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STUDY OF NICKEL COMPLEXES OF SOME AMINO ACID DERIVATIVES

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Synthesis of nickel complexes of 6-methoxy-3-methylcoumariloylamino acids and related 5,7-dibromo derivatives (IV-VI) are described. Magnetic susceptibility, IR and Visible spectra of these complexes are investigated. All nickel complexes were found to have specific antimicrobial activity against number of microorganisms.

Key Words: Nickel Complexes; Coumarilic Acid Derivatives; Biological Activity

Introduction

In previous studies, many copper complexes of some amino acid derivatives were reported[1,2]. Recently, copper complexes of substituted coumariloylamino acid derivatives were examined[3]. However, spectroscopic and biological studies of nickel complexes of substituted coumariloylamino acids have not yet been studied.

The present investigation involves the preparation of nickel complexes of 6-methoxy-3-methyl-coumariloylamino acids and related 5,7-dibromo derivatives (IV-VI) as well as studying their spectroscopic, magnetic susceptibility and biological properties.

Experimental

Melting points were determined using an electrothermal melting point apparatus and are uncorrected. Thin layer chromatography (TLC, R_f value) was performed on silica-gel-G using benzene-ethyl acetate (2:1) and iodine-KI (20%) as detection reagent. Benzidine, ninhydrin were used for the detection of amino acid derivatives (spot reactions). The microanalysis were performed by microanalytical center at Cairo University. Infrared spectra were recorded (Table I) using Shimadzu IR spectrometer (IR 440). Samples were mixed with KBr and all spectra were scanned in the range 5050-300 cm^{-1} Visible spectra were obtained in the range 900-500 nm. (11, 111-20,000 cm^{-1}) in the liquid phase using Perkin Elmer λ_{3b} spectrometer. Magnetic susceptibility measurements were obtained at room temperature using Guoy method[4].

6-Methoxy-3-methyl-coumariloylamino acids (I, II)

The titled compounds were prepared as reported in our recent work[3].

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Table 1

Frequencies in cm $^{-1}$ of IR absorption peaks

Compd No.	νOH)	ν(C=O)	°CC=C)	δ(NH)	ν(C–O)
I	3390	1730	1607	1555	1140
IV	3380	1720	1707	1552	1135
II	3340	1720	1605	1572	1150
V	3340	1713	1603	1570	1145
III	3380	1730	1605	1577	1140
VI	3380	1721	1603	1577	1135

5,7-Dibromo-6-methoxy-3-methyl-coumariloyl-DL-leucine (III)

5,7-Dibromo-6-methoxy-3-methyl-coumariloyl-chloride (0.005 mole) was dissolved in benzene (20 ml) and added dropwise to a solution of DL-leucine (0.005 mole) in 1 M NaOH (30 ml) at 7°C. The reaction mixture was stirred at 10°C for 75 min., followed by three hours stirring at room temperature. The benzene layer was separated out and the aqueous layer cooled to 0°C and acidified with 2 M HCl until become acidic to congo red (pH = 5). The separated crude product was filtered off, washed with cold water and recrystallized from ethanol-water, yield (70%), m.p. 300-2°C R_f (0.82) [cf. Fig. 1].

Analysis: $C_{17}H_{19}Br_2NO_5$

Calcd: C, 42.77, H, 3.98, N, 2.94

Found: C, 42.82, H, 4.02, N, 2.09

Preparation of Nickel Complexes of (1:1) *Molar Ratio (IV-VI)*

A 0.01 M solution of 6-methoxy-3-methyl-coumariloylamino acid or related 5,7-dibromo derivative (ligands I-III) in absolute ethanol was introduced into 10 ml measuring flask. The mixture was brought to the mark by the addition of hot ethanolic solution of nickel chloride. The mixture was stirred for 15 min, which on cooling, nickel complexes were separated out, recrystallized from ethanol-water and examined.

Results and Discussion

Chemistry

Coupling of 6-methoxy-3-methyl-coumariloyl chloride or related 5,7-dibromo derivative with the appropriate amino acids in benzene-sodium hydroxide medium at 7°C afforded the desired 6-methoxy-3-methyl-coumariloylamino acids and related 5,7-dibromo derivative (I-III). The time required for the completion of the reaction was monitored by TLC. Compounds (I-III) were chromatographically homogeneous and did not respond to ninhydrin reaction. Complete acid hydrolysis of (III) (6M-HCl, 100°C, 24 hours), followed by subsequent paper chromatography afforded ninhydrin positive spot of leucine.

Nickel complexes of 6-methoxy-3-methyl-coumariloylamino acids and related 5,7-dibromo derivative (IV-VI) of 1:1 molar ratio were prepared by add-

ing alcoholic solution of nickel chloride to alcoholic solution of the appropriate ligands (I-III). On cooling, the desired nickel complex were separated out. Nickel was determined complexometrically as reported before[5].

The characteristic IR absorption frequencies of the ligands revealed an absorption feature which resolved in the range 3400-3200 cm^{-1} and this absorption peak was attributed to ν(OH). In addition to that peak, a strong absorption peak was clearly resolved in the range 1730-1710 cm^{-1} and this absorption frequency was most probably attributed to $\nu(C=O)$ stretching mode. The band appeared in the range 1150-1135 cm^{-1} was attributed to $\nu(C-O)$ of the furan ring. The strong absorption feature located at ~1600 cm^{-1} was assigned to $\nu(C=C)$ of the phenyl ring. The IR spectra of nickel complexes revealed a strong and extremely broad absorption feature observed in the range 3400-3200 cm^{-1} and this absorption feature was attributed to ν(OH) of coordinated water molecules[6]. ν(NH) Stretching mode is hidden behind the strong ν(OH).

By comparing the IR spectra of the ligands and Ni^{+2} complexes, it was clear to observe a frequency shift of $\nu(C=O)$ to lower frequency upon complexation, also $\nu(C-O)$ was slightly shifted to lower frequency. From the observed frequency shift, we suggested that complexation occurred via the coordination sites carbonyl oxygen and furan ring oxygen.

The effective magnetic moment (μ_{eff}) were measured at room temperature and listed in Table II. The values of magnetic moments indicated the presence

Table II

Absorption peaks and magnetic susceptibility data

Complex No.	Colour	μ_{eff} B.M.	Absorption peaks (cm^{-1})		
IV	Green	2.93	—	12,500	15,384
V	Green	2.93	—	12,500	15,384
VI	Green	3.01	12,077	12,500	15,152

Table III

Minimal inhibitory concentration (MIC in μg/ml) of the biologically active compounds

Compd. No.	*B. subtilis*	*B. cereus*	*E. coli*	*S. typhosa*	*Cand. utilis*
I	250	500	500	500	—*
II	250	250	250	500	—
III	250	250	250	250	—*
IV	50	100	50	50	—
V	25	25	25	50	—
VI	10	10	10	15	100

*Biological inactive compound (MIC > 500 μg/ml).

of two unpaired electrons in these complexes. The relatively low values of (μ_{eff}) suggested that these Ni^{2+} complexes may have an octahedral structure[7].

The absorption peaks in the visible region are listed in Table III. Two peaks were clearly resolved at ~12,500 and ~15,300 cm^{-1}. The first peak was attributed to $^3T_{1g} \leftarrow {}^3A_{2g}$ (ν_2), while the second peak was assigned as the spin forbidden $^1E_g \leftarrow {}^3A_{2g}$ which frequently observed in Ni^{+2} complexes and attributed to spin-orbit coupling or configuration interaction[8].

We conclude from our experimental data that Ni^{+2} ion is octahedrally coordinated.

Biology

The antimicrobial activities of the synthesized nickel complex derivatives (IV-VI) were tested using the hole plate and filter paper disc methods[9-13]. All compounds were tested against gram-positive and gram-negative bacteria: *Bacillus substilis* ICC strain), *Bacillus cereus*, (NRRL-B-569), *Escherichia coli* (NRRL-B-210); *Salmonella typhosa* (NRRL-B-573), and selected fungi; *Candida utilis*. The results were compared with activity of parent compounds (I-III) which were found to possess a various antimicrobial activity against all tested bacteria (MIC 250-500 μg/ml) and were inactive against *Candida utilis*. The data for the minimal inhibitory concentrations (MIC in μg/ml) of the active compounds are summarized in Table III.

The nickel complexes of 6-methoxy-3-methyl-coumarilolyl-L-phe (IV) and corresponding L-Tyr (V) were found to possess a moderate antibacterial activity against all tested gram-positive and gram-negative bacteria (MICs ranging from 25 to 50 μg/ml). The nickel complex derivatives (IV, V) were found to be inactive against the tested fungi (cf. Table III).

The nickel complex of 5,7-dibromo-6-methoxy-3-methyl-coumoriloyl-DL-Leu (VI) was found to possess a high antibacterial activity against all tested bacteria (MICs 10-15 μg/ml) and had a moderate activity against *Candida utilis* (MIC 100 μg/ml).

The present investigation indicated that introducing of nickel atom to 6-methoxy-3-methyl-coumariloylamino acid residues induce specific biological properties of the nickel complexes (IV, V). Moreover, the presence of bromine atoms in combination with nickel atom improve the biological activity of the synthesized nickel complex derivative (VI).

References

1 A M El-Naggar, M R Zaher and A M Abd-El-Salam *J appl Chem & Biotechnol* **26** (1976) 305
2 A M El-Naggar, M R Zaher and A M Abd El-Salam *Egypt J Chem* **18** (1975) 43
3 T M Ibrahim, A A Shabana, H A Hammad *Anglo-Egypt Conf (II)* (1991) (*Accepted*)
4 F P Dwyer and D P Mellor *Chelating Agents and Metal Chelates* Academic Press New York (1964)
5 J Lewis and R G Wilkins *Modern Coordination Chemistry* Interscience Publ Co New York (1964)
6 K Nakamato *Infrared Spectra of Inorganic and Coordination Compounds* Wiley Interscience, New York (1970)

7 R S Drago *Physical Methods in Inorganic Chemisatry* Litton Educational Publ Inc New Delhi (1965)
8 A B P Lever *Inorganic Electronic Spectroscopy* Elseiver Publ Co New York (1968)
9 J G Carlson, H G Douglas and H D Bissel *J Bacteriol* **55** (1948) 607
10 G W Irving, T D Fontaine and S P Dolittle *J Bacteriol* **52** (1946) 10
11 J G Vincent and H W Vincent *Proc Soc Exp Biol Med* **55** (1944) 162
12 J A Epstein, E J Foley I, Perrine and S W Lee, *J Lab Clin Med* **29** (1944) 319
13 A M El-Naggar, F S M Ahmed, M F Badie and K M Kamel *Int J Peptide Protein Res* **22** (1983) 251