

# New Complexes of Nickel (II) Using 4-Hydroxy-2-Oxo-2H-Chromene-3-Carboxamide as Ligand

Dije Dehari, Ahmed Jashari, Shefket Dehari, Agim Shabani

**Abstract**—New complexes of nickel (II) have been synthesized in the reaction mixture of nickel (II) acetate and 4-hydroxy-2-oxo-2H-chromene-3-carboxamide. Bis(4-hydroxy-2-oxo-2H-chromene-3-carboxamidato-O,O)nickel (II) and diaquabis(4-hydroxy-2-oxo-2H-chromene-3-carboxamidato-O,O)nickel (II) were characterized by elemental analysis, IR spectroscopy and ESI mass spectrometry. Elemental analysis and mass spectrometry data of the complexes suggests the stoichiometry of 1:2 (metal-ligand).

**Keywords**—Nickel complexes, 4-hydroxy-2-oxo-2H-chromene-3-carboxamide, IR spectroscopy, mass spectrometry.

## I. INTRODUCTION

COUMARIN is a structural unit of many natural and synthetic compounds which endows them with a wide range of physiological and pharmacological activities as antibacterial [2], [3], antiviral [4], [5], bactericidal [6], fungicidal [7], anti-inflammatory [8], and anticoagulants [9]. The interest has grown up when remarkable anticancer [10]–[13] and lately anti-HIV [14], [15] activities of some coumarins were confirmed. Especially the coumarin derivative 4-hydroxy-2-oxo-2H-chromene-3-carboxamide (1) attracted our attention as potentially very active compound in live cells, because of the functional groups connected to each other in the six-member pyranon system. Furthermore, those are very polar groups, (keto, hydroxy and amido) which are able to create interactions (as hydrogen bond for example) with the large biomolecules as guest-host systems. Also, the geometric position of those groups is perfect to embrace metal cations. Theoretically, its deprotonated species especially should show pronounced ability for complexation. Namely, this compound can serve as a versatile polyfunctional ligand being included as:

- a) an ion
- b) a ligand coordinated through:
  - the nitrogen atom and deprotonated hydroxyl group
  - the carbonyl oxygen atom from the amido group and deprotonated hydroxyl group,
  - the nitrogen atom and the carbonyl oxygen atom from the pyranon ring
  - the carbonyl oxygen atom from the amido group and the

carbonyl oxygen atom from the pyranon ring

c) a neutral molecule

Many researchers synthesized the complexes of transition metals with coumarin derivatives because these complexes that contain coumarin as a ligand show anticoagulant properties [16], [17] and antitumor activity [18], [19]. Kostova et al. have shown the cytotoxic potential of coumarins complexed with cerium, lanthanum, zirconium and neodymium [20]–[22].

In this work we have shown the synthesis of nickel complexes with 4-hydroxy-2-oxo-2H-chromene-3-carboxamide as ligand using triethylamine for the deprotonation of hydroxyl group in C–4 position.

## II. MATERIAL AND METHODS

Melting points were determined on a Reichert heating plate and are uncorrected. C, H elemental analysis was carried out with Coleman Model 33. N elemental analysis was carried out by the Dumas method. NMR spectra were recorded on a Bruker 400 MHz instrument using DMSO- $d_6$  as solvent and tetramethylsilane as internal standard. Infrared spectra (KBr pellets) were measured on a Perkin-Elmer System 2000 FT IR. ESI-tof mass spectra were measured using an LCT mass spectrometer (Waters) equipped with a lockspray dual-electrospray ion source combined with Waters alliance 2695 HPLC unit.

All the reagents and solvents were obtained from commercial sources and were used without further purification.

### A. Preparation of Ligand

10g (60mmol) of 4-hydroxycoumarin were poured in round-bottom flask and 5g (80mmol) of urea were added. The flask was stopped with glass stopper and the compounds were mixed well. Afterwards, the flask was mounted on the vertical condenser which was previously inducted in the domestic microwave oven through the manually madden hole. The power was set to 850W and the timer to 5min. After this time the mixture was left to cold and then it was dissolved in worm ethanol. After crystallization white needles of the pure product were formed. Anal. Calc. for  $C_{10}H_7NO_4$ : C 58.54%; H 3.44%; N 6.83%, found: C 58.02%, H 3.12%, N 6.16%. IR (KBr,  $cm^{-1}$ ): 3353 (vasNH), 3201 (vsNH), 3500-3100 (vOH – overwrite), 1702 (vC=O, pyr), 1643 (vC=O, amide).  $^1H$ -NMR ( $\delta$ , ppm, Fig. 3): 7.90 (s, 1H,  $NH_2$ ), 7.63 (s, 1H,  $NH_2$ ), 6.73 (dd, 1H, Ar), 6.57 (td, 1H, Ar) and 6.21 (m, 2H, Ar). ESI-MS

Dije Dehari, Ahmed Jashari, Shefket Dehari, and Agim Shabani are with the State University of Tetovo, Faculty of Mathematical and Natural Sciences, Department of Chemistry, 1200 Tetovo, Macedonia (tel: +38971797661; e-mail: dije.dehari@yahoo.com).

$m/z$  206.0 ( $M+H^+$ ).

#### B. Preparation of Ni Complex (**1a**)

124mg (0.5mmol) of  $Ni(OAc)_2 \cdot 4H_2O$  were measured and dissolved in 15ml dried methanol in room temperature. Also, 1mmol (205mg) of the ligand (**1**) were measured and dissolved in 15ml dried methanol and 0.2ml triethylamine were added in room temperature. The solution of the ligand was added in the nickel solution and the reaction mixture was refluxed for 25min at 50°C. The light green nickel complex precipitated, filtered and washed with ethanol and diethyleter.

Anal. calc. for  $C_{20}H_{12}N_2NiO_8$ : C, 51.44; H, 2.59; N, 6.00; Found: C, 50.92; H, 2.24; N, 5.67. IR (KBr,  $cm^{-1}$ ): 3298, 1695, 1622, 1505, 1199, 1039, 762, 674. ESI-MS ( $m/z$ ) 467.0 ( $M+H^+$ ); Mp: 220°C (decomp).

#### C. Preparation of Ni Complex (**1b**)

124mg (0.5mmol) of  $Ni(OAc)_2 \cdot 4H_2O$  were measured and dissolved in 15ml methanol + 5ml  $H_2O$  in room temperature. Also, 1mmol (205mg) of the ligand (**1**) were measured and dissolved in 15ml methanol and 0.2ml triethylamine were added in room temperature. The solution of the ligand was added in the nickel solution and the reaction mixture was refluxed for 20min at 40°C. The greenish nickel complex precipitated, filtered and washed with ethanol and diethyleter.

Anal. calc. for  $C_{20}H_{16}N_2NiO_{10}$ : C, 47.75; H, 3.21; N, 5.57; Found: C, 46.92; H, 3.14; N, 5.47. IR (KBr,  $cm^{-1}$ ): 3417, 1694, 1620, 1559, 1490, 1476, 767, 679. ESI-MS  $m/z$  502.02 ( $M+H^+$ ); Mp: 215°C (decomp).

### III. RESULTS AND DISCUSSIONS

In the pre-search of the literature poor information was found for the compound **1**. It was found that it was synthesized by Scarborough and Gould [1] in 1961, using direct method of melting 4-hydroxycoumarin with urea according to the reaction gave in the Fig. 1. However, this procedure was repeated over and over and the compound was obtained but in very moderate yields (ca. 25%). On the other hand, we attempt to melt this mixture using microwave irradiation. In this case, when the mixture was melted in domestic microwave oven, on 850 W for 3-5 minutes, the result was slightly better obtaining 30-35% yield.

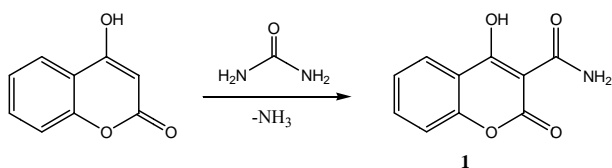


Fig. 1 Synthesis of the 4-Hydroxy-2-Oxo-2H-Chromene-3-Carboxamide (**1**)

#### A. Elemental Analysis

The elemental analysis data match very well with those calculated and they show that nickel is coordinated with ligand in 1:2 ratio.

#### B. IR Spectra

On the measured IR spectra of ligand (**1**) it can be noticed that two bands are present on 3353 and 3201 $cm^{-1}$  from the antisymmetric and symmetric stretching vibrations of the  $NH_2$  groups [23]. Also two  $C=O$  vibrational bands on 1702 and 1643 $cm^{-1}$ , one from the carbonyl group attached on the pyrane ring and the other from the amide group [24]. The hydroxyl group shows at 3440 $cm^{-1}$  (Fig. 2).

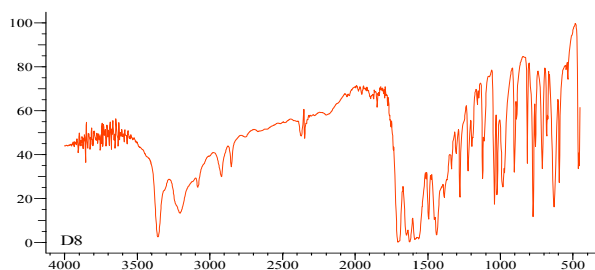


Fig. 2 IR spectrum of ligand (**1**)

The complex (**1a**) shows a band of amino groups at 3298 $cm^{-1}$ . The  $C=O$  bands of amido groups appear at the 1622 $cm^{-1}$  which shows that the ligand is coordinated with nickel (II) through carbonyl groups and deprotonated fenolik groups. The free carbonyl groups of piranon ring appear at 1695 $cm^{-1}$  (Fig. 4).

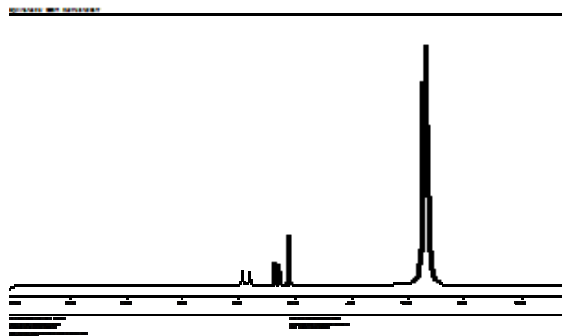


Fig. 3  $^1H$ -NMR spectrum of ligand (**1**)

The complex (**1b**) shows a broad band of hydroxyl groups at 3600-3300 $cm^{-1}$  with maximum absorption in the 3417 $cm^{-1}$ . These bands show the coordinated water molecules to the Ni (II) ion in the complex. The  $C=O$  bands of amido groups appear at the 1620 $cm^{-1}$  which also shows that the ligand is coordinated with nickel (II) through carbonyl groups and deprotonated fenol groups. The free carbonyl groups of piranon ring appear at 1694 $cm^{-1}$  (Fig. 5).

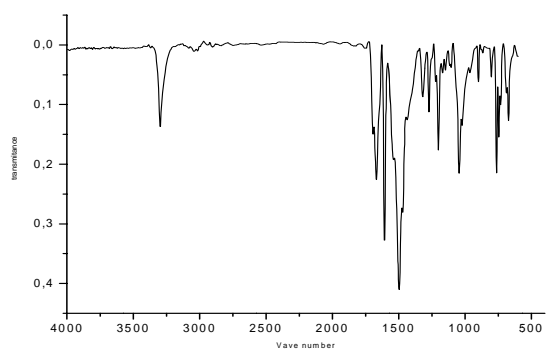


Fig. 4 IR spectrum of Ni complex (1a)

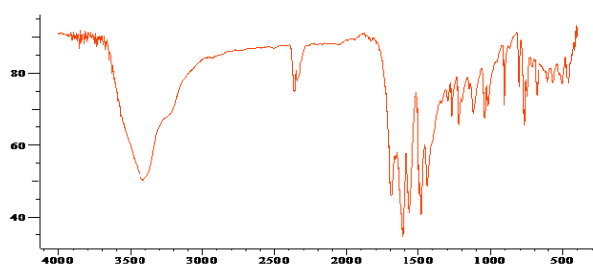


Fig. 5 IR spectrum of Ni complex (1b)

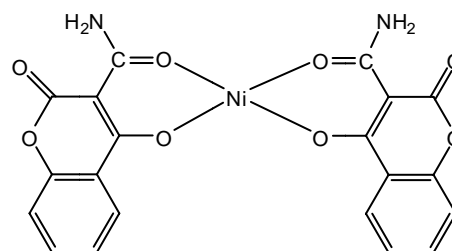
### C. Mass Spectra

The  $m/z$  value of ligand (**1**) confirms the structure as shown in Fig. 1. The  $m/z$  values of complexes prove that complexes were formed in the above mentioned ratio. The experimental values of ESI-MS are almost the same with theoretically

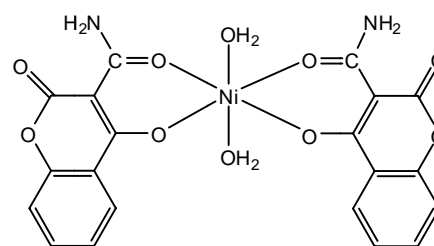
calculated (Table I). The mass spectrums of complexes (**1a**) and (**1b**) are shown in Figs. 7 and 8.

TABLE I  
MASS SPECTERS OF LIGAND AND Ni(II) COMPLEXES

| Compound                                | $m/z$ Calc. (M) | $m/z$ Found                |
|---|-----------------|----------------------------|
| $C_{10}H_7NO_4$ ( <b>1</b> )            | 205.04          | 206.0(M + H <sup>+</sup> ) |
| $C_{20}H_{12}N_2NiO_8$ ( <b>1a</b> )    | 465.99          | 467.0(M + H <sup>+</sup> ) |
| $C_{20}H_{16}N_2NiO_{10}$ ( <b>1b</b> ) | 502.02          | 500.9(M - H <sup>+</sup> ) |



(1a)



(1b)

Fig. 6 Suggested structures of Ni complexes

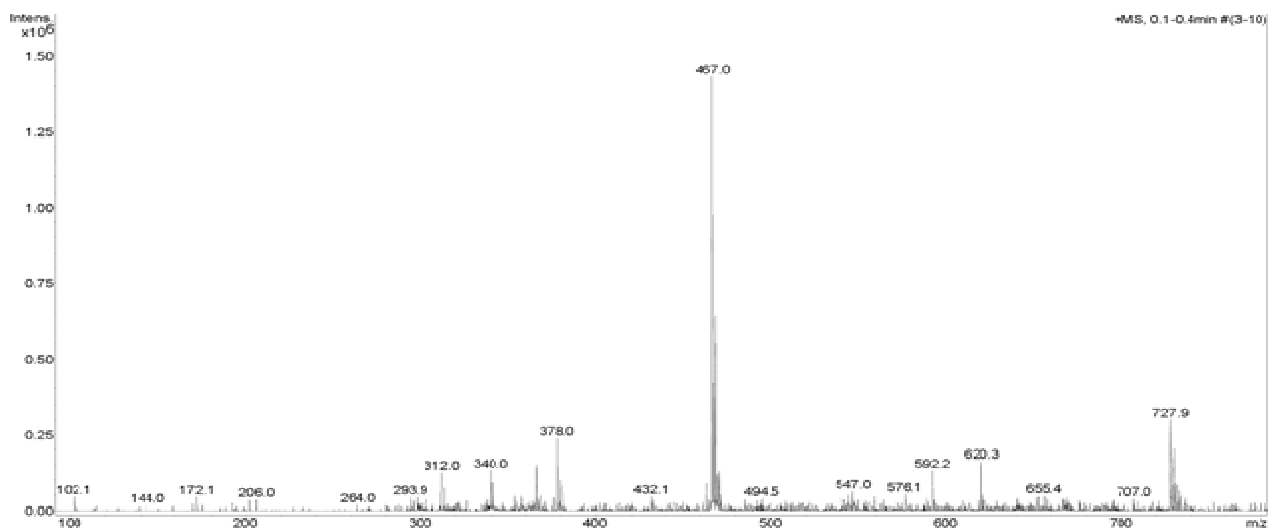
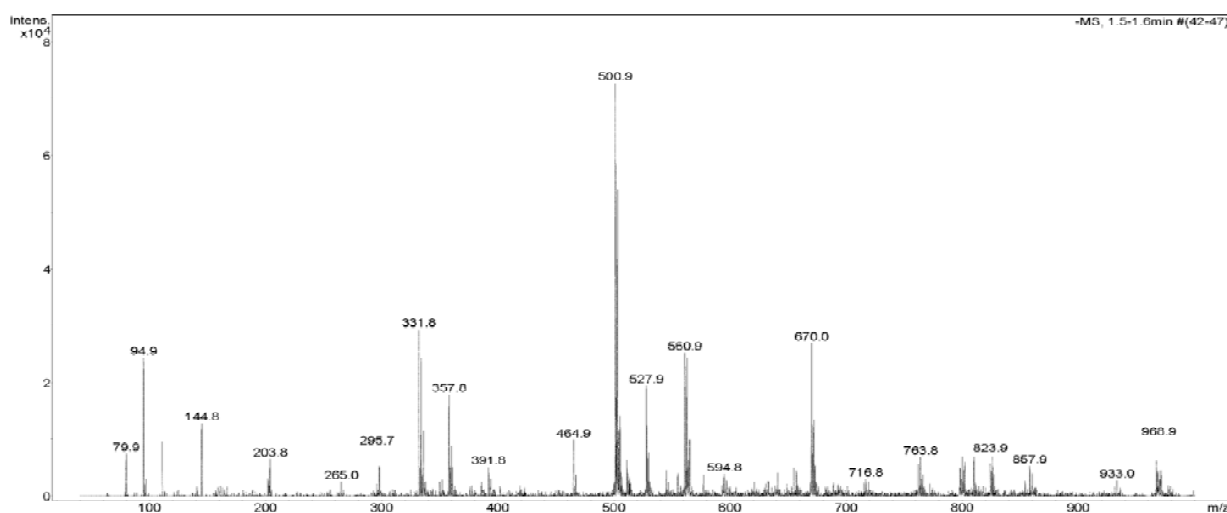


Fig. 7 Mass spectrum of Ni complex (1a)

Fig. 8 Mass spectrum of Ni complex (**1b**)

## ACKNOWLEDGMENT

D. D. thanks the DAAD Programme “Stability Pact for South Eastern Europe” for financial support during her stay at the Faculty of Chemistry and Mineralogy, Universität Leipzig, Germany.

D. D. also thanks Prof. Dr. Eva Marie Hey-Hawkins for her help while working in her laboratories.

## REFERENCES

- [1] H. Scarborough, W. Gould, The Reaction of Urea with Cyclic 1,3-Dicarbonyl and Other Active Hydrogen Compounds. *J. Org. Chem.*, vol. 26, no.10, pp. 3720-3723, 1961.
- [2] M. Al-Haiza, M. Mostafa, M. El-Kady, Synthesis and Biological Evaluation of Some New Coumarin Derivatives. *Molecules*, vol. 8, pp. 275-286, 2003.
- [3] C. Dutton, J. Sutcliffe, B. Yang, 4-Hydroxy coumarin derivatives with antibacterial activity. *PCT Int. Appl. US1993/006308*, 1994.
- [4] V. Parmar, K. Bisht, R. Jain, S. Singh, S. Sharma, S. Gupta, S. Malhotra, O. Tyagi, A. Vardhan, H. Pati, D. Berghe, A. Vlietinck, Synthesis, Antimicrobial and Antiviral Activities of Novel Polyphenolic Compounds. *Ind. J. Chem. Sec. B*, vol. 35, pp. 220-232, 1996.
- [5] T. Ishikawa, K. Kotake, H. Ishii, Synthesis of Toddacoumaquinone, a Coumarin-Naphthoquinone Dimer and Its Antiviral Activities. *Chemical & Pharmaceutical Bulletin*, vol. 43, no. 6, pp. 1039-1041, 1995.
- [6] A. El-Sayed, O. Abd-Allah, Synthetic and biological studies on coumarinhydrazone derivatives. *Phosphorus, Sulfur and Silicon Relat. Elem.*, vol. 170, pp. 75-86, 2001.
- [7] A. El-Agrody, M. Abd El-Latif, N. El-Hady, A. Fakery, A. Bedair, Heteroaromatization with 4-Hydroxycoumarin Part II: Synthesis of Some New Pyrano[2,3-d]pyrimidines, [1,2,4]triazolo[1,5-c]pyrimidines and Pyrimido[1,6-b]-[1,2,4]triazine Derivatives. *Molecules*, vol. 6, pp. 519-527, 2001.
- [8] A. Emmanuel-Giota, K. Fylaktakidou, D. Litina, K. Litinas, D. Nicolaides, Synthesis and biological evaluation of several 3-(coumarin-4-yl)tetrahydroisoxazole and 3-(coumarin-4-yl)dihydropyrazole derivatives. *J. Heterocyclic Chem.*, vol. 38, pp. 717-722, 2001.
- [9] W. Barker, M. Hermodson, K. Link, 4-Hydroxycoumarins. Synthesis of the metabolites and some other derivatives of warfarin. *J. Med. Chem.*, vol. 14, pp. 167-169, 1971.
- [10] Z. Nofal, M. El-Zahar, S. El-Karim, Novel Coumarin Derivatives with Expected Biological Activity. *Molecules*, vol. 5, pp. 99-113, 2000.
- [11] L. Raev, E. Voinov, I. Ivanov, D. Popov, Antitumor activity of some coumarin derivatives. *Pharmazie*, vol. 45, pp. 696-698, 1990.
- [12] P. Valenti, A. Rampa, M. Recanatini, A. Bisi, F. Belluti, P. Da Re, M. Carrara, L. Cima, Synthesis, cytotoxicity and SAR of simple geiparvarin analogues. *Anticancer Drug Des.*, vol. 12, no. 6, pp. 443-451, 1997.
- [13] A. Shah, Y. Naliapara, D. Sureja, N. Motohashi, M. Kawase, C. Miskolci, D. Szabo, J. Molnar, 6,12-Dihydro-1-Benzopyrano[3,4-b][1,4]Benzothiazin-6-ones. Synthesis and MDR Reversal in Tumor Cells. *Anticancer research*, vol. 18, pp. 3001-3004, 1998.
- [14] H. Skulnick, P. Johnson, P. Aristoff, J. Morris, K. Lovasz, Structure-Based Design of Nonpeptidic HIV Protease Inhibitors: The Sulfonamide-Substituted Cyclooctylpyranones. *J. Med. Chem.*, vol. 40, pp. 1149-1164, 1997.
- [15] C. Spino, M. Dodier, S. Sotheeswaren, Anti-HIV coumarins from calophyllum seed oil. *Bioinorg. & Med. Chem. Lett.*, vol. 8, pp. 3475-3478, 1998.
- [16] D. Jiang, R. Deng, J. Wu, Synthesis and properties of lanthanide compounds of 3-sulfo-4-hydroxycoumarin. *Wuji Huaxue*, vol. 5, pp. 21-28, 1989.
- [17] R. Deng, J. Wu, L. Long, Lanthanide complexes of bis(4-hydroxy-3-coumarinyl) acetic acid and their anticoagulant action. *Bull. Soc. Chim. Belg.*, vol. 101, pp. 439-443, 1992.
- [18] I. Kostova, I. Manolov, S. Konstantinov, M. Karaivanova. Synthesis, physicochemical characterisation and cytotoxic screening of new complexes of cerium, lanthanum and neodymium with Warfarin and Coumachlor sodium salts. *Eur. J. Med. Chem.*, vol. 34, pp. 63-68, 1999.
- [19] I. Manolov, I. Kostova, T. Netzeva, S. Konstantinov, M. Karaivanova, Cytotoxic activity of cerium complexes with coumarin derivatives. Molecular modeling of the ligands. *Arch. Pharm.*, vol. 333, pp. 93-98, 2000.
- [20] I. Kostova, G. Momekov, M. Zaharieva, M. Karaivanova, Cytotoxic activity of new lanthanum complexes of bis-coumarins. *Eur. J. Med. Chem.*, vol. 40, pp. 542-551, 2005.
- [21] I. Kostova, I. Manolov, G. Momekov, Cytotoxic activity of new neodymium (III) complexes of bis-coumarins. *Eur. J. Med. Chem.*, vol. 39, pp. 765-775, 2004.
- [22] I. Kostova, I. Manolov, M. Karaivanova, Synthesis, physicochemical characterization, and cytotoxic screening of new zirconium complexes with coumarin derivatives. *Arch. Pharm.*, vol. 334, pp. 157-162, 2001.
- [23] E. Pretsch, P. Buhlmann, M. Badertscher, *Structure Determination of Organic Compounds*, Berlin Heidelberg: Springer-Verlag, 2009, p. 292.
- [24] E. Pretsch, P. Buhlmann, M. Badertscher, *Structure Determination of Organic Compounds*, Berlin Heidelberg: Springer-Verlag, 2009, p. 317.