

# Ni(II) Coordination Compound with Acetaminophen

## Synthesis and Characterization

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*The study deals with the synthesis and physico-chemical characterization of a new metal complex of Ni(II) with a bioactive ligand, namely acetaminophen (paracetamol). The synthesis of the coordination compound was monitored by the means of TLC and characterized by several techniques such as elemental analysis, FTIR spectroscopy and hyphenated thermogravimetric analysis (TG/DTG/HF). The results indicated that the coordinative compound contains the metal and ligand in a molar ratio of 1:2, as well coordination and lattice water. Also, the thermal stability and decomposition under non-isothermal conditions were investigated.*

*Keywords: acetaminophen nickel(II) complex, coordination compound, paracetamol, thermal behaviour, hyphenated techniques, nickel oxide*

Metal coordinative compounds are nowadays an independent and highly-developed domain in the field of chemistry due to the fact that numerous scientific and technical fields require the synthesis of such compounds. Medicinal chemistry developed enormously in the last two decades and nowadays is focused on drug design and both organic and inorganic synthesis, and the last one is mainly represented by metal coordinative compounds [1].

Acetaminophen (N-(4-hydroxyphenyl)ethanamide, N-acetyl-p-aminophenol or trivial name Paracetamol) is a highly-accessible and widely used drug, sold over-the-counter in numerous countries for reducing pyrexia in children and adults and as well as a pain reliever, having similar properties with those of acetylsalicylic acid, but with weaker anti-inflammatory effects [2]. It is generally recommended for patients suffering of gastroesophageal reflux disease, being better tolerated than acetylsalicylic acid and having an overall tolerability equivalent to that of ibuprofen [3].

Acetaminophen (ACPH) acts as an analgesic in mild arthritis, but is ineffective in the treatment of inflammation, and swelling of the joint [4-6].

By far, most of the over-the-counter drugs containing acetaminophen (ACPH) as active substance with/without other active substance are used in cold and flu pharmaceutical formulations [7], but are also used in treatment of different types of aches and neuralgia [8].

The chemical structure of acetaminophen (ACPH) is presented in figure 1.

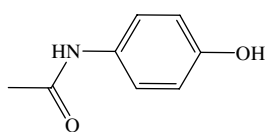


Fig.1. Chemical structure of acetaminophen (ACPH)

Transition metals are involved in essential biological processes in both humans and mammals bodies, but as well in plants since they are cofactors of metalloproteins and also act as regulator elements. An average human body contains at least 60 elements in major, minor and trace quantities, 25 of them being considered to have an essential role in health of humans. Nielsen [9] described the chemistry, metabolism, deficiency signs, toxicology functions, mode of action, dietary and clinical considerations over nickel and its compounds for humans. It was considered that nickel is not clearly associated with a biochemical function on humans, but is a cofactor and structural component in specific metalloenzymes in superior organisms due to the fact that plays a crucial role in bacteria, plants and invertebrates. Nickel-containing enzymes consist in urease, hydrogenase and reductase. In superior animals, nickel may be involved in pathways using vitamin B12 or/and vitamin B9. Being known the fact that nickel is essential for several animals can act as a presumption that is necessary for humans too. It has been suggested that the dietary requirement for humans is around 25-35µg/day. In humans, a high concentration of nickel was found in adrenal and thyroid glands (up to 132 µg/kg) while most organs contains a considerable lower quantity (up to 50 µg/kg) [9].

The increasing interest in the domain complexes containing metal ions and biological active ligands is sustained by the considerably numerous scientific studies regarding the synthesis, physico-chemical characterization and biological activity of coordination compounds containing essential trace elements such as Cr(III), Fe(III), Co(II), Ni(II), Cu(II) and Zn(II). Following a previous study which dealt with the synthesis and solid-state characterization of a Zn(II) complex with ACPH ligand [10], we set our goal in the synthesis and characterization of a Ni(II) coordination compound with acetaminophen.

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## Experimental part

All chemicals used were of analytical purity and used without further purification. Acetaminophen (Sigma-Aldrich),  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (Reactivul București) and ethanol 96% (Chimopar SA, București) were used. The composition of the metal complex (C, H and N) was determined by elemental analysis using a Vario El Cube analyzer. The Ni(II) content was determined by complexometric titration with EDTA, in  $\text{NH}_3/\text{NH}_4\text{Cl}$  buffer solution at  $\text{pH} \sim 10$ , in the presence of Murexide as indicator, by a standard analytical procedure.

Melting point was determined on a Böetius PHMK (Veb Analytik Dresden) instrument, and thin-layer chromatography was carried out on silica gel-coated plates 60F<sub>254</sub> Merck using hexane:methanol 3:7 as eluant. The FTIR spectra of ligand and Ni(II) coordinative compound were obtained on the Perkin Elmer SPECTRUM 100 spectrometer using the UATR technique on 4000-650  $\text{cm}^{-1}$  spectral range and in KBr pellet on a Jasco FT/IR-410 spectrophotometer for the product of thermal decomposition of Ni(II) complex, respectively, on 4000-400  $\text{cm}^{-1}$  spectral range.

Thermal analysis of prepared complex was carried out by TG-DTG-HF method using a Perkin-Elmer DIAMOND equipment. Samples about 6 mg were heated in aluminium crucibles, up to 550 °C at a heating rate  $\beta = 10 \text{ }^\circ\text{C} \cdot \text{min}^{-1}$ , in dynamic air atmosphere.

### Synthesis of Ni(II) metal complex

The synthesis of the complex was carried out in aqueous-alcoholic medium, by the reaction of ACPH and  $[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2$ . Into a round bottom flask, to a solution (30 mL) containing  $[\text{Ni}(\text{H}_2\text{O})_6](\text{NO}_3)_2$  (1.4540g, 5 mmol) in water, a diluted ethanolic solution (40 mL) of ACPH (1.5116g, 10 mmol) was added dropwise under intense stirring. The mixture was then heated under reflux for 8h, and then was allowed to cool down at room temperature. After cooling, the volume of solvent (distilled water) was reduced to half under reduced pressure (40 °C / 10 mmHg). The concentrated solution was stored in a covered beaker at 5°C, and after 6 days a pale green compound separated as a crystalline solid, which was filtered off under vacuum, washed with distilled water (3 x 5 mL) and dried for 48 h at 30°C.

### $[\text{Ni}(\text{ACPH})_2(\text{OH})_2]^{2+}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ metal complex

Crystalline pale green solid (2.5626g, 4.6 mmol, yield 91.8%), m.p. (Böetius) = 117 °C (decomp.), TLC one spot;

Chemical formula:  $\text{C}_{16}\text{H}_{26}\text{N}_4\text{NiO}_{14}$ ; molar mass: 557.09  $\text{g} \cdot \text{mol}^{-1}$ ;

FTIR (UATR,  $\text{cm}^{-1}$ ): 3702-2894 (broad), 3322, 1598 (intense), 1562, 1436, 1369, 1324, 1227, 1011, 804, 737, 691.

Complex	C / %		H / %		N / %		Ni / %	
	calc.	found	calc.	found	calc.	found	calc.	found
$[\text{Ni}(\text{ACPH})_2(\text{OH})_2]^{2+}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$	34.50	35.02	4.70	4.92	10.06	9.85	10.54	10.17

$\beta$ ( $^\circ\text{C} \cdot \text{min}^{-1}$ )	Process	$T_i$ (°C)	$T_f$ (°C)	$T_{\text{peak DTG}}$ (°C)	$T_{\text{onset HF}}$ (°C)	$T_{\text{peak HF}}$ (°C)	$\Delta H$ ( $\text{J} \cdot \text{g}^{-1}$ )	$\Delta m$ (%)
10	I	53	90	75	60	70	18.03	6.19
	II	115	175	127	112	116	41.09	6.91
	III	249	320	250; 290	201	235	-65.25	30.12
	IV	320	410	370	350	385	-143.67	42.65

## Results and discussions

The present study was undertaken in order to characterize the metal complex by elemental analysis, FT-IR spectroscopy and thermal analysis.

### Elemental analysis

The results of elemental analysis and molecular formula of the metal complex are listed in table 1. The obtained results are in good agreement with the ones calculated for the suggested formula.

### Thermal decomposition

In our previous papers [11-20], we have presented the applications of thermoanalytical methods and hyphenated techniques (TG-DTG-HF-FTIR) in the preformulation stages in solid state form of pharmaceuticals and thermal behaviour of some new compounds with biological activity, respectively. The TG/DTG/HF curves of the metal complex obtained during heating in air atmosphere are shown in figure 2.

The TG curve of the metal complex presents four thermal decomposition processes leading to a final decomposition residue of 13.41% mass. The first step of decomposition in the temperature range 53-90 °C associated with a maximum of DTG<sub>peak</sub> at 75 °C corresponds to the loss of two moles of water with a mass loss of 6.19% (calcd. 6.47%). This elimination is an endothermic event which occurs at a considerably low temperature, suggesting a weak bonding of water in the complex structure. This water loss can be associated, according to literature [21] to the lattice water. The second decomposition step occurred in the range of 115-175 °C with a DTG<sub>max</sub> = 127 °C corresponds to the loss of another

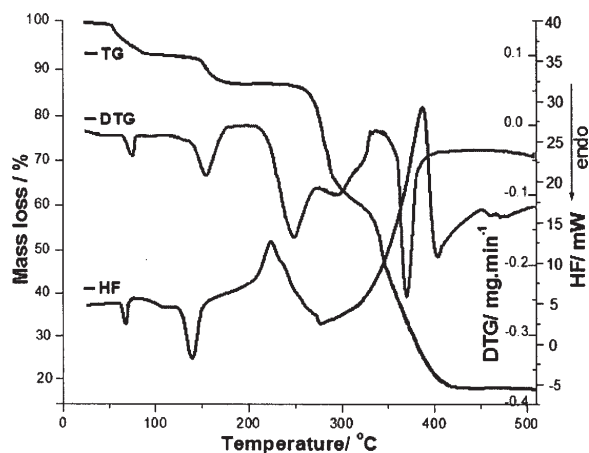


Fig.2. The thermoanalytical curves TG/DTG/HF obtained in air at  $\beta = 10 \text{ }^\circ\text{C} \cdot \text{min}^{-1}$  for the analysed Ni(II) complex

Table 1  
ELEMENTAL ANALYSIS DATA

Table 2  
THERMOANALYTICAL DATA OF  
THE ANALYZED COMPLEX

two moles of water with  $\Delta m_{\text{experimental}} = 6.91\%$  (calcd. 6.47%). Due to the fact that this loss of water occurs at temperatures above 110 °C, leads to the conclusion that it corresponds to coordinated water, not to lattice water [21].

The third decomposition step is not a single one, but an overlapping of two processes according to the Heat Flow profile. The exothermic and endothermic peaks observed in the 249-320°C temperature range are probably due exo- and endothermic reactions that take place simultaneously such as breaking and rearrangement of the bonds as well as some moieties oxidative degradation because the heating takes place in an oxidative atmosphere.

In the final step, the oxidative degradation of the organic ligand, as well as the nitrate anions elimination occurs. As a result of these transformations, the last process is a very strong exothermic one as can be seen on the HF curve. All these degradation steps finally lead to nickel (II) oxide (calculated mass loss = 13.41 %; experimental mass loss = 14.23 %). The nature of final product was confirmed by FTIR spectroscopy.

Taking into account all the above presented data, the complex can be formulated as  $[\text{Ni}(\text{ACPH})_2(\text{OH})_2]^{2+}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ . The thermal analysis results of the Ni(II) complex with acetaminophen, determined in non-isothermal conditions are summarized in table 2.

ACPH ligand coordinates to  $\text{Ni}^{2+}$  in the stoichiometric ratio 2:1 by the oxygen atoms from phenolic hydroxyl and amidic carbonyl. These data are in good agreement with previous published results in the domain of metal complex of paracetamol [10, 22-24].

#### Spectroscopic description

In order to evaluate the formation of the coordinative entity, UATR-FTIR spectroscopy was used. The main strategy used was the corroboration of data obtained for free ligand (ACPH) and the one for the metal complex, in the 4000-650  $\text{cm}^{-1}$  spectral region (fig. 3).

As previously published [10], the analysis of UATR-FTIR spectrum of ACPH, reveals several characteristic absorption bands at 3322  $\text{cm}^{-1}$  (stretching vibrations of -NH group) and 3160-3108  $\text{cm}^{-1}$  (stretching vibrations of -OH groups), respectively. The intense and sharp absorption band at 1650  $\text{cm}^{-1}$  in the spectrum of ACPH can be assigned to stretching of C=O functional group. These three functional groups (-NH, -OH and -C=O) were mainly analysed because they can be involved in the formation of the coordinative compound, so a modification of their intensity and/or shifting in the spectrum of the complex is expected.

In order to evaluate the formation of the coordinative compound, and as well to determine which functional groups are involved in the dative bond ligand-metal, a comparative analysis of the FTIR spectrum of Ni(II)

complex with the one of ACPH was realized (fig. 3). Due to the fact that no quantitative analysis was realized, but only a qualitative one, we studied mainly the shifting of maximum corresponding to characteristic bands to lower/higher wavenumbers, but as well the modification of their aspect. As previously described in one of our papers [10], FTIR spectrum of ACPH molecule presents characteristic bands for the -OH stretching vibrations between 3160-3108  $\text{cm}^{-1}$ , while in the case of  $[\text{Ni}(\text{ACPH})_2(\text{OH})_2]^{2+}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$  this broad band became even larger (3702-2894  $\text{cm}^{-1}$ ), due to the overlapping with the vibrations of water (coordination and lattice) in its structure. The shifting of the maximum indicated also indicates the involvement of the -OH group in the formation of the metal complex. As can be noticed, the band from 3322  $\text{cm}^{-1}$  that corresponds to the -NH group is not shifted to different wavenumbers, indicating the fact that this group does not participate in the formation of -HN-Ni dative bond. The most relevant shifting of a band, accompanied by the modification of its aspect (band with sharp and weak shoulder) occurs for the one corresponding to the C=O stretching vibration, suggesting that coordination occurs through this group. In a previous study regarding the spectroscopic evaluation of a Zn(II) metal complex with ACPH [10], the shifting of this signal occurred to a higher wavenumber (from 1650  $\text{cm}^{-1}$  up to 1694  $\text{cm}^{-1}$ ), while in the case of metal complex of Ni(II) with ACPH, the shifting of this band takes place to a significantly lower wavenumber (from 1650  $\text{cm}^{-1}$  down to 1598  $\text{cm}^{-1}$ ). The formation of the metal complex is also sustained by the apparition of two new sharp absorption bands at 737  $\text{cm}^{-1}$  and 691  $\text{cm}^{-1}$  in the spectrum of the Ni(II) complex, without having a correspondence in the spectrum of free ligand. These two new bands can be attributed to vibrations of nickel-ligand bonds, namely  $\text{HO} \rightarrow \text{Ni}$  and  $\text{C}=\text{O} \rightarrow \text{Ni}$ , respectively.

The analysis of TG curve obtained in air at  $\beta = 10^\circ\text{C} \cdot \text{min}^{-1}$  for the analysed Ni(II) complex (fig. 2), leads to the conclusion that the final decomposition product is stable in the temperature range 410-510 °C. In order to determine the composition of this product, for the remaining solid, an FTIR spectrum was drawn up. As expected, the reduced number of bands from FTIR spectrum indicates the formation of a relatively simple product, characterised by only few vibrational modes. Due to the fact that the thermal treatment was carried out in oxidative atmosphere (synthetic air), nickel (II) oxide was presumed to be formed. By the comparison with the FTIR bands mentioned in the literature [25] for pure NiO (namely 418.57  $\text{cm}^{-1}$ , 677.04  $\text{cm}^{-1}$ , 1629.90  $\text{cm}^{-1}$ , 2924.18  $\text{cm}^{-1}$  and 3431.48  $\text{cm}^{-1}$ ), the FTIR spectra that was drawn up for the sample proven that the decomposition product is NiO (fig. 4).

According to spectroscopic data, and by corroboration to thermal behaviour of complex and the results from

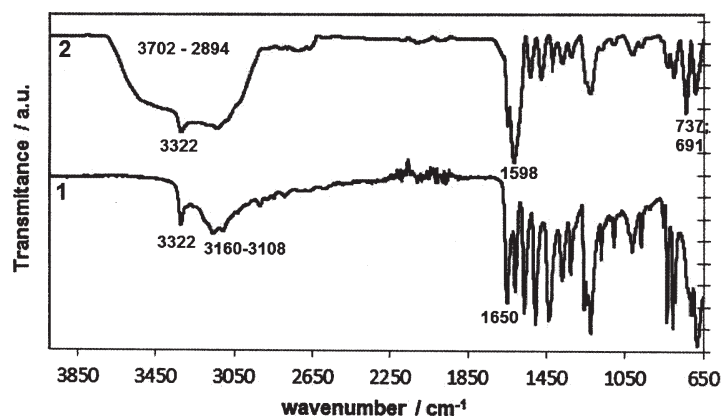


Fig.3. Comparative FTIR spectra of (1) ACPH- ligand; (2)-  $[\text{Ni}(\text{ACPH})_2(\text{OH})_2]^{2+}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$

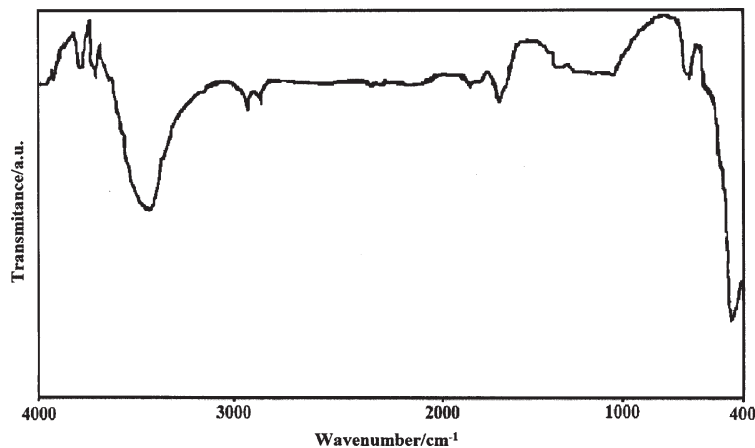


Fig.4. FTIR spectra for the decomposition product of Ni(II)-ACPH complex at 510 °C

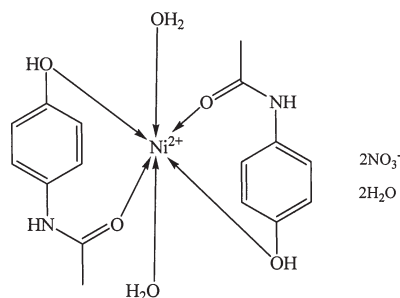


Fig. 5. The proposed structure of  $[\text{Ni}(\text{ACPH})_2(\text{OH}_2)_2]^{2+}(\text{NO}_3^-)_2 \cdot 2\text{H}_2\text{O}$  complex

elemental analysis, a proposed structure for the metal complex is presented in figure 5.

### Conclusions

In our study, a Ni(II)-ACPH coordinative compound was synthesized. The physico-chemical characterization was realized by means of elemental analysis, FTIR spectroscopy and TG-DTG-HF technique. The thermal analysis showed processes such as water elimination, breakage and oxidative destruction of the organic ligand.

Thermal decomposition of this complex allowed establishing the number and nature of water molecules and the composition, but also the intervals of thermal stability. After the water elimination in two distinctive steps, the anhydrous metal complex undergo an oxidative degradation leading to nickel(II) oxide as final residue.

From the IR data, it is obvious that the formation of complex occurs by both  $-\text{OH}$  and  $-\text{C}=\text{O}$  groups from ACPH. The broad absorption band in the  $3702\text{--}2894\text{ cm}^{-1}$  range represents a proof for the water presence in the complex structure.

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