

Synthesis and Characterization of Transition Metal Complexes of Chlorpromazine

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Abstract The chlorpromazine (CP) complexes of the transition metal ions, Zn(II), Cd(II) and Hg(II), have been synthesized. The complexes have been characterized by their elemental analysis, molar conductivity, magnetic susceptibility, UV-Visible, IR and ¹H-NMR data. The molecular formulations of the new mononuclear complexes have been found to be [ZnBr(C₁₇H₁₉ClN₂S.HCl)₂]Br, [CdBr(C₁₇H₁₉ClN₂S.HCl)₂]Br.H₂O, [Cd(C₁₇H₁₉ClN₂S.HCl)₂]I₂ and [HgBr((C₁₇H₁₉ClN₂S.HBr)₂)Br.2H₂O, where the ligand chlorpromazine or CP = C₁₇H₁₉ClN₂S. The complexes, [ZnBr(C₁₇H₁₉ClN₂S.HCl)₂]Br, [CdBr(C₁₇H₁₉ClN₂S.HCl)₂]Br.H₂O, and [HgBr((C₁₇H₁₉ClN₂S.HBr)₂)Br.2H₂O, behave in DMF solutions as 1:1 electrolytes while the other complex, [Cd(C₁₇H₁₉ClN₂S.HCl)₂]I₂, shows an ionic ratio of 1:2 in solution. Molecular structures have been proposed showing a square pyramidal environment around each metal center with an sp³d hybridization for the five-coordinate complexes, [ZnBr(C₁₇H₁₉ClN₂S.HCl)₂]Br, [CdBr(C₁₇H₁₉ClN₂S.HCl)₂]Br.H₂O, and [HgBr((C₁₇H₁₉ClN₂S.HBr)₂)Br.2H₂O. In the four-coordinate [Cd(C₁₇H₁₉ClN₂S.HCl)₂]I₂ complex, the Cd(II) center with an sp³ hybridization has a tetrahedral environment around it.

Keywords Chlorpromazine, Metal Complexes, Synthesis, Characterization, Analysis

1. Introduction

The N-alkylamino phenothiazine derivatives (NPTZs) including chlorpromazine (CP) are biologically active heterocyclic compounds. Structurally, CP is a phenothiazine substituted with chlorine and *tert*-alkylamine groups at 2 and 10 positions, respectively (Fig. 1). The NPTZ derivatives find extensive applications in the field of medicine as antipsychotic, anxiolytic, antiemetic and inodilationdrugs[1-3].

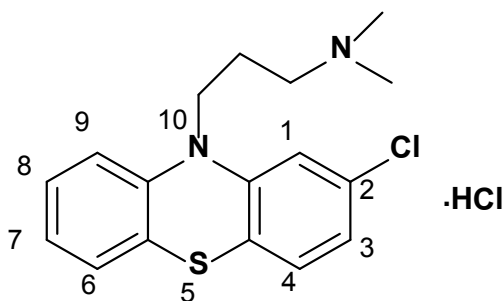


Figure 1. Molecular structure of chlorpromazine hydrochloride

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 some 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 some 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]. We here report the synthesis and characterization of four transition metal complexes with CP.HCl as the main ligand.

2. Experimental

2.1. Materials

Metal salts, zinc bromide, cadmium bromide, cadmium iodide and mercuric bromide, and the ligand, chlorpromazine hydrochloride (CP.HCl; 99% pure) (Aldrich/Sigma Chemical Company) were used as supplied.

All solvents such as methanol, ethanol, diethyl ether, dimethyl sulfoxide, dimethyl formamide and DMSO-d₆ (Cambridge isotope laboratories Inc.) were of ACS reagent grade and were used without further purification. Double

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distilled water was used in all preparations.

2.2. Physical Measurements

Elemental analyses of complexes were performed by Microanalysis Laboratory, University of Illinois, Urbana-Champaign, IL. Molar conductance was determined with the 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. ¹H-NMR spectra were recorded on a JEOL-300MHz FT-NMR spectrometer in DMSO-d₆. Mass magnetic susceptibilities of the complexes were measured at room temperature with a Johnson Matthey magnetic susceptibility balance which uses HgCo(SCN)₄ as a calibrant.

2.3. General Synthesis of Complexes

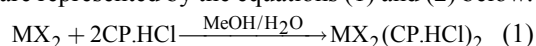
A solution of the transition metal salt (x mmol) (ZnBr₂, CdBr₂, CdI₂ and HgBr₂) dissolved in a minimum volume of MeOH was slowly added with stirring to a concentrated methanolic solution of CP.HCl (2x mmol) and refluxed overnight. Each reaction mixture was cooled overnight at 0°C and the precipitated 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 CaSO₄ in a desiccator. Each crude product was recrystallized twice from a hot saturated solution of the crude sample in

methanol. The yield was determined.

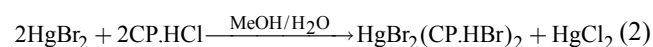
3. Results and Discussion

The elemental analysis data listed in Table 1 show that the theoretical values are in agreement with the experimental ones. Physical properties of the new metal-CP.HCl complexes are presented in Table 2. Complexes are colored, microcrystalline, and relatively stable at room temperature with percent yields ranging from 71 to 93. The complexes are slightly soluble in common polar solvents such as MeOH and readily soluble in DMF and DMSO. All complexes except Zn(II) complex are insoluble in water.

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



where M = Zn(II) or Cd(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-CP.HCl complexes

Complex, molecular formula	Ionic formula* (mol. Wt, g/mol)	%C exp (Theor)	%H exp (Theor)	%N exp (Theor)
ZnBr ₂ (CP.HCl) ₂	[ZnBr(C ₁₇ H ₁₉ ClN ₂ S.HCl) ₂]Br (935.86)	43.09 (43.6)	4.42 (4.3)	5.89 (5.98)
CdBr ₂ (CP.HCl) ₂ .H ₂ O	[CdBr(C ₁₇ H ₁₉ ClN ₂ S.HCl) ₂]Br.H ₂ O (1000.89)	40.55 (40.79)	3.84 (4.22)	5.50 (5.59)
CdI ₂ (CP.HCl) ₂	[Cd(C ₁₇ H ₁₉ ClN ₂ S.HCl) ₂] ₂ (1076.88)	37.46 (37.9)	3.49 (3.74)	5.02 (5.2)
HgBr ₂ (CP.HBr) ₂ .2H ₂ O	[HgBr(C ₁₇ H ₁₉ ClN ₂ S.HBr) ₂]Br.2H ₂ O (1071.07)	34.11 (34.14)	3.28 (3.7)	4.6 (4.68)

*Based on conductances shown in Table 2.

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

Complex	Melting point (°C)	Molar conductance (mho cm ² mol ⁻¹)* (Ionic ratio)	Mass magnetic susceptibility (10 ⁻⁶ cgs)	Color	Yield (%)
ZnBr ₂ (CP.HCl) ₂	55-63	103.6 (1:1 electrolyte)	4.15	Lt. purple	71.0
CdBr ₂ (CP.HCl) ₂ .H ₂ O	50-59	103.6 (1:1 electrolyte)	5.89	Lt. purple	89.8
CdI ₂ (CP.HCl) ₂	60-70	124.3* 217.6** (1:2 electrolyte)	1.39 (2.17)	Lt. yellow	72.6
HgBr ₂ (CP.HBr) ₂ .2H ₂ O	52-60	82.88 (1:1 electrolyte)	5.35 (3.84)	Lt. gray-ish-yellow	93.2

* 1.00 mM complex solution in DMF and ** acetonitrile

The molar conductances for the complexes, measured in DMF and acetonitrile solutions, presented in Table 2 indicate that all complexes behave as 1:1 electrolytes (except CdI_2 complex which has 1:2 ionic ratio). Magnetic data of the complexes differ from the normal behavior of the d^{10} metal ions, Zn(II), Cd(II) and Hg(II), which are probably due to impurities[20]. The molecular formulations listed in Table 1 show that each complex contains a metal center and two chlorpromazine hydrochloride molecules as principal ligands. The other ligands include bromide and iodide ions. Additionally, complexes of CdBr_2 and HgBr_2 contain one and two H_2O molecules, respectively, as water of hydration.

The UV-Visible spectral data of the ligand (CP.HCl) and its complexes are presented in Table 3. The maximum absorption band at 254.50 nm for CP.HCl with a high molar absorptivity ($\epsilon = 1.69 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) suggesting a $\pi \rightarrow \pi^*$ transition is shifted for the metal-CP.HCl complexes to a lower wavelength with high varying molar absorptivities ($\epsilon = (0.595 - 4.07) 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) indicating intraligand transitions of the $\pi \rightarrow \pi^*$ type that undergo hypsochromic shifts, confirming the metal-CP complexation[15-23].

Relevant IR absorption frequencies of the CP.HCl ligand and its metal complexes are presented in Table 4. In the uncomplexed CPHCl, the presence of a broad band in the 2000-2730 cm^{-1} range is assigned to the interaction of the quaternary ammonium ion, $(\text{R}_3\text{NH})^+$ ion with a halide ion[12-15,21,22]. In the IR spectra of the metal-CP.HCl

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 3000-2800 cm^{-1} region in the spectrum of CP.HCl may be assigned to the heterocyclic nitrogen atom carrying an alkyl amine side chain[21,22]. This band of CP.HCl shows a shift upon complexation suggesting its coordination to the metal(II) center[10-14]. In addition, CdBr_2 and HgBr_2 complexes show a broad band in the 3250-3560 cm^{-1} region, supporting the hydrogen bonded OH interactions of the water of hydration. The Hg(II) complex spectrum shows that bands in the 600-700 cm^{-1} and 715-740 cm^{-1} regions, attributable to the heterocyclic C-S-C modes, undergo a shift, suggesting heterocyclic sulfur atom as a coordination site[12,15,22]. The ^1H NMR data for the ligand, CP.HCl, and its complexes are presented in Table 5. Comparing the absorption peaks/multiplets and the chemical shifts of the uncomplexed ligand with those of corresponding complexes, it could be inferred that some of the resonance signals experience shifts upon complexation. Especially, in the free CP.HCl ligand, the broad singlet which occurs far down field (δ 10.80), attributable to the exocyclic $(\text{R}_3\text{NH})^+$ proton, has shifted upfield on complexation indicating a change in this proton environment. This indirectly supports the existence of intramolecular hydrogen bonding between $(\text{R}_3\text{NH})^+$ and X^- of the MX_3 moiety[12,15,24].

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

Complex/Ligand	λ_{max} (nm)	Molar absorptivity ($10^4, \text{M}^{-1} \text{ cm}^{-1}$)	Transition
CP.HCl	254.50	1.69	$\pi \rightarrow \pi^*$
$\text{ZnBr}_2(\text{CP.HCl})_2$	252.50	1.25	$\pi \rightarrow \pi^*$
$\text{CdBr}_2(\text{CP.HCl})_2 \cdot \text{H}_2\text{O}$	239.50	4.07	$\pi \rightarrow \pi^*$
$\text{CdI}_2(\text{CP.HCl})_2$	255.50	1.12	$\pi \rightarrow \pi^*$
$\text{HgBr}_2(\text{CP.HBr})_2 \cdot 2\text{H}_2\text{O}$	237.50	0.595	$\pi \rightarrow \pi^*$

Table 4. Important IR absorptions of CP.HCl and its metal complexes

Complex/ Ligand	Absorption of (R_3NH^+) (cm^{-1})	Absorption of $(>\text{N-R}^1)$ (cm^{-1})	Absorption of (C-S-C) (cm^{-1})	Absorption of (OH) (cm^{-1})
CP.HCl	2730-2000	3000-2800	750	-
$\text{ZnBr}_2(\text{CP.HCl})_2$	2900-2750	3100-2930	754	-
$\text{CdBr}_2(\text{CP.HCl})_2 \cdot \text{H}_2\text{O}$	2820-2600	3200-2860	754	3550-3250
$\text{CdI}_2(\text{CP.HCl})_2$	2810-2640	3200-2900	752	-
$\text{HgBr}_2(\text{CP.HBr})_2 \cdot 2\text{H}_2\text{O}$	2820-2675	3200-2940	752	3600-3230

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

Ligand/Complex	Chemical shift (multiplicity, protons)
CP.HCl	2.08 (m,2H), 2.68 (s,6H), 3.13 (t,2H), 4.00 (t,2H), 6.95-730 (m,7H), 10.80 (br.s, 1H).
$\text{ZnBr}_2(\text{CP.HCl})_2$	2.00-2.05 (m,2H), 2.73 (s,6H) 3.11-3.16 (t,2H), 3.94-3.99 (t,2H), 7.13-7.22 (m,7H), 9.35 (br.s,1H).
$\text{CdBr}_2(\text{CP.HCl})_2 \cdot \text{H}_2\text{O}$	2.00-2.05 (m,2H), 2.74 (s,6H), 3.11-3.16 (t,2H), 3.994-3.997 (t,2H), 7.01-7.22 (m,7H), 9.37 (br.s,1H).
$\text{CdI}_2(\text{CP.HCl})_2$	1.99-2.04 (m,2H), 2.74 (s,6H), 3.11-3.16 (t,2H), 3.94-3.99 (t,2H), 7.13-7.22 (m,7H), 9.25 (br.s,1H)
$\text{HgBr}_2(\text{CP.HBr})_2 \cdot 2\text{H}_2\text{O}$	2.02-2.08 (m,2H), 2.79 (s,6H), 3.11-3.16 (t,2H), 3.94-3.99 (t,2H), 7.02-7.22 (m,7H), 9.32 (br.s,1H).

* In DMSO-d_6

Crystals of sufficient quality required to permit x-ray crystallographic analysis of the complexes could not be grown. Based on the discussed analytical data, tentative square pyramidal structures have been proposed for the complexes (Fig. 2.a-2.c). Similar structures have been reported for other phenothiazine-transition metal complexes[12-15,24]. A square pyramidal geometry around each M(II) metal center (sp^3d hybridized), due to the steric constraints of the bidentate ligand not favoring a trigonal bipyramidal arrangement, involves two CP.HCl ligands and a monodentate bromide ion. With the relatively hard acids, Zn(II) and Cd(II) (Fig. 2.a), the CP.HCl binds through its heterocyclic N atom (as a hard base) directly and through the exocyclic N atom indirectly through the H-bonding with a halide ion. The scorpion tail like N-alkylamino group with its flexible bending mode is well suited for this kind of intramolecular H-bonding in NPTZs. The two protonated (CPH⁺) ligands coordinate to the MX₃ unit of the compound through two N atoms resulting in a square planar MX₂N₂ unit, which along with an axial M-X bond represents a square-pyramidal geometry for each complex. In the [HgBr(C₁₇H₁₉ClN₂S.HBr)₂][Br.2H₂O] complex (Fig. 2.b), the relatively soft acid, Hg(II) binds to the CP ligand through its heterocyclic S atom (as a soft base) directly and through the exocyclic N atom indirectly through its H-bonding with a halide ion. In the [Cd(C₁₇H₁₉ClN₂S.HCl)₂]₂ complex (Fig. 2.c), the Cd(II) center with an sp^3 hybridization has a tetrahedral environment around it[14,15]. Similar transition metal complex structures have been reported in the literature[10-15].

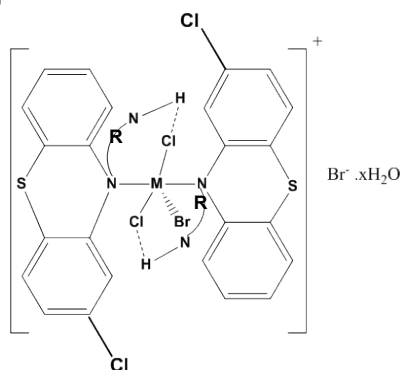


Figure 2a. Proposed square pyramidal structure for the complex ion, [MBr(CP.HCl)₂]⁺, where R = -C₃H₆, M = Zn(II) or Cd(II) and x = 0 for Zn(II) and 1 for Cd(II)

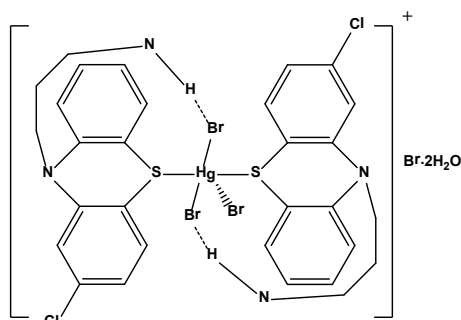


Figure 2b. Proposed square pyramidal structure for the complex ion, [HgBr(CP.HBr)₂]⁺

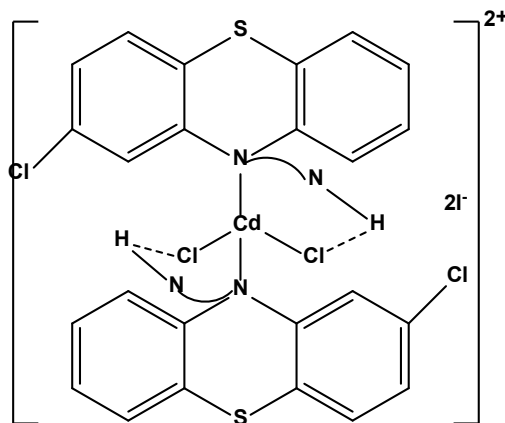


Figure 2c. Proposed tetrahedral structure for the complex ion, [Cd(CP.HCl)₂]²⁺

4. Conclusions

Four transition metal-chlorpromazine complexes have been successfully prepared and characterized based on their spectroscopic data. Square-pyramidal and tetrahedral geometries have been proposed for the new complexes. The future work would be on the determination of antioxidant and free radical scavenging activities of these complexes using standard assays.

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