

Synthesis and characterization of Co(II), Ni(II), Cu(II) and Zn(II) complexes with 3-salicylidenehydrazono-2-indolinone

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Abstract: Complexes of Co(II), Ni(II), Cu(II) and Zn(II) with 3-salicylidenehydrazono-2-indolinone were prepared. Their structure was established to be [MLCl]Cl by using elemental analysis and molar conductivity, as well as AA, FTIR, UV/VIS and ¹H-NMR spectroscopic methods. The spectral studies indicated a square-planar geometry for the Ni(II) and Cu(II) complexes and a tetrahedral one for the Co(II) and Zn(II) complexes. The complexes were tested for antibacterial activity against *Staphylococcus aureus*, *Enterococcus D*, *Proteus mirabilis*, *Escherichia coli*, *Bacillus anthracis*, *Pseudomonas aeruginosa* and *Candida albicans*.

Keywords: isatin, salicylaldehyde, transition metal complexes, FTIR, UV/VIS, ¹H-NMR, antibacterial activity.

INTRODUCTION

The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis, which stemmed from the interest in the biological and pharmacological properties of its derivatives.¹ It is also known that mono- and bis-hydrazones find wide application in medicine as active physiological preparations, due to their antibacterial, tuberculostatic, fungicidal properties^{2,3} as well as activities against certain types of cancers and microorganisms. Benzylidene derivatives have also found wide application, not only because of their strong activity against some microorganisms, but also because they can act as free radical scavengers. Many coordination compounds of transition metals with Schiff bases show greater activity than the ligands alone.^{2–5}

The present paper describes the synthesis of the salicylaldehyde β -hydrazone of isatin (L), and the preparation and spectral characteristics of its Co(II), Ni(II), Cu(II) and Zn(II)

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complexes. The synthesized compounds were tested for antibacterial activity against *Staphylococcus aureus* ATCC 6538, *Enterococcus D*, *Proteus mirabilis*, *Escherichia coli* 95, *Bacillus anthracis*, *Pseudomonas aeruginosa* and *Candida albicans* ATCC 10231 by the disk method and also by the standard minimum inhibitory concentration (MIC) of serial dilution test.

EXPERIMENTAL

Materials, methods and instruments

The chemical used were of AR grade.

Microanalysis for carbon, hydrogen and nitrogen was carried out with a Carlo Erba 1106 microanalyser. The chloride content was determined by the Mohr method. The metal contents were determined using a Virial AA-457 Double beam spectrometer. The molar conductivity of the complexes was measured with an Iskra Conductivity Meter 0.67 using 10^{-3} mol dm⁻³ solutions in DMF. The Fourier transformed infrared (FTIR) spectra were recorded using a Michaelson Bomen MB-series spectrophotometer, using the KBr pellet (1 mg/100 mg) technique. The electronic spectra (UV/VIS) were recorded on a Perkin-Elmer Lambda 15 UV/VIS spectrophotometer using 10^{-3} mol dm⁻³ solutions in DMF. The nuclear magnetic resonance (¹H-NMR) spectra were obtained in DMSO solution with a GEMINI-200 "HF NMR" spectrometer.

For the disk method, stock solutions of 15 mg cm⁻³ concentration were made with a solvent mixture of 50 % DMF and 50 % 0.1 mol dm⁻³ NaOH. Onto disks, 2×10^{-6} dm³ of stock solution was dropped, and then dried at room temperature. Suspensions were made from the 24-hour blood agar culture of the bacteria and incubated at 310 K for 3 h. The bacterial suspension was transferred to the antibacterial test medium and the disk was placed on it. After incubation at 310 K for 18 h, the incubation zones were measured (mm). The antimicrobial activity was determined by following the bacterial growth at 37 °C in the nutrition medium for 24 h. The concentration of the tested compounds at which no increase of optical density was observed after an incubation time of 24 h, were accepted as the minimal inhibitory concentration (MIC).⁶

Synthesis of ligands and complexes

Synthesis of salicylaldehyde β-hydrazone of isatin. The β-hydrazone of isatin (synthesized by a standard procedure^{4,5}) was dissolved in the minimum amount of 95 % ethanol. To this solution, salicylaldehyde was added in an equimolar amount under continuous refluxing for about 45 min. The mixture was acidified with H₂SO₄ to pH 4 – 4.5. The colored product was filtered, washed with ethanol and dried *in vacuo* over CaCl₂.

Synthesis of the complexes. For the synthesis of the complexes, the salicylaldehyde β-hydrazone of isatin was dissolved in the minimum amount of 95 % ethanol. To this refluxing solution, metal(II) chloride was added in equimolar amounts. The refluxing was continued for about 2 h. The colored products were filtered, washed with ethanol and dried *in vacuo* over CaCl₂.

RESULTS AND DISCUSSION

The results of elemental analysis and some physical characteristics of the obtained compounds are given in Table I. The complexes were synthesized using a 1:1 mole ratio of all reactants. The elemental analysis (Table I) of the complexes indicates a 1:1 metal to ligand stoichiometry, too. The complexes are air-stable, non-hygroscopic, with high melting points, insoluble in H₂O, but partly soluble in ethanol. They are also soluble in certain solvents such as DMF and DMSO. The molar conductivities of 10^{-3} mol dm⁻³ solutions of the complexes in DMF (Table I) indicate that the complexes behave as electrolytes⁶ in DMF.

TABLE I. Analytical and physical data of the investigated compounds

Comp.	Yield/%	Color	M.p./°C	Analysis (%) found (Calcd)					Mol. cond. S cm ² mol ⁻¹
				C	H	N	Cl	M	
L	89.65	light-red	175	66.90 (67.92)	4.10 (4.15)	15.60 (15.84)	–	–	–
[CoLCl]-Cl	35.12	blue	190	45.65 (45.69)	2.50 (2.54)	10.73 (10.66)	14.85 (14.95)	18.09 (18.02)	89
[CuLCl]-Cl	45.63	brown	195	45.00 (45.17)	2.12 (2.51)	10.23 (10.54)	17.65 (17.82)	15.69 (15.93)	90
[NiLCl]-Cl	41.25	dark-red	184	45.35 (45.72)	2.35 (2.54)	10.45 (10.66)	18.10 (18.02)	15.01 (14.95)	88
[ZnLCl]-Cl	36.06	red	203	45.02 (44.95)	3.00 (2.49)	10.40 (10.48)	17.69 (17.73)	16.69 (16.33)	85

Electronic absorption spectra

The spectral data of the compounds in DMF are presented in Table II. There are two absorption bands, assigned to $n-\pi^*$ and $\pi-\pi^*$ transitions, in the electronic spectrum of the ligand. These transitions are also found in the spectra of the complexes, but they are shifted towards lower and higher frequencies, confirming the coordination of the ligand to the metallic ions.

TABLE II. Electronic spectral data and magnetic moments of the complexes recorded in DMF [frequency(cm⁻¹)/ ϵ_{\max} ·10⁻³ (mol⁻¹ dm³ cm⁻¹)]

Compound	$\nu(10^3 \text{ cm}^{-1})/\epsilon$	geometry	$\mu_{\text{eff}}/\mu_{\text{B}}$
Ligand	36.8/1637 30.8/1627	–	–
[CoLCl]-Cl	37.7/751 29.9/698 16.4/391 15.9/451	Tetrahedral	4.56
[CuLCl]-Cl	15.5/381 37.7/732 25.9/614 21.4/412	Square-planar	1.88
[NiLCl]-Cl	15.5/384 37.7/761 28.5/623 18.9/596	Square-planar	diam.
[ZnLCl]-Cl	13.5/488 37.8/847 29.5/573 26.9/514	Tetrahedral	–

The visible electronic absorption spectrum of the cobalt(II) complex is dominated by the highest energy ${}^4A_2 \rightarrow {}^4T_1(P)$ transition, which is a typical one for tetrahedral Co(II) complexes. The magnetic moment value (Table II) and the blue color of the cobalt(II) complex, also suggest tetrahedral stereochemistry.^{6,12}

The electronic spectrum of the copper complex exhibits bands at 21400 cm^{-1} and 15500 cm^{-1} which can be assigned to ${}^2B_{1g} \rightarrow {}^2A_1$ and ${}^2B_{1g} \rightarrow {}^2E_{1g}$ transitions.^{8,17} These transitions, as well as the measured value of the magnetic moment ($\mu_{\text{eff}} = 1.88\ \mu_B$) suggest a square-planar stereochemistry of the compound.

The electronic spectrum of the nickel complex shows the two bands at 18900 cm^{-1} and 13500 cm^{-1} which are attributed to ${}^1A_{1g} \rightarrow {}^1A_{2g}$ and ${}^1A_{1g} \rightarrow {}^1B_{2g}$ transitions.⁸ These transitions, as well as the measured value of the magnetic moment ($\mu_{\text{eff}} = 0$) suggest a square-planar stereochemistry of the compound.

Since the zinc ion has d^{10} configuration, the absorption at 26900 cm^{-1} could be assigned to a charge transfer transition.^{4,5} However, taking into account the spectrum and the configuration of the zinc(II) ion, a tetrahedral geometry⁸ could be assumed for its complex.

Infrared spectra

The main frequencies and their assignments are presented in Table III.

An –OH stretching vibration appears at $\approx 3541\text{ cm}^{-1}$ in the spectrum of ligand. This band is strong, probably, because of intramolecular hydrogen bond formation between the nitrogen atom of azomethine group and the hydrogen atom of the –OH group. This functional group also shows a specific in-plane deformation vibration. The large band at $\approx 1340\text{ cm}^{-1}$ confirms the intramolecular hydrogen bonding of this group. The salicylaldehyde β -hydrazone of isatin also shows a –C(H)=N stretching band at 1585 cm^{-1} ,⁷ and a band at 1359 cm^{-1} , assigned to the vibration frequency of the phenolic C–O group.

TABLE III. FTIR spectral data of the compounds [frequency (cm^{-1})]

Compound	Assignment of bands ^a							
	$\nu(\text{OH})$	$\nu(\text{NH})$	$\nu(\text{C=O})$	$\nu(\text{C=N})^1$	$\nu(\text{CH=N})^2$	$\nu(\text{C-O})$	M-N	M-O
L	$3541m; l$	$3400m$	$1730s$	$1615m$	$1585w$	$1359w$	–	–
[CoLCl]·Cl	–	$3400m$	$1706m$	$1616w$	$1545w$	$1386m$	$455m$	$487m$
[CuLCl]·Cl	–	$3400m$	$1704m$	$1618w$	$1560w$	$1367m$	$461m$	$498m$
[NiLCl]·Cl	–	$3376m$	$1698s$	$1615w$	$1545w$	$1378m$	$440w$	$498w$
[ZnLCl]·Cl	–	$3361s$	$1685s$	$1616w$	$1550w$	$1368m$	$458m$	$491m$

^aRelative intensity: *s*–strong, *m*–medium, *w*–weak, *l*–large; ¹Vibrations of group from the β -hydrazone of isatine; ²Vibrations of the azomethine group

The characteristics of the FTIR spectra of all complexes are in agreement with the suggested structural formulae. The disappearance of the phenolic (OH) bond indicates the deprotonation of this group and cleavage of the hydrogen bond, with involvement of the oxygen atom in bonding with the metal.⁷ In the complexes, the band assigned to the vibra-

tion frequency of the phenolic C–O group undergoes positive shifts, indicating that the Schiff base is bonded to the metallic ions through the phenolic oxygen atoms.¹⁰ The bands corresponding to $\nu(\text{C}=\text{N})$ are shifted to lower frequencies ($\Delta\nu = 5\text{--}23\text{ cm}^{-1}$) in the spectrum of the complexes. This indicates that the C=N group is a coordination site of the ligand. It also can be seen that the bands corresponding to $\nu(\text{C}=\text{O})$ are shifted to lower frequencies ($\Delta\nu = 11\text{--}24\text{ cm}^{-1}$) in the spectra of the complexes. This indicates that the C=O group is also a coordination site of the ligand.^{5,7,8}

Thus, knowledge gained from the infrared spectra provides clear evidence that the ligand is bonded as a tridentate by the nitrogen and oxygen atom from the isatin as well as through the oxygen atom from the salicylaldehyde part of the molecule.

Nuclear magnetic resonance

¹H-NMR data of the ligand and complexes are listed in Table IV.

In the spectrum of β -HI, the –NH group resonance signal is observed as a singlet at 8.234 ppm. The –NH₂ group resonance signal appears as a singlet at 10.694 ppm. The characteristic two doublets and two triplets of the substituted phenyl ring in this spectrum are observed at 6.839–7.375 ppm.

The signal of the –NH₂ group is not found in the spectrum of salicylaldehyde β -hydrazone of isatin, but a signal of a hydroxyl group appears at 12.56 ppm. In the spectrum of the ligand, the –NH group resonance signal is also observed as a singlet at 8.054 ppm. The signal of the azomethine HC=N proton is at 8.598 ppm. Thus, the appearance of the azomethine proton signal and the disappearance of the –NH₂ group resonance signal both suggest condensation of the β -HI and carbonyl components.^{11,15}

TABLE IV. ¹H-NMR data (δ /ppm) of the compounds

Compound	$\delta(\text{OH})$	$\delta(\text{NH}_2)$	$\delta(\text{NH})$	$\delta(=\text{CH})$	$\delta(\text{phenyl}^1)$	$\delta(\text{phenyl}^2)$
β HI	–	10.694 (s; 1H)	8.324 (s; 1H)	–	6.839–7.375 (m; 4H)	–
L	12.56 (s; 1H)	–	8.354 (s; 1H)	8.598 (s; 1H)	6.853–7.169 (m; 4H)	7.188–7.391 (m; 4H)
[CoLCl]·Cl	–	–	8.250 (s; 1H)	8.581 (s; 1H)	6.850–7.195 (m; 4H)	7.180–7.398 (m; 4H)
[CuLCl]·Cl	–	–	8.256 (s; 1H)	8.580 (s; 1H)	6.849–7.196 (m; 4H)	7.181–7.399 (m; 4H)
[NiLCl]·Cl	–	–	8.255 (s; 1H)	8.581 (s; 1H)	6.849–7.195 (m; 4H)	7.180–7.399 (m; 4H)
[ZnLCl]·Cl	–	–	8.258 (s; 1H)	8.581 (s; 1H)	6.850–7.195 (m; 4H)	7.179–7.399 (m; 4H)

¹phenyl from the isatin part of the molecule; ²phenyl from the salicylaldehyde part of the molecule

The main difference in the spectrum of complexes is the absence of the OH proton located at 12.56 ppm in the free ligand. This indicates deprotonation of this group during coordination with metallic ion.^{6,7} Also, a downfield shift of –NH and =CH group resonance signal in the complex compounds is related with a decrease of the electron density and deshielding of both protons, as a result of the participation of the adjacent C=O and C=N groups in the coordination.^{13,14}

The structural formula of the complexes shown in Fig. 1 is consistent with the above mentioned data.

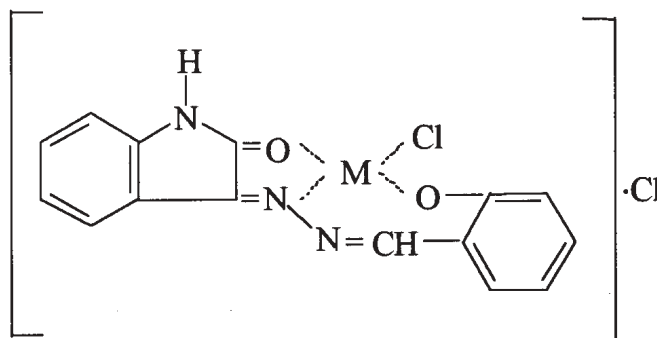


Fig. 1. The structure of the coordination compounds.

Antimicrobial activity

The experimental inhibition zones (mm) and the MIC values are shown in Table V. As can be seen, all the compounds have different antibacterial activity *in vitro* against the tested bacterial organisms.^{15,16}

The results show that the bis-Schiff base exhibits the best activity against *Staphylococcus aureus*.

TABLE V. Range of inhibition zones (mm) and MIC values ($\mu\text{g cm}^{-3}$) of the investigated compounds

Compound	<i>E. coli</i>		<i>P. mirabilis</i>		<i>S. aureus</i>		<i>E. group D</i>		<i>B. anthracis</i>		<i>P. aeruginosa</i>		<i>C. albicans</i>	
	mm	MIC	mm	MIC	mm	MIC	mm	MIC	mm	MIC	mm	MIC	mm	MIC
L	11	50–200	10	200–500	14	50–200	10	200–500	10	200–500	10	200–500	14	20–200
[CoLCl]·Cl	22	<50	19	<50	22	<50	19	<50	23	<50	22	<50	26	<50
[CuLCl]·Cl	22	<50	20	<50	22	<50	20	<50	23	<50	22	<50	26	<50
[NiLCl]·Cl	21	50–200	19	<50	21	<50	16	50–200	20	<50	20	<50	25	<50
[ZnLCl]·Cl	22	<50	21	<50	22	<50	20	<50	23	<50	21	<50	27	<50

An influence of the central ion of the complexes in the antimicrobial activity against the tested gram-positive and gram-negative organisms and yeast is evident. The results also show that the complexes have an enhanced activity compared to the ligand itself. This is

especially shown against *Candida albicans*. The metal activity decreases in the order $Zn \geq Cu > Co > Ni$.

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ИЗВОД

СИНТЕЗА И КАРАКТЕРИЗАЦИЈА Co(II), Ni(II), Cu(II) И Zn(II) КОМПЛЕКСА СА 3-САЛИЦИЛИДЕНХИДРАЗОНО-2-ИНДОЛИНОНОМ

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Синтетисани су комплекси Co(II), Ni(II), Cu(II) и Zn(II) са 3-салицилиденхидразоно-2-индолиноном. Изоловани комплекси су окарактерисани елементалном микроанализом, мерењем моларне проводљивости, магнетне суцептибилности, АА, FTIR, UV/VIS и ¹H-NMR спектроскопским методама. Утврђена је квадратно-планарна геометрија за Ni(II) и Cu(II), као и тетраедарска геометрија за Co(II) и Zn(II) комплексе. Синтетисаним једињењима је испитана биолошка активност у односу на *Staphylococcus aureus*, *Enterococcus D*, *Proteus mirabilis*, *Escherichia coli*, *Bacillus anthracis*, *Pseudomonas aeruginosa* и *Candida albicans*.

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