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Anil Kumar Bansal, Rajesh Kumar Yadav, Raaz Maheshwari, Babita Gupta and Megha Bansal

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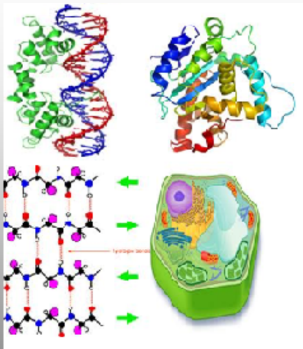

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RESEARCH PAPER

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Synthesis, Characterization and Biocidal Studies of Some Newly Synthesized Medicinally Important Compounds

Anil Kumar Bansal*, Rajesh Kumar Yadav, Raaz Maheshwari***, Babita Gupta**** and Megha Bansal****
Department of Chemistry, S.S. Jain Subodh P.G. College, Rambagh Circle Jaipur (India)*
Department of Environmental Science, S.S. Jain Subodh P.G. College, Rambagh Circle Jaipur** (India). Department of Chemistry, SBRMGC, Nagaur, Rajasthan (India) ***,
Department of Chemistry, University of Rajasthan, Jaipur (India) ****

ABSTRACT

Transition metal complexes containing bidentate N, O donor ligand i.e. 5-isopropenyl-2-methyl-2-cyclohexenoxime (IPMCO) and 5-isopropenyl-2-methyl-2-cyclohexenosemicarbazone (IPMCSC) have been synthesized and characterized by elemental analysis, molar conductivity, magnetic susceptibility measurements and various spectral (IR, electronic and ^{1}H NMR) studies. All the metal complexes are (ML_2Cl_2) type, where M=Co^{II}, Ni^{II}, Cu^{II} and L=IPMCO, IPMCSC. All the complexes are of high spin type and found to have six co-ordinated geometry. The biological activities of the ligand and metal complexes have been screened in vitro against bacteria and pathogenic fungi to study capacity to inhibit their growth. The complexes showed enhanced values than those of ligand as IPMCO, IPMCSC.

Key words: Carvone, Hydroxylamine Hydrochloride, Semicarbazide Hydrochloride, Biocidal Activities.

INTRODUCTION

The co-ordination and organometalic chemistry of metal nitrogen, metal oxygen and metal sulfur bonded compounds have come to occupy a prominent position in the researches due to their economical importance in the field of agriculture (Reddy and Reddy, 2000), medicinal and industrial chemistry.

The rapid development in co-ordination chemistry of transition metal is mainly attributed to the industry, economic and environmental importance of transition of metal and significant biological importance of metal complexes (Offiong, et al. 2000). Very few system are reported, showing the relationship between thermal stability metal chelates and structure of chelating reagents (Wendlandt, 1957), Hill et al. 1976 studied the thermal properties of metal chelates with different type of complexing ligands. Such studies on the thermal decomposition and kinetics of metal chelates with azomethine ligand have been done by few workers (Paradeshi and Bhobe, 1983). Azomethine and their transition metal complexes have remarkable potential for inhibitory growth to various pathogenic, microorganisms and this property has been exploited in pharmacological application (Keefer, 1984). The biological properties of semicarbazone, thiosemicarbazone and oximes are often related to the metal ion coordination. Semicarbazone and oximes derivatives of various aldehyde, ketone and their transition metal complexes possess wide biological activities (Patole et al. 2004). The copper complexes of furan oxime, semicarbazone and thiosemicarbazone derivatives are found to be potent cytotoxic in both murine and human tissue cultured cell lines as well as tumors (Hall et al. 1997, West et al, 1993 and West et al, 1998). The coordinating properties of some semi carbazone metallic complexes have also been studied. Previously, authors have reported spectral and structural studies of oxovandium (IV) and dioxouranium (VI) complexes of some acyclic monoterpene constituents of essential oil (Sharma et al. 2003). It is well known fact that both the transition elements and essential oils play important role in human life. In this paper, we report the synthesis, characterzation and biocidal studies of new metallic complexes obtained from transition metal chloride and the oxime, semicarbazone derivatives of 5-isopropenyl-2-methyl-1-cyclohexenone (Carvone). Carvon is cyclic monoterpene and important constituent of spearmint and caraway oil.

EXPERIMENTAL

Physical measurements

The IR spectra were recorded with KBr pellets in the 4002-225 cm^{-1} range on a Shimadzu (Japan) FT-IR 8400 spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol 300 MHz FT-NMR system and electronic spectra were recorded on a varioancary 50 Bio U.V./visible spectrophotometer (Department of Chemistry, University of Rajasthn, Jaipur). Magnetic moments were measured on a Gouy balance. Molar conductances were measured in 10^{-4} M DMF on a □p-based conductivity meter model 1601/E. Elemental analyses were performed at the CDRI Lucknow. Metal content was measured by complexometric titration with EDTA (Vogel's, 1985). Chloride content was determined by the Volhard'smethod (Vogel's, 1989).

Antibacterial activities of these compounds on selected bacteria (*Staphylococcus aureus* Gram (+), *E. coli* Gram (–) and selected fungi (*A. niger*, *A. flavus*) were carried out using the filter paper scrap diffusion method (Bryant, 1988).

MATERIAL AND METHODS

All the metal salts were of analar grade (BDH) and due to Merck. They were used in the form of chlorides without further purification. Carvon was likewise purchased form Merck and used as supplied. Semicarbazide hydrochloride purchased from BDH also and recrystallized from hot H_2O. Solvents were purified by the method as mentioned in the literature.

Synthesis of 5-isopropenyl-2-methyl-2-cyclohexenoxime (IPMCO)

An aqueous solution of ($50cm^3$) hydroxylamine hydrochloride (0.6949g/10 mmol) and crystalline NaOH (0.23g/10 mmol) was added dropwise with constant stirring to an ethanolic solution ($50cm^3$) of 5-isopropenyl-2-methyl-2-cyclohexenene (Carvone) (1.5022 g/10mmol) and the reaction mixture was stirred (on slightly heating) at about 10-12 hrs. After this, reaction mixture was cooled at 0°C and IPMCO precipated as white slacked solid upon cooling. The mixture was filtered of and recrystallized from a H_2O-EtOH mixture and dried on vaccuo (m.p. 80°C, yield 89%).

Synthesis of 5-isopropenyl-2-methyl-1-cyclohexenosemicarbazone (IPMCSC)

An aqueous solution of (50 cm^3) semicarbazide hydrochloride (1.1153g/10 mmol) and crystalline $MeCO_2Na$ (1.3606g/10mmol) was added dropwise with constant stirring to an ethanolic solution ($50cm^3$) of 5-isopropenyl-2-methyl-2-cyclohexenone (carvone) (1.5022g/10 mmol) and the reaction mixture was boiled under reflux on a water bath. After 2 hrs refluxing IPMCSC precipitated as white solid upon cooling. The mixture was filtered off and finally recrystallized from a H_2O-EtOH mixture and dried on vacco (m.p. 130°C, yield 85%).

Preparation of complexes

Most of complexes were prepared in anhydrous EtOH. The metal complexes were prepared by mixing a hot EtOH solution of ligand IPMCO & IPMCSC (0.02 mol) with an EtOH solution of the respective metal chloride (0.01 mmol). The reaction mixture was boiled under reflux on a water bath for 6-8 h. then allowed to cool to room temperature. The resulting solid was filtered-off, washed several times with anhydrous EtOHand dried under reduced pressure. All the complexes were synthesized by the same method.

RESULTS AND DISCUSSION

The reaction of metal chloride with ligand IPMCO (I), IPMCSC (II) in 1:2 molar ratio results in formation of complexes as Fig. I, II.

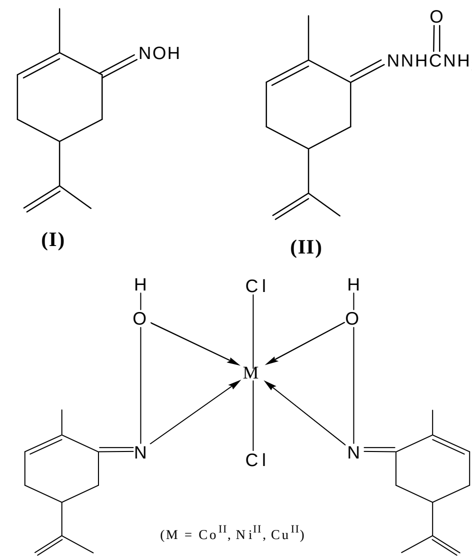

Fig. 1. Proposed structure formula for the complexes

Analytical data of the new complexes with molar conductance are given in (Table-I). All the complexes are non hygroscopic in nature, insoluble in water and soluble in common organic solvents like DMSO, DMF etc. All the newly synthesized complexes are stable at room temperature and decompose on heating at ~ 300°C.

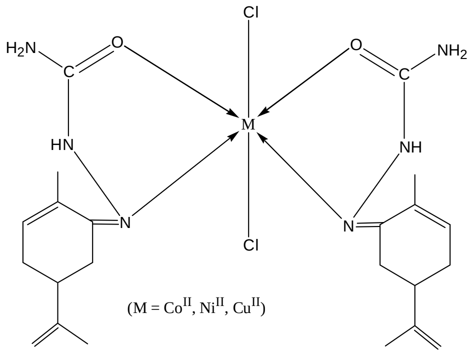

Fig. 2. Proposed structure formula for the complexes.

INFRARED SPECTRA

A comparative interpretation of the IR spectral data (Table 2) suggest that IPMCO and IPMCSC acts as bidentate ligand in the synthesized complexes using N and O as donor atom. The results are as summarized:

1. The IR spectra of IPMCO shows strong broad band at 3360-3365 cm^{-1} assigned to v (OH) str. Vibration. In the frequency range 2915-3030 cm^{-1} appears the typical band of aliphatic CH group. In the spectrum of IPMCO the v(C=C) and v(C=N) assigned two band at 1605 cm^{-1} and 1620 cm^{-1}.
2. The IR spectra of IPMCSC also show two strong band at 3470 cm^{-1}, 3280 cm^{-1} respectively to v(N–H) asymmetric and v(N–H) symmetric vibration of the terminal NH_2 group. The N–H str. Vibration of the imino group is attributed at 3315 cm^{-1}. The band at 1610 cm^{-1} is due to v(C=N) while the other at 953 cm^{-1} is assigned to v(N–H). The str. Vibration band of the carbonyl group lies at 1670 cm^{-1}.
3. The comparison between IPMCO, IPMCSC with its metal complexes allow us to determine, the co-ordinating atom is present in all the species.
4. The IPMCO and IPMCSC both acts as bidentate ligand through nitrogen atom of (C=N) group and oxygen atom of (OH) group in IPMCO and (C=O) group in IPMCSC.
5. The mode of complexation is supported by the following observation: In the IPMCO (C=N) and (OH) moved to lower wave number and in IPMCSC (C=N) and (C=O) shows downward shifts.
6. The appearance of new band for v(M–N), v(M–O), v(M–Cl) occurs in the 435-470, 340-390 and 303-312 cm^{-1} region. This indicates that N, O atom are involved in coordination.

Electronic spectra: Metal complexes of IPMCO

The magnetic moment measurement of the Co (II) complexes at RT lie in the range 4.30-5.20 B.M. corresponding to three unpaired electron. The electronic spectra of the cobalt (II) complexes exhibit absorption in the region 8693-18656 cm^{-1} which are assigned to $^4T_{1g} \rightarrow {}^4T_{2g}$ (v_1), $^4T_{1g} \rightarrow {}^4A_{2g}$ (v_2) and $^4T_{1g} \rightarrow {}^4T_{1g}$ (v_3) respectively. These transitions suggest in octahedral environment (Figgis and Lewis, 1964 and Wilkinson, and Cotton, 1988) around the cobalt ion. At RT, Ni (II) complexes show magnetic moment in the range 2.80-3.50. These values correspond to a high spin configuration and show the presence of an octahedral environment around the nickel (II) ion in the complexes. The electronic spectra of the complexes display three absorption bands in the range 9997-1625 cm^{-1} and 24867 cm^{-1}. These bands may be assigned to the three spin allowed transition: $^3A_{2g} \rightarrow {}^3T_{2g}$ (v_1), $^3A_{2g} \rightarrow {}^3T_{1g}$ (v_2) and $^3A_{2g} \rightarrow {}^3T_{1g}$ (v_3) respectively corresponding to an octahedral geometry (Lever, 1968). The magnetic moment measurement of the Cu (II) complexes at RT lie in the range 1.70-2.20 B.M. corresponding to one unpaired electron.

The electronic spectra of the copper (II) complex display bands in the range 10219-1448 cm^{-1} and one charge transfer band at 20181 cm^{-1}. These bands may be assigned to the following transition as $^2B_{1g}$□$^2A_{1g}$ (v_1), $^2B_{1g}$□^2E_g (v_3). The electronic band position is in good agreement with the distorted octahedral geometry of the Cu^{II} complexes (Lever, 1984, Dutta and Syamal, 1993). This transition suggests D_{4h} symmetry.

Metal complexes of IPMCSC

The electronic spectra of the Co (II) complexes exhibit a broad and two shoulders in 8827-21710 cm^{-1} range. These band may be assigned to $^4T_{1g}$□$^4T_{2g}$ (v_1), $^4T_{1g}$□$^4A_{2g}$ (v_2) and $^4T_{1g}$□$^4T_{1g}$ (v_3), respectively. The lower value of the v_2/v_1 may be due to the distortion of the octahedral structure (Lever, 1984). This is consistent with the very broad nature of v_1 band, which may be best assigned to the envelope of the transition from ^4E_g ($^4T_{1g}$) to components $^4B_{2g}$ and ^4E_g of $^4T_{2g}$ characteristic of a tetragonally distorted octahedral environment (Tian et al, 1995). The magnetic moment value corresponds to three unpaired electron.

The electronic spectra of Ni(II) complexes shows two well defined band in the region 10526-16642 cm^{-1}, assignable to $^3A_{2g}$ □□$^3T_{2g}$ (v_1) and $^3A_{2g}$ □□$^3T_{1g}$ ($F_{1,}$ v) transition, respectively, in octahedral structure. The third d-d transition band (v_3), which may be obscured by the more intense charge transfer band is calculated the theoretically and found to be at 24876 cm^{-1}. The magnetic moment value for nickel complex is reported in Table (I) corresponding to two unpaired electron. Hence octahedral geometry was proposed for nickel complexes (Lewis and Wilkins, 1967).

The electronic spectra of the Cu (II) complex show two characteristic bands in 14300-20800 cm^{-1} range and a charge transfer band at 34200 cm^{-1}. These bands have been assigned to the following transition in order of increasing energy: $^2B_{1g}$□$^3A_{1g}$ (v_1), $^2B_{1g}$□^2Eg (v_2) the third band being assigned to a charge transfer transition. The magnetic moment to of Cu (II) complexes corresponding to one unpaired electron. Hence a distorted octahedral geometry was proposed for the copper complex (Cassella and Gullotti, 1981).

The absorption band appearing in the UV domain is considered to the characteristic of the ligand. The assignment of n–□ and □–□* transition as being due to (C=O) group.

^{1}H NMR spectra

The ^{1}H NMR spectra of IPMCO and IPMCSC were recorded in D_6-DMSO. In the spectrum of IPMCO following signals were observed: □ 2.10 (s, 6H, 2CH$_3$), 3.22 (m, 4H, 2CH$_2$), 4.89 (t, 1H, =CH), 2.40 (m, 1H, CH), 4.95 (m, 2H, =CH$_2$), 9.76 broad (s, 1H, C=NOH).

In the spectrum of IPMCSC, following signals were recorded: □ 2.10 (s, 6H, 2CH$_3$), 3.22 (m, 4H, 2CH$_2$), 4.89 (t, 1H =CH), 2.40 (m, 1H, CH), 4.95 (m, 2H, =CH$_2$), 8.75 (s, 1H, NH), 6.53 (s, 2H, NH$_2$). The proton n.m.r. spectra did not show significant difference between ligand and its metal complexes. On the basis of above analysis the following (Fig. I, II) may be suggested for the complexes.

BIOCIDAL STUDIES

The newly synthesized complexes show antimicrobial activity on selected bacteria *Staphylococcus aureus* Gram (+) and *E. coli* Gram (–) and some selected fungi *A. niger*and *A. flavus*. The filter paper scraps diffusion method used for testing the antimicrobial activity of IPMCO, IPMCSC and its metal complexes. The results of biocidal tests on the complexes are shows in (Table 3) and reveals that the metal complexes are more potent than the parent ligand. Hence, they may serve as vehicles for activation of the ligand as principle cytotoxic species (Petering, 1973).

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Table 1: Elemental analysis and physical characteristic for IPMCO, IPMCSC and their metal complexes.

S. N.	Compound	Empirical formula	Colour	Yield (%)	Analysis (Found/Calcd) (%) C	H	N	M	Cl	Molar cond^a (□$^{-1}$ cm^{2}mol^{-1})	□□(B.M.)
1.	IPMCO	$C_{10}H_{15}ON$	White	89	72.65	9.01	8.01	-	-	-	-
					(72.72)	(9.09)	(8.48)				
2.	IPMCSC	$C_{10}H_{17}ON_3$	Yellow	85	63.70	7.89	19.89	-	-	-	-
					(63.76)	(8.21)	(20.28)				
3.	$[Co(IPMCO)_2Cl_2]$	$[Co(C_{10}H_{15}ON)_2Cl_2]$	Brown	78	51.99	5.40	5.59	12.80	14.93	0.85	4.21
					(52.18)	(6.52)	(6.08)	(12.81)	(15.43)	(0.87)	(3.88)
4.	$[Ni(IPMCO)_2Cl_2]$	$[Ni(C_{10}H_{15}ON)_2Cl_2]$	Yellowish	72	52.10	5.59	5.92	12.55	15.39	1.15	2.80
					(52.20)	(6.52)	(6.09)	(12.76)	(15.44)	(1.25)	(2.84)
5.	$[Cu(IPMCO)_2Cl_2]$	$[Cu(C_{10}H_{15}ON)_2Cl_2]$	Green	79	50.60	5.90	5.60	12.60	14.40	1.45	1.89
					(51.66)	(6.45)	(6.02)	(13.67)	(15.28)	(1.56)	(1.73)
6.	$[Co(IPMCSC)_2Cl_2]$	$[Co(C_{11}H_{17}ON_3)_2Cl_2]$	Brown	76	48.49	6.03	14.40	9.90	13.02	0.80	4.73
					(48.53)	(6.25)	(15.44)	(10.83)	(13.05)	(0.89)	(3.88)
7.	$[Ni(IPMCSC)_2Cl_2]$	$[Ni(C_{11}H_{17}ON_3)_2Cl_2]$	Green	75	47.95	5.60	14.76	9.80	12.01	1.15	2.82
					(48.55)	(6.25)	(15.44)	(10.79)	(13.05)	(1.26)	(2.84)
8.	$[Cu(IPMCSC)_2Cl_2]$	$[Cu(C_{11}H_{17}ON_3)_2Cl_2]$	Brown	73	47.80	5.89	14.32	10.90	17.96	1.49	1.92
					(48.12)	(6.19)	(15.31)	(11.58)	(12.94)	(1.54)	(1.73)

Table 2 : Main infrared absorption frequencies (cm^{-1}) and electronic spectral band (cm^{-1}) ($\square_{max}$ M^{-1}cm^{-1}) for compounds.

S. No.	Compound	I.R. Spectral vibration (cm^{-1})									Electronic spectral bands cm^{-1} ($\square_{max}$ M^{-1} cm^{-1})		
		ν(OH)	ν(NH$_2$)	ν(NH)	ν(C=O)	ν(C=N)	ν(N–N)	ν(M–N)	ν(M-O)	ν(M–Cl)			
1.	IPMCO	3365	-	-	-	1610	-	-	-	-	-	-	-
2.	IPMCSC	-	3470 3280 s	3315	1670	1615	953	-	-	-	-	-	-
3.	$[Co(IPMCO)_2Cl_2]$	3362	-	-	-	1605	-	435	345	390	8693 (53)	14476 (68)	18656 (91)
4.	$[Ni(IPMCO)_2Cl_2]$	3360	-	-	-	1595	-	420	392	390	9997 (36)	16257 (66)	24867 (121)
5.	$[Cu(IPMCO)_2Cl_2]$	3363	-	-	-	1590	-	443	377	350	10219 (62)	14448 (76)	20164 (127)
6.	$[Co(IPMCSC)_2Cl_2]$	-	3410 3240 s	3275	1655	1605	945	470	385	320	8827 (57)	14541 (73)	21055 (97)
7.	$[Ni(IPMCSC)_2Cl_2]$	-	3420 3240 s	3300	1667	1595	665	455	357	395	10526 (42)	16642 (73)	24876 (127)
8.	$[Cu(IPMCSC)_2Cl_2]$	-	3398 3245 s	3280	1697	1605	950	467	344	325	10348 (65)	14640 (81)	20234 (132)

Table 3. Antimicrobial activity data for IPMCO, IPMCSC and their complexes

S. No.	Compound	Average value of bacteria static diameter (mm)[a]			
		Bacteria		Fungal	
		S. aureus	*E. coli*	*A. niger*	*A. flaves*
1.	IPMCO	11.5	10.4	11.4	10.9
2.	IPMCSC	13.4	13.1	12.6	11.6
3.	$[Co(IPMCO)_2Cl_2]$	12.2	11.2	12.4	11.4
4.	$[Ni(IPMCO)_2Cl_2]$	15.4	13.4	14.6	16.7
5.	$[Cu(IPMCO)_2Cl_2]$	16.4	15.2	18.4	18.2
6.	$[Co(IPMCSC)_2Cl_2]$	14.6	15.2	14.2	12.4
7.	$[Ni(IPMCSC)_2Cl_2]$	17.8	18.4	16.4	14.6
8.	$[Cu(IPMCSC)_2Cl_2]$	20.6	20.5	19.6	18.9

a = Average value from four experiment

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Corresponding author: Dr. Raaz Maheshwari, Department of Chemistry, SBRMGC, Nagaur, Rajasthan (India). **Email id:** **subodhproject@yahoo.com / drraazgreenchemacs@gmail.com / drraazecoethics151260@gmail.com**