The Antibacterial Effect of Mechanically Synthesized Copper (II) and Silver (I) Complexes with Cefuroxime on Some Cephalosporin-Resistant Bacteria

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ABSTRACT

Due to the potential for complication to alter a drug's pharmacological, toxicological, and physical-chemical characteristics, it is an essential stage in the creation of new medicines. These results provide the first solvent-free synthesis of cefuroxime copper (II) and silver (I) complexes (mechanochemical). Physicochemical techniques, such as infrared spectroscopy, were used to characterize the complexes. Composition, temperature of melting, solubility, conductivity, and sensitivity to visible light are all factors. The location of the complexes was influenced by these findings. For example, it has been reported that the formulations [Cu(CFU)2H2O] and [Ag(CFU)NO3], where CFU stands for cefuroxime, are effective. A discussion on antimicrobial therapy using the disc diffusion technique, the complexes were evaluated for antibacterial activity against a wide variety of microorganisms. Bacillus subtitles, Streptococcus pneumonia, Typhi is the name for this subtype of Salmonella. Resistance to methicillin in Klebsiella pneumonia and Escherichia coli Infections caused by Staph aureus (Staph aureus), Pseudomonas aeruginosa, and MRSA. The evidence suggests this is the case. The activity of complexes is increased in comparison to the free ligand.

INTRODUCTION

Many factors, such as the spread of new infectious illnesses and the global population's increasing old age, make disease treatment a complex and important issue. Tremendous numbers of germs that is now immune to antibiotics. There are a plethora of medicinal choices; medicines with chemotherapeutic agents, while there has to be continual surveillance of antibiotic resistance. have increased substantially during the last several decades, finding novel molecules that may be able to eliminate bacteria and other pathogens an action, maybe the result of a chain of events, In contrast to common types, Years of research have resulted in certain antimicrobial medicines with clinical Pathogenic microorganisms have become immune [1]. Antibiotic Resistance: An Evolving Phenomenon If a bacterium undergoes a change that decreases or reduces the intensity of a drug's, chemical's, or other substance's antibiotics, antiviral drugs, and other medicines used to treat or stop infections. Microbiological contamination increase in number and severity of injury caused. This service is provided by a number of different bacterial systems. Some Antibiotic resistance occurs when bacteria acquire defense mechanisms to withstand treatment with antimicrobials. Some people may attempt to delay the drugs, while some may transition to other antibiotics with relative ease. Place of assault, preventing it from disrupting normal bacterial activity. Since the development of modern antibiotics, there the issue of resistance remains the most important synthetic a person with a PhD or postdoctoral research experience who focuses on chemistry [2]. Treatment options are becoming more limited as drug-resistant bacteria evolve. To recover, new medicine is needed or the current drug has to be increased. New antibiotic treatments are desperately needed. Despite a decline in the exploration and creation of new pharmaceuticals [3].

Similarly to penicillin’s, cephalosporin’s are efficient against bacteria because they prevent their reproduction. Same antibacterial effects to those of other beta-lactam drugs (like penicillin), but without the side effects. may avoid the majority of -lactamase problems. Cephalosporin’s’ ability to inhibit, Membrane peptidoglycan assembly A bacterial cell's outer membrane. Peptidoglycan plays a crucial part in structural integrity of the cell membrane. Thus, transpeptidation is finished. Transpeptidases play a crucial part in peptidoglycan production. Penicillin-binding proteins (PBPs) [4] are proteins that bind penicillin. A decrease in the affinity of existing PBP components or the development of a new -lactam-insensitive PBP are two possible mechanisms by which cephalosporin-based treatments become ineffective. Citrobacterfreundii, Enterobacter cloacae, and Klebsiella pneumonia are just a few of the bacteria that have evolved to cause food poisoning. The diversity of Escherichia coli and Neustria gonorrhoea strains. Illness that cannot be treated with cephalosporins. Morganellamorganii strains, Proteus vulgaris, Pseudomonas aeruginosa, and Providence rettgeri are examples of bacteria that may cause skin infections.

Salmonella and Pseudomonas aeruginosa co-infection exhibiting variable levels of cephalosporin resistance the usage of silver and its many compounds goes back medicines used to prevent the spread of germs in hospitals. Silver sulfadiazine is the chemical name for this compound. Have a lot of supporters due to the fact that it is highly antibacterial and may be absorbed by the skin. Varied species of yeasts and bacteria [1]. The antibacterial properties of copper and copper alloys are well-documented. Substances with antibacterial properties were used by ancient societies. The metal copper was used long before the term "microbe" was ever thought of to have achieved prominence by the nineteenth century [6].

MATERIALS AND METHODS

High-quality chemicals were utilized in all of the experiments. We utilized them as they were originally provided to us by Bristol Scientific Company Limited. The ligand in this scenario is chloride of copper and cefuroxime (Cfu) metal Metal ions may also form dehydrates, such as with silver nitrate (H3O) and copper chloride (H2O). IR The spectra of KBr pellet complexes were collected in between 4000 and 4000 cm-1, which is the range covered by an FTIR spectrometer while searching for metals. Atomic absorption spectroscopy was used for the analysis. Using a Perkin-Elmer 3110 UV-Vis Spectrometer We collected UV2550 Shimazu spectra. Instrument for gauging light between 200 and 800 nm in wavelength. Formation of Complicated Substances The literature-based research strategy [9] was used, and the results were producing all metal compounds using mechanical synthesis. Process Adding 0.025 g of copper chloride to 10 mmol (4.25 g) of cefuroxime The amount of dehydrate used was calculated to be 10 mmol (or 1.705 g), and modified their method of crushing ingredients by switching to a mortar and pestle. Then the two parts Twenty (20) minutes in a blender, food processor, or crusher will yield powder that is uniform and fine. After the powder keg exploded, dried with a mortar and pestle before being stored in desiccators. When moving from one phase to the next, we followed the same procedure. A combination of silver nitrate and cefuroxime (1.699 grammes) (10 mmol) (10mmol, 4.25g).

Equation for reaction

$$CuCl_2.2H_2O + CFU \rightarrow [Cu(CFU)2H_2O] + Cl_2$$
$$AgNO_3 + CFU \rightarrow [Ag(CFU)NO_3]$$
Where CFU = Cefuroxime

RESULTS AND DISCUSSION

Both the copper ion complex and the silver ion complex are air-stable powders; however the former has a pale green colour while the latter is bright white. In polar solvents like water, both complexes might potentially dissociate. Ingredients: distilled water, methanol, ethanol, and dimethylsulfoxide (DMSO). Considering that the complexes are soluble in polar solvents, it is safe to assume that they are polar molecules. Equivalents, parallels, and comparisons started off as the number [11]. Amount to the structures of However, copper only has to be heated to 110 degrees Fahrenheit to melt, whereas silver requires 1200 degrees (Table 1). To rephrase, ligand has a substantially lower melting point than Initiation of a complex creation leads to other chemical processes and making the complicated plain to see [12]. The "molar conductivity" of a substance is a measure of how (Table) varies from 3.6-4.5 Scm2/mol for the complexes. Based on this evidence, it seems likely that the chemicals in issue are not electrolytes [13]. Infrared Radiation Spectral analysis via infrared microscopy of various compounds and ligands Extensive examples may be seen in Table 2. An interval is assigned using research done in the past on ligand mixtures metal complexes used in drug design and other compounds [11]. The the natural frequency of vibration of the unbound ligand was determined to be 3190 cm1. The frequency v (O-H) is being stretched because of As a result of the complication procedure, the complexes develop. Look see the group playing over there! The wavelength of 3560 cm-1 in the free ligand has also been attributed to v. (N-H2) Changes in the position of the amine group. Still, the 1550 cm-1 band was this is because v(C=N) is a vibrating variable. Something like the original discovery was made. Created by a focused team of experts [14]. v(C=O) vibrations may be responsible for the strong band. For the free ligand, spectral stretching was seen at The crucial bands of the metal were detected at a wavelength of 1720 cm1.

Any chemical with a smaller wavelength shift ligand couples lose strength (Table 2). The Two new spectral bands arise at 620 and 630 cm1. rate at which v(M-O) stretching provides an explanation for complexes indications of progress toward completion of the complexes.

Structure of the complexes

This study's inquiry established that cefuroxime links with metal ions through its carboxylate anion's oxygen atoms and the water molecule. carbonyl-oxygen atom-complexes Identifying a 5th coordinate (Fig 1 and 2). Which is why similarly to what we've already reported [8].

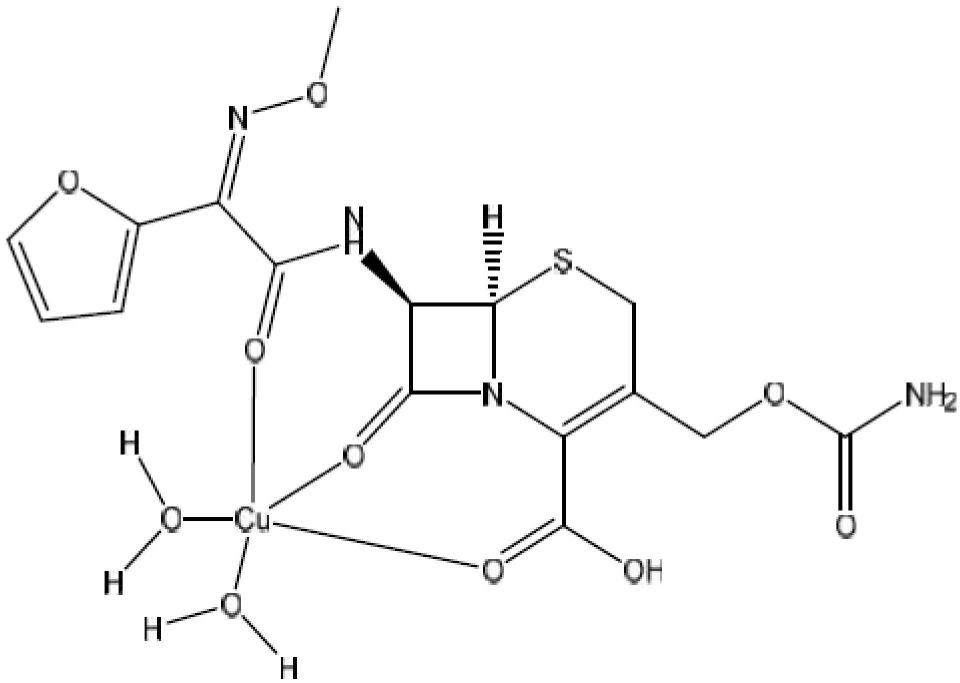

Figure 1: Copper complex of cefuroxime

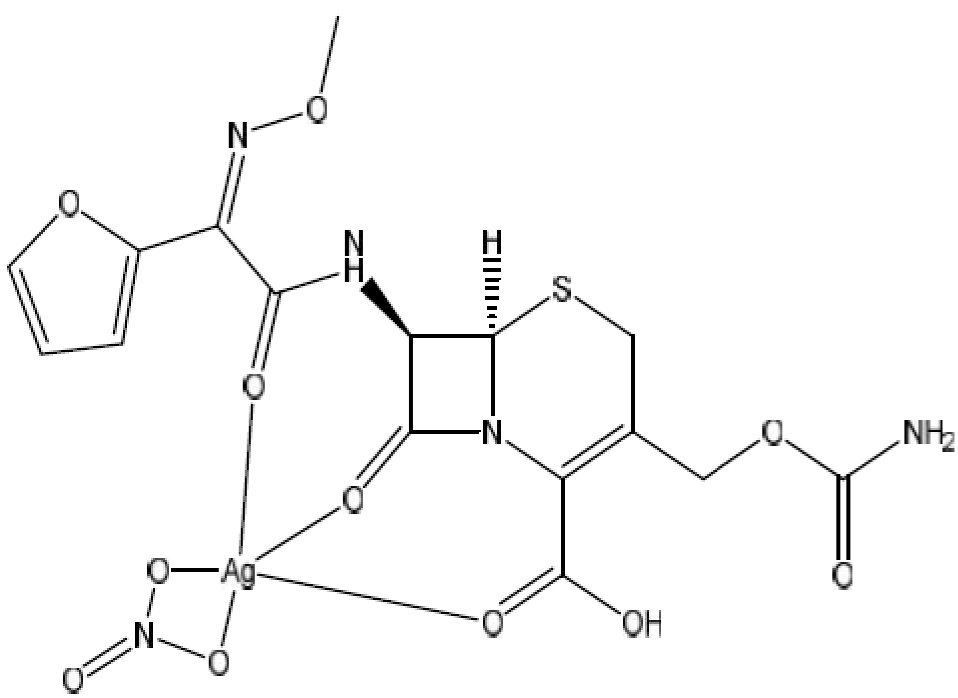

Figure 2: Silver complex of cefuroxime

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	3484	$n\rightarrow\pi^*$
		301	3322	MLCT
		313	3195	MLCT

Table 4: 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
	20	11±0.9	14±0.1	0.0±0.0	17±0.5	0.0±0.0	12±0.3	8.0±0.7	7.0±0.4
	30	15±0.2	17±1.0	0.0±0.0	23±0.4	0.0±0.0	15±0.5	11±0.6	9.0±0.4

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

Table 5: 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)2H_2O]	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)NO_3]	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)NO3] has MIC of 4mg/mL on *S. pneumoniae* and 6 mg/mL on both *E.coli and P.aeruginosa* (Table5).

Table 6 : Minimum Bactericidal concentration (MBC) 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	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
	10	S	S	S	S	S	S	S	S

The MBC result also shows that both the ligand and the complexes have MBC ranging from 6-10 mg/mL on microorganism
tested (Table 6).

CONCLUTION

Five candidate coordinated complexes were found via research on both substances Kinetic analysis of ligand inhibition zones Structures that had been built in advance revealed signs of increasing the cephalosporin's already impressive antibacterial properties bacterium that is more immune to the ligand.

REFERENCE

[1] *Marcela R. Metal Complexes as Antimicrobial Agents. Faculty of Biochemistry and Pharmacy, National University of Roario, Argentina, 2010.*

[2] Tacconelli E., De Angelis G., Cataldo MA.,Pozzi E., and Cauda R. "Does Antibiotic Exposure increase the risk of Methicillin-resistant Staphylococcus aureus (MRSA) Isolation? A systematic Review and Meta-analysis". J. Antimicrob. Chemother. 2008, 61 (1): 26–38.

[3] McNulty CA., Boyle P., Nichols T., Clappison P., and Davey P."The public's Attitudes to and Compliance with Antibiotics". J. Antimicrob. Chemother. 2007, 60 Suppl 1: i63–8.

[4] Sayed H. A., Ilka K., Beate S., Matthias B., Yahya M., Cornelia G., Reinhard H., and Neubert H. Effect of Different Metal Ions on the Biological Properties of Cefadroxil. Pharmaceuticals, 2009,2, 184-193.

[5] Dancer S. J. The problem of cephalosporin.J. of Antimicrobial Chemotherapy. 2015, 48 (4):463- 478.

[6] Dollwet H. H. A. and Sorenson J. R. J. Historic uses of Copper Compounds in Medicine. Trace Elements in Medicine, 1985,2(2): 80-87

[7] ZaharievaJ. T., Milanova M., TodorovskyD. Mechanochemical Synthesis of Thenoyl trifluoroacetone-1, 10-Phenanthroline Europium complex. Russian J. of Inorganic Chemistry, 2007, 52(4): 518-523.

[8] N.P. Ndahi, M.B. Fugu, I. waziri and Y.A. Geidam. Effect of Mechanochemically Synthesized Copper (II) and Silver (I) Complexes on Some Cephalosporin Resistance Bacteria. International J. of Innovative Research and Devolopment, 2017,6(7): 262-269

[9] Houria K., Channing C. A., Song-Jong H., Robert C. B., and Jason G. Direct Synthesis and NMR Characterization of Calcium Alanate. J. of Alloys and Compounds, 2007, 264-266

[10] I. Waziri, G.A Mala, M.B. Fugu, B. Isa and U. Umaru. Synthesis, Spectral Characterization and Antimicrobial Activity of Some Metal Complexes of Mixed Antibiotics. Chemistry Research J.,2017, 2(2): 46-52

[11]Ogunniran, K.O., Ajanku K. O., James O.O., Ajani O. O., Adekoya J. A., and Nwinyi O. C. Synthesis, Characterization, Antimicrobial Activity and Toxicology Study of Some Metal Complexes of Mixed Antibiotics. African J. of Pure and Applied Chemistry, 2008, 2(7): 069-074

[12]Taghreed H. A., Amer J. J., and Abbas O. H. Synthesis, Characterization and Antibacterial Activity of Some Metal ion with 2-aminophenol and Tributylphosphine. Research J. of Pharmaceutical, Biological & Chemical Sciences, 2017, 8(3): 1-8

[13]Adedibu C. T., Uche B. E., Aaron Y. I., and Christiana A. O. Mechanically- induced Solventless Synthesis of Cobalt and Nickel Complexes of Cimitidine. The Electronic J. of Chemistry, 2011, 3(2): 94- 103

[14] Oladipo MA. Woods JAO. Odunola OA. Synthesis, Vibrational Spectra and Magnetic Properties of Cobalt (II), Nickel (II) and Copper (II) Complexes of Barbituric Acid. Science Focus, 2005, 10(1): 49-52.

[15]Korany A. Ali, Mokhles M. Abd-Elzaher and Khaled Mahmoud. Synthesis and Anticancer Properties of Silver (I) Complexes Containing 2,6- Bis (substituted) Pyridine Derivatives, International J. of Medicinal Chemistry 2013, Volume 2013: 1-7

