

Stability of the complexes of some lanthanides with coumarin derivatives. II. Neodymium(III)-acenocoumarol

IRENA P. KOSTOVA¹*
ILIA I. MANOLOV²
MARITZA K. RADULOVA³

¹ Department of Chemistry
Faculty of Pharmacy, Medical University
Sofia 1000, Bulgaria

² Department of Industrial Pharmacy
Faculty of Pharmacy, Medical University
Sofia 1000, Bulgaria

³ Department of Technology
Faculty of Pharmacy, Medical University
Sofia 1000, Bulgaria

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A complex of neodymium(III) with 4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one (acenocoumarol) was synthesized by mixing water solutions of neodymium(III) nitrate and the ligand (metal to ligand molar ratio of 1:3). The complex was characterized and identified by elemental analysis, conductivity, IR, ¹H NMR and mass spectral data. DTA and TGA were applied to study the composition of the compound. Elemental and mass spectral analysis of the complex indicated the formation of a compound of the composition NdR₃ × 6H₂O, where R = C₁₉H₁₄NO₆⁻. The reaction of neodymium(III) with acenocoumarol was studied in detail by the spectrophotometric method. The stepwise formation of three complexes, *vis.*, NdR²⁺, NdR₂⁺ and NdR₃ was established in the pH region studied (pH 3.0–7.5). The equilibrium constants for 1:1, 1:2 and 1:3 complexes were determined to be log K₁ = 6.20 ± 0.06; log K₂ = 3.46 ± 0.07 and log K₃ = 2.58 ± 0.05, respectively.

Keywords: neodymium(III) complex, 4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one (acenocoumarol), stability

Coumarin derivatives are of interest because of their biological activities (1) and complexing ability (2–7). Nowadays, many studies report complexes of coumarin derivatives with rare earth metals, that possess biological activity. Thus, lanthanide complexes of 3-sulfo-4-hydroxycoumarin (8) and bis-(4-hydroxy-3-coumarinyl)-acetic acid (9) have been synthesized and characterized. The complexes have revealed good anticoagulant action. Coumarin derivatives have been found to exhibit anticoagulant and plant growth regulating properties. The complexes of lanthanides (cerium, lanthanum and neodymium) with acenocoumarol were assayed for acute intraperitoneal and peroral toxicity and for their influence on blood clotting time.

As a result of our earlier work, the cytotoxic profile of some complexes of 7-hydroxy-4-methylcoumarin, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-1-benzopyran-2-one, 4-hydroxy-3-[1-(4-chlorophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one and 4-hydroxy-3-[1-(4-

* Correspondence, e-mail: irenakostova@yahoo.com

-nitrophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one (acenocoumarol) with lanthanides against P3HR1, K-562 and THP-1 cell lines has been proven (10–12).

In the present investigation, the complexation reaction of neodymium(III) with (acenocoumarol) has been studied.

EXPERIMENTAL

Reagents

The compounds used for preparing the solutions were *p.a.* grade (Merck, Germany) products: $\text{Nd}(\text{NO}_3)_3 \times 6\text{H}_2\text{O}$ and 4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one (acenocoumarol). 4-Hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-2H-1-benzopyran-2-one sodium salt (acenocoumarol sodium) was used as the ligand for the metal complex preparation.

Synthesis

The complex was synthesized by mixing water solutions of the neodymium(III) salt and the ligand in the metal to ligand molar ratio of 1: 3. The reaction mixture was stirred with an electromagnetic stirrer at 25 °C for one hour and a precipitate was obtained. The precipitate was filtered, washed several times with water and dried in a desiccator to a constant mass.

The complex was insoluble in water, slightly soluble in methanol and ethanol and very soluble in DMSO. Its physicochemical characteristics, such as the melting point and molar conductance, were measured.

Analytical methods and instruments

Elemental analysis were performed using Vario EL V2.3 CHNS Modus Elementar Analysensysteme (Germany).

Water content was determined by Metrohm (Switzerland) E55 Karl Fisher Titrator and thermogravimetrically. The metal ion was determined after mineralization and thermogravimetrically. The presence of the sodium ion was checked by means of flame photometry (Perkin-Elmer 4 000 AA, USA).

DTA and TGA analyses were carried out using a derivatograph produced by MOM (Hungary). Samples 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 Al_2O_3 .

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

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

IR spectra (Nujol) were recorded on a IR-spectrometer FTIR-8101M Shimadzu (3800–400 cm^{-1}) (Japan) and on a IR-spectrometer Perkin-Elmer GX Auto image system (700–200 cm^{-1}) (USA).

Purity check was performed by TLC (Kieselgel 60 F₂₅₄ Merck, Germany) using cyclohexane-chloroform-acetic acid (10:10:4 V/V/V) as the mobile phase.

¹H NMR spectra were recorded at room temperature on a Bruker WP 100 (100 MHz) spectrometer (Germany) in DMSO-d₆. Chemical shifts are given in ppm.

Mass spectra were recorded on a Jeol JMS D 300 (Japan) double focusing mass spectrometer 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 reaction of neodymium(III) with acenocoumarol was studied in detail by the spectrophotometric method.

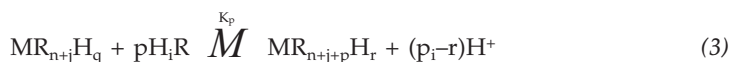
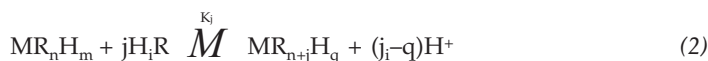
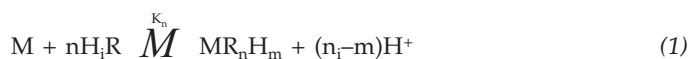
The pH of the solutions was adjusted using highly dilute solutions of sodium hydroxide and nitric acid, which slightly influenced the ionic strength. The ionic strength of solutions was maintained constant (0.01 mol L⁻¹) using 1 mol L⁻¹ KNO₃ solution.

A Metrohm 744 pH-meter and a Hewlett-Packard 8452 A diode array spectrophotometer were employed for pH and absorption measurements, respectively. Each pH value was determined five times and the respective spectra were recorded.

All experiments were carried out in 96% ethanol which was found to be an appropriate solvent for concentrations of the order of 10⁻⁵ mol L⁻¹.

Computational approach

The system neodymium(III)-acenocoumarol 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_m and MR_{n+j}H_q and MR_{n+j+p}H_r are the complexes.

The following equations may be written for the above equilibria:

$$A = \varepsilon_1 c_M - [H]^{(n_i-m)} A / c_R^n K_n \quad (4)$$

$$A = \varepsilon_1 c_M + c_R^j (\varepsilon_2 c_M - A) K_j / [H]^{(j_i-q)} \quad (5)$$

$$A = \varepsilon_2 c_M - [H]^{(j_i-q)} (A - \varepsilon_1 c_M) / K_j c_R^j \quad (6)$$

$$A = \varepsilon_2 c_M + c_R^p (\varepsilon_2 c_M - A) K_p / [H]^{(p_i-r)} \quad (7)$$

$$A = \varepsilon_3 c_M - [H]^{(p_i-r)} (A - \varepsilon_2 c_M) / K_p c_R^p \quad (8)$$

where A is absorbance, ε_1 , ε_2 and ε_3 are molar absorptivities of complexes MR_nH_m , $MR_{n+j}H_q$ and $MR_{n+j+p}H_r$, respectively, c_M is the concentration of the metal, c_R = concentration of the ligand, K_n , K_j and K_p are equilibrium constants of complexes MR_nH_m , $MR_{n+j}H_q$ and $MR_{n+j+p}H_r$, respectively.

Eqs. (4) to (8) were used for the interpretation of absorbance as a function of the increasing ligand concentration at constant pH.

The following method was used to evaluate the values of ε_1 , ε_2 and ε_3 . Functions A vs. $A/[H]^{(n_i-m)}$, A vs. $(\varepsilon_2 c_M - A)/[H]^{(j_i-q)}$ and A vs. $(\varepsilon_3 c_M - A)/[H]^{(p_i-r)}$ were computed from the absorbance at different pH values and different ligand concentrations, recorded at a suitable wavelength. The values of ε_1 , ε_2 and ε_3 at that wavelength were then deduced from the above plots. Consequently, the better values were substituted in the logarithmic transformations (9)–(11):

$$\log (A/(\varepsilon_1 c_M - A)) = n \log c_R + (n_i-m) \text{pH} + \log K_n \quad (9)$$

$$\log (A - \varepsilon_1 c_M)/(\varepsilon_2 c_M - A) = j \log c_R + (j_i-q) \text{pH} + \log K_j \quad (10)$$

$$\log (A - \varepsilon_2 c_M)/(\varepsilon_3 c_M - A) = p \log c_R + (p_i-r) \text{pH} + \log K_p \quad (11)$$

The values of (n_i-m) , (j_i-q) and (p_i-r) were obtained from the slopes of the linear plots obtained using Eqs. (9) to (11). The stability constants were then calculated from the plot of pH vs. $-\log c_R$, for the equation with the left hand side being zero, and also by plotting $\log (A/(\varepsilon_1 c_M - A))$ vs. pH and other similar terms vs. pH: $\log (A - \varepsilon_1 c_M)/(\varepsilon_2 c_M - A)$ and $\log (A - \varepsilon_2 c_M)/(\varepsilon_3 c_M - A)$.

A set of pH – absorbance curves for solutions containing a constant excess of ligand was established [see Eqs. (12)–(14)]. These were the solutions having the same values of $\varepsilon = (A - A_{OR})/c_M$ (where A_{OR} is absorbance due to the ligand). Under such conditions simple logarithmic plots are valid whose slopes give directly the ratio of the number of coordinated ligand molecules to that of the protons liberated during complexation:

$$\text{pH} = n/(n_i-m) (-\log c_R) + \text{constant} \quad (12)$$

$$\text{pH} = j/(j_i-q) (-\log c_R) + \text{constant} \quad (13)$$

$$\text{pH} = p/(p_i-r) (-\log c_R) + \text{constant} \quad (14)$$

To establish the existence of polynuclear complexes, especially dinuclear complexes, solutions containing a constant excess of ligand but a varying metal ion concentration were examined. The ratio of the number of metal ions complexed to that of the protons liberated, using Eq. (15) follows:

$$\text{pH} = (m-1)/m(-\log c_M) + \text{constant} \quad (15)$$

RESULTS AND DISCUSSION

Physico-chemical and spectral evidence

The data of the elemental analysis (found/calculated), for $\text{NdR}_3 \cdot 6\text{H}_2\text{O}$ ($\text{R} = \text{C}_{19}\text{H}_{14}\text{NO}_6^-$) are (%): C 52.48/52.29, H 4.10/4.13, N 3.01/3.21, H_2O 7.95/8.25, Nd 10.83/11.01. The molar conductivity of the same complex was $< 14 \text{ S cm}^2 \text{ mol}^{-1}$, indicating that the complex is a non-electrolyte. The complex is a highly melting solid (m.p. $> 300 \text{ }^\circ\text{C}$) and it decomposes before melting.

The composition of the complex was confirmed by DTA and TGA. There is a clearly manifested endothermic peak ($\sim 105 \text{ }^\circ\text{C}$) at the beginning of the DTA curve. A steady mass loss is recorded on heating up to $\sim 220 \text{ }^\circ\text{C}$, which corresponds to the elimination of 6 molecules of water per molecule of the neodymium(III) complex. This mass loss, determined also by the Karl Fisher analysis, is correlated with the intensity of endothermic effects and with the respective mass decreases. On heating the complex, the decomposition step corresponds to the loss of ligand molecules, which is in agreement with the proposed composition of the complex. Exothermic effect ($500 \text{ }^\circ\text{C}$) dominates in the thermogram of the complex, resulting from the decomposition of organic matter. A further mass loss recorded up to $750 \text{ }^\circ\text{C}$ indicates the formation of a thermally stable metal oxide. The results of DTA and TGA are presented in Table I.

Table I. DTA and TGA data of acenocoumarol, its sodium salt and Nd(III) complex

Compound	Thermal effect	T ($^\circ\text{C}$)	Mass loss (Δm , %)
acenocoumarol ($\text{C}_{19}\text{H}_{15}\text{NO}_6$)	Endo	240, 465	1.6, 30.7
	Exo	540, 620, 738	42.0, 58.0, 80.6
acenocoumarol sodium salt ($\text{C}_{19}\text{H}_{14}\text{NaNO}_6$)	Endo	170	10.2
	Exo	300	40.9
	Endo	450	47.7
	Exo	480	56.8
	Endo	630	65.9
acenocoumarol Nd(III)-complex ($\text{NdR}_3 \cdot 6\text{H}_2\text{O}$)	Endo	105, 220	4.00, 8.00
	Exo	350, 500	25.9, 46.0
	Endo	750	75.3

The mode of bonding of the ligand to Nd(III) was elucidated by recording the IR spectrum of the complex as compared with the spectrum of the free ligand. Acenocoumarol, acenocoumarol sodium and of the neodymium(III) complex with acenocoumarol are presented in Table II.

The band at 1715 cm^{-1} of acenocoumarol sodium salt can be attributed to the stretching vibrations of the keto-carbonyl group of the side chains; the band at 1653 cm^{-1}

Table II. IR spectra of acenocoumarol its sodium salt and Nd(III) complex

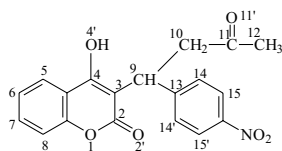
Compound	ν_{OH}	$\nu_{\text{C=O}}^{\text{a}}$	$\nu_{\text{C=O}}^{\text{b}}$	$\nu_{\text{C=C}}$	ν_{Ar}	$\nu_{\text{C-C}}$	$\nu_{\text{C-O}}$	$\nu_{\text{C-O-C}}$
acenocoumarol ($\text{C}_{19}\text{H}_{15}\text{NO}_6$)	3295	1686	1619	1572	1512	1249–1212	1173	1101
acenocoumarol sodium salt ($\text{C}_{19}\text{H}_{14}\text{NaNO}_6$)	3364	1715	1653	1595	1516	1267–1226	1163	1076
acenocoumarol Nd(III) complex ($\text{NdR}_3 \cdot 6\text{H}_2\text{O}$)	3392	1697	1650	1598	1514	1281–1229	1179	1111

^a keto carbonyl group

^b lactone carbonyl group

corresponds to the carbonyl group of the lacton ring and the band at 1595 cm^{-1} can be related to the stretching vibrations of the conjugated $\text{C}=\text{C}$ system. Vibrations at 1516 cm^{-1} correspond to the aromatic system. A broad band, characteristic of ν_{OH} of coordinated water was observed in the range $3300\text{--}3400\text{ cm}^{-1}$ in the spectrum of the complex. The weak band observed at 3295 cm^{-1} in the spectrum of the free ligand is missing in the spectrum of the complex. The $\nu_{\text{C=O}}$ band at 1715 cm^{-1} exhibits a shift of 20 cm^{-1} to lower wavenumber values on complexation, which may be taken as evidence for the participation of the $\text{C}=\text{O}$ group in coordination. The C-C and C-O stretch and the C-O-C band are all shifted to a higher frequency ($1281\text{--}1229$, 1179 and 1111 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 (13).

Table III. ^1H NMR spectra of acenocoumarol, its Na-salt and its Nd(III)



Compound	δ (ppm)				
	$\text{H}_5\text{--H}_8^{\text{a}}$	H_9^{a}	H_{10}^{a}	H_{12}^{a}	$\text{H}_{14,15,16}^{\text{a}}$
acenocoumarol ($\text{C}_{19}\text{H}_{15}\text{NO}_6$)	7.36–7.66 m	4.18 s	3.47	1.94	7.83–8.12 dd
acenocoumarol sodium salt ($\text{C}_{19}\text{H}_{14}\text{NaNO}_6$)	6.95–7.40 m	5.05 t	3.40 d	3.05 s	7.60–8.10 dd
acenocoumarol Nd(III) complex ($\text{NdR}_3 \cdot 6\text{H}_2\text{O}$)	7.20–7.60 m	6.80 s	3.50 bs	1.90 s	7.50–7.90 dd

^a Atom numbering is in agreement with the structure enclosed.

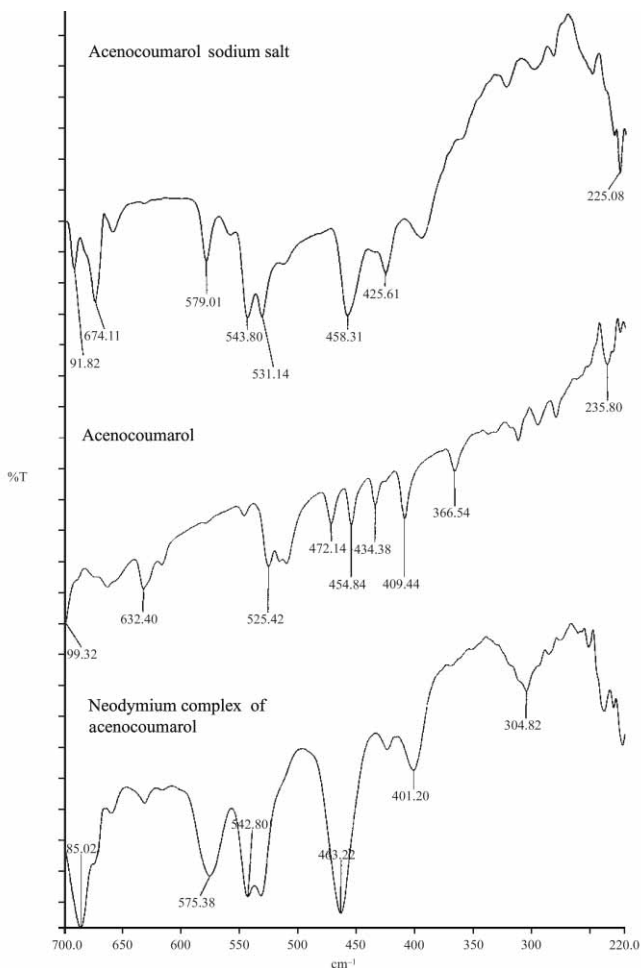


Fig. 1. IR spectra of acenocoumarol, its sodium salt and Nd(III) complex in the range 700–220 cm^{-1} .

The neodymium(III) complex spectrum showed new bands, in comparison with that of the free ligand, at 463 and 305 cm^{-1} , and they were assigned to metal-oxygen stretching vibrations (Fig. 1).

According to ^1H NMR spectra metal ion coordination with the ligand by means of C=O oxygen atom took place. Typical chemical shifts of the ^1H NMR spectra in DMSO- d_6 are presented in Table III. It is evident that in the case of the neodymium(III) complex there was a strong positive shift effect for H_9 and a weaker one for H_{10} . Chemical shifts of H_9 and H_{10} protons in the complex were attributed to coordination of the ligand to neodymium(III).

Table IV. Mass spectral data of acenocoumarol, its Na-salt and its Nd(III)

Compound	M/z	(%)
acenocoumarol (C ₁₉ H ₁₅ NO ₆)	354	100
	295	17
	163	27
acenocoumarol sodium salt (C ₁₉ H ₁₄ NaNO ₆)	375	17
	352	22
	176	100
Nd(III) acenocoumarol complex (NdR ₃ ·6H ₂ O)	1200 NdR ₃	0.03
	847 NdR ₂	0.17
	496 NdR	0.5
	354	33
	295	27
	176	20
	163	18

The mass spectra analysis confirmed the metal/ligand ratio 1:3 in the investigated complex (Table IV). The mass spectral fragmentation of the complex is presented in Figs. 2 and 3. As seen from Table IV, the first three peaks in the spectrum of neodymium(III) complex spectrum (although with low intensity) correspond to the complex formation and the other ones to that of the ligand.

Spectrophotometric and pH studies

A family of curves (Fig. 4) was obtained at λ_{\max} = 316 nm at constant pH and fixed concentration of the metal ion but with varying concentration of the ligand. The curves indicate that at constant pH the absorbance increases if the ligand concentration is raised.

The absorption of the complex remained constant for more than 24 h. The complexation reaction was reversible within the pH range 3.0–7.5.

Only mononuclear complexes were formed in solution with the excess of the ligand in the entire pH region used. Absence of polynuclear complexes is inferred from the overlapping of pH *vs.* (A/c_R) curves at different c_M values.

The pH-absorbance curves were interpreted in two ways: by the logarithmic method of analysis and the corresponding solution method.

Assuming general equilibria (1)–(3), the following results were obtained on the basis of transformations (4)–(8) as well as on the basis of the results of logarithmic analysis according to Eqs. (9)–(11).

At 316 nm the plots of $A = f(A/c_R)$, A *vs.* $(A - A_{01})/c_R$ and A *vs.* $(A - A_{02})/c_R$ were drawn (Fig. 5) to obtain the values of A_{01} , A_{02} and A_{03} . With the help of these values, plots of $\text{pH} = f[\log A/(A_{01} - A)]$ at $\text{pH} = 3.0\text{--}4.5$, $\text{pH} = f[\log (A - A_{01})/(A_{02} - A)]$ at $\text{pH} = 5\text{--}6$ and $\text{pH} = f[\log (A - A_{02})/(A_{03} - A)]$ at $\text{pH} = 6.5\text{--}7.5$ (Fig. 6) were obtained. The plots indicate that only one molecule of acenocoumarol is successively coordinated and only

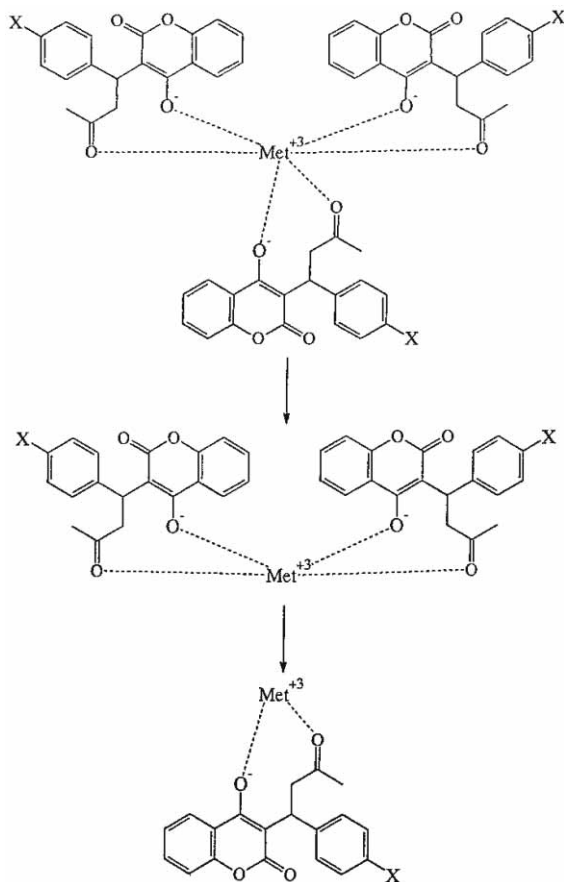
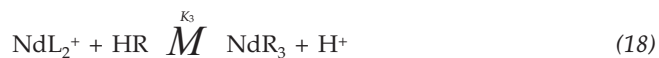
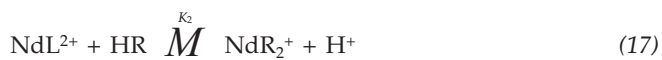
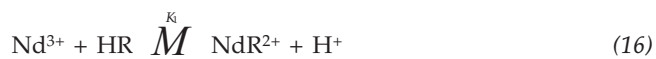


Fig. 2. Mass spectral fragmentation of the neodymium(III)-acencoumarol complex

one proton is liberated in each step of complexation in the presence of a large excess of the ligand. Therefore, equilibria (16), (17) and (18) can be assumed in different pH regions:



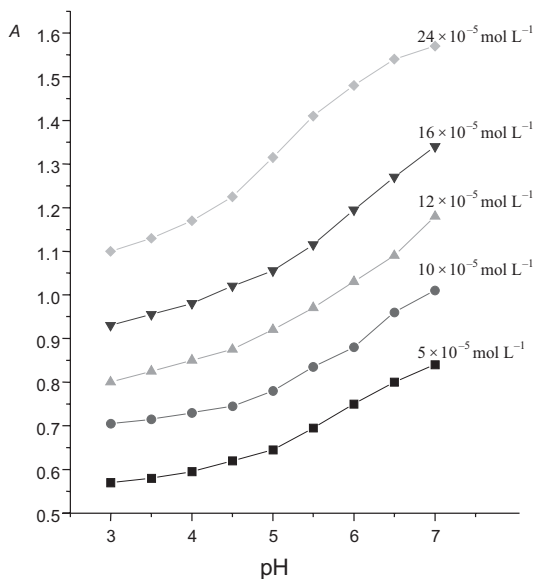


Fig. 4. Absorbance vs. pH curves at various ligand concentrations (316 nm).

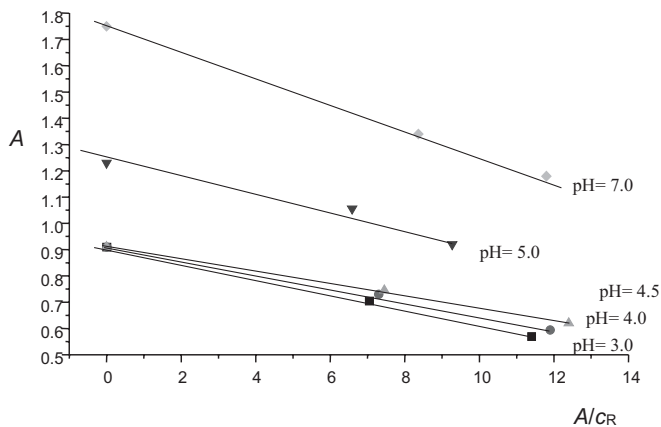


Fig. 5. Analysis of absorbance-pH curves at 316 nm
 $[A = f\left(\frac{A}{c_R}\right), \text{pH } 3.0\text{--}4.5; A = f\left(\frac{A - A_{01}}{c_R}\right), \text{pH } 5.0\text{--}6.0; A = f\left(\frac{A - A_{02}}{c_R}\right), \text{pH } 6.5\text{--}7.5].$

The dissociation constant of the acencoumarol ligand was determined pH-metrically and was found to be $\text{p}K_{\text{ai}} = 5.15$.

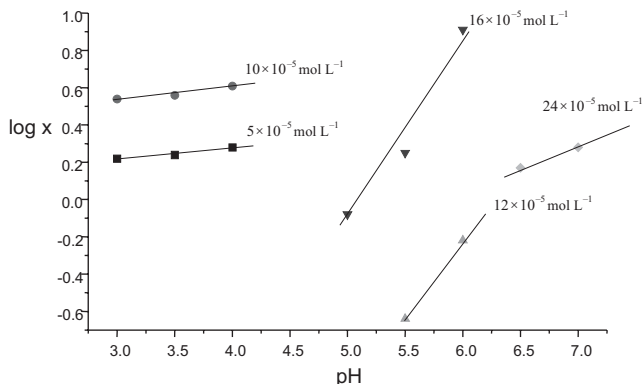


Fig. 6. Logarithmic analysis of pH-absorbance curves (316 nm) [$\log x_{\text{NdR}_2^+} = \log \frac{A}{A_{01} - A}$ (pH 3.0–4.5); $\log x_{\text{NdR}_2^+} = \log \frac{A - A_{01}}{A_{02} - A}$ (pH 5.0–6.0); $\log x_{\text{NdR}_3} = \log \frac{A - A_{02}}{A_{03} - A}$ (pH 6.5–7.5)].

The values of molar absorptivities of the three complexes were found to be $\epsilon_1 = 2.275 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$, $\epsilon_2 = 3.075 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ and $\epsilon_3 = 4.375 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$, respectively.

The values of stepwise stability constants (mean \pm SD, $n \geq 3$ of the three complexes) were found to be $\log K_1 = 6.20 \pm 0.06$ for NdR_2^+ , $\log K_2 = 3.46 \pm 0.07$ for NdR_2^+ and $\log K_3 = 2.58 \pm 0.05$ for NdR_3 .

CONCLUSIONS

Stepwise formation of three complexes of Nd(III) with acenocoumarol, depending upon the concentration of the ligand and pH, has been established. Liberation of one additional proton in different pH ranges indicates the stepwise formation of the three complexes.

All the three complexes formed are mononuclear, *vis.* NdR_2^+ , NdR_2^+ and NdR_3 . The 1:1 complex prevails in acidic solutions (pH 3.0–4.5) and 1:3 complex is formed at pH > 6.5, while 1:2 complex is present in the intermediate pH range (pH 5.0–6.0).

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S A Ž E T A K

Stabilnost kompleksa nekih lantanida s derivatima kumarina.

II. Neodimij(III)-acenokumarol

IRENA P. KOSTOVA, ILIA MANOLOV i MARITZA K. RADULOVA

Neodimijev(III) kompleks s acenokumarolom pripravljen je mješajući vodenu otopinu neodimijevog(III) nitrata i liganda u molarnom omjeru metala i liganda 1:3. Kompleks je karakteriziran i identificiran elementarnom analizom, konduktometrijom, IR, ^1H NMR, masenom spektroskopijom, DTA i TGA. Analize ukazuju na sastav kompleksa $\text{NdR}_3 \cdot 6\text{H}_2\text{O}$, gdje je $\text{R} = \text{C}_{19}\text{H}_{14}\text{NO}_6^-$. Reakcija neodimij(III) s acenokumarolom praćena je spektrofotometrijski. U pH području 3,0 do 7,5 utvrđeno je postupno stvaranje triju kompleksa, NdR_2^+ , NdR_2^+ i NdR_3 . Konstante ravnoteže za 1:1, 1:2 i 1:3 komplekse bile su $\log K_1 = 6,20 \pm 0,06$, $\log K_2 = 3,46 \pm 0,07$, odnosno $\log K_3 = 2,58 \pm 0,05$.

Cljučne riječi: neodimijev(III) kompleks, 4-hidroksi-3-[1-(4-nitrofenil)-3-oksobutil]-2H-1-benzopiran-2-on (acenokumarol), stabilnost

Department of Chemistry, Department of Industrial Pharmacy and Department of Technology Faculty of Pharmacy, Medical University, Bulgaria