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Synthesis, Characterization, and Biological Activity of Some Metal Complexes derived from Isatin.

Ream Nafea, Abeer A. Faheim^a, Zeinab A. El-Shafiey^a, EmanHelmy^b

International

^aChemistry Department, Faculty of Science (Girl's), Al-Azhar University, Nasr-City, Cairo, Egypt,
^bThe Regional Center For Mycology and Biotechnology, Al-Azhar University, Nasr-City, Cairo, Egypt

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Abstract

Condensation of isatin with 2-amino-5-chloropyridene readily gives rise to Schiff-base ligand, L. Its reactions with Co(II) and Cd(II) ions give a series of new complexes. All the synthesized metal complexes were found to be coloured, nonhygroscobic in nature, stable in air. The metal complexes structurally characterized with spectroscopic methods, magnetic, and conductivity measurements. The data showed that the Schiff base ligand, L, behaves as a tridentate via nitrogen atom of azomethine group, oxygen atom of isatin carbonyl and nitrogen atom of pyridine ring moiety. The results obtained from magnetic moments, electronic spectra, mass spectra and elemental analyses confirmed the octahedral geometry around the central metal ions.

Keywords: Schiff-base ligand; metal complexes; biological activity.

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Introduction

Schiff bases derived from an amino and carbonyl compound are an important class of ligands that coordinate to metal ions via azomethine nitrogen and have been studied extensively. Schiff's bases have been widely used as ligands because they form highly stable coordination compounds and have good solubility in common solvents. These Schiff's base metal derivatives have considerable interest in biological systems, contributing to the knowledge of their structure and behavior in various activities [1]. In azomethine derivatives, the C=N linkage is essential for biological activity, several azomethine have been reported to possess remarkable antibacterial, antifungal and anticancer activities [2].

Isatin has been known for about 150 years and has been found, like oxindole and endogenous recently polyfunctional heterocyclic compounds, to exhibit biological activity in mammals [3]. Isatin also is a synthetically versatile substrate that can be used to prepare a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis [4]. Schiff bases of isatin are known to possess a wide range of pharmacological properties including antibacterial [5], anticonvulsant [6], antifungal [7]. Bis-Schiff bases are characterized by their capacity to completely co-ordinate a metal ion, forming chelate rings [8]. The Schiff bases of isatin have also been used as ligands for complexation of metals such as copper II [2].

Correspondence

Abeer A. Faheim

Chemistry Department, Faculty of Science (Girl's), Al-Azhar University, Nasr-City, Cairo, Egypt These complexes catalyzed the oxidation of carbohydrates. Bis-Schiff bases can act as inhibitors of human α -thrombin. Recently it has been reported that a bis-imine of isatin has antimicrobial properties and affects cell viability [7].

2. Experimental.

2.1. Analysis and Physical Measurements

All chemical used in the present work were of highest purity available (BDH, Fluka, Sigma or Merck products). They include: isatin, 2-amino-5-chloropyridine, hydrated metal chloride salts namely, $\{CoCl_3.6H_2O \text{ and } CdCl_2.2H_2O \}$, ethanol, methanol, distilled water, double-distilled water.

Microanalysesof carbon, hydrogen and nitrogen were performed using a Perkin-Elmer CHN 2400 elemental analyzer at Micro Analytical Center, Cairo University, Giza, Egypt. Infrared spectra of studied samples were recorded as KBr discs on a Perkin-Elmer 437 IR spectrometer covering the frequency range 400-4000 cm⁻¹.The ¹H-NMR spectra of ligand were recorded in DMF. The solid reflectance measurements were measured at room temperature in the UV-Vis. regions in the wavelength (200-800 nm) were made with UV-VIS-NIR shimadzu 310 Pc. The thermo gravimetric analyses (TGA) were carried out in dynamic nitrogen atmosphere (20 mL min⁻¹) with a heating rate of 10 °C min⁻¹ and temperature range 20-1000 °C using shimadzu TG-50 H and DTA-60 H thermal analyzers. Magnetic susceptibilities were measured by the Gouy method at room temperature using a Johnson Matthey, alfa product; model MKI magnetic susceptibility balance at the Micro Analytical Center, Cairo University, Giza, Egypt.

Melting or decomposition point was measured by electronic melting point apparatus : Griffin & George made in Britain.

2.2. Synthesis of the organic ligand.

An ethanoic solution of (20 mL) of 0.01 M was added to a solution of 0.01 M isatin dissolved in (20 mL) of ethanol. The mixture was reflexed for 4 hours on water bath and a red solid compound was separated.

2.3. Synthesis of the metal complexes.

The metal complexeswere synthesized by an ethanoic solution of $(5.0 \times 10^{-3} \text{ M})$ of ligand L was added to a solution of $(5.0 \times 10^{-3} \text{ M})$ of the hydrated metal chloride salts dissolved in (20 mL) of ethanol. The reaction mixture was refluxed for 6 hrs. under stirring at room temperature.

2.4. Assessment of antimicrobial activity.

The potential antimicrobial effects of ligand L and its Co(II) and Cd(II) complexes were investigated by using modified disc diffusion method [9] at the Regional Center for Mycology and Biotechnology Al-Azhar University, Cairo, Egypt. three Gram-positive bacteria, *namely Streptococcu mutants, Enterococcus faecalis and*

Lactobacillus bulgaricus and one Gram-negative bacteria, namely Porphyromonasgingivalis. these bacterial strains were chosen as they are known human pathogens [14] in addition to tow fungi, namely Candida albicans, and Crytococcusneoformaswere used in the study. Gentamycinand Ketoconazole were used as positive reference standards for bacteria and fungi respectively.

3. Results and discussion

All the synthesized metal complexes were found to be coloured, nonhygroscobic in nature, stable in air. The metal complexes were found to be insoluble in water and most organic solvent but soluble in DMF and DMSO. The melting point of the complexes were found to be $> 300 \degree$ C Table 1.

3.1. Molar conductance measurements

The molar conductance measurement for 1×10^{-3} M of Co(II) andCd(II), complexes in DMSO at room temperature, Table 1 indicates that these complexes are non-electrolytes.

Table(1): Analytical data and some physical properties of the Schiff base ligand, (L) and its metal complexes.

Com			Molecular		Elemental analysis, found (calcd)					
pd. No.	Empirical formula	Colour	weight	С	Н	Ν	Cl	М		
L	C ₁₃ H ₈ N ₃ OCl	Orange	257.71	60.49 (60.59)	3.76 (3.14)	15.367 (16.31)	12.89 (13.76)			
1	$[Co(L)Cl_2.H_2O].2H_2O \\ [CoC_{13}H_8N_3OCl_3.3H_2O \\]$	Brown	440.46	34.39 (35.36)	3.10 (3.20)	8.50 (9.52)	23.54 (24.08)	13.85 (13.35)		
2	$\begin{array}{l} [Cd(L)Cl_{2}.H_{2}O] \\ [CdC_{13}H_{8}N_{3}OCl_{3}.H_{2}O] \end{array}$	Pale orange	459.69	35.42 (34.01)	2.34 (2.20)	9.06 (9.16)	24.01 (23.17)	23.55 (24.49)		

3.2. Infrared spectra and mode of bonding

In order to ascertain the mode of bonding, the IR spectrum of the free ligand was compared with those of its metal complexes. The main vibration frequencies of the ligand in comparison with its metal complexes are listed in Table 2 and represented in Figure 1. The spectra of the free ligand show two strong bands at 1736 and 1612 cm¹ characteristics to the ν C=O (Isatin) and ν C=N (azomethine) respectively, indicating the formation of the Schiff base product. These bands are shifted towards lower or higher frequencies in the spectra of all metal complexes 1603-1497 cm⁻¹ compared with the free Schiff base indicating the involvement of the isatin C=O oxygen and azothemine nitrogen in chelation with the metal ions, the coordination of nitrogen to the metal ion would be expected to change the electron density of the azomethine link and thus cause a shift in the vC=N group[10]. The intense band at 1466 cm⁻¹ present in the IR spectra of the free ligand may be assigned to the vC=N (pyridine ring), however, the spectra of all complexes show the shift of this band indicating the participation of the pyridine nitrogen atom in

coordination , moreover, The observed broad band at 3449 cm⁻¹ in the IR spectrum of the ligand, was attributed to NH of the isatin ring [11]. The IR spectrum displays also medium bands at 735 cm⁻¹ may be assigned to vC-Cl of the ligand [12]. The IR spectra of the complexes exhibited additional bands at 934-947 cm⁻¹ due to skeletal vibration of pyridine ring breathing mode ,the shift of this band comparing to the free ligand suggesting the participation of ring nitrogen in complex formation[13].

Another evidence for the coordination is the observance of new bands in the far IR region at 570–505, 520–440, and 432–524 cm⁻¹ which may be due to vM-O, vM-N (azomethine), and vM-N (pyridine) respectively, that are not observed in the spectrum of the free ligands [14, 15].

Furthermore, observed broad bands appear at 3402-3354 cm⁻¹ in all complexes indicates the existence of coordinated/lattice water molecules [16]. The nature of water molecules was detected using the thermal gravimetric analysis technique as clear letter.

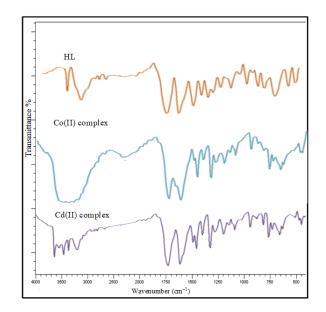


Figure (1): IR spectra of ligand L and its metal complexes

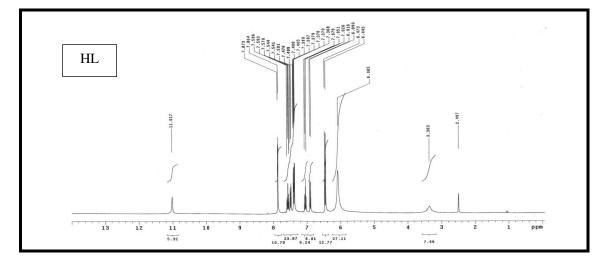
Table 2 : Significant IR – spectral bands, $\upsilon((cm^{-1}))$ of Schiff base ligand, L and its metal complexes

Comp.	v(H ₂ O)	v (C=O) (isatin, moiety)	v(C=N) azome	Pyridine v(C=N)	v(NH)	v(M-O)	v(M-N)
Ligand L		1756	1612	1466	3449		
$[Co(L)Cl_2.H_2O]_2H_2O$	3379	1728	1650	1404	3456	664	478
$[Cd(L)Cl_2.H_2O]$	3364	1728	1650	1404	3456	664	455

3.3. ¹H NMR spectroscopy

The ¹H NMR spectra were obtained in DMSO– d_6 as well as DMSO- d_6 + D₂O in order to confirm the coordination sites of the ligand, L to its diamagnetic

Cd(II) complex. Chemical shifts were reported in parts per million (ppm). The spectra of diamagnetic Cd(II) complex show similar NMR pattern as clear from Figure (2) and its chemical shifts in comparison with the parent ligand, Lare listed in Table 3.



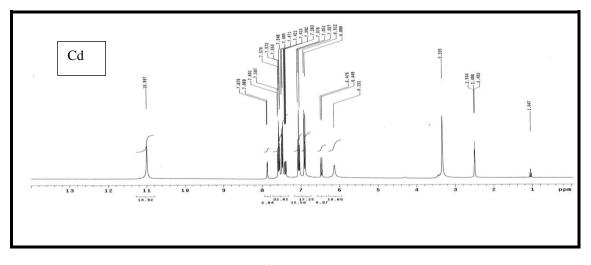


Figure (2)¹H NMR spectrum of Schiff base ligand L

Table (3)¹H NMR data (ppm) for Schiff base ligand, L and its diamagnetic Cd(II) complex

Compound	δ Phenyl	δ pyridine	δ ΝΗ	
L	6.443-75.96	7.864-7.873	11.017	
2	6.886 -7.576	7.597-7.876	10.997	

3.4. Electronic spectra and Magnetic behavior of the metal complexes

The electronic spectra of the ligand, L and its complexes were recorded in DMF at room temperature and all data are given in Table4.Two absorption speaks were observed in the absorption spectrum of the free ligand is characterized mainly by Three absorption bands in the region 242-419 nm which may be assigned to and change transfer transition the longer wave length band is assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ intramolecular charge transfer while the other due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of the benzene and pyridine moieties[17] .Upon interaction of the ligand with the selected metal ions and comparison of the spectrum of the free ligand and its Co(II) and Cd(II) complexes, the bands of the free ligand were existed in all complexes spectra with slight shift to the blue or red region. Also, new bands were observed in the spectra of the complexes which are listed in Table --- This change can be taken as a positive evidence of complex formation[18]. The electronic spectra of Co (II) (1-5)complex showed two absorption bands at 419 and 725nm assigned to the transition ⁴ T_{1g} (F) \rightarrow ⁴ T_{1g}(P) and ⁴T_{1g}(F) \rightarrow ⁴A_{2g}(F),respectively suggesting and the octahedral structure and magnetic moment value is 7.97 B.M. [19,20], showing three unpaired electrons which is within the value corresponding to high spin (sp³d² structure) octahedral complexes of Co(ll) ion (ref).this value higher than the spin only value (3.87)due to the high orbital contribution to the magnetic moment.

The molar magnetic susceptibility values for powder sample of the complexes were measured at room temperature and used to calculate the corrected magneticmoments per metal ion using Pascal's constants showed that Cd(II) complex is diamagnetic in nature with no d-d or f-f transitions. The octahedral structure may be suggested according to all previous data and analysis.

Compd.	$\mu_{\rm eff}.^{(a)}(B.M.)$	Absorption bands (nm)					
No		ππ*	$n-\pi^*$	CTI ^(b)	d-d transition		
L		242	300	419			
1	4.97	237	256	299	419,725		
2	Diamagnetic	227	297	418			

Table (4): Magnetic moment and electronic spectral data of L, ligand and its metal complexes

(a) μ_{eff} is an experimental effective magnetic moment calculated

(b) Charge transfer interaction

3.7. Thermo gravimetric analysis.

The thermal methods of analysis are widely used to

investigate, thermal decomposition, thermal stability, solid state reactions, purity, reaction kinetics, evolved gas analysis as well as to verify the status of associated water / solvent into inside or outside the inner coordination sphere of the central metal ion supports the elemental analyses and confirms the structure of the metal complexes [21-23].

The thermogravimetric analysis (TGA) of the ligand L and its Co(II), Cd(II), Fe(III) and La(III) complexes carried out under nitrogen atmosphere at heating rate 20 $^{\circ}$ C / min up to 1000 $^{\circ}$ C are shown in Figure3 while Table 5 lists the temperature range ($^{\circ}$ C), partial mass losses (%) together with the assignments of each decomposition step based on mass calculation and nature of the peaks in each stage of decomposition. In all the TG curves, the results show good agreement with the calculated formulas as suggested from the analytical data Table 5. The obtained data indicated that :

- The coordinated water molecules were substantially eliminated from the complexes at higher temperatures than the hydrated water.[24]
- The thermogram of the ligand ($C_{13}H_8N_3OCl$) show three steps. The first stage of decomposition at the temperature range 45-522 °C with observed mass loss 24.64(25.04) % found (calculated) which due to the loss of, HCl and CO molecules. The second stage at temp. 522 – 604 °C the observed mass loss is 11.56 (10.10) due to the loss of CN. The third stage of decomposition at temp. rang 604 – 764 °C, the observed mass loss is 50.03(50.38) This is due to the loss of C₆H₅, N₂, and C₂H₂ Leaving Carbon residue.
- The thermal decomposition process of Co(II) complex showedfour weight loss steps. The first step of decomposition occurred within the temperature range of 46 –147 °C correspond to

the loss of two water molecules of hydration and with estimated mass loss 8.53% (calc. 8.15 %). The second step of decomposition was carried out in the range of 147 -211 °C correspond to the one coordinated H₂O and one HCl loss of molecules with estimated mass loss 12.95%(calc.12.34 %).The third stepofdecomposition occurred in the range of 211 -557 °C with mass loss of three CN and tow C₂H₂ molecules with estimated massloss 28.79 %(calc. 29.46%). The final step was carried out within the rang e of 557 -696 °C with mass loss of CO and C₅H₃ fragment with estimated mass loss of 21.29% (calc. 20.62 %), leaving behind CoCl₂ as a decomposition residual.

The thermal decomposition process of Cd(II) complex showed three weight loss steps. The first step of decomposition occurred within the temperature range of 130-299 °C correspond to the loss of one coordinated H₂O molecules with estimated mass loss 4.16% (calc. 3.94%). The second step of decomposition was carried out in the range of 279-442 °C correspond to the loss of one HCl and one CN molecules with estimated mass loss 12.95% (calc. 13.62 %). The third step was carried out within the range of 422-722 °C with mass loss of one CO, two CN, two HCl and C₉H₅ fragment with estimated mass loss of 58.15% (calc. 57.95%), leaving behind Cd as a decomposition residual.

Comp.	Stage	Temp. range	Weight	t loss%	Evolved moiety	Composition of the residue
1		(°C)	Found	Calc.		
L	Ι	45-522	24.64	25.04	HCl, CO	$C_{12}H_7N_3$
$(C_{13}H_8N_3OCI)$	II	522-604	11.35	10.10	CN	$C_{11}H_7N_2$
	III	604-764	50.03	50.38	C_6H_5, C_2H_2, N_2	3C (13.98%)
$[Co(L)Cl_2(H_2O)]2H_2O$	Ι	46-147	8.53	8.15	2H ₂ O Lattice	Co(C ₁₃ H ₈ NOCl ₂)H ₂ O
Co C ₁₃ H ₈ N ₃ OCl ₃ 3H ₂ O	II	147-211	12.95	12.34	H ₂ O,Coord, HCl	$Co(C_{13}H_7N_3OCl)$
	III	211-557	28.79	29.46	$3CN+2C_2H_2$	$Co(C_6H_3OCl)$
	IV	557-696	21.29	20.62	CO+C ₅ H ₃	CoCl ₂ (29.43%)
$[Cd(L)Cl_2(H_2O)]$	Ι	130-299	4.16	3.94	H ₂ O Coord	Cd (C ₁₃ H ₈ N ₃ OCl ₃)
Cd C ₁₃ H ₈ N ₃ OCl ₃ H ₂ O	II	279-442	12.95	13.62	HCl, CN	Cd(C ₁₂ H ₇ N ₃ OCl ₂)
	III	442-722	58.15	57.95	CO,2CN,2HCl,C ₉ H ₅	Cd (24.49%)

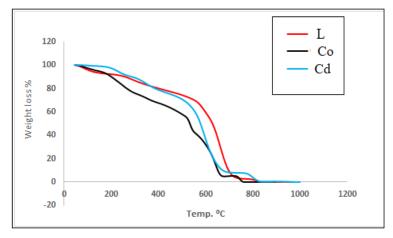


Figure (3): Thermogram of ligand and its metal complexes

3.6.2. Evaluation of the antimicrobial activity of synthesized compounds.

The antimicrobial activities of ligand L and its synthesized metal complexes were tested in vitro against series of organisms to increase the chance of detecting antibiotic principles in tested materials. The activity was determined by measuring the inhibition zone diameter values (mm) of the complexes against the organisms. The screening data in addition to the calculated percent activity index are given in Table 6 and are graphically presented in Figures 7 and 8 Analyzing the tabulated results indicated that:

- 1-The ligand L and its Co(II)and Cd(II) complexes, possessed a broad spectrum of activity towards all sensitive organisms.
- 2- Co(II) and Cd(II) complexes, display high activity towards all sensitive organisms.
- 5- Antimicrobial activity of the synthesized complexes is promising, so determining the minimum inhibitory concentration (MIC) for the synthesized complexes is recommended .

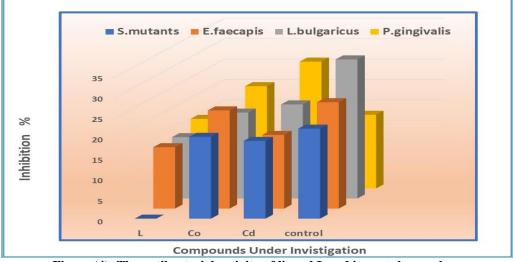


Figure (4): The antibacterial activity of ligand L and its metal complexes.

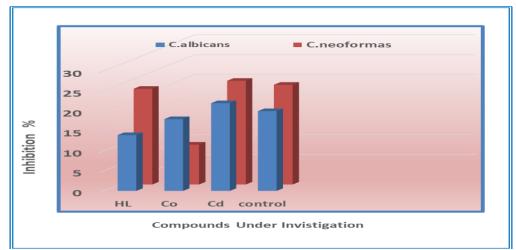


Figure (5): The antifungal activity of ligand L and its metal complexes.

Table (6) Antibacterial	and antifungal	activity of t	he ligand and	its metal complexes

Strain	Gram positive bacteria		Gram negative bacterial		Fungi	
Compoun d	Streptococc u mutants	Enterococcu s faecalis	Lactobacillu s bulgaricus	Porphyromonasgingivali s	Candid a albicans	Crytococcusneoforma s
L	NA	15	15	17	14	20
1	20	24	21	25	18	10
2	19	18	23	31	22	26
Standard	22	26	34	18	20	25

The test was done using the diffusion agar technique. Well diameter 6.0 nm (100 μ l was tested). Positive control for fungi: Ketoconazole 100 μ g/ml

*NA: No activity

Positive control for bacteria. Gentamycin $4\mu g/ml$ The sample was tested at 10 mg/ml concentration.

Conclusion

In this work, the synthesis and characterization of a new tri-dentate Schiff base derived from isatin, and 2-aminocl-pyridine were investigated by experimental and theoretical approaches. It is tentatively proposed that the Schiff base L coordinates through nitrogen atom of azomethine group, oxygen atom of isatin carbonyl and nitrogen atom of pyridine ring moiety, forming a stable chelate ring structure. Based on the above interpretations, the octahedral structures for all complexes are proposed with chemical formula $[Co(L)Cl_2(H_2O)]2H_2O$ $[Cd(L)Cl_2(H_2O)].$ and Furthermore, the electronic structures of the L ligand and also Co(II)- L, and Cd(II)-L complexes were optimized by IR, UV, and TGA analysis. The obtained results are in good agreement with the experimental data.

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