



New metal(II) complexes with ceftazidime Schiff base

Research article

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Abstract

Schiff base obtained from ceftazidime and thiophene-2-carbaldehyde reacts with transition metallic ions Co(II) and Ni(II) to give octahedral $[ML_2(H_2O)_2]Cl_2$ complexes. These complexes were characterized by physicochemical and spectroscopic methods. The spectra IR indicated that the ligand is a bidentate chelating agent. The molar conductivities of the complexes measured in DMF indicated their electrolyte nature. The antibacterial activity of the metal complexes was found to be better than that of free Schiff base.

Keywords: Schiff base, metallic complexes, ceftazidime, thiophene-2-carbaldehyde, antibacterial activity

1. INTRODUCTION

Metalloantibiotics chemistry is becoming an emerging area of research due to the demand for new metal based antibacterial compounds. The serious medical problem of bacterial resistance and the rate at which it develops have led to increasing levels of resistance to

classical antibiotics among Gram positive and Gram negative organisms [1,2].

Cephalosporin antibiotics are the most important class of drugs against infectious diseases caused by bacteria and their interactions in human body were recently studied. The biological activity of these antibiotics is attributed to the β -lactam ring.

Ceftazidime having the chemical name (6*R*,7*R*,*Z*)-7-(2-(2-aminothiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetamido)-8-oxo-3-(pyridinium-1-ylmethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate is a third-generation cephalosporin antibiotic, with a large antibacterial spectrum, extended to *Pseudomonas* [3]. However, its clinical efficiency is currently drastically reduced by the global emergence of the extended-spectrum and / or AmpC β -lactamases [4].

The literature data regarding the antibacterial efficiency of metal complexes with Schiff base derived from cephalosporins and different aldehydes revealed that they exhibit an increased biological activity upon coordination [5-13]. The improvement of the antibacterial properties of metal complexes may be explained on the basis of Overtone's concept [14] of cell permeability and Tweedy's chelation theory [15].

As a continuation of our research work in metal complexes with drugs [16-19], we report here the synthesis of two new compounds of transition metallic ions Co(II) and Ni(II) with a new Schiff base derived from ceftazidime (Figure 1) and thiophene-2-carbaldehyde. The structural features of the Schiff base and metal complexes were investigated by analytical and spectral techniques and then, evaluated for their antibacterial activity against some bacterial strains.

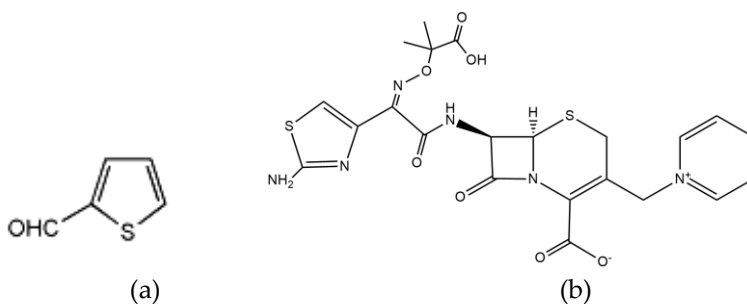


Figure 1. Structural formulae of thiophene-2-carbaldehyde (a) and ceftazidime (b)

2. MATERIALS AND METHODS

2.1. Materials

The chemicals ceftazidime and thiophene-2-carbaldehyde (E. Merk, Germany) were used without further purification. All metal salts used were chloride ($\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$). Solvents used were analytical grade.

2.2. Apparatus and equipment

Chemical analysis of carbon, hydrogen and nitrogen was performed by using M.L.W. microelementary CHN analyser. The metal contents of the complexes were determined by atomic absorption technique using Varian-AA775 spectrophotometer. The IR spectra were recorded on a PerkinElmer 157 instrument in anhydrous KBr pellets in the range $4000\text{-}400\text{ cm}^{-1}$. Electronic spectra by diffuse reflectance technique, with MgO as standard, were recorded in the range $5000\text{-}50000\text{ cm}^{-1}$, on a Jasco V670 spectrophotometer. The molar conductivities were determined by using OK-102 conductivity meter.

2.3. Antibacterial activity study

The *in vitro* biological screening effects of the compounds were tested against two Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) and two Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) clinically isolated bacterial strains by the well diffusion method using agar nutrient as the medium. According to the common procedure that is used in hospitals, the diffusion method was done as follows: on an agar plate inoculated with bacterial strains, a well was made and filled with the test solution by means of a micropipette. The plate thus prepared was incubated at 30°C for 72 hours during which the test solution diffused and the growth of the inoculated bacterial strains was influenced. Then, the developed inhibition zone was measured.

2.4. Synthesis of the Schiff base (L)

A solution of ceftazidime (1mmol in 40mL ethanol) was dropwise added under continuous stirring to a solution of thiophene-2-carbaldehyde (1mmol in 10mL ethanol). The pH of the solution was adjusted to 7 with 0.5M KOH in ethanol. The reaction mixture was refluxed for 3h at 70°C. The precipitate obtained was filtered off, washed with ethanol and dried under vacuum. Recrystallization from hot ethanol gave purified Schiff base ligand.

$C_{27}H_{24}S_3O_7N_6$ yield: 70 %, color: yellow; elemental analysis, found (calcd.) %: C, 51.85(51.93); H, 3.57(3.82); N, 11.26(11.46).

2.5. Synthesis of the metal complexes

The metal complexes were prepared following the same method. To a hot solution of 1 mmol metal salt in 15 mL ethanol was dropwise added and with stirring a solution obtained by dissolving 2 mmol Schiff base in 20 mL ethanol. The pH of the solution was adjusted to 7 with 0.5M KOH in ethanol. This resulting mixture was refluxed for 4 h at a temperature of 70° C. The obtained colored product was separated by filtration, washed with ethanol and diethyl ether and finally dried under vacuum over anhydrous $CaCl_2$.

[CoL₂(H₂O)₂]Cl₂: $CoC_{54}H_{52}S_6O_{16}N_{12}Cl_2$ yield: 70 %, color: red brown; elemental analysis, found (calcd.) %: C, 44.48(44.81); H, 3.57(3.59); N, 12.96(11.61); Co, 4.19(4.07); $\lambda_M=120 \Omega^{-1}cm^{-2}mol^{-1}$.

[NiL₂(H₂O)₂]Cl₂: $NiC_{54}H_{52}S_6O_{16}N_{12}Cl_2$, yield: 80 %, color: dark brown; elemental analysis, found (calcd.) %: C, 43.48(44.82); H, 3.57(3.59); N, 11.96(11.62); Ni, 4.19(4.06); $\lambda_M=125 \Omega^{-1}cm^{-2}mol^{-1}$.

3. RESULTS AND DISCUSSION

The Schiff base ligand was prepared by refluxing the appropriate amount of ceftazidime with thiophene-2-carbaldehyde in ethanol. The metal complexes were prepared by the stoichiometric reaction of the corresponding metal(II) chloride with the ligand Schiff base in a molar

ratio M : L of 1 : 2. The complexes were obtained as air-stable colored amorphous solids. They are insoluble in water, partially soluble in common organic solvents, totally soluble in DMF. The molar conductivities of the complexes measured in DMF ($10^{-3} \text{ mol}\cdot\text{L}^{-1}$ at room temperature) have high values ($120\text{-}125 \text{ }\Omega^{-1}\text{cm}^2\text{mol}^{-1}$) indicated their electrolyte nature [20]. The elemental analysis and the physical measurements permit the suggestion of the molecular formulae: $[\text{ML}_2(\text{H}_2\text{O})_2]\text{Cl}_2$ where L = Schiff base and M = Co(II) and Ni(II) .

3.1. Structural investigation

IR spectra were recorded ($4000\text{-}400 \text{ cm}^{-1}$) for ceftazidime, Schiff base and for each metal complex in order to demonstrate the formation and the coordination mode of the Schiff base ligand. The relevant IR data are presented in Table 1.

Table 1. IR spectra (frequency: ν , cm^{-1}) of ceftazidime, Schiff base and metal complexes

Compound	$\nu(\text{H}_2\text{O})$	$\nu(\text{NH}_2)_{\text{asym}}$ $\nu(\text{NH}_2)_{\text{sym}}$	$\nu(\text{C}=\text{O})$ $\beta\text{-lact}$ $\nu(\text{C}=\text{O})$ amidă	$\nu(\text{C}=\text{N})$ azm.	$\delta\text{r}(\text{H}_2\text{O})$ $\delta\text{w}(\text{H}_2\text{O})$ Coord. water	$\nu(\text{C-S})$ Tiofen	$\nu(\text{M-N})$
Ceftazidime	-	3408 3306	1739 1640	-	-	-	-
Schiff base(L)	-	-	1740 1640	1630	-	755	-
$[\text{CoL}_2(\text{H}_2\text{O})_2]\text{Cl}_2$	3530	-	1739 1640	1620	863 539	750	420
$[\text{NiL}_2(\text{H}_2\text{O})_2]\text{Cl}_2$	3545	-	1739 1640	1615	857 541	745	427

A comparison of the IR spectra of the complexes and those of the free Schiff base ligand allow us to determine the coordination sites that could be involved in chelation process.

The spectra of the complexes contain a broad band around 3530 and 3545 cm^{-1} attributed to $\nu(\text{H}_2\text{O})$. Additionally, the coordinated water presents $\delta\text{r}(\text{H}_2\text{O})$ rocking at 863 and 857 cm^{-1} and $\delta\text{w}(\text{H}_2\text{O})$ wagging at 539 and 545 cm^{-1} [21].

The band at 1630 cm^{-1} attributed to $\nu(\text{HC}=\text{N})$ in the Schiff base spectrum is shifted to lower values in the complexes at 1620 and 1615 cm^{-1} , which suggests that the Schiff base is coordinated to the metallic ion by the N atom of the azomethine group [22]. The metal complexes are also characterized by the appearance of some new bands at 420 and 427 cm^{-1} , which are assigned to $\nu(\text{M-N})$ stretching frequencies, respectively [23].

The absorption band at 755 cm^{-1} in the ligand spectrum attributed to the $\nu(\text{C-S})$ frequency, appears shifted by 5 or 10 cm^{-1} to lower frequencies in the spectra of the metal complexes, which indicates the participation of the sulphur ion in coordination with the metal ion [21]. Since the IR spectrum is recorded up to 400 cm^{-1} , the possible bands that appear below this value, respectively those attributed to the M-S bond (around 310-315 cm^{-1}) could not be detected.

In conclusion, we can say that the Schiff base ligand is bidentately coordinated to the metallic ions with N atom from azomethine group and the sulphur atom from the thiophene ring.

3.2. Electronic spectra

In order to obtain information regarding the coordination geometry of the complexes, the electronic spectra were determined and the ligand field parameters: splitting energy ($10Dq$), interelectronic repulsion parameter (B) and nephelauxetic ratio (β) were calculated (Table 2).

Table 2. Absorption maxima from electronic spectra and crystal field parameters for metal complexes.

Compound	Absorption maxima/ cm^{-1}	Assignments	Crystal field parameters		
			$10Dq/\text{cm}^{-1}$	B/cm^{-1}	β
[CoL ₂ (H ₂ O) ₂]Cl ₂	22115 (ν_3)	$^4T_{1g}(\text{F}) \rightarrow ^4T_{1g}(\text{P})$	1140	883	0.811
	10140 (ν_1)	$^4T_{1g} \rightarrow ^4T_{2g}(\text{F})$			
[NiL ₂ (H ₂ O) ₂]Cl ₂	16330 (ν_2)	$^3A_{2g} \rightarrow ^3T_{1g}(\text{F})$	1070	642	0.617
	10725 (ν_1)	$^3A_{2g} \rightarrow ^3T_{2g}(\text{F})$			

The absorption bands observed in the UV-Vis regions at 38460 and 28985 cm^{-1} in the electronic spectrum of the ligand are assigned to

intraligand $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of $-C=C$ -(aromatic ring) and $-C=N$ -(azomethine) groups, respectively. These bands also appear in the electronic spectra of the complexes, but they are shifted to lower values, which proves the coordination of the ligand to the central metallic ions.

The electronic spectra of the Co(II) complex display two bands at 10140 cm^{-1} (ν_1) and 22115 cm^{-1} (ν_3), which are assigned to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1); ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (ν_3) transitions, respectively. These are the characteristic bands of high spin octahedral Co(II) complexes [24]. The ligand field parameters (Dq , B , β) are calculated using E. König equations [23, 25], when only ν_3 and ν_1 bands are observed in the electronic spectra and the values are well within the range reported for the octahedral complexes:

$$10Dq = 2 \nu_1 - \nu_3 + 15B \quad (1)$$

$$B = \frac{1}{30} \left[-(2\nu_1 - \nu_3) + \sqrt{\{-\nu_1^2 + \nu_3^2 + \nu_1 \nu_3\}} \right] \quad (2)$$

$$\beta = \frac{B_{\text{complex}}}{B_{\text{ion liber}}} \quad (3)$$

The electronic spectrum of Ni(II) complex presents two $d \rightarrow d$ absorption bands at 10725 cm^{-1} (ν_1) and 16330 cm^{-1} (ν_2) in an octahedral environment corresponding to ${}^3A_{2g} \rightarrow {}^3T_{2g}(F)$ (ν_1) and ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ (ν_2), transitions, respectively [24, 25]. For d^8 ions in an octahedral environment, the energy of ν_1 corresponds to $10Dq$ and the value of Dq is obtained from it. When ν_2 and ν_1 absorption maxima are known, the ligand field parameter B is calculated using the following equation of E. König:

$$B = (2 \nu_1^2 + \nu_2^2 - 3 \nu_1 \nu_2) / (15\nu_2 - 27\nu_1) \quad (4)$$

The values obtained for Dq , B , β are in agreement with the experimental ones for Ni(II) octahedral complexes [26].

On the basis of the above data the proposed structures for the synthesized complexes are shown in Figure 2.

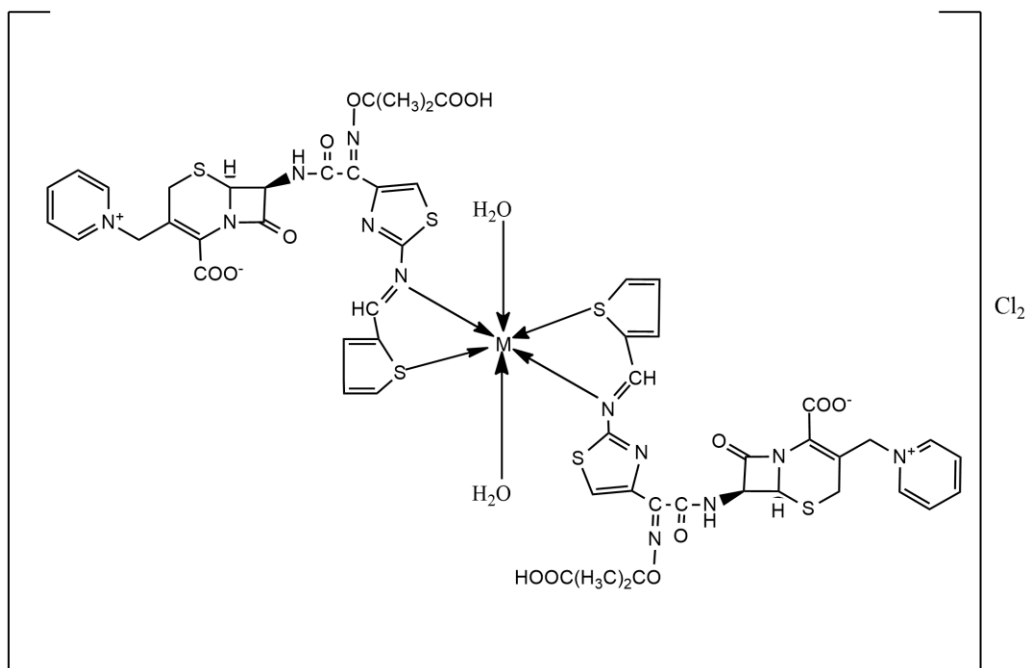


Figure 2. Proposed structure of the metal complexes where M= Co(II) and Ni(II)

3.3. Antibacterial activity

A major problem in public health is the resistance of new bacterial strains to current antibiotics. Over the past years, researchers have studied the synthesis of new metal complexes with new organic ligands and tested them for antimicrobial activity.

In this work we tested the synthesized compounds for *in vitro* antibacterial activity against two Gram-negative (*E. coli*, *P. aeruginosa*) and two Gram-positive (*S. aureus*, *B. subtilis*) bacterial strains by measuring the size of the bacteriostatic diameter (Table 3).

The obtained results were compared with those of free drug. The solvent DMF alone does not show any antibacterial effect.

Table 3. The inhibition diameter zone (mm) of Schiff base and complexes against bacterial strains

Compound	<i>E. coli</i>	<i>P.aeruginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>
Ceftazidime	30	33	32	30
Schiff base (L)	32	33	33	32
[CoL ₂ (H ₂ O) ₂]Cl ₂	32	35	35	32
[NiL ₂ (H ₂ O) ₂]Cl ₂	35	35	37	35
DMF	-	-	-	-

The complexes exhibit better antibacterial activity than the Schiff base and their inhibitory effects on the growth of bacterial strains vary in the following order: Ni(II) > Co(II).

4. CONCLUSION

Two new metal(II) complexes with the Schiff base ligand derived from ceftazidime and thiophene-2-carbaldehyde were synthesized and characterized. Data from IR spectra concluded that the Schiff base behaves as a bidentate ligand coordinated in the complexes. Electronic spectra indicate an octahedral geometry for Co(II) and Ni(II) complexes. The results from the biological activity demonstrated that the complexes have better activity than that of free ligand.

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