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Synthesis, Spectral, Magnetic and Antibacterial Properties of Copper(II) Complexes of Quaternary and Tertiary N-Donor Ligands

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New complexes of Cu(II) with propantheline bromide [PP Bromide] with quaternary nitrogen and amitriptyline hydrochloride [AMTHCl] with tertiary nitrogen were prepared and their structures were elucidated by elemental analyses, IR, ^{1}H NMR, electronic spectra, ESR spectra and conductivity measurements. The spectral data suggest the monodentate nature in the complexes, a tetragonally distorted octahedral geometry is proposed for the complexes. The results of the antibacterial activity studies show that the complexes strongly inhibit *Eschearichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella*.

Key Words: Cu(II) complexes, Propantheline bromide, Amitriptyline hydrochloride, Antibacterial activity.

INTRODUCTION

Propantheline bromide [PPBr, 2-hydroxyethyl diisopropyl methyl ammonium bromide xanthene-9-carboxylate] is found to exhibit anticholinergic parasympatholytic and spasmolytic action[1-3] and hence used in medicinal chemistry. Amitriptyline hydrochloride [AMTHCl, 3-(10*H*-dihydro-5*H*-dibenzo-[a,b]-cydopentene-5-ylidene)-N,N-dimethyl-1,1-propanamine] is found to exhibit antidepressant with antianxiety and antihistamine properties[4-6]. Literature survey reveals that very less work has been reported on the study of complexing abilities of these two ligands. Recently PPBr has been proposed as a monodentate ligand[7]. Herein, the synthetic and spectroscopic studies of Cu(II) complexes of propantheline bromide and amitripytyline hydrochloride are reported. These synthesized complexes were also screened for antibacterial activity.

EXPERIMENTAL

All chemicals used in this work were of AnalR grade. Solvents were used after distillation. Propantheline bromide and amitriptyline hydrochloride

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were received as a gift samples from Searle (India) Ltd, Mumbai and Sun Pharmaceutical Ltd., Mumbai, respectively.

The carbon, hydrogen and nitrogen micro analyses were done on a Carlo Erba 1108 Heraeus instrument. The ^{1}H NMR spectra were obtained with an AMX-400 FT NMR. Spectrometer using TMS as internal standard. The infrared spectra were recorded in KBr pellets on a Perkin-Elmer spectrophotometer. The magnetic susceptibility of the complex were measured with Gouy balance using $Hg[Co(SCN)_2]$ as calibrant. A Dupont 9900 thermal analyzer with a 951 TGA module was used for recording TG curves in air at a heating rate of 6 °/min. The molar conductance of the new complexes in DMSO (10^{-4} M) were measured using Phillips model PR 9500 conductivity bridge. The electronic spectra were recorded on Perkan-Elmer 580 Spectrophotometer.

The analyses of the metal content, sulphur, chloride, bromide, nitrate, acetate and perchlorate were carried out by literature methods[8].

Preparation of complexes: All the complexes were prepared according to the following general method. In 50 mL of the appropriate ethanolic solution (2.5 mmol copper(II) salt ($CuX_2{\cdot}nH_2O$; $X = Cl^-$, Br^-, NO_3^-, CH_3COO^- and ClO_4^-; n = 0, 1, 2, …) added to 50 mL of (5 m mol) ethanolic solution of propantheline bromide and amitriptyline hydrochloride slowly and separately with continuous stirring. The solution was kept to room temperature for about 0.5 h the reaction mixture was then warmed on a water bath at 70-80 ºC for about 4 h. The coloured precipitates obtained in each case after cooling to room temperature were filtered washed several times with absolute alcohol, finally with ether and dried in an evacuated desiccator over anhydrous silica gel. The copper(II) acetate complex was prepared in aqueous media. Yield: 61-85 %.

RESULTS AND DISCUSSION

Analytical data given in Table-1 indicate the formation of the complexes $[Cu(PP)_2X_2(H_2O)_2]$ and $[Cu(AMT)_2X_2(H_2O)_2]$ where $X = Cl^-$, NO_3^-, CH_3COO^-, ClO_4^-. All the new complexes are insoluble in water, ethanol, chloroform and carbon tetrachloride but soluble in DMSO and DMF. Molar conductance of these complexes (10^{-4} M) in DMSO lie in the range 11.4-31.3 ohm^{-1} cm^2 mol^{-1} indicating them to be non-ionic[9]. Elemental analysis of the complexes reveals 1:2 stoichiometry.

Electronic spectra and magnetic moments: The copper(II) complexes studied have effective magnetic moment in the range 1.80-1.91 BM indicting that they are mononuclear with no interaction between copper atoms[10]. The magnetic moment of the complexes and electronic spectral data are given in Table-2. The values indicate a slight distortion in the geometry of the complexes.

TABLE-1
PHYSICAL, ANALYTICAL AND MOLAR CONDUCTANCE DATA OF COPPER(II) COMPLEXES

Complex (colour)	Yield (%)	Decomp. temp. (ºC)	m.w. Found (calcd.)	Elemental analysis (%): Found (Calcd.)					λ_m ohm^{-1} cm^2 mol^{-1}
				C	H	N	X	M	
$[Cu(PP)_2(H_2O)_2Cl_2]$	85	290-292	868.09	60.48	6.42	3.11	8.01	7.31	13.2
(Reddish brown)			(877.47)	(60.17)	(6.61)	(3.19)	(8.08)	(7.24)	
$[Cu(PP)_2(H_2O)_2Br_2]$	73	285-287	948.21	54.13	6.06	2.85	16.41	6.64	18.6
(Brown)			(966.38)	(54.64)	(6.00)	(2.90)	(16.54)	(6.58)	
$[Cu(PP)_2(H_2O)_2(N0_3)_2]$	62	295-297	948.83	56.08	6.28	6.07	–	6.76	20.2
(Reddish brown)			(930.57)	(56.74)	(6.23)	(6.02)	–	(6.83)	
$[Cu(PP)_2(H_2O)_2(Cl0_4)_2]$	63	162-164	–	52.98	5.71	2.80	7.07	6.40	11.4
(Greenish gray)			(1005.84)	(52.49)	(5.77)	(2.78)	(7.05)	(6.32)	
$[Cu(PP)_2(H_2O)_2(CH_3COO)_2]$	61	253-255	935.75	62.90	6.87	3.05	–	6.78	12.5
(Blue)			(924.66)	(62.29)	(6.92)	(3.03)	–	(6.87)	
$[Cu(AMT)_2(H_2O)_2Cl_2]$	81	242-244	733.15	65.89	6.91	3.88	9.71	8.68	22.8
(Green)			(725.22)	(66.19)	(6.89)	(3.86)	(9.78)	(8.76)	
$[Cu(AMT)_2(H_2O)_2Br_2]$	80	231-233	799.87	58.43	6.15	3.46	19.54	7.88	31.3
(Green)			(814.13)	(58.96)	(6.14)	(3.44)	(19.63)	(7.80)	
$[Cu(AMT)_2(H_2O)_2(CH_3COO)_2]$	54	220-222	763.55	68.98	7.22	3.64	–	8.27	25.8
(Green)			(772.41)	(68.36)	(7.25)	(3.63)	–	(8.23)	

TABLE-2
ELECTRONIC SPECTRAL BANDS AND MAGNETIC MOMENT OF COPPER(II) COMPLEXES

Complex	Electronic spectral bands (cm^{-1})				μ_{eff} (BM)
$[Cu(PP)_2(H_2O)_2Cl_2]$	10537	20366	47846	–	1.82
$[Cu(PP)_2(H_2O)_2Br_2]$	10928	22421	31347	47619	1.84
$[Cu(PP)_2(H_2O)_2(NO_3)_2]$	10752	22883	31056	47169	1.81
$[Cu(PP)_2(H_2O)_2(ClO_4)_2]$	11061	22153	33276	48076	1.91
$[Cu(PP)_2(H_2O)_2(CH_3COO)_2]$	10750	22380	29761	47846	1.89
$[Cu(AMT)_2(H_2O)_2Cl_2]$	11198	20576	29664	46950	1.80
$[Cu(AMT)_2(H_2O)_2Br_2]$	11223	22522	30675	46512	1.88
$[Cu(AMT)_2(H_2O)_2(CH_3COO)_2]$	11150	20210	29890	46315	1.86

The copper(II) complexes display two bands in the visible region. One broad absorption band observed in the region 10537-11223 cm^{-1} being assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2B_{2g}$ transitions while the second band at 18450-22883 cm^{-1} can be attributed to $^2B_{1g} \rightarrow {}^2E_g$ transitions suggesting a distorted octahedral configuration[11,12]. The band that appears near 30000-40000 cm^{-1} might be charge transfer origin. The room temperature magnetic moment of the complexes lie in the range 1.80-191 BM. This value supports a distorted octahedral symmetry of copper(II) in these complexes.

ESR Spectral studies: The ESR spectra of copper(II) complexes of PP and AMT were recorded at room temperature. The $g_{\|}$ and $g_{\perp}$ and related parameters were calculated and indicated in Table-3.

TABLE-3
ESR SPECTRAL PARAMETERS OF COPPER(II) COMPLEXES

Complex	$g_{\|}$	g_{iso}	$g_{\perp}$	G	g_{ava}
$[Cu(PP)_2(H_2O)_2Cl_2)$	2.2054	2.0601	1.9582	2.0831	2.0406
$[Cu(PP)_2(H_2O)_2Br_2]$	2.1232	2.0534	2.0173	1.9912	2.0526
$[Cu(AMT)_2(H_2O)Cl_2]$	2.2681	2.1293	2.0535	1.8830	2.1248
$[Cu(AMT)_2(H_2O)_2(NO_3)_2]$	2.2202	2.1034	2.0326	1.9758	2.0951

The X-band ESR spectra of the hexa-coordinate copper(II) complexes of PP and AMT are characteristics of rhombic symmetry and gives three distinct g-values with $g_{\perp} < g_{iso} < g_{\|}$. The values of $g_{\|}$ are greater than $g_{\perp}$ in the complexes. This sight elongation along the four fold symmetry axis Z, the orbital of the unpaired electron is still dx^2-y^2 because Jahn-Tellar induced distortion[13] generally favours dx^2-y^2.

The g_{av} = 1/3 g + 2/3 $g_{\perp}$ and these evaluated values (Table-3) are in agreement with an arbitrarily non degenerate state. The $g_{\perp}$ values < 2.3 indicate the covalent character of metal ligand bond. The axial symmetry parameter G less than 4 indicates exchange interaction in the magnetically equivalent copper(II) ion in the unit cell of PP and AMT complexes[14,15].

IR Spectra: The IR spectral data of the ligands and their representative copper (II) complexes are presented in Table-4. In the IR spectra of the ligand PP a strong band in the region 3000-2960 cm^{-1} can be attributed to the quaternary nitrogen atom of the side chain attached to alkyl group combined with bromide ion[16]. The sharp peaks occurring at 1150, 1725 and 2320 cm^{-1} in the ligand PP are due to ν(C-O-C) and ν(COO) band present at 1150 and 1725 cm^{-1}, respectively in the ligand remain in the same position in the spectra of the complexes suggesting that none of the oxygen atoms have taken part in bonding with copper(II) ion. The broad band around 3000-2960 cm^{-1} has completely disappeared in the spectra of complexes indicating the quaternary nitrogen of the side chain is the site of coordination.

TABLE-4
CHARACTERISTIC IR BANDS (cm^{-1}) OF THE LIGANDS AND THEIR COPPER(II) COMPLEXES

Compound	ν(Q.N$^+$-CH$_3$)	ν(-N-CH)	ν(COO)	ν(C-O-C)	ν(OH)	ν(Cu-N)
Propantheline bromide	3000-2960	2320	1725	1150	-	-
$[Cu(PP)_2(H_2O)_2Cl_2]$	-	2325	1720	1170	3440	420
$[Cu(PP)_2(H_2O)_2Br_2]$	-	2330	1728	1180	3420	418
$[Cu(AMT)_2(H_2O)_2(NO_3)_2]$	-	2320	1715	1170	3430	422
$[Cu(PP)_2(H_2O)_2(ClO_4)_2]$	-	2325	1720	1170	3425	425
$Cu(PP)_2(H_2O)_2(CH_3COO)_2]$	-	2320	1725	1175	3420	420

Q=quaternary

Compound	ν(N-CH$_3$)	ν(=CH)	ν(-CH$_3$)	ν(OH)	ν(Cu-N)	ν(Cu-X)
Amitriptyline hydrochloride	2600-2400	1590	2920		-	-
$[Cu(AMT)_2(H_2O)_2Cl_2]$	-	1600	2950	3500	420	290
$[Cu(AMT)_2(H_2O)_2Br_2]$	-	1605	2955	3450	422	275
$[Cu(AMT)_2(H_2O)_2(CH_3COO)_2]$	-	1610	2950	3420	420	-

A broad band appearing in many organic compounds in the range 2700-2200 cm^{-1} can be assigned to tertiary nitrogen attached to alkyl group combined with halogen[17]. The IR spectra of the ligand AMT show a broad band in the region 2600-2400 cm^{-1} which is due to alkyl nitrogen. In the IR spectra in the corresponding copper(II) complexes, this band has totally disappeared showing that the tertiary nitrogen of the side chain of the ligand is coordinated to the copper(II) ion. Thus, IR spectra show that AMT acts as a monodentate ligand by coordination through the tertiary nitrogen atom of the side chain. In addition to this all the new complexes exhibit a band at 3500 cm^{-1} which may be assigned to δ-OH of H_2O and a band of medium intensity around 1620 cm^{-1} can be attributed to $-OH_2$ coordinated water molecules[18]. The non ligand band at 420 cm^{-1} may be assigned to ν(Cu-N)[19]. The bands at 3040-2900 cm^{-1} is assigned to aromatic ν(C-H) which do not show appreciable change in ligand and their copper(II) complexes.

^{1}H NMR: The ligand PP exhibits a triplet at δ 1.14 ppm which is assigned to $C-(CH_3)_4$. The sharp signal (singlet) at δ 3.35 ppm is due to the quaternary nitrogen attached to the alkyl group *i.e.*, $N-CH_3$. The sharp signal at δ 3.45 ppm is attributed to $N-CH_2$. the multiplets at δ 7.15 ppm are due to aromatic protons.

In the spectra of the complexes all these resonance signals are retained by broadening the line due to paramagnetism of the complex, but a sharp signal at δ 3.35 ppm has completely disappeared indicating that the CH_3 group of quaternary nitrogen get lost during the coordination of ligand to the copper(II) ion.

The ligand AMT exhibits a triplet at δ 5.80 ppm that is assigned to olefinic proton that is = CH. The sharp signal at δ 3.16 ppm is assigned to $N-CH_2$ and the multiplets centered at δ 2.42 ppm are attributed to $-CH_2$ groups (6H). The singlet at δ 3.37 ppm is assigned to $N-CH_3$. The other multiplets at δ 7.07 ppm are assigned to aromatic protons.

In the ^{1}H NMR of the complexes all the above resonance signals are retained except a sharp singlet at δ 3.37 ppm which disappears there by suggesting the involvement of tertiary nitrogen atom in coordination with copper(II) ion. Thus ^{1}H NMR supports the conclusion drawn on the basis of IR data regarding the involvement of tertiary nitrogen atom of the side chain in bonding with copper(II) ion.

The chemical shift of the representative groups of the ligand PP and AMT and their complexes are summarized in Table-5.

On the basis of chemical analysis and various physico chemical studies, a tentatively distorted octahedral geometry for the copper(II) complexes is proposed.

Antibacterial activity: The ligands and a few complexes were screened for antibacterial activity by disk diffusion method[20] against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella*. Nutrient agar broth was melted in a water bath and cooled to 45 ºC with gentle shaking to bring about uniform cooling. It was inoculated with 0.5

mL of a 18-24 h old culture aseptically and mixed well by gentle shaking before pouring in to the sterilized petri dishes. The poured material was allowed to set (1-2 h). Sterilized filter paper dishes (Whatmann filter paper no. 41) were loaded with known volume of the test compound of known strength using micro pipette to get the disk of desired concentration[21]. The disks are placed over the growth media seeded with microorganism, left for diffusion and incubated at 37 °C for 24 h. The antibiotic amikacin was also screened under similar conditions for comparison as standard.

TABLE-5

^{1}H NMR DATA (ppm) OF THE LIGANDS AND COPPER(II) COMPLEXES

Compound	-C-$(CH_3)_4$	-O-CH_2	-N-CH_3	-N-$(CH)_2$	-N-$(CH)_2$	C-H	Ar-H
PP Bromide	1.14 t	4.37 s	3.35 s	3.45 m	3.74 m	2.67 s	7.15 m
$[Cu(PP)_2(H_2O)_2Cl_2]$	1.14 t	4.37 s	-	4.32 m	3.74 m	2.65 s	7.15 m
Compound	-N-CH_3	=CH	-$(CH_2)_3$	N-CH_2	Ar-H	N^+-HCl	
AMT.HCl	3.37 s	5.80 t	2.42 m	3.16 s	7.07 m	10.79 s	
$[Cu(AMT)_2(H_2O)_2Cl_2]$	-	5.78 t	2.40 m	3.12 s	7.05 m	-	

s = singlet, t = triplet, m = multiplet; PP = Propantheline; AMT = hydrochloride

The inhibition zones were measured in millimeter and results are presented in Table-6. The results reveal that the new complexes exhibit promising activity against all tested organisms than the free ligand. The results also reveal that copper(II) PP complexes exhibit more antibacterial activity than copper(II) AMT complexes.

TABLE-6

ANTIBACTERIAL ACTIVITY: INHIBITION ZONE IN mm

Compound	*E. coli*		*S. aureus*		*Pseudomonas*		*Klebsiella*	
	25 µg	40 µg	25 µg	40 µg	25 µg	40 µg	25 µg	40 µg
PP.Bromide	0.0	8.2	0.0	8.1	0.0	8.6	0.0	8.3
$[Cu(PP)_2(H_2O)_2Cl_2]$	6.6	11.6	6.7	12.2	7.4	13.7	6.8	11.1
$[Cu(PP)_2(H_2O)_2Br_2]$	7.2	12.5	8.1	13.1	8.2	14.1	7.3	12.5
$[Cu(PP)_2(H_2O)_2(CH_3COO)_2]$	8.5	14.8	9.1	15.7	9.5	16.3	7.5	13.6
AMT.HCl	0.0	7.1	0.0	8.3	0.0	8.3	0.0	8.6
$[Cu(AMT)_2(H_2O)_2Cl_2]$	6.8	12.3	7.1	15.6	8.1	13.6	6.7	12.3
$[Cu(AMT)_2(H_2O)_2Br_2]$	7.1	13.5	8.2	16.3	8.1	14.2	7.1	12.5
$[Cu(AMT)_2(H_2O)_2(CH_3COO)_2]$	7.5	13.9	8.3	16.1	8.2	15.3	7.2	12.8
Amikacin (30 µg)	–	25.0	–	22.0	–	24.0	–	20.0

Each value is the average of four replicates; DMSO (solvent): No inhibition; Control amikacin (30 µg); Diameter of disk = 6.5 mm.

PP = Propantheline; AMT = amitriptyline.

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