

Stability of the complexes of some lanthanides with coumarin derivatives. I. Cerium(III)-4-methyl-7-hydroxycoumarin

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A complex of cerium(III) with 4-methyl-7-hydroxycoumarin was synthesized by mixing water solutions of cerium(III) nitrate and 4-methyl-7-hydroxycoumarin sodium salt in a metal-to-ligand molar ratio of 1:2. The complex was characterized and identified by elemental analysis, conductometry, IR, ¹H and ¹³C NMR-spectroscopy, mass spectral data, DTA and TGA. Thermal analysis of the complex indicated the formation of a compound of the composition CeR₂(OH)·5H₂O, R standing for the ligand.

The reaction of cerium(III) with 4-methyl-7-hydroxycoumarin was studied in detail by the spectrophotometric method. The stepwise formation of two complexes, *vis.*, CeR²⁺ and CeR₂⁺, was established in the pH region studied. The equilibrium constants for 1:1 and 1:2 complexes were determined to be 10.72 and 9.22, respectively.

Keywords: Ce(III)-4-methyl-7-hydroxycoumarin, complex stability

Coumarin derivatives are of interest because of their physiological, photodynamic, anticoagulant, spasmolytic, bacteriostatic and antitumor activity (1). They are also extensively used as analytical reagents. Coumarins and their derivatives have been studied extensively for their complexation with metal ions (2). A number of dioxouranium(VI) and titanium(IV) complexes with hydroxycoumarins, *e.g.*, 3-hydroxycoumarin and 7,8-dihydroxy-4-methylcoumarin, *etc.*, have been studied spectrophotometrically and it has been observed that depending upon pH, 1:1, 1:2 and 1:3 complexes are formed in the solution (3, 4).

8-Substituted-4-methyl-7-hydroxycoumarin (5–7) and 6-substituted-4-methyl-7-hydroxycoumarin (8) have been investigated for their complexing ability. These coumarin derivatives have been found to exhibit anticoagulant and plant growth regulating properties (9). 4-Methyl-7-hydroxycoumarin complexes with several metals might be applicable as anticoagulants and spasmolytic agents (10).

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The complexes of rare earth ions have aroused much interest. Cerium ion is a subject of increasing interest in bioinorganic and coordination chemistry (11, 12).

As a result of our earlier work, the cytotoxic profile of some complexes of 4-methyl-7-hydroxycoumarin, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-1-benzopyran-2-one, 4-hydroxy-3-[1-(4-chlorophenyl)-3-oxobutyl]-2*H*-1-benzopyran-2-one and 4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2*H*-1-benzopyran-2-one with lanthanides against P3HR1, K-562 and THP-1 cell lines has been proven (13–15).

Although solution chemistry of transition metal complexes with 4-methyl-7-hydroxycoumarin, substituted at positions 3, 6 or 8, has been reported, no work has been done on the synthesis and structural aspects of solid complexes of 4-methyl-7-hydroxycoumarin sodium salt.

In the present investigation, complexation reaction of cerium(III) with 4-methyl-7-hydroxycoumarin has been studied. The pharmacological properties of cerium(III) complex with 4-methyl-7-hydroxycoumarin have already been reported (13). This compound was assayed for acute intraperitoneal and peroral toxicity, influence on blood clotting time and for spasmolytic activity and showed marginal cytotoxic activity against transformed leukemic cell lines (P3HR1 and THP-1) as compared to cerium(III) nitrate.

EXPERIMENTAL

Reagents

The compounds used to prepare the solutions were Merck (Germany) products, *p.a.* grade: $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ and 4-methyl-7-hydroxy-2*H*-1-benzopyran-2-one (4-methyl-7-hydroxycoumarin) (Mendiaxon, Hymecromone). 4-Methyl-7-hydroxy-2*H*-1-benzopyran-2-one sodium salt (Mendiaxon sodium) was used as a ligand. Mendiaxon sodium was prepared by the following procedure: 4-methyl-7-hydroxycoumarin (1.76 g, 10 mmol) was added to sodium hydroxide (0.038 g, 9.5 mmol) in 30 mL water. The mixture was stirred vigorously at room temperature for an hour until it got clear. The solution was filtered and the filtrate was evaporated to dryness by a vacuum evaporator. The viscous residue was recrystallized from ethyl acetate (yield 1.7 g, 86 %, m.p. > 300 °C). Purity control was performed by TLC on Alufolien Kieselgel 60 F₂₅₄, 0.2 mm thickness with fluorescent indicator (Merck, Germany) (mobile phase: hexane/acetone, 2:1).

The complex was synthesized by mixing water solutions of Ce(III) salt and the ligand, in a metal to ligand molar ratio of 1:2. The reaction mixture was stirred with an electromagnetic stirrer at 25 °C for one hour and a precipitate was obtained. It was filtered, washed several times with water and dried in a desiccator to a constant mass.

The complex of Ce(III) with 4-methyl-7-hydroxycoumarin was insoluble in water, slightly soluble in methanol and ethanol and freely soluble in DMSO. Its physicochemical characteristics, such as the melting point and molar conductance, were measured.

Analytical methods and instruments

Carbon and hydrogen were determined by elemental analysis using Vario EL V2.3 CHNS Modus (Elementar Analysen Systeme, Germany).

Melting points were determined using a Boetius melting point apparatus (Boetius Franz Kustner, Germany) and are uncorrected.

Al-foils Kieselgel 60 F₂₅₄ (Merck, Germany) developed by cyclohexane/chloroform/acetic acid (10:10:4, V/V/V) were used for TLC purity control at 254 nm.

The metal ion was determined after mineralization and thermogravimetrically. The presence of the sodium ion was checked by means of flame photometry (Perkin-Elmer 5000 AA, USA).

Water content was determined by Metrohm (Switzerland) E55 Karl Fisher Titrator and thermogravimetrically.

DTA and TGA analyses were carried out using a derivatograph produced by MOM (Hungary). Samples with particles smaller than 0.25 mm were placed in platinum crucibles. The heating rate was 10 °C min⁻¹ up to 900 °C. The inert substance was Al₂O₃.

Conductometric measurements were carried out in 10⁻³ mol L⁻¹ solutions in DMSO at 25 °C by a Metrohm 660 AG-9101 conductometer with a platinum electrode and a cell with the cell constant of 0.79 cm⁻¹.

IR spectra (Nujol) were recorded on a IR-spectrometer FTIR-8101M Shimadzu (Japan) (range 3800–4000 cm⁻¹).

¹H NMR and ¹³C NMR spectra were recorded at room temperature in DMSO-d₆ on a Bruker WP 100 (100 MHz) spectrometer (Germany) and a Bruker 250 WM (62.9 MHz) spectrometer, respectively. Chemical shifts are given in ppm, downfield from TMS.

Mass spectra were recorded on a Jeol JMS D 300 double focusing mass spectrometer (Japan) coupled to a JMA 2000 data system. The compounds were introduced with a direct inlet probe, heated from 50 °C to 400 °C at a rate of 100 °C min⁻¹. The ionization current was 300 mA, the accelerating voltage 3 kV and the chamber temperature 150 °C.

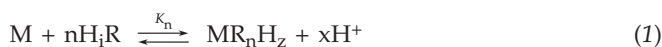
Stability constants

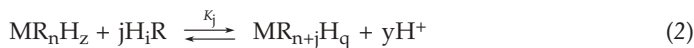
The pH of the solutions was adjusted using sodium hydroxide and nitric acid of concentrations low enough not to affect ionic strength. The ionic strength of solutions was maintained constant at 0.01 mol L⁻¹ using 1 mol L⁻¹ KNO₃ solution.

A Metrohm 744 pH-meter and a Hewlett-Packard 8452 A diode array spectrophotometer (Germany) were employed for pH and absorption measurements, respectively. Five determinations of each pH value and the respective spectra were recorded.

Computational approach

The system Ce(III)-4-methyl-7-hydroxycoumarin was investigated spectrophotometrically, assuming the following general equilibria in solutions using the excess of the ligand:





where M is the metal ion, H_iR is a ligand, MR_nH_z and MR_{n+j}H_q are the complexes, K_n and K_j are equilibrium constants of complexes MR_nH_z and MR_{n+j}H_q, respectively, x = ni-z, y = ji-q are stoichiometry coefficients.

The following straight line equations were then derived and used to interpret the above complexation equilibria:

$$A = \varepsilon_1 c_M - [\text{H}]^x A / c_R^n K_n \quad (3)$$

$$A = \varepsilon_1 c_M + c_R^j (\varepsilon_2 c_M - A) K_j / \text{H}^j \alpha^j \quad (4)$$

$$A = \varepsilon_2 c_M - [\text{H}]^y \alpha^j (A - \varepsilon_1 c_M) K_j c_R^j \quad (5)$$

where A is absorbance, ε₁ and ε₂ are molar absorptivities of complexes MR_nH_z and MR_{n+j}H_q, respectively, c_M is the concentration of the metal, c_R is the concentration of the ligand, and α^j = 1 + K_{ai}/H ± 1, where K_{ai} is the dissociation constant of the ligand.

According to equations (3) to (5) various functions such as A vs. A(H)^x, A vs. (ε₂ c_M - A)/[H]^y α^j or A vs. [H]^y α^j/(A - ε₁ c_M) were computed from the absorbance values at different pH values in solutions with the excess of the ligand; these were plotted to get the values of ε₁ and ε₂. The calculated true values of ε₁ and ε₂ were inserted in appropriate logarithmic equations (6) and (7):

$$\log (A / (\varepsilon_1 c_M - A) + n \log x = n \log c_R + x \text{ pH} + \log K_n \quad (6)$$

$$\log (A - \varepsilon_1 c_M) / (\varepsilon_2 c_M - A) + j \log y = j \log c_R + y \text{ pH} + \log K_j \quad (7)$$

Accurate values of x and y follow from the slope of these plots for solutions with a constant excess of the ligand.

A set of absorbance-pH curves was established for solutions having equal values of absorbance ε = (A - A_{OR})/c_M (where A_{OR} is absorbance due to the ligand). Under such conditions simple logarithmic plots, *i.e.* pH vs. log c_R, are valid, whose slopes give directly the ratio of the number of coordinated ligands to that of the protons liberated during complexation:

$$\text{pH} = n/x (-\log c_R + \log \alpha) + \text{constant} \quad (8)$$

$$\text{pH} = j/y (-\log c_R + \log \alpha) + \text{constant} \quad (9)$$

The nuclearity of the complex was examined plotting (A - A_{OR})/c_M = f(pH) for various c_M values. The slope of these curves was found to be independent of the metal ion concentration so that m - 1 = 0 and m = 1 in eq. (10). If the slope of such plots reaches α, only a mononuclear complex is formed:

$$\text{pH} = (m-1)/n(-\log c_M) + \text{constant} \quad (10)$$

The same forms of equations (3) to (7) were used for the interpretation of absorbance as a function of the increasing ligand concentration at constant pH. The number of coordinated ligands was derived from the plots of A vs. A/c_R^n , A vs. $c_R^j/(\varepsilon_2 c_M - A)$ or A vs. $(A - \varepsilon_1 c_M)/c_R^j$.

RESULTS AND DISCUSSION

Physicochemical and spectral evidence

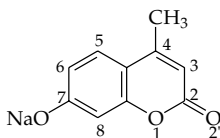
Elemental analysis of $\text{CeR}_2(\text{OH}) \cdot 5\text{H}_2\text{O}$ ($\text{R} = \text{C}_{10}\text{H}_7\text{O}_3^-$) gives the following calculated/found percentage: C 40.20/39.71, H 4.19/3.77, Ce 23.45/24.80, H_2O 15.07/15.00. Molar conductivities of the above complex and of the ligand are $2.11 \text{ S cm}^2 \text{ mol}^{-1}$ and $39.6 \text{ S cm}^2 \text{ mol}^{-1}$, respectively, indicating that the complex is a non-electrolyte. Melting point of the complex is 162°C and that of the ligand is $> 300^\circ\text{C}$.

There is a clear endothermic effect ($\sim 120^\circ\text{C}$) at the beginning of the DTA-curve of the complex, which is due to the hygroscopic moisture released. A steady mass loss is recorded on heating up to $\sim 230^\circ\text{C}$, which corresponds to the elimination of 5 molecules of water per molecule of the cerium(III) complex. This mass loss correlates with the Karl Fisher analysis and the endothermic effect intensity. On heating the complex, the decomposition step corresponds to the loss of ligand molecules, which is in agreement with the composition of the complex. Exothermic effect ($500\text{--}550^\circ\text{C}$) dominates in the thermogram of the complex, resulting from the decomposition of organic matter. A further mass loss recorded up to 900°C indicates the formation of a thermally stable metal oxide.

The mode of binding of the ligand to Ce(III) was elucidated by recording the IR spectra of the complex as compared with the spectra of the free ligand. The bands of the ligand appear at 3655, 1726, 1603, 1576, 1290, 1140, 1070–976, 831, 613 and 484 cm^{-1} . The band at 1726 cm^{-1} can be attributed to the stretching vibrations of the carbonyl group; two bands at 1603 and 1576 cm^{-1} can be related to the stretching vibrations of the conjugated system. A broad band, characteristic of ν_{OH} of coordinated water was observed in the range $3500\text{--}3400 \text{ cm}^{-1}$ in the spectrum of the complex. The weak band observed at 3655 cm^{-1} in the spectrum of the free ligand was shifted to a lower wavenumber (3490 cm^{-1}) in the complex. This assignment is corroborated by the occurrence of the corresponding rocking mode in the range $840\text{--}830 \text{ cm}^{-1}$. The C=O band at 1726 cm^{-1} exhibits a shift of $50\text{--}60 \text{ cm}^{-1}$ to lower wavenumber values on complexation, which may be taken as evidence for the participation of the C=O group in coordination. The most notable change observed upon complex formation is a shift of the C=O stretch to a lower frequencies. The C–C and C–O stretch and the C–O–C band are all shifted to higher frequencies (1277 , 1159 and 1076 cm^{-1}) in the complex. Similar frequency shifts were observed for the other complexes and are attributed to complexation of the positive ion with the carbonyl oxygen (16).

Coordination of metal ion with ligand through oxygen atom of C=O group was documented owing to data of ^1H NMR and ^{13}C NMR spectra (Tables I and II).

Table I. ^1H NMR spectra of 4-methyl-7-hydroxycoumarin sodium salt and its Ce(III) complex



$\text{C}_n\text{-H}$	Multiplicity of the signal	δ (ppm)	
		Ligand ($\text{C}_{10}\text{H}_7\text{O}_3\text{Na}$)	Ce(III) complex
$\text{C}_8\text{-H}$	s, 1H	5.9	6.8
$\text{C}_6\text{-H}$	d, 1H, $J = 7$ Hz	6.2	6.9
$\text{C}_5\text{-H}$	d, 1H, $J = 7$ Hz	7.2	7.7
$\text{C}_3\text{-H}$	s, 1H	5.5	6.1
CH_3	s, 3H	2.1	2.3

Table II. ^{13}C NMR spectra of 4-methyl-7-hydroxycoumarin sodium salt and its Ce(III) complex

C_n	δ (ppm)	
	Ligand ($\text{C}_{10}\text{H}_7\text{O}_3\text{Na}$)	Ce(III) complex
CH_3	18.08	18.11
C_5	101.44	102.18
C_3	103.03	110.25
C_4	104.13	111.91
C_6	118.66	112.87
C_8	125.03	126.63
$\text{C}_{4'}$	153.56	153.57
$\text{C}_{8'}$	157.46	155.13
C_7	162.02	160.29
C=O	175.99	161.16

In the case of the cerium(III) complex, it was evident that there was a strong positive shift effect for H_8 and weaker ones for H_3 , H_5 and H_6 . Chemical shifts of these protons in the complex were attributed to coordination of the ligand to cerium(III).

The ligand and the complex showed ten signals in the ^{13}C NMR spectra for ten carbons, respectively, of the coumarin moiety. Due to electron transfer from the carbonyl oxygen atom to cerium(III), chemical shifts to higher ppm were observed for the neighboring C-3 and C-4 carbon atoms of the complex and they confirmed the expected coordination of the ligand through the carbonyl oxygen atom. The other carbon atoms were only slightly affected by the coordination of the metal. The most notable change observed upon complex formation was the chemical shift of the C=O to lower ppm.

The mass spectra analyses confirmed the metal/ligand ratio 1:2 in the investigated complex. MS data for 4-methyl-7-hydroxy-2H-1-benzopyran-2-one sodium salt were: m/z (% of base peak): 198 (80), 176 (100), 154 (60), 136 (60), 120 (17), 107 (22) and for cerium complex: 352.8 (17), 306.8 (5), 288.8 (5), 176.8 (100), 154 (35), 136 (35), 120 (14), 106.9 (17). As it is seen from the above results, the first peak in the cerium(III) complex spectrum (although with low intensity) corresponds to the mass of the complex formation and the second ones to that of the ligand.

Spectrophotometric study

The reaction of cerium(III) with 4-methyl-7-hydroxycoumarin was studied in detail by the spectrophotometric method. The absorption spectra at different pH and different concentrations of the ligand and a fixed concentration of the metal ion for the complexes are given in Fig. 1.

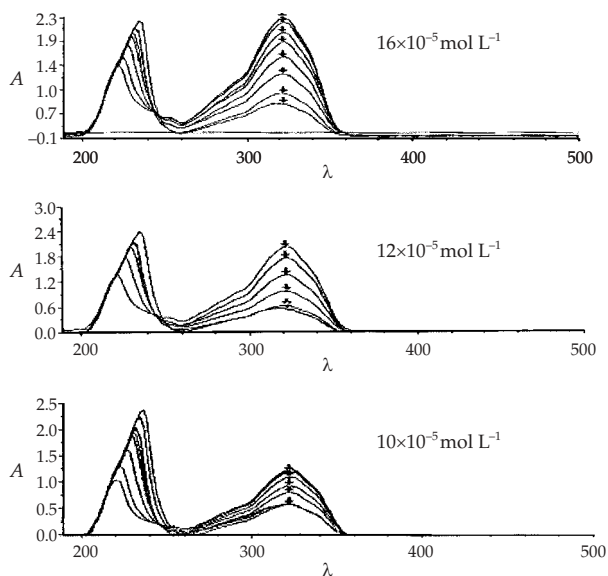


Fig. 1. Absorption spectra of the Ce(III) complex in 4-methyl-7-hydroxycoumarin at pH = 1.5–4.0 and various concentrations of the ligand.

pH-absorbance curves. – A family of curves (Fig. 2) was obtained at λ_{\max} of 322 nm at a fixed concentration of the metal ion but with varying ligand concentration. The absorption of the complex remained constant for more than 24 h. The complexation reaction was reversible within the pH range 1.5–4.0. Subsequent studies have, therefore, been limited upto pH 4.0 only. The curves obtained at different pH values keeping c_{R^n} and c_{R^j} constant were analyzed, assuming general equilibria (1) and (2) by means of equations (3) to (5). Molar absorptivities of the two complexes (CeR^{2+} and CeR_2^+) were then obtained by the method of successive approximation.

Comparable values of ϵ_1 and ϵ_2 were also obtained from the plots of A vs. A/c_{R^n} and A vs. $c_{R^j}/(\epsilon_2 c_M - A)$ at constant pH values (Fig. 3). The above calculated values of ϵ_1 and

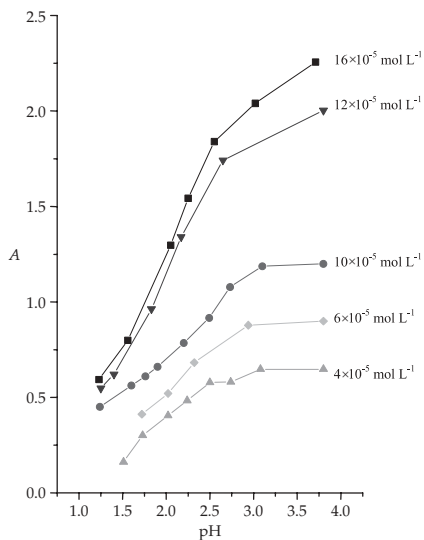


Fig. 2. Absorbance-pH curves at various ligand concentrations ($\lambda = 322 \text{ nm}$).

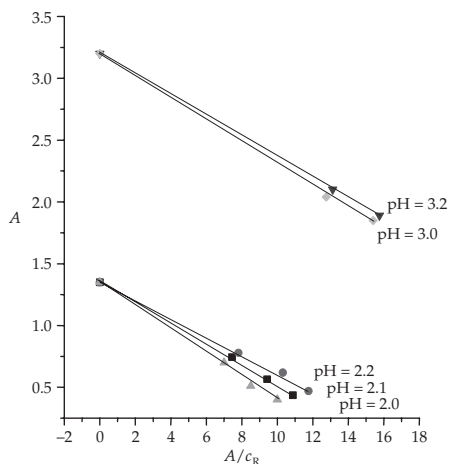


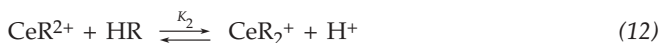
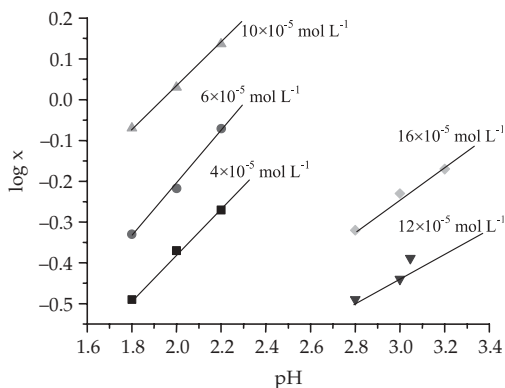
Fig. 3. Analysis of absorbance-pH curves.

ϵ_2 were put in appropriate logarithmic equations (6)–(7) and plots pH *vs.* $\log A/(A_{01}-A)$ and pH *vs.* $\log(A-A_{01})/(A_{02}-A)$ were found almost equal to unity and thus the values of x and y were obtained (Fig. 4).

Sets of absorbance-pH curves were further analyzed using equations (6)–(9) by the method of corresponding solutions. From the slope of the curves pH *vs.* $-\log C_R$, comparable values of x and y were obtained.

It can thus be inferred that up to pH 4.0 4-methyl-7-hydroxycoumarin is successively coordinated with Ce(III) in two steps with liberation of the only proton in each complexation step. The following course of the reaction is suggested:

Fig. 4. Logarithmic analysis of absorbance-pH curves (at pH 1.5–2.2: $x_{\text{CeR}^{2+}} = \frac{A}{A_{01} - A}$; at pH 2.8–4.0: $x_{\text{CeR}_2^+} = \frac{A - A_{01}}{A_{02} - A}$).



From the absorbance-pH plots, it is deduced that the above mentioned complexes are formed in different pH intervals: CeR^{2+} at pH = 1.5–2.2 and CeR_2^+ at pH = 2.8–4.0. Molar absorptivities of the complexes were found to be $\epsilon_1 = 3.37 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ and $\epsilon_2 = 8 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$, respectively.

Equilibrium constants. – The dissociation constant (K_{ai}) of the ligand, 4-methyl-7-hydroxycoumarin, determined pH-metrically was found to be 8.79.

The equilibrium constants of CeR^{2+} and CeR_2^+ complexes were calculated from the following equations:

$$\log \left(\frac{A}{(\epsilon_1 c_M - A) [1 + K_{\text{ai}}/(\text{H})]} \right) = \log c_R + \text{pH} + \log K_1 \quad (13)$$

$$\log \left(\frac{A - \epsilon_1 c_M}{(\epsilon_2 c_M - A) [1 + K_{\text{ai}}/(\text{H})]} \right) = \log c_R + \text{pH} + \log K_2 \quad (14)$$

The values of stepwise stability constants of the complexes were found to be $\log K_1 = 10.72 \pm 0.05$ and $\log K_2 = 9.22 \pm 0.07$, respectively (mean \pm SD, $n \geq 3$).

CONCLUSIONS

The current studies show that the Ce(III) complex with 4-methyl-7-hydroxycoumarin possesses a good stability. The synthesis and characterization of this complex seem to be very important in view of its possible pharmaceutical application.

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S A Ž E T A K

**Stabilnost kompleksa nekih lantanida s derivatima kumarina.
I. Cerijev(III)-4-metil-7-hidroksikumarin**

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Kompleks cerijevog(III) iona s 4-metil-7-hidroksikumarinom priređen je mješanjem vodene otopine cerijevog(III) nitrata i natrijeve soli 4-metil-7-hidroksikumarina u moalrnom omjeru 1:2. Kompleks je karakteriziran i identificiran elementarnom analizom, konduktometrijski, IR, ^1H i ^{13}C NMR-spektroskopijom, DTA, TGA i spektrometrijom masa. Termičkom analizom utvrđen je sastav kompleksa kao $\text{Ce}(\text{R})_2(\text{OH})\cdot 5\text{H}_2\text{O}$. Reakcija cerijevog(III) iona s 4-metil-7-hidroksikumarinom praćena je spektrofotometrijski. U proučavanom pH području utvrđeno je stupnjevito nastajanje dva kompleksa, CeR_2^{2+} i CeR_2^+ . Konstante ravnoteže za 1:1 i 1:2 komplekse bile su 10,72, odnosno 9,22.

Ključne riječi: Ce(III)-4-metil-7-hidroksikumarin, stabilnost kompleksa

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