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Aliphatic and Piperidinic Phenothiazine Drugs as Ligands for Copper(II) Ions

OLIMPIA MARIANA MICU, OANA ADRIANA JINGA, ANCA VALUTA, IOANA JITARU
University "Politechmica", Faculty of Industrial Chemistry, 1 Polizu St.,Bucharest, Romania

Abstract

New Cu(II) complexes with phenothiazine derivatives as ligands, having the general formula ***: [Cu$\mathcal{L}X_2]_2$*** *($\mathcal{L}$ =10-(3-dimethylaminopropyl) phenothiazine,noted pmz ; X= Cl^- , CH_3COO^- or $\mathcal{L}$ = 10/2-(1'-methyl –2'-piperdyl) ethyl-2'-methylthiophenothiazine, noted, tdz ; X = Cl^-) ;* ***[Cu$\mathcal{L}^+X_3$]*** *($\mathcal{L}^+Cl$ =10-(3-dimethylaminopropyl) phenothiazine hydrochloride,noted cpzH or 10/2-(1'-methyl –2'-piperdyl) ethyl-2'-methylthiophenothiazine hydrochloride, noted tdzH ; X=Cl^-) and* ***[Cu $\mathcal{L}_2$ X_2]*** *($\mathcal{L}$ = pmz,tdz ; X = Cl^-).The complexes were characterised by elemental chemical analyses, molecular electrical conductivity, electronic, epr and FT-IR spectra.The estimation of the electronic densities in MO diagram calculations confirm the experimental data and suppositions about the structural formulas of the isolated complexes.The formation of such complexes may be the support of a possible action mechanism of the phenothiazine drugs in Wilson's disease.*

Introduction

The metal complexing effect of the phenothiazines derivatives may constitute the common cause of their action at the molecular level and, over the last thirty years the interaction between phenothiazine and metal ions has been extensively studied [1-8].For example, it has been shown in literature that the antitumoral and antipsyhotic activities of phenothiazine may occur by formation of Cu(II) (from enzimes) charge transfer complexes with phenothiazine derivatives[9,10].

This paper is a part of a general one studying the complex properties of some antipsychotic drugs from the thioxanthene and phenothiazine groups.The first article from this series was published in this journal [11].

Two aliphatic phenothiazines:inactive - promazine (**pmz**) and active- thorazine (chlorpromazine hydrochloride, **cpzH-Cl**) pharmacological form and two piperidinic phenothiazines : inactive - thioridazine (**tdz**) and active - thioridazine hydrochloride, **tdzH-Cl** pharmacological form , respectively, were used as ligands for Cu(II) ion, in this paper.

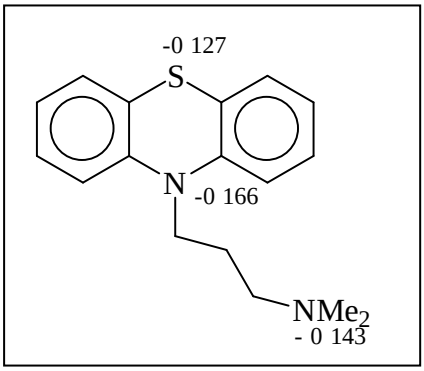
Under well established conditions, the following complex compounds have been obtained $[Cu\mathcal{L}X_2]_2$ ($\mathcal{L}$ =10-(3-dimethylaminopropyl) phenothiazine, **pmz** ; X= Cl^- , CH_3COO^- or $\mathcal{L}$ = 10/2-(1'-methyl –2'-piperidyl) ethyl-2'-methylthiophenothiazine, **tdz** ; X = Cl^-) ; $[Cu\mathcal{L}^+X_3]$ ($\mathcal{L}^+Cl$ =10-(3-dimethylaminopropyl) phenothiazine hydrochloride, **cpzH** or 10/2-

(1'-methyl –2'-piperidyl) ethyl-2'-methylthiophenothiazine hydrochloride, **tdzH** ; X=Cl^-) and [Cu $\mathcal{L}_2$ X_2] ($\mathcal{L}$ = **pmz,tdz** ; X = Cl^-).

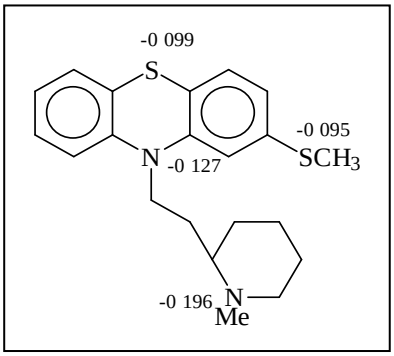
Elemental chemical analysis, electrical conductivity measurements, electronic, epr and FT-IR spectra have been used for the characteization of new complex compounds. The estimation of the electronic densities in MO diagram calculations confirms the coordination manner of the phenothiazine derivatives toward Cu(II), in good agreement with the experimental data.

Inactive pharmaceutical forms

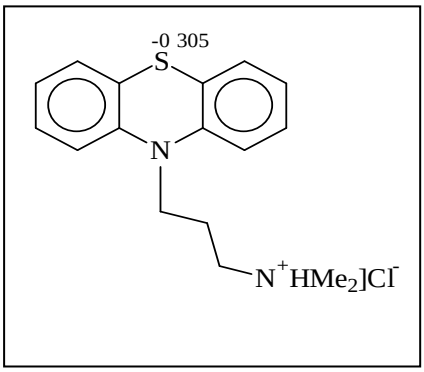
Promazine (pmz)



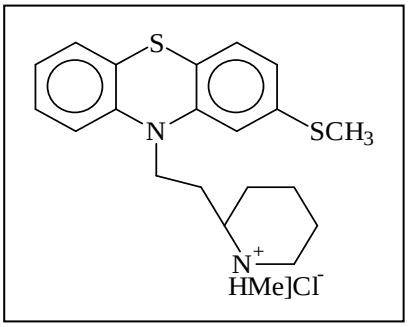
Thioridazine (tdz)



Active pharmaceutical forms



Chlorpromazine hydrochloride (cpzH)



Thioridazine hydrochloride (tdz)

Materials and Methods

Syntheses of complexes:

[Cu$\mathcal{L}X_2]_2$ (*$\mathcal{L}$ =10-(3-dimethylaminopropyl) phenothiazine,* ***pmz*** *; X= Cl^- , CH_3COO^- or $\mathcal{L}$ = 10/2-(1'-methyl –2'-piperdyl) ethyl-2'-methylthiophenothiazine,* ***tdz*** *; X = Cl^-)* complexes have been prepared at reflux, during five hours, in ethanol of $\mathcal{L}$ and CuX_2 (X=Cl^-, CH_3COO^-) in a molar ratio 1:1,when a pale green solution was obtained. After solvent evaporation by heating in a water bath, the obtained solids (dark green for X=Cl^- and brown for X=CH_3COO) were filtered , washed with ethanol-water(1:1 mixture) and dried in air.Yield 60-65%.

[Cu $\mathcal{L}_2$ X_2] (*$\mathcal{L}$ =* ***pmz,tdz*** *; X = Cl^-*) complexes have been similarly prepared using a molar ratio CuX_2: *$\mathcal{L}$ = 1:2.* The solid compounds have a dark brown colour. Yield 75-80%.

[CuL⁺X₃] *(L⁺Cl =10-(3-dimethylaminopropyl) phenothiazine hydrochloride,* ***cpzH,*** *10/2-(1'-methyl –2'-piperdyl) ethyl-2'-methylthiophenothiazine hydrochloride,****tdzH*** *; X=Cl⁻*) have been isolated by boiling in reflux, during ten hours,of an aqueous slightly acidulated (pH = 3.5-4) solution of CuX_2 and an ethanolic solution of *L⁺Cl* (*L⁺* = cpzH,tdzH) in 1:1 molar ratio.After the solvent evaporation in air, the obtained solids were triturated with cold ethanol-diethylether 1:1 mixture and dried in a dessicator on P_4O_{10}. Yield 65-70%.

Analysis (mass percentages) :

Found for: (**1**}$[Cu(pmz)Cl_2]_2$ ($CuC_{17}H_{24}N_2SCl_2$)	Cu,15.54; N,3.90; S,7.15;Cl,15.93
Calcd.	Cu,14.54; N,3.86; S,7.34;Cl,16.26
Found for: (**2**) $[Cu(pmz)(CH_3COO)_3]_2$ ($CuC_{21}H_{27}N_2S$)	Cu,12.95;N,6.10; S,6.12
Calcd.	Cu,13.13 ;N,5.80;S,6.62
Found for (**3**) $[Cu(pmz)_2Cl_2]_2$($CuC_{34}H_{48}N_4S_2Cl_2$)	Cu,9.10; N,8.20; S,7.95;Cl,10.10
Calcd.	Cu,8.60 N,7.58; S,8.66;Cl,9.61
Found for : (**4**) $[Cu(tdz)Cl_2]_2$ ($CuC_{21}H_{31}N_2S_2Cl_2$)	Cu,1190; N,2.90; S,7.10;Cl,16.25
Calcd.	Cu,11.90; N,3.10; S,8.45;Cl,15.30
Found for : (**5**) $[Cu(tdz)_2Cl_2]_2$($CuC_{42}H_{62}N_4S_4Cl_2$)	Cu, 6.90; N,8.20; S,7.95;Cl,7.80
Calcd.	Cu,7.30; N,7.30; S,8.50 ;Cl,7.15
Found for : (**6**) $[Cu(cpzH)Cl_3]$ ($CuC_{17}H_{25}N_2SCl_3$)	Cu,12.70; N,3.75; S,7.80;Cl,18.10
Calcd.	Cu,12.30; N,3.50; S,7.50;Cl,18.10
Found for: (**7**) $[Cu(tdzH)Cl_3]$ ($CuC_{21}H_{42}N_2S_2Cl_3$)	Cu,11.20; N,4.05; S,6.50;Cl,17.93
Calcd.	Cu,11.74; N,3.80; S,7.15;Cl,18.80

Electronic spectra have been recorded at room temperature on a VSU-2G spectrophotometer using MgO as standard sample.

EPR spectra have been registred on polycrystalline powders by using a spectrophotometer of the type ART-IFIN Bucharest in the 9000 MHz frequency ranges with a magnetic field modulation of 100 kHz.

Molar electrical conductivitie**s** have been recorded in DMF solutions at 25^0C, with an OK 102/1 Radelkis Conductometer with a 0.1 S – 0.5 S measuring range.

FT-IR spectra have been recorded with a Perkin-Elmer spectrophotometer using KBr pellets as refference.

Results and Discussions

The proposed formulas of the three general types of Cu(II) complexes with studied phenothiazines derivatives (*L* and *L⁺*) are supported by elemental chemical data and molar conductivity measurements **(Table1)**. All complex compounds are of the nonelectrolyte type.

Table 1 . Molar conductivity and data of electronic and epr spectra

Complex compound	Conductivity($\mu S.cm^2.mol^{-1}$) [Type of electrolyte]	Visible band λ (nm)	epr parameters
(1)	35.20 [nonelectrolyte]	650-720	slightly paramagnetic
(3)	35.00 [nonelectrolyte]	680-750	g_{II} = 2.035 $g_{\perp}$ = 2.130
(4)	25.70 [nonelectrolyte]	700-750	slightly paramagnetic
(5)	20.10 [nonelectrolyte]	690-760	g_{II} = 2.060 $g_{\perp}$= 2.200
(6)	25.50 [nonelectrolyte]	690-740	g_{II} = 2.040 $g_{\perp}$ = 2.210
(7)	35.10 [nonelectrolyte]	680-730	g_{II} = 2.020 $g_{\perp}$ = 2.270

The electronic spectra of all Cu(II) – phenothiazine derivatives ($\mathcal{L}$ and $\mathcal{L}^+$) present a large, asymetric band in vizibil range (650-750 nm) that suggest a strong distorted tetrahedral up to square planar geometry of the complexes (Jahn-Teller effect and nonequivalency of the ligands)[12]. In all synthetized complexes the maximum coordination number is four, very probable due to the bulk ligands used.

Further information about the stereochemistry of the complexes have been obtained from their epr spectra. The $[Cu\mathcal{L}X_2]_2$ complexes are slightly paramagnetic due to of a partial compensation of Cu(II)(d^9) electronic spins (the compensation of Cu(II) electronic spins in the dinuclear complexes is not total, due to the large distance between Cu(II) ions).
The $[Cu\mathcal{L}^+X_3]$ complexes present a epr signal with different values of g parameters, characteristic to the strongly distorted configurations (table 1).

The FT-IR spectra have been recorded particularly, to confirm our suppositions regarding the coordination manner of the phenothiazine derivative and of the anions Cl^- and CH_3COO^-.For comparision, the IR spectra of the free ligands (promazine and thorazine) have also been registered; characteristic frequencies of the C-heterocyclic N (at 1520 cm^{-1} and 1650 cm^{-1}), C-heterocyclic S (at 670 cm^{-1} and 750 cm^{-1}) and N-CH_3 (at 2810 cm^{-1}) were observed **(Table 2)**.

The most important conclusions from the IR spectra of the isolated complexes were:

- in the spectra of $[Cu\mathcal{L}X_2]_2$ ($\mathcal{L}$ = pmz ; X= Cl^- , CH_3COO^- or $\mathcal{L}$ = tdz ; X = Cl^-) complexes, the shifting of the C-heterocyclic S and of the N-CH_3 frequencies to lower values (640 cm^{-1}, 705 cm^{-1} and 2790 cm^{-1}, respectively) is a consequence of $\mathcal{L}$ coordination as a bidentate ligand, through endocyclic sulphur and amine nitrogen from the N(10) side chain;
- the frequency of the carboxyl group ($\nu_{as(OCO)}$) from the spectrum of $[Cu(pmz)(CH_3COO)_2]_2$ complex is obscured by some specific bands of the phenothiazine derivatives, but $\nu_{s(OCO)}$ occurs at 1610 cm^{-1} as a well defined, sharp and intense band indicating the coordination of CH_3COO^- ion;
- in the spectra of $[Cu\ \mathcal{L}_2\ X_2]$ ($\mathcal{L}$ = pmz,tdz ; X = Cl^- , CH_3COO^-) complexes, the shifting of N-CH_3 group frequency to lower value (in comparison with that of free ligands) is very probable a consequence of $\mathcal{L}$ coordination as a monodentate ligand through amine nitrogen from side chain;
- in the spectra of $[Cu\mathcal{L}^+X_3]$ ($\mathcal{L}^+$ = cpzH, tdzH ; X=Cl^-) complexes, the C-cyclicS frequency is shifted to lower value as a consequence of monodentate coordination of the ligands, through endocyclic sulphur ;
- the characteristic S-CH_3 frequency (1325 cm^{-1}) from the IR spectra of thioridazine occurs in the spectra of complexes at the same value;
- specific frequencies of the Cu-N, Cu-S and respectively Cu-Cl occur in the far IR range [13].

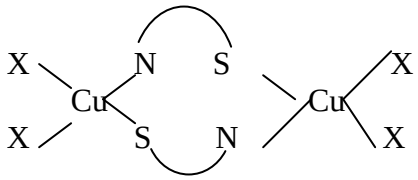
The estimation of the electronic densities in MO diagram calculations confirm our experimental data and supposition referring to the structural formulae of the studied complexes . In **(Figure 1)** are presented the proposed structural formulae for complexes of inactive and active pharmaceutical forms of the sudied phenothiazine derivatives.

In the $[Cu\mathcal{L}^+X_3]$ complexes, intramolecular hydrogen bonding between the negative center, CuX_3^- and the positive part of quaternary ammonium of the ligands is possible to form.

Table 2. IR characteristic frequencies of the studied complexes

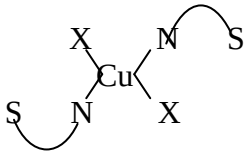
Compound	$\nu_{C\text{-}Ncyclic}$	$\nu_{C\text{-}Scyclic}$	$\nu_{N\text{-}CH3}$	$\nu_{S\text{-}CH3}$	ν_{OCO}	$\nu_{Cu\text{-}N}$	$\nu_{Cu\text{-}S}$ $\nu_{Cu\text{-}S}$
pmz	1520 1650	670 750	2810	-	-	-	-
$[Cu(pmz)Cl_2]_2$	1530 1650	640 705	2790	-	-	410 390	350 327
$[Cu(pmz)(CH_3COO)_2]_2$	1520 1660	640 700	2750	-	1610	415 390	355 340
$[Cu(pmz)_2Cl_2]$	1520 1660	670 745	2700	-	-	410 375	- 320
$[Cu(cpzH)Cl_3]$	1520 1650	650 720	2800	-	-	-	380 320
tdz	1520 1610 1660	670 750	2850	1325	-	-	-
$[Cu(tdz)Cl_2]_2$	1530 1650	635 720	2790	1320	-	420 395	350 320
$[Cu(tdz)_2Cl_2]$	1520 1650	670 750	2780	1325	-	420 380	320 315
$[Cu(tdzH)Cl_3]$	1530 1640	640 700	2845	1325	-	-	360 310

Coordination of inactive forms



(1),(2) and **(4)**

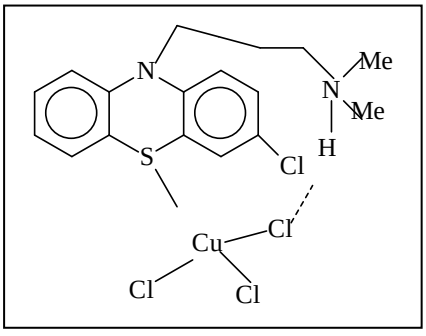
where N S is :**pmz**



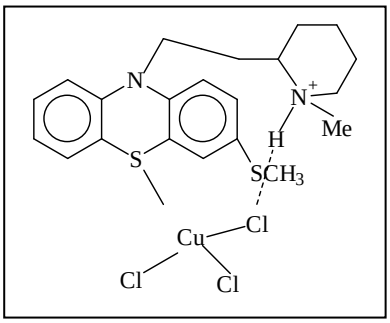
(3) and **(5)**

where N S is **tdz**

Coordination of active forms



(6)



(7)

Figure 1. Structural proposed formulae of the isolated complexes

Conclusions

Three general types of Cu (II) complexes with phenothiazine derivatives in their inactive ($\mathcal{L}$) and active ($\mathcal{L}^{+}Cl$) pharmaceutical forms have been obtained:

- $[Cu\mathcal{L}X_2]_2$ ($\mathcal{L}$ = pmz ; X= Cl^- , CH_3COO^- or $\mathcal{L}$ = tdz ; X = Cl^-) ;
- $[Cu\ \mathcal{L}_2\ X_2]$ ($\mathcal{L}$ = pmz, tdz; X = Cl^-, CH_3COO^-) and
- $[Cu\mathcal{L}^{+}X_3]$ ($\mathcal{L}^{+}$ = cpzH, tdzH; X=Cl^-).

The ligands in inactive pharmaceutical form act as bidentate (through endocyclic sulphur and amine nitrogen (10) from the side chain of phenothiazine derivatives) forming bridges in dimeric complexes or as monodentate (through endocyclic sulphur) in monomeric complexes. The active pharmaceutical forms coordinate as positively, monodentate (through endocyclic sulphur) ligands.

The estimation of the electronic densities in MO calculations supports the suppositions about the structure of complexes.

The formation of such complexes may be the support of a possible action mechanism of the phenothiazine drugs in Wilson's disease [11].

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