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New coordination compounds of citric acid and polyamines with lanthanide ions - potential application in monitoring the treatment of cancer diseases

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ABSTRACT

Non-covalent interaction in the binary systems of polyamines (putrescine, spermidine, spermine) with citric acid and complex formation in the binary as well as ternary systems of lanthanide(III) ions, citric acid and polyamine have been investigated. The studies were performed in aqueous solution. The overall stability constants of the complexes were determined using the potentiometric method with computer analysis of the data. Only mononuclear type of complexes were found in the ternary systems and polyamines were located in the outer as well as inner coordination sphere. Non-covalent interaction between biogenic amines and citric acid in the binary and ternary systems were confirmed on the basis of the equilibrium constants analysis and spectroscopic studies.

1. Introduction

Citric acid (Cit) is one of the fruit acids which is commonly found in living organisms. In the human body citric acid is an active site of metalloenzymes and plays a crucial role in the Krebs cycle (citric acid cycle - CAC) [1–5]. Citric acid and its compounds are used in medicine as supplements and drugs as well as in cosmetics as an antioxidant and acidity regulator. Significant properties of the complex formation of citric acid are associated with the character of their functional carboxyl and hydroxyl groups. The relatively low protonation value of the carboxyl groups makes them a potential coordination site of metal ions in the low pH values. Moreover, chelate complexes of citric acid enhance the bioavailability and assimilability of metal ions in biological systems [6–8].

Polyamines (PA) especially biogenic amines such as: putrescine (Put), spermidine (Spd), and spermine (Spm) are essential amines in living systems, Fig. 1. The complex formation of polyamines could be used in the treatment of disease e.g. cancer. Platinum complexes containing bridging polyamines in their structure are successfully used in cancer therapy [9]. Polyamines in physiological condition are protonated and are able to form non-covalent complexes with negatively charged biomolecules occurring in the cells of e.g. phosphate groups of polynucleotides. Such types of interaction prevent protein denaturation and coagulation as well as stabilize the structure of nucleic acids [10–14].

The weak noncovalent interactions play important role in biological systems, e.g. in processes of molecular recognition and in enzymatic reactions. Molecular complexes in which weak noncovalent interactions take place are formed when a protonated ligand interacts with negatively charged molecules involved or not in coordination sphere [10,15–17].

Lanthanide(III) ions and their complexes are commonly used in medicine because of their anti-coagulating, anti-inflammatory, anti-allergic and anti-cancer properties. The magnetic properties of gadolinium(III) complexes have been adopted for the widely used magnetic resonance imaging method [18,19] Moreover, the complexes of cerium (III), lanthanum(III) and neodymium(III) with coumarin and its derivatives have been proved to effectively activity in human leukemia cells in initial clinical trials [20]. The complexes of cerium(III) ions with bipyridine and phenanthroline have been reported to effectively inhibit cancer cell growth in vitro [21].

The latest medical research indicates that elevated polyamine concentrations indicate the formation of various types of human cancers. However, the explanation of the detailed mechanism of action of polyamines in many biochemical and metabolic processes at the molecular level requires further research. The main purpose of this work

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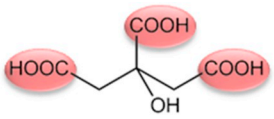
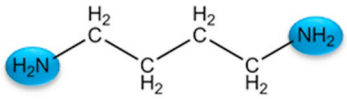


Citric acid (Cit)



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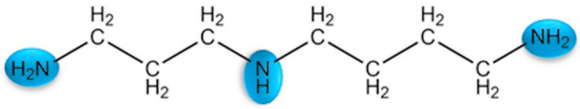
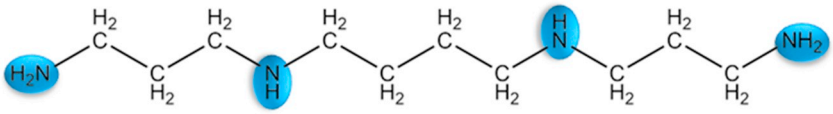


Spermidine (Spd)



Spermine (Spm)

Fig. 1. Formulae of studied ligands.

Table 1
The overall protonation constants of polyamines and citric acid.

Species	Overall protonation constants (logβ)			
	Putrescine (Put)	Spermidine (Spd)	Spermine (Spm)	Citric acid (Cit)
HL	9.35 [31]	10.97 [32]	10.91 [33]	5.29 [28]
H_2L	16.35 [31]	21.03 [32]	21.28 [33]	9.63 [28]
H_3L	–	29.49 [32]	30.39 [33]	12.67 [28]
H_4L	–	–	38.67 [33]	–

Table 2
The overall stability constants (logβ) and equilibrium constants of formation (logK_e) of adducts in the system of citric acid (Cit)/polyamine (PA) (standard deviation are given in parenthesis).

Species	Putrescine (Put)		Spermidine (Spd)		Spermine (Spm)	
	logβ	logK_e	logβ	logK_e	logβ	logK_e
$CitH_6PA$	–	–	–	–	56.36(5)	8.06
$CitH_5PA$	–	–	42.14(2)	3.02	51.61(5)	7.55
$CitH_4PA$	32.77(3)	6.79	38.10(2)	3.22	44.60(3)	5.93
$CitH_3PA$	28.62(3)	6.88	32.68(3)	3.19	35.87(3)	5.48
$CitH_2PA$	23.22(2)	6.87	24.67(3)	3.64	–	–
CitHPA	–	–	15.56(2)	4.59	–	–

was to investigate the type of interactions between lanthanide (III) ions/citric acid/polyamines and the impact of these interactions on the detection of polyamine levels. This paper presents the results of equilibrium and spectroscopic studies of the binary systems polyamines/citric acid or lanthanide(III) ions and ternary systems lanthanide(III) ions/citric acid/polyamines.

2. Material and methods

2.1. Materials

Citric acid (Cit) and free 99% pure polyamines (putrescine, spermidine, spermine) were purchased from Sigma-Aldrich and were used without further purification, Fig. 1.

Nitrates of the polyamines (Put, Spd, Spm) were obtained by mixing one chemical equivalent of the amine suspended in methanol with the required chemical equivalents of a water-methanol solution of HNO_3. The white salts were recrystallised, washed with methanol, and dried in a desiccator over P_4O_{10}. Lanthanum(III), neodymium(III), europium (III), gadolinium(III), terbium(III), holmium(III) and lutetium(III) nitrates were obtained from Sigma-Aldrich and used without further purification. All solutions were prepared using demineralized carbonate-free water (conductivity 0.055 μS). The concentrations of metal ions were determined by the method of Inductively Coupled Plasma Optical Emission Spectrometry (ICP OES).

2.2. Equilibrium study

Potentiometric titrations were carried out using a Titrando 905 Metrohm equipped with an autoburette with an i-electrode Metrohm 6.0280.300 calibrated in terms of concentration of hydrogen ions prior to each titration [22–27]. Before each series of measurements, the pH-meter indication was corrected with the use of two standard buffer solutions of pH 4.002 and pH 9.225 at 20 ± 1Å C. All potentiometric titrations were performed in an atmosphere of neutral gas (helium - Ultra High Purity), at the constant ionic strength of 0.1 M (KNO_3), temperature 20 ± 1 °C (titration dish placed in thermostatic bath set at this temperature), in the pH range from 2.5 to 10.5, using as a titrant CO_2-

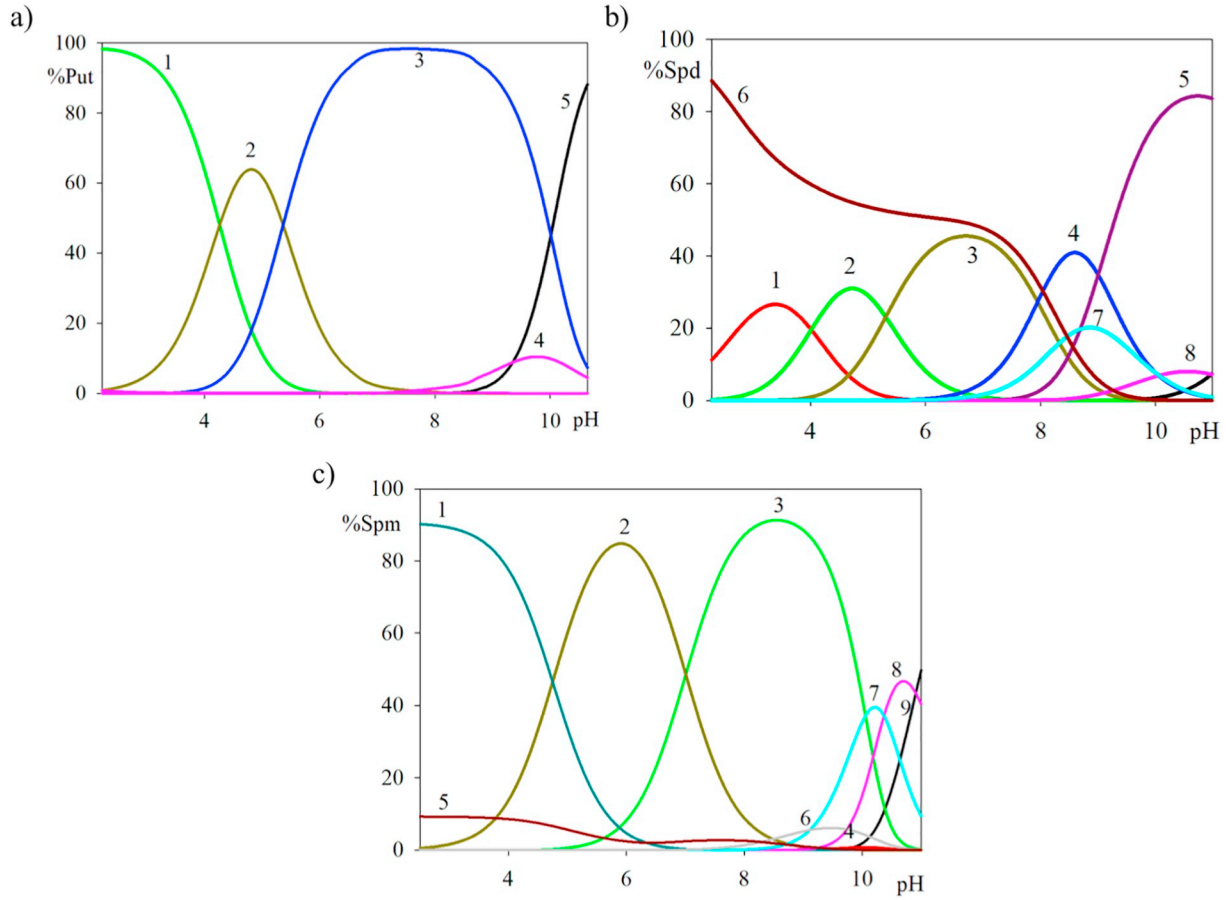


Fig. 2. Distribution diagrams for the studied systems: a) 1 - (Cit)H_4(Put); 2 - (Cit)H_3(Put); 3 - (Cit)H_2(Put); 4 - HPut; 5 - Put; b) 1 - (Cit)H_5(Spd); 2 - (Cit)H_4(Spd); 3 - (Cit)H_3(Spd); 4 - (Cit)H_2(Spd); 5 - (Cit)H(Spd); 6 - H_2Spd; 5 - HSpd; c) 1 - (Cit)H_6(Spm); 2 - (Cit)H_5(Spm); 3 - (Cit)H_4(Spm); 4 - (Cit)H_3(Spm); 5 - H_4Spm; 6 - H_3Spm; 7 - H_2Spm; 8 - HSpm; the percentage of the species refers to polyamine; $c_{PA} = c_{Cit} = 1 \times 10^{-3}$ M (for the sake of simplicity, ion charges in potentiometric description of the complexes were omitted).

free NaOH at a concentration of 0.1885 M. The concentration of citric acid and polyamines was 0.001 M and the metal to ligand ratio was 1:1 in the binary systems and 1:1:1 in the ternary systems. The selection of the model and the determination of the stability constants of the complexes were made using the HYPERQUAD program and the determined ionic product for water was $pK_w = 13.78$ [22,24–26]. The computer program uses the non-linear method of least squares to minimize the sum (S) of the squares of residuals between the observed quantities (f^{obs}) and those calculated on the basis of the model (f^{calc}).

$$S = \sum_{i=1}^{n} w_i (f_i^{obs} - f_i^{calc})^2$$

n – number of measurements, w_i – statistical weight.

The stability constant of the complexes formed in the ternary complexes could be evaluated by the following equilibria (charge was omitted for simplicity):

$$oM + pCit + qPA + rH \leftrightarrows M_oCit_pPA_qH_r$$

$$\beta = \frac{M_oCit_pPA_qH_r}{[M]^o[Cit]^p[PA]^q[H]^r}$$

The calculations were performed using 150–350 points for each job (eight or more titrations were performed for each particular system), taking into account only that part of the potentiometric curve where precipitate was not observed. Hydrolysis constants of metal ions were taken from our previous paper and were taken into account in the computer analysis of potentiometric data [28]. The iteration procedure allows the types (stoichiometry) and thermodynamically stability of the complexes formed in the studied systems to be determined. The testing began with the simplest hypothesis and the models were then expanded to include progressively more species, after which the results were scrutinized to eliminate the species rejected by the refinement processes. The correctness of the assumed model was verified by analysis of the standard deviations, the convergence of the experimental data with those obtained for the model evaluated by the Hamilton test and chi squared test [26,29,30]. The distribution diagrams of particular forms were obtained using the HySS (Hyperquad Simulation and Speciation) program [22].

2.3. Infrared spectroscopy

IR spectra measurements were performed by dissolving the relevant species (citric acid, polyamines and metal ions) in D_2O and adjusting pH by addition of NaOD or DCl. The pH values were corrected according to the formula pD = pH meter readings + 0.4 [27]. IR spectra were measured for the binary and ternary systems with ratios of 1:1 and 1:1:1, respectively. The metal concentration for the IR studies was 0.25 M. IR spectra were recorded on an IR Spirit Fourier Transform Infrared Spectrophotometer spectrometer (Shimadzu).

2.4. UV–vis and luminescence spectroscopy

Samples for spectroscopic measurements were prepared in ultrahigh quality water. Water was doubly distilled and purified using a

Table 3
The overall stability constants (logβ) and equilibrium constants of formation (logK_e) of binary complexes in the systems of lanthanide ions/polyamine (standard deviation are given in parenthesis).

	Species	Putrescine (Put)		Spermidine (Spd)		Spermine (Spm)	
		logβ	logK_e	logβ	logK_e	logβ	logK_e
La^{3+}	MLH	–	–	–	–	14.84(9)	3.93
	ML	–	–	6.00(3)	6.00	6.15(1)	6.15
	ML(OH)	−6.50(6)	7.26	−3.65(2)	4.10	−5.50(7)	2.10
	$ML(OH)_2$	−16.40(4)	3.87	−14.37(4)	3.04	–	–
Nd^{3+}	MLH	–	–	–	–	16.97(1)	6.06
	ML	–	–	7.63(1)	7.63	7.71(2)	7.71
	ML(OH)	−4.80(3)	8.96	−1.57(1)	4.55	−2.72(1)	3.33
	$ML(OH)_2$	−15.90(8)	2.66	−12.90(4)	2.43	–	–
Eu^{3+}	MLH	–	–	–	–	17.86(9)	6.95
	ML	–	–	8.84(1)	8.84	8.35(1)	8.35
	ML(OH)	−4.10(4)	9.66	−0.55(2)	4.37	−2.60(7)	2.81
	$ML(OH)_2$	−14.53(9)	2.34	−11.45(3)	2.86	–	–
Gd^{3+}	MLH	–	–	–	–	18.02(1)	7.11
	ML	–	–	8.64(1)	8.64	8.68(1)	8.68
	ML(OH)	−3.94(3)	9.82	−0.77(2)	4.34	−2.27(2)	2.81
	$ML(OH)_2$	−15.06(7)	2.64	−12.46(9)	2.07	–	–
Tb^{3+}	MLH	–	–	–	–	17.84(4)	6.93
	ML	–	–	9.04(4)	9.04	7.97(5)	7.97
	ML(OH)	−3.29(3)	10.47	1.08(2)	5.81	–	–
	$ML(OH)_2$	−12.90(6)	4.16	−8.69(3)	3.99	–	–
Ho^{3+}	MLH	–	–	–	–	18.05(3)	7.14
	ML	–	–	8.98(1)	8.98	8.65(5)	8.65
	ML(OH)	−3.69(2)	10.07	−0.55(3)	4.26	−1.57(5)	3.53
	$ML(OH)_2$	−13.00(5)	2.89	−11.73(5)	2.57	–	–
Lu^{3+}	MLH	–	–	–	–	18.45(2)	7.54
	ML	–	–	10.24(1)	10.24	8.49(3)	8.49
	ML(OH)	−2.88(2)	10.88	0.67(3)	4.19	–	–
	$ML(OH)_2$	−13.55(4)	3.10	−10.02(4)	3.06	–	–

Simplicity Ultrapure Water System (Millipore). The UV absorption spectra were recorded with a Cary 300Bio (Varian) spectrophotometer. Emission spectra were measured on a Hitachi F7000 spectrophotometer using 2.5/2.5-nm slit widths. UV–Vis absorption and steady-state emission spectra were recorded at room temperature in quartz cells. In luminescence studies samples were excited at 395 nm for Eu(III) system and 370 nm for Tb(III) systems. The absorbance of the solutions at the excitation wavelength of 395 nm and 370 nm were lower than 0.2 absorbance units.

3. Results and discussion

3.1. Potentiometric measurements

Protonation constants of citric acid (Cit) and polyamines (PA) were determined in previous publications and are given in the Table 1.

The relatively high protonation constants of polyamines also caused the amino groups to occur in protonated form at high pH values. On the other hand the citric acid molecule in the same conditions is fully deprotonated. On the basis of the analysis of the protonation constants of the studied ligands, it was found that positively charged polyamines can interact with negatively charged citric acid in biological systems.

3.1.1. The systems of citric acid/polyamines

As we found earlier, a change in the acid-base equilibria is observed as a result of non-covalent interactions between bioligands [29,34]. Due to the release of protons accompanying the formation of adducts, these processes can be studied by the potentiometric method:

$$H_xCit + H_yPA \leftrightarrows CitH_{(x+y-n)}PA + nH^+$$

Computer analysis of potentiometric data has shown the formation of adducts in the systems of citric acid (Cit) with polyamines (PA). Molecular complexes of the $CitH_{(x+y-n)}PA$ type were identified in all the studied systems. The composition and overall stability constants (logβ) as well as the equilibrium constants of the species formation (logK_e) are presented in Table 2.

As follows from the values of the successive protonation constants of the ligands studied, the protonated amine groups of polyamines are the potential positive reaction centres in the studied pH range, where deprotonated carboxyl groups of citric acid are the potential negative centres. As found earlier, for similar systems [29,35], the results suggest the presence of an ion-ion type interaction between Cit and PA. Computer analysis of the potentiometric titration data indicates that the molecular complexes $(Cit)H_4(Put)$, $(Cit)H_5(Spd)$, $(Cit)H_6(Spm)$ already appear in detectable concentrations in the Cit/PA systems at pH < 2, when citric acid has at least one deprotonated carboxyl group, Fig. 2.

With increasing pH, the next carboxyl group of citric acid is deprotonated and adducts $(Cit)H_3(Put)$, $(Cit)H_4(Spd)$, $(Cit)H_5(Spm)$ are formed, Table 2. These molecular complexes appear at a pH of about 3 in all studied systems and start to disappear at pH = 7 for $(Cit)H_3(Put)$ as well as $(Cit)H_4(Spd)$, and pH = 9.0 for $(Cit)H_5(Spm)$, Fig. 2. The equilibrium constants calculated according to the equilibriums:

$$H_2Cit + H_2Put \leftrightarrows (Cit)H_4(Put) \qquad \log K_e = 6.79$$

$$H_2Cit + H_3Spd \leftrightarrows (Cit)H_5(Spd) \qquad \log K_e = 3.02$$

$$H_2Cit + H_4Spm \leftrightarrows (Cit)H_6(Spm) \qquad \log K_e = 8.06$$

suggest that weak interaction between citric acid and putrescine or spermine have the same character. The acid-base properties of spermine result from the fact that the molecule has two independent small amino fragments ($(H_2N)(CH_2)_3(NH_2)$) separated by a tetramethylene chain [36]. The relatively lower value of logK_e for $(Cit)H_5(Spd)$ suggests that not all protonated amine groups are involved in weak interaction (Table 2). The lowest tendency to create adducts in the system Cit/Spd is observed on the distribution curves because all the molecular complexes formed binds of about 25% of bioligands. Moreover, adducts formed by the interaction of citric acid with putrescine or spermine involved about 60–80% of the ligands present in the system. The highest value of stability constants (logβ) were found for citric acid with spermine compounds. Weak interactions of the ion-ion type were observed in all the studied systems until the full deprotonation of polyamines.

3.1.2. Systems of lanthanide(III) ions/polyamines

Computer analysis of potentiometric titration data for the systems Ln(III)/PA (Ln = lanthanide(III) ion) indicated the formation of MHL and ML as well as the ML(OH) and $ML(OH)_2$ type of complexes. In the system with putrescine only hydroxocomplexes were identified. The overall stability constants of the complexes (logβ) and the equilibrium constants of the species formation (logK_e) are presented in Table 3.

The equilibrium constants of polyamine complexes with lanthanide (III) ions were determined on the basis of the proposed reactions of their formation:

$$Ln^{3+} + HPA \leftrightarrows LnHPA$$

$$Ln^{3+} + PA \leftrightarrows LnPA$$

$$LnPA + H_2O \leftrightarrows LnPA(OH) + H^+$$

$$LnPA(OH) + H_2O \leftrightarrows LnPA(OH)_2 + H^+$$

For all lanthanide(III) ions with biogenic amines the complexation reaction begins at pH 7.0–8.5 with the formation of Ln(Put)(OH) for the systems with putrescine, Ln(Spd) for spermidine and Ln(HSpm) for spermine, Fig. 3, Fig. 4 and Supplementary Fig. S1-S3.

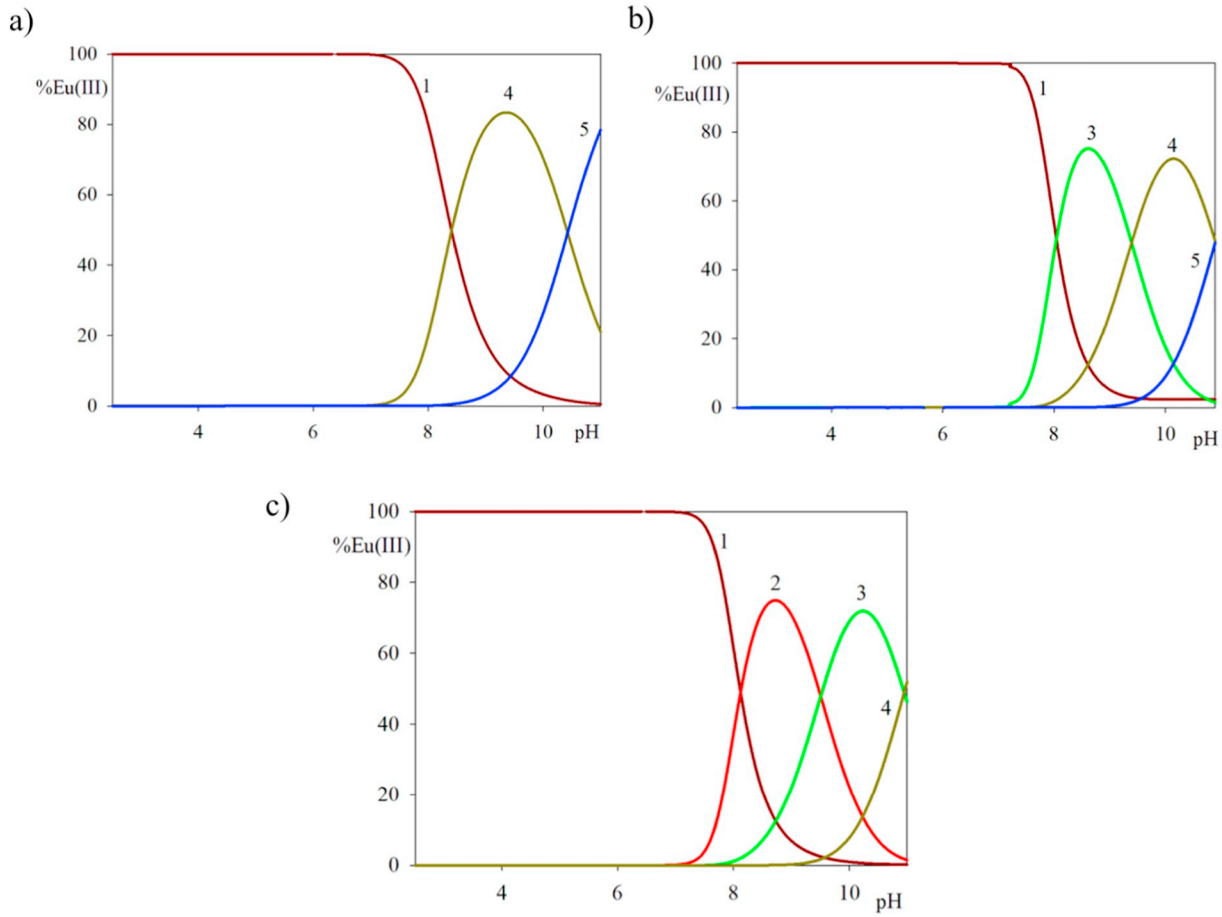


Fig. 3. Distribution diagrams for the Eu(III)/PA systems: a) 1 - Eu^{3+}; 4 - Eu(Put)(OH); 5 - $Eu(Put)(OH)_2$; b) 1 - Eu^{3+}; 3 - Eu(Spd); 4 - Eu(Spd)(OH); 5 - $Eu(Spd)(OH)_2$; c) 1 - Eu^{3+}; 2 - Eu(HSpm); 3 - Eu(Spm); 4 - Eu(Spm)(OH); 5 - $Eu(Spm)(OH)_2$; the percentage of the species refers to metal ions; $c_{metal\ ion} = 1 \times 10^{-3}$ M; $c_{PA} = 1 \times 10^{-3}$ M.

Protonated complexes were identified only in systems with spermine. These species are dominant at pH 8.5–9.0 binding the maximum amount of metal ions (10% for La(III), 30% for Nd(II) and > 85% for the rest of the studied lanthanide(III) ions), Fig. 3c and Supplementary Fig. S3. Fully deprotonated spermidine and spermine start the ML type complex formation at a pH of about 7.0 for Spd and at 8.0 for Spm. Ln(Spd) and Ln(Spm) complexes are dominant at a pH of about 9.0 and 10.0 respectively, binding the maximum amount of metal ions (40% for La(III) and > 85% for the rest of the studied lanthanide(III) ions in the system with spermidine and 50% for Nd(III) and Ho(III) as well as > 80% for the rest). Complexes with Tb(III) in the system with spermidine dominate at pH 8.0 and bind only 30% of metal ions introduced to the system, but in the system with spermine they bind > 95% of metal ions at a pH above 10.0, Fig. 3b,c and Supplementary Fig. S2, S3. Monohydroxocomplexes of the ML(OH) type were formed in all systems, except with terbium and lutetium in systems with spermine and > 50% of lanthanide(III) ions participated in the formation of this type of compound. In the system with Put as well as Spd the maximum amount of lanthanide(III) ions (25–95%, respectively) were binding at pH 9.0 for Tb(III) and 10.0 for the rest Ln(III), Fig. 3a,b and Supplementary Fig. S1, S2. In the system with Spm the Ln(Spm)(OH) complexes start forming at a pH above 10.0 and the maximum amount of lanthanide(III) ions bound was 15–80%, respectively; La(III) the least and Nd(III) the most. Moreover, in the systems Tb(III)/Spm and Lu(III)/Spm no hydroxocomplexes were formed, Fig. 3 and Supplementary Fig. S1-S3. For Put and Spd above pH 10.0 dihydroxocomplexes were observed.

3.1.3. *The systems of lanthanide(III) ions/citric acid/polyamines*

In ternary systems formation of complexes of citric acid (Cit) and polyamines (PA) with lanthanide(III) ions (La(III), Nd(III), Eu(III), Gd(III), Tb(III), Ho(III), Lu(III)) were studied. The formation of the $LnCitH_xPA$ type of complexes (where x = 0–6) and hydroxocomplexes $LnCitPA(OH)_x$ (where x = 1–2) was found. The stability constants ($\log\beta$) and equilibrium constants ($\log K_e$) of the complexes are listed in Table 4. Equilibrium constants of ternary complexes were determined based on the proposal reaction of their formation (for the sake of simplicity, ion charges in potentiometric description of the complexes were omitted):

$$Ln^{3+} + H_2Cit + H_4PA \leftrightarrows LnCitH_6PA$$

$$LnHCit + H_4PA \leftrightarrows LnCitH_5PA \text{ or } Ln^{3+} + H_2Cit + H_3PA \leftrightarrows LnCitH_5PA$$

$$LnCit + H_4PA \leftrightarrows LnCitH_4PA \text{ or } Ln^{3+} + H_2Cit + H_2PA \leftrightarrows LnCitH_4PA$$

$$LnCit + H_3PA \leftrightarrows LnCitH_3PA$$

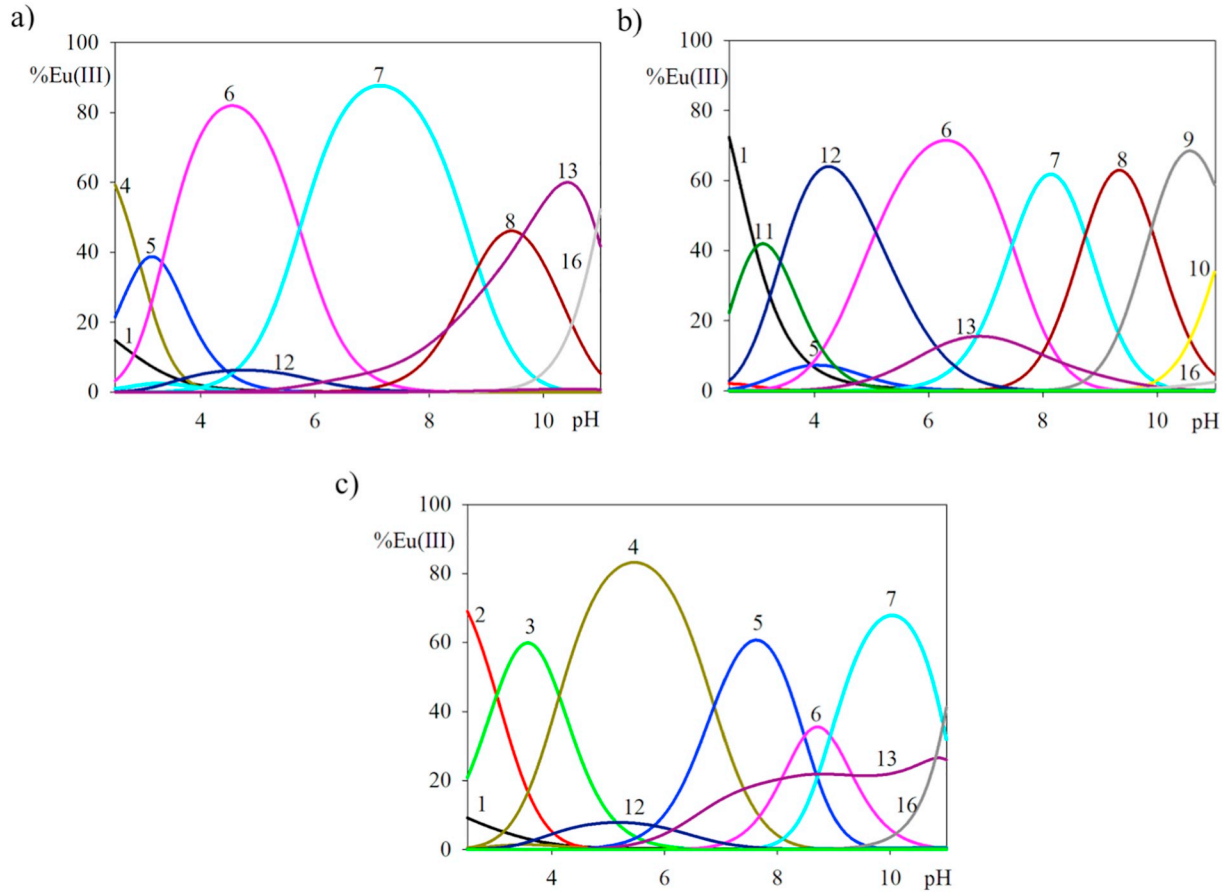


Fig. 4. Distribution diagrams for the studied systems: a) Eu(III)/Cit/Put b) Eu(III)/Cit/Spd;
c) Eu(III)/Cit/Spm; 1 - Eu^{3+}; 2 - $EuCitH_6PA$; 3 - $EuCitH_5PA$; 4 - $EuCitH_4PA$; 5 - $EuCitH_3PA$;
6 -$EuCitH_2PA$; 7 - EuCitHPA; 8 - EuCitPA; 9 - EuCitPA (OH); 10 - EuCitPA $(OH)_2$; 11 - Eu(HCit);
12 - EuCit;13 - Eu(Cit)(OH); 14- Eu(Cit)$(OH)_2$; 15 - $Eu(OH)_2$; 16 - $Eu(OH)_3$ (PA-polyamine); the percentage of the species refers to metal ions; $c_{metal\ ion} = 1 \times 10^{-3}$ M;
$c_{Cit} = 1 \times 10^{-3}$ M;
$c_{PA} = 1 \times 10^{-3}$ M.

$LnCit + H_2PA \leftrightarrows LnCitH_2PA$

$LnCit + HPA \leftrightarrows LnCitHPA$

$LnCit + PA \leftrightarrows LnCitPA$

$LnCitPA + H_2O \leftrightarrows LnCitPA(OH) + H^+$

$LnCitPA(OH) + H_2O \leftrightarrows LnCitPA(OH)_2 + H^+$

The occurrence of the suggested complexes in the studied systems was verified by analysis of the standard deviations and convergence of the experimental data with a theoretical curve obtained for chosen model.

Ternary complexes are dominant, except the Eu(III)/Cit/Spd and Tb (III)/Cit/Spd systems, and bind 60%–100% of lanthanide(III) ions. At low pH value fully protonated polyamines are located in the outer coordination sphere of metal ions and interact with binary complexes formed in the Ln(III)/Cit systems. Increasing pH value leads to deprotonation of amino groups of polyamines and PAs are involved in the inner coordination sphere of metal ions and at the same time interact with coordinated citric acid. Non-covalent bonds disappear together with full deprotonation of polyamines. At higher pH the monohydroxocomplexes Ln(Cit)(OH) are found in this type of compound; both ligands and the OH^- group are directly coordinated to the Ln(III).

3.2. Spectroscopic studies

3.2.1. IR spectroscopy

On the basis of analysis of IR spectra of d-electron metal ion/citric acid/polyamine systems, the complex formation and involvement of carboxyl groups from citric acid in coordination were confirmed. The IR spectra were recorded for ternary complexes with fully protonated amine and fully deprotonated citric acid at pH their dominance only for ternary systems. Comparison of the spectrum of free ligand, binary systems and spectrum of ternary complexes showed the disappearance of the bands assigned to the stretching vibrations of C═O bonds and stretching vibrations of the C—O bonds (Fig. 5 and Supplementary Fig. S7). It was not possible to record the spectra for binary compounds Ln (III)/PAs a precipitate of studied complexes appeared in the required concentrations of samples. Because IR spectra recording need high concentrations of the complexes, it was impossible to record them at higher pH values because of precipitate formation. The new band at 1700 cm^{-1} on spectra of lanthanide(III) ion/citric acid/polyamine systems additionally confirms the participation of the polyamine in non-covalent interactions with citric acid.

Table 4
The overall stability constants (logβ) and equilibrium constants of formation (logK_e) of ternary complexes in the system of lanthanide(III) ions/citric acid/polyamine (standard deviation are given in parenthesis).

	Species	Putrescine (Put)		Spermidine (Spd)		Spermine (Spm)	
		logβ	logK_e	logβ	logK_e	logβ	logK_e
La^{3+}	$MCitH_6PA$	–	–	–	–	61.24(4)	12.94
	$MCitH_5PA$	–	–	49.35(1)	5.21	58.09(4)	8.67
	$MCitH_4PA$	40.89(1)	14.91	46.17(1)	5.99	53.66(3)	7.91
	$MCitH_3PA$	37.65(1)	10.55	42.28(1)	5.77	45.27(4)	7.80
	$MCitH_2PA$	33.79(1)	10.36	33.79(2)	5.68	36.50(3)	8.14
	MCitHPA	25.30(1)	8.87	24.21(8)	6.16	27.10(4)	9.11
	MCitPA	15.92(1)	8.84	15.59(2)	8.51	–	–
Nd^{3+}	$MCitH_6PA$	–	–	–	–	58.48(4)	10.18
	$MCitH_5PA$	–	–	46.20(2)	2.06	55.66(3)	6.67
	$MCitH_4PA$	37.24(5)	11.26	43.17(3)	3.42	51.37(3)	5.92
	$MCitH_3PA$	34.09(5)	7.42	39.59(2)	3.38	43.83(3)	6.66
	$MCitH_2PA$	30.94(6)	7.81	32.27(3)	4.46	35.33(2)	7.27
	MCitHPA	23.91(4)	7.78	23.96(2)	6.21	26.13(2)	8.44
	MCitPA	15.10(4)	8.32	14.96(1)	8.18	–	–
Eu^{3+}	$MCitH_6PA$	–	–	–	–	57.88(5)	9.58
	$MCitH_5PA$	–	–	–	–	54.86(5)	5.78
	$MCitH_4PA$	34.86(3)	8.88	–	–	50.73(4)	5.05
	$MCitH_3PA$	31.92(3)	5.16	38.59(8)	2.25	43.85(4)	6.45
	$MCitH_2PA$	28.60(2)	5.24	34.66(1)	6.63	35.37(4)	7.08
	MCitHPA	22.87(1)	6.51	27.20(1)	9.23	26.43(4)	8.51
	MCitPA	14.01(1)	7.00	18.46(1)	11.46	–	–
	MCitPA(OH)	–	–	8.56(1)	3.87	–	–
	$MCitPA(OH)_2$	–	–	−2.68(2)	2.51	–	–
GGd^{3+}	$MCitH_6PA$	–	–	–	–	57.57(5)	9.27
	$MCitH_5PA$	–	–	–	–	54.58(5)	5.64
	$MCitH_4PA$	32.93(5)	6.95	–	–	50.12(4)	5.59
	$MCitH_3PA$	–	–	39.15(1)	3.86	42.76(4)	6.51
	$MCitH_2PA$	26.87(2)	4.66	32.63(1)	5.74	33.90(4)	6.76
	MCitHPA	20.76(3)	5.55	24.34(1)	7.51	24.47(4)	7.70
	MCitPA	12.00(3)	6.14	14.91(1)	9.05	–	–
	MCitPA(OH)	1.37(5)	3.13	4.70(1)	3.55	–	–
Tb^{3+}	$MCitH_6PA$	–	–	–	–	57.91(5)	9.61
	$MCitH_5PA$	–	–	–	–	55.08(5)	6.14
	$MCitH_4PA$	32.26(8)	6.28	42.55(3)	2.79	50.65(4)	5.53
	$MCitH_3PA$	29.84(3)	3.22	39.54(1)	3.60	43.50(4)	6.66
	$MCitH_2PA$	26.85(1)	4.05	33.41(1)	5.93	34.59(4)	6.86
	MCitHPA	20.97(1)	5.17	25.61(1)	8.19	25.36(4)	8.00
	MCitPA	12.56(1)	6.11	16.63(1)	10.18	–	–
	MCitPA(OH)	–	–	6.62(1)	3.76	–	–
Ho^{3+}	$MCitH_6PA$	–	–	–	–	58.43(4)	10.13
	$MCitH_5PA$	–	–	–	–	55.46(4)	6.20
	$MCitH_4PA$	32.78(4)	6.80	–	–	51.13(3)	5.58
	$MCitH_3PA$	–	–	39.52(4)	3.15	42.81(3)	6.54
	$MCitH_2PA$	26.99(2)	3.76	34.33(3)	6.42	34.82(4)	6.66
	MCitHPA	21.63(1)	5.40	26.77(3)	8.92	25.83(3)	8.04
	MCitPA	13.08(1)	6.20	17.83(3)	10.95	–	–
	MCitPA(OH)	–	–	8.14(3)	4.08	–	–
	$MCitPA(OH)_2$	–	–	−3.73(3)	1.88	–	–
Lu^{3+}	$MCitH_6PA$	–	–	–	–	60.22(4)	11.92
	$MCitH_5PA$	–	–	46.73(4)	2.59	57.13(4)	8.56
	$MCitH_4PA$	33.65(2)	7.67	44.24(2)	4.85	52.78(3)	7.50
	$MCitH_3PA$	31.12(1)	4.87	40.29(2)	4.19	45.19(3)	8.19
	$MCitH_2PA$	27.65(1)	4.69	33.26(3)	5.62	36.31(3)	8.42
	MCitHPA	22.54(1)	6.98	23.65(2)	6.07	26.98(4)	9.46
	MCitPA	13.51(1)	6.90	15.36(2)	8.75	–	–

3.2.2. UV–vis spectroscopy

The intensity of certain transitions in the absorption spectra of Ln (III) ions is very sensitive to changes in the environment of these ions, while the intensity of the remaining bands changes slightly [37–39]. Such transitions are called hypersensitive transitions. Hypersensitive transition is the $^4I_{9/2}$-$^2H_{9/2}$ transition in the Nd(III) ion. The absorption bands in the range of the hypersensitive transitions allow evaluation of the formation of Nd(III) complexes [40,41]. However, due to the weak nature of f-f transitions, the sensitivity of the absorption measurements is limited. The Nd(III) ion was chosen for the studies because it has the highest molar absorption coefficient, ε, in the whole lanthanide series.

The UV–Vis spectra of ternary system Nd/Cit/Put were recorded at the pH values of domination of individual species in the range of the hypersensitive transition $^4I_{9/2}$ – $^2H_{9/2}$, Fig. 6 and Supplementary Fig.

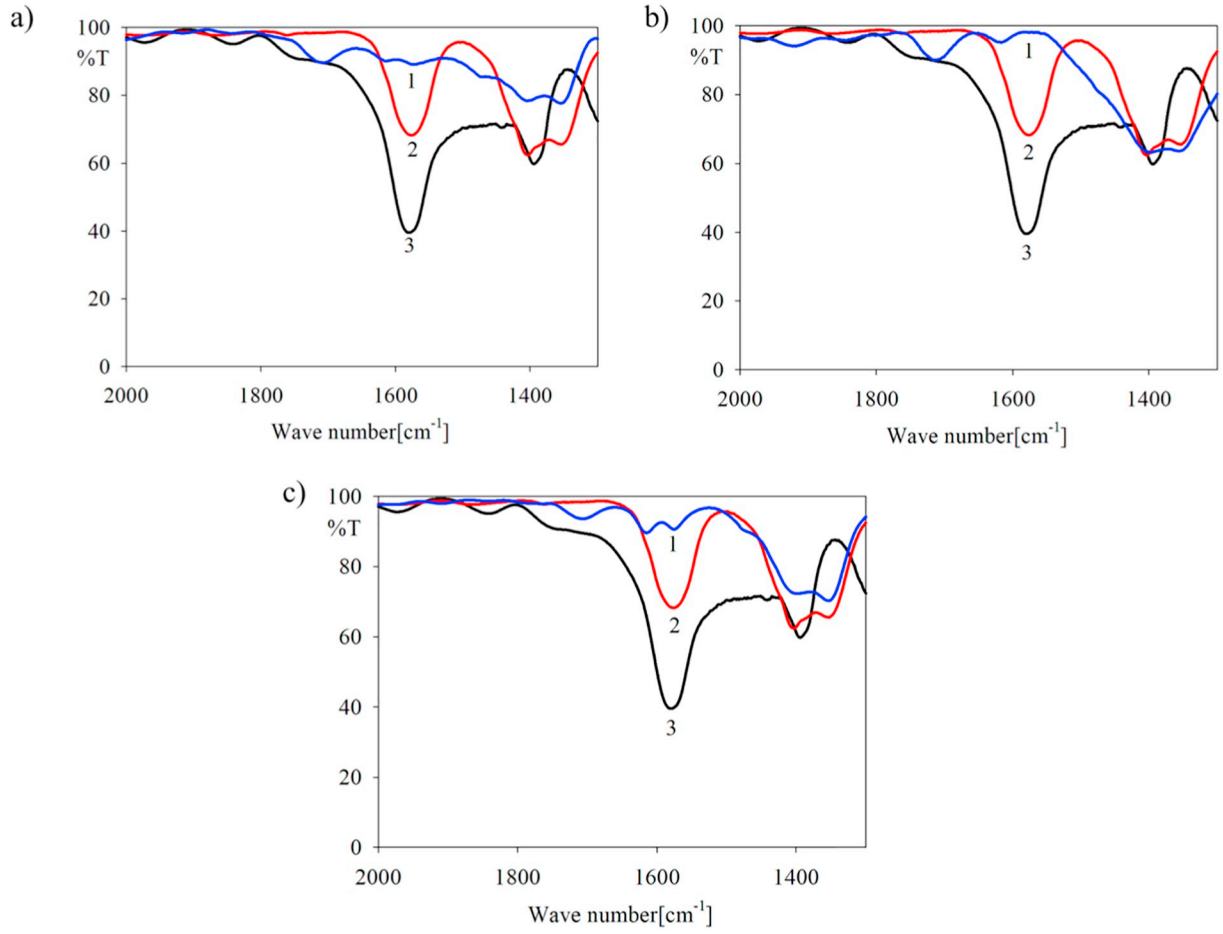


Fig. 5. IR spectra of selected systems: a) Eu(III)/Cit/Put; b) Eu(III)/Cit/Spd; c) Eu(III)/Cit/Spm;
1 - Eu(III)/Cit/PA, 2 - Eu(III)/Cit, 3 - Cit; $c_{Eu} = 1 \times 10^{-3}$ mol dm^{-3}; $c_{Cit} = c_{PA} = 1 \times 10^{-3}$ mol dm^{-3}.

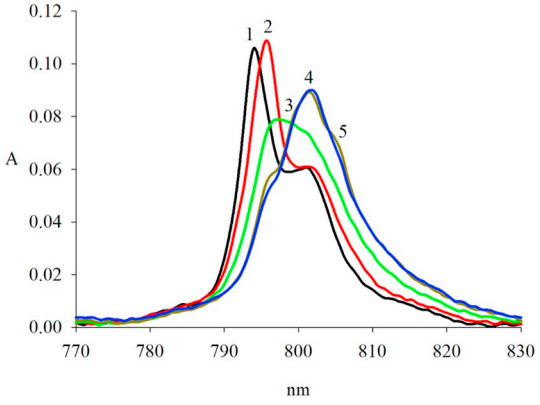


Fig. 6. The absorption spectrum of Nd(III) ion in the system Nd(III)/Cit/Put in the range of the transition
$^4I_{9/2} - {}^2H_{9/2}$; 1 - pH = 2.5, 2 - pH = 5.1, 3 - pH = 7.9, 4 - pH = 9.9, 5 - pH = 11.0; $c_{Nd} = 1 \times 10^{-3}$ mol dm^{-3};
$c_{Cit} = c_{Put} = 1 \times 10^{-3}$ mol dm^{-3}.

S10. The shape of each spectrum and location of the maximum are different for subsequent pH values. The spectrum of the solution recorded at pH 2.5 showed maximum absorption at 793 nm. This solution contained an Nd(III) ion, protonated polyamine, and partially deprotonated citric acid. The shift of the maximum absorption at pH 5.1 and at pH 7.9 to 795.6 nm, and 797.5 nm, respectively and reduction of the intensity of band, revealed the further deprotonation of citric acid and the onset of deprotonation of polyamine. The changes of intensity and shape of bands also indicate modification of the coordination sphere of the Nd(III) ion. The increase in pH to 9.9 resulted in the disappearance of the band at 795 nm and an increase in the intensity of the band at 801.7 nm; further increase in the pH value did not cause any changes.

3.2.3. Luminescence spectroscopy

The emission spectra of water solutions of the studied binary Ln (III)/PA systems and ternary Ln(III)/Cit/PA systems were recorded at the pH values of domination of the species. For the binary and ternary systems containing an Eu(III) ion the emissions were observed from the nondegenerate $^5D_0$ excited state to the energy level ^7F_j (j = 0, 1, 2, 3, 4) of the ground state (Figs. 7, 8), whereas for the binary and ternary systems containing a Tb(III) ion the emission was observed from the $^5D_4$ excited state to the energy level ^7F_j (j = 6, 5, 4, 2) of the ground state (Fig. 9 and Supplementary Fig. S11). During excitation with λ = 394 nm strong emissions were found in the regions corresponding to the transitions $^5D_0$-$^7F_1$, $^5D_0$-$^7F_2$, while medium strong emissions corresponded to the transition $^5D_0$-$^7F_4$ for all the studied binary Eu(III)/PA systems. For the ternary systems of the Eu(III) ion the strongest emissions were found in the regions corresponding to the transition

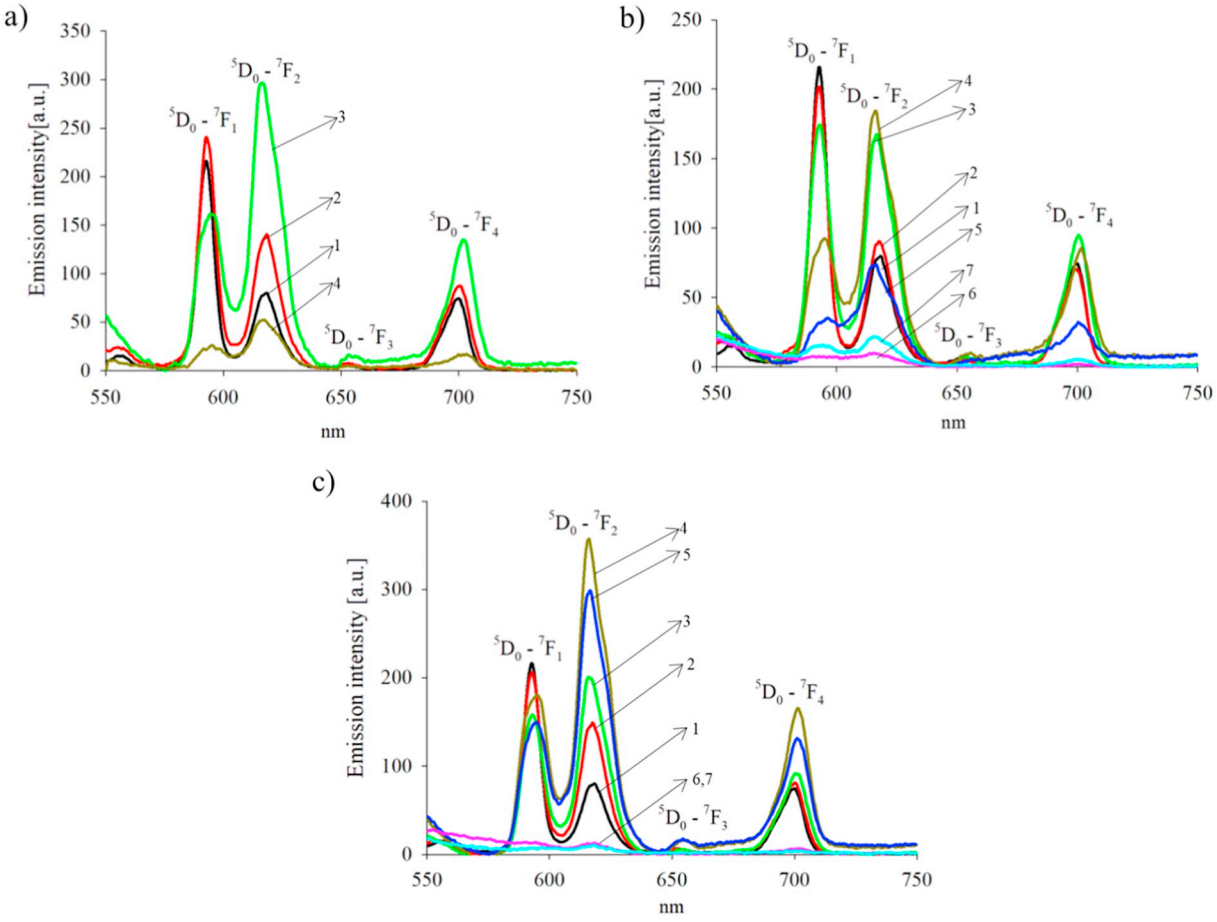


Fig. 7. Emission spectra of the systems: a) Eu(III)/Put: 1 - Eu(III), 2 - Eu(III)/Put pH = 7.4, 3 - Eu(III)/Put pH = 8.4, 4 - Eu(III)/Put pH = 11.0; b) Eu(III)/Spd: 1 - Eu (III), 2 - Eu(III)/Spd pH = 7.2, 3 - Eu(III)/Spd pH = 8.0,
4 - Eu(III)/Spd pH = 8.5, 5 - Eu(III)/Spd pH = 9.4, 6 - Eu(III)/Spd pH = 10.1, 7 - Eu(III)/Spd pH = 11.0;
c) Eu(III)/Spm: 1 - Eu(III), 2 - Eu(III)/Spm pH = 7.3, 3 - Eu(III)/Spm pH = 8.0,
4 - Eu(III)/Spm pH = 8.8, 5 - Eu(III)/Spm pH = 9.5, 6 - Eu(III)/Spm pH = 10.2, 7 - Eu(III)/Spm pH = 11.0;
$c_{Eu} = 1 \times 10^{-3}$ mol dm^{-3}; $c_{Cit} = c_{PA} = 1 \times 10^{-3}$ mol dm^{-3}.

$^5D_0$-$^7F_2$, while medium strong emissions corresponded to the transitions $^5D_0$-$^7F_1$, $^5D_0$-$^7F_4$. For binary systems Tb(III)/PA during excitation with 370 nm the most intensive emissions were observed in the region corresponding to $^5D_4$-$^7F_5$, and medium strong emissions in the regions of rest transitions of the Tb(III) ion. Upon excitation for the ternary system of the Tb(III) ion the most intensive emissions were found in the region corresponding to the transition $^5D_4$-$^7F_5$, while medium strong emissions in the region corresponding to the transition $^5D_4$-$^7F_6$.

As expected, with increasing pH the intensity of the bands $^5D_0$-^7F_j in Eu(III) ion, changed. For binary systems Eu(III)/PA the intensity of the band $^5D_0$-$^7F_1$ decreased with increasing pH. The highest intensity of the band ($^5D_0$-$^7F_1$) was found for the uncoordinated Eu(III) ion. Moreover, with increasing pH the intensity of the second band $^5D_0$-$^7F_2$ changed, and the highest intensity of the band was observed at pH 8.4 for Eu(III)/Put, 8.5 for Eu(III)/Spd, and 8.8 for Eu(III)/Spm. It worth noting that for ternary Ln(III)/PA/Cit systems a regular increase of emission intensity was observed with increasing pH. For the ternary system of the Eu(III) ion the highest intensity of the band $^5D_0$-$^7F_2$ was observed at pH 10. for Eu(III)/Put/Cit, 9.3 for Eu(III)/Spd/Cit, and 8.7 and 11.0 for Eu(III)/Spm/Cit.

The luminescence intensities of the systems Eu(III)/PA have been analysed to determine the ratio $\eta = I_{em}618/I_{em}593$. (Table 5). Compared to the aqua complex $Eu(H_2O)_9^{3+}$ where the value is low (0.40) with increasing pH in the presence of polyamines the value η increased. While, in our previous studies for systems Ln(III)/Cit the values were similar [28].

This observation reveals the gradual replacement of water molecules in the internal coordination spheres of the central europium(III) ion with amino groups of polyamines. Moreover, the highest emission intensity was found for the Eu(III)/Spm system which confirms the most extensive changes in the coordination sphere of the lanthanide(III) ion due to the coordination of tetraamine. Analyzing the luminescence intensities of the ternary systems Eu(III)/Cit/PA/, it was found that the ratio $\eta = I_{em}618/I_{em}593$ (Table 6) also indicates changes in the coordination sphare of europium(III) ions.

Comparing the luminescence intensities on the emission spectra of europium(III) or terbium(III) ions and their binary and ternary complexes, it can be concluded that Eu(III) or Tb(III) luminescence was enhanced by four to eight orders of magnitude in the presence of both ligands: citric acid and polyamines (Put, Spd or Spm). The increase in

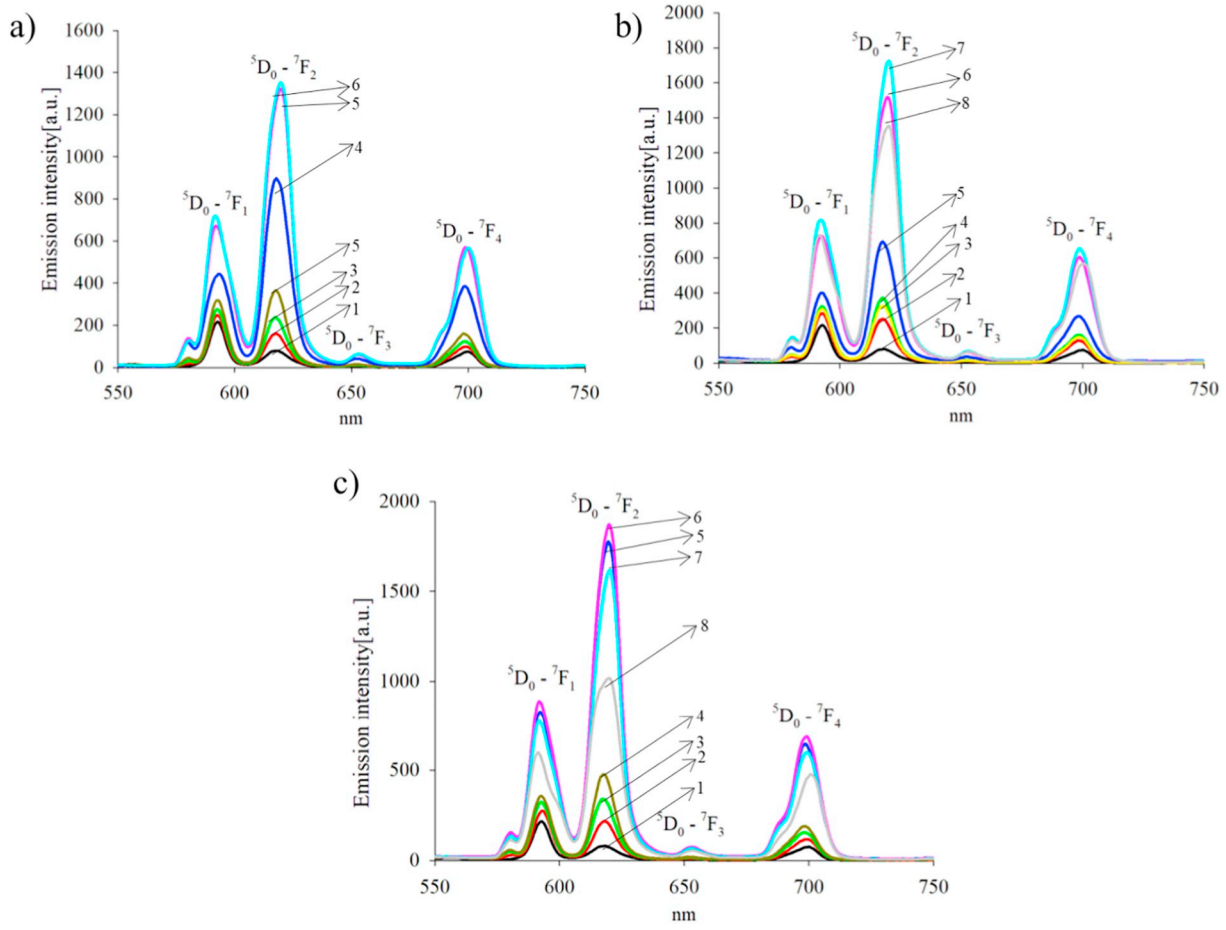


Fig. 8. Emission spectra of the systems a) Eu(III)/Cit/Put: 1 - Eu(III), 2 - Eu(III)/Cit/Put pH = 2.5, 3 - Eu(III)/Cit/Put pH = 3.1, 4 - Eu(III)/Cit/Put pH = 4.6, 5 - Eu(III)/Cit/Put pH = 7.1, 6 - Eu(III)/Cit/Put pH = 9.4, 7 - Eu(III)/Cit/Put pH = 10.3; b) Eu(III)/Cit/Spd: 1 - Eu(III), 2 - Eu(III)/Cit/Spd pH = 3.0, 3 - Eu(III)/Cit/Spd pH = 4.1, 4 - Eu(III)/Cit/Spd pH = 5.0, 5 - Eu(III)/Cit/Spd pH = 6.3, 6 - Eu(III)/Cit/Spd pH = 8.2, 7 - Eu(III)/Cit/Spd pH = 9.3, 8 - Eu(III)/Cit/Spd pH = 10.5; c) Eu(III)/Cit/Spm: 1 - Eu(III), 2 - Eu(III)/Cit/Spm pH = 2.5, 3 - Eu(III)/Cit/Spm pH = 3.5, 4 - Eu(III)/Cit/Spm pH = 5.4, 5 - Eu(III)/Cit/Spm pH = 7.6, 6 - Eu(III)/Cit/Spm pH = 8.7, 7 - Eu(III)/Cit/Spm pH = 10.0, 8 - Eu(III)/Cit/Spm pH = 11.0;
$c_{Eu} = 1 \times 10^{-3}$ mol dm^{-3}; $c_{Cit} = c_{PA} = 1 \times 10^{-3}$ mol dm^{-3}.

the intensity of bands indicate changes in the coordination sphere of Eu (III) or Tb(III) ion emission by adding further donor atoms to the metal ion(III) [42–44].

4. Conclusions

The formation of binary and ternary complexes containing citric acid (Cit), polyamine (PA) (putrescine, sprmidine and spermine) as well as lanthanide(III) ions (La(III), Nd(III), Eu(III), Gd(III), Tb(III), Ho(III) and Lu(III)) was studied using potentiometric and spectroscopic methods. The formation of weak interactions of the ion-ion type was found in systems Cit/PA. The lowest tendency to form such interactions was observed for the Cit/Spd system, while the highest tendency was found for the Cit/Spm system. For binary complexes of Ln(III)/PA it was found that putrescine with lanthanide(III) ions formed only hydroxocomplexes, while spermidine and spermine, apart from hydroxocomplexes, also formed LnHPA, LnPA complexes. In the ternary system formation of $LnCitH_xPA$ type complexes (where x = 0-6) and hydroxocomplexes $LnCitPA(OH)_x$ (where x = 1-2) was observed, it was found that the structures of the studied compounds depend on pH value. At low pH value, fully protonated polyamines are located in the outer coordination sphere of lanthanide(III) ions and interact with binary complexes Ln(III)Cit. However, deprotonation of amino groups of polyamines at higher pH leads to the involvement of PAs in the inner coordination sphere of metal ions and at the same time interaction with coordinated citric acid. Non-covalent bonds disappear together with full deprotonation of polyamines. A further increase in pH causes the formation of monohydroxocomplexes Ln(Cit)(OH). The stability constants of these complexes increase with decreasing ionic radius that within the group for lanthanide ions decreases from lanthanum to lutetium, unlike the coordination number. Additionally, the absorption spectra of Nd(III)/Cit/PA systems and IR spectra confirm the occurrence of non-covalent interaction.

Photoluminescence studies of Tb(III), Eu(III) and their complexes with polyamines and/or citric acid reveal the formation of compounds. Luminescence studies of binary and ternary systems showed that the intensity of Eu(III) and Tb(III) is greatly enhanced in the presence of citric acid and polyamine.

For now, it is not possible to formulate a general conclusion that the increase in polyamine concentration is specifically related to the

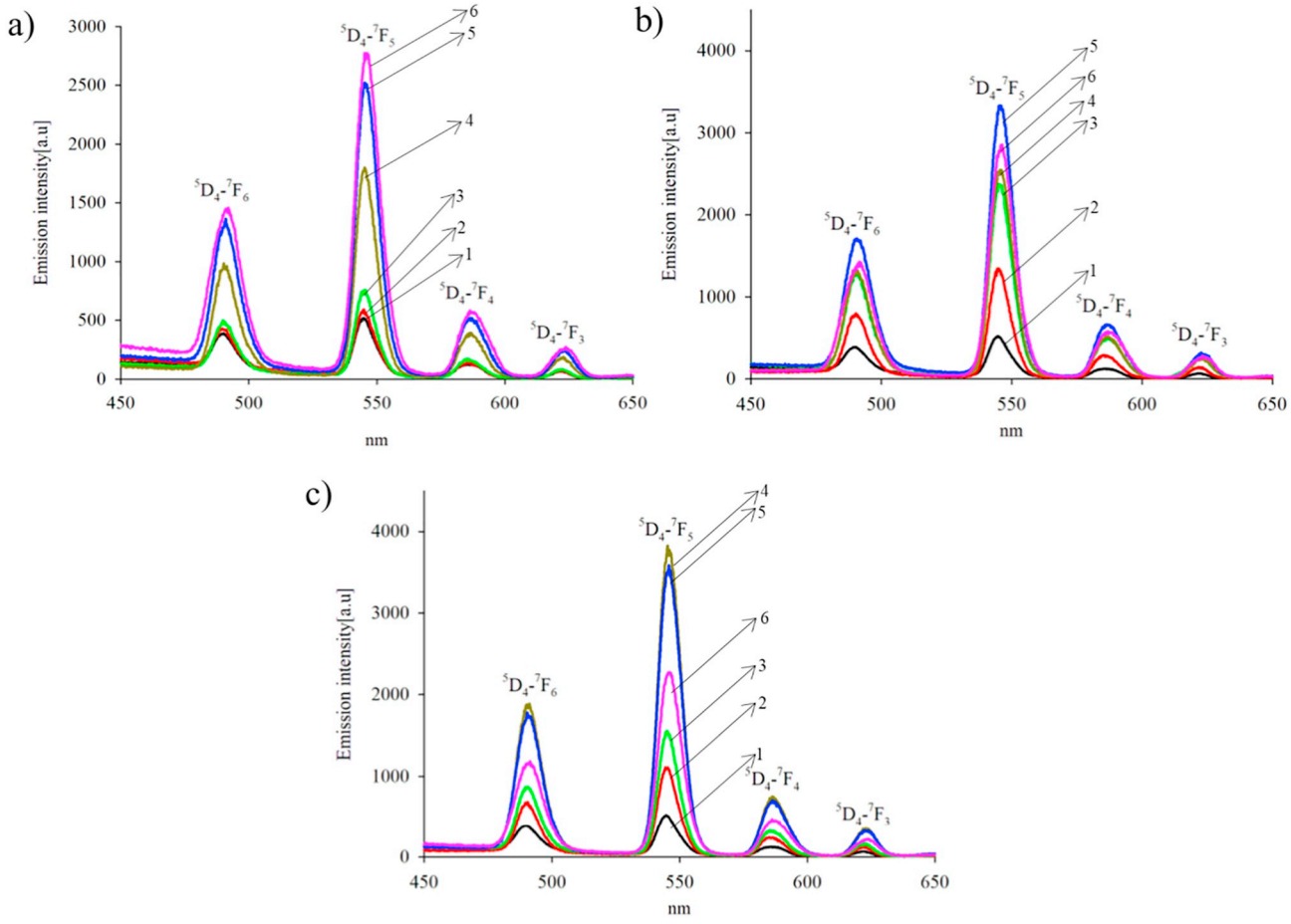


Fig. 9. Emission spectra of the systems a) Tb(III)/Cit/Put: 1 - Tb(III), 2 - Tb(III)/Cit/Put pH = 2.5, 3 - Tb(III)/Cit/Put pH = 4.8, 4 - Tb(III)/Cit/Put pH = 8.4, 5 - Tb(III)/Cit/Put pH = 9.5, 6 - Tb(III)/Cit/Put pH = 11.0; b) Tb(III)/Cit/Spd: 1 - Tb(III), 2 - Tb(III)/Cit/Spd pH = 4.9, 3 - Tb(III)/Cit/Spd pH = 7.0, 4 - Tb(III)/Cit/Spd pH = 8.4, 5 - Tb(III)/Cit/Spd pH = 9.5, 6 - Tb(III)/Cit/Spd pH = 11.0; c) Tb(III)/Cit/Spm: 1 - Tb(III), 2 - Tb(III)/Cit/Spm pH = 3.7, 3 - Tb(III)/Cit/Spm pH = 5.7, 4 - Tb(III)/Cit/Spm pH = 7.9, 5 - Tb(III)/Cit/Spm pH = 9.9, 6 - Tb(III)/Cit/Spm pH = 11.0 $c_{Tb} = 1 \times 10^{-3}$ mol dm^{-3}; $c_{Cit} = c_{PA} = 1 \times 10^{-3}$ mol dm^{-3}.

Table 5
The $\eta = I_{em}618/I_{em}593$ of binary complexes in lanthanide ions/polyamine systems.

Species	$\eta = I_{em}618/I_{em}593$		
	Putrescine (Put)	Spermidine (Spd)	Spermine (Spm)
EuLH	–	–	1.26
EuL	–	0.95	1.99
EuL(OH)	1.83	1.97	2.01
$EuL(OH)_2$	1.95	2.09	–

Table 6
The $\eta = I_{em}618/I_{em}593$ of ternary complexes in lanthanide ions/citric acid/polyamine systems.

Species	$\eta = I_{em}618/I_{em}593$		
	Putrescine (Put)	Spermidine (Spd)	Spermine (Spm)
$EuCitH_6PA$	–	–	0.78
$EuCitH_5PA$	–	–	1.05
$EuCitH_4PA$	0.87	–	1.34
$EuCitH_3PA$	1.15	0.90	2.05
$EuCitH_2PA$	2.01	1.14	2.01
EuCitHPA	1.83	1.69	1.79
EuCitPA	1.86	2.08	–
EuCitPA(OH)	–	2.10	–
$EuCitPA(OH)_2$	–	1.85	–

neoplastic process and is a reflection of its rapid growth Due to the very significant role of polyamines in the growth of tumors, they may be useful in the near future to develop more effective forms of therapy. This paper may offer a basis for further discussion on application of studied complexes in medicine to detect changes of polyamine level in living organisms.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2019.110715.

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