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Antimicrobial and Toxicological Studies of Mixed Ligand Transition Metal Complexes of Schiff Bases

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Abstract: Mixed ligand transition metal complexes of Cu^{+2}, Ni^{+2} and Co^{+2} ions with Schiff base ligands (SB-1 & SB-2) derived from the condensation of O-hydroxy benzaldehyde with amino phenols and nitrogen donor amine bases, e.g. ethylenediamine, 2-aminopyridine, O-Phenylenediamine or thiocyanate have been synthesized. Their conventional physical and chemical analyses have been done. Their anti-bacterial and anti-fungal activity have been evaluated including toxicological studies.

Key words: Biological activity, toxicological studies, Schiff base

Introduction

Most of the insecticides in their early stage of the inorganic compounds having bad odour and very ugly to look at (Bhuiyan *et al.*, 1991). The production of effective poisons in their regard begin since from the middle of 19 th century. The arsenate compounds of Ca, Pb, S and paris green [$Cu(C_2H_3O_2)_2$. 3 $Cu(AsO_2)$] were remarkable among them.
The chlorinated species of 8-hydroxyquinoline has been proved as anti-bacterial and anti-fungal agents (Meyer *et al.*, 1980) and the di-iodo derivative is administered to overcome Zn deficiency in animals (Dell, 1980). Derivatives of Cu with 8-hydroxyquinoline are anti-fouling agents (Nakazawa and Yamauchi, 1980) and 8-hydroxyquinoline itself protect the industrial and fungi in them. (Kulieve *et al.*, 1979 a and Kulieve *et al.*, 1979 b) 3-aminopyridine has strong anti-convulsive effects. (Baranyi *et al.*, 1979 and Szente *et al.*, 1984). Some mixed ligand complexes of Cu^{+2}, Ni^{+2} and Co^{+2} ion with Schiff base ligands (SB-1 & SB-2) and amine bases or thiocyanate have been prepared and their anti-microbial and toxicological studies have been carried out.

Materials and Methods

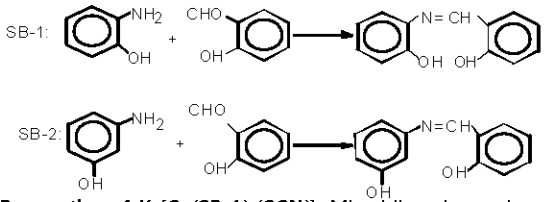
The test organisms (both bacteria and fungi) were collected from the Department of Pharmacy and Botany, Rajshahi University, Bangladesh. All steps of the work were carried out at the Molecular Genetics Laboratory, Department of Pharmacy and Plant Pathology Laboratory, Department of Botany, Rajshahi University. Ten healthy growing (32-45 gm) albino rats were collected from Rajshahi districts and placed in mesh bottomed cases.

Antibacterial activity: These complexes were screened for anti-bacterial activity against *S. aureus*, and *B. megatrium* (gm positive), *S. dysentry* and *Salmonella* (gm negative) organism using disc diffusion technique (Gnanamanickam *et al.*, 1980) at 50 μg/ disc. Concentrations of each compound was mixed in nutrient agar media. The results were compared with standard antibiotics, of Kanamycin and Dimethyl sulfoxide (DMSO) which were used as control.

Antifungal activity: The antifungal activity of the complexes was carried out against *Colletotrichum* sp., *Aspergillus nidulans*, *Botryodiplodia* sp., *Bipolaris sorokiniana* (on PDA medium) and *Treponemap aledium* (on Sabouraud=s medium) using disc diffusion technique (Gnanamanickam *et al.*, *1980*).

Toxicological studies: Each compound was administered in 5 different doses (0.01, 0.02, 0.03, 0.04 and 0.05%). In the primary screening, a constant dose (0.1 ml/rat/day) of the solutions were administered intraperitonealy into experimental groups consisting of two male albino rats by means of disposable oral feeding needle (Prasada *et al.*, 1993).
The experiment was continued and the animals were observed for 7 days for their behavioural and autonomic signs. Weight of the rats was taken every day. The toxicity was measured by comparing the weight taken of the experimental group rats with that of the control group rats considering the weight gain of the control group rats as 100%.

Preparation of Schiff bases (SB-1 & SB-2): The Schiff bases (SB-1 & SB-2) were prepared by the condensation of O-hydroxy benzaldehyde with o and m-amino phenol.
1.7 gm, 0.014 mol of O-hydroxy benzaldehyde in 20 ml absolute ethanol was added to 30 ml ethanolic solution of 1.5 gm, 0.014 mol of o-amino phenol or m-amino phenol. The mixture was heated to reduce the volume to 25 ml, then it was cooled in ice-bath. The black crystalline product was isolated and washed with hot ethanol. The prepared Schiff bases were obtained in pure form, after the treatment of column chromatography which shows a single spot in TLC (Thin layer chromatography) in all the cases.



Preparation of K [Cu(SB-1) (SCN)]: Mixed ligand complex of Cu^{+2} with Schiff base ligand (SB-1) and thiocyanate has been prepared (Islam *et al.*, 2000).

General method for the preparation of [M(SB-2) (NN)] [M=Cu $^{+2}$, Ni^{+2} and Co $^{+2}$, NN = $C_2H_8N_2$, $C_5H_6N_2$ and $C_6H_8N_2$]: A 25 ml of ethanolic solution of the metal chloride (0.005 mol) [$CuCl_2$. $2H_2O$. $NiCl_2$. $6H_2O$. $CoCl_2$. $6H_2O$] was added to 30 ml of an ethanolic solution of the above prepared Schiff base (SB-2) (0.005 mol). Then 20 ml of a ethanolic solution of [$C_2H_8N_2$,or$C_5H_6N_2$ or $C_6H_8N_2$]

Table 1: Analytical data and physical properties

Complexes	Color	Metal %	M. P. or dec. temp.	Molar Condectome (Ohm^{-1} cm^2 mol^{-1})	Magnetic moment in B.M
K[Cu(SB-1)(SCN)]]	Yellowish	16.99 (15.54)	175-177	29	1.95
[Cu(SB-2). $C_5H_6N_2$]	Greenish	17.14 (17.89)	228-230	30	1.91
[Cu({SB-2). $C_2H_8N_2$]	Greenish	18.86 (17.99)	208-210	40	1.89
[Cu({SB-2). $C_6H_8N_2$]	Greenish	16.52 (16.05)	160-162	35	1.90
[Ni({SB-2). $C_5H_6N_2$]	Pale yellow	16.05(15.25)	225-227	35	Diam
[Ni({SB-2). $C_2H_8N_2$]	Red brick	17.69 (18.15)	288-290 D	36	Diam
[Co(SB-2). $C_5H_6N_2$]	Black	16.10 (17.95)	206-208	38	3.0
[Co(SB-2).$C_6H_8N_2$]	Black	15.51 (14.12)	186-188	42	2.0

D = Decomposition point

Table 2: Antibacterial activity of the complexes

Complexes	Diameter of zone of inhibition of mycelial growth (mm)			
	S. aureus (+ve)	*B. megatrium* (+ve)	*S. dysentry* (-ve)	*Salmonella* (-ve)
K[Cu(SB-1)(SCN)]	24	30	26	28
[Cu(SB-2). $C_5H_6N_2$]	19	29	18	24
[Cu({SB-2). $C_2H_8N_2$]	23	24	25	23
[Cu({SB-2). $C_6H_8N_2$]	22	22	23	20
[Ni({SB-2). $C_5H_6N_2$]	22	14	22	20
[Ni({SB-2). $C_2H_8N_2$]	-	8	-	8
[Co(SB-2). $C_5H_6N_2$]	14	18	17	15
[Co(SB-2).$C_6H_8N_2$]	17	20	17	19

Table 3: Antifungal activity of the complexes

Complexes	Diameter of zone of inhibition of mycelial growth (mm)				
	T. paledium	*Bipolaris sorokiniana*	*Botryodiplo dia* sp.	*A. nidulans*	*Colletotri-chum.*sp.
K[Cu(SB-1)(SCN)]	20	-	-	8	-
[Cu(SB-2). $C_5H_6N_2$]	22	10	8	-	-
[Cu({SB-2). $C_2H_8N_2$]	28	15	9	-	8
[Cu({SB-2). $C_6H_8N_2$]	- -	-	-	-	
[Ni({SB-2). $C_5H_6N_2$]	10	-	-	-	-
[Ni({SB-2). $C_2H_8N_2$]	17	-	-	-	-
[Co(SB-2). $C_5H_6N_2$]	8 -	-	-	-	
[Co(SB-2).$C_6H_8N_2$]	25	-	-	9	-

Table 4 : Toxicity studies on albino rats

Group no.	Basal diet	Initial weight of (the rats (gm)	Samples (lower doses) were administered 0.1 Ml/day/rat	Weight (gm) or death occurred/day				
				1st day	2nd day	3rd day	4th day	5th day
1	+	43	A	40	38	Dead	-	-
2	+	45	B	44	39	Dead	-	-
3	+	38.5	C	37	36	31	28	Dead
4	+	32	D	32	31	31.5	29	Dead
5	+	34	-	35.5	37	39	42	44.5

\+ indicates diet added; - = indicates sample not added.
A = [Cu(SB-2). $C_5H_6N_2$]; C = [Ni(SB-2). $C_2H_8N_2$]; B = K[Cu(SB-1) (SCN)]; D = [Ni(SB-2). $C_5H_6N_2$].

(0.005 mol) was added to the metal-Schiff base solution. The resulting mixture was boiled on a water-bath for 5 min. and cooled. The complexes were separated, washed with hot ethanol and dried in vacuo over P_4O_{10}. The prepared complexes were obtained in pure form after the treatment of column chromatography which shows a single spot in TLC in all the cases.

Results and Discussion

The complexes were characterized on the basis of elemental analysis, melting point, conductance, magnetic measurement, infrared and electronic spectra. The physico-chemical study suggested the square planar structure for Cu^{+2}, Ni^{+2} and Co^{+2} complexes, Elemental analysis along with other data are presented in Table 1. The conductance values revealed that all of the complexes were of 1:1 electrolytes, (Geary, 1971). Magnetic measurement indicate that the copper complexes (1) - (4) are paramagnetic and show magnetic moment (1.89-1.95 B.M.) corresponding to one unpaired electron. The Ni complexes are all diamagnetic in nature. The Co complexes (7) - (8) have magnetic moment of 2.0 B 3.0 B.M, indicative of square planar structure (Islam, 1986).Generally more

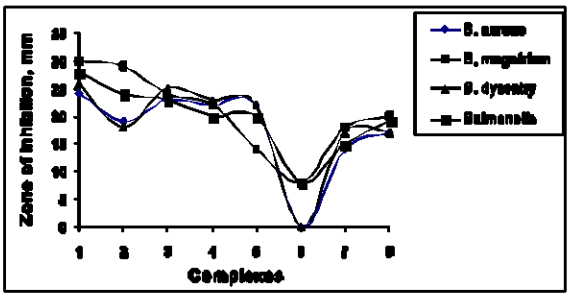


Fig. 1: Bacteriocidal activity of metal complexes.

1 = K[Cu(SB-1) (SCN)] 2 = [Cu(SB-2).$C_5H_6N_2$]
3 = [Cu(SB-2).$C_2H_8N_2$] 4 = [Cu(SB-2).$C_6H_8N_2$]
5 = [Ni(SB-2).$C_5H_6N_2$] 6 = [Ni(SB-2).$C_2H_8N_2$]
7 = [Co(SB-2).$C_5H_6N_2$] 8 = [Co(SB-2).$C_6H_8N_2$]

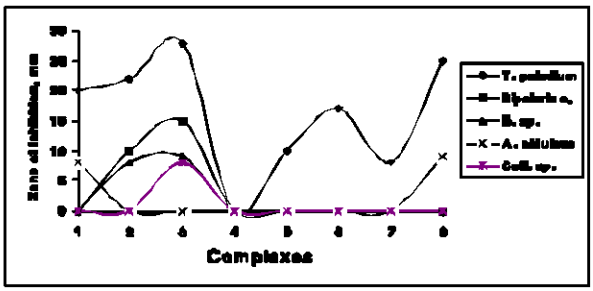


Fig. 2: Fungicidal activity of metal complexes.

1 = K[Cu(SB-1) (SCN)] 2 = [Cu(SB-2).$C_5H_6N_2$]
3 = [Cu(SB-2).$C_2H_8N_2$] 4 = [Cu(SB-2).$C_6H_8N_2$]
5 = [Ni(SB-2).$C_5H_6N_2$] 6 = [Ni(SB-2).$C_2H_8N_2$]
7 = [Co(SB-2).$C_5H_6N_2$] 8 = [Co(SB-2).$C_6H_8N_2$]

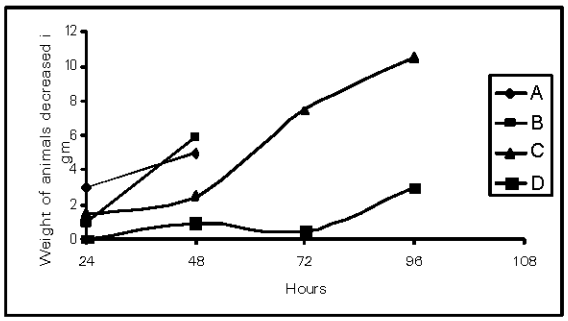


Fig. 3: A plot of weight of animals decreased per day

A = [Cu(SB-2).$C_5H_6N_2$] B = K[Cu(SB-1) (SCN)]
C = [Ni(SB-2).$C_2H_8N_2$] D = [Ni(SB-2).$C_5H_6N_2$]

susceptible the test organism, the larger is the zone of inhibition. Antimicrobial activities of the test samples are expressed by measuring the zone of inhibition observed around the area.

The results revealed that the complexes are more microbial toxic than the free metal ions or ligands. The complexes containing 2-aminopyridine and O-Phenylenediamine as secondary ligands are much more microbial active than the other complexes. Moreover, the complex K[Cu (SB-1)(SCN)] shows the highest anti-bacterial activity against all bacteria tested. Fig 1 (Table 2) show that the highest inhibition of growth occurred on complex no.1 against the bacterium *B. megatrium* and the lowest on complex no. 6 both against the bacteria *B. megatrium* and *Salmonella* sp. Fig. 1, it may be concluded that most of the complex have anti-bacterial effect except complex no. 6, which have less anti-bacterial effect.

The results of the anti-fungal activity of the complexes are recorded in Table 3. From the zone of inhibition, it is observed that all the complexes showed significant activity towards *T. paledium* sp. except [Cu(SB-2). $C_6H_8N_2$], and it is more effective among the complexes tested. It is evident form Fig. 2 that the highest anti-fungal activity was shown in the complex no. 3 against *T. paledium* (28 mm) and the lowest against *Colletotrichum* sp. (8 mm). From Fig. 2 it is clear that all the complexes shown anti-fungal activities against *T. paledium* except complex no. 4. Rest of the complexes have more or less intermediary anti-fungal effect against the tests fungi.

A plot of animal weight decreased per day (Fig.3), when these compounds were administered to the animals, onset of death in the animals was found to be quicker with higher doses, but delayed with the lower doses. Remarkably, it was observed that the animals showed the symptoms of drowsiness and general weakness before death. The complexes A and B are comparatively more toxic and/or quick acting poison than that of C and D. So all the complexes (A, B, C, D) tested might be considered as toxic complexes. From Fig. 3, (Table 4) it is shown that the administration of complex A, B, C and D, on rats, they became gradually decreased their weight on comparison with control. In case of complex A and B, the rats died on 3rd days and in case of complex C and D, the weight became reduced up to 4th days and died on 5th days of doses administrations.

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