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Antimicrobial Studies of Mixed Ligand Transition Metal Complexes of Cu(II) and Cd(II) with Maleic Acid and Heterocyclic Bases

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Abstract Mixed ligand transition metal complexes of Cu(II) and Cd(II) ions were synthesized, where maleic acid as primary ligand and heterocyclic amine bases as a secondary ligands have been used, respectively. The prepared complexes, [Cu(MA)(1,10-Phen)], [Cu(MA)$(Py)_2$] and [Cd(MA)$(IQ)_2$] were characterized by their conventional physical and chemical analyses. The complexes were tested for their antimicrobial activity against ten bacterial strains *Streptococcus-β-haemolyticus* (Gram positive), *Vacillus megterium* (Gram positive), *Bacillus suvtilis* (Gram positive), *Sarcina lutea* (Gram positive), *Salmonella typhi* (Gram negative), *Shigella boydii* (Gram negative), *Shigella shiga* (Gram negative), *Klebsiella Sp.* (Gram negative), *Escherichia coli* (Gram negative) and *Shigella sonnei* (Gram negative). The antifungal activities were evaluated against five fungi *Fusarium Sp.*, *Penicillium Sp.*, *Trichoderma Sp.*, *Aspergillus Sp.* and *Aspergillus nidulans.* Disc diffusion methods were employed, with Kanamycin as the standard antibiotic, for antimicrobial assays. The complexes containing 1,10-phenanthroline and Isoquinoline as secondary ligands were much more microbial active than other complexes. The complex [Cu(MA)(1,10-Phen)] showed the highest fungicidal activity against all fungi tested. In addition, [Cd(MA)$(IQ)_2$] showed satisfactory activity against pathogenic bacteria and fungi. (MA=Maleic acid, py=pyridine, 1,10-Phen=1,10-Phenanthroline and IQ=Isoqunoline).

Keywords Biological Activity, Maleic Acid, Heterocyclic Amine Bases, Mixed Ligand Transition Metal Complexes

1. Introduction

Inorganic compounds play an important role in biological processes and it has been established that many organic compounds used in medicine are activated by metal ions metabolism[1]. Metal complexes of ligands possess a variety of applications in the biological, analytical, clinical and industrial areas[2]. In recent times, transition metal complexes of ligands have gained considerable attention due to their remarkable antifungal, antibacterial and antitumor activities[3-6].

Pathogenic microorganisoms cause different life threatening infections such as tuberculosis, Cancer, AIDS etc. and they are also an important cause of morbidity and mortality in immunocompromised patients. Synthetic chemical compounds constitute important sources of various bioactive compounds such as antibacterial[4], antifungal[5] and anticancer[6] compounds. The synthesized chemical compounds, which are used for the treatment of infectious diseases, are known as chemotherapeutic agents. Every year thousands of compounds are synthesized with an aim to find a potential chemotherapeutic agent to combat pathogenic microorganisms. The mixed ligand complexes of Co(II), Ni(II), Cu(II) and Zn(II) with Schiff bases were synthesized and the antimicrobial activities were measured[7]. Fe(III), Ni(II), Co(II), Cu(II) and Cd(II) complexes with thiazoline and their fungicidal activity has been evaluated[8]. Metal chelation or complexation is involved in many important biological processes, where the coordination can occur between a variety of metal ions and a wide range of ligands[9]. Many types of ligand are known and the properties of their derived metal chelate have been investigated[10]. Prior to 1980, search for anticancer drugs was focused primarily on organic compounds[11].

Antimicrobial activity of the metal complexes of Fe(III), Co(II) and Ni(II) with cyanex-272 have been tested and found most of them has substantial activity against microorganism[12].

Heterocyclic bases have a great important in biological and industrial fields. Most of the heterocyclic bases are used as corrosion inhibitors and as antibacterial, anticonvulsive, antifungal and antifouling agents[13]. The chlorinated species of 8-hydroxyquinoline has been proved as antibacterial and antifungal agent[14] and di-iodo derivative is administered to overcome Zn deficiency in animal[15]. Derivatives of Cu(II) with 8-hydroxywuinoline are antifouling agents[16] and it itself prospects the industrial and fungi in them[17]. 3-aminopyridine has strong anticonvulsive effects[18,19].

Biologically relevant metal complexes have several requirements in terms of their synthetic design. A biologically active metal complex should have a sufficiently high thermodynamically stability to deliver the metal to the active site. Generally, drug combinations have proven to be an essential feature of antimicrobial treatment due to a number of important considerations such as they increase activity through the use of compounds with synergistic or additive activity, they increase the spectrum of activity, they decrease required doses.

In biological process, mixed ligand complexes play an important role by many instances in which enzymes are known to be activated by metal ions[20-22]. The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance. Metal complexation is a process by which certain inorganic metal ions coordinate with organic functional groups through ionic bonds and ion dipole interactions to form organometallic hybrids having many interesting properties and applications.

This present study was undertaken to prepare some mixed ligand transition metal complexes of Cu(II) and Cd(II) ions with maleic acid as primary and heterocyclic bases as secondary ligands. The physicochemical properties and characterization of the complexes were carried out by elemental analysis, magnetic susceptibilities, FTIR, UV-Visible. The antimicrobial activities of the synthesized compounds were evaluated against ten bacterial strains *Streptococcus-β-haemolyticus* (Gram positive), *Vacillus megterium* (Gram positive), *Bacillus suvtilis* (Gram positive), *Sarcina lutea* (Gram positive), *Salmonella typhi* (Gram negative), *Shigella boydii* (Gram negative), *Shigella shiga* (Gram negative), *Klebsiella Sp.* (Gram negative), *Escherichia coli* (Gram negative) and *Shigella sonnei* (Gram negative). The antifungal activities were reported against five fungi *Fusarium Sp.*, *Penicillium Sp.*, *Trichoderma Sp.*, *Aspergillus Sp.* and *Aspergillus nidulans* to find out as antibacterial and antifungal agents.

2. Material and Methods

The mixed ligand transition metal complexes were obtained from the Inorganic Chemistry Research Laboratory of University of Rajshahi, Bangladesh where these were prepared and characterized[23]. The tested bacteria and fungi were collected from the department of batany, University of Rajshahi. All steps of the work were carried out at the Plant Pathology and Mycology laboratory, Department of Botany, University of Rajshahi, Bangladesh. Nutrient agar and potato dextrose agar were used as fungicidal and bacteriological media, respectively.

Preparation of Complexes

Preparation of Cu(II) complexes: The solution of copper chloride(0.001 mol) in ethanol(20 ml) was mixed with the solution of maleic acid(0.001 mol) in ethanol(20 ml) and the mixtures were refluxed for 30 minutes. No precipitate was observed. Then 20 ml of an ethanolic solution of heterocyclic amine bases (eg, 2 mmol for monodentate ligands of IQ, Py, 2-Pic, 4-Pic and 1 m mole for bidentate ligands of 2-Apy, 3-Apy, AMP, 1,10-Phen, 2,2'-Dpyl) were added to the resulting mixture over a hot plate with constant stirring. The volume of the solution was reduced to a half and allowed to cool. The precipitate formed and was filtered, washed several times with ethanol and then dried in desiccator over anhydrous $CaCl_2$.

Preparation of the Cd(II) complexes: CdI_2 (0.01 mol) was dissolved in ethanol to which on alcoholic solution of maleic acid (0.01 mol) was added. The mixture was then refluxed on a water bath for an hour and then the calculated amount of an alcoholic solution of bases (Q, IQ, 8-HQ, 2-Pic, 4-Pic, Py, AMP, 1,10-Phen, 2,2'-Dpyl) were added. The mixture was again refluxed on a water bath for an hour and then cooled. The precipitate were filtered and washed several times with distilled water and finally with ethanol and then dried in a vacuum over anhydrous $CaCl_2$.

Antibacterial Assay

For primary selection of the complexes as therapeutic agents, the disc diffusion method[24] is used in vitro antibacterial screening. The method is highly effective for rapidly growing microorganisms and the activities of the test complexes are expressed by measuring the diameter of the zone of inhibition. Generally, the more susceptible the test organism, the larger is the zone of inhibition. The method is essentially a qualitative or semi quantitative test indicating sensitivity or resistance of microorganisms to the test materials as well as the bacteriostatic or bactericidal activity of a compound[25]. The complexes were screened for antibacterial activity against *Streptococcus-β-haemolyticus* (Gram positive), *Vacillus megterium* (Gram positive), *Bacillus suvtilis* (Gram positive), *Sarcina lutea* (Gram positive), *Salmonella typhi* (Gram negative), *Shigella boydii* (Gram negative), *Shigella shiga* (Gram negative), *Klebsiella Sp.* (Gram negative), *Escherichia coli* (Gram negative) and *Shigella sonnei* (Gram negative). The activities were carried out with the help of disc diffusion technique[26,27]. The complexes were dissolved separately in dimethyl sulfoxide (DMSO) to get a concentration of 100 μg $disc^{-1}$. Antibacterial activity was compared with the standard

Kanamycin (30 µg disc^{-1}).

Antifungal Assay

The antifungal activity of the complexes carried out against *Fusarium Sp.*, *Penicillium Sp.*, *Trichoderma Sp.*, *Aspergillus Sp.* and *Aspergillus nidulans.* with the help of disc diffusion technique[26,27]. The complexes were dissolved separately in dimethyl sulfoxide (DMSO) to get a concentration of 100, 150 and 200 µg disc^{-1}. Antifungal activity of the complexes was compared with the standard Nystratin.

3. Results and Discussion

The complexes were characterized on the basis of elementary analysis, Melting point and conductance magnetic measurement, Infrared and electronic spectra. These characterizations confirmed the coordination of transition metal with ligands.

Antibacterial Activity

The antibacterial activities of the complexes [Cu(MA)(1,10-Phen)] and [Cd(MA)(IQ)$_2$] were determined at the concentration of 100 µg disc^{-1} against a series of Gram positive and Gram negative pathogenic organisms(Shown in Table 1). The results show that the mixed ligands complexes are more active than their parent ligands against the same microorganism. The increase in the antimicrobial activity of the mixed ligand complexes may be due to the effect of the metal ion on the normal cell processes. The copper complex, [Cu(MA)(1,10-Phen.)] showed more activity against the tested bacteria than others. The zones of inhibition were found as 27, 28 and 30 mm against *Klebsiella Sp. (-ve), Sarcina lutea (+ve), Shigalla sonnei (-ve), Bacillus megterium (+ve)*, respectively in complex of [Cu(MA)(1,10-Phen.)] while rest of the complexes have more or less intermediary antibacterial effect against the tested bacteria.

Antifungal Activity

The antifungal activities of the complexes, [Cu(MA)(1,10-Phen)], [Cu(MA)(Py)$_2$] and [Cd(MA)(IQ)$_2$] were studied and results were presented in the Table 2. The highest zone of inhibition 25, 26 and 27 mm of Trichoderma Sp. were measured in complex of [Cu(MA)(1,10-Phen.)] while rest of the complexes have more or less intermediary antifungal effect against the test fungi. Our present investigation show how these complexes can be used as antifungal agent. As different ligands modify the antifungal activity of the complexes so, proper ligand selection may reveal metal complexes to be potent antifungal agents. Therefore, the present findings may also open a new search for these complexes for use in fungal diseases.

Table 1. Results of the antibacterial activities of the complexes

Bacteria code	Name of the bacteria	Strain No.	Diameter of inhibition zone (mm)			
			[Cu(MA)(1,10-Phen)]		**[Cd(MA)(IQ)$_2$]**	
			100 µg/disc	Kanamycin 30 µg/disc	100 µg/disc	Kanamycin 30 µg/disc
A002	Streptococcus-*β*-haemolyticus (+ve)	CRL	25	22	32	25
B002	Bacillus megterium (+ve)	QL-38	27	24	28	29
C002	Bacillus subtilis (+ve)	QL-40	22	21	30	22
D002	Sarcina lutea (+ve)	QL-166	28	24	18	21
E002	Salmonella typhi (-ve)	-	19	20	26	20
F002	Shigella boydii (-ve)	AL-17313	25	26	27	18
G002	Shigella shiga (-ve)	ATCC-26107	23	19	19	21
H002	Klebsiella Sp. (-ve)	-	30	28	20	26
I002	Escherichia coli (-ve)	FPFC-1407	25	24	25	28
K002	Shigalla sonnei (-ve)	AJ-8992	30	22	24	20

Table 2. Results of the antifungal activities of the complexes

Name of the Fungi	Diameter of inhibition zone (mm)									
	[Cu(MA)(1,10-Phen)]			[Cu(MA)(Py)$_2$]			[Cd(MA)(IQ)$_2$]			Nystratin 30 µg/disc
	100 µg/disc	150 µg/disc	200 µg/disc	100 µg/disc	150 µg/disc	200 µg/disc	100 µg/disc	150 µg/disc	200 µg/disc	
Aspergillus Sp.	17	15	22	6	21	34	15	12	17	14/15/16
Trichoderma Sp.	25	26	27	11	14	18	14	15	18	17/19/18
Penicillium Sp.	15	16	18	19	21	21	14	17	21	14/14/13
Fusarium Sp.	16	17	19	23	27	29	12	14	15	10/11/11
Aspergillus nidulans	8	13	16	10	12	11	13	15	18	14/13/15

4. Conclusions

The Mixed ligand complexes were synthesized and characterized by their conventional physical and chemical analyses. The complexes were tested for their antimicrobial activity against ten bacterial strains *Streptococcus-β-haemolyticus* (Gram positive), *Vacillus megterium* (Gram positive), *Bacillus suvtilis* (Gram positive), *Sarcina lutea* (Gram positive), *Salmonella typhi* (Gram negative), *Shigella boydii* (Gram negative), *Shigella shiga* (Gram negative), *Klebsiella Sp.* (Gram negative), *Escherichia coli* (Gram negative) and *Shigella sonnei* (Gram negative). The antifungal activities were evaluated against five fungi *Fusarium Sp.*, *Penicillium Sp.*, *Trichoderma Sp.*, *Aspergillus Sp.* and *Aspergillus nidulans.* The Copper complex showed biocidal activity against bacteria and fungi. Further studies of the copper complex may explore its clinical implications in the world life threatening infection.

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