

# Antifungal Investigations of Synthesized new Transitional Bivalent Metal Complexes Derived from 4-Methyl phenol

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## Abstract

In this work new series complexes of Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Au(III) were prepared and characterized using a new azo ligand (HMDP) from coupling reaction of 4- Aminoacetophenone with 4-methyl phenol. The structures of the free ligand and the complexes were characterized using several techniques, including molar conductance, elemental analysis (C.H.N), electronic spectral, magnetic measurements, <sup>1</sup>HNMR, FT-IR, and mass. The data values indicated octahedral geometry with a genral formula [ML<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] for Co(II), Cu(II), Ni(II), Zn(II) and Cd(II) metal ions, and square planar geometry [ML(H<sub>2</sub>O) Cl] Cl for Au(III) central ion, in which ligand behaves as abidentate donor. The metal ion complexes showed higher significant antimicrobial activity against C. albicans fungi comparing to their corresponding ligand.

**Keywords:** New Azo ligand, complexes, 4-methyl phenol, p-cresol, C. albicans.

## 1. Introduction

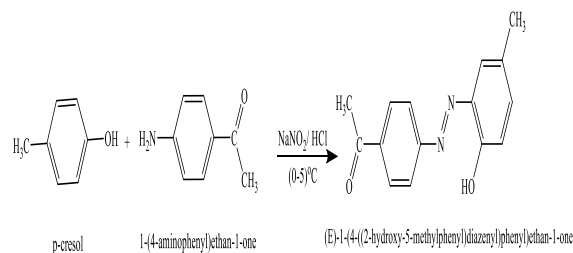
Azo ligands have a lot of interest in a different fields especially in the coordination chemistry due to their stability, sensitivity, and selectivity twarads metal ions in their diffenet oxidation states [1-3]. p-crecol azo compounds considered as an important type of homocyclic azo ligands which have an ability to coordinate as abidentate through one nitrogen atom of azo group and oxygen atom of hydroxyl group [4], Five member ring that formed after the coordination contribute significantly to increase the stability of the complexes, as well as the biological inhibiting of these compounds towards many types of bactria and fungi, In addition to their effectiveness as anti-cancer [5, 6]. The aim of our work concentrated on synthesis of new azo ligand as a derivative of p-crecol, and styding its coordination with Co(II), Cu(II), Ni(II), Zn(II), Cd(II), and Au(III) ions and then biological inhiption towards C. albicans fungi.

## 2. Experemental

All of the chemicals that used in the present studies supplied by Sigma Aldrich and BHD companies, with high percentage of purity. Elemental analysis was performed employing the element analyzer, microanalytically units of 1180 C.H.N. 1700, Double beam Shimadzu spectrophotometer model 1700 was used for recording of the electronic spectra, while FT\_IR sperctra were measured by Shimadzo FTIR-8400 spectrophotometer, <sup>1</sup>H-NMR at DMSO-d<sub>6</sub> solvent operating by Bruker3000MHz, Switzerland. AB Sciex Q-Trap 3200 LC-MS/MS was used to record mass spectra. A balance magnetic MSB-MKI was performing the magnetic susceptibility.

### Synthesis of Azo ligand (HMDP)

Azo ligand (HMDP) was prepared by coupling reaction of (2.7gm, 0.005 moles) 4- aminoacetophenone which mixed with (4) ml of concentrated HCl in (30) ml of distilled water, then (1.4gm, 0.002`mole) of cold solution of NaNO<sub>2</sub> was added with stirring. The temperature of the reaction was maintained between (0-5) 0C. Diazonium salt solution prepared above was added dropwise to the alkaline solution of p-cresol. The reaction mixture was stirred for (10-20) minutes maintaining the temperature of (5-10) 0C until the precipitation of ligand was appeared, filtered, dreied, and recrystallized from proper solution, as shown in Scheme(1).



### Scheme 1: Synthesis of Azo compound (HMDP)

#### Synthesis of Solid Complexes

The complexes with mole ratio (HMDP:M) (2:1) were prepared by dissolving (0.914 g ; 0.001mol) of (HMDP) in (15) ml of ethanol. Each of metal chloride salts (0.001 mol): CoCl<sub>2</sub>.6H<sub>2</sub>O, NiCl<sub>2</sub>.6H<sub>2</sub>O, CuCl<sub>2</sub>.2H<sub>2</sub>O, ZnCl<sub>2</sub>.H<sub>2</sub>O, CdCl<sub>2</sub>.H<sub>2</sub>O, and NaAuCl<sub>4</sub>.2H<sub>2</sub>O has been dissolved in ethanol (15) ml, and mixed with ethanolic solution of a ligand, then refluxed for (1) hr. The complexes are separated, and the product of each complex was filtered, washed with distilled water, and dried under vacuum. Some of the physical features and analytical data for the ligand and the complexes were summarized in Table (1).

**Table (1) :Some of Physical Features of (HMDP) ligand and the solid complexes**

Compound (Molecular Formula)	Colour (product%)	M.Wt.	m.p	Element Analysis (calculated) Found
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				C	H	N	M
(HMDP) (C15 H14 N2 O2)	yellow 75%	254	222	(70.85) 70.88	(5.55) 5.52	(11.02) 11.00	-----
[Co(HMDP) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] (C30H29N4O6Co)	Red 78%	600.5	270	(60.00) 60.02	(4.87) 4.85	(9.33)	(9.81)
[Ni(HMDP) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] (C30H29N4O6Ni)	Red 80%	600.2	310 Dec.	(60.03) 60.00	(4.87) 4.90	(9.33) 9.31	(9.78) 9.80
[Cu(HMDP) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] (C30H29N4O6Cu)	Red 75%	605.1	308 Dec	(59.55) 59.57	(4.83) 4.80	(9.26) 9.27	(10.50) 10.48
[Zn(HMDP) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] (C30H29N4O6Zn)	Deep red 82%	606.9	278	(59.37) 59.35	(4.82) 4.84	(9.23) 9.22	(10.77) 10.77
[Cd(HMDP) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ] (C30H29N4O6Cd)	Deep red 85%	654.0	286	(55.10) 55.08	(4.47) 4.44	(8.57) 8.60	(17.19) 17.20
[Au (HMDP) (H <sub>2</sub> O) Cl]Cl (C15H15Cl2N2O3Au)	Deep Orange 81%	539.1	219	(33.42) 33.45	(2.80) 2.78	(5.20) 5.23	(36.53) -----

### Antifungal Activity

The Antifungal activity of (HMDP) and the complexes were tested against *Candida albicans*. fungi by using Agar-diffusion method Stock. The solutions were prepared by dissolving free ligand and complexes in DMSO solvent with a concentrations(10, 20 and 50 )ppm. The nutrient agar medium was poured into petridish, [1] ml of the tested microorganism was spread over the solid nutrient agar plates with help of a spreader.(0.1) ml of the test solutions were added in the spots of the inoculated solid media. After evaporating process of the solvent Perti dishes were placed at low temperature for two hours to allow the diffusion of the chemical materials and then incubated at 37°C for 48 hours.

### 3. Results and Discscution

<sup>1</sup>HNMR spectrum of (HMDP) ligand in DMSO-d<sub>6</sub> solvent exhibited a signels (s,3H, -CH<sub>3</sub>) protons at (2.55), and (2.51) ppm, while the signales of the Aromatic protons (m, Ar-H) [7] were appeared between (7.46-8.335) ppm, the single at (9.33) ppm due to the proton of hydroxyl group [8] (s,1H,-OH) which is disappeared in [Cd(HMDP)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] complex as a result of participation of this group in the coordination process, also the signal at (6.22) ppm was appeared in the complex spectrum which is indicating existence of H<sub>2</sub>O molecules inside the coordination sphere, as shown in figures (1), and (2)

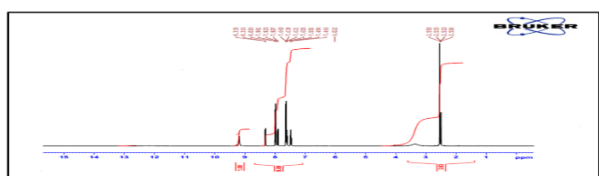


Fig.1: <sup>1</sup>HNMR Spectra of Azo ligand (HMDP).

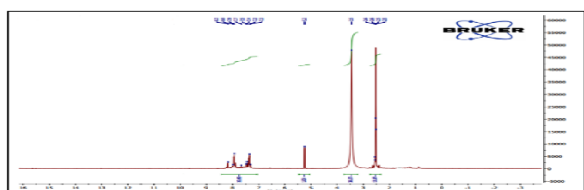


Fig.2: <sup>1</sup>HNMR Spectra of [Cd(HMDP)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] complex

FT-IR spectrum of the free ligand (LMDP) showed a broad beak at (3439) cm – due to interaction of phenolic ν(O-H), and ν(O-H) of H<sub>2</sub>O molecules [9], This peak was shifted in the complexes spectra as a result of participation of aqua molecules, and phenol group after it,s deprotonation in the coordination process. A noticeable change in position and intensity was seen on the ν(N=N) [2, 10] value at (1597) cm – in (LMDP) comparing to complexes spectra that indicating the coordination through one nitrogen atoms of azo group, Finally new peaks were appeared in the complexes spectra for ν(M-N) [11] at (424- 499) cm-, and ν(M-O) [12, 13] at (520- 547) cm – which gives further evidence of occurance the coordination between the metal ion and (LMDP) ligand as showed in figures ( 3- 6 ), and Table (2)

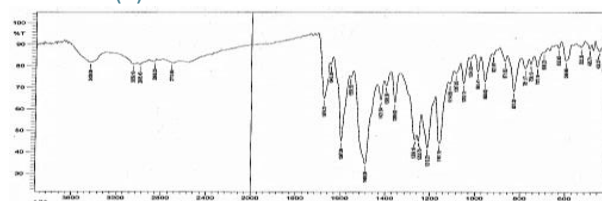


Fig.3 :FT-IR spectrum of (HMDP) ligand

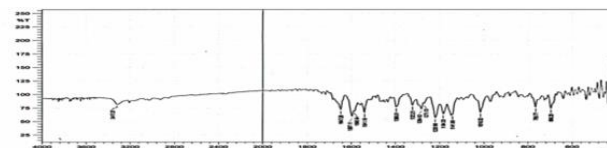


Fig.4 :FT-IR spectrum of [Ni(HMDP)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] complex

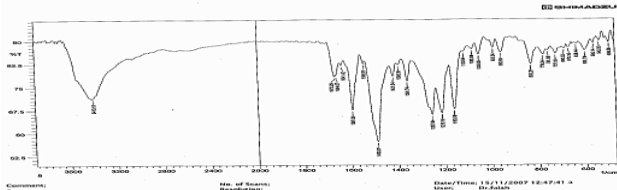


Fig.5 :FT-IR spectrum of [Cu(HMDP)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] complex

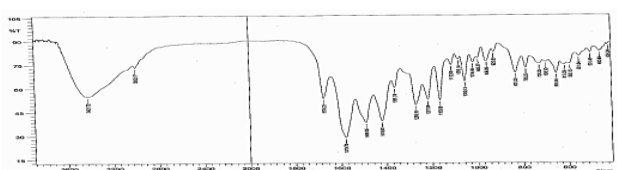


Fig.(6) :FT-IR spectrum of [Au(HMDP) (H<sub>2</sub>O) Cl] Cl compl

Table( 2) : Values of FT-IR ferquencies(cm-) for (HMDP) ligand, and it,s complexes

Compounds	ν(O-H)phe +ν(O-H) H <sub>2</sub> O	ν (C-H)or.	ν (C-H)al.	ν (C=O)	ν(N=N)	ν (C-OH)	ν(M-N)	ν(M-O)
L	3439 wbr	3064w	2924 w	1674s	1597 m	1161s	---	---
[Co( L) <sub>2</sub> ( H <sub>2</sub> O) <sub>2</sub> ]	3423 wbr	3003w	2962w	1671m	1477s	1155s	497 w	530 w

[Ni(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	3421 wbr	3003w	2937w	1668m	1490m	1159s	466 w	520 w
[Cu(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	3381 wbr	3005w	2901w	1674m	1491m	1163m	424 w	547 w
[Zn(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	3421 wbr	3006w	2831w	1674m	1494m	1161m	499w	532w
[Cd(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	3390 wbr	3171w	2935w	1674m	1481m	1163m	484w	521w
[Au(L(H <sub>2</sub> O)Cl)Cl]	3390 wbr	3171w	2935w	1671m	1490m	1162m	484w	521w

(b : broad, w: weak, m: medium, s: strong ), (L: (HMDP) )

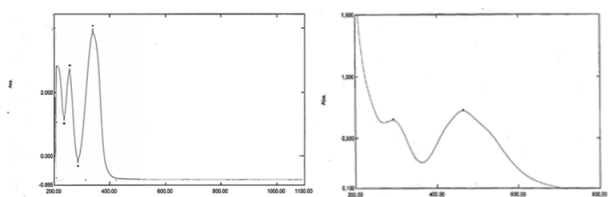
Molar conductivity measurements of the complexes in DMF solvent at a concentration M is summarized in Table (3), their values between (5.45–21.65) S.cm<sup>2</sup>.mole<sup>-1</sup> confirmed the non-electrolyte nature of all metal ions (II) complexes, except Au (III) complex is 87.17 S.cm<sup>2</sup>.mole<sup>-1</sup>, indicates the presence of one chlorid ions outside the coordination sphere, also the magnetic susceptibility of the

synthesized complexes confirmed the number of unpaired electrons in the electronic configuration of Co(II), Ni(II), and Cu(II) metal ions [14], while their values of Zn(II), Cd(II), and Au(III) refers to the diamagnetic nature of these complexes on the other hand the values of magnetic moment indicating the octahedral geometry for all of the complexes [15] except the square planar geometry of Au(III) complex, as shown in table (2)

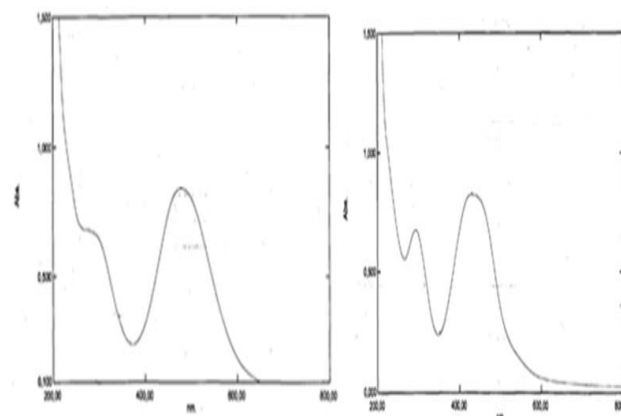
**Table (2) :Molar conductivity in DMF & Magnetic moment of (HMDP) and the complexes.**

Complexes formula	$\Lambda_M$ (S.cm <sup>2</sup> .mol <sup>-1</sup> ) in DMF	$\mu_{eff}$ (B.M)	Geometry (Hybridization)
[Co(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	15.36	3.78	O.h distorted (sp <sup>3</sup> d <sup>2</sup> )
[Ni(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	11.51	2.98	O.h regular (sp <sup>3</sup> d <sup>2</sup> )
[Cu(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	10.77	1.78	O.h distorted (sp <sup>3</sup> d <sup>2</sup> )
[Zn(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	14.32	0.00	O.h regular (sp <sup>3</sup> d <sup>2</sup> )
[Cd(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	8.60	0.00	O.h regular (sp <sup>3</sup> d <sup>2</sup> )
[Au(L(H <sub>2</sub> O)Cl)Cl]	87.17	0.00	S.P (dsp <sup>2</sup> )

Electronic spectrum of (HMDP) ligand showed ( $\pi$ - $\pi^*$ ) transitions at (368) nm, and ( $n$ - $\pi^*$ ) transition at (430) nm, as a result of coordination process intra ligand charge transfer where appeared in the complexes spectra between (377-385) nm, while (MLCT) where emerged between (430 -496) nm, as shown in Figures (7- 10), and Table (4).



Fig(7) :Uv-Vis spectrum of (HMDP) Fig(8) :Uv-Vis spectrum of [Co(HMDP)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]



Fig(9) :Uv-Vis spectrum of [Ni(HMDP)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] Fig(10) :Uv-Vis spectrum of [Cu(HMDP)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]

**Table (3) : Electronic transitions of (HMDP) and it,s complexes**

Compound	$\lambda$ nm	$\bar{\nu}$ (cm <sup>-1</sup> )	Assignment
L(HMDB)	368	(27173)	intra-ligand $\pi \rightarrow \pi^*$
	430	(23255)	$n \rightarrow \pi^*$
[Co(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	380	(26315)	intra-ligand $n \rightarrow \pi^*$
	486	(20576)	4T <sub>1g</sub> (F) $\rightarrow$ 4T <sub>2g</sub> (P)
[Ni(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	379	(26385)	intra-ligand $n \rightarrow \pi^*$
	490	(20408)	[(v <sub>1</sub> )3A <sub>2g</sub> (F)] $\rightarrow$ 3T <sub>2g</sub> (F)]
[Cu(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	381	(26246) (21141)	C.T
	468		2E <sub>g</sub> $\rightarrow$ 2T <sub>2g</sub>
[Zn(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	383	(26109)	intra-ligand $n \rightarrow \pi^*$
	474	(21097)	(MLCT)
[Cd(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	385	(25974)	intra-ligand $n \rightarrow \pi^*$
	476	(21008)	(MLCT)
[Au(L(H <sub>2</sub> O)Cl)Cl]	377	(26525)	intra-ligand $n \rightarrow \pi^*$
	496	(20162)	(MLCT)

According to the previous results octahedral geometry of the synthesized complexes with a general formula [M(HMDB)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>] were proposed, the ligand (HMDB) occupied four coordination locations, and behaved as

bidentate through one nitrogen atom of azo group, and oxygen atom of phenolic group after deprotonation, while the residual locations were occupied by aqua molecules, on the other hand Au(III) complex manifested the square

planer geometry in which one (HMDB) molecule coordinated with this central ion as abidentate, while aqua molecule, and chloride ion coordinated as a monodentate, as shown in figure(11).

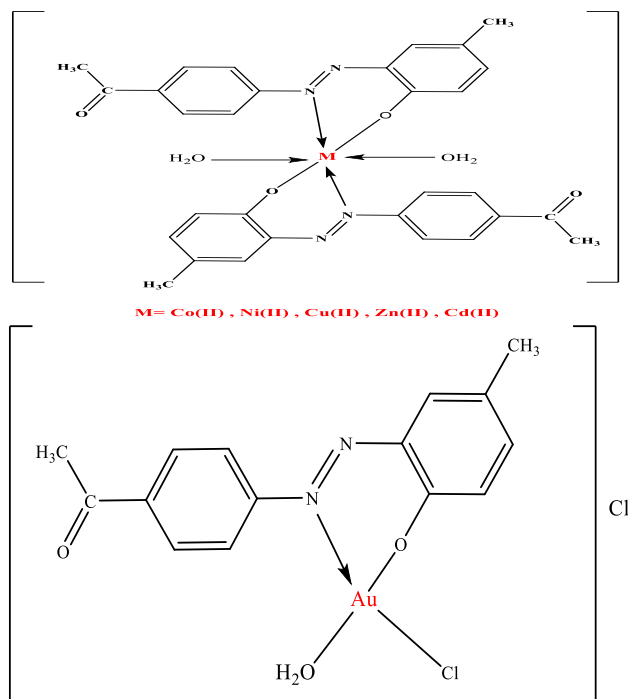
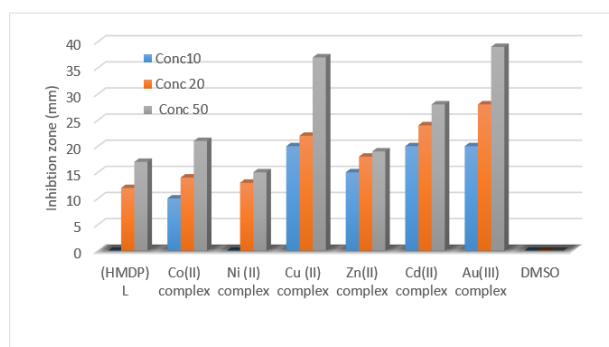


Fig (11) : Proposed structure of the synthesized complex

Antifungal activity of the free ligand and its complexes were studied against *C. albicans* type, at three types of concentrations [7, 14], and (50) ppm in DMSO solvent, the results confirmed the inhibition activity of (HMDB) ligand and the complexes, The complexes showed more activity comparing to the free ligand may be due to the toxicity effect of the metal ion on the normal cell processes, also the inhibition ability increase with increase of the concentration, as shown in figure (12).

#### 4. Conclusion:

New series of complexes of Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Au(III) ions with azo ligand (HMDB) as a derivative of p-cresol were synthesized and characterized with speed method, and high stability. All of these complexes have an octahedral geometry except Au(III) complex which has square planer shape. Finally the complexes have good inhibition activity against *C. albicans* fungi comparing their free ligand (HMDB).



Fig(12) : Inhibition Zones of (HMDB), and its complexes against *C. albicans* fungi

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