	S	S	S	NA	NA	NA	NA
[Cu(CFU) $2H_2O$]	2	R	R	NA	R	NA	NA	NA	NA
	4	R	R	NA	R	NA	NA	NA	NA
	6	R	S	NA	R	NA	NA	NA	NA
	8	S	S	NA	R	NA	NA	NA	NA
	10	S	S	NA	S	NA	NA	NA	NA
[Ag(CFU)NO_3]	2	R	R	R	R	R	R	R	R
	4	R	R	R	R	R	R	R	R
	6	R	S	R	R	R	R	R	S
	8	R	S	S	S	R	R	S	S

Microanalysis

The microanalysis of the metal complexes is presented in Table 4. The results revealed that the percentages of Carbon (C), Hydrogen (H), and Nitrogen (N) are in good agreement with the proposed structures. The data suggest that the complexes are formulated as [Cu(L)2H2O][\text{Cu(L)}_2\text{H}_2\text{O}][Cu(L)2H2O] and [Ag(L)NO3][\text{Ag(L)NO}_3][Ag(L)NO3], where L = CFU.

Antimicrobial Studies

Transition metal complexes play a significant role in biological studies due to their antimicrobial and anticancer properties [15]. Extensive investigations into metal complexes have highlighted their potential [18]. This study synthesized new Cu(II) and Ag(I) complexes with cefuroxime using a mechanochemical method and evaluated their antimicrobial effects.

Both the ligand and the metal complexes were tested against various gram-positive and gram-negative bacteria, including *Streptococcus pneumoniae*, *Bacillus subtilis*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Escherichia coli*, Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The results indicated that the complexes exhibited superior antimicrobial activity compared to the free ligand. Specifically, the complexes were most effective against *Bacillus subtilis*, followed by *Staphylococcus aureus*. However, *Escherichia coli* and *Pseudomonas aeruginosa* were not inhibited by either the ligand or the complexes at any concentration (Table 5). Notably, the complexes inhibited *Klebsiella pneumoniae* at concentrations of 20 and 30 mg/mL, whereas the ligand showed lesser activity at these concentrations.

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The Minimum Bactericidal Concentration (MBC) results revealed that both the ligand and the complexes had MBC values ranging from 6 to 10 mg/mL against the tested microorganisms (Table 7).

Conclusion

The analysis of both compounds suggests that five-coordinated complexes are formed. The inhibition zone measurements for both the ligand and the complexes demonstrated that the synthesized complexes exhibit enhanced antibacterial activity against cephalosporin-resistant bacteria compared to the free ligand.

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