



COORDINATION COMPOUNDS OF Co(II), Ni(II), Cu(II) and Zn(II) WITH URSODEOXYCHOLIC ACID

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Complexes of Co(II), Ni(II), Cu(II) and Zn(II) with the anion of ursodeoxycholic acid (UDC) as ligand, of $M(UDC)_2 \cdot nH_2O$ type ($M = Cu(II)$, $n = 2$; $M = Co(II)$, $Zn(II)$, $n = 3$; $M = Ni(II)$, $n = 11$) have been prepared and characterized by elemental analysis, IR, UV-VIS and EPR spectroscopy, as well as magnetic measurements.

INTRODUCTION

In recent years steroidal structures have become increasingly important in a number of fields, such as pharmacology, biomimetic, supramolecular chemistry and nanotechnology. Many studies were performed to evaluate the ability of bile acids to act as shuttles to deliver drugs specifically to the liver and biliary system.¹

It is well known that metals accumulate in the liver causing serious problems. Using chelating agents which facilitate urinary excretion may be a solution for solving these problems, but it has the disadvantage of potentially damaging the kidneys. An alternative for the excretion of such metals via bile and feces is to use bile acids and derivatives as chelating agents.² Progress in understanding how bile acids interact with metal ions in solution depends on knowing their coordination to the metal ions.^{3,4}

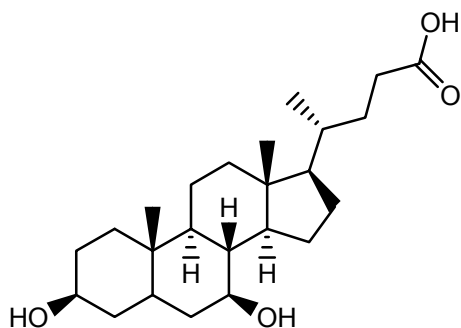
On the other hand, the need to find a safe and highly selective cure for neoplastic diseases remains a major challenge for modern science. The discovery of the antitumor efficacy of cisplatin and some related platinum complexes has stimulated the search for other metals with antineoplastic properties. Different metal complexes, such as complexes of zinc, copper and cobalt, are found to be promising compounds for the design of new

anticancer agents. Binding molecules containing a transition metal to bile acids have been synthesized and characterized, this new family of compounds named Bamets having citostatic activity.^{5,6}

The purpose of this paper was to study the coordination compounds of Co(II), Ni(II), Cu(II), Zn(II) with ursodeoxycholic acid, a naturally occurring tertiary dihydroxy hydrophilic bile acid with interesting properties. The capacity of different bile acids to coordinate metal ions has also been reported in several publications.^{7,8,9} Ursodeoxycholic acid is used successfully in the treatment of primary biliary cirrhosis.^{10,11} It is found in large quantities in bear bile. Also its taurine and glycine conjugates appear to protect against cholestasis and toxicity induced by the hydrophobic bile acids.^{12,13} This protective effect can be attributed to its ability to block the deleterious actions and encourage the choleresis of toxic bile acids.¹⁴ While some bile acids are known to be colon tumor promoter (*eg.* deoxycholic acid), others such as ursodeoxycholic acid are chemopreventive, perhaps by inducing cellular differentiation and cellular senescence in colon epithelial cells.¹⁵ As a pharmaceutical, it reduces the rate at which the intestine absorbs cholesterol molecules breaking up micelles containing cholesterol, for this reason being used to dissolve cholesterol gallstones in patients who want an alternative to surgery. Also, ursodeoxycholic acid

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reduces elevated liver enzyme levels by facilitating bile flow through the liver and protecting liver cells. For children it is used in biliary atresia, which is a cause of neonatal jaundice.¹⁶



Ursodeoxycholic acid

EXPERIMENTAL

Reagents: Ursodeoxycholic acid (Calbiochem product); all other reagents used were purchased from Merck.

Synthesis of sodium ursodeoxycholate ($\text{NaC}_{24}\text{H}_{39}\text{O}_4$). Ursodeoxycholic acid was dissolved in water containing an

equivalent amount of sodium hydroxide, and then the solution was evaporated to dryness on a water bath.

Synthesis of metal ursodeoxycholate complexes. Sodium ursodeoxycholate was dissolved in water at room temperature and aqueous solution of metal salt ($\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$; $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$; $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$; $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$) was added to this solution, under vigorous stirring. The precipitates were filtered, washed several times with distilled water to eliminate unreacted metal salt and sodium ursodeoxycholate and then desiccated over P_4O_{10} . All of the solid complexes obtained were identified by elemental chemical and physico-chemical analysis. The metal contents was determined by atomic absorption spectrophotometry and C, H content by microcombustion method. The results are presented in Table 1.

The IR spectra of the coordination compounds were recorded on KBr pellets with a Jasco FTIR 4100 spectrophotometer in the $4000\text{-}400\text{ cm}^{-1}$ range.

The electronic spectra were recorded on a UV4 Unicam spectrophotometer in the $900\text{-}200\text{ nm}$ range (MgO as standard).

The magnetic measurements on solid samples were measured by Faraday method with Mohr salt as a standard, at room temperature. The diamagnetic corrections were made by Pascal's constant.

EPR spectra were measured on powders at 9.5 GHz (X-band) on a Bruker E500 CW spectrometer.

Table 1

Elemental chemical analysis and magnetic moments for the coordination compounds of transition metals containing anion of ursodeoxycholic acid as ligand

Compound	Colour	Found/calculated (%)		μ_{eff} (B.M.)
		C	H	
$\text{Co}(\text{UDC})_2 \cdot 3\text{H}_2\text{O}$	Pink	64.04/64.28	9.36/9.37	5.0
$\text{Cu}(\text{UDC})_2 \cdot 2\text{H}_2\text{O}$	Olive green	65.20/65.25	9.21/9.28	2.44
$\text{Ni}(\text{UDC})_2 \cdot 11\text{H}_2\text{O}$	Light green	55.08/55.38	8.37/9.61	3.30
$\text{Zn}(\text{UDC})_2 \cdot 3\text{H}_2\text{O}$	White	63.66/63.82	9.07/9.30	0

RESULTS AND DISCUSSION

The complexes $\text{M}(\text{UDC})_2 \cdot n\text{H}_2\text{O}$ type ($\text{M} = \text{Cu}(\text{II}), n = 2; \text{M} = \text{Co}(\text{II}), \text{Zn}(\text{II}), n = 3; \text{M} = \text{Ni}(\text{II}), n = 11$) were prepared by mixing aqueous solutions of metal salts and ursodeoxycholic acid sodium salt (UDCNa) in a stoichiometric ratio, at room temperature. The compounds are insoluble in water and also in most organic solvents. They are soluble in warm DMSO. Elemental analysis results are in good agreement with the proposed composition of the complexes (Table 1).

In order to obtain information about the coordination manner of the ligands FTIR spectroscopic measurements in the $4000 - 400\text{ cm}^{-1}$ range for all coordination complex were performed (Table 2). IR spectra of all the coordination compounds at room temperature show strong absorption bands due to asymmetric stretching vibrations of the coordinated carboxylate group (ν_{as}) at $1562 - 1586\text{ cm}^{-1}$ and symmetric stretching vibrations (ν_{s}) at $1413 - 1415\text{ cm}^{-1}$.

Table 2

The characteristic frequency data of IR spectra for coordination compounds and their assignments.

Compound	OH	CH	COO^-_{as}	COO^-_{s}	$\Delta\nu$
$\text{Co}(\text{UDC})_2 \cdot 3\text{H}_2\text{O}$	3390	2935, 2866	1569	1414	155
$\text{Cu}(\text{UDC})_2 \cdot 2\text{H}_2\text{O}$	3387	2936, 2866	1613, 1561	1416	197, 145
$\text{Ni}(\text{UDC})_2 \cdot 11\text{H}_2\text{O}$	3398	2936, 2866	1563	1413	153
$\text{Zn}(\text{UDC})_2 \cdot 3\text{H}_2\text{O}$	3415	2935, 2866	1586	1414	172
UDCNa	3388	2932, 2864	1558	1405	153

The coordination modes of the ligand to the metal ion are assigned on the basis of the magnitude of separation ($\Delta\nu$) of the $\nu_{as}(\text{COO})$ and $\nu_s(\text{COO})$ bands and are compared with the sodium salt of the ursodeoxycholic acid (Table 2). According to literature data, $\Delta\nu$ for monodentate mode are usually much greater than the ionic complexes, $\Delta\nu$ for chelating mode are significantly less than the ionic complexes and $\Delta\nu$ for bridging mode are greater than those of chelating (bidentate) complexes and close to the ionic values.^{17,18} Taking into account that in case of sodium cholate, the carboxylate groups are coordinated in a pseudo-chelating mode to Na^+ through a water molecule,¹⁹ we propose that in our complexes, excepting $\text{Cu}(\text{UDC})_2 \cdot 2\text{H}_2\text{O}$, both carboxylate groups coordinate to the metal ion (Co^{2+} , Ni^{2+} , Zn^{2+}) in a pseudo-chelating mode, each of them through a water molecule. In case of $\text{Cu}(\text{UDC})_2 \cdot 2\text{H}_2\text{O}$ one carboxylate group coordinates with Cu^{2+} in a monodentate mode ($\Delta\nu = 197 \text{ cm}^{-1}$) and the other carboxylate group in a pseudo-chelating mode ($\Delta\nu = 145 \text{ cm}^{-1}$) through a water molecule. According to Refs.,^{7,19,20} in case of deoxycholate anion, both hydroxyl groups on the steroid ring coordinate with metal ions in crystal. Because of similarity between deoxycholate anion and ursodeoxycholate anion, we can assume that the hydroxyl groups of ursodeoxycholate anion will bind to the metal ions in order to satisfy its coordination geometries.

The broad, very intense band occurring centered at $\sim 3400 \text{ cm}^{-1}$ in all of these spectra confirms the

presence of water molecules in these complex compounds.

The electronic absorption spectra are often very helpful in the evaluation of results furnished by other methods of structural investigation. The electronic spectral measurements were used to assign the stereochemistries of the metal ions in the complexes based on the positions and number of d-d transition peaks. The electronic absorption spectra of the ligand and its complexes were recorded in the 900-200 nm range, at room temperature.

The reflectance spectrum of the pink $\text{Co}(\text{II})$ complex displays an absorption band at 570 nm which can be attributed to the ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}(\text{P})$ (ν_3) transition, characteristic to $\text{Co}(\text{II})$ (d^7) ion in an octahedral environment (Figure 1a).²¹ With the increase of temperature, the color of complex varied from pink to blue, this fact indicating that the configuration of $\text{Co}(\text{II})$ changed from octahedral to tetrahedral. The UV-VIS spectrum of $\text{Co}(\text{UDC})_2$ obtained by heating of $\text{Co}(\text{UDC})_2 \cdot 3\text{H}_2\text{O}$ at $110 \text{ }^\circ\text{C}$ for two hours, exhibits a characteristic band in the range 500 – 700 nm (with a maximum at 615 nm). This band may be assigned to the ${}^4\text{A}_2(\text{F}) \rightarrow {}^4\text{T}_1(\text{P})$ (ν_3) transition characteristic to Co^{2+} (d^7) in tetrahedral configuration (Figure 1b).

The solid state electronic spectrum of $\text{Ni}(\text{II})$ complex exhibits the characteristic features of Ni^{2+} (d^8) ion in a distorted octahedral environment. The two bands located at 408 nm and 700 nm are assigned to the ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ (ν_2) and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$ (ν_3) transitions (Figure 2).

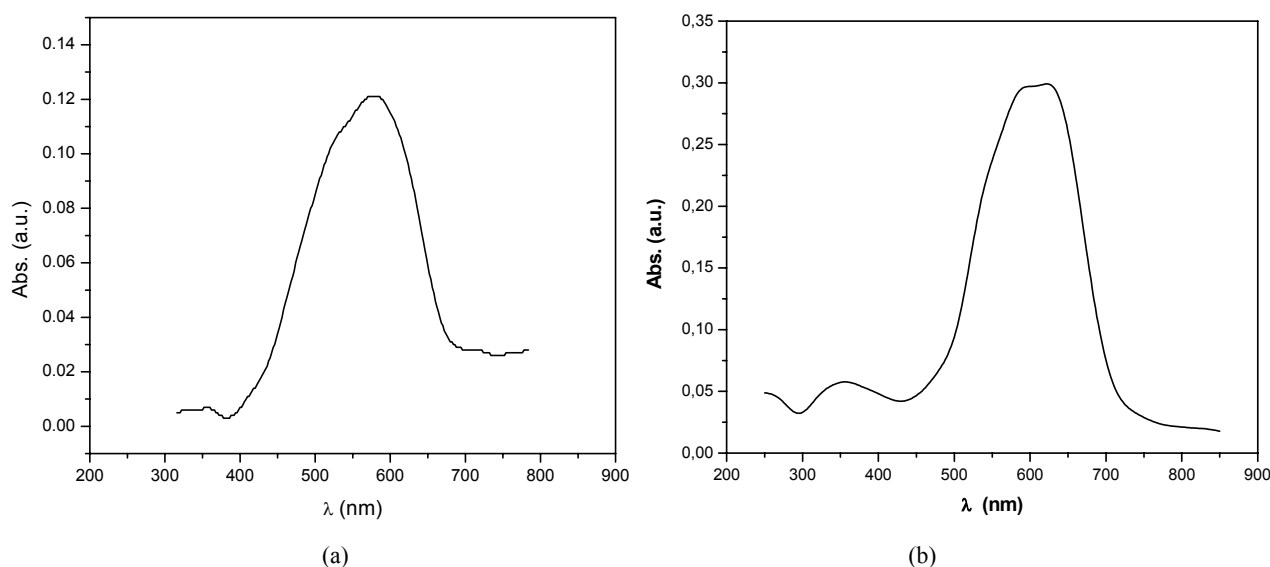
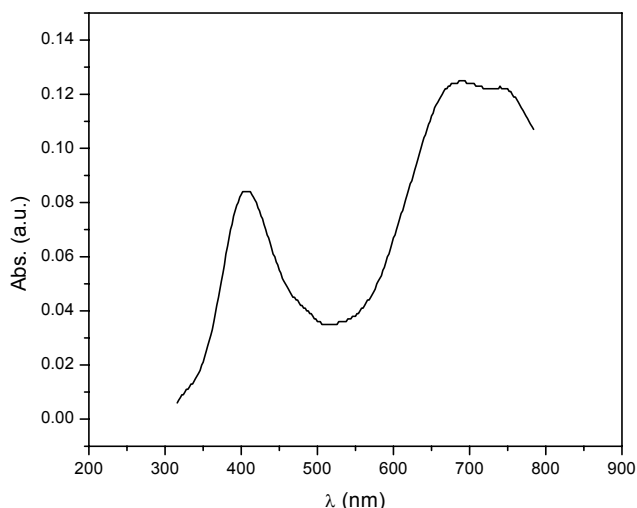
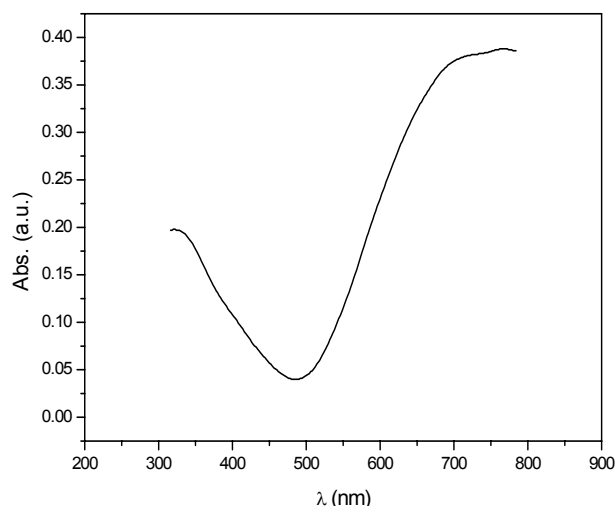


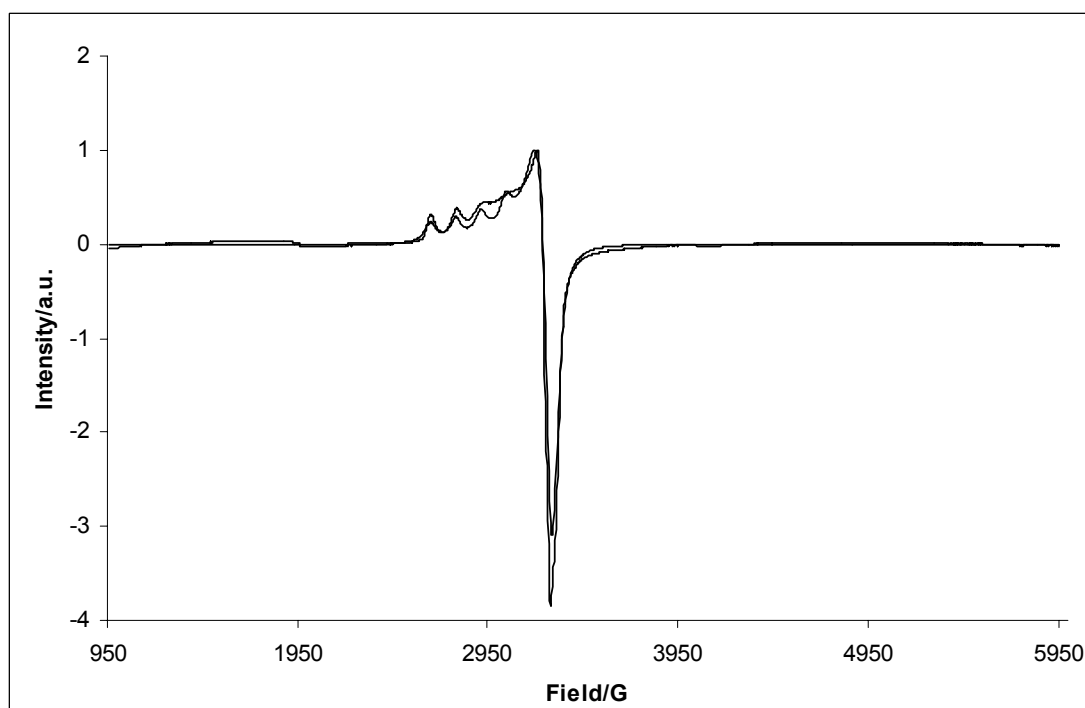
Fig. 1 – UV-VIS spectra of $\text{Co}(\text{UDC})_2 \cdot 3\text{H}_2\text{O}$ (Oh configuration) (a) and $\text{Co}(\text{UDC})_2$ (Td configuration) (b).

Fig. 2 – UV-VIS spectra of Ni(UDC)₂·11H₂O.Fig. 3 – UV-VIS spectra of Cu(UDC)₂·2H₂O.

The reflectance spectrum of Cu(UDC)₂·2H₂O consists in a broad absorption band centered at ~ 710 nm (Figure 3). The position and the intensity of this band suggest a distorted octahedral environment around the Cu(II) (d⁹) ion, most probably a square bipyramidal distorted one. The band is assigned to the ²E → ²A₁. Though three transitions are expected in this case (d_{xz}, d_{yz} → d_{x²-}

y², d_{xy} → d_{x²-y²) they are very close in energy and often appear in the form of one broad band envelope.²²}

The EPR spectrum of Cu(UDC)₂·2H₂O is shown in Figure 4 together with its simulated spectrum – the latter gives the following parameters g₁ = 2.0811, g₂ = 2.1035, g₃ = 2.3912 which confirm the geometry proposed for this compound.

Fig. 4 – EPR spectrum of Cu(UDC)₂·2H₂O at 10 K. Upper trace: experimental; lower trace: simulated spectrum with parameters g₁ = 2.0811, g₂ = 2.1035, g₃ = 2.3912.

The effective magnetic moment (μ = 5 BM) found for the Co(II) complex suggest a high spin octahedral arrangement (theoretical values 4.7 –

5.2 BM). The same geometry can be attributed to Ni(UDC)₂·11H₂O on the basis of magnetic moment value (μ = 3.30 BM). The Cu(II) complex shows a

slightly higher value (2.44 BM) of the magnetic moment as the one characteristic for a system with an unpaired electron (1.73 BM, $g = 2$). The Zn(II) complex is diamagnetic as expected for a d^{10} configuration (Table 1).²³

A series of investigations concerning the effects of the synthesized coordination compounds on viability and proliferation of cultured tumor and nontumor cells and also evaluation of their putative antiviral activity are in progress.

CONCLUSIONS

In this study, four coordination compounds of Co(II), Ni(II), Cu(II) and Zn(II) containing ursodeoxycholate anion as ligand have been synthesized and characterized by various physico-chemical methods. Molecular formulae were established correlating all these data. By analogy with the literature data, we concluded that in all the complexes, excepting $\text{Cu(UDC)}_2 \cdot 2\text{H}_2\text{O}$, both carboxylate groups coordinate to the metal ion in a pseudo-chelating mode, each of them through a water molecule. In case of $\text{Cu(UDC)}_2 \cdot 2\text{H}_2\text{O}$ one carboxylate group coordinates with Cu^{2+} in a monodentate mode and the other carboxylate group in a pseudo-chelating mode through a water molecule. The octahedral coordination geometries of metal ions are completed by hydroxyl groups of ursodeoxycholate anion in crystal. The magnetic moments confirm the stereochemistries proposed for these coordination compounds.

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