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SYNTHESIS, PHYSICO-CHEMICAL CHARACTERIZATION AND BIOLOGIC ACTIVITY OF A NEW NICKEL COMPLEX WITH 2-CYANOGUANIDINE

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abstract: A new complex of nickel with 2-cyanoguanidine and acrilato ion as ligands was synthesised. The physico-chemical characterisation revealed the unidentate coordination mode of ligands as well as the metallic ion octahedral stereochemistry. The biological tests have highlighted a narrow but very good antimicrobial activity.

key words: nickel complex; 2-cyanoguanidine; acrylato ion; biological activity.

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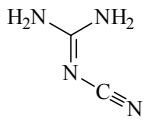
1. Introduction

2-Cyanoguanidine (cnge) and its derivatives have found a number of uses in chemical synthesis as well as in biochemistry. Some derivatives of 2-cyanoguanidine have potent antisecretory and/or antiulcer activities [1] or are effective smooth muscle relaxants [2]. N,N'-disubstituted cyanoguanidines can be selective inhibitors of factor Xa (trypsin-like serine protease factor), which is a highly effective approach to the prevention and treatment of arterial and venous thromboembolism [3]. On the other hand, 2-cyanoguanidine is a versatile ligand which can coordinate either as unidentate or bridging bidentate, leading stable compounds with both hard and soft metals. There is not information regarding the biological properties of these complexes until now.



2-cyanoguanidine (cnge)

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This paper reports the synthesis of a nickel complex with 2-cyanoguanidine and acrylato ligands.

2. Experimental

The compound was synthesized from commercially available starting materials used without further purification. IR spectra were recorded in KBr pellets with an FTIR-Biorad 135 instrument in 400-4000 cm^{-1} range. The diffuse-reflectance spectrum was recorded between 200 and 900 nm on a JASCO V-570 spectrophotometer, by using MgO as a standard.

Elemental analyses (C, H, N) were performed with a Perkin Elmer PE 2400 instrument.

Synthesis of $[Ni(C_2H_4N_4)_2(C_3H_3O_2)_2(H_2O)_2]H_2O$ (**1**): An aqueous mixture of nickel hidroxocarbonate (0.952 g, 8 mmol), acrylic acid (2.2 ml, 32 mmol) and 2-cyanoguanidine (1.35 g, 16 mmol) was stirred at room temperature for one hour. The pale green obtained solution was filtered off. The filtrate was allowed to slowly evaporate at room temperature. The pale green crystals formed were filtered off, washed with small amounts of cooled ethylic alcohol and air-dried.

Elemental chemical analyses $NiC_{10}H_{20}N_8O_7$: 28.39 C; 4.76 H; 26.49 N, 13.87 Ni %, (found); 28.24 C; 4.86 H; 26.57 N, 13.79 Ni % (calcd). Selected IR data (KBr, cm^{-1}): $\nu(H_2O)$, 3400sh, m; $\nu_{as}(NH_2)$, 3352m; $\nu_s(NH_2)$, 3216m; $\nu(C\equiv N)$, 2225s, 2181m; $\nu(C=N)$, 1657s; 1639s; $\nu_{as}(OCO)$, 1598vs; $\delta_{as}(NH_2)$, 1565s, 1539s; δ(CH), 1427s; $\nu_s(OCO)$, 1363m; ν(C-N), 1032m; γ(CH), 1004s, 955m; $\gamma(NH_2)$, 671m; $\delta(OCO)$, 685m; $\rho_w(H_2O)$, 626w. Diffuse reflectance spectrum: 395 nm; 665 nm, 745 and 1145 nm.

The antimicrobial activity of the investigated compound was tested against bacterial and fungal strains belonging to the following genera and species: Gram positive (methicillin resistant *Staphylococcus (S.) aureus, Bacillus (B.) subtilis, Bacillus (B.) ceres*), Gram-negative (*Escherichia (E.) coli, Salmonella (S.) enteritidis, Shigelle flexure*, *Enterobacter*) and *Candida (C.) albicans*. The microbial strains were identified by aid of VITEK I automatic system. VITEK cards for identification and susceptibility testing (GNS-522) were inoculated and incubated according to the manufacturer's recommendations. The results were interpreted by using software version AMS R09.1. In our experiments there were used bacterial suspensions of $1.5x10^8$ CFU/mL or 0,5 McFarland density obtained from 15-18 h bacterial cultures developed on solid media. The antimicrobial activity was tested on Mueller- Hinton medium recommended for the bacterial strains and Yeast Peptone Glucose (YPG) medium for *C. albicans*. It was used the solutions of the new compound in water with 1000 µg/mL concentration.

The qualitative screening was performed by an adapted disk diffusion method. Petri dishes with Mueller Hinton (for bacterial strains) /YPG (for yeasts) medium were seeded with bacterial inoculums as for the classical antibiotic susceptibility testing disk diffusion method [4÷6]; 5 mm diameter paper filter disks were placed on the seeded medium, at 30 mm distance. Subsequently, the disks were impregnated with 5 µL tested compound solution (1000 µg/ mL concentration). The plates were left at room temperature for 20-30 minutes and then incubated at 37°C for 24 hrs. The positive results were read as the occurrence of an inhibition zone of microbial growth around the disk.

3. Results and discussion

The synthesis of $[Ni(cnge)_2(Acr)_2(H_2O)_2]H_2O$ **1** was achieved by the reaction of $NiCO_3 \cdot Ni(OH)_2$, acrylic acid (HAcr) and 2-cyanoguanidine in 1:4:2 ratio, according to the experimental conditions.

3.1. Infrared and electronic spectra

The infrared spectrum of **1** shows the characteristic vibration bands of the 2-cyanoguanidine, acrilato ion and water molecule. The bands assigned to the stretching vibrations of nitrile group are significantly shifted towards higher wavenumbers in comparison with the spectrum of 2-cyanoguanidine. This behavior is in accord with a coordination through its nitrile part.

The acrylato ions coordination mode can be identified due to $\nu_{as}(COO)$ and $\nu_s(COO)$ bands. A $\Delta = \nu_{as}(COO) - \nu_s(COO)$ value higher than the ionic one of 203 cm^{-1} observed for sodium acrylate, indicates an unidentate coordination mode, while a $\Delta < 203$ cm^{-1} value indicates a bidentate (chelation/bridging) coordination mode [7]. The $\nu_{as}(COO)$ and $\nu_s(COO)$ bands associated with the acrylato fragment in complex generate a Δ value of 235 cm^{-1} indicating an unidentate coordination mode. The IR spectrum also displays bands around 3400 and 626 cm^{-1}, assigned to $\nu(OH)$ and $\rho_w(H_2O)$ vibrations for coordinated water molecules [8].

The electronic spectrum of **1** is typical for an octahedral nickel(II) ion [9]. The three absorption bands at 395 nm, 665 nm and 1145 nm are assigned to the spin-allowed d–d transitions: $^3A_{2g} \rightarrow {}^3T_{1g}(P)$, $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g} \rightarrow {}^3T_{2g}(F)$, respectively. A weak absorption due to the $^3A_{2g} \rightarrow {}^1E_g$ spin forbidden transition is observed at 745 nm. These data allow the calculation of the ligand filed parameters, $10Dq$ and Racah (B): $10Dq$ = 8730 cm^{-1}; B = 959 cm^{-1}. The value of the nephelauxetic parameter, β, is 0.92.

In summary, the synthesized compound contains the nickel ion octahedral coordinated by two nitrogen atoms from the nitrile group of 2-cyanoguanidine molecules and four oxygen atoms provided by acrilato ions and water molecules.

3.2. Biological activity

The *in vitro* screening of the antimicrobial properties was performed by broth microdilution method, in order to establish the minimal inhibitory concentration (MIC), against Gram-positive (*S. aureus, B. subtilis, B. ceres*), Gram-negative (*E. coli, S. enteritidis, Shigelle flexure*, *Enterobacter*), as well as *C. albicans*, using both reference and clinical, multidrug resistant strains. Our results showed that the tested compound exhibits a narrow antimicrobial spectrum, being active only against *B. subtilis* (MIC 62.5 μg/cm^3) and *Shigelle flexure* (MIC 1.95 μg/cm^3).

It is to be noticed the very good bactericidal effect of complex on *Shigelle flexure* (with a low MIC of 1.95 μg/cm^3).

4. Conclusion

A new complex $[Ni(cnge)_2(Acr)_2(H_2O)_2]H_2O$ was synthesised and physico-chemical and biological characterized.

IR spectrum is consistent with the presence of 2-cyanoguanidine N-bound to the nickel(II) ion through its nitrile part as well as acrylato ion coordinated in an unidentate fashion.

The compound exhibits a narrow antimicrobial spectrum, but with a remarkable activity against *Shigelle flexure*.

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