



SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF COORDINATION POLYMERS DERIVED FROM BISTETRAHYDRO PHTHALAMIC ACID OF TRIMETHOPREM DRUG

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Article History:

Received: 28.05.2023

Revised: 22.06.2023

Accepted: 18.07.2023

Abstract

The trimethoprem drug was condensed with tetrahydrothalic anhydride. The resultant Bis tetrahydrophalamic acid of trimethoprem namely; 2, 4-Bis (5-carboxycyclohex-1-en-6-carbonyl)-(3, 4, 5-trimethoxyphenyl) methyl pyrimidine, characterised duly. The coordination polymers of this bis ligand were BTPT prepared by using metal ions viz; Cu⁺², CO⁺², Ni⁺², Mn⁺², and Zn⁺². The coordination polymers and parent ligand BTPT were analysed by metal: ligand ratio, spectral features, magnetic moment, large molecular weight and thermogravimetry. The antimicrobial activity of all the Mn⁺ ligands and polymers were evaluated by Agar-cup-method.

Keywords: Coordination polymers, Spectral study, metalaalts ligand, magnetic moment, Spectral study, thermogravimetry, Number average molecular weight Mn⁺.

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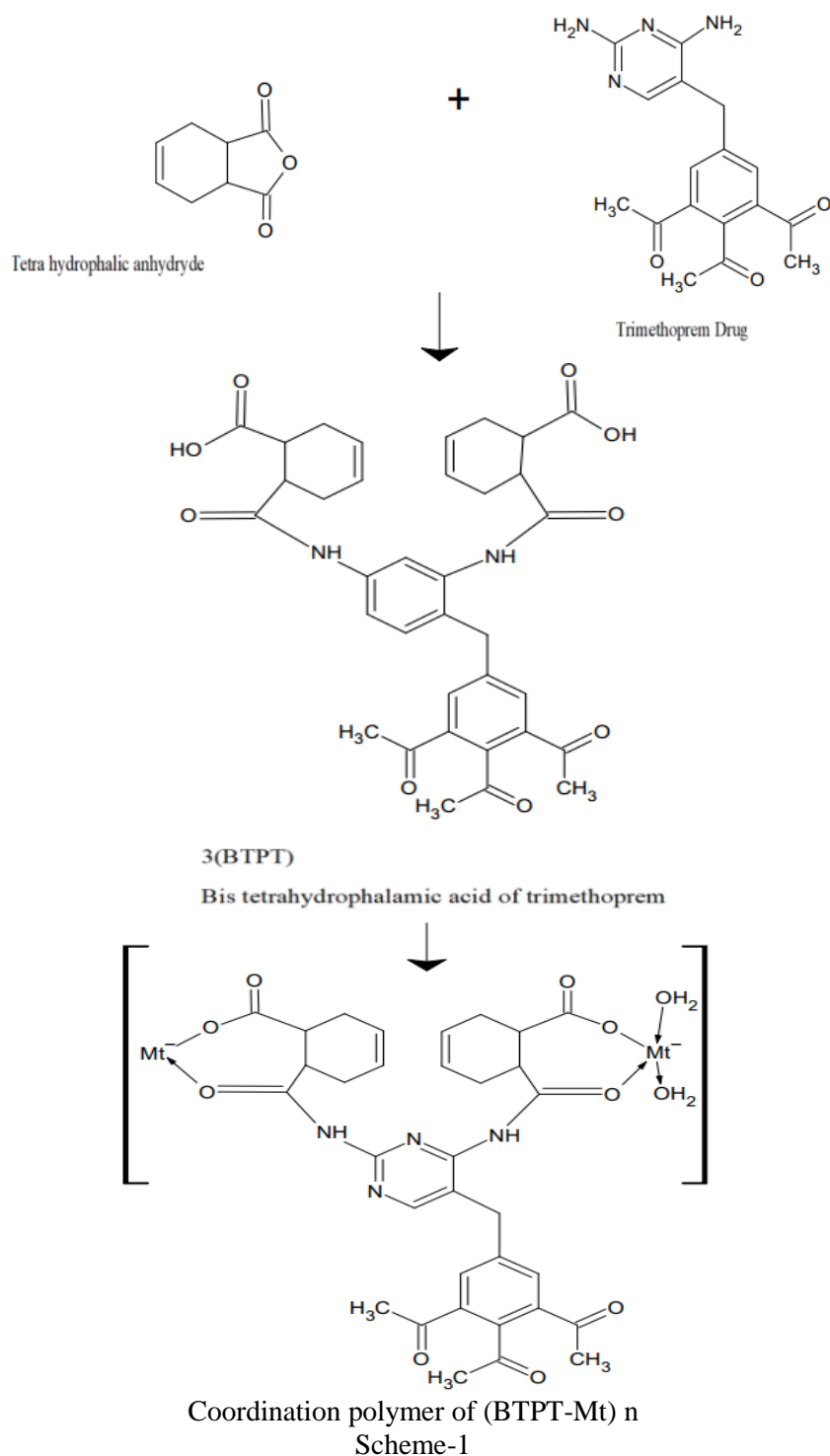
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DOI: 10.48047/ecb/2023.12.si10.00205

INTRODUCTION

The application of transition metal complexes of organic as well as drug molecules as medicinal compounds has been more articulated, Their activity reported as anti-infective, antidiabetic, anti-septic, antifungal and more particularly anticancer [1] The review [2] represent the metal complexes are use some of carboxylic acid – metal complexes are used as anticancer drug [3-10] Many researchers did the work on metal complexes of phthalamic acid derivatives [11-16].

Recently the present authors [17] reported the metal complexes of tetrahydrophthalamic acid with sulfa drugs moieties, In continues of this work[17], the present paper comprises the coordination polymers based on bis tetrahydrophthalamic acid of trimethoprim drug. This may enhance the antimicrobial activity of present complexes up to some extent. The route of research work is shown as follow.



EXPERIMENTAL Material: All the chemicals, reagent etc are procured from local market as pure grade and were used without purification.

MEASUREMENTS:

Infrared spectra (FT-IR) were scanned in KBr on Perkin Elmer spectrum GX spectrophotometer (FT-IR) instrument. ¹H NMR ¹³C NMR spectra were acquired at 400 MHz on a Bruker NMR spectrometer using DMSO-d₆ (residual peak at ~2.5 or ~3.5 °K) as a solvent as well as TMS an internal reference standard. Micro analytical (C, N, H) data were obtained by using a Perkin-Elmer 2400 CHN elemental analyzer. The solid diffuse electronic spectra were recorded on a Beckman DK-24 spectrophotometer with MgO as a reference. Magnetic moments were determined by the Gouy method with mercury tetra thiocyanetocobaltate (II), [HgCo (NCS)₄] as a calibrant and were for correcting molar susceptibility Pascal's constant [18]. The thermogravimetric analysis studies were carried out with a model Perkin Elmer thermogravimetry analyzer at a heating rate of a 10°C min⁻¹ under in N₂ gas. The metal content of the coordination polymers was estimated by method reported [19]. Number average molecular weight (M_n) of coordination polymers was estimated by nonaqueous conductometric titration. It was carried out in pyridine solution against standard sodium methanoate in pyridine solution as a titrant, The number average molecular weight of each sample was calculated according to method reported in literature [20]. The melting point was checked by the standard open capillary method.

Synthesis of ligand Bis tetrahydrophthalamic acid of trimethoprem BTPT (3)

A solution of trimethoprenol (0.1 mol) was added gradually to stirred solution of tetrahydrophthalic anhydride (0.2 mol) and keeping the temperature of the mixture to 10-15°C for an 2 hour (scheme 1). The obtained ensuing solution was poured into ice

water in which the reaction product precipitated. The final white precipitates were filtered, washed and purified. Yield was 75%; Decomposition temp.: 265-270°C; Elemental Analysis calculated for show in the spectral features of BTPT are as follows.

Bis Ligand

IR bands, cm⁻¹:

3400-3300(NH, COOH), 3050, 2880, 1590, 1500(C-H), 1780-1600 (CO), 1270-1245(C-N) 1600, 1465(C=C) and 1120(R-O-R)

PMR signal, δ ppm: 11.50 (s, 2H,-OH)

6.50-8.00 (m, 3H, aromatic-H),

2.80-3.00 (q, 4H, -CH₂),

2.35-2, 10 (t, 8H, -CH₂),

5.70 (q, 4H, -CH=CH-)

3.90 (s, 2H, -CH₂) and

3.90 (s, 12H,-OCH₃)

LC-MS (m/z): 595, 9 (M⁺)

Synthesis of coordination polymers (4a-f)

All coordination polymers were synthesized similarly by using stoichiometric ligand and various metal (II) salts. The general Synthesis is given below here.

First the bis ligand BTPT (59.4 g, 0.05m) was dissolved in DMSO solvent up to clear solution. To the warm solution added 0.1 m aqueous NaOH soluble maintaing with PH 7-8. The pasty mass was obtained and it was dissolved by addition of water and make to mark up to 500ml. So it is solution of disodium salt of BTPT of 0.1 M solution and 50 ml contain 2.97 g BTPT ligand. Now take 50 ml of BTPT solution in beaker and metal acetate (0.05m) in water was added into it. Stirred well, The precipitation digested on water bath, filtered washed and dried. Details of all five co-ordinate polymer are given in Table-1.

Table -1. Analysis of Ligand And Its Coordination Polymers

Ligands and its Coordination Polymers	mol. Wt.	Yield %	Elemental analysis (%)			
			C% Cald.	H% Cald.	N% Cald.	M% Cald.
			Found	Found	Found	Found
C30H34N4O9	594	68	60.6	5.76	9.42	-
			60.5	5.7	9.4	-
C30H32N4O9Cu ₂ ·2H ₂ O	692.54	69	52.06	5.24	8.09	9.18
			52	5.2	8	9.1
C30H32N4O9Ni ₂ ·2H ₂ O	687.71	68	52.42	5.28	8.15	8.54
			52.4	5.2	8.1	8.5
C30H32N4O9Co ₂ ·2H ₂ O	687.94	72	52.41	5.28	8.15	8.57
			52.4	5.2	8.1	8.5

C30H32N4O9Zn2+.2H2O	694.38	71	51.92	5.23	8.07	9.42
			51.9	5.2	8	9.4
C30H32N4O9Mn2+.2H2O	683.94	69	52.71	5.31	8.2	8.04
			52.7	5.3	8.1	8

BIOLOGICAL ACTIVITY

Antibacterial activity (in vitro) of Ligand BTPT and its contained polymers (BTPT-Mt)_n was evaluated against gram +ve bacteria (shown in table-1) [21,22] by agar diffusion method. The wells were dug in broth media with help of a sterile metallic borer. The test sample (1mg/ml in DMSO) was introduced in the wells. The reference antibacterial drug, ciprofloxacin was taken as a standard. The bacteria culture were introduced in to wells at CFU. The plates were then incubated immediately at 35°C for one day. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth Inhibition was compared with the standard drug. The control plate of DMSO in the biological screening placed separately and it resulted there is no antibacterial activity of DMSO.

The ligand BTPT on TGA analysis show the initial weight lost of 12.48% due to dicarboxylic. The theoretical value for decarboxylation is 12.68%. This is almost agreed with the predicted the product structure at BTPT.

Similarly Antifungal activity (in vitro) of ligand and the coordination polymers (shown in table1) was also tested against various fungi the antifungal drug, ketoconazole was used as a standard, Antifungal screening for all compounds and positive control was performed for 3 mg sample. The fungal strains were grown and maintained on potato dextrose agar plates, The cultures of the fungi were purified by single spore isolation technique. Each compounds in DMSO solution was prepared for testing against spore germination of each fungus. The fungal culture plates were inoculated and incubated (1000 ppm) at 25±2°C for 5 days. The plates were then observed and the diameter of the zone of inhibition (in mm) were measured. The percentage inhibition for fungi growth was calculated after 5 days using the formula given below:

$$\text{Percentage of inhibition} = 100(X-Y)/X$$

Where,

X Area of colony in control plate

Y Area of colony in test plate

RESULTS AND DISCUSSION

The synthesis of BTPT was performed by simple condensation reaction of tetrahydrophthalic

anhydride with trimethoprem drug. To the best of our knowledge BTPT has not been reported previously.

The FTIR spectrum of represent the BTPT bands of tetrahydroperphthaliv acid amide and trimethoprem moieties. The only discernible bands due to formation of new groups i.e. -COOH and -CONH are observed. The bands 3308 cm⁻¹ and 1730 cm⁻¹ are arisen respectively due to OH of COOH and CO of COOH stretching vibration, the bands due to around CONH also observed 3255 and 1680 cm⁻¹.

The NMR spectrum BTPT show signal due to proton present in the trimethoprem and tetrahydro phthalic acid moieties. The differentiate signals are at 10-89 ppm for COOH and 9.16 ppm for CONH protons. These further confirmed by ¹³C NMR value i.e 168.11 and 171.79 attributed to carboxylic carbon and amide carbon respectively. The ligand BTPT started to lose weight because of thermal degradation, Thermogram of product BTPT (Fig. 1) indicated that, the degradation occurred into two steps. First stage of degradation started from 180°C to 320°C might be attributed to decarboxylation of product BTPT. The value of wt. loss 14.7% is consistent with the theoretical value 14.81%. The second major stage 320°C to 700°C may attributed to the BTPT decomposition/ pyrolysis. The 4-5% char residue remained at 700°C.

SYNTHESIS OF COORDINATION POLYMERS

Physical properties

Elemental contain BTPT and its in good agreement with predicted structures. All the coordination polymers exhibited 1:1 metal a ligand (M: L) stoichiometry. The structure of coordination polymers were consistent with the FTIR, electronic spectra and TGA. The geometry of the central metal ion was confirmed by electronic spectra and magnetic susceptibility measurements. The degrees of polymerization (DP) for all coordination polymers are in the range of 5 to 6. All the data provides good evidence that the chelates are polymeric in nature. The suggested structure of the coordination polymers is shown in scheme 1.

Infrared spectra

Inspection of the IR spectrum of free ligand with those of spectra of coordination polymers results that the difference were observed. The band at 3526cm⁻¹. For carboxylic acid in ligand was

disappeared from the spectra of coordination polymers. However this coordination polymers exhibit more broadened band in their spectra at 2980-2990 cm^{-1} indicating the presence of coordinated water molecules [23]. The coordinated water in all the polymeric metal (II) complexes presents different peaks at 900-995 cm^{-1} (rocking) and 760-765 cm^{-1} (wagging). Whereas none of these vibrations appear in the spectrum at ligand. A strong band at 160 20 cm^{-1} in the spectra of coordination polymer are mainly due to COO^- anion. This indicates the involvement of oxygen atom of hydroxy group of $-\text{COOH}$ group in bonding with metal ion [24]. The band in the 625 – 640 cm^{-1} bands, Which were not present in the spectra of coordination polymers which indicates for $-\text{M}-\text{O}$ coordination bond.[25]. These overall data suggest that the carboxylate-O groups are involved in coordination with the metal (II) ion in coordination polymers, These Features confirmed the proposed structure of coordination polymers as shown in scheme – 1.

Magnetic moments and electronic spectral data

The geometry of the coordination polymers were obtained from their diffuse electronic spectral data

and magnetic moment values. The diffuse electronic spectrum of the $[\text{Cu}(\text{BTPT})(\text{H}_2\text{O})_2]_n$ shows two broad bands around 15,921 cm^{-1} and 22,726 cm^{-1} due to the $2\text{T}_{2g} \rightarrow 2\text{E}_g$ transitions and charge transfer, respectively, This suggested a distorted octahedral structure for the $[\text{Cu}(\text{BTPT})(\text{H}_2\text{O})]_n$ polymer. Which was further confirmed by its μ_{eff} value 1.98 B.M. The $[\text{Ni}(\text{BTPT})(\text{H}_2\text{O})_2]_n$ coordination polymer gives two absorption bands at 15,588 cm^{-1} , 22,960 cm^{-1} and 9,883 cm^{-1} due to $3\text{A}_{2g} \rightarrow 3\text{T}_{1g}(\text{F})$ and $3\text{A}_{2g} \rightarrow 3\text{T}_{1g}(\text{P})$ and $3\text{A}_{2g} \rightarrow 3\text{T}_{2g}$ transitions respectively. The $[\text{Co}(\text{BTPT})(\text{H}_2\text{O})_2]_n$ polymer gives two absorption bands at 22,956 cm^{-1} ,

15,547 cm^{-1} and 9,838 cm^{-1} corresponding to $4\text{T}_{1g}(\text{F}) \rightarrow 4\text{T}_{1g}(\text{P})$, $4\text{T}_{1g}(\text{F}) \rightarrow 4\text{A}_{2g}(\text{F})$ and $4\text{T}_{1g}(\text{F}) \rightarrow 4\text{T}_{2g}(\text{F})$ transitions respectively, indicated distorted octahedral configuration for the $[\text{Ni}(\text{BTPT})(\text{H}_2\text{O})]_n$ and $[\text{Co}(\text{BTPT})(\text{H}_2\text{O})]_n$ polymers [26]. This configuration was further confirmed by its μ_{eff} value 3.10 B.M and 4.41 B.M.

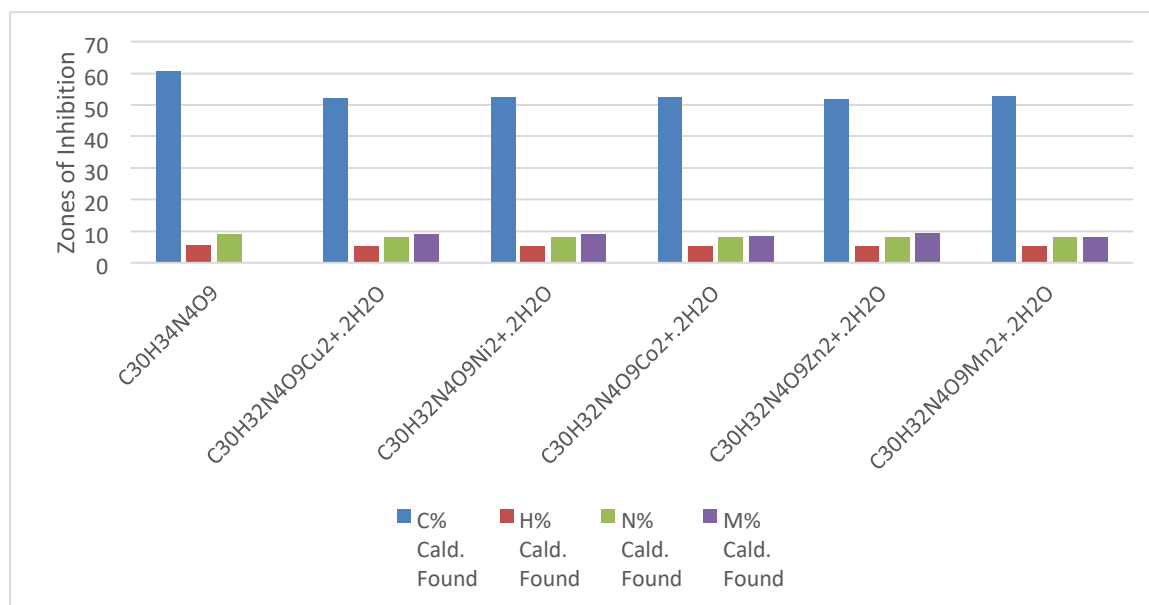


Fig.1 Antimicrobial activity of ligand and its coordination polymers

The spectrum of $[\text{Mn}(\text{BTPT})(\text{H}_2\text{O})_2]_n$ show weak bands at 16,452, 17,740 and 23,176 cm^{-1} assigned to the transition $6\text{A}_{1g} \rightarrow 4\text{T}_{1g}(4\text{G})$, $6\text{A}_{1g} \rightarrow 4\text{T}_{2g}$ and $6\text{A}_{1g} \rightarrow 4\text{A}_{1g}, 4\text{E}_g$ respectively, suggesting an distorted octahedral structure for the $[\text{Mn}(\text{BTPT})(\text{H}_2\text{O})]_n$ polymer [27]. This configuration was further confirmed by its μ_{eff} value 5.81 B.M. AS the spectrum of the $[\text{Zn}(\text{BTPT})(\text{H}_2\text{O})_2]_n$ polymer is not well intereprted, but its μ_{eff} value shows that it

is diamagnetic as expected examination of the magnetic moments μ_{eff} of all coordination polymers reveled that all polymers except Zn(II) metal ion polymer are paramagnetic while Zn(II) metal ion polymer is diamagnetic.

Thermal analysis

The thermal behaviour of all the samples to determined by Perkin Elmer TGA analyzer. In all

the coordination polymers, decomposition occurred in two steps (Fig 1). First step occurred between 100°C and 200°C which might be due to loss of associated water molecules. Second step occurred between 200°C and 700°C, exhibits a mass loss corresponding to decomposition of ligand part in polymer. The weight loss of coordination polymers was noticed between 300 and 600°C. The rate of degradation is high between 400- 600°C. Then may be due to acceleration of degradation by metal oxide form 'in situ'. Each polymer loses about 80% of its weight when heated up to 700°C on the basis of the relative decomposition (% weight loss) and the nature of thermogram, the coordination polymers may be arranged in order of their increasing stability as: Cu<Ni<Co<Zn<Mn.

Biological activity

The histogram (Fig 2) shows that the antibacterial activity of bis ligand BTPT and its coordination polymers agent both gram – positive and gram – negative bacteria. The zone of inhibition (ZOI) is in the range of 18 mm to 38 mm depending upon the nature of compound. The results also show that the copper coordination polymer bears higher toxicity. For bacteria this might be due to increase in the lipophilic behaviour of metal atom, which favours its permeation through the lipid bacterial membrane. Thus increasing the hydrophobic character and liposolubility of the molecule in cell, and hence enhances the biological utilization preparation of test sample. The biological activity of compounds also depends on nature of the ligand, concentration, lipophilicity, nature of metal ion, coordination sites and geometry of the complex.

Antifungal activity

Similarly as antibacterial activity the antifungal activity of ligand and its coordination polymer exhibit good antifungal activity of their histogram shown in fig 2.

Conclusion

The bis ligand and its coordination polymers were prepared in good amount of yield and were duly characterized. In the coordination polymers ligand coordinates to central metal atom with 4 coordination bonds along with two as coordinated water molecule. The structure of ligand and its coordination polymers are agreed spectral and thermal studies. The geometry of the central metal ion was confirmed by electronic spectra and magnetic moments. All the data confirmed that the chelates are polymeric in nature. All these polymers do not melt up to 400°C. The polymers have

moderate thermal stability and good antimicrobial activity.

Acknowledgments:

The authors would like to thank the Department of Chemistry, PAHER University, Udaipur, Rajasthan, for providing the infrastructure to carry out the research work.

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