

Article

Thermodynamic Study on the Dissociation and Complexation of Coumarinic Acid with Neodymium(III) and Dioxouranium(VI) in Aqueous Media

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Abstract: In the frame of a systematic study on the sequestering ability of natural antioxidants towards metal cations, the complexation of coumarin-3-carboxylic acid (HCCA) with neodymium(III) and dioxouranium(VI) (uranyl, UO_2^{2+}), and overall stability constants of the resulting complexes, were evaluated from the pH-potentiometric titration data at 37 °C and in an aqueous solution (i.e., 0.16 mol/L NaClO_4). The graphic representation of the complex's concentration curves is given by the distribution diagrams, which provide a depiction of all the species present in the solution in the selected pH ranges. The protonation constant of HCCA was also determined to evaluate the competition of the ligand for the metal cations and H^+ . The ligand-to-metal concentration ratio was varied between 1 and 10, and the hydrogen ion concentration was decreased stepwise until the incipient precipitation of a basic salt of the metal, which occurred at different values depending on the specific metal cation and the ligand to metal ratio. Speciation profiles obtained by potentiometric titrations and supported by UV-Vis data show that a complexation occurs at a ligand-to-Nd(III) and to $-\text{UO}_2^{2+}$ ratio of 1:1 and 2:1, with different degrees of deprotonation: $\text{Nd}(\text{OH})(\text{CCA})^+$, $\text{UO}_2(\text{OH})(\text{CCA})$, $\text{UO}_2(\text{OH})_2(\text{CCA})^-$, and $\text{Nd}(\text{OH})(\text{CCA})_2$, $\text{UO}_2(\text{CCA})_2$ and $(\text{UO}_2)_2(\text{OH})_2(\text{CCA})_2$.

Keywords: coumarin-3-carboxylic acid; Nd(III) complexes; UO_2^{2+} complexes; sequestering ability; stability constants



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1. Introduction

The poisoning action of toxic metal ions represents one of the most important problems for health. In this context, metal chelation therapy was proposed more than 50 years ago for the treatment of pathologies produced in the body by an overload of a metal ion, and it is the most efficient therapeutic approach [1,2]. The choice of the most adequate chelating agent is related to the specificity and stability of the metal–chelator complexes. Metal chelation therapy involves the use of a chelating agent, which consists of an organic molecule that possesses a chelator located at one terminus of the agent and an active functionality located at the other end of the molecule to connect with the vector molecule [3]. Among chelators, the most used are macrocyclic ligands, which are to be preferred with respect to their acyclic counterparts from a thermodynamic and kinetic point of view. Their drawback is related to their slow binding kinetics, which necessitates high temperatures. Coumarin and its derivatives can form complexes with different metal ions, and therefore, in principle, can be used in specific chelation therapies. This class of ligands can form complexes with several toxic metal ions, and has attracted the interest of researchers, also in consideration of their antibiotic, anticoagulant, anticancer and anti-inflammatory properties [4]. Complexes of this class of ligands with several transitions, lanthanide and actinide metal ions have been studied previously to gain insight into their coordination chemistry and their biological activity [5–15]. Some reviews summarize the advances in various medicinal applications of metal complexes of coumarins [15–18]. It was reported that the biological activity of some

coumarin derivatives significantly improves by binding to metal ions; this behavior could be attributed to an increase in the lipophilicity of the systems. However, the relationship between the structure and properties of complexes is still unknown. Nevertheless, to achieve insight into the factors controlling the metal complex biological activity, it is first necessary to know the binding properties of coumarins to the metal ions. In 2001, attempts to determine the structure of a copper(II) complex of coumarin-3-carboxylic acid (HCCA), analyzing spectroscopic data, suggested a binuclear structure [4]. Synthesis was carried out using copper(II) chloride as the salt yielding a very insoluble product. Overall complexes of Ni(II), Co(II), Zn(II) and Mn(II) with HCCA were studied at experimental and theoretical levels. The complexes were characterized by elemental analyses, FT-IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and UV-Vis spectroscopy, and by magnetic susceptibility measurements [19]. Recently, we have reported on the complexation of HCCA with Al(III) and Fe(III), in aqueous solutions at 37 °C and in 0.16 M NaCl, to evaluate the selectivity of this ligand towards bioavailable metal cations [20].

HCCA exhibits two different coordination sites (Figure 1): it can play as monodentate or bidentate ligand via carboxylic moiety involving one or both oxygen atoms, respectively, as well as bidentate ligand through the lactone and the carboxylic oxygen to realize a high stabilized 6-membered metallocycle. Simultaneous bidentate and monodentate coordination mode by the free carbonyl oxygen was shown in the presence of lanthanides [12].

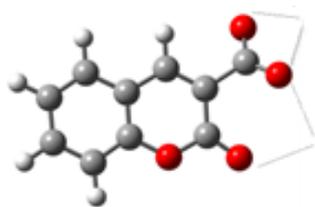


Figure 1. Coordination sites of HCCA.

In view of its potential application as a chelating agent, herein we present a study on the complexation ability of coumarin-3-carboxylic acid towards neodymium(III) and dioxouranium(VI) (uranyl, UO_2^{2+}) under the physiological conditions of temperature and ionic strength (i.e., 37 °C and 0.16 mol/L NaClO_4), evaluating the stability constants of the complexes and the corresponding structures by potentiometric measurements and UV-Vis spectrophotometry. This work is the first one entirely in an aqueous medium; although the ligand's antioxidant activity involves water as a natural solvent in the biological media, most of the studies reported in the literature refers to measurements carried out in mixed solvents, due to the low solubility in water of HCCA.

2. Materials and Methods

2.1. Chemicals

Sodium hydroxide titrant solutions, perchloric acid and sodium perchlorate stock solutions were prepared and standardized as previously described [21]. Neodymium and uranyl perchlorate stock solutions were prepared and standardized as reported previously [22]. HCCA ($\geq 99\%$, Sigma–Aldrich, Munich, Germany), kept in a desiccator over silica gel, was used without further purification. The ionic strength of all the solutions was adjusted to 0.16 mol/L at 37 °C by adding the appropriate amount of NaClO_4 as the background electrolyte. All solutions were freshly prepared with double-distilled water.

2.2. Potentiometry and Spectrophotometry

The potentiometric apparatus used to carry out the titrations was described previously [21]. The glass electrodes were manufactured by Metrohm (Swiss) and acquired, after the addition of the reagents, a constant potential within 45–60 min that remained unchanged within ± 0.01 mV. To avoid carbonate interference, a slow stream of nitrogen

gas was passed into the test solutions, kept under magnetic stirring during titrations. The cell assembly was placed in a thermostat kept at $(37.0 \pm 0.1)^\circ\text{C}$.

The complexation equilibria were studied, at 37°C and in $0.16\text{ mol/L NaClO}_4$, by measuring, with a glass electrode (GE), the competition of HCCA for H^+ and metal cations. Measurements were performed as potentiometric titrations with cell (G)



in which RE is the reference electrode ($\text{Ag} \mid \text{AgCl} \mid 0.01\text{ mol/L NaCl} \mid 0.15\text{ mol/L NaClO}_4 \mid 0.16\text{ mol/L NaClO}_4$) and the Test Solution contained $C_M\text{ mol/L M}(\text{ClO}_4)_n$ (i.e., $\text{Nd}(\text{ClO}_4)_3$ and $\text{UO}_2(\text{ClO}_4)_2$), $C_L\text{ mol/L HCCA}$, $C_A\text{ mol/L HClO}_4$, $C_B\text{ mol/L NaOH}$, and $(0.16 - nC_M - C_A - C_B)\text{ mol/L NaClO}_4$. The EMF of cell (G) can be written, in mV, at the temperature of 37°C , as Equation (1):

$$E = E^\circ + 61.54 \log[\text{H}^+] + E_j \quad (1)$$

where E° was constant for each series of measurements and E_j is the liquid junction potential, which is a function of $[\text{H}^+]$ only [23]. E_j value under our experimental conditions (i.e., 37°C and $0.16\text{ mol/L NaClO}_4$) was determined by acid-base titration with cell (G) when metal ions and HCCA were absent. The data for $[\text{H}^+] \leq 0.100\text{ mol/L}$ could be well approximated by the linear slope $E_j([\text{H}^+])_I = -j_I[\text{H}^+]$. The value of j (mV/M) is 337 ± 1 .

Each titration was divided into two parts. In the first part, E° was determined in the absence of HCCA and metal cations; in the $[\text{H}^+]$ range 10^{-4} – 10^{-2} mol/L values constant to within 0.1 mV were calculated according to the Gran's method [24,25]. In the second part, after the addition of the reagents, the acidity was stepwise decreased by adding known volumes of NaOH standard solution. The concentration of HCCA (C_L) was varied within 1 and $5 \cdot 10^{-3}\text{ mol/L}$, while the concentration of metal ions (C_M) ranged within 0.5 and $5 \cdot 10^{-3}\text{ mol/L}$, and the ligand to metal concentration ratio was varied within 1 and 10 . The hydrogen ion concentration was varied from $1 \cdot 10^{-2}\text{ mol/L}$ (pH 2.0) to incipient precipitation of a neutral salt, which takes place in the range $[\text{H}^+] = (3.2\text{--}0.032) \cdot 10^{-5}\text{ mol/L}$ (pH 4.5–6.5) depending on the specific metal ion and on the ligand-to-metal ratio. The primary C_M , C_L , C_A , C_B and $[\text{H}^+]$ data form the basis of the treatment to obtain the stability constants.

The spectrophotometric measurements were carried out with a Varian Cary 50 Scan UV Visible Spectrophotometer. Absorbance values between 210 and 450 nm were measured each 1 nm . The temperature of the cell holder was kept at $(37.0 \pm 0.3)^\circ\text{C}$ by a Grant circulating water bath. Matched quartz cells of thickness 1 cm were employed. The absorbance, A_λ , was recorded to 0.001 units. The acquisition of data was controlled with the aid of a computer connected to the instrument.

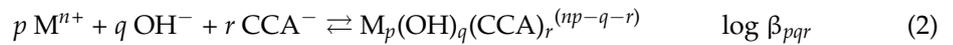
2.3. Synthesis of the Complexes

An amount of 0.560 g of $\text{Nd}(\text{ClO}_4)_3$ (0.119 mmol) and 0.435 g of $\text{UO}_2(\text{ClO}_4)_2$ (0.2196 mmol) stock solutions were added to 10.0 mg (0.0521 mmol) and 5.0 mg of coumarin-3-carboxylic acid, respectively, and then dissolved in water (i.e., 100 mL) under constant stirring and at 37°C over a period of 24 h .

Taking into account the distribution diagrams of the metal ions in the presence of HCCA, the pH of these solutions was controlled (i.e., pH = 6 and pH = 4 for neodymium and uranyl, respectively). The complexation resulted in pallid yellow aqueous solutions and two solids, white for neodymium and orange for uranyl, the latter removed by filtration. Aqueous solutions, as well as solids, dissolved in DMSO, and opportunely diluted with water, were analyzed by UV-Visible spectroscopy.

3. Results

The experimental data (C_M , C_L , C_A , C_B , $[H^+]$), processed by graphical, as well as numerical procedures, were explained according to the general equilibrium reported in the Equation (2):



The graphical methods consist essentially in the comparison of experimental plots with model functions [26]. To explain the experimental data, the simple hypothesis was made that the main reaction products are binary ($q = 0$) complexes, mononuclear in metal ion ($p = 1$), formed according to equilibrium (3):



The validity of this assumption was tested by constructing the graphs Z as a function of $\log ([HCCA]/[H_3O^+])$ from the primary data. Z represents the average number of ligand for metal ion, as reported in Equation (4):

$$Z = (C_A - [HCCA] - [CCA^-])/C_B \quad (4)$$

Thus, when complexes of general formula $M(CCA)_r^{(n-r)}$ predominate, the points Z versus $\log ([HCCA]/[H_3O^+])$, at different C_L and C_M , should fall on a unique curve. The experimental functions Z for Nd^{3+} -HCCA and UO_2^{2+} -HCCA are reported in Figure 2a,b, respectively.

Table 1. Formation of complexes of coumarin-3-carboxylic acid with Nd^{3+} and UO_2^{2+} according to Equation (2). Values of $\log \beta$ in $NaClO_4$ 0.16 mol/L at 37 °C were obtained by numerical procedure. Standard deviations are reported as 3σ .

Metal Ions	Species	$\log \beta \pm 3\sigma$
Nd^{3+}	$Nd(OH)(CCA)^+$	9.2 ± 0.1
	$Nd(OH)(CCA)_2$	11.9 ± 0.3
UO_2^{2+}	$UO_2(CCA)_2$	8.2 ± 0.1
	$UO_2(OH)(CCA)$	13.0 ± 0.3
	$UO_2(OH)_2(CCA)^-$	21.6 ± 0.1
	$(UO_2)_2(OH)_2(CCA)_2$	28.9 ± 0.3

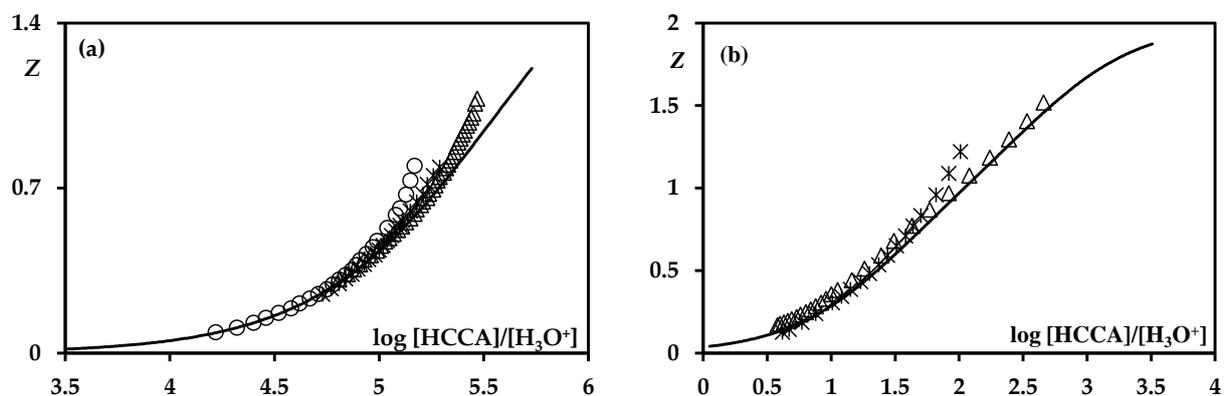


Figure 2. Z as a function of $\log([HCCA]/[H_3O^+])$ for (a) Nd^{3+} -HCCA and (b) UO_2^{2+} -HCCA systems. Triangles (0.5, 5); diamond (5, 5); circles (1, 2). The curve was calculated with the constants obtained by numerical treatment and reported in Table 1.

As Figure 2 shows, most of the experimental points fall on a unique curve, which tends to 2, though a careful inspection of the graphs shows that small, but systematic, deviations from the model including only simple complexes were observed. These deviations

were evidence that some additional species are present. The probable composition of the complexes, responsible for these deviations, was obtained by numerical treatment by the least-square program SUPERQUAD [27], to seek the minimum of the function:

$$U = \sum (E_i^{\text{obs}} - E_i^{\text{cal}})^2 \quad (2)$$

where $E^{\text{obs}} = E + j [\text{H}_3\text{O}^+] = E^\circ + 0.06154 \log [\text{H}_3\text{O}^+]$ and E^{cal} is a value calculated for a given set of parameters.

The most probable p , q and r values and the corresponding constants $\log \beta_{pqr}$ (Equation (2)) were achieved by varying systematically the stability constants of a chosen ternary species (p, q, r) to obtain the best data fitting. In the numerical treatments, the acidic constant of coumarin-3-carboxylic acid, according to equilibrium (5) and reported with the relative standard deviation (3σ), was kept invariant.



This constant, unknown from the literature, was determined by potentiometric measurements under the same experimental conditions used for the evaluation of the stability constants between ligand and metal ions (i.e., at 37 °C and in 0.16 mol/L NaClO_4).

Considering the low solubility of HCCA in an aqueous solution [20], all the experiments were carried out by adding an exactly weighed quantity of solid ligand in the titration's apparatus. When equilibria (2) and (5) take place, HCCA dissolved into the aqueous medium. In the numerical treatment, the constants of the predominant hydrolysis products of Nd^{3+} and UO_2^{2+} , taken from the literature [28], (i.e., $\text{Nd}(\text{OH})^{2+}$ and $\text{Nd}_2(\text{OH})_2^{4+}$, $(\text{UO}_2)_2(\text{OH})_2^{2+}$, $(\text{UO}_2)_3(\text{OH})_5^+$, $\text{UO}_2(\text{OH})^+$ and $(\text{UO}_2)_3(\text{OH})_4^{2+}$, respectively), were kept invariant and were used to construct the distribution diagrams reported in Figure 3a,b. In the construction of these diagrams, the same pH range investigated for the study of the complexes was considered. As can be seen in Figure 3a, the only hydrolytical species of neodymium is $\text{Nd}(\text{OH})^{2+}$, which nevertheless does not reach percentages greater than 10%. In regard to uranyl ion (Figure 3b), the complexes $(\text{UO}_2)_2(\text{OH})_2^{2+}$ and $(\text{UO}_2)_3(\text{OH})_5^+$ are the predominant hydrolytical species, while $(\text{UO}_2)_3(\text{OH})_4^{2+}$ and $\text{UO}_2(\text{OH})^+$ are minor species, with percentages that do not exceed 10% and 1%, respectively.

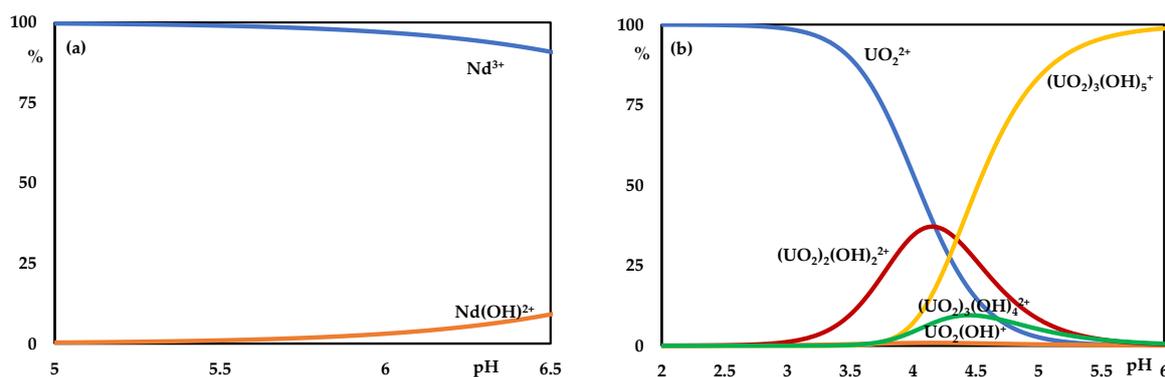


Figure 3. Distribution diagrams of hydrolytical species of (a) Nd^{3+} ($C_M = 1.0$ mM) and (b) UO_2^{2+} ($C_M = 2.5$ mM).

The results obtained for the neodymium- and uranyl-HCCA systems are reported in Table 1. For the neodymium-HCCA system, experimental data were explained with the formation of one complex, and the best minimum was obtained with the $\text{Nd}(\text{OH})\text{CCA}^+$ species. A substantial decrease in the square error sum U (66.85%) was obtained considering also the presence of $\text{Nd}(\text{OH})(\text{CCA})_2$. No other complexes improved the fit.

Moreover, the uranyl-HCCA system data were explained with one complex: the best model comprised $\text{UO}_2(\text{CCA})_2$. Different models that consider the presence of two species were also tested; among these, the best fit was obtained with the presence of $\text{UO}_2(\text{CCA})_2$ and $\text{UO}_2(\text{OH})(\text{CCA})$, which corresponds to a decreasing of U (57%). A lower

error square sum (71%) was still obtained on adding the species $\text{UO}_2(\text{OH})_2(\text{CCA})^-$. Finally, the inclusion of the polynuclear complexes $(\text{UO}_2)_2(\text{OH})_2(\text{CCA})_2$, though present in small amounts, lowers the minimum of the square error sum by more than 40%. No other species, introduced to improve the fit, was retained. Speciation profiles show that in an aqueous solution a complexation occurs at 1:1 and 2:1 ligand-to-cations ratio with different degrees of deprotonation for both cations. A direct comparison between species with the same stoichiometry shows that the complex of uranyl is more stable than that of neodymium (i.e., 13.0 vs. 9.2).

4. Discussion

In this work, we have investigated the acid–base equilibrium of coumarinic acid and the chelating properties of its deprotonated form towards neodymium and uranyl at 37 °C and in 0.16 mol/L NaClO_4 . Coumarinic acid anion forms 1:1 and 2:1 complexes with both metal ions. The uranyl ion is also capable to form a polynuclear complex with stoichiometry 2:2. Furthermore, from the data reported in Table 1, it may be noted that the complex $\text{UO}_2(\text{OH})(\text{CCA})$ is stronger than the corresponding neodymium species, $\text{Nd}(\text{OH})(\text{CCA})^+$.

The stability constants reported in Table 1 were used to represent the distribution diagrams (Figure 4a,b), in which the percentage of metal cations into the complexes as a function of pH is depicted.

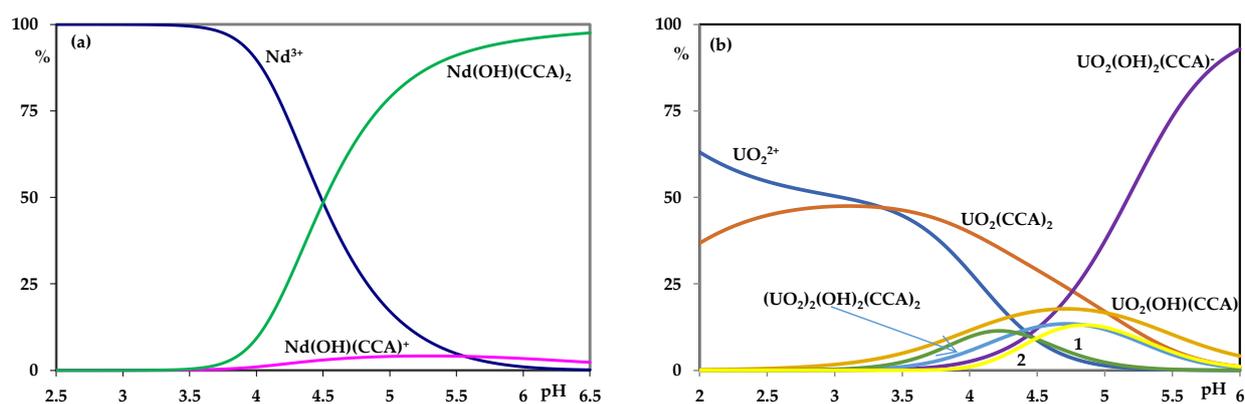


Figure 4. Distribution diagrams in the presence of HCCA of (a) Nd^{3+} ($C_M = 1.0$ mM and $C_L = 2.0$ mM) and (b) UO_2^{2+} ($C_M = 2.5$ mM and $C_L = 2.5$ mM). One (green line) and 2 (yellow line) in (b) are the hydrolytical species $(\text{UO}_2)_2(\text{OH})_2^{2+}$ and $(\text{UO}_2)_3(\text{OH})_5^+$, respectively.

As can be seen in Figure 4a, the complexation between HCCA and Nd(III) starts at a pH higher than 3.5 with the neutral species $\text{Nd}(\text{OH})(\text{CCA})_2$, which is predominant in the whole pH range. The complex $\text{Nd}(\text{OH})(\text{CCA})^+$, instead, is a minor species with a percentage that does not reach values higher than 5%. The neodymium hydrolytical species $\text{Nd}(\text{OH})^{2+}$ does not exist in the pH range investigated, supporting that the complexes between the ligand and metal ion could also involve the hydroxyl group.

Regarding the system UO_2^{2+} -HCCA (Figure 4b), all of the complexes reach significant percentages. The complexation starts from pH 2 with the formation of the neutral species $\text{UO}_2(\text{CCA})_2$, which is predominant until pH 5. The anionic complex $\text{UO}_2(\text{OH})_2(\text{CCA})^-$ is the main from pH 5, while the other two minor species, $(\text{UO}_2)_2(\text{OH})_2(\text{CCA})_2$ and $\text{UO}_2(\text{OH})(\text{CCA})$, start to have significant percentages at the same pH value (i.e., 4) and coexist in the whole investigated pH range. As can be seen in Figure 4b, the percentage of the predominant uranyl hydrolytical complexes, $(\text{UO}_2)_2(\text{OH})_2^{2+}$ and $(\text{UO}_2)_3(\text{OH})_5^+$, decreases drastically in the presence of coumarin-3-carboxylic acid, confirming that the complexes between UO_2^{2+} and HCCA could be mixed species involving hydroxyl ion too.

To verify the effective formation of the complexes, a comparison of the UV-Vis spectra for free ligand and coordinated species is reported in Figure 5.

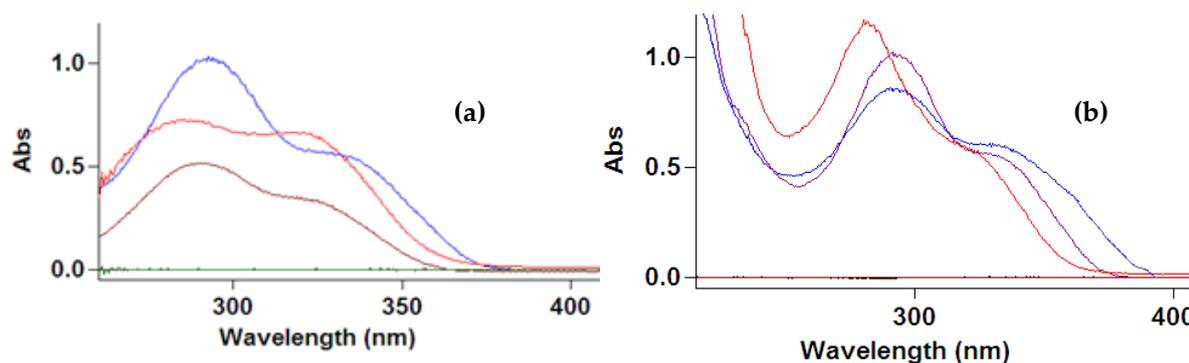


Figure 5. UV-Vis spectra of (a) Nd^{3+} -HCCA: free ligand (blue line), solution (brown line) and solid (red line); (b) UO_2^{2+} -HCCA: free ligand (violet line), solution (red line) and solid (blue line).

According to the literature [19], the UV-Vis spectrum of free coumarin-3-carboxylic acid shows two characteristic absorption bands, at 333 nm (low intensity) and 292.5 nm. The addition of the metal cations, Nd^{3+} or UO_2^{2+} , in the aqueous suspension containing HCCA, brought solid ligand into the aqueous phase as soluble complexes. Figure 5 shows the absorption spectra of the Nd^{3+} -HCCA (brown line in Figure 5a) and UO_2^{2+} -HCCA (red line in Figure 5b) complexes. Due to the low electronic rearrangement, which is induced on the ligand upon complex formation, the free ligand absorption spectrum was not significantly affected by the complexation.

Indeed, the band at 333 nm undergoes, in both spectra, a slight blue shift (i.e., at 320 nm). The most interesting spectral change can be detected for the band at 292.5 nm, which undergoes a significant hypsochromic shift, especially for the uranyl system (i.e., at 280 nm). As a further product of both syntheses, a solid was obtained, which was dissolved in a 1:1 ethanol:water mixture and analyzed, after the appropriate dilution with water, spectrophotometrically (red line in Figure 5a and blue line in Figure 5b). The UV-Vis spectra of these complexes show analogous spectral features to those analyzed before, suggesting that these insoluble species are formed by the soluble complexes, possibly upon the additional inclusion of a ligand or a hydroxide in the metal coordination sphere, in order to obtain a neutral species of the type $\text{M}_p(\text{OH})_q(\text{CCA})_r$.

All the complexes' spectra contain a broad band in the UV region (i.e., at $\lambda = 320$ nm), with tailing into the visible region. These bands were assigned to a ligand to metal charge transfer transition.

The molar absorption coefficients of the complexes are reported in Figure 6: for the two complexes of neodymium, i.e., $\text{Nd}(\text{OH})(\text{CCA})^+$ and $\text{Nd}(\text{OH})(\text{CCA})_2$, ϵ values of 5870 and $4360 \text{ M}^{-1}\text{cm}^{-1}$, respectively, were recorded at λ_{max} of 290 nm. Higher ϵ values are obtained for the uranyl-HCCA system, which are $4 \cdot 10^5$ for the neutral species and $7 \cdot 10^5$ for the charged one.

Our results can only be partially compared with those proposed by Georgieva et al. [15] and by Martin et al. [29]; in these works, the complex of formula $\text{Nd}(\text{CCA})_2(\text{NO}_3)(\text{H}_2\text{O})$ was synthesized and characterized by spectroscopic and computational methods. According to our hypothesis, the spectroscopic results suggest that CCA^- is bidentate bound to the metal ion through the carboxylic and the carbonylic moiety. The model calculations of both bidentate modes of CCA^- to $\text{Nd}(\text{III})$ showed that the bidentate binding form through the carboxylic and the carbonylic oxygen atoms is energetically preferred as compared to that through both the carboxylic atoms.

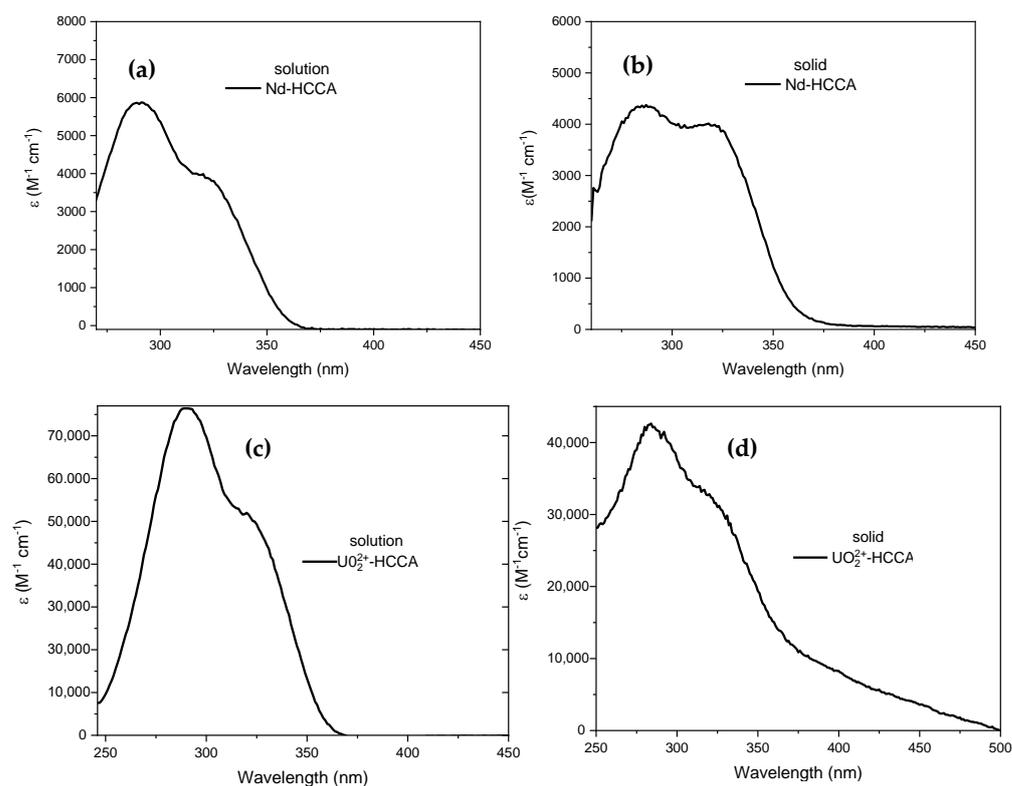


Figure 6. Absorption spectra of (a,b) neodymium-HCCA and (c,d) uranyl-HCCA complexes, obtained by analyzing solution and solid, respectively.

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