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Synthesis, Characterization and Antibacterial Activity of Copper(II) Complexes with N-Vanillidene-2-amino-4-phenylthiazole

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Condensation of 2-amino-4-phenylthiazole with vanillin yielded a potentially bidentate Schiff base (VAAT) which formed a series of Cu(II) complexes of the type $[Cu(VAAT)X_2]$ in presence of different counter anions such as chloride, bromide, nitrate, acetate and perchlorate. These complexes were characterized by elemental analysis, molar conductance, magnetic susceptibility measurements and IR spectral studies. Spectral studies revealed that the ligand is bonded to the metal ion through azomethine nitrogen and ring nitrogen atoms. The ligand as well as the complexes were screened for their antibacterial activity against selected bacterial stains such as *P. aeruginosa, K. pneumoniae, B. megaterium, V. cholerae, S. typhi*. It has been observed that the complexes are more potent bactericides than the ligand and the activity varied with the change in the coordinating anion.

Key Words: N-Vanillidene-2-amino-4-phenylthiazole, Copper(II) complexes, Co-ligands, Antibacterial activity.

INTRODUCTION

Schiff bases form an interesting class of chelating ligands that has use in the coordination chemistry of transition, inner transition and main group elements[1-4]. Among the prodigious number and variety of Schiff base complexes those derived from heterocyclic systems particularly those containing thiazole ring system find extensive applications in various fields[5,6]. The antibacterial activities of vanillin Schiff bases are well documented in literature[7,8]. Condensation of 2-amino-4-phenylthiazole with vanillin produces a potentially bidentate ligand, which is versatile in forming a series of complexes with some transition metal ions under well-defined conditions. In this communication, we report the synthesis, characterization and antibacterial activities of a series of copper(II) complexes with N-vanillidene-2-amino-4-phenylthiazole (VAAT) and different counter anions. The effect of co-ligands on antibacterial activity of the complexes is also discussed.

EXPERIMENTAL

AnalaR grade chemicals and commercially available solvents purchased from SRL, Aldrich, Fischer *etc.*, were used for synthesis. The metal contents of the complexes were analyzed using atomic absorption spectrophotometer (GBC Avanta). Carbon, hydrogen and nitrogen contents were analysed using a Heraeus Carlo Erba 1108-CHN analyzer. Sulphur content in the complexes was determined gravimetrically. Infrared spectra were recorded on a Shimadzu FTIR 8000 spectrophotometer and far IR spectra were recorded on a polytec FIR 30 Fourier spectrometer. Proton NMR spectrum of the ligand was recorded on a Jeol GSX 400 NB 400 MHz FTNMR spectrometer using $CDCl_3$ as solvent. Molar conductance measurements were conducted using 10^{-3} solutions of complexes in methanol on a Systronics conductivity meter type 304. Magnetic susceptibility measurements of the complexes were measured with a Gouy type magnetic balance at room temperature. Antibacterial activity of the complexes were determined by paper disc method[9].

2-Amino-4-phenylthiazole was prepared by reported method[10]. To a 0.01 M solution of 2-amino-4-phenylthiazole in toluene (30 mL), a 0.01 M solution of vanillin in toluene (20 mL) was added and the resulting mixture was refluxed on a water-bath for 6 h. On concentration and cooling orange coloured crystals of the ligand separated out from solution. This was filtered, washed successively with toluene and ether and then dried. The ligand was further purified by recrystallization from toluene. The metal complexes were prepared by the following general procedure.

A methanolic solution of corresponding copper(II) salt (0.01 M) was added to a hot solution of ligand (0.01 M) in methanol. The resulting solution was then refluxed for 4 h after adjusting pH to 6-7. On concentration and cooling, brown coloured metal complexes separated out. The complex was filtered, washed successively with methanol and ether and then dried in vacuum.

RESULTS AND DISCUSSION

Formation of the complexes can be represented by the following eqn.

$$CuX_2 + VAAT \rightarrow [Cu(VAAT)X_2]$$

where $X = Cl^-$, Br^-, OAc^-, NO_3^-, or ClO_4^-

The complexes obtained are listed in Table-1. All the complexes are coloured and posses good keeping qualities. They are non-hygroscopic solids soluble in common organic solvents like methanol, DMSO, $CHCl_3$, *etc*. Formulation of the complexes has been done on the basis of their elemental analytical data, molar conductance and magnetic susceptibility measurements. Molar conductance values of the complexes adequately support the non-electrolytic nature of the complexes[11].

TABLE-1
ANALYTICAL DATA OF THE Cu(II) COMPLEXES OF VAAT

Compound	Yield (%)	% Analysis found (calculated)					Molar conductance $\Omega^{-1}mol^{-2}cm^2$	μ_{eff} (BM)
		Cu	C	H	N	S		
VAAT	82	–	66.43 (66.23)	4.35 (4.22)	9.18 (9.09)	10.42 (10.38)	–	–
$[Cu(VAAT)Cl_2]$	72	18.26 (18.50)	60.48 (60.79)	3.26 (3.79)	8.84 (8.17)	9.82 (9.34)	26.2	1.84
$[Cu(VAAT)Br_2]$	74	11.92 (11.95)	38.48 (38.38)	2.41 (2.44)	5.19 (5.27)	6.22 (6.02)	24.1	1.86
$[Cu(VAAT)(ClO_4)_2]$	80	13.82 (13.49)	44.52 (44.20)	2.51 (2.76)	5.54 (5.95)	6.38 (6.80)	27.3	1.82
$[Cu(VAAT)(NO_3)_2]$	78	12.38 (12.88)	41.38 (41.97)	2.57 (2.62)	8.42 (8.47)	6.33 (6.45)	26.9	1.83
$[Cu(VAAT)(CH_3COO)_2]$	75	12.97 (12.87)	52.54 (52.29)	2.62 (2.65)	5.36 (5.72)	6.42 (6.54)	28.7	1.83

Analytical data indicates that condensation of vanillin with 2-amino-4-phenylthiazole occurred in 1:1 molar ratio. The structure of the ligand has been established by IR and proton NMR spectral studies

Infrared spectrum of the ligand exhibited a medium intensity band at *ca.* 1635 cm^{-1}, characteristic of the ν(C=N) vibration of the azomethine moiety[12]. Vibration characteristic of the ring ν(C=N) has been observed at *ca.* 1595 cm^{-1} and vibrations characteristic of thiazole ring moiety[13] at *ca.* 1510, 1460 and 1045 cm^{-1}.The absence of $-NH_2$ peak in the spectrum of the ligand compared to that of 2-amino-4-phenylthiazole suggests that the expected imino compound is formed.

The proton NMR spectrum[13] of the ligand exhibited a multiplet signal at δ 7.2-8.1 characteristic of the aromatic protons, a sharp singlet at δ 6.4 characteristic of thiazole ring hydrogen and at δ 4.2 characteristic of $-OCH_3$ group.

The IR spectral data of the complexes along with their tentative assignments are presented in Table-2. The peak due to azomethine group is shifted to lower frequencies by about 15-25 cm^{-1} in all the compexes. The peak due to ring ν(C=N) is also shifted to lower frequencies by about 8-10 cm^{-1} in all the complexes indicating the coordination of the ligand[14] to metal by azomethine nitrogen and ring nitrogen atom, respectively. The bands due to >C–S–C< vibration, –OH vibration and $–OCH_3$ vibration remain almost unchanged. Hence it is assigned that the ligand acts in a neutral bidentate fashion to form complexes.

TABLE-2
INFRARED SPECTRAL DATA (cm^{-1}) OF Cu(II)-VAAT COMPLEXES

Compound	Assignments					
	Azo-methine ν(C=N)	Ring ν(C=N)	ν(-OCH_3)	ν(-OH)	ν(C-S-C)	ν(Cu-N)
VAAT	1335	1595	2177	3280	686	–
[Cu(VAAT)Cl_2]	1613	1585	2174	3283	684	572
[Cu(VAAT)Br_2]	1618	1585	2177	3284	682	578
[Cu(VAAT)$(NO_3)_2$]	1618	1587	2175	3284	684	572
[Cu(VAAT)$(ClO_4)_2$]	1612	1584	2174	3286	683	575
[Cu(VAAT)$(CH_3COO)_2$]	1614	1582	2175	3285	684	573

In the spectrum of nitrate complex three well-defined peaks are obtained at *ca.* 1029, 1346 and 1383 cm^{-1}. Here ν_5-ν_1 is about 150 cm^{-1} which suggests that nitrate group is coordinated in a monodentate manner[15]. In the acetate complex, two bands have been observed at *ca.* 1636 and 1403 cm^{-1} which may be assigned to antisymmetric and symmetric (COO^-) stretching vibrations, respectively suggesting that the coordination of acetate is in a monodentate fashion[16]. In the far IR spectra of the complexes the non-ligand bands appearing at *ca.* 320 and 300 cm^{-1} for chloro and bromo complexes are assignable to ν(Cu–Cl) and ν(Cu–Br) stretching vibrations, respectively[17]. These complexes exhibit medium intensity bands in the region *ca.* 575-570 cm^{-1} which are assignable to ν(M–N) vibration[17]. The band at *ca.* 1130 cm^{-1} is assignable to ν_4 vibration of monodentate perchlorate group. The peaks at *ca.* 1060, 640 and 925 cm^{-1} corresponds to ν_1, ν_3 and ν_2 vibrations, respectively of monodentate perchlorate group[18].

Antibacterial activity

The ligand and the metal complexes have been screened *in vitro* for their antibacterial activity against five bacteria - *P. aeruginosa, K. pneumonia, S.typhi, V. cholera* and *B. megaterium* to study the effect of anions on biological properties and the results obtained are presented in Table-3.

All the complexes are more potent bactericides than the ligand. This can be explained on the basis of chelation theory[19]. On chelation, the polarity of the metal ion will be reduced to a great extent due to the overlap of the ligand orbital. Chelation increases polarization of π electrons over the whole chelate ring and increases lipophilicity of the complex[20]. This enhanced lipophilicity of the complexes leads to breakdown of the permeability barrier of the cell and this retards the normal cell process[21]. Hence the metal complexes possess an increased antibacterial activity. Apart from chelation, there are some other factors, which determine the antibacterial

activity of the complexes, *viz.*, nature of the ligand, nature of the metal ion, coordinating sites, geometry of the complex, hydrophilicity, lipophilicity and presence of co-ligands[22].

TABLE-3
ANTIBACTERIAL ACTIVITIES OF VAAT AND ITS Cu(II) COMPLEXES

Name of bacteria / Name of compd.	Zone of inhibition (mm)				
	PA	KP	VC	BM	ST
VAAT	2	2	8	6	8
$[Cu(VAAT)Cl_2]$	4	8	8	6	8
$[Cu(VAAT)(ClO_4)_2]$	10	2	8	6	8
$[Cu(VAAT)Br_2]$	22	12	8	8	8
$[Cu(VAAT)(NO_3)_2]$	18	16	10	6	10
$[Cu(VAAT)(CH_3COO)_2]$	28	18	8	10	8

PA = *P. aeruginosa*; KP = *K. pneumonia*; VC = *V. cholera*; BM = *B. megaterium*; ST = *S. typhi*

All the tested complexes had different antibacterial activity against the bacterial stains.

The zones of inhibition of the ligand against *K. pneumonia* and *P. aeruginosa* are very low while it is marginally high for other three bacteria. Among the tested complexes the acetate complex produces very high inhibition zone against *P. aeruginosa* and *K. pneumonia* and a fairly high inhibition zone against *B. megaterium*. The bromide complex also exhibits high inhibition zone against *K. pneumonia* and *P. aeruginosa*. The nitrate complex is an effective bactericide against all tested bacteria except *B. megaterium*. The least effective bactericides are chloride and perchlorate complexes. The former is effective against *K. pneumonia* and latter against *P. aeruginosa* only. All the complexes are less effective against *S. typhi* and *V. cholera* except the nitrate complex. Here the difference in antibacterial activity of the complexes can be attributed to different anions present in the complexes[23].

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