

Research Paper :

Complexes of transition metals with tridentate N-(2-thiazole) benzamide-2'-carboxylic acid and oxine

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ABSTRACT

Complexes of the type $[ML_2]$ and $[MLL'.H_2O]$ [where, M = Cu(II), Ni(II), Co(II), Zn(II) and Mn(II); HL = N-(2-thiazole)-2'-carboxylic acid; and L' = oxine] have been synthesized. The complexes are octahedral in nature. The synthesized ligand behaves as tridentate OON donor. The characterization of the complexes has been done on the basis of analytical, molar conductance, magnetic susceptibility, molecular weight, infrared and electronic spectral data. Antibacterial activity of these ligands and their metal complexes has been determined on gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria at 37°C and antifungal activity has been determined on common fungi viz., *Aspergillus niger*, *Aspergillus nidulense* and *Candida albicans* at 28°C. It has been found that the biocidal activity of these ligands increases on being coordinated with suitable metal ion.

Key words : I.R./electronic spectra/mixed ligand complexes/ternary complexes/metal chelates

Oxine, heterocyclic acids and their derivatives have long been established as potential antimicrobial agents and drugs^{1,2}. The information about the role of metal complexes in biological systems, their concentration and presence in different equilibrium is of immense importance. Conflicting reports exist in the literature about the N, S and O, donor ligands and their transition metal complexes which play an important role in the biocidal action of biological systems and their metal complexes have been found more biological active in comparison to either the free ligands or the involved metal ions³⁻⁸. Similar observations have been noted on the oxine⁹ and its transition metal complexes¹⁰.

In view of the biological importance of the thiazole moiety, several workers have studied the coordination behavior of simple and substituted thiazoles with transition¹¹⁻¹⁴ and non transition metal ions¹⁵. In continuation of our earlier work¹⁶⁻²⁶, it was therefore, thought worthwhile to undertake studies on binary and ternary metal complexes involving N-(2-thiazole) benzamide-2'-carboxylic acid and oxine as ligand with a view to explore their biocidal activity.

MATERIALS AND METHODS

All the chemicals used were of analytical reagent grade.

Synthesis of N-(2-thiazole) benzamide-2'-carboxylic acid and metal chelates :

N-(2-thiazole) benzamide-2'-carboxylic acid (TBCA)

was synthesized by constant stirring followed by refluxing (5 hours) equimolar amount of phthalic anhydride and 2-amino thiazole. The compound thus obtained was filtered, washed with benzene and recrystallised (melting point 184°C). The metal complexes have been synthesized as reported earlier¹⁷.

Physical measurements :

The infrared spectra of the ligands and their corresponding metal complexes were recorded on Perkin-Elmer-521 spectrophotometer. The electronic spectra of metal complexes were recorded on Cary-14 spectrophotometer using DMSO as solvent. Molar conductance of the complexes was measured in their DMSO solution using Toshniwal conductivity meter. Elemental analyses were carried out by microanalytical technique and metal contents were estimated by standard methods²⁷. The molecular weight of the compounds was determined by cryoscopic method in dimethylsulfoxide (DMSO). Magnetic measurements were carried out at room temperature by Gouy's method. The values were corrected for diamagnetism by applying Pascal's constant. Thermal gravimetric analysis was carried out at Regional Sophisticated Instrumentation Center, Nagpur in a constant flow of nitrogen keeping the heating rate 15°C min⁻¹ for each run.

RESULTS AND DISCUSSION

The results obtained from the present investigation are below :

Elemental analyses, molecular weight determination and conductance measurement :

The complexes were found thermally stable and insoluble in water. The molar conductance of the complexes in DMSO (10^{-3} M) solution was found in the range $0.02-2.0 \text{ ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$, indicating the non-electrolytic nature²⁸. The 1:2 type of stoichiometry in the case of binary complexes and 1:1:1 type of stoichiometry in the case of ternary complexes were concluded from their elemental analyses and molecular weight measurement data (Table 1). The presence of water molecule is confirmed by thermal gravimetric analysis and infrared spectra of the complexes.

Thermalgravimetric analysis :

On gradual heating above the room temperature, the hydrated metal complexes dehydrated completely within the temperature range $110-165^\circ\text{C}$. The complexes were found thermally stable and decomposed in the temperature range $280-470^\circ\text{C}$. The resultant products were the metal hydroxides in all cases. The corresponding weight loss in the dehydration and decomposition process is well in agreement with the calculated values.

Infrared studies :

The appearance of new bands around $3,580-3,450 \text{ cm}^{-1}$ and $1,575 \text{ cm}^{-1}$ indicate the antisymmetric and symmetric OH stretching and H-OH bending modes. The amide I band appearing at $1,735 \text{ cm}^{-1}$ in case of ligand (TBCA) shifted to lower wave number (25 cm^{-1}) in the complexes, indicating coordination through carbonyl oxygen atom of the amide group²⁹. A slight decrease in the NH (amide II) band is observed, supporting the involvement of carbonyl oxygen in bonding. The NH band at $3,150 \text{ cm}^{-1}$ remain unaffected in the case of complexes (involving TBCA as ligand), indicating that imine nitrogen is not forming any bond with metal ion. The carboxylic group stretching frequency of TBCA is lowered from $1,680$ to $1,660 \text{ cm}^{-1}$ showing the coordination of carboxylic group³⁰. A band in the region $1,535-1,475 \text{ cm}^{-1}$ occurred due to the presence of thiazole ring in TBCA. The spectral features are indicative of non-involvement of thiazole sulfur in bonding³¹. The OH (phenolic) stretching frequency at $3,270 \text{ cm}^{-1}$ in free oxine is absent in the spectra of $\text{M}[\text{TBCA}][\text{OX}]\cdot\text{H}_2\text{O}$ complexes, indicating the involvement of phenolic group in complexation. A band at $1,500 \text{ cm}^{-1}$ may be assigned to C = N bond. This band is

Table 1 : Elemental analysis, magnetic moment and molecular weight data of ligand and metal complexes

Compound	Analysis (Found/calculated)					$\mu_{\text{eff.}}$ B.M. 303°K	Molecular weight (Found/calcd.)
	C	H	N	S	M		
TBC	53.25 (53.22)	3.27 (3.25)	11.24 (11.28)	12.87 (12.92)	-	-	241 (248)
Cu [TBCA] ₂	47.29 (47.35)	2.51 (2.53)	10.08 (10.04)	11.51 (11.49)	11.31 (11.38)	1.96	549 (558)
Ni [TBCA] ₂	47.42 (47.76)	2.57 (2.55)	10.08 (10.13)	11.61 (11.59)	10.55 (10.61)	3.09	545 (553)
Co [TBCA] ₂	47.79 (47.74)	2.58 (2.55)	10.15 (10.12)	11.51 (11.58)	10.58 (10.65)	4.95	542 (553)
Zn [TBCA] ₂	47.21 (47.19)	2.55 (2.52)	10.53 (10.01)	17.09 (17.14)	11.62 (11.68)	Diam.	551 (559)
Mn [TBCA] ₂	48.12 (48.09)	2.61 (2.57)	10.23 (10.19)	11.72 (11.67)	9.89 (9.99)	4.91	538 (549)
Cu [TBCA][OX], H ₂ O	50.11 (50.09)	3.22 (3.19)	8.85 (8.88)	6.82 (6.78)	13.37 (13.43)	2.02	466 (473)
Ni [TBCA][OX], H ₂ O	51.35 (51.31)	3.23 (3.22)	8.92 (8.97)	6.79 (6.85)	12.43 (12.54)	3.13	460 (468)
Co [TBCA][OX], H ₂ O	51.54 (51.29)	3.19 (3.23)	8.91 (8.97)	6.71 (6.68)	12.63 (12.58)	5.05	455 (468)
Zn [TBCA][OX], H ₂ O	50.58 (50.59)	3.21 (3.18)	8.90 (8.85)	6.69 (6.75)	13.71 (13.77)	Diam.	465 (474)
Mn [TBCA][OX], H ₂ O	51.82 (51.73)	3.19 (3.25)	9.09 (9.05)	6.83 (6.90)	11.77 (11.83)	4.97	456 (464)

lowered in the case of metal complexes $M[TBCA]_2$ and $M[TBCA][OX].H_2O$ probably due to the formation of M-N bond. The strong bands in the region 1,175-1,125 cm^{-1} depict the presence of coordinated oxine³². Some new bands which were absent in the spectra of free ligands, have been observed at 600-400 cm^{-1} in the spectra of complexes. The appearance of these bands in the region 480-460 and 430-400 cm^{-1} , is probably due to the formation of M-O and M-N bond respectively³³. No M-S bond could be observed in $M[TCBA]_2$ and $M[TBCA][OX].H_2O$ complexes, which exhibits that S is not taking part in complexation³⁴.

Electronic spectra and magnetic studies :

The magnetic moments of Cu(II), Ni(II), Co(II) and Mn(II) complexes calculated from corrected magnetic susceptibility and electronic spectral data are given in Table 1 and 2. The observed magnetic moment of the complexes suggests the octahedral geometry around the metal ion³⁵. The electronic spectra of the copper complexes show only band around 14,000 cm^{-1} due to ${}^2E_g \rightarrow {}^2T_{2g}$ transitions³⁶. Three bands observed ~8,500, 14,200 and 26,200 cm^{-1} in the spectra of nickel complexes, due to three spin allowed transitions from ${}^3A_{2g} \rightarrow {}^3T_{2g}(F)$, ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and ${}^3A_{2g} \rightarrow {}^3T_{1g}(P)$, respectively in octahedral environment³⁷. Three bands observed in the

spectra of cobalt complexes around 8,300, 16,300 and 22,000 cm^{-1} , may be due to ${}^4T_{1g} \rightarrow {}^4T_{2g}(F)$, ${}^4T_{1g} \rightarrow {}^4A_{2g}(F)$ and ${}^4T_{1g} \rightarrow {}^4T_{1g}(P)$ transitions, respectively which supported the octahedral environment. Three bands around 19,500, 23,400 and 28,500 cm^{-1} are due to the transitions ${}^6A_{1g} \rightarrow {}^4T_{1g}(G)$, ${}^6A_{1g} \rightarrow {}^4E_g$, ${}^4A_{1g}(G)$ and ${}^6A_{1g} \rightarrow {}^4E_g(D)$, respectively for manganese complexes supporting the octahedral geometry³⁷. The ligand field parameters Dq, B, b, LFSE and % covalency have been evaluated (Table 2) for the studied complexes. The Racah interelectronic repulsion parameter is less than free ion value suggesting considerable covalent character of the bond. The calculated values of n_2/n_1 ratio is within the range expected for octahedral environment³⁸.

On the basis of elemental analysis, infrared spectra, molar conductance and molecular weight determination data, the zinc complexes were proposed to have an octahedral geometry.

Antibacterial and antifungal activity :

To study the microbial properties of potentially active substances *in vitro*, a number of methods³⁹ have been employed with their limitations and disadvantages. Irrespective of the methods given, however, following general and necessary conditions have to be maintained in each case.

Table 2 : Electronic spectral data of metal complexes

Complex	Band maxima	Dq cm^{-1}	B cm^{-1}	β cm^{-1}	LFSE $k.cal.mol^{-1}$	ν_2/ν_1	% covalency (δ)
Cu[TBCA] ₂	14,044	1,404	-	-	24.068	-	-
Ni[TBCA] ₂	8,586 14,120 26,230	858	972	0.933	29.417	1.644	7.181
Co[TBCA] ₂	8,530 16,366 21,551	783	821	0.845	13.422	1.918	18.343
Mn[TBCA] ₂	19,245 23,876 28,350	702	639	0.665	-	-	50.376
Cu[TBCA][OX].H ₂ O	14,140	1,414	-	-	24.240	-	-
Ni[TBCA][OX].H ₂ O	8,482 14,238 26,155	848	996	0.956	29.074	1.678	4.602
Co[TBCA][OX].H ₂ O	8,273 16,310 22,145	803	909	0.936	13.765	1.971	6.837
Mn[TBCA][OX].H ₂ O	19,722 23,238 28,880	732	806	0.839	-	-	19.189

– The substance under examination is brought in an intimate contact with microorganism against which the activity is to be studied.

– Favourable conditions have to be maintained for the optimum growth of the microorganism in absence of other antimicrobial agent except the substance under examination in suitable growth media.

– To escape from the environmental contaminations, all the operations have to be conducted using aseptic technique⁴⁰.

For the most satisfactory growth of microorganism, the proper temperature, pH, necessary nutrients and growth media free from other microorganism have been provided for the preparation of culture of pathogenic bacteria and fungi, using aseptic technique⁴⁰. The culture media used for the slant and broth was sterilized by moist heat sterilization method⁴¹. All the utensils used were sterilized by suitable methods. The incubating period for bacteria was kept 24 hours at 37°C temperature and for fungi, *Aspergillus niger*,

Aspergillus nidulense for 96 hours at 28°C and *Candida albicans* for 48 hours at 28°C.

Culture media for growing bacteria⁴² :

Peptone	0.6%
Pancreatic digest of casein	0.4%
Yeast extract	0.3%

Beaf extract	0.15%
Dextrose	0.1%
Agar(only for slant)	1.5%
Water to make total volume	100 ml
pH adjusted to 6.5 to 6.6	

Culture media for growing fungi⁴² :

Peptone	1%
Dextrose	2%
Agar(only for slant)	2.5%
Water to make total volume	100 ml
pH adjusted to 5.4	

Serial dilution method^{42,43} was adopted to study the antibacterial and antifungal activity of the compounds. In this method, graded dilutions of the test compound in a nutrient medium are inoculated with the organism under examination using aseptic technique and incubated under suitable conditions. The minimum concentration of test compound preventing detectable growth in MIC, the antibacterial and antifungal activity of binary, ternary complexes and involved ligands have been tested on said bacteria and fungi. A close and comparative study of Table 3 reveal that the ligands are active against the bacteria and fungi used. In these investigations, it is found that the activity of oxine is enhanced when it is chelated with suitable metal ion. It has been reported¹ that 1:2 chelate of metal-oxine penetrates the cell and dissociates 1:1 half

Table 3 : Antibacterial and antifungal activity of the ligands and metal complexes*

Compound	Bacteria		Fungi		
	<i>S. aureus</i>	<i>E. coli</i>	<i>A. niger</i>	<i>A. nidulense</i>	<i>Calbicans</i>
OX	290.02	277.48	292.91	315.44	319.97
TBCA	255.86	230.68	238.47	277.46	235.42
Cu [OX].H ₂ O	99.77	96.91	70.54	82.83	89.15
Ni [OX].H ₂ O	79.68	83.20	54.49	66.10	73.91
Co [OX].H ₂ O	66.97	52.52	39.53	54.29	56.17
Zn [OX].H ₂ O	102.52	102.95	91.24	98.09	92.01
Mn[OX].H ₂ O	100.13	99.67	86.13	90.24	91.05
Cu [TBCA] ₂	112.59	100.12	95.24	92.12	91.23
Ni [TBCA] ₂	100.29	91.05	83.87	80.51	81.66
Co [TBCA] ₂	79.12	76.51	73.28	70.11	72.46
Zn [TBCA] ₂	129.39	116.25	113.24	115.58	114.20
Mn[TBCA] ₂	120.25	111.58	101.68	103.86	105.38
Cu [TBCA][OX].H ₂ O	38.55	37.13	31.24	31.36	34.54
Ni [TBCA][OX].H ₂ O	31.28	30.43	29.65	29.87	30.38
Co [TBCA][OX].H ₂ O	28.05	24.18	23.13	25.46	26.69
Zn [TBCA][OX].H ₂ O	45.23	40.56	38.12	42.65	41.87
Mn[TBCA][OX].H ₂ O	42.11	38.46	36.56	40.12	40.68

TBCA = N-(2thiazole) benzamide-2'carbopxylic acid ; OX = Oxine

* Values are minimum inhibitory concentration in µmol/L

chelate and free oxine. The half chelate would become the toxic entity. Gershon and Parmegiani⁴ supported the above mechanism and indicated that biocidal activity of metal-oxine is not due to the release of oxine within the cell but due to the dissociated 1:1 complex such as that reported¹. The comparable activity of the ternary complexes to that of binary complexes may be due to the dissociation of the complexes at the site of action.

Both the 1:1 cationic complexes thus formed may be acting as toxic moieties at the site of action reinforcing the total activity. Thus in the ternary complexes in addition to 1:1 metal-oxine, 1:1 metal-TBCA may also act as toxic agent which increases the activity. A comparatively faster diffusion of the complex as a whole through the cells may be one of the important factor. It is evident that these complexes are stable and chemically inert having no specific Center

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