PHYSICO-CHEMICAL AND BIOLOGICAL STUDIES ON THE COORDINATION COMPOUNDS OF N-(2-CARBAMOYLFURANYL)-C-(3'-CARBOXY-2'-HYDROXYPHENYL) AZETIDIN-2-ONE

Praveen Kr. Gupta¹, Dinesh Kumar², Amit Kumar^{3,*} and Durga Dass⁴

¹Department of Chemistry, Maharishi Markandeshwar (Deemed to be University)

Mullana-133207, Ambala, (Haryana) India

²Department of Chemistry, National Institute of Technology,

Kurukshetra-136118(Haryana) India

³Department of Chemistry, Indira Gandhi National College, Ladwa,

Kurukshetra-136132, (Haryana) India

⁴Department of Chemistry, Shri Krishan Institute of Engg. & Tech.,

Kurukshetra-136118, (Haryana) India

*E-mail: amitvash76@gmail.com

ABSTRACT

The Schiff base, N-(2-carbamoylfuranyl)-3'-carboxy-2'-hydroxybenzylideneimine reacts with chloro acetyl chloride and forms N-(2-carbamoylfuranyl)-C-(3'-carboxy-2'-hydroxyphenyl) azetidin-2-one, LH₃ (I). This is a cyclization reaction and occurs in triethylamine's presence. A MeOH solution of LH₃ reacts with Co(II) and Ni(II) ions leads to the formation of coordination compounds i.e. [Co(LH)(MeOH)]₂ and [Ni(LH)].

Various characterization tools like elemental analyses, molar conductance, magnetic measurements, Infra red and reflectance spectral studies have been used to characterize these compounds. Both the compounds show non-electrolytic behavior i.e. molar conductivity lies in the range 1.6 to 5.2 mho cm² mol⁻¹ in DMF. The denticity of the ligand is Four i.e. it behaves like a dibasic tetradentate OONO donor ligand in its complexes. [Co(LH)(MeOH)]₂ is dimer and the [Ni(LH)] is monomeric in diphenyl. [Ni(LH)] shows square-planar while [Co(LH)(MeOH)]₂ shows an octahedral structure. LH₃ (I) and its complexes while testing with *E.Coli*. (Gram Negative) and *S. Aureus* (Gram-positive) bacteria show antibacterial activities.

Keywords: Azetidin-2-One, Coordination Compounds, Magnetic Susceptibility, Antibacterial, Complexometric, Magnetically Dilute.

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INTRODUCTION

Azetidin-2-ones commonly known as β -lactams are derivatives of azetidines having a carbonyl group in the second position. Most common antibiotics like cephalosporins, penicillins etc show their activity due to the presence of lactam ring in them.

Azetidin-2-ones have a broad range of biological applications¹ like antimicrobial, antibacterial, anti-inflammatory, anticonvulsant and antitubercular.¹⁻⁸ They are also effective on the central nervous system⁹. Due to its ring strain¹⁰ the azetidin-2-one, acts as building unit for the synthesis of a large number of organic molecules.

This manuscript includes the syntheses and characterization of N-(2-carbamoylfuranyl)-C-(3'-carboxy-2'-hydroxyphenyl)azetidin-2-one, LH₃ (I) and its compounds with Co(II) and Ni(II) ions.

EXPERIMENTAL

Furoic acid hydrazide [Aldrich]; nickel (II) acetate, cobalt (II) acetate, methanol, acetone, ethyl acetate, triethylamine, chloroacetyl chloride and dioxane [Ranbaxy] were used for the syntheses. The synthesis of 3-Formylsalicylic acid was done as per the published procedure.¹¹

Analyses and Physical Measurements

Before the estimation of metal ions, their organic skeleton must be decomposed. It was done by heating the compound with conc. HNO_3 and then the dissolution of residue in the least amount of conc. HCl . Metal ions were estimated as follows:

The estimation of Co(II) and Ni(II) contents was done by the complexometric method using EDTA soln. The C, H and N contents of LH_3 and its coordination compounds were determined by CHN Eager analyzer model-300.

[CAC: Chloroacetyl chloride; TEA: Triethylamine]

Scheme-I: Preparation of N-(2-carbamoylfuranyl)-C-(3'-carboxy-2'-hydroxyphenyl) azetidin-2-one (I)

Scheme-II: Preparation of coordination compounds of N-(2-carbamoylfuranyl)-C-(3'-carboxy-2'-hydroxyphenyl) azetidin-2-one (I)

The S and Cl contents were estimated gravimetrically. Rast method was used for the determination of the molecular weight¹². The IR and reflectance spectra were recorded by Beckman-20 spectrophotometer. The magnetic susceptibility measurements were carried out as per the mentioned procedures.¹³

Synthesis of the Schiff base [N-(2-carbamoylfuranyl)-3'-carboxy-2'-hydroxybenzylideneimine]

The titled compound was synthesized by following the published procedure.¹⁴

Synthesis of N-(2-carbamoylfuranyl)-C-(3'-carboxy-2'-hydroxyphenyl)azetidin-2-one (I)

A dioxane solution (50 mL) of the Schiff base (2.74 g, 10 mmol) was stirred with the dropwise addition of chloroacetyl chloride (2.26 g, 20 mmol) in presence of triethylamine (3.03 g, 30 mmol). Volume of the

filtrate was reduced to half. Triethylamine hydrochloride formed was filtered off and the the solution was kept aside for 24 h and the solid product formed was filtered, washed with dioxane and recrystallized from CHCl_3 . The compound was dried in vacuo. Yield = 26%. Anal: (**I**, $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_6\text{Cl}$) (obsd: C, 51.03%; H, 3.17%; N, 7.84%; Cl, 10.28%. calc.: C, 51.36%; H, 3.14%; N, 7.99%; Cl, 10.13%); IR bands (KBr): 2895 cm^{-1} [$\nu(\text{O—H})$ (intramolecular H-bonding)], 1745 cm^{-1} [$\nu(\text{C=O})$ (β -lactam)], 1670 cm^{-1} [$\nu(\text{C=O})$ (amide)], 1540 cm^{-1} [$\nu(\text{C—O})\phi$], 1414 cm^{-1} [$\nu(\text{C—N})$ (β -lactam)], 1080 cm^{-1} [$\nu(\text{C—O—C})$ (furan)] and 750 cm^{-1} [$\nu(\text{C—Cl})$ (β -lactam)].

Syntheses of Coordination Compounds of I

A methanolic solution (30-50 mL) of the metal salt (10 mmol) was added to a methanolic solution (50 mL) of **I** (3.50 g, 10 mmol) and the mixture was then refluxed for 3-4 h. The solid products formed were filtered, washed with methanol and were then dried as mentioned above. Yield = 45-65%.

RESULTS AND DISCUSSION

N-(2-Carbamoylfuranyl)-C-(3'-carboxy-2'-hydroxyphenyl)azetidin-2-one, LH_3 (**I**) was synthesized by the reaction of chloroacetyl chloride on the Schiff base, N-(2-carbamoylfuranyl)-3'-carboxy-2'-hydroxybenzylideneimine. The reaction of **I** with metal salts in 1:1 molar ratio in methanol produces the coordination compounds of the types, $[\text{Co}(\text{LH})(\text{MeOH})_2]$ and $[\text{Ni}(\text{LH})]$. The coordination compounds are insoluble in H_2O , MeOH and EtOH. They are partially soluble in CHCl_3 , Me_2CO , C_6H_6 and completely soluble in DMSO and DMF. They are non-electrolytes ($\Lambda_M = 1.6\text{-}5.2\text{ mho cm}^2\text{ mol}^{-1}$) in DMF. The analytical data of **I** and its coordination compounds are given in Table-1.

Table-1: Analytical, Molar Conductance (Λ_M) and Molecular Weight Data of I and its Coordination Compounds

Compound	Mol. Formula	Λ_M ($\text{mho cm}^2\text{ mol}^{-1}$)	Mol. Wt Obsd. (Cal.)	Obsd(Cal)%				
				M	C	H	N	Cl
LH_3 (I)	$\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}_6\text{Cl}$		349.0 ^a (350.5)	-	51.03 (51.36)	3.17 (3.14)	7.84 (7.99)	10.28 (10.13)
$[\text{Co}(\text{LH})(\text{MeOH})_2]$	$\text{Co}_2\text{C}_{32}\text{H}_{26}\text{N}_4\text{O}_{14}\text{Cl}_2$	1.6	855.3 ^b (878.8)	13.07 (13.40)	43.52 (43.69)	2.88 (2.96)	6.32 (6.37)	8.16 (8.08)
$[\text{Ni}(\text{LH})]$	$\text{NiC}_{15}\text{H}_9\text{N}_2\text{O}_6\text{Cl}$	5.2	436.6 ^b (407.2)	14.05 (14.42)	44.16 (44.20)	2.17 (2.21)	6.83 (6.88)	8.92 (8.72)

Abbreviations: ^aMass Spectral Data, ^bRast Method Data

Infrared Spectral Studies

The infrared spectra of the LH_3 (**I**) and its coordination compounds were mentioned in Table-2. The $\nu(\text{C—N})$ (β -lactam) stretch¹⁵ in **I** at 1414 cm^{-1} confirms the conversion of Schiff base to azetidinone. A (C—Cl) (β -lactam) stretch¹⁶ at 750 cm^{-1} further supports the same. A strong band due to intramolecular H-bonded OH group of phenolic and/or carboxylic acid moieties¹⁷ at 2895 cm^{-1} in **I** get disappears in its coordination compounds showing the deprotonation of the OH groups followed by the involvement of phenolic and carboxylic acid O atoms towards coordination.

The presence of a broadband between $3350\text{-}3450\text{ cm}^{-1}$ due to the $\nu(\text{O—H})(\text{MeOH})$ stretch and the decrease of the $\nu(\text{C—O})(\text{MeOH})$ stretch from 1034 cm^{-1} to lower energy by 58 cm^{-1} in the coordination compounds of Co(II) ions with **I** indicate the involvement of the O atom of MeOH towards coordination¹⁸. The presence of $\nu(\text{C=O})(\text{amide})$ stretch at 1670 cm^{-1} in **I** shows its occurrence in keto form. $[\text{Ni}(\text{LH})]$ shows the same band which indicates the non-involvement of this keto O atom towards coordination.

In $[\text{Co}(\text{LH})(\text{MeOH})_2]$ the absence of $\nu(\text{C=O})(\text{amide})$ stretch and presence of a band at 1255 cm^{-1} due to $\nu(\text{C(OH)})$ (enolic) stretch indicating the conversion of $-\text{C(O)NH}-$ moiety (keto-form) into $-\text{C(OH)=N}-$ moiety (enol-form). It shows the coordination through the enolic O atom. A decrease of $29\text{-}44\text{ cm}^{-1}$ in $\nu(\text{C—N})$ (β -lactam) stretch of **I** in the complexes shows the involvement of its N atom towards coordination¹⁹. The appearance of $\nu(\text{C=O})(\beta\text{-lactam})$ stretch²⁰ at 1745 cm^{-1} in the coordination compounds i.e. at the same frequency as in **I** indicates the non-involvement of O atom of β -lactam moiety towards coordination. The

carboxylate moiety coordinates in a monodentate manner²¹ in the coordination compounds as indicated by the energy difference of 205-206 cm⁻¹ in the $\nu_{as}(\text{COO})$ and $\nu_s(\text{COO})$ stretches which appears between 1535-1548 cm⁻¹ and 1330-1342 cm⁻¹ respectively. [Ni(LH)] and [Co(LH)(MeOH)]₂ show a higher shift by 10 and 20 cm⁻¹ respectively in the $\nu(\text{C—O})$ (phenolic) stretch²² supporting the involvement of phenolic O atom towards coordination. The appearance of $\nu(\text{C—Cl})$ (β -lactam) stretch¹⁶ at 750 cm⁻¹ in the coordination compounds i.e. at the same frequency as in **I** indicates its non-involvement towards coordination. A decrease of $\nu(\text{C—O—C})$ (furan moiety)²³ stretch of the ligand at 1080 cm⁻¹ by 45 cm⁻¹ in [Ni(LH)] shows its involvement in coordination, while it remains unchanged in [Co(LH)(MeOH)]₂. Some non-ligand bands in these coordination compounds are assigned to the $\nu(\text{M—O})$ (545-560 cm⁻¹) and the $\nu(\text{M—N})$ (425-440 cm⁻¹) and these bands are in the expected order of increasing energy: $\nu(\text{M—N}) < \nu(\text{M—O})$.²⁴

Reflectance Spectral Studies

[Co(LH)(MeOH)]₂ shows three bands at 8930, 13200, 20200 cm⁻¹ due to ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(v_1)$, ${}^4T_{1g}(F) \rightarrow {}^4A_{2g}(v_2)$ and ${}^4T_{1g}(F) \rightarrow {}^4T_{1g}(v_3)$ transitions, respectively, indicating its octahedral geometry²⁵. The various spectral parameters are: ν_3/ν_1 value = 2.26, $Dq = 1011$ cm⁻¹, $B' = 830$ cm⁻¹, $\beta = B'/B = 0.85$, $\beta^0 = 15\%$ and CFSE = -96.6 kJ mol⁻¹. The ligand is strong field²⁶ in nature and its coordination compounds shows covalence as indicated by the reduction of Racah parameter from its the free ion value of 971 cm⁻¹ to 830 cm⁻¹ and the β^0 value of 15%. (Table-2).

Table-2: IR, Reflectance Spectral Data (cm⁻¹) and Magnetic Moments of Coordination Compounds of I

Compound	$\nu_{as}(\text{COO})$	$\nu_s(\text{COO})$	$\nu(\text{C—O})$ (phenolic)	$\nu(\text{C—N})$ (β -lactam)	$\nu(\text{C—O})$ (enolic)	$\nu(\text{C—O})$ (MeOH)	$\nu_{\max}$	Mag. Moment (B. M.)
LH ₃ (I)	—	—	1540	1414	—	—	—	Diamagnetic
[Co(LH)(MeOH)] ₂	1548	1342	1560	1385	1255	976	8930, 13200, 20200	4.76
[Ni(LH)]	1535	1330	1550	1370	—	—	—	Diamagnetic

Magnetic Measurements

The magnetic moments of [Co(LH)(MeOH)]₂ is 4.76 B.M supporting its octahedral geometry.²⁷ [Ni(LH)] is diamagnetic.

Based on analytical data, molecular weight, valence requirements, spectral and magnetic studies, it is proposed that **I** behaves as a dibasic tetradentate OONO donor ligand in the monomeric, diamagnetic, four-coordinate, square-planar compound [Ni(LH)] (**III**) and dimeric, six-coordinate, high-spin octahedral compound [Co(LH)(MeOH)]₂ (**II**) (Fig.-1).

Antibacterial Studies

The antibacterial activity of ligand (**I**) and its complexes were tested against bacteria, *E.Coli* (Gram-negative) and *S. aureus* (Gram-positive) by using disc diffusion method (Table-3). The entire procedure and results are following our published paper.²⁸

Determination of Minimum Inhibitory Concentration (MIC)

The entire procedure of determination of MIC (Table-4) and the results are in accordance with our published paper.¹⁵

Table-3: Antibacterial Activity of I and its Coordination Compounds (Zone of Inhibition in mm)

Compound	E.Coli (Gram negative)	S. Aureus (Gram positive)
LH ₃ (I)	7	6
[Co(LH)(MeOH)] ₂	7	8
[Ni(LH)]	7	10

Fig.-1

Table-4: Minimum Inhibitory Concentration (MIC) of I and its Coordination Compounds ((μg/ml)

Compound	<i>E. Coli</i> (Gram negative)	<i>S. Aureus</i> (Gram positive)
LH ₃ (I)	32	32
[Co(LH)(MeOH)] ₂	32	64
[Ni(LH)]	64	64

CONCLUSION

The elemental analyses, IR, reflectance and magnetic susceptibility measurements suggest an octahedral structure for [Co(LH)(MeOH)]₂ (II) and a square-planar structure for [Ni(LH)] (III). Both the complexes shows antibacterial activities while testing with *E. Coli* (Gram Negative) and *S. Aureus* (Gram-positive) bacteria.

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