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Research Article

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Synthesis, Characterization, and Biological Activities of 4'-(1H-Benzimidazol-2-yl)-2, 2':6', 2''-terpyridine and its Copper Complex

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ABSTRACT

Terpyridine derivatives and their metal ion complexes have many applications in the fields of supramolecular chemistry, medicinal chemistry and material science. There has been only a few studies on 4' heteroaryl substituted – 2, 2': 6', 2'' – terpyridines and their metal ion complexes which may be useful as pharmacological agents. In recent years there has been considerable interest in developing 4'- substituted terpyridines and their metal complexes as anticancer drugs, anti-oxidants and as antimicrobials.
synthesized (a) 4'-(1H-benzimidazole-2-yl)- 2,2':6',2'' – terpyridine (bitpy) was incorporated with copper perchlorate finally this complex was characterized by elemental analysis, IR, UV-visible and 1H NMR, and cyclic voltammetry. Application of this complex also were studied.

Keywords: Ligand; Complex; Copper perchlorate; Antimicrobial activity; Bitpy.

INTRODUCTION

The coordination chemistry of nitrogen donor ligands is an active and interesting area of research. Organic compounds containing pyridine rings play significant roles in many biological reactions [1]. Also many transition and heavy metal cations play active roles in several biological processes. Polypyridines are becoming increasingly important in many areas[2]. Several hundred metal polypyridine complexes have been prepared and used over the past few decades[3]. Much of the interest in these compounds stem from their possible applications.
Among the polypyridine, terpyridine derivatives with three nitrogen atoms acting as tridentate ligands to coordinate with various transition metal ions have been extensively studied[4]. Coordination chemistry of 2, 2':6', 2''-terpyridine particularly those substituted at the 4'- position has been attracting growing attention in many areas. The popularity of 2, 2':6', 2'' - terpyridine (tpy) as a ligand is easy to understand. Several types of derivatised tpy, particularly those substituted at the 4'- position are also readily accessible[5,6]. Terpyridine can bind to both low and high oxidation state metal ions almost always in tridentate fashion[7,8]. Bidentate and monodenate co-ordinations of tpy derivatives to metal ions are also known[9]. Since tpy was first prepared over 100 years ago[10-11], its coordination chemistry along with those of its substituted (Xtpy) analogues have been widely investigated[7].
4'- Aryl substituted 2, 2':6', 2''- terpyridines find relevance in areas like supramolecular chemistry. The metallosupramolecular species may be constructed from a number of metal ions linked by suitable tpy ligands.

These species may act as molecular wires, while two and three dimensional species may be used for harvesting light energy[12]. The symmetry of 4'- substituted- tpy ligands makes their units ideal metal binding domains for use in coordination oligomers and other supramolecular systems[13-15]. The metal binding domains in tpy are in favour of self – assembly of metallopolymers and metal cycles[16]. 2,2':6',2'' -Terpyridine ligands particularly those substituted at the 4'- position have been attracting attention in the design of supramolecular building blocks based on metal directed self - assembly. The metal - tpy units are incorporated into coordination polymers, dentrimers and other supramolecular structures.

Medicinal inorganic chemistry has become an important research area since the validation of cisplatin as an effective anti-cancer agent in humans[17-19]. The rich coordination chemistry of transition metal ions with organic ligands provides suitable candidates in the design of chemotherapeutic drugs for various diseases. In this respect, the metal ion complexes of terpyridine derivatives have been extensively explored as antimicrobial, antiprotozoal, antitubercular, antioxidant and anticancer agents. The terpyridine - metal complexes are attributed with these biological properties, because they are able to bind the DNA molecules present in the living systems. Complexes of terpyridine ligands can bind to DNA by metal coordination as well as π stacking interactions.

The terpyridine - metal complexes also exhibit interesting photophysical properties. The terpyridines are highly useful building blocks for the creation of wide range of transition metal complexes with interesting photophysical, electrochemical and catalytic properties. Consequently metal-terpyridine complexes have been explored extensively for their use in desensitized solar cells[20], two - photon lurninescent systems[21] as well as light emitting devices[22].

In view of these fascinating properties and applications of metal complexes of derivatives of 2, 2':6',2''- terpyridine, we ventured to synthesize and characterize 4'- substituted terpyridine ligand such as 4'- (1H- benzimidazol-2-yl) - and their coordination compound with bivalent copper perchlorate. We also ventured to study the electrochemical properties and biological properties (anti -microbial, antioxidant and antiproliferative activities) of the newly synthesized compounds. In this context a survey of related recent studies has been made and the related literature is presented here in a chronological manner. The survey of related studies is of immense importance in deciding the research design including the synthetic strategies for the present investigation.

EXPERIMENTAL SECTION

Materials

The starting materials required for the synthesis of terpyridine ligands, namely, 1,2-diaminobenzene, tartaric acid, sodium periodate and 2-acetyl pyridine were obtained from Sigma-Aldrich Chemicals, Bangalore and used as received. Common reagents like ammonium acetate, glacial acetic acid, hydrochloric acid, ammonia solution and sodium hydroxide were purchased from SD Fine Chemicals, India. 2,2'-Bipyridine and 1,10-phenanthroline were received from Sigma-Aldrich and used as received. Ferrocene carboxaldehyde was purchased from Sigma-Aldrich chemicals. Reagents required for synthesis of metal (II) complexe such as Copper(II)perchloratehexahydrate, was purchased from Sigma-Aldrich Chemicals. Solvents like methanol, acetonitrile, ethyleneglycol, ethanol, dimethylsulfoxide, acetone, dimethylformamide, tetrahydrofuran of analytical grade were purchased from SRL Chemicals and used as received. Chemicals/solvents used in various analytical techniques like KBr (IR grade), and tetrabutylammoniumperchlorate (for CV) were obtained from Sigma-Aldrich Chemicals.

Synthesis and Characterization of 4'-(1H-Benzimidazol-2-yl) 2,2':6',2''-terpyridine (bitpy)

4'-(1H-Benzimidazol-2-yl)-2,2':6',2''-terpyridine(bitpy) was synthesized using a known procedure available in literature [23] Firstly 1,2-bis(1H-benzimidazol-2-yl)ethane-1,2-diol was prepared by mixing dl- tartaric acid (1.5 g,10 mmol) and benzene -1,2- diamine (2.16, 20 mmol) with 50 ml of 4N HCl and refluxing the mixture for 24h. The solution was cooled to room temperature and then kept in a refrigerator overnight. The green colored crystals were filtered and re-dissolved in ethanol and the solution refluxed with the decolorizing agent, charcoal for 2h. Ammonia solution was added to get the curd white precipitate of 1,2-bis(1H- benzimidazol- 2-yl) ethan-1,2 diol. The precipitate was filtered, washed with water (3x5 ml) and then air dried (yield: 1.76, 60 %), (Figure 2).

The starting material benzimidazole carboxaldehyde was prepared by interacting 1,2-bis (1H-benzimidazol-2-yl)ethan-1,2diol (1g, 3.4 mmol) methanolic solution with methanolic solution of NaIO4 (0.73g, 3.4mmol) added drop wise with constant stirring for 2h. The curd white precipitate of benzimidazole carboxaldehyde formed was filtered, washed with hot water (3x15 ml) and air dried (yield: 1.96g, 85 %), (Figure 3).

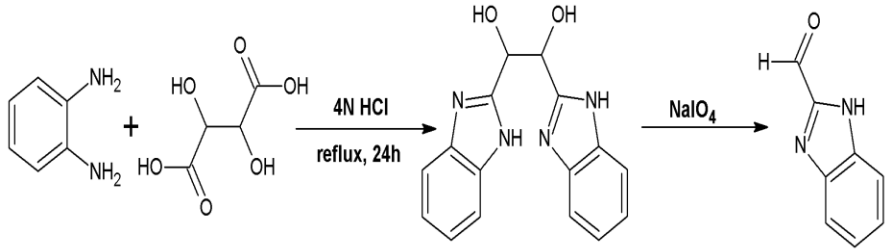

Figure 1: Synthesis of benzimidazole carboxaldehyde

2- Acetyl pyridine (1.12 mL,10 mmol) and 1H-benzimidazole-2-carboxaldehyde (0.73 mg, 5 mmol) were intimately mixed using a mortar and pestle till the formation of an orange red powder (about 10 minutes) .The powder was added to a suspension of ammonium acetate (2.5g) in glacial acetic acid and heated to reflex for 3h. The crude product was filtered, washed with water (5mL) and cold ethanol (5 mL). It was column chromatographed in silica gel column using
1:1 methanol dichloromethane system to get the pure product (yield: 1.43g, 82 %), (Figure 2).

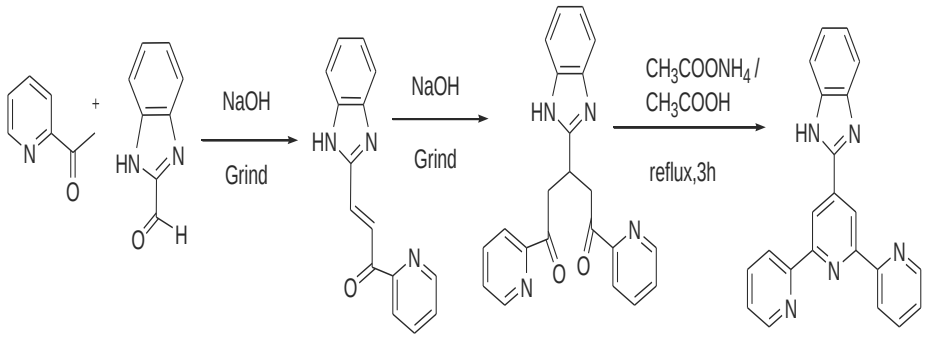

Figure 2: Synthesis of benzimidazolyl terpyridine

RESULT AND DISCUSSION

The analytical and mass spectral data obtained for 4'-(1H-benzimidazol-2-yl)-2,2':6', 2''-terpyridine (bitpy) (L1) are provided in Table 1.

Table 3.1: Elemental Analysis, Conductance and Mass Spectral Data for bitpy.

S. No	Compound	% Found (Calculated)				λ_M (S cm^2mol^{-1})	Molecular Ion Peak (m/z)
		C	H	N	M		
1	bitpy	75.43 (75.64)	4.33 (4.29)	20.00 (20.05)	-	-	349
2	$[Cu(bitpy)_2(ClO_4)_2]$	55.27 (55.25)	2.99 (3.16)	14.32 (14.64)	6.15 (6.14)	38.5	955.71

1H NMR Spectral Study on Benzimidazolyl terpyridine (bitpy)

The ^1H NMR spectrum of bitpy was recorded in $CuCl_3$. The spectrum is shown in Fig 3.1 and its resonance signals are listed in Table 3.2. The spectrum of bitpy shows signals due to protons at different positions of terpyridine moiety. Helen Elsbernd and James K.Beattie [24-25] have investigated the ^1H NMR spectrum of 2, 2':6', 2''-terpyridine. According to them the protons at 3, 4, 5 and 6 and symmetrically related protons at 3'', 4'', 5'' and 6'' positions form a four spin system and the central ring protons at 3', 4' and positions for a three-spin system in the NMR of terpyridine moiety. It is also reported that the chemical shifts of protons on terminal rings are independent of the nature of the substituent at the 4'-position [26-30]. The observed resonance signals and their assignments are provided in Table 3.2. The signals observed at δ 2.029 and 2.047 ppm may be due to impurities. Thus the spectrum of bitpy illustrates the presence of pyridine rings, imidazole ring, and fused benzene ring in bitpy molecule. Thus the structure of bitpy is confirmed based on elemental analysis, mass, infrared, UV-visible and NMR spectra.

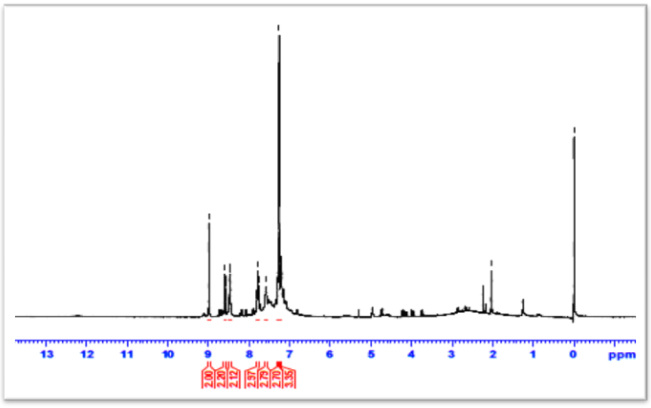

Figure 3: NMR Spectrum of Ligand

Table 2: 1H NMR chemical shifts (δ ppm) for L

S. No	Chemical shift	Assignment
1	7.198	H5 / H5'' of tpy
2	7.765	H4 / H4'' of tpy
3	8.463	H3' / H5' of tpy
4	8.592	H6 / H6'' of tpy
5	8.602	H3 / H3'' of tpy
6	8.989 - 8.602	H of NH of imidazole
7	7.206 - 7.802	H of benzene ring

IR Absorption Frequencies (cm-1) for bitpy (L) and its Copper Complex

The ligand L (bitpy) has five possible potential coordination sites viz. two imidazole N and three terpyridine N atoms. A comparison of the IR spectra of the metal complexes with that of the ligand suggests the actual coordination sites of the ligand. Also the mode of coordination of the perchlorate groups to the metal centre may be inferred from the IR spectra of the metal complexes. Ligand shows its molecular ion peak at m/z=349.0 (Fig.3.3) which confirms it molecular mass and molecular formula. Further, elemental analysis, conductivity data, magnetic moments, UV–visible spectra and mass spectra of the complexes have been measured to assign the stoichiometries and stereochemistries of the metal ion complexes.

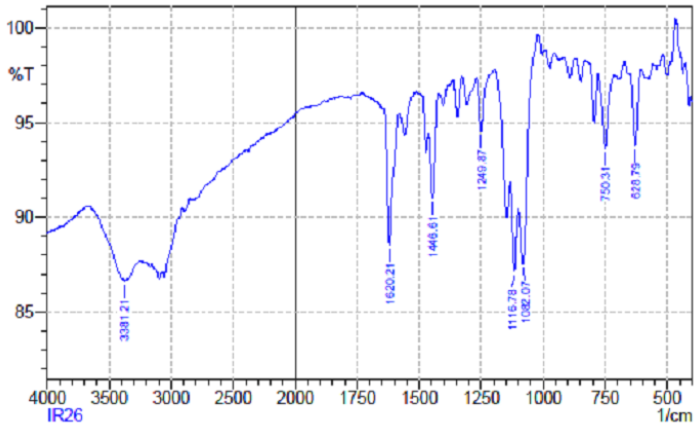

Figure 4: FT-IR Spectrum of Copper Complex

Redox Behavior of [Cu(bitpy)2(ClO4)2], Complex 2

This complex in its cyclic voltammograms (Fig 3.4) scanned at 50, 100 and 200 mVs-1 records cathodic peak potentials (Epc) at 1.0026, 1.099 and 1.361 V respectively featuring the reduction of CuII to CuI species, while the anodic peak potential values measured at 1.379, 1.548 and 1.649 V respectively feature the reoxidation of CuI species to CuII species on reversing the scan 160, 161. The peak potential separations have been calculated at 376, 449 and 288 mV for the scans operated at 50, 100 and 200 mVs-1 respectively. The calculated peak separation values are higher than 200 mV for this copper(II) complex revealing that an irreversible redox process is

involving a CuII/CuI redox couple. The peak current ratios (Ipa/Ipc) have been measured at 0.508, 0.418 and 1.924 when scanned at 50, 100 and 200 mVs-1 respectively. These peak current ratios measured at 50 and 100 mVs-1 which are less than unity indicate that the electron transfer is followed by chemical reaction i.e. EC mechanism is followed in the process but, at 200 mVs-1 it is not so. For this complex the E1/2 values have been determined at 1.191, 1.324 and 1.505 V at 50,100 and 200 mVs-1 respectively. These positive values of E1/2 suggest that the benzimidazolyl terpyridine (bitpy) ligand exhibits considerable σ-donating ability so as to form a stable chelate complex. Hence reduction of CuII species becomes very difficult.

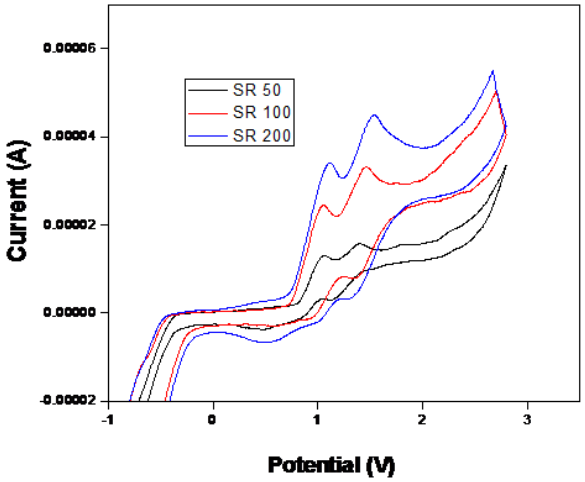

Figure 5: Cyclic Voltammograms of Copper Complex at 50,100 and 200 mVs-

Investigation of Biological Properties of Benzimidazolyl terpyridine and its Copper Complex

Antioxidant Activity Screening:
***In Vitro* Evaluation of Antioxidant Activities by DPPH Assay**

Sl.No	Test Drug	Concentration (µg/mL)	Absorbance	% DPPH Scavenging Activity
1.	bitpy(L)	05	0.19	50.00
		10	0.10	73.68
		15	0.05	86.84
		20	0.02	94.74
2.	$[Cu(bitpy)_2(ClO_4)_2]$ Complex	05	0.19	50.00
		10	0.10	73.68
		15	0.07	81.58
		20	0.03	92.11
3.	Control (Ethanol)	-	0.38	-

***Invitro* Antimicrobial Activity Screening**

Sl. No	Test Drug	Zone of Inhibition (mm)											
		S. aureus			*B. subtilis*			*K. aerogenes*			*E. coli*		
		100 mg/L	250 mg/L	500 mg/L	100 mg/L	250 mg/L	500 mg/L	100 mg/L	250 mg/L	500 mg/L	100 mg/L	250 mg/L	500 mg/L
1	bitpy(L1)	17	20	24	12	16	18	8	8	10	15	16	20
3	$[Cu(bitpy)_2(ClO_4)_2]$ Complex	14	16	20	14	15	18	18	20	24	13	16	18

Note: Zone size less than 15 mm – Least active; 16 – 20 mm– moderatively active; Above 20 mm – highly active

Table 3 : Antifungal Activities of bitpy(L) and its Metal Complexes

Sl. No	Test Drug	Zone of Inhibition (mm)					
		Aspergillus niger			*Candida albicans*		
		100 mg/L	250 mg/L	500 mg/L	100 mg/L	250 mg/L	500 mg/L
1	bitpy(L1)	16	16	20	15	18	19
3	$[Cu(bitpy)_2(ClO_4)_2]$ Complex	15	16	19	10	14	16

Note: Zone size less than 15 mm - Least active; 16 – 20 mm - moderatively active; Above 20 mm – highly active

Streptococcus aureus *Bacillus subtilis* *Aspergillus niger*

Escherichia coli *Klebsiella* *aerogenes*

Figure 6: Antibacterial and Antifungal Activities of Ligand, 1 bitpy

Antifungal Activities of Copper Complex:

Streptococcus aureus, Bacillus subtilis, Klebsiellaaerogenes and Escherichia coli

REFERENCES

[1] M. G. Abd El Wahed. *J Serb Chem Soc*. **2003**, 68, 463-69.
[2] M. Cargill Thompson. *Coord Chem Rev.* **1997,** 160, 1-10.
[3] V. Balzani; A. Juris; M. Venturi; S. Campagna; S. Serroni. *Chem. Rev.* **1996**, 96, 759-63.
[4] E. C. Constable. *Coord. Chem. Rev*. **2008**, 252, 842.
[5] Malcom A. Halcrow. Coord Chem Rev, **2005**, 249, 2880-88.
[6] R. A. Fallahpour. *Synthesis*. **2003**, 155.
[7] G. Chelucci; R. P. Thummel. *Chem Rev*. **2002**, 102, 3129-36.
[8] E. C. Constable. *Adv Inorg Chem Radiochem*. **1986**, 30, 69-75.
[9] T. J. Meyer; M. H. V. Huynh. *Inorg Chem*. **2003**, 42, 8140-46.
[10] C. Piguet; G. Bernardinelli; G. Hopfgartner, *Chem Rev*. 1997, 97, 2005-07.

[11] G. T. Morgan; F. H. Burstall. *J Chem Soc*. **1932**, 20.
[12] G. T. Morgan; F. H. Burstall. J.Chem.Soc., **1937**, 2, 1649-54.
[13] M. D. Ward. *Chem Soc Rev*. **1995**, 121-27.
[14] E. C. Constable; A. M. W. Cargill Thompson. *J Chem Soc Dalton Trans*. **1992**, 2, 3467-73.
[15] E. C. Constable, A. M. W. Cargill Thompson, D. A. Tocher, V.Balzani, L.de Cola(eds). Supramolecular Chemistry, Kluwer, Dordrecht, **1992**,41 219-223.
[16] E. C. Constable , L. Fabbrizzi, A. Poggi(eds). Transition Metals in Supramolecular Chemistry, Kluwer, Dordrecht, **1994**, 3,81-89.
[17] R. P. Thummel, J. A. McCleverty, T. J. Meyer(Eds), Comprehensive Coordination Chemistry II, Elsevier, Oxford, **2004** (1) 41-49.
[18] B. Rosenberg; L. Van Camp; T. Krigas. *Nature*, **1965,** 200, 698-704.
[19] B. Rosenberg; L. Van Camp; E. B. Grimley; J. Thomson. *J Biol Chem*. 1967, 242,1347-55.
[20] J. Wilson; S. J. Lippard. *Chem Rev.* **2014,** 114, 4470-79.
[21] Reynal, E; Palomares; *Eur J Inorg* Chem. **2011**, 8, 4509-18.
[22] L. S. Natarajan; A. Toulmin; A. Chew; S. W. Magennus. *Dalton Trans*. **2010,** 39, 108-17.
[23] R. C. Evans; P. Douglas; C. J. Winscom. *Coord Chem Rev.* **2006**, 250, 2093.
[24] D. A. Durham; G. H. Frost; F. A. Hart. *J Inorg Nucl Chem.* **2002**, 31, 833.
[25] G. Ciantelli; P. Legittimo;0 F. Pantani. *Anal. Chim. Acta*. **1969,** 53, 303-11.
[26] H. Elsbernd; James K. Beattie. *J Inorg Nucl Chem.* **1972**, 34, 771-80.
[27] S. Musumeci; E. Rizzarelli; S. Sammartano; R. P. Bonomo, *J Inorg Nucl Chem.* **1974**,36,853.
[28] L. C. Kamra; G. H. Ayres; *Anal Chim Acta*. **1976**, 81, 117.
[29] J. M. Rao; M. C. Hughes; D. J. Macero. *Inorg Chim Acta*.**1976**, 16, 231-41.
[30] E. C. Constable; J. Lewis. *Polyhedron*. **1982**, 1, 303-10.
[31] E. C. Constable; J. Lewis; M. C. Liptrot; P. R. Raithby; M. Schroder. *Polyhedron*, **1983**, 2, 301-11.