

Transition Metal Complexes of Ethopropazine: Synthesis and Characterization

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Abstract Ethopropazine (EP) or profenamine is a phenothiazine derivative, N¹⁰-(2-diethylaminopropyl)phenothiazine (Figure.1), used as an antiparkinsonian drug that has anticholinergic, antihistamine, and antiadrenergic actions. Transition metal complexes of ZnBr₂, CdBr₂, CdI₂, and HgBr₂ have been synthesized using EP as the main ligand and purified by recrystallization in MeOH. These products have been characterized based on their elemental analysis, molar conductance, magnetic susceptibility, IR and ¹H-NMR data. The molecular formulations of the new mononuclear complexes have been found to be [Zn(C₁₉H₂₄N₂S.HCl)₂]Br₂, [Cd(C₁₉H₂₄N₂S.HCl)₂]Br₂, [Cd(C₁₉H₂₄N₂S.HCl)₂]I₂ and [Hg(C₁₉H₂₄N₂S.HCl)(C₁₉H₂₄N₂S.HBr)(OH₂)]Br₂, where the ligand, EP = C₁₉H₂₄N₂S. All the complexes show an ionic ratio of 1:2 in acetonitrile solutions. Molecular structures have been proposed. The four-coordinate complex cations of [Zn(C₁₉H₂₄N₂S.HCl)₂]Br₂, [Cd(C₁₉H₂₄N₂S.HCl)₂]Br₂, and [Cd(C₁₉H₂₄N₂S.HCl)₂]I₂ contain an sp³ hybridized metal(II) center each with a tetrahedral environment. On the other hand, six-coordinate cationic species of [Hg(C₁₉H₂₄N₂S.HCl)(C₁₉H₂₄N₂S.HBr)(OH₂)]Br₂ complex with an sp³d² hybridized metal center exhibits the octahedral geometry.

Keywords Ethopropazine Hydrochloride, Transition Metal Complexes, Synthesis, Characterization, Analysis

1. Introduction

The study of metal-N-alkylphenothiazine complexes has been growing into a research field having special interest both in preparative and biological activities[1]. N-alkylphenothiazines (NPTZs) are biologically active heterocyclic compounds. Ethopropazine or profenamine (parsidol, parsidan or parkin), is a phenothiazine derivative, N-10-(2-diethylaminopropyl)phenothiazine (Figure.1), used as an antiparkinsonian agent that has anticholinergic, antihistamine, and antiadrenergic actions. Considering the fact that some platinum(II)-NPTZ complexes are used as antitumor agents[2], it is likely that other transition metal-NAPTZ complexes would behave as more potent and/or less toxic drugs than the free ligands themselves. Furthermore, a considerable increase in the fungicidal activity of some NPTZs due to their complexation with copper(II)[3,4] and uranium oxide[5] has been reported.

Previously, some studies of transition metal-NPTZ complexes have been reported by several workers[4-16]. Keshavan and co-workers[4-7] have synthesized and characterized compounds of selected NPTZs with molybdenum(IV), tungsten(IV), ruthenium(II/III) and copper(II). Keshavan and Janardhan[7] and Gowda and

Jayarama[8] have reported mononuclear copper(II) and zinc(II) complexes of NPTZs. Kroener et al.[9] have studied the X-ray crystal structures of several cis- and trans-bis(2,2'-bipyridine)-bis(phenothiazine-S) ruthenium (II) hexafluorophosphates. Made Gowda et al. have previously studied the synthesis and characterization of coordination compounds of NPTZs with rhodium (II/III), rhenium (VII), iridium (III/IV), molybdenum (IV/V), zinc(II), palladium(II) and mercury(II)[10-16]. Chaitanya Lakshmi et al have reported transition metal-pyridoxine complexes[17-19]. In continuation of the project on the coordination chemistry of NPTZ com-plexe, the study of synthesis and characterization of transition metal complexes using EP.HCl, as the main ligand, is reported.

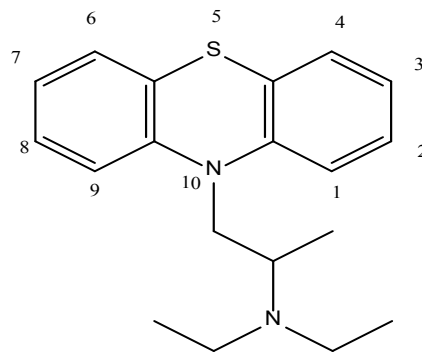


Figure. 1. Molecular structure of ethopropazine

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2. Experimental

2.1. Materials

Metal salts, zinc bromide, cadmium bromide, cadmium iodide and mercuric bromide, and the ligand, ethopropazine hydrochloride (99% purity) from Aldrich/Sigma Chemical Company were used as supplied.

All solvents such as methanol, ethanol, diethyl ether, dimethyl sulfoxide, dimethyl formamide and DMSO- d_6 (Cambridge isotope laboratories Inc.) were of ACS reagent grade and were used without further purification. Double distilled water was used in all preparations.

2.2. Physical Measurements

Elemental analyses of the complexes were performed by the Microanalysis Laboratory, University of Illinois, Urbana-Champaign, IL. Molar conductance was determined with a Conductance-Resistance meter. UV-Visible spectra were recorded on a Shimadzu UV1601 spectrophotometer. The infrared spectra were recorded on a Shimadzu FTIR 8400 spectrometer using potassium bromide pellets. $^1\text{H-NMR}$ spectra were recorded on a JEOL-300 MHz FT-NMR spectrometer in DMSO- d_6 . Mass magnetic susceptibilities of the complexes were measured at room temperature with a Johnson Matthey magnetic susceptibility balance which uses $\text{HgCo}(\text{SCN})_4$ as a calibrant.

2.3. General Synthesis of Complexes

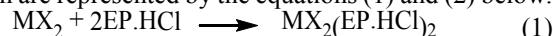
A solution of the transition metal salt (x mmol) (ZnBr_2 , CdBr_2 , CdI_2 and HgBr_2) dissolved in a minimum volume of MeOH was slowly added with stirring to a concentrated methanolic solution of EP.HCl ($2x$ mmol) and refluxed overnight. Each reaction mixture was cooled overnight at 0°C and the precipitated product isolated by suction filtration

through a medium-glass fritted funnel. The product was washed with small amounts of cold water first followed by methanol, air-dried, and dried in vacuo over anhydrous CaSO_4 in a desiccator. Each crude product was recrystallized twice from its hot saturated solution in methanol. The yield was determined.

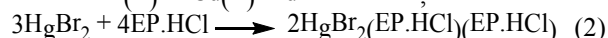
3. Results and Discussion

The elemental analysis data of the new metal-EP.HCl complexes listed in Table 1 show that the theoretical values are in agreement with the experimental ones. Physical properties of the complexes are presented in Table 2. All the complexes are colorless, except $\text{ZnBr}_2(\text{EP.HCl})_2$, which is grayish. They are microcrystalline and stable at room temperature with percent yields ranging from 47 to 83. They have a narrow range of melting points indicating their relative purity. The complexes are slightly soluble in common polar solvents such as MeOH and readily soluble in DMF and DMSO.

The stoichiometric reactions involved in the complex formation are represented by the equations (1) and (2) below.



Where $\text{M} = \text{Zn}(\text{II})$ or $\text{Cd}(\text{II})$ and X is Br or I,



In the reaction for the formation of Hg(II) complex (eq. (2)), the larger Hg(II) ion as a soft acid tends to preferentially coordinate with the soft base Br^- as compared to the relatively harder Cl^- ion of the ligand. The molecular formulations and structures of the complexes were determined on the basis of elemental analysis, molar conductance, UV-Vis, IR, and NMR data.

Table 1. Elemental data of the metal-EP-HCl complexes

Complex, molecular formula	Ionic formula* (molar mass, g/mol)	%C, exp (calcd.)	%H, exp (calcd.)	%N, exp (calcd.)
$\text{ZnBr}_2(\text{EP.HCl})_2$	$[\text{Zn}(\text{C}_{19}\text{H}_{24}\text{N}_2\text{S.HCl})_2]\text{Br}_2$ (923.07)	49.97 (49.44)	5.62 (5.46)	6.18 (6.07)
$\text{CdBr}_2(\text{EP.HCl})_2$	$[\text{Cd}(\text{C}_{19}\text{H}_{24}\text{N}_2\text{S.HCl})_2]\text{Br}_2$ (970.09)	46.82 (47.00)	5.20 (4.90)	5.73 (5.70)
$\text{CdI}_2(\text{EP.HCl})_2$	$[\text{Cd}(\text{C}_{19}\text{H}_{24}\text{N}_2\text{S.HCl})_2]\text{I}_2$ (1064.1)	42.29 (42.00)	4.57 (4.50)	5.15 (5.20)
$\text{HgBr}_2(\text{EPHCl})(\text{EPHBr}).2\text{H}_2\text{O}$	$[\text{Hg}(\text{C}_{19}\text{H}_{24}\text{N}_2\text{S.HCl})(\text{C}_{19}\text{H}_{24}\text{N}_2\text{S.HBr})(\text{OH}_2)]\text{Br}_2$ (1058.3)	40.30 (40.07)	4.30 (4.74)	5.03 (4.92)

*Based on molar conductances shown in Table 2.

Table 2. Physical properties of the metal-EP-HCl complexes

Complex	Melting point ($^\circ\text{C}$)	Molar conductance ($\text{mho cm}^2 \text{ mol}^{-1}$)* (ionic ratio)	Mass magnetic susceptibility (10^{-6} cgs)	Color	Yield (%)
$\text{ZnBr}_2(\text{EP.HCl})_2$	160-163	196 (1:2 electrolyte)	-0.705	Lt. grayish	82.9
$\text{CdBr}_2(\text{EP.HCl})_2$	160-165	238 (1:2 electrolyte)	-0.22	colorless	46.7
$\text{CdI}_2(\text{EP.HCl})_2$	142-145	228 (1:2 electrolyte)	-0.05	colorless	67.2
$\text{HgBr}_2(\text{EPHCl})(\text{EPHBr}).2\text{H}_2\text{O}$	169-170	184 (1:2 electrolyte)	-0.60	colorless	62.4

* 1.00 mM complex solution in acetonitrile

The molar conductances for the complexes, measured in acetonitrile solution, presented in Table 2 indicate that all complexes behave as 1:2 electrolytes. Mass magnetic susceptibilities (X_m) for the complexes are in the range of -0.05×10^{-6} to -0.705×10^{-6} c.g.s at 23°C (Table.2). The magnetic data are consistent with the metal systems which are of low spin (diamagnetic) type due to the absence of unpaired electrons in the metal(II) d-subshell. The metal ions containing a common d-electron configuration of d^{10} exhibit diamagnetism, as expected.

The molecular formulations listed in Table 1 show that each complex contains a metal(II) center and two ethopropazine hydrohalide molecules as principal ligands.. Additionally, the complex of $HgBr_2$ contains two H_2O molecules as water of hydration.

The UV-Visible spectral data of the ligand (EP.HCl) and its complexes are presented in Table 3. The broad bands observed in the region of 260-307 nm in the spectra of all complexes can be attributed to the intraligand transitions. The molar absorptivities of the complexes falling in the range of 4.58×10^4 to 5.49×10^4 L mol⁻¹ cm⁻¹, are higher than that of the ligand in the free state which is 1.74×10^4 L mol⁻¹ cm⁻¹. The shift in the bands in UV- Vis spectra are attributed to the intramolecular transitions of $\pi \rightarrow \pi^*$ type. This may be taken as an indirect evidence for the involvement of N atoms of EP in the coordination process. The electronic spectra confirm the complexation between metal ions and the EP.HX ligand[15-23].

Relevant IR absorption frequencies of the EP.HCl ligand and its metal complexes are presented in Table 4. In the uncomplexed EPHCl, the presence of a broad band in the 2080-2700 cm⁻¹ range is assigned to the interaction of the quaternary ammonium ion, $(R_3NH)^+$, with a halide ion[12-15,21,22]. In the IR spectra of the complexes, this band has shifted with diminished intensity suggesting that the exocyclic N atom of the alkylamino group is indirectly involved in coordination with the metal center. A band observed in the 3047-2870 cm⁻¹ region in the spectrum of EP.HCl may be assigned to the heterocyclic nitrogen atom carrying an alkyl amine side chain[21,22]. This band of EP.HCl shows a shift upon complexation suggesting its coordination to the metal(II) center[10-14]. In addition, $HgBr_2$ complex shows a broad band in the 3240-3600 cm⁻¹ region, supporting the hydrogen bonded OH interactions of the water molecules. Additionally, the Hg(II) complex

spectrum shows that bands in the 680-700 cm⁻¹ region, attributable to the heterocyclic C-S-C modes, undergo a shift, suggesting the involvement of heterocyclic S atom as a coordination site[12,15,22]. The ¹H-NMR data for the ligand, EP.HCl, and its complexes are presented in Figure. 2 and Table 5. Some general trends exist in the proton-NMR spectra of the EPHCl ligand and all its complexes. In the spectra of the uncomplexed EP.HCl and its complexes, the broad singlet due to the quaternary ammonium ion, $(R_3NH)^+$, of the free ligand, which occurs far downfield (δ 10.3), has shifted upfield in the spectra of all the complexes indicating the existence of H-bonding between the exocyclic N atom and the halogen atom bonded to the metal(II) center [12,15,24].

Crystals of sufficient quality required for x-ray crystallographic analysis of the complexes could not be grown. Based on the discussed analytical data, tentative structures have been proposed for the complexes based on several factors (Figure. 3.a-3.b). Similar structures have been reported for other transition metal complexes of phenothiazines and pyridoxine[12-15,17-19,24]. The ionic ratio from the molar conductance data is found to be 1:2 for all the complexes, thus supporting the formula as $[M(EP.HCl)_2]^{2+} 2X^-$ for the zinc(II) and cadmium(II) complexes. The ionic formula for the Hg(II) complex is $[Hg(EP.HCl)(EP.HBr)(OH_2)_2]^{2+} 2Br^-$. The four-coordinate complex cations of the Zn(II) and Cd(II) complexes contain an sp^3 hybridized metal(II) center with a tetrahedral environment (3.a). On the other hand, the six-coordinate cationic species of Hg(II) complex with an sp^3d^2 hybridized metal center exhibits the octahedral geometry (3.b). The presence of hydrogen bond between the exocyclic N atom and the halogen atom bonded to the M(II) center is confirmed by the upfield shift of the broad singlet at 10.3 ppm in the ¹H-NMR spectra of the complexes. The $[Hg(EPHCl)(EPHBr)(OH_2)_2]Br_2$ complex containing a Br^- ion in place of original Cl^- ion as part of the EP ligand can be justified based on the Pearson's HSAB interactions. Since Hg(II) is a soft acid, it prefers to coordinate with a soft base. The source of Br^- ion is the reactant $HgBr_2$ used in the reaction. The distorted octahedral geometry is supported by its diamagnetic behaviour evident from the magnetic susceptibility data (Table 2)[14,15]. Similar transition metal complex structures have been reported in the literature[10-15].

Table 3. UV-Visible spectral data of the metal-EP.HCl complexes

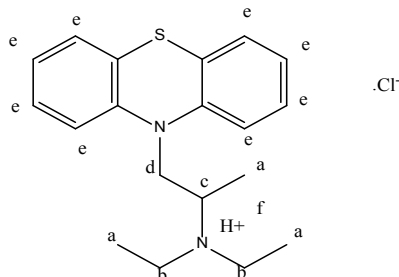
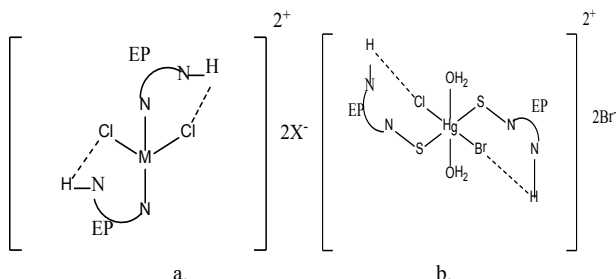
Complex/Ligand	λ_{max} (nm)	Molar absorptivity (ϵ) (10^4 , L mol ⁻¹ cm ⁻¹)	Transition
EP.HCl	260.5	1.74	$\pi \rightarrow \pi^*$
$ZnBr_2(EP.HCl)_2$	262.5	4.58	$\pi \rightarrow \pi^*$
$CdBr_2(EP.HCl)_2$	261.0	4.92	$\pi \rightarrow \pi^*$
$CdI_2(EP.HCl)_2$	260.5	5.49	$\pi \rightarrow \pi^*$
$HgBr_2(EP.HCl)(EP.HBr).2H_2O$	262.0	5.34	$\pi \rightarrow \pi^*$

Table 4. Important IR absorption bands of EP.HCl and its metal complexes

Complex/Ligand	Absorption of (R_3NH^+) (cm^{-1})	Absorption of ($>N-R^1$) (cm^{-1})	Absorption of (C-S-C) (cm^{-1})	Absorption of (OH) (cm^{-1})
EP.HCl	2700-2080	3047-2870	700-680	-
ZnBr ₂ (EP.HCl) ₂	2500-2100	3088-2880	700-680	-
CdBr ₂ (EP.HCl) ₂	2450-2200	3055-2864	700-680	-
CdI ₂ (EP.HCl) ₂	2560-2100	3091-2872	700-680	-
HgBr ₂ (EP.HCl)(EP.HBr).2H ₂ O	2550-2100	3055-2868	690-625	3600-3240

Table 5. ¹H-NMR data of EP.HCl and its metal complexes*

Ligand/Complex	Chemical shift (multiplicity, protons) (Fig. 2)
EP.HCl	(a) 1.15-1.30 (m,9H), (b) 3.05-3.20 (m,4H), (c) 3.57 (m,1H), (d) 4.15- 4.55 (m,2H), (e) 7.00-7.36 (m,8H), (f) <u>10.30</u> (br.s,1H)
ZnBr ₂ (EP.HCl) ₂	(a) 1.18-1.32 (m,9H), (b) 3.15-3.38 (m,4H), (c) 3.57 (m,1H), (d) 4.16-4.43 (m,2H), (e) 7.00-7.29 (m,8H), (f) <u>9.19</u> (br.s,1H)
CdBr ₂ (EP.HCl) ₂	(a) 1.18-1.30 (m,9H), (b) 3.15-3.33 (m,4H), (c) 3.57 (m,1H), (d) 4.16-4.4 (m,2H), (e) 7.00-7.29 (m,8H), (f) <u>9.11</u> (br.s, 1H)
CdI ₂ (EP.HCl) ₂	(a) 1.17-1.30 (m,9H), (b) 3.17-3.38 (m,4H), (c) 3.57 (m, 1H) (d) 4.16-4.37 (m, 2H), (e) 7.00-7.29 (m, 8H), (f) <u>8.91</u> (br.s,1H)
HgBr ₂ (EP.HCl)(EP.HBr).2H ₂ O	(a) 1.17-1.30 (m,9H), (b) 3.27-3.37 (m,4H), (c) 3.57 (m,1H), (e) 7.24-7.29 (m,8H), (f) <u>9.22</u> (br.s, 1H)

* In DMSO-d₆**Figure 2.** Molecular structure of the EP.HCl ligand showing different types of protons**Figure 3.** a. Proposed general structure for the $[M(EP.HCl)_2]^{2+}$ complex ions, where $M = Zn(II)$ and $Cd(II)$; $X = Br^-$ or I^- ; b. Proposed structure for the $[Hg(EPHCl)(EPHBr)(OH)_2]^{2+}$ complex ion

4. Conclusions

Transition metal(II)- ethopropazine hydrochloride complexes ethopropazine hydrochloride have been prepared and characterized using such analytical data as elemental analysis, molar conductance, magnetic susceptibility, IR and ¹H-NMR. The molecular structures of the metal complexes have been presented. The future plan of work includes the determination of free radical and antioxidant activities using standard assays.

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