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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2011, Vol. 27, No. (4):
Pg. 1465-1473

Preparation Ligand 5-(3-chlorophenyl)-1,3,4-oxadiazole-2-thiol by New Method and Complexation with Transition Metals

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(Received: September 25, 2011; Accepted: October 26, 2011)

ABSTRACT

A ligand 5-(3-chlorophenyl)-1,3,4-oxadiazol-2-thiol (CPoxSH) synthesized by two methods and its Zn(II), Cd(II), Hg(II), Mn(II), Co(II), and Ni(II) complexes were synthesized. The ligand were prepared by two methods, microwave and classic method, *m*-chlorobenzol hydrazine(A) was prepared the hydrazinolysis of methyl *m*-chlorobenzoate(B) with hydrazine hydrate in abs. ethanol. Refluxing of *m*-chlorobenzol hydrazine(C) in basic medium with carbon disulfide CS_2 to give 5-(3-chlorophenyl)-1,3,4-oxadiazol-2-thiol (D). And complexation with [HgX_2] (X= Cl, Br, SCN)(1:1), and [$Hg(OAc)_2$] (1:2) mole proportion of ligand. Reaction of $MCl_2.xH_2O$ [M(II)= Cd, Zn, Mn, Co, Ni] and [$M(OAc)_2.xH_2O$ [M = Cd, Zn, Co, Ni] with ligand by (1:2) mole proportion. The preparation ligand and complexes were characterized by element analysis, IR spectral data , ^1H and ^{13}C-{^1H} NMR data.

Key words: Oxadiazole, Transition metal, Thione, complexes, microwave,

INTRODUCTION

In the family of heterocyclic compounds, nitrogen containing heterocycles with an oxygen atom and complexes are considered as an important class of compounds in medicinal chemistry because of their interesting diversified biological application[1]. During the past years considerable evidences have also accumulated to demonstrate the efficacy of 1,3,4-oxadiazoles including antibacterial, anti-inflammatory, antimalarial, antitubercular, antihypoglycemic, anticancer, antileishmanial, antiviral, anticonvulsant and insecticidal properties[1-4]. In some cases, metal complexes of these ligands shown higher anticancer activity than the free ligand, and some of thes complexes classified as clinical agents for therapy of human leukaemias[5-10].

The use of microwaves in organic synthesis has increased dramatically in the last years, receiving widespread acceptance and becoming an indispensable tool[5]. Microwave technology has become a powerful tool in organic

synthesis, since by employing this technique it is generally possible to prepare organic compounds very fast, with high purity and better yields compared to other more conventional methods[6-7].

In this paper, the first time, the syntheses of ligand [5-(*m*-chlorophenyl) -1,3,4-oxadiazole-2-thione(CPoxSH)] by two methods, in the first method using the classic synthetic method of the ligand is depicted in (Scheme 1), while using microwave technology in the second method (scheme 2) and syntheses and characterization of some transition metal complexes with this ligand.

EXPERIMENTAL

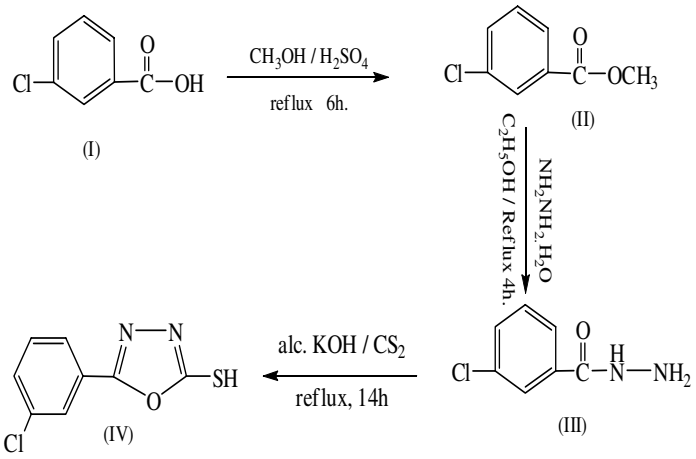
General

All chemicals were commercially available used and received (Except the CPoxSH ligand is prepared by down method). Melting points were determined on an electrothermal 9300 melting point apparatus. ^1H and ^{13}C NMR spectra in ä units (ppm) relative to an internal standard of tetramethylsilane on ^1H and ^{13}C NMR in DMSO-d6 (Brucker 400 MHz, in AL al-Bayt University). IR spectra were recorded on a shimadzu FT.IR. 8400 spectrometer in the 200 – 4000 cm^{-1} range using CsI discs. Elemental analysis were carried out on a CHN analyzer type 1106(Carlo –Erba in AL al-Bayt University).

Synthesis of 5-(3-chlorophenyl)-1,3,4-oxadiazole-2-thiol(CPoxSH)

1- By classic method

The ligand 5- (3-chlorophenyl)-1,3,4-oxadiazole-2-thiol (Scheme 1) was prepared as follows:



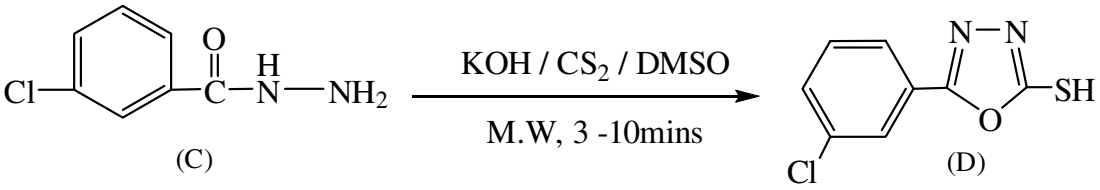
Scheme 1: Synthesis of the ligand

A mixture of m-chlorobenzoic acid hydrazide[11] (10mmole, 1.715g) dissolved in ethanol (50cm^3),KOH (20mmole, 0.112 g) in (60cm^3) ethanol and CS_2 (20mmole , 1.2 cm^3) was refluxed on a water bath for 14h, until the evolution of H_2S gas ceased. The resultant mixture was acidified with acetic acid and the white solid which separated was filtered and recrystallized from ethanol. Yield 76 %, m. p. 170-172 °C.

By Micro Wave method

In this new method for ligand 5- (3-chlorophenyl)-1,3,4-oxadiazole-2-thiol synthesis using microwave heating. When dipole molecules such as m-chlorobenzoic acid hydrazide are exposed to an electric field, they align with the field. When the field oscillates the molecules realign over and over. This results in molecular friction, which produces heating. Because this heating occurs within the sample, the reactants experience rapid, uniform heating. In conventional heating, the reaction vessel is heated first, and the temperatures are greatest near the walls. Thus reactions occur more rapidly with microwave heating, and there are

fewer side reactions, because there are fewer hot spots that might trigger them. Here with rapid, efficient microwave heating, reflux for 14h is not needed as a catalyst, as it is with conventional heating.



Scheme 2: Synthesis of the ligand via microwave irradiation

Synthesis of $[HgCl_2(CPoxSH)]_2$ complex

A solution of CPoxSH (0.1g, 0.47mmole) in EtOH (10cm^3) was added to solution of $HgCl_2$ (0.128g, 0.47mmole) in EtOH (10cm^3). The mixture was stirred at room temperature for 2hr. The white solid thus formed was filtered off and washed with EtOH and recrystallized from ethanol and acetone as white powder (yield 87%). The $[HgBr_2(CPoxSH)]_2$, $[Hg(SCN)_2(CPoxSH)]_2$ complexes is prepared by similar method.

Synthesis of $[Hg(CPoxS)_2]$ complex

A solution of CPoxSH (0.2g, 0.94mmole) in EtOH (15cm^3) was added to solution of $Hg(oAc)_2$ (0.128g, 0.47mmole) in warm EtOH (20cm^3) present Et_3N (0.3 cm^3) as a base. The mixture was stirred at room temperature for 3hr. The white solid thus formed was filtered off and washed with EtOH and recrystallized from ethanol and acetone as white powder (yield 76%).

Synthesis of $[CdCl_2(CPoxSH)_2]$ complex

A solution of CPoxSH (0.2g, 0.94mmole) in EtOH (30cm^3) was added to solution of $CdCl_2$ (0.09g, 0.47mmole) in warm EtOH (15cm^3). The mixture was stirred at room temperature for 1.5hr. The yellow solid thus formed was filtered off and washed with EtOH and recrystallized from ethanol and acetone as yellow powder (yield 91%). The $[Cd(NO_3)_2(CPoxSH)_2]$, $[ZnCl_2(CPoxSH)_2]$, $[NiCl_2(CPoxSH)_2]$, $[MnCl_2(CPoxSH)_2]$, $[CoCl_2(CPoxSH)_2]$ complexes is prepared by similar method.

Synthesis of $[Cd(H_2O)_2(CPoxS)_2]$ complex

A solution of CPoxSH (0.5g, 2.35mmole) in EtOH (45cm^3) was added to solution of $Cd(oAc)_2.xH_2O$ (0.271g, 1.175mmole) in warm EtOH (40cm^3) present Et_3N (0.3cm^3) as a base. The mixture was stirred at room temperature for 2hr. The milky solid thus formed was filtered off and washed with EtOH and recrystallized from ethanol as milky(off white) powder (yield 80%). The $[Zn(H_2O)_2(CPoxS)_2]$, $[Co(H_2O)_2(CPoxS)_2]$, $[Ni(H_2O)_2(CPoxS)_2]$ complexes is prepared by similar method.

RESULTS AND DISCUSSION

Synthesis of ligand and complexes

The oxadiazole ligand exist as two toutomeric conformations exhibiting thiol(I) – thione(II) isomers involving (-N=C-SH) and (-NH-C=S) group in the thiol – thione equilibrium(Fig.1). On deprotonation the resulting anions can also have thiol – thione isomerism with negative charge is either on the thiol sulfur atom or the amide nitrogen atom.

Reaction of $[HgX_2]$ (X= Cl, Br, SCN) with CPoxSH ligand in ethanol solution (1 :1) molar ratio gave tetrahedral complexes of the type $[HgX_2(CPoxSH)]_2$ (Fig.2). The halogen and pesudohalogen was coordinated as a bidentate bridging and monodentate to mercury(II) ions , while the oxadiazole ligand (CPoxSH) behaves as monodentate ligand coordinated via sulfur atoms to mercury(II) ion.

While the react between oxadiazole ligand with $MCl_2.xH_2O$ [M = Cd, Zn, Mn, Co, Ni] in ethanol solution (1:2) molar ratio gave tetrahedral complexes of the type $[MCl_2(CPoxSH)_2]$(Fig. 3). The oxadiazole ligand behaves as monodentate ligand coordinated

Table 1: Elemental analysis and physical properties of prepared compounds

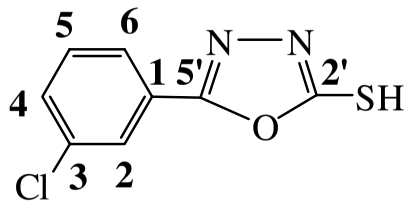
Seq.	Complexes	Color	mp °C	Yield%	CHN Found (Cacl.) %		
					C	H	N
	CPoxSH	Off with	170-172	76	45.65(45.14)	1.15(1.14)	13.16(13.17)
1	$[HgCl_2(CPoxSH)]_2$	White	235-238	87	18.94 (19.80)	1.15(1.25)	5.65(5.77)
2	$[HgBr_2(CPoxSH)]_2$	White	300d	76			
3	$[Hg(SCN)_2(CPoxSH)]_2$	White	225d	61	22.94 (19.80)	1.10(1.14)	10.65(10.56)
4	$[ZnCl_2(CPoxSH)]$	Yellow	215-218	65	33.96 (34.09)	2.09(2.15)	9.65(9.94)
5	$[CdCl_2(CPoxSH)]$	Yellow	221-224	91	31.46 (31.74)	1.93(1.98)	8.99(9.18)
6	$Cd(NO_3)_2(CPoxSH)]$	Milky	149-152	73			
7	$[MnCl_2(CPoxSH)]$	White	197-200	81			
8	$[CoCl_2(CPoxSH)]$	Blue	265d	72			
9	$[NiCl_2(CPoxSH)]$	Greenish yellow	235-237	75			
10	$[Hg(CPoxS)_2]$	White	243-245	85	30.80 (30.80)	1.25(1.29)	9.32(8.98)
11	$[Zn(H_2O)_2(CPoxS)_2]$	Yellow	276d	84	36.25 (36.62)	2..36(2.31)	10.65(10.68)
12	$[Cd(H_2O)_2(CPoxS)_2]$	Off white	175d	80	33.61 (33.61)	2.32(2.12)	9.88(5.77)
13	$[Co(H_2O)_2(CPoxS)_2]$	Light blue	265-269	79			
14	$[Ni(H_2O)_2(CPoxS)_2]$	Greenish yellow	250d	87	35.99 (37.10)	2.35(2.33)	10.68(10.82)

Table 2: IR spectra data cm^{-1} of the ligand and complexes (1-14)

Seq.	ν(OH)	ν(NH)	ν(SH)	ν(C=N)	ν(C=S)	ν(N-N)	ν(C-Cl)	ν(M-S)	ν(M-N)	ν(M-O)
CPoxSH	-	3152m	-	1636s	1556m	1067s	576s	-	-	-
1	-	3210w	-	1642s	1538m	1088m	565m	321m	-	-
2	-	3157m	-	1651s	1531m	1076s	586m	332w	-	-
3	-	3187m	-	1938s	1521s	1066s	567s	303m	-	-
4	-	-	2565m	1610m	1567s	1091s	598m	-	476w	-
5	-	-	2552w	1625s	1583s	1087s	560m	-	492m	-
6	-	-	2632m	1632s	1564m	1052s	587m	-	482m	-
7	-	-	2556w	1630s	1560m	1088s	550m	-	523w	-
8	-	-	2576w	1621s	1542s	1078s	553m	-	474w	-
9	-	-	2540m	1641m	1523s	1077s	590m	-	512m	-
10	3412m	-	-	1632s	1552m	1066s	576m	321w		-
11	3423b	-	-	1639s	1532s	1076m	565m	331w	507w	440w
12	3432b	-	-	1632m	1550m	1100m	574w	325m	521s	395m
13	3398m	-	-	1640m	1562m	1078s	587w	315m	543w	415w
14	3421b	-	-	1623m	1573m	1072m	576m	298w	521m	389w

s = Strong , w = Weak , m = Medium, b= Broad

Table 3: ^{1}H, ^{13}C-NMR spectra data ppm of the ligand and some complexes prepared



Complex	Seq.	δSH	δNH	δphenyl	δC-1	δC-2,4	δC-3	δC-5	δC-6	δC-2'	δC-5'
CPoxSH		10.7		7.180-7.530	131.800	128.500	134.400	124.500	125.700	178.81	160.71
$[HgCl_2(CPoxSH)]_2$	(1)	-	5.744	6.990-7.875	131.863	131.822	134.438	125.101	125.965	169.975	162.894
$[Hg(SCN)_2(CPoxSH)]_2$	(3)	-	6.435	7.346-7.854	131.933	130.092	134.668	124.961	125.765	170.774	161.754
$[CdCl_2(CPoxSH)_2]$	(5)	9.36		7.573-7.853	131.930	131.930	134.514	125.096	125.184	171.432	159.922
$[ZnCl_2(CPoxSH)_2]$	( )	8.67		7.587-7.856	131.918	126.060	134.516	125.054	125.298	170.565	161.167
$[Zn(H_2O)_2(CPoxS)_2]$	(11)	-		7.540-7.772	131.564	130,981	134.266	124.249	125.454	173.755	162.114
$[Cd(H_2O)_2(CPoxS)_2]$	(12)	-		7.500-7.782	131.700	126.956	134.272	124.582	125.514	171.765	160.744

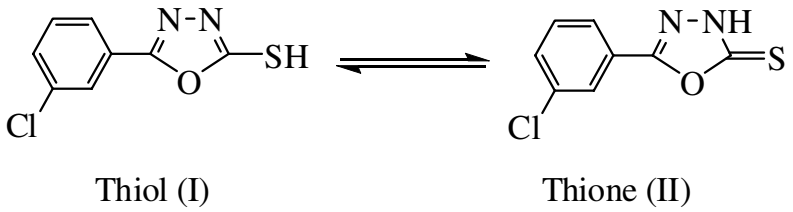


Fig. 1: The structure of thione ligands (LH)

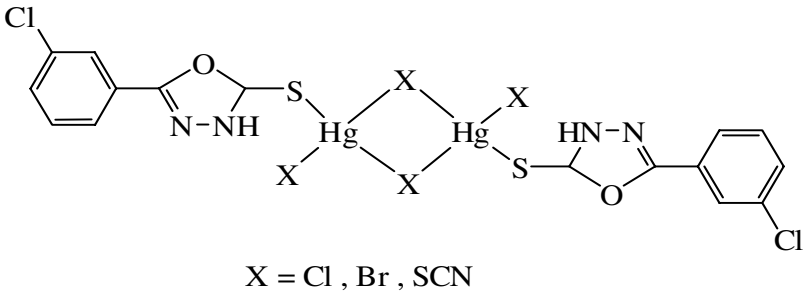


Fig. 2: The structure formula of the complexes$[HgX_2(CPoxSH)]_2$

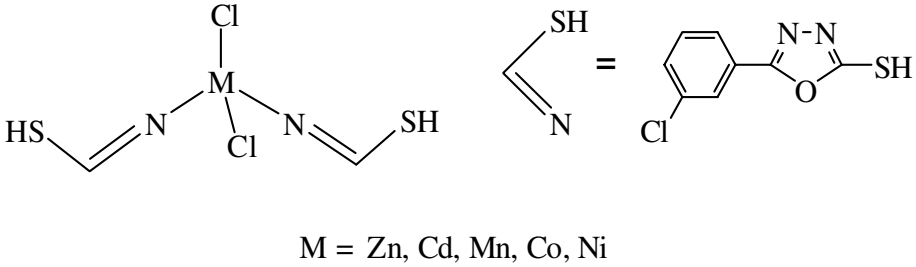


Fig. 3: The structure formula of the complexes $[MCl_2(CPoxSH)_2]$

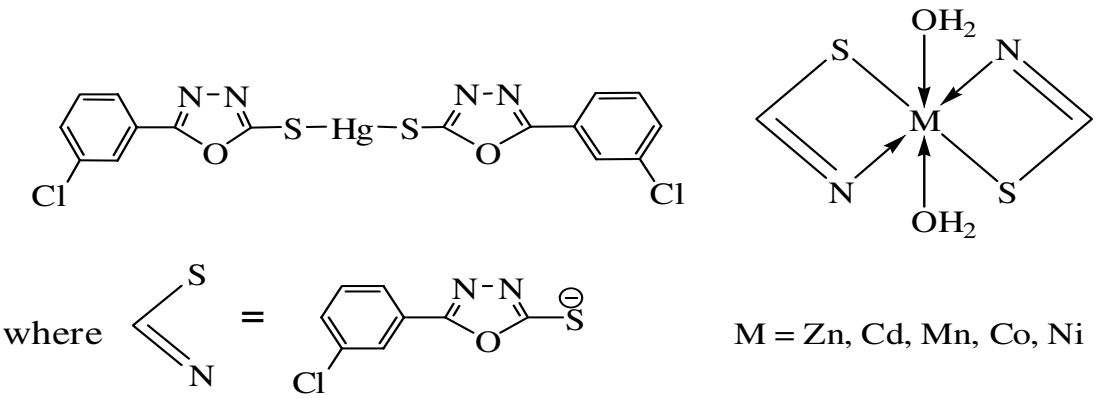


Fig. 4: The structure formula of the$[Hg(CPoxS)_2]$ and $[M(H_2O)_2(CPoxS)_2]$ complexes

from nitrogen atom of oxadiazole ring and the chloride ligand coordinate as monodentate ligand to metal(II) ions.

The deprotonated complexes of the type $[Hg(CPoxS)_2]$ were readily precipitated by reaction of $[Hg(OAc)_2]$ with two mole proportion of CPoxSH in the presence Et_3N as a base. The thionate were coordinated as monodentate ligand to mercury through sulfur atom of thione group. But with $[M(OAc)_2.xH_2O]$ give octahedral complexes of the type $[M(H_2O)_2(CPoxS)_2]$ and the thionate were coordinated as bidentate ligand to metal ion through the sulfur and nitrogen atoms.

Characterization of complexes

The prepared complexes were identified by IR spectra, element analysis and some them by ^1H and ^{13}C-{^1H} NMR. spectra and their data are listed in Tables 1-3.

Infrared spectra

The infrared spectra of CPoxSH ligand and complexes 1-14 recorded in the 4000 – 200 cm^{-1} range with CsI disk (the data of spectra shown in table 2). In the IR spectra of the ligand, the band at 1636 cm^{-1} was assigned to ν(C=N)[12], while that at 3152 cm^{-1} to ν(N-H). These observations suggest that the ligand exists in the thione form (Fig. 1) in the solid state. A strong band at 1092 cm^{-1} was attributed to (N-N) of the oxadiazole ring[13]. Bands located at 1563, 1110, 950, and 555 cm^{-1} were assigned to C=C aromatic ring, C-O-C symmetrical stretching, C-O-C asymmetrical stretching for oxadiazole ring and C-Cl band[14], respectively.

The spectra of complexes

1. $[HgX_2(CPoxSH)]_2$ when (X = Cl, Br, SCN)(Fig 2), a band due to *í*(NH) is visible in the region (3252-3175)cm^{-1}, suggesting the non-involvement of the nitrogen in the coordination. The shift of the (N-N) to high frequency and positive shift of the C=N band indicate the coordinated of the ligand to the metal center through the sulfur atoms, and show a new medium bands in the region (303-332) cm^{-1} assigned to Hg-S[15]. The IR spectra of the $[HgX_2(CPoxSH)]_2$ complex shown two strong band at 2069cm^{-1} and 2113$cm^{-1}$was assigned to SCN terminal and bridging bond, respectively[16]
2. $[Hg(CPoxS)_2]$ (Fig 4). The IR spectra is show a strong at 1641 cm^{-1} was assigned to (C=N)[12]. A positive shift in C=N and N-N indicate that the C=N group is uncoordinated, and a negative shift in C=S and the appearance of a band at 321cm^{-1} to Hg-S[15] indicate the ligand coordination through the sulfur atoms.
3. $[MCl_2(CPoxSH)_2]$ when [M = Cd, Zn, Mn, Co, Ni]. The IR spectra of complexes show a bands in the region (2540–2632)cm^{-1} due to (SH), suggesting the non-involvement of –SH in coordination. And the shift of (N–N) to lower energy and the weakening of the (C=N) band indicates the coordination of C=N to the metal centre through the nitrogen atoms. This view is further supported by the appearance of a band corresponding to the metal–nitrogen stretching vibration[17] at (474–523)cm^{-1} in the complexes.
4. $[M(H_2O)_2(CPoxS)_2]$ when [M = Cd, Zn, Mn, Co, Ni](Fig 4). The IR spectra of these complexes show a bands in the region (1623-1640)cm^{-1} was assigned to (C=N)[17]. The appearance of a bands in the region (298-331)cm^{-1} to M-S [15] and bands in the region (507-543)cm^{-1} to M-N[17] indicate the ligand coordination behaves as a bidentate chelate through the sulfur and nitrogen atoms. A bands observe in the region (389-440)cm^{-1} die to (M-O) bond[18]

^1H- and ^{13}C-NMR spectra

The ^1H and ^{13}C-{^1H} NMR data of some the prepared complexes are given in Table 3.

The ^1H-NMR spectrum of the ligand exhibits a sharp singlet at 10.7 ppm due to -SH, indicating the thiol form of the ligand in the solution state (Fig 1). The aromatic protons were observed

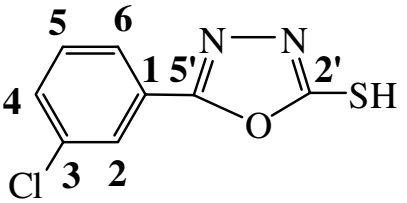


Fig. 5: The number of carbon atoms

in the region 7.18–7.53 ppm. The ^{13}C-NMR spectrum shows peaks at 134.19 (C-3), 128.50 (C-2,4), 125.0 (C-5) and 131.45 (C-6) ppm for the aromatic ring[19]. The peaks observed at 159.71 and 178.81 ppm are due to C-5' and C-2' (C=S)[19], respectively, of the oxadiazole ring (Fig. 5).

In the ^{1}H-NMR spectrum of the $[HgCl_2(CPoxSH)]_2$ and $[Hg(SCN)_2(CPoxSH)]_2$ complexes, the signal due to –SH is no longer present and a new peak at 8.12 and 7.96 ppm, respectively, due to –NH is observed. This suggests the existence of ligand in the thione form in the complexes (Fig. 3) and the non-involvement of –NH in the coordination. The aromatic protons are observed in the region 7.10–7.59 and 7.23-7.68 ppm respectively. And the negative shift in the chemical shift in ^{13}C-NMR spectrum of C=S indicate the ligand coordinated through the sulfur atom with mercury metal[15] and a new beak is appeared in spectrum of the second complex at 112ppm due to SCN group and this is indicate the complex is formation. But in the ^{1}H-NMR spectrum of the $[CdCl_2(CPoxSH)_2]$ and $[ZnCl_2(CPoxSH)_2]$ complexes, a signal beak at 10.86 and 10.76ppm due to –SH respectively. This indicate the ligand is coordinated through nitrogen atom[20]. The aromatic protons are observed in the region 7.15–7.79 and 7.35-7.76 ppm respectively. ^{13}C-{^{1}H} n.m.r. spectra have also been recorded and data are given in table 3.

ACKNOWLEDGEMENTS

We thank Prof. Subhi A. Al-Jibori (Department of Chemistry, College of Science, University of Tikrit) and AL al-Bayt University for measuring the NMR spectra.

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