

Supramolecular Compounds of β -cyclodextrins as a Material for the Pharmaceutical Industry

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Abstract – The binary systems $\text{Eu(L)}_3(\text{ClO}_4)_3 \cdot 2\text{H}_2\text{O}$ and ternary systems $\text{EuL}_3(\text{CD})_3 \cdot 2\text{H}_2\text{O}$ were synthesized. The structural features of the systems were analyzed. The composition and structure of the synthesized complex compounds were studied by NMR spectroscopy, IR spectroscopy, X-ray phase analysis, thermal analysis, and luminescence analysis. It was revealed that during formation of the ternary system, the amino acid enters the cyclodextrin cavity and is preserved by hydrogen bonds; coordination with Eu^{3+} is due to the carboxyl group (COO^-), which is outside the cyclodextrin cavity. It was assumed that the spatial structure of the ternary system includes metal, amino acid, and β -cyclodextrin, where the ion of europium is used as a metal. It is used to track drug transportation in the biological systems.

Keywords – cyclodextrin; amino acids; inclusion complexes; complexes of amino acids with rare-earth elements.

I. INTRODUCTION

Chemistry of complex cyclodextrins (CD) compounds is one of the most promising areas of modern supramolecular

chemistry. It is due to the unique combination of properties which the systems can have [1].

The most popular application is the pharmaceutical industry, since it is in contact with the development of vector drug delivery to living systems [2, 3].

Binary systems of the CD-guest type have been studied [2]. There are data on complex-inclusions of amino acids in the modified β -CD, as well as on the complexes of CD with metal ions. In particular, their use as carriers for metal-containing nano-particles [3] was described.

When considering ternary systems, relatively small molecules, benzene or propanol, usually appear as the third component. However, ternary systems 'metal-ion-CD guest' are an exception [4]. Metal-ion-amino acid-CD systems are of great interest both from theoretical and practical points of view.

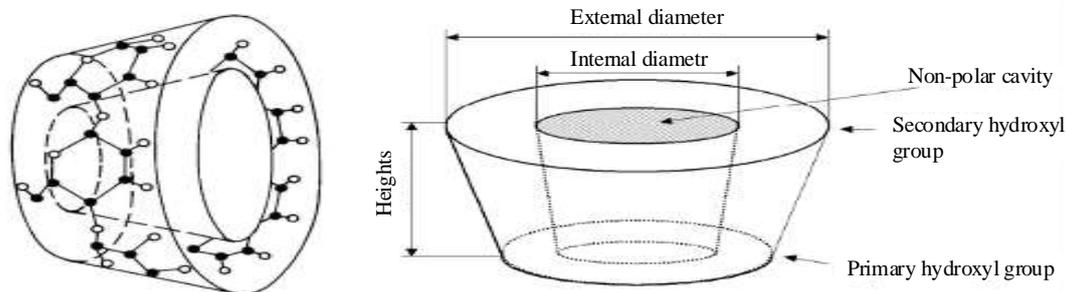


Fig. 1. Compound structure diagram

The article presents the results of studies on the complex system β -cyclodextrin – amino acid – rare-earth element (REE) which helps track drug transportation in biological systems.

II. METHODS AND MATERIALS

To produce complex compounds, methods and parameters that would affect properties and forms of the product were selected. The data on cyclodextrin produced using different methods play a key role in choosing the best method and conditions for achieving the most desirable result [4,5,8,9]. Synthesis of binary complex compounds in the β -cyclodextrin (β -CD) - amino acid - $\text{Eu}_3 +$ system was carried out according to the known method [6, 7, 10].

The structural formula of binary Eu (III) / amino acid complexes (phenylalanine, tyrosine) determined using complexometry and computational elemental analysis, corresponds to $\text{Eu}(\text{L})_3(\text{ClO}_4)_3 \cdot 2\text{H}_2\text{O}$.

The next stage was synthesis of supramolecular compounds - ternary complexes of $\text{EuL}_3(\text{CD})_3 \cdot 2\text{H}_2\text{O}$.

The metal concentration was determined by complexometric titration [4]. The amount of carbon and hydrogen was determined by elemental microanalysis using VARIO MICRO CUBE in a stream of oxygen at a furnace temperature of 1200 °C.

Thermal analysis was performed using NETSCH STA 409 PC / PG synchronous thermal analyzer. The analysis was carried out in the temperature range of 25-1000 ° C with a heating rate of 10 K/min. Data analysis shows that the composition of the system corresponds to the formula given above.

III. RESULTS

Analysis of Figures 1–3 and Table 1 shows that thermal destruction of β -CD systems with $\text{Eu}(\text{Phe})_3$ and β -CD with $\text{Eu}(\text{Tyr})_3$ are characterized by several thermal effects on the DTA curve which corresponds to the mass loss on the TG (thermogravimetric) and DTG (differential – thermogravimetric) curves.

Low-temperature endo-effects ($T_{\text{max}} = 80.7$ and 108°C) accompanied by a weight loss (3.93%, 11.83%) at 128°C for the system with phenylalanine and at 136°C for the system with tyrosine are water desorption. When heated, complex compounds begin to decompose in the range of $168\text{--}227^\circ\text{C}$ with a weight loss of 17.48% for the systems with phenylalanine and in the range of $136\text{--}260^\circ\text{C}$ with a weight loss of 10.93% - for the systems with tyrosine.

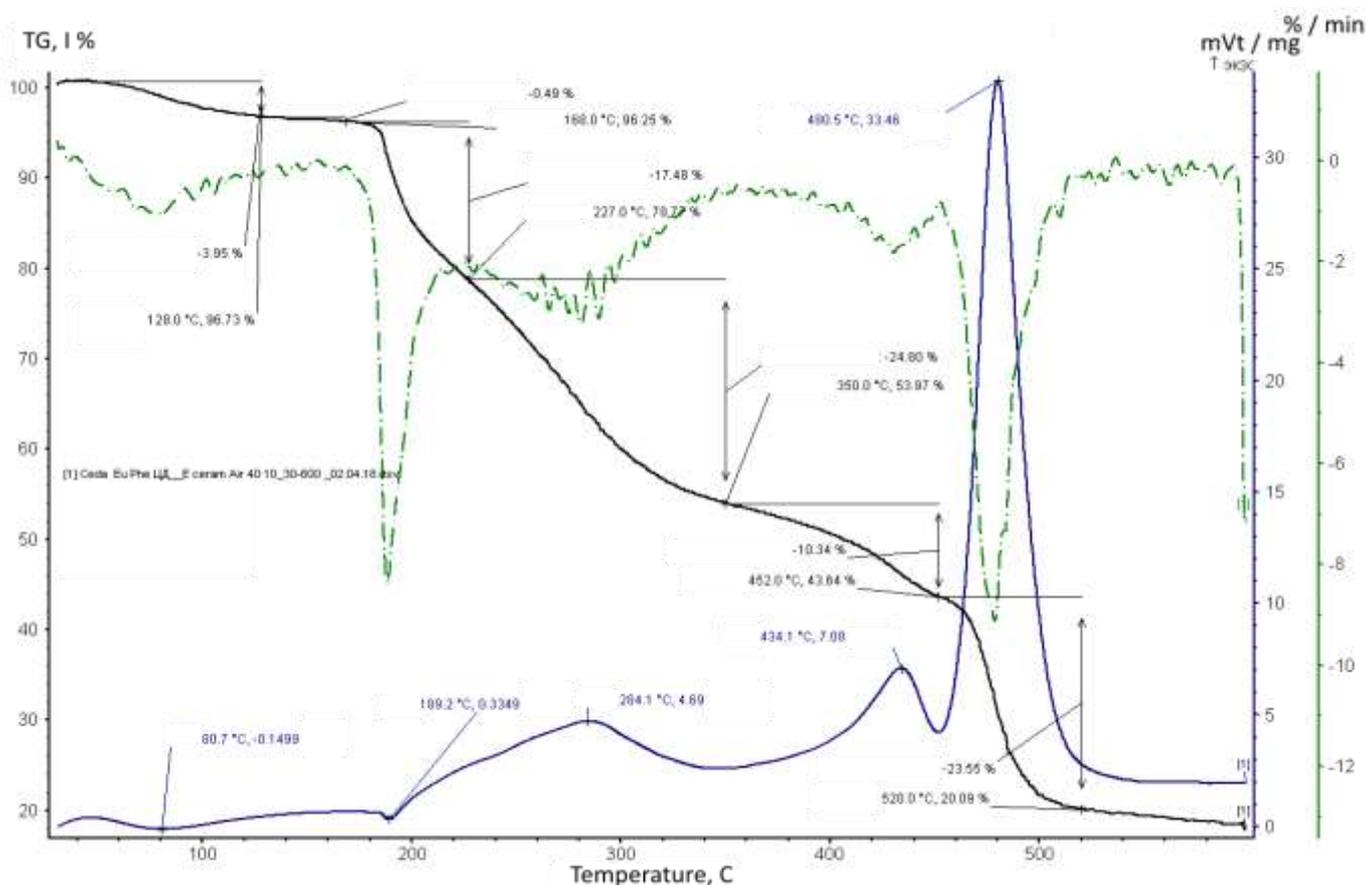


Fig. 2. Thermogram of the β -cyclodextrin complex with $\text{Eu}(\text{Phe})_3$

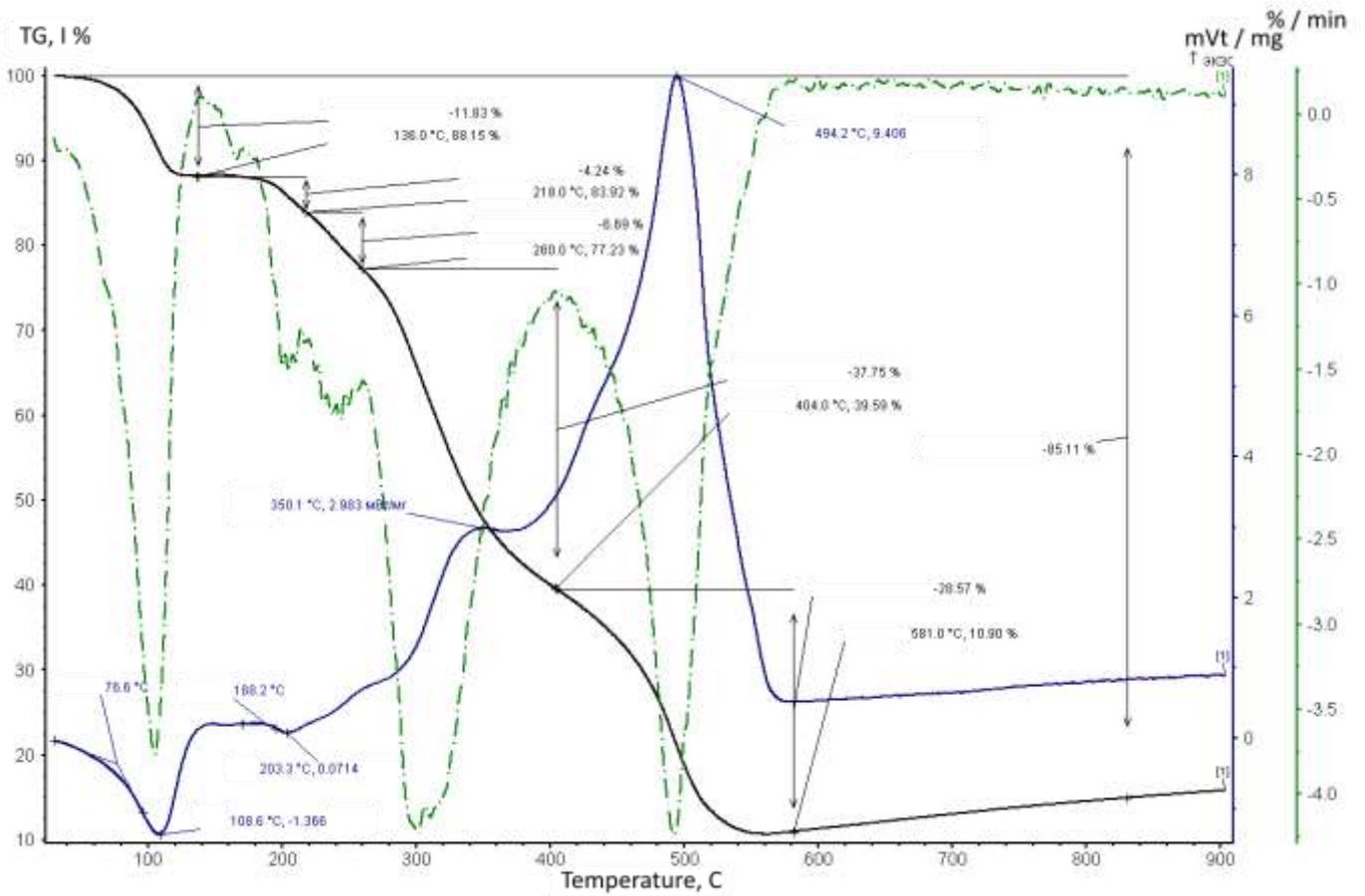


Fig. 3. Thermogram of the β -cyclodextrin complex with $\text{Eu}(\text{Tyr})_3$

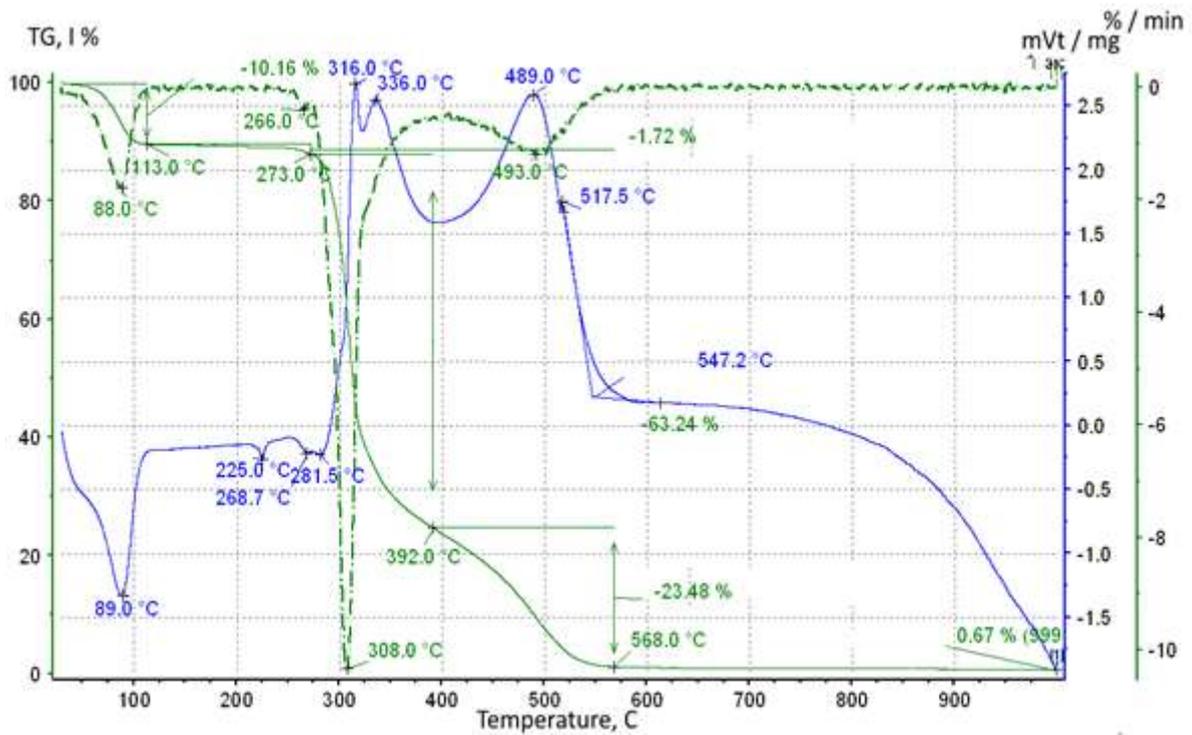


Fig. 4. β -cyclodextrin thermogram.

At 189.2 °C, a small endo-effect is observed. It corresponds to the beginning of the melting of the system with phenylalanine. For the system with tyrosine, the effect is observed at 203.3 °C. At $t = 227 - 520$ °C, for the system with phenylalanine and at $t = 260 - 581$ °C for the system with tyrosine, sharp weight loss is observed. It corresponds to thermo-oxidative destruction of the system. Exo-effects at 284.1, 434.1 and 480 °C for the system with phenylalanine and 350 and 494 °C for the system with tyrosine correspond to this process. Residual mass corresponds to lanthanide oxide.

Thus, formation of an inclusion system enhances the binding of water in the CD, but reduces thermal stability of the CD itself. Figure 2 shows the thermogram of β -cyclodextrin for comparison with the inclusion β -CD system.

Thermograms (Fig. 2–4) show that the low-temperature endoeffect ($T_{max} = 88$ °C) accompanied by a weight loss (10.16%) in the range of 20–150 °C refers to water desorption: calculation shows that the internal cavity of β -CD contains 7 water molecules.

When heated, cyclodextrin begins to decompose in the temperature range of 230–280 °C. The difference in the data on thermal destruction of CD is due to a large variety of methods for production and purification, as well as storage characteristics of CD. The thermogram shows small endoeffects at 225 °C and 268 °C with a total weight loss of 1.72%, accompanied by an endo-effect at 281 °C which corresponds to the CD melting. The β -CD melting is accompanied by oxidative destruction which destroys hydroxyl groups and glucopyranose units of cyclic oligosaccharide. This process corresponds to two intense exoeffects at 336 °C and 489 °C (with approximately equal energy / enthalpy) with a mass loss of 63.24% and 23.48%, respectively. A narrow peak of the exoeffect at 316 °C is imposed on them.

IR-spectroscopy (VERTEX 70 (BRUKER)) shows that in the ternary system, there are absorption bands characteristic of both β -CD and guest molecules (amino acids) (Table 2, Fig. 5).

TABLE I. DATA OF THERMOGRAMS OF β -CD COMPLEXES

	Samples		Description
	β -CD with $Eu(Phen)_3$	β -CD with $Eu(Tyr)_3$	
H ₂ O	80,7 °C	108 °C	Low-temperature endo-effect caused by water desorption
Endoeffects	189 °C	188-203 °C	Beginning of the melting process
Compound mass	227 - 520 °C	260 - 581 °C	Combustion of the main mass of the compound
remainder	20 %	10,90 %	Eu ₂ O ₃
Exoeffects	284 °C 434 °C 480 °C	350 °C 494 °C	Characterize the loss of main mass

TABLE II. FREQUENCIES IN THE IR SPECTRA FOR TERNARY COMPLEXES

	Atom grouping	Oscillation type	Frequency interval, cm ⁻¹
β -CD- Eu(Phen) ₃	OH	v	3400-3200
	NH ₂	v	3130-3030
	COO ⁻	v _s	
v _{as}			1604
v _s			1452
v _{as}			1583
β -CD- Eu(Tyr) ₃			

The spectra of solid-state NMR ¹³C were measured using JEOL ECA-400; the spectra were measured in a 4 mm rotor using a “wPMLG-3” technique at a rotational speed of 11.2 kHz; the amount of accumulation was 30. For ¹³C, the CP MAS method was used, the sample rotation speed was 15 kHz. According to NMR data, formation of the system was confirmed. According to the ¹³C NMR spectra for Eu (Phen) 3CD3 system and sources of phenylalanine and CD, phenylalanine interacts with cyclodextrin. Analysis of the NMR spectra shows changes in the chemical shifts of both the ligand and the CD (Fig. 6).

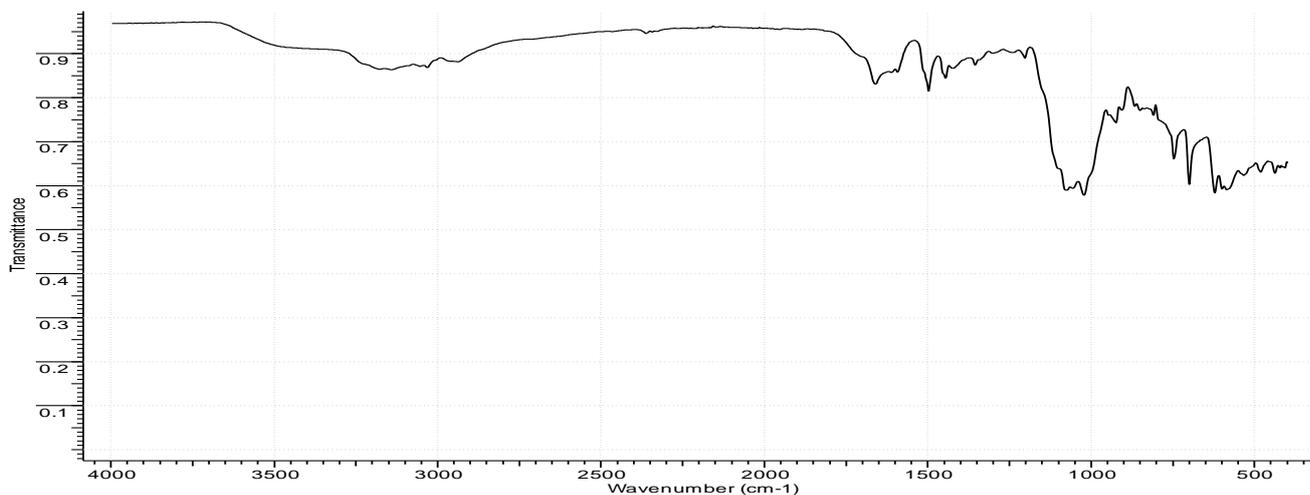


Fig. 5. IR spectrum of the β -cyclodextrin complex with $\text{Eu}(\text{Phe})_3$

The ROESY spectra were also recorded (Fig. 6). The presence of all cross-peaks in the spectra of all systems indicates spatial proximity of protons 3 and 5 of cyclodextrin and phenyl protons of amino acids. According to the data, amino acid molecules encapsulated in the cavity are involved β -cyclodextrin system formation.

According to the XRD data (energy dispersive X-ray fluorescence spectrometer EDX-800HS Shimadzu), the following system formation mechanism can be used: when the system is dissolved, dissolved $\text{Eu}(\text{Tyr})_3$ system is distributed and its entry into the CD cavity is accompanied by formation of intermolecular contacts, hydrogen bonds and hydrophobic interactions.

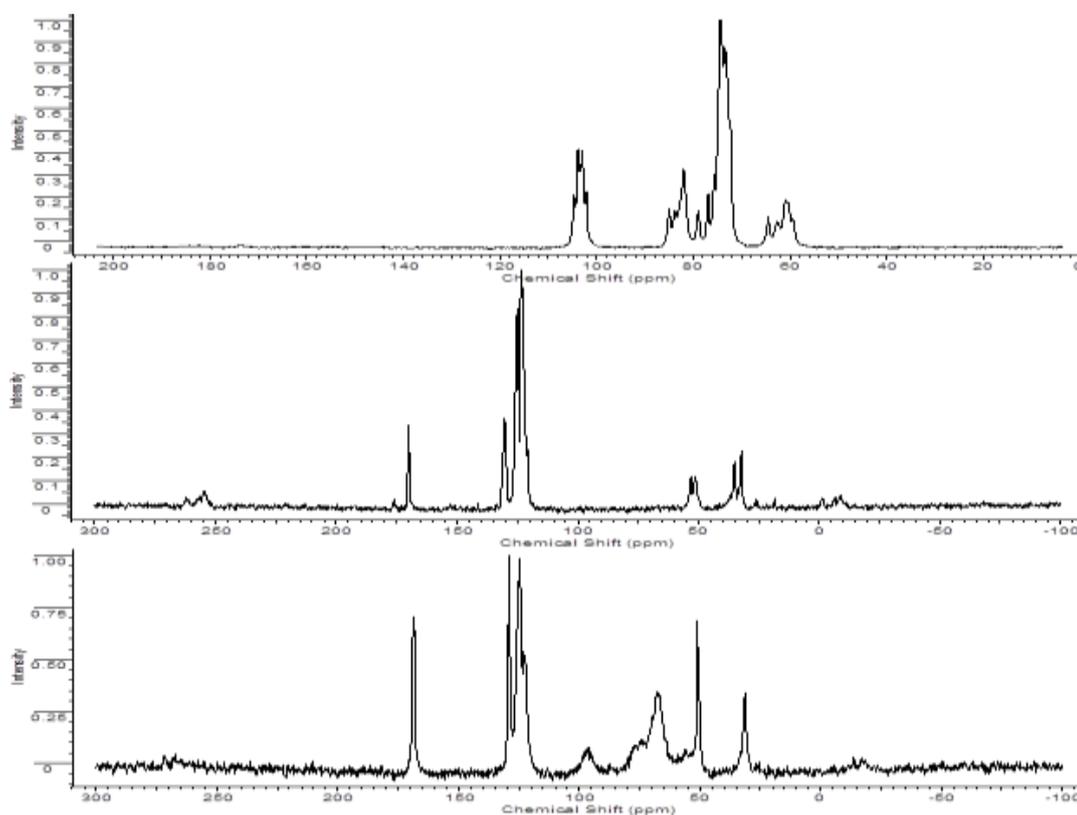


Fig. 6. NMR spectra ^{13}C with phenylalanine CD, $\text{Eu}(\text{Phen})_3(\text{CD})_3$.

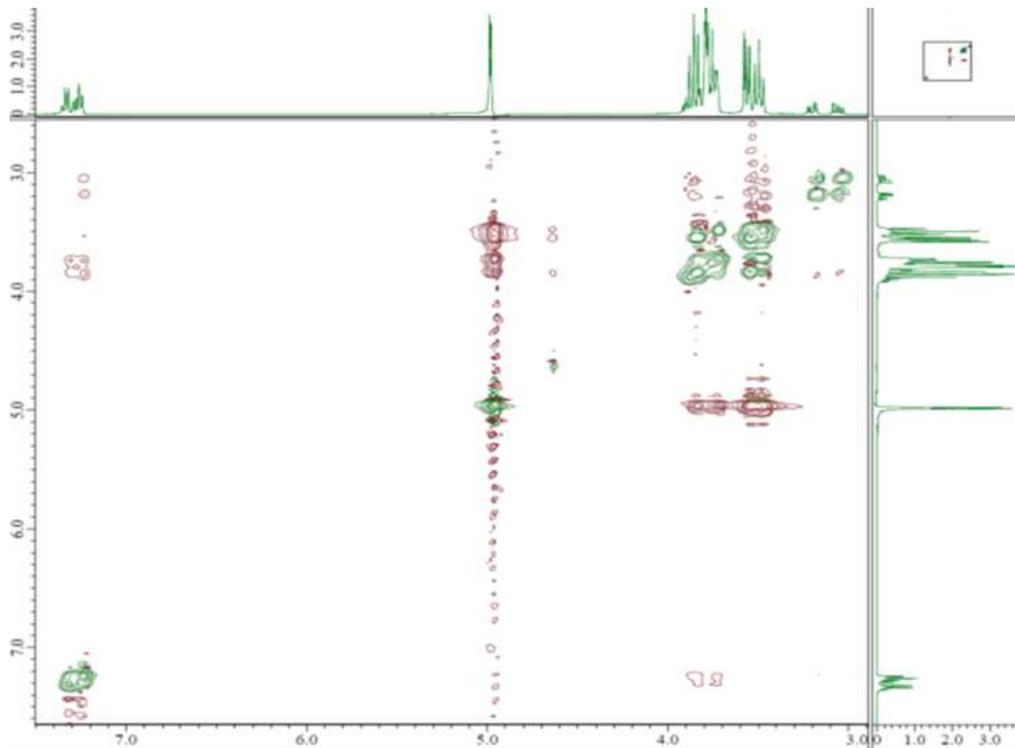


Fig. 7. ROESY spectrum of inclusion of the β-cyclodextrin complex with phenylalanine

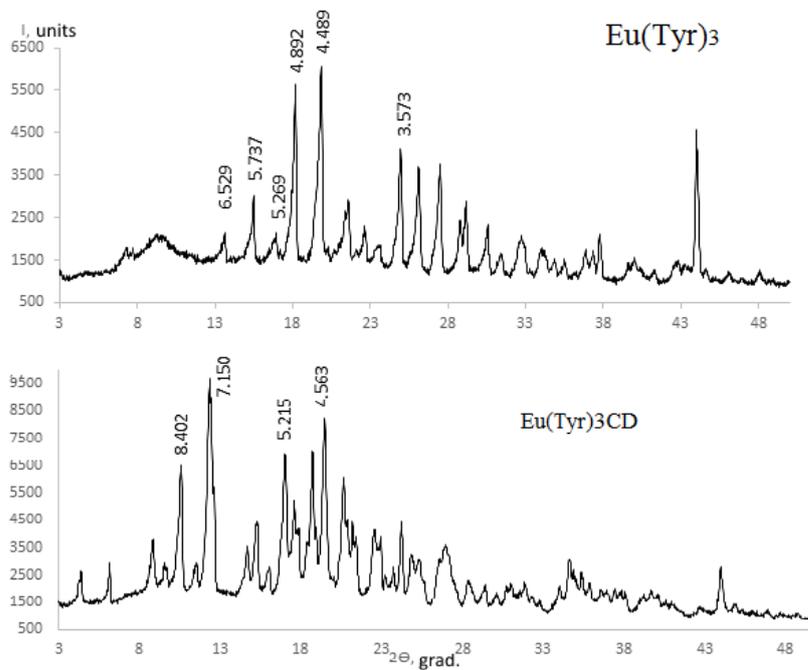


Fig. 8. Diffractograms $\text{Eu}(\text{Tyr})_3$ of the β-CD complex with $\text{Eu}(\text{Tyr})_3$

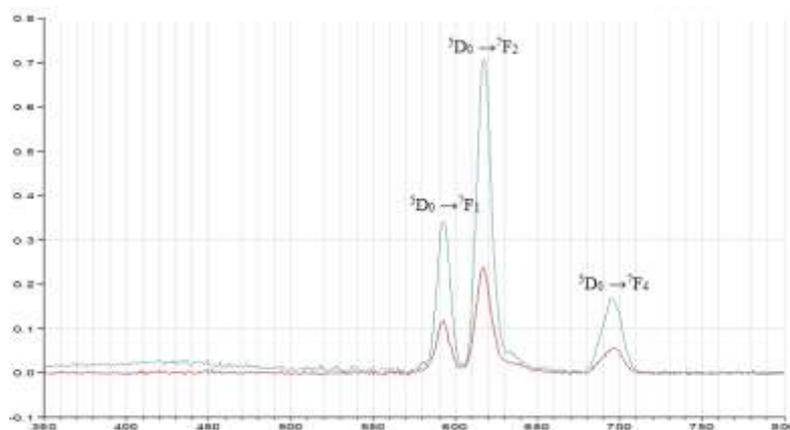


Fig. 9. The luminescence spectrum of $\text{Eu}(\text{Phen})_3(\text{CD})_3$

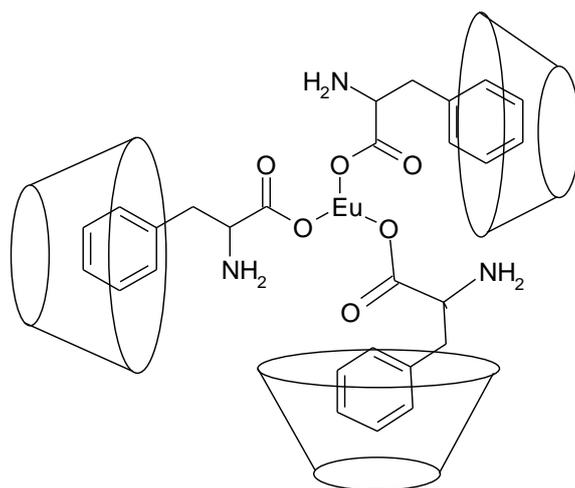


Fig. 10. Formula of $\text{Eu}(\text{Phen})_3(\beta\text{-CD})_3$

The spectra of excitation, recording, and luminescence kinetics were measured (Fluorat-02-Panorama (Lumex) spectrofluorometer). For recording, solid samples of the complex compounds were used; recording was conducted at a room temperature. Terbium benzoate was used as a standard for determining relative integral luminescence intensities, since benzoic acid is the simplest representative of aromatic carboxylic acids, and its complex compound with terbium (III) has luminescence in the visible region.

In the luminescence spectra at room and liquid nitrogen temperatures, there are three main peaks of europium Eu^{3+} in the region of ~ 594 nm, ~ 616 nm, ~ 693 nm which correspond to $^5\text{D}_0 \rightarrow ^7\text{F}_1$, $^5\text{D}_0 \rightarrow ^7\text{F}_2$, $^5\text{D}_0 \rightarrow ^7\text{F}_4$ electronic europium transitions. The highest intensity is accompanied by the $^5\text{D}_0 \rightarrow ^7\text{F}_2$ electronic transition with a maximum at ~ 616 nm. Thus, Eu^{3+} is included in the structure of the coordination compound. At the temperature of liquid nitrogen, intensity of the peaks increases due to temperature luminescence quenching.

Based on all the data, the structural formula of the ternary system is as follows:

IV. CONCLUSION

1) Within the research objectives, binary systems $\text{Eu}(\text{L})_3(\text{ClO}_4)_3 \cdot 2\text{H}_2\text{O}$ and ternary systems $\text{Eu}(\text{L})_3(\text{CD})_3 \cdot 2\text{H}_2\text{O}$ (q.e. Eu 8) were synthesized. The systems were studied using the thermogravimetric analysis, IR spectrometric analysis, X-ray phase analysis, solid-state ^{13}C NMR, and luminescence.

2) According to the data of physicochemical measurements, the composition and structure of complex compounds were confirmed. It has been suggested that during formation of the ternary system, the amino acid enters the cyclodextrin cavity and is preserved by hydrogen bonds; coordination with Eu^{3+} is due to the carboxyl group (COO^-) which is outside the cyclodextrin cavity.

3) The structure of the ternary system was formed.

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