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Synthesis, Spectral and Biological Studies of Transition Metal Complexes of 2-(4-Nitrophenylaminocarbonyl)benzoic Acid

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In this study Cr(III), Co(II), Ni(II), Cu(II) and Zn(II) complexes of 2-(4-nitrophenylaminocarbonyl)benzoic acid have been prepared and were characterized by physical, analytical and spectroscopic studies. On the basis of electronic spectra and magnetic susceptibility measurements in conjunction with infrared spectra, six coordinated octahedral structure has been proposed to Cr^{3+}, Co^{3+} and Ni^{2+} complexes. In case of Cu^{2+} and Zn^{2+}, they form four coordinated complexes. The ligand and its metal complexes have been tested for their *in vitro* antimicrobial activity against three bacterial strains, *Mycobacterium smegmatis* (gram +ve), *Escherichia coli* (gram -ve), *Pseudomonas aeuroginosa* (gram -ve) and three fungal strains, *Nigrospora oryzae*, *Aspergillus niger* and *Candida albicans*. The antimicrobial activities of the metal complexes were found to be more than those of 2-(4-nitrophenylaminocarbonyl)benzoic acid alone.

Key Words: 4-Nitroaniline, Phthalic anhydride, Metal ions, Antimicrobial activity.

INTRODUCTION

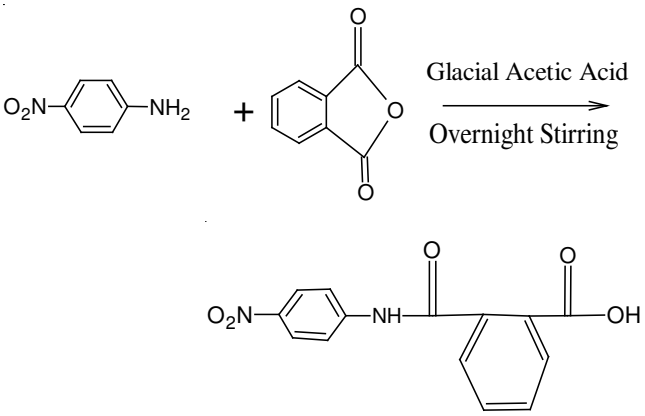
Transitions metal complexes with soft or hard donor groups have been used extensively in coordination and organometallic chemistry[1]. Reaction of coordinated ligands model systems of biological interest, analytical chemistry, agriculture and optical display devices[2-4]. Resistance to the presently accessible antibiotics has motivated the search for new agents to inhibit bacterial activity. Among such agents, metal complexes of biologically active ligands are attractive as both ligands and metal ions can interact with different steps of pathogenic life cycles[5-7]. Much work has been done by bioinorganic as well as medicinal chemists to establish the relationship between the metal ions and their complexes as antitumour and antibacterial agents[8-12]. It is however remarkable that some biologically active compounds may become more carcinostatic and bacteriostatic upon chelation[13]. There is currently a resurgency of interest in the biochemistry as well as the coordination chemistry of bivalent Cr, Co, Ni, Cu and Zn due to their biological importance.

In view of this, the present work presents the synthesis, characterization and biological activity of M^{2+} (M = Cr, Co, Ni, Cu, Zn) with 2-(4-nitrophenylaminocarbonyl)benzoic acid as ligand. Aniline derivatives have been actively investigated because of their fascinating biological and diverse ligational behaviour towards metal ions and novel structural features in their complexes[14-25].

EXPERIMENTAL

All the chemicals used were of analytical grade and were obtained from Merck. IR spectra were recorded on a spectrum 100 FTIR spectrophotometer Perkin Elmer USA. UV-Visible spectra were obtained in DMSO by Agilent 8453-spectrophotometer using ChemStation software. Melting points were determined by a melting point meter M5000 from KRUSS Optronic.

Synthesis of ligand: 2-(4-Nitrophenylaminocarbonyl)-benzoic acid was made as described previously[19,26] (**Scheme-I**).



Scheme-I: Synthesis of 2-(4-nitrophenylaminocarbonyl)benzoic acid

Synthesis of metal complexes

Synthesis of Cu(II)-complex: 2-(4-Nitrophenylaminocarbonyl)benzoic acid (0.01 mol, 0.286 g) was suspended in acetone (100 mL) in a 250 mL two necked round bottom flask and then treated with triethylamine (0.45 mL). The mixture was refluxed for 2-3 h. Then $CuCl_2 \cdot 2H_2O$ (0.005 mol) was added to the reaction flask with constant stirring and the reaction mixture was again refluxed for 8-10 h. A dark green precipitate was formed. The solvent was evaporated and the remaining mass was recrystallized from $CHCl_3$/ *n*-hexane mixture (1:1) and was stored in a moisture-free environment.

The Ni(II), Cr(II), Co(II) and Zn(II) complexes were made similarly from the hydrated chlorides.

Biological studies

Antibacterial studies: The ligand as well as its metal complexes were screened against *Mycobacterium smegmatis*, *Escherichia coli* and *Pseudomonas aeuroginosa* by using the paper disc diffusion method[17], nutrient agar medium (peptone, beef extract, NaCl and agar-agar) and 5 mm diameter paper discs (Whatman No. 1). The compounds *i.e.*, ligand precursor and its complexes, were dissolved (30 µg) in DMF (0.01 mL). The filter paper disc were soaked in these solutions, dried and then placed in petri plates previously seeded with the test organisms. The plates were incubated for 24 h at 37 ºC and the inhibition zone in the region of each disc was measured.

Antifungal activities: The antifungal activity of the ligand and its metal complexes were evaluated against *Nigrospora oryzae*, *Aspergillus niger* and *Candida albicans* by the agar plate technique using the reported method[27].

RESULTS AND DISCUSSION

2-(4-Nitrophenylaminocarbonyl)benzoic acid reacted with solutions of metal ions to give coloured amorphous complexes of general formulae ML_2 and $ML_2(H_2O)_2$ as shown by elemental analysis (Table-1). They were insoluble in common organic solvents and soluble in DMF and DMSO[23].

Electronic spectral analysis: Data obtained from the electronic spectroscopy are tabulated in Table-2. For the chromium complex two peaks at 15898 and 23770 cm^{-1} were assigned to $^4A_{2g} \rightarrow {}^4T_{2g}$ and $^4A_{2g} \rightarrow {}^4T_{1g}$(f) *d-d* transitions, respectively. The appearance of these two bands confirms octahedral (O_h) geometry for this complex. The electronic spectrum of the Cu(II)-complex showed bands at 31055 and 19820 cm^{-1} and are assigned, respectively, to charge transfer and $E_g \leftarrow {}^2T_{2g}$ transitions. These two band are in agreement with those usually observed for square planar Cu(II)-complexes[28]. The electronic spectrum of the Co(II) complex showed bands at 7373, 17213 and 20613 cm^{-1} assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ transitions, respectively, corresponding to octahedral geometry. The Ni(II)-complex also exhibited three spin-allowed bands at 26312, 15433 and 9789 cm^{-1}, assigned, respectively, to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{2g}(P)$ transitions, consistent with well defined octahedral geometry. The diamagnetic Zn(II)-complex did not show any *d-d* transition.

Magnetic moment: The magnetic moment value for the Cr(III)-complex was found to be 3.81 BM (Table-2) which suggests an octahedral geometry for this complex[29]. The magnetic moment for value Cu(II)-complex (1.79 BM) also favours its square planar geometry. The magnetic moment value (3.12 BM) showed two unpaired electron per Ni(II) ion and is indicative of octahedral environment for Ni(II). Similarly the magnetic moment of the Co(II)-complex (4.76 BM) is consistent with octahedral geometry[29]. The Zn(II) complex was found to be diamagnetic.

IR spectral analysis: The IR stretching frequencies and assignments are given in Table-3. A carboxylate ligand can bind to the metal in monodentate or bidentate fashion, resulting in changes in the relativepositions of the asymmetric and symmetric stretching vibrations[30]. The IR spectra of the complexes give a separation value ($\Delta\nu$) less than 200 cm^{-1}, which confirms that the coordination is bidentate[31,32]. A strong band at 3479-3437 cm^{-1}, characteristic of the NH group and present in the spectrum of the ligand precursor persists in the

TABLE-1
ELEMENTAL ANALYSIS DATA OF LIGAND AND ITS METAL COMPLEXES

Compound	C % obs. (calcd.)	H % obs. (calcd.)	N % obs. (calcd.)	M % obs. (calcd.)
Ligand	58.43 (58.95)	3.07 (3.16)	9.63 (9.82)	–
Cr(III)-complex	50.87 (51.09)	2.33 (2.73)	8.23 (8.51)	7.77 (7.90)
Ni(II)-complex	50.34 (50.57)	2.57 (2.71)	8.19 (8.42)	8.45 (8.83)
Co(II)-complex	50.43 (50.55)	2.67 (2.70)	8.61 (8.41)	8.47 (8.86)
Cu(II)-complex	52.87 (53.06)	2.54 (2.84)	8.43 (8.84)	10.56 (11.14)
Zn(II)-complex	52.30 (52.90)	2.67 (2.83)	8.57 (8.81)	11.10 (11.47)

Ligand: 2-(4-Nitrophenylaminocarbonyl)benzoic acid.

TABLE-2
PHYSICAL PROPERTIES OF LIGAND AND ITS METAL COMPLEXES

Compound	Colour	Physical state	m.p. (ºC)	μ_{eff} (BM)	Conductance (µS/cm)	Yield (%)	λ_{max} (cm^{-1})
Ligand	Yellowish brown	Crystalline	230	–	–	75	–
Cr(III)-complex	Dark green	Amorphous	>280	3.81	121	68	15898, 23770
Ni(II)-complex	Brownish yellow	Amorphous	>290	3.12	19	70	6312, 15433, 9789
Co(II)-complex	Light pink	Amorphous	>291	4.76	33	56	7373, 17213, 20613
Cu(II)-complex	Green	Amorphous	>285	1.79	12	62	31055, 19820
Zn(II)-complex	White	Amorphous	>267	Diamagnetic	14	43	27123

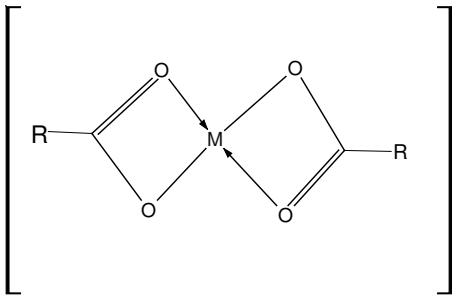
Ligand: 2-(4-nitrophenylaminocarbonyl)benzoic acid.

TABLE-3
IR STRETCHING FREQUENCIES (cm^{-1}) OF THE VARIOUS FUNCTIONAL GROUPS OF LIGAND AND ITS METAL COMPLEXES

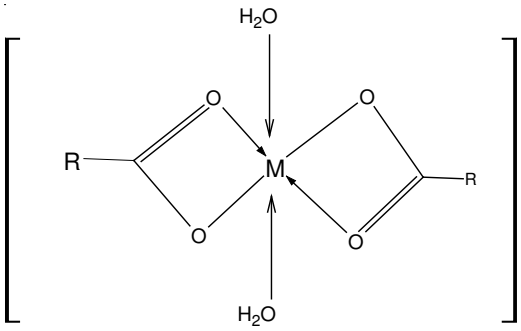
Compound	C=O (cm^{-1})	NH (cm^{-1})	(COO^-) asym. (cm^{-1})	(COO^-) sym (cm^{-1})	Δν (cm^{-1})	(OH) (cm^{-1})	C-H (cm^{-1})	N-O asym. (cm^{-1})	H_2O (cm^{-1})	C-O-C (cm^{-1})	C-N (cm^{-1})
4-Nitroaniline	–	3479	–	–	–	–	794	1504	–	–	–
Phthalic anhydride	1762	–	–	–	–	–	798	–	–	1280	–
Ligand	1702	3379	1595	1377	218	2853	798	1518	–	–	1306
Cr(III)-complex	1730	3373	1553	1415	138	–	794	1525	3667	–	1295
Ni(II)-complex	1729	3378	1566	1381	185	–	709	1519	3643	–	1300
Co(II)-complex	1728	3376	1550	1378	172	–	783	1521	3455	–	1308
Cu(II)-complex	1729	3378	1552	1384	168	–	708	1514	–	–	1290
Zn(II)-complex	1732	3370	1559	1376	183	–	722	1513	–	–	1298

Ligand: 2-(4-Nitrophenylaminocarbonyl)benzoic acid. (–): Absent.

spectra of all metal complexes. This shows that NH group does not participate *via* intra or intermolecular interactions[33]. Peaks above 3400 cm^{-1} in the Co(II), Ni(II) and Cr(II) complexes, indicated the presence of coordinated water[17]. These were not present in the Cu(II) and Zn(II) complexes, suggesting that the coordination number in these compounds is only four. All the above discussion is consistent with the structures in Fig. 1.



M=Cu^{2+},Zn^{2+}



M=Cr^{3+},Co^{2+}, Ni^{2+}

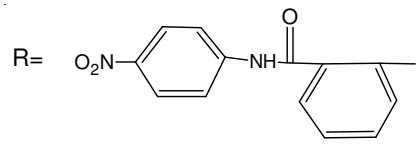


Fig. 1. Proposed structures of metal complexes

Biological studies

Antibacterial studies: Metal complexes were screened against *Mycobacterium smegmatis*, *Escherichia coli* and *Pseudomonas aeuroginosa* by the paper disc diffusion method[17]. Studies of *in vitro* antibacterial activity of metal complexes exhibit appreciable antibacterial activity (Table-4) that is in accordance with our previous studies[34,35]. This enhanced antibacterial activity may be due to an increase in cell permeability of the lipophilic metal conjugates, which allows intracellular drug accumulation. It is also likely that the intracellular reduction of these metal compounds may lead to higher cytoplasmic concentration of metal species, which prove lethal for bacteria.

TABLE-4
ANTIBACTERIAL ACTIVITY OF LIGAND AND ITS METAL COMPLEXES

Compound	Bacterial strain inhibition zone (mm)		
	E. coli	*Pseudomonas aeuroginosa*	*Mycobacterium smegmatis*
Sulphadimidine	+++	+++	++
Ligand	+	–	+
Cr(III)-complex	+ +	+	+
Ni(II)-complex	+	+ +	–
Co(II)-complex	+ +	+ +	+ +
Cu(II)-complex	+ +	+ +	+ + +
Zn(II)-complex	+ + +	+	+ +

Ligand: 2-(4-Nitrophenylaminocarbonyl)benzoic acid. Inhibition zone = + 0-5 mm, ++ 6-0 mm, +++, 11-15mm, – inactive.

TABLE-5
ANTIFUNGAL ACTIVITY OF LIGAND AND ITS METAL COMPLEXES

Compound	*Nigrospora oryzae*			*Aspergillus niger*			*Candida albicans*		
	100 (μg/mL)	500 (μg/mL)	1000 (μg/mL)	100 (μg/mL)	500 (μg/mL)	1000 (μg/mL)	100 (μg/mL)	500 (μg/mL)	1000 (μg/mL)
Ketoconazole	10.5	15.8	27.9	15.5	23.8	31.9	12.3	17.7	33.9
Ligand	7.2	12.1	21.4	–	2.4	5.6	10.3	15.3	22.2
Cr(III)-complex	10.2	14.3	16.0	17.2	23.0	26.5	19.5	33.6	45.2
Ni(II)-complex	9.0	13.5	25.8	10.2	14.5	19.4	22.4	38.3	56.2
Co(II)-complex	15.2	33.5	54.4	16.2	30.3	44.5	13.3	24.5	34.4
Cu(II)-complex	22.6	47.5	63.4	17.3	27.7	54.2	21.5	35.2	49.4
Zn(II)-complex	21.2	35.5	53.4	15.2	28.3	39.5	13.3	29.5	39.4

Ligand: 2-(4-Nitrophenylaminocarbonyl)benzoic acid. (–): Inactive.

Antifungal studies: The antifungal activity of all the synthesized metal complexes was determined against three fungal strains namely; *Nigrospora oryzae*, *Aspergillus niger* and *Candida albicans* by the agar plate technique and the results are recorded in Table-5. It was observed that metal complexes are more active than the corresponding ligand and toxicity increases with increasing concentration[36].

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