

Promazine Complexes of Transition Metal Ions: Synthesis

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Abstract Psychotherapeutic, antiemetic, and antihistamine activities are exhibited by some of the N-alkylaminophenothiazine derivatives including promazine (P). The N-alkylamine side chain is implicated in the aforementioned pharmacological activities. Several promazine (P.HCl or C₁₇H₂₀N₂S.HCl) 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 proposed. These complexes behave in DMF solutions as 1:1 electrolytes. Molecular structures have been proposed showing a square pyramidal environment around each metal center with an sp³d hybridization for the five-coordinate complexes, [ZnBr(C₁₇H₂₀N₂S.HCl)₂]Br, [CdBr(C₁₇H₂₀N₂S.HCl)₂]Br, [CdI(C₁₇H₂₀N₂S.HCl)₂]I.H₂O and [HgBr((C₁₇H₂₀N₂S.HCl)₂)]Br.

Keywords Promazine, Metal Complexes, Synthesis, Characterization, Elemental and Spectroscopic Analyses

1. Introduction

N-Alkylphenothiazines (NAPTZs) are biologically active heterocyclic compounds with the general structure shown in Fig. 1. Their research was initially stimulated by the discovery of the anthelmintic action of N-substituted and C-substituted derivatives¹. However, in recent years coordinating behavior of NAPTZs has gained much importance due to their extensive applications in industry, medicine, and chemical analysis². Some of the NAPTZ ligands including promazine (P) are used as psychotherapeutic, antiemetic, and antihistamine drugs. The N-alkylamine side chain is considered to be responsible for the aforesaid pharmacological activities[1-3].

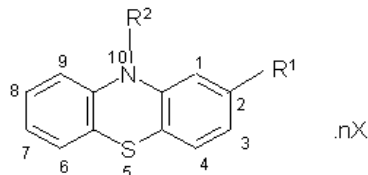


Figure 1. General molecular structure of phenothiazine derivatives

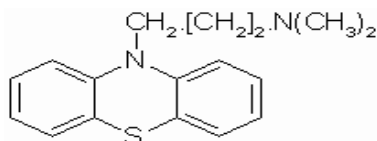


Figure 2. Molecular structure of promazine

Among the NAPTZ derivatives, promazine (trade name Sparine), 10-(3-dimethylaminopropyl)phenothiazine, belongs to the aliphatic phenothiazine class of antipsychotics. It is also used as moderate sedative. The structure of promazine is shown in Fig. 2.

Previously, some studies of transition metal-NAPTZ complexes have been reported by several workers[4-16]. Keshavan and co-workers[4-7] have synthesized and characterized compounds of selected NAPTZs with molybdenum(IV), tungsten(IV), ruthenium(II/III) and copper(II) ions. Keshavan and Janardhan[7], and Gowda and Jayarama [8] have reported mononuclear copper(II) and zinc(II) complexes of NAPTZs. 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 NAPTZs 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 the synthesis and free-radical scavenging activities of transition metal (II)-pyridoxine complexes[17-19]. In this report, the synthesis and characterization of the transition metal complexes with P.HCl as the main ligand is presented.

2. Experimental

2.1. Materials

Metal salts, zinc bromide, cadmium bromide, cadmium iodide and mercuric bromide, and the ligand, promazine hydrochloride (P.HCl; 99% purity) were obtained from Al-

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drich/Sigma Chemical Company, USA. All organic 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

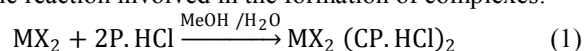
Elemental analyses of complexes were performed by Microanalysis Laboratory, University of Illinois, Urbana-Champaign, IL. Molar conductance was determined with the Conductance-Resistance meter. Melting points were determined on a Melt-Temp apparatus from Laboratory Devices, Cambridge, MA. Shimadzu UV1601 spectrophotometer was used to measure uv-visible spectra and absorbances of analyte solutions. The infrared spectra were recorded using potassium bromide discs on a Shimadzu FTIR 8400 spectrometer. ^1H -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 known concentration of the transition metal salt (x mmol) (ZnBr_2 , CdBr_2 , CdI_2 and HgBr_2) in a minimum volume of MeOH was slowly added with stirring to a concentrated methanolic solution of P.HCl ($2x$ mmol) and refluxed

overnight. Each reaction mixture cooled overnight at 0°C precipitated a product, which was isolated by suction filtration through a medium-glass fritted funnel. The product was washed with small amounts of cold water first followed by MeOH, air-dried, and dried *in vacuo* over anhydrous CaSO_4 in a desiccator. Each crude product was recrystallized twice from a hot saturated solution in MeOH and dried as before. The yield was determined.

The following general equation represents the stoichiometric reaction involved in the formation of complexes:



Where M = Zn(II), Cu(II) or Hg(II) and X is Br $^-$ or I $^-$.

3. Results and Discussion

The molecular formulations and structures of the complexes were determined on the basis of elemental analysis, molar conductance, UV-Vis, IR, and NMR data. The complexes are slightly soluble in common polar solvents such as MeOH and EtOH and readily soluble in acetone, acetonitrile, nitromethane, DMF, and DMSO (0.4 g – 2.0 g per 100 mL). All products except Zn(II) complex are insoluble in water.

The physical properties of the new metal-P.HCl complexes are presented in Table 1. Complexes are colored, crystalline/microcrystalline, and relatively stable above room temperature as indicated by their melting point ranges with percent yields ranging from 82 to 93.

Table 1. Physical properties of metal-P.HCl complexes

Complex	Melting point ($^\circ\text{C}$)	Molar conductance ($\text{ohm}^{-1} \text{ cm}^2 \text{ mol}^{-1}$) in nitromethane	Mass magnetic Susceptibility (10^{-6} cgs)	Color	% Yield
$\text{ZnBr}_2(\text{P.HCl})_2$	90-110	93.24 (1:1) (electrolyte)	-0.16 (diamagnetic)	colorless	93.3
$\text{CdBr}_2(\text{P.HCl})_2$	138-145	114.0 (1:1) (electrolyte)	-0.38 (diamagnetic)	colorless	87.1
$\text{CdI}_2(\text{P.HCl})_2$	118-130	93.24 (1:1) (electrolyte)	0.69 (slightly paramagnetic)	colorless	90.9
$\text{HgBr}_2(\text{P.HCl})_2$	100-120	103.6 (1:1) (electrolyte)	0.70 (slightly paramagnetic)	light greenish	81.7

Table 2. Elemental analyses of metal-P.HCl complexes

Complex	Molecular Formula (Mol wt: g/mol)	%C exp. (Theor.)	%H exp. (Theor.)	%N exp. (Theor.)
$\text{ZnBr}_2(\text{P.HCl})_2$	$[\text{ZnBr}(\text{C}_{17}\text{H}_{21}\text{Cl}_2\text{N}_2\text{S}_2)]\text{Br}$ (867.03)	46.80 (47.10)	4.85 (4.88)	6.12 (6.13)
$\text{CdBr}_2(\text{P.HCl})_2$	$[\text{CdBr}(\text{C}_{17}\text{H}_{21}\text{Cl}_2\text{N}_2\text{S}_2)]\text{Br}$ (914.05)	44.67 (44.68)	4.60 (4.63)	6.12 (6.13)
$\text{CdI}_2(\text{P.HCl})_2 \cdot \text{H}_2\text{O}$	$[\text{CdI}(\text{C}_{17}\text{H}_{21}\text{Cl}_2\text{N}_2\text{S}_2)]\text{I} \cdot \text{H}_2\text{O}$ (1020.3)	39.40 (39.79)	4.01 (4.31)	5.43 (5.45)
$\text{HgBr}_2(\text{P.HCl})_2$	$[\text{HgBr}(\text{C}_{17}\text{H}_{21}\text{Cl}_2\text{N}_2\text{S}_2)]\text{Br}$ (1008.1)	40.54 (40.75)	4.23 (4.22)	5.67 (5.59)

Table 3. UV-Visible spectral data of P.HCl and its metal complexes

Complex/Ligand	λ_{max} (nm)	Molar absorptivity (ϵ) ($10^4, \text{M}^{-1} \text{ cm}^{-1}$)	Transition
P.HCl	259.0	1.42	$\pi \rightarrow \pi^*$
	306.5	0.22	
$\text{ZnBr}_2(\text{P.HCl})_2$	258.0	3.83	$\pi \rightarrow \pi^*$
	306.5	0.58	
$\text{CdI}_2(\text{P.HCl})_2 \cdot \text{H}_2\text{O}$	258.0	4.54	$\pi \rightarrow \pi^*$
	306.5	0.62	
$\text{CdBr}_2(\text{P.HCl})_2$	259.0	4.11	$\pi \rightarrow \pi^*$
	306.5	0.68	
$\text{HgBr}_2(\text{P.HCl})_2$	258.0	4.54	$\pi \rightarrow \pi^*$
	306.5	0.63	

Table 4. Important IR absorptions of P.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 (C-N) (cm^{-1})
P.HCl Ligand	2689-2515	3053-2853	771-748	1038 & 972
ZnBr ₂ (P.HCl) ₂	2764-2650	3054-2862	760	1036 & 972
CdBr ₂ (P.HCl) ₂	2837-2639	3019-2837	758	1035 & 973
CdI ₂ (P.HCl) ₂ .H ₂ O*	3067-2652	3067-2789	760	1035 & 970
HgBr ₂ (P.HCl) ₂	2716-2608	3069-2813	759	1036 & 972

* indicates OH absorption band at 3225-3400 cm^{-1} **Table 5.** Proton-NMR data of P.HCl and its metal complexes*

Ligand/Complex	δ Chemical shift (multiplicity, protons)
P.HCl	2.0 (m, 2H), 2.68 (s, 6H), 3.13- 3.15 (t, 2H), 3.94 – 3.98 (t, 2H), 7.1-7.2 (m, 7H), 10.80 (br.s, 1H).
ZnBr ₂ (P.HCl) ₂	2.02-2.07 (m, 2H), 2.73 (s, 6H), 3.12-3.17 (t, 2H), 3.93-3.97 (t, 2H), 7.09-7.21 (m, 7H), 9.39 (br.s, 1H).
CdBr ₂ (P.HCl) ₂	2.05 – 2.08 (m, 2H), 2.74 (s, 6H), 3.12 – 3.18 (t, 2H), 3.93 – 3.98 (t, 2H), 6.98-7.21 (m, 7H) 9.39 (br.s, 1H).
CdI ₂ (P.HCl) ₂ .H ₂ O	2.01 – 2.06 (m, 2H), 2.80 (s, 6H), 3.12-3.17 (t, 2H), 3.93-3.97 (t, 2H), 6.98-7.24 (m, 7H), 9.27 (br.s, 1H)
HgBr ₂ (P.HCl) ₂	2.02-2.07 (m, 2H), 2.73 (s, 6H), 3.12-3.17 (t, 2H), 3.93-3.98 (t, 2H), 7.09-7.21 (m, 7H), 9.42 (br.s, 1H).

* In DMSO-d₆

All complexes behave as 1:1 electrolytes as shown by their molar conductance data, which are presented in Table 1. The overall magnetic data of the complexes show the low spin nature of the d^{10} metal ions with two of them, Cd(II)I₂ and Hg(II)Br₂, deviating slightly which probably can be attributed to the presence of paramagnetic impurities[20]. Elemental analysis results listed in Table 2 show that the theoretical values for C, H, N are in agreement with the experimental ones. The complexes contain one metal center and two promazine hydrochlorides as principal ligands. The other ligands include bromide or iodide ions. Additionally, CdI₂ complex contains one H₂O molecule as the water of hydration.

The UV-Visible spectral data of the ligand (P.HCl) and its metal-complexes are presented in Table 3. The broad bands observed in the UV region of 255 – 310 nm in the spectra of all complexes can be attributed to the intraligand transitions[15-23]. The molar absorptivities (ϵ) of the complexes falling in the range of 5.8×10^3 to 4.55×10^4 M⁻¹ cm⁻¹, are higher than those of the ligand in the free state which are 2.2×10^3 M⁻¹ cm⁻¹ and 1.42×10^4 M⁻¹ cm⁻¹ at 306.5 nm and 259 nm, respectively. The increased molar absorptivities can be attributed to the transitions of $\pi - \pi^*$ type (hypsochromic shift). This may be taken as an indirect evidence for involvement of the N atoms in the coordination process, confirming the complex formation between metal and ligand[15-23].

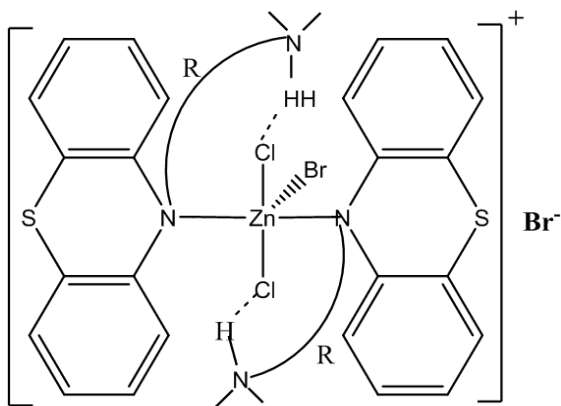
Infrared spectral data of P.HCl ligand and its complexes are presented in Table 4. In the free P.HCl ligand spectrum, a strong band observed at ~ 2500 -2700 cm^{-1} region is attributable to the interactions of a halide ion with the exocyclic quarternary ammonium ion (R_3NH^+). In the spectra of Zn(II), Cd(II) and Hg(II) complexes, this band shifts to a higher wave number with diminished intensity indicating weakening of the hydrogen bonding between the nitrogen atom of the exocyclic quarternary ammonium ion (R_3NH^+) and halide ions.[12-15,21,22]. A band observed in the 3000-2800 cm^{-1} region in the spectrum of P.HCl may be

assigned to the heterocyclic nitrogen atom carrying an alkyl amine side chain[21,22]. This band of P.HCl shows a shift upon complexation suggesting its coordination to the metal(II) center [10-14]. The broad absorption band ~ 3200 -3400 cm^{-1} supports the H-bonded OH interactions of the water of hydration in CdI₂ complex. In the free ligand, the vibrations of heterocyclic $\nu(C-S-C)$ are different from their Cd(II) and Hg(II) complexes, due to the coordination of the heterocyclic S atom to the metal center as compared to the Zn(II) center which is bonded to the heterocyclic N atom [12,15,22].

The ¹H NMR data for the ligand, P.HCl, and its complexes are presented in Table 5. A comparison of the nature of important peaks/multiplets and their chemical shifts of the spectra reveals that the resonance signals of the uncomplexed ligand have experienced small shifts upon coordination to metal ions. The above spectral changes indicate the involvement of its exocyclic N atom and a heterocyclic N or S atom as donor coordination sites. The broad singlet peak in the free ligand (δ 10.80) shifted upfield in the complexes is attributed to the complex formation via intramolecular H-bonding between exocyclic (R_3NH^+) and Cl⁻ of the N₂MX₃ or S₂MX₃ moiety of the complex[12,15,24].

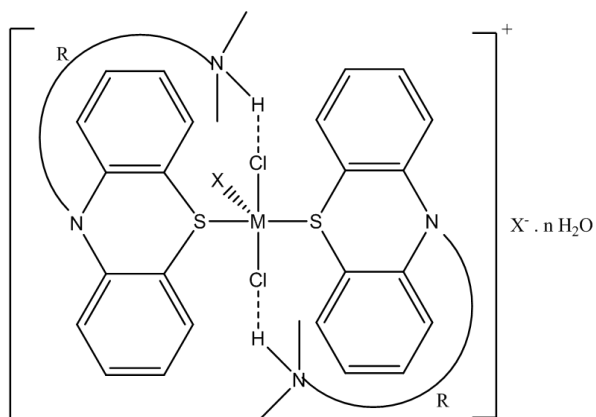
Crystals of sufficient quality required to permit x-ray crystallographic analysis of the complexes could not be grown. Based on the discussed analytical data, tentative square pyramidal structures have been proposed for all the complexes (Figs. 3A and 3B.). Similar structures have been reported for other phenothiazine-transition metal complexes[12-15,24]. The Zn(II), Cd(II) and Hg(II) complexes have the general ionic formula $[MX(P.HCl)_2]X$, where M = metal(II) center with d^{10} configuration and X = Br⁻ or I⁻. According to the valence bond theory, the five-coordinate Zn(II), Cd(II) and Hg(II) centers of the complexes involve sp^3d hybridized atomic orbitals. In the complexes, each central metal ion forms a square planar base unit containing two M-N or M-S bonds with heterocyclic N/S atoms of two promazine hydrochloride ligands, two M-Cl bonds with

each chloride ion which in turn is hydrogen-bonded to the nitrogen atom of the exocyclic quarternary ammonium ion of the ligand, and one axial M-Br or M-I bond within the inner coordination sphere. The heterocyclic N atom as the coordination site for a small/hard Zn(II) ion and the heterocyclic S atom as the site for a relatively larger/softer Cd(II) or Hg(II) ion in the complexes can be justified based on the Pearson's HSAB interactions. In coordination, the hard acid Zn(II), prefers a hard N end while the softer acid, Cd(II) or Hg(II), prefers to coordinate with a softer S site of the ligand. Each complex has a distorted square pyramidal geometry around the metal(II) center and the distortion can be attributed to the chelating effect of the bidentate P.HCl ligand. The scorpion tail like N-alkylamino (R) group with its flexible bending mode is well suited for this kind of intramolecular H-bonding in the ligands, NAPTZs[11-19]. The structures (Figs. 3A and 3B) are supported by the low-spin nature of the complexes.



Here for the promazine (P) ligand: $R = (CH_2)_3N(CH_3)_2$;

Figure 3A. Proposed structure of $[ZnBr(P.HCl)_2]Br$. $R = (CH_2)_3N(CH_3)_2$



Here for the promazine (P) ligand: $R = (CH_2)_3N(CH_3)_2$; X^- is Br^- or I^- and $n = 0$ or 1

Figure 3B. Proposed general molecular structure for the Complexes, $[CdBr(P.HCl)_2]Br$, $[CdI(P.HCl)_2] \cdot nH_2O$ and $[HgBr(P.HCl)_2]Br$

4. Conclusions

Transition metal-promazine hydrochloride complexes

have been prepared and characterized based on their spectroscopic data. A distorted square-pyramidal structure has been proposed for the new complexes. The future work would be on the determination of *in vitro* antioxidant and free radical scavenging activities of these complexes using standard assays.

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