ANTIFUNGAL ACTIVITY OF MIXED LIGAND TRANSITION METAL COMPLEXES OF SOME DIBASIC ACID AND HETEROCYCLIC BASES

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Abstract: *Mixed ligand transition metal complexes of Cu (II), Co (III), Rh (III) and Pt (IV) ions with dibasic acids viz., diphenic acid and adipic acid as primary ligands and amine bases as secondary ligands have been synthesized. Their conventional physical and chemical analyses have been done. The antifungal activities have been evaluated by Disc Diffusion method employed for antifungal assays against two pathogenic fungi. All the complexes show moderate antifungal activity. The highest inhibition of growth occurred on complex [Cu (DA)(8-HQ)] against the fungi Botryodiplodia theobromae and the lowest on complex [Rh (DA)(8-HQ)(H_2 O)$_2$] against the fungi Colletotrichum gloesparioides penz.*

Key words: *Biological Activity, diphenic acid, heterocylic amine, mixed ligand complexes*

1 Introduction

Mixed ligand complexes of dibasic acids and heterocyclic bases have been studied over the past few decades [1] not only because of their intriguing coordination chemistry, but also because of their pronounced biological activities against microbes, viruses and cancer cells [2]. The complexes of platinum metal are very important from medical point of view. Some complexes of platinum exhibit anti-tumor activity [3]. On the other hand, Ni (II), Co (II), Fe (II) and Cu (II) complexes with thiazoline and their fungicidal activity have been evaluated [4]. The metal complexes of phthalic acid have been studied both from pharmacological [5] and industrial (Nippon Synthetic Chemical Industry Co. Ltd.) point of view as indicated by available literature. Heterocyclic bases have a great importance in biological and industrial fields. The chlorinated species of 8-hydroxyquinoline has been proved as antifungal agents [6]. Derivatives of Cu with 8-hydroxyquinoline are antifouling agent [7] and itself protects the industrial and fungi in them [8]. Recently, we have reported antifungal activities of some mixed ligand complexes of transition metals with malonic acid (Reza *et al*., 2003) maleic acid (Islam *et al*., 2003), and phthalic acid (Reza *et al*., 2003) and heterocyclic bases. As part of our ongoing work on mixed ligand complexes, we report here the synthesis, characterization of Pt (IV), Co (III), Cu (II) and Rh (III) ions with diphenic acid or adipic acid as primary and heterocyclic bases, viz., Quinoline (Q), 8-hydroxyquinoline (8-HQ) as secondary ligands. Their antifungal activities carried out to perform primary selection of these complexes as the therapeutic agents.

2 Materials and Methods

2.1 General method of complex Preparation: Chloride or nitrate salts of various metals (1 mmol) ($Cu(NO_3)_2.3H_2O$, $CoCl_3.6\ H_2O$, Cl_6H_2Pt aq ,$RhCl_3.\ H_2O$) were dissolved in absolute ethanol (20-50 mL). The solution was heated if necessary and filtered to obtain a clear solution of the metal salt. Ethanolic solution of dibasic acids were added in the calculated ratio and mixed with constant stirring. If a pseudo precipitate formed, that was collected and dissolved in acetone. Then 25 mL of an ethanolic solution of amine bases (e.g. 1-2 mmol of Py, Q, IQ, 8-HQ) was added to the resulting mixture. If immediate precipitation of the complex did not occur, the volume of the mixture was

reduced by heating on a magnetic regulator hot plate with constant stirring and then it was cooled in an ice-bath. The product formed was isolated, washed with a small amount of ethanol and finally dried in a desiccator over anhydrous $CaCl_2$.

2.2 Antifungal test: Tow fungi viz., *Botryodiplodia theobromae* and *Colletotrichum gloesparioides penz* were collected from Department of Botany, University of Rajshahi and selected for anti-microbial test. The test was performed in plant pathology laboratory, Department of Botany, University of Rajshahi. Potato Dextrose Agar was used as fungicidal media. The complexes were dissolved separately in dimethyl sulfoxide (DMSO) to get a concentration of 80, 50 and 30 μg $disc^{-1}$ respectively. Then in vitro anti-microbial activity of these complexes was carried out by disc diffusion method (Bauer et al, 1966). The diameter of the zone of inhibition produced by the complexes was compared with Fluconazol (80, 50 and 30 μg $disc^{-1}$ respectively).

3 Results and Discussion

The complexes were characterized on the basis of elemental analysis, melting point, conductance, magnetic measurement and infrared spectra (Table 1). The infrared spectra of the complexes confirmed the coordination of metal ion with ligands. The observed magnetic moment values of Pt (IV) and Rh (III) (3, 4) indicated that these complexes are diamagnetic.

Table 1 Analytical data and physical properties of the complexes

Complex no.	Complexes	Color	Metal (%)	M.P.or dec.temp (±5°)	Molar conductance ($ohm^{-1}cm^2mole^{-1}$)	Magnetic Moment (BM)
1	[Co(DA)(8-HQ)]	Brown	0.06 (10.35)	180	15.48	3.90
2	[Cu(DA)(8-HQ)]	Brown	14.18(14.00)	240	10.12	1.76
3	$[Pt(A)_2(Q)_2]$	Pale orange	39.20(39.11)	240	11.2	0.53
4	$[Rh(DA)(8\text{-}HQ)(H_2O)_2]$	Brown	8.56 (28.30)	250(d)	12.61	0.51

Where A = $C_6H_6O_4$, DA = $C_{14}H_8O_4$, 8-HQ = C_9H_6NO, Q = C_9H_7N, d = decomposition

Table 2 Result of the anti-fungal activity of the complexes against *Botryodiplodia theobromae*

Complex no.*	Zone of inhibition of mycelial growth, (mm).		
	80μg/disc	50μg/disc	30μg/disc
1	15	13	12
2	16	13	12
3	12	10	8
4	11	9	7
Control	6	--	--

***** Complexes: Please see Table 1

Table 3 Results of the anti-fungal activity of the complexes against *Colletotrichum gloesparioides penz.*

Complex no.*	Zone of inhibition of mycelial growth, (mm).		
	80μg/disc	50μg/disc	30μg/disc
1	12	10	8
2	13	11	10
3	11	9	8
4	10	8	7
Control	6	--	--

***** Complexes: Please see Table 1

For Cu (II), and Co (II) complexes (1, 2) the values of magnetic moment lies between 1.73-3.90 BM. All the metal complexes showed moderate antifungal activity

compared with standard Fluconazol. This is an interesting finding as very few reports have been made on metal complexes as antifungal agents [8]. Our present investigation show how these complexes can be used as antifungal agent (Table 2 & 3). 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.

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