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RESEARCH ARTICLE

Rare-earth element complexes with complexones, heparin, and antibiotics in biosystems for use as electrode-active materials in membrane ion-selective electrodes

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Abstract

Objectives. The creation of ion-selective electrodes (ISEs) based on rare-earth element (REE) complexes in environmentally friendly biosystems is of interest due to the increased relevance of environmental management. The work sets out to study the possibility of using REE complexes for creating ISEs sensitive to cefazolin. The created potentiometric sensors can be used for rapid determination of antibiotics in microvolume samples.

Methods. The work presents the synthesis of electrode-active REE complexes with cefazolin. In order to identify the obtained electrode-active substances and investigate their physicochemical characteristics, the following methods were used: elemental analysis with a scanning electron microscope, infrared spectroscopy, simultaneous thermal analysis, and potentiometry.

Results. Previously unstudied complexes of cerium and lutetium with cefazolin were obtained for use as an electrode-active substance for creating ISEs. The physicochemical characteristics of the complexes were investigated. For the created ISEs, the following characteristics were studied: performance characteristics, the dependence of electrode potentials on the analyte concentration, stability, and the response time of the electrode placed in the sample under study. The created membrane electrodes are stable, have a concentration range of operation of pC 1–3, and can be used in the pH range 4–8. Testing of the selectivity of the ISEs with respect to Na^+ and K^+ ions showed that the electrodes are effective even in a thousandfold excess. The performance of the electrodes was tested using model systems.

Conclusions. Novel REE–cefazolin complexes were successfully demonstrated for use as electrode-active substances for the manufacture of membrane ISEs sensitive to cephalosporin antibiotics.

Keywords
coordination compounds of rare-earth elements, complexons, heparin, cefazolin complexes, cephalosporins, ion-selective electrodes

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НАУЧНАЯ СТАТЬЯ

Комплексы редкоземельных элементов в биосистемах с комплексонами, гепарином, антибиотиками для применения в качестве электродактивного вещества мембранных ионселективных электродов

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Аннотация

Цели. В настоящее время остро стоит вопрос сохранения благоприятной экологической обстановки на планете, поэтому интересны работы по созданию ионселективных электродов (ИСЭ) на базе комплексов редкоземельных элементов (РЗЭ) в экологически безопасных биосистемах. Цель работы — изучить возможности использования комплексов РЗЭ для создания ИСЭ с откликом на цефазолин. Создаваемые потенциометрические сенсоры позволят проводить экспрессное определение антибиотиков в микрообъемных пробах.

Методы. В работе реализован синтез электродактивных комплексов РЗЭ с цефазолином. Для идентификации полученных электродактивных веществ и изучения их физико-химических характеристик использованы элементный анализ с помощью растрового электронного микроскопа, инфракрасная спектроскопия, синхронный термический анализ и потенциометрия.

Результаты. Получены ранее не исследованные комплексы церия и лютеция с цефазолином с целью их использования в качестве электродактивного вещества для создания ИСЭ. Изучены их физико-химические характеристики. Для созданных ИСЭ исследованы их эксплуатационные характеристики, зависимость электродных потенциалов от концентрации аналита, а также изучены стабильность созданных ИСЭ и время отклика сигнала электрода, помещенного в исследуемую пробу. Созданные мембранные электроды стабильны, имеют концентрационный диапазон эксплуатации pC 1–3 и могут быть использованы в диапазоне pH 4–8. Проверка селективности ИСЭ по отношению к ионам Na^+ и K^+ показала, что электроды эффективны даже при их тысячекратном присутствии. Работоспособность электродов проверена на модельных объектах.

Выводы. Показано, что впервые созданные комплексы РЗЭ с цефазолином могут успешно использоваться в качестве электродактивных веществ для изготовления мембранных ИСЭ на цефалоспориновые антибиотики.

Ключевые слова
координационные соединения редкоземельных элементов, комплексоны, гепарин, комплексы цефазолина, цефалоспорины, ионселективные электроды

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INTRODUCTION

The rapid development of the chemistry of complex compounds of rare-earth elements (REEs) has resulted in the accumulation of a large body of factual material on the physicochemical properties of the created complexes and their areas of application based on their unique properties. The individuality of individual representatives of REEs was first noted by Dmitri Mendeleev as "one of the true strengtheners of the Periodic Law" [1].

Today, environmental management is the focus of much attention. Therefore, studies on REE complexation processes in various biosystems are of particular interest, for example, when used in environmentally friendly complexones derivatives of succinic acid (CDSA). To minimize the negative impact of humans on the environment, not only are the methods of REE extraction and separation being improved, but also the various methods for their secondary utilization. The use of iminodisuccinic acid for the extraction of some REEs by adsorption was described [2]. In passing, attention should also be paid to the inverse problem involving the patented synthesis of iminodisuccinic acid using lanthanide catalysts [3].

Combined with the fact that these ligands in natural conditions are capable of rapid decomposition and do not accumulate in waste [4–7], the unique ability of CDSA to exhibit high complexing properties has found them a wide range of applications, including in "green chemistry" [8–11]. Of interest are the results of studying lanthanide complexes with biuret [12].

The introduction of REE ions into biosystems (for example, the human body) significantly increases the effectiveness of blood anticoagulants such as heparin. In investigating the complexation of heparin with REE, we conducted a thermochemical study of neodymium complexes with heparin. The dehydration of the Nd complex with heparin, which already begins at a temperature of 40°C, continues up to 190°C. Following dehydration at 190°C and up to 420°C, the glycosidic bond and carbon skeleton of heparin are decomposed. At a temperature of 400–450°C, some of the combustion products combine with neodymium to form $Nd_2(SO_4)_3$. During further decomposition (above 600°C), this is decomposed to neodymium oxysulfate $Nd_2O_2SO_4$ [13]. The lanthanide atoms are shown to be coordinated by heparin through carboxylate, hydroxyl, sulfonate, and aminosulfonate groups at a denticity of 4 [14].

The present paper presents the results of studying the processes of complexation of REEs with antibiotics, in particular, with cefazolin. It was previously shown that cefazolin in REE metal complexes is bidentate [15] due to the formation of coordination bonds through the amide and carboxylate groups.

Research into novel antibacterial agents is in demand due to their potential uses in the chemical and pharmaceutical industries. While antibiotics represent a widespread group of medicinal compounds, identifying their potential hazards to human health is one of the urgent problems of modern analytical chemistry. Diverse areas in which it is necessary to determine and control the content of antibiotics include pharmaceuticals, biological fluids of the human and animal body, food products, and wastewater from pharmaceutical enterprises [16].

Cephalosporin antibiotics are typically studied by spectroscopic, chromatographic, electrochemical, and other methods. The main methods used for determining cephalexin, cefuroxime, and cefixime in medicinal and biological media are chromatography [17, 18], spectroscopy [19], and voltammetry [20, 21]. However, such methods generally require expensive equipment, reagents, and qualified operators; moreover, they take a long time to complete and do not allow for rapid determination of antibiotic content in clinical and biochemical laboratories. Conversely, potentiometric sensors have shown the possibility of rapid determination of active substances even in microvolume samples [16, 22]. The rapid determination of antibiotics in biological fluids and dosage forms of drugs is necessary for studying physiological and biochemical processes occurring in the body, as well as for ensuring effective drug controls.

It has been established that molecules with antimicrobial activity are necessarily amphiphilic, i.e., also include hydrophobic regions [23]. The low water solubility of sufficiently hydrophobic REE complexes with cefazolin permits their use as an electrode-active substance in the manufacture of membrane ion-selective electrodes (ISEs) sensitive to cephalosporin antibiotics.

Thus, the present work is aimed at developing a new direction of research of the physicochemical characteristics of REE complexes with cefazolin to establish the possibility of creating ISEs sensitive to cefazolin.

EXPERIMENTAL

The potentiometric characteristics of the REE complexes with cefazolin were determined and the pH of the medium was monitored using an I-160MP ion meter (*Izmeritelnaya Tekhnika*, Moscow, Russia). The electrode response time was measured with a stopwatch. To record IR spectra, samples were prepared in the form of tablets with KBr (reagent grade, *Baza No. 1 Khimreaktivov*, Russia). The spectra of the samples containing 2 mg of the test substance per 200 mg of KBr were recorded with an Alpha Fourier transform infrared spectrometer (*Bruker*, Germany) in the range of 4000–400 cm^{-1}. Simultaneous thermal analysis of the samples was performed with an STA 449 F3 Jupiter simultaneous thermal analyzer (*Netzsch Group*, Germany) in an air atmosphere. Elemental chemical analysis of the samples was carried out with a JEOL JSM-6610LV scanning electron microscope equipped with an Oxford INCA energy dispersive spectrometer (*Oxford Instruments*, United Kingdom).

An ISE sensitive to cefazolin was created using cefazolin sodium salt (NaCzl, *Deko*, Moscow, Russia). The exact concentrations of REE chlorides solutions prepared from reagents of chemical purity grade (*Khimkraft*, Russia) were established by complexometric titration [24].

Electrode-active substances were obtained by mixing aqueous solutions of cerium or lutetium chloride and sodium cefazolin in a molar ratio of 1 : 4. Next, the resultant substances were separated by centrifugation and dried at room temperature (20°C) in a desiccator over a layer of silica gel. The thus obtained samples were stored in a desiccator over a layer of silica gel in a closed cabinet to avoid exposure to light. The stock solution of cefazolin having a concentration of 0.1 *M* was prepared by dissolving a weighed sample to form a basis for additional solutions obtained by dilution. Membranes were prepared using S-70 polyvinyl chloride (PVC, *SAYANKHIMPLAST*, Russia), dioctyl phthalate (DOP, *Khimprom-M*, Russia), and cyclohexanone (*Baza No. 1 Khimreaktivov*, Russia). The created ion-selective membranes contained 1 wt % electroactive substance, 1 wt % DOP, and 98 wt % PVC.

Before the experiment, the ISEs were soaked for 1 h in a 0.01 *M* cefazolin solution. The electrode potentials were recorded in the following electrochemical cell:

Ag	AgCl	Cefazolin solution (0.01 *M*) + + KCl solution (0.1 *M*)	Ion-selective membrane	Test solution	Saturated KCl solution	AgCl	Ag

RESULTS AND DISCUSSION

Table presents the calculated and experimentally determined elemental compositions of the metal complex. On the basis of the obtained data, the inner sphere of the metal complex can be unambiguously determined, with the exception of hydrogen atoms, which cannot be detected by X-ray electron microprobe analysis.

According to the obtained data, the samples do not contain sodium and chlorine. The composition of the inner sphere of the metal complex was established to correspond to the molar ratio [metal] : [ligand] = 1 : 3.

The similarity of the obtained spectra when comparing the IR spectra of pure sodium salt and synthesized compounds (Fig. 1) confirms that the interaction of cefazolin sodium salt with REE cations does not cause changes in the chemical structure of cefazolin.

Interpretation of the IR spectrum of cefazolin sodium salt showed that the broad band at 3430 cm^{-1} corresponds to vibrations of the hydroxyl group, which participates in the formation of hydrogen bonds with coordinated water molecules [25, 26].

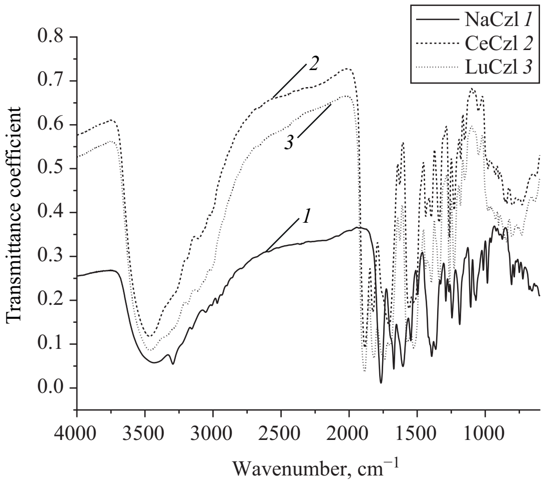

Fig. 1. IR spectra of (*1*) cefazolin, (*2*) cerium metal complex, and (*3*) lutetium metal complex

Table. Results of elemental analysis

Sample	Molecular formula	Elemental composition	C, %	N, %	O, %	S, %	Me, %
CeCzl_3	$C_{42}H_{42}CeN_{24}O_{12}S_9$	Calculated	33.51	22.34	12.76	19.15	9.30
		Found	34.94	22.34	13.05	19.72	9.36
LuCzl_3	$C_{42}H_{42}LuN_{24}O_{12}S_9$	Calculated	31.68	21.11	15.07	18.12	10.99
		Found	31.66	21.07	15.05	18.09	10.95

According to the published research data [26, 27], the carboxyl group is characterized by a wavenumber of 1761 cm^{-1}, while the band at 1680 cm^{-1} corresponds to the amide group –C=O. These wavenumbers of the characteristic absorption bands of the carboxyl and amide groups of cefazolin agree with the data given in an earlier work [19]; here, the shift of the band at 1545 cm^{-1} for symmetric stretching vibrations of the carboxyl group is noted to imply coordination through this group. We consequently assigned the band at 1490 cm^{-1} to vibrations of C=C of the aromatic structure. The bands at 1241, 1183, 1100, and 1062 cm^{-1} characterize vibrations of the CN group.

The presented spectra of our samples show a shift of the hydroxyl group band (3439 cm^{-1}), a shift of the amide –C=O vibration band (1681 cm^{-1}), and a shift of the symmetrical stretching vibration band of the carboxyl group (1566 cm^{-1}).

Since no significant shifts of the CN vibration bands were found, it can be concluded that nitrogen atoms do not participate in the coordination.

The coincidence of the ν(C–S–C) stretching vibration bands in both the sodium salt (669 cm^{-1}) and the metal complexes (670 cm^{-1}) of the thiazole ring indicates that the sulfur atom does not participate in the complexation process. A similar picture was also observed in the spectrum of the lutetium metal complex.

Taking into account the shifts of the absorption bands of the amide and carboxylate groups, we conclude that cefazolin is coordinated bidentately through the amide and carboxylate groups.

Figure 2 presents the results of thermal analysis of CeCzl (thermogravimetry (TG) and differential scanning calorimetry (DSC) curves). The mass loss in the temperature range from 39 to 120°C is due to the evaporation of the adsorption and crystallization water: the mass change in this range was 1.48%, while the mass change in the range from 100 to 120°C was 0.31%. The peak at 222.7°C corresponds to the destruction of the metal complex structure and oxidation of the ligand [15].

The evaluation of ISE stability confirmed that potential drift remains approximately constant, amounting to 2–5 mV/day. According to the stopwatch, the response time is about 45 s for 10^{-1}–10^{-3} *M* solutions. Figure 3 depicts the dependence graphs of the ISE potentials on the cefazolin concentration both for membranes with the cerium metal complex and those used with the lutetium metal complex.

In the range of negative decimal logarithms of concentrations of pC 1–3, the experimental points are described by a straight-line equation. The linear portion of the electrode function indicates the possibility of practical use of the ISE for determining cefazolin. We also took into account that the operation of the electrode can be affected by both the pH of the medium and the presence of accompanying cations. The selectivity coefficients for Na$^+$ and K$^+$ ($1.5 \cdot 10^{-3}$ and $1.4 \cdot 10^{-3}$, respectively) were

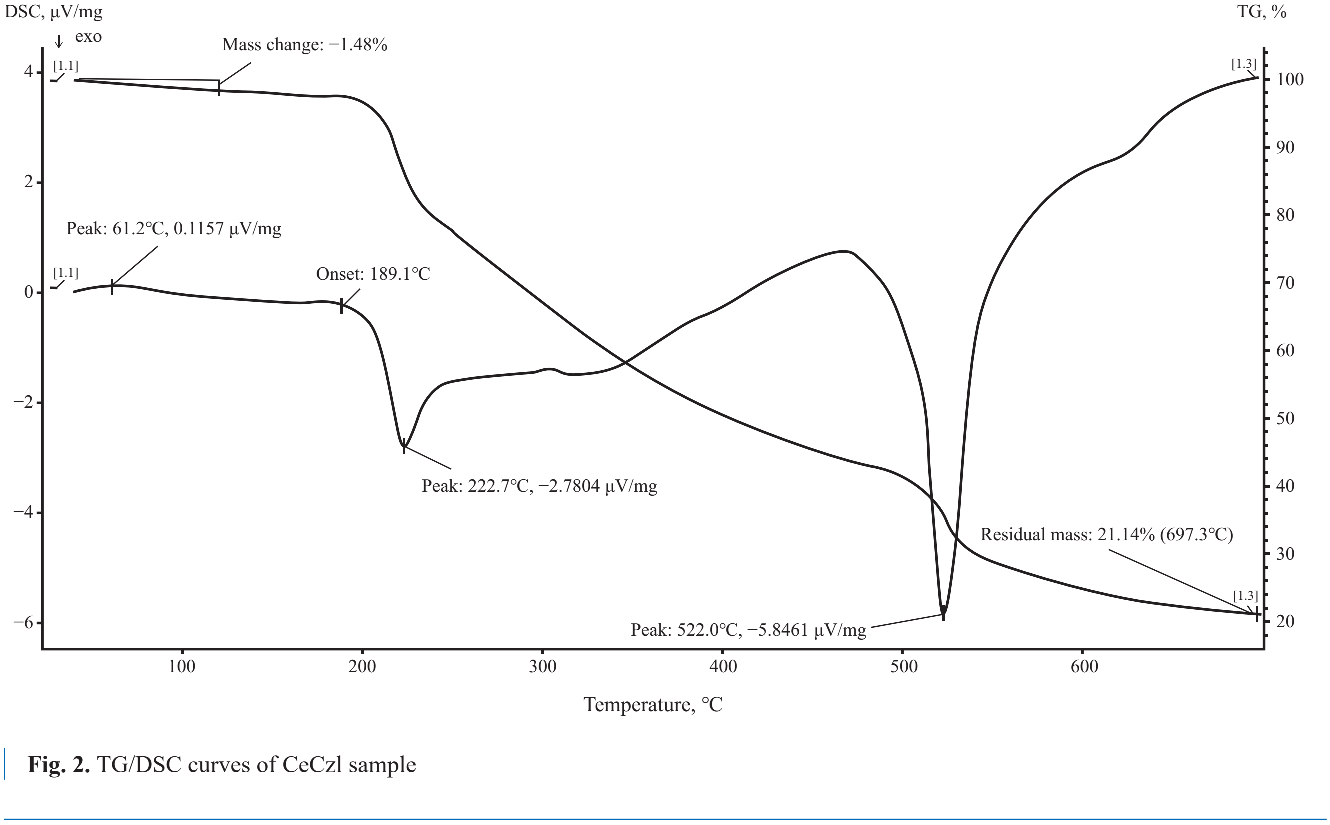

Fig. 2. TG/DSC curves of CeCzl sample

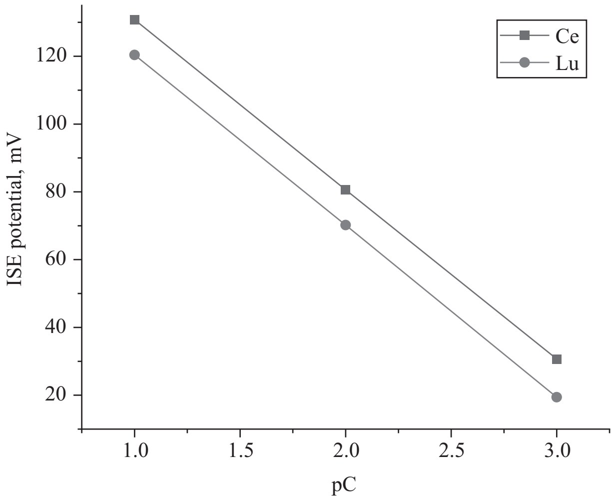

Fig. 3. Dependence of the ISE potentials of (*1*) the metal complex of cerium and (*2*) the metal complex of lutetium on the cefazolin concentration

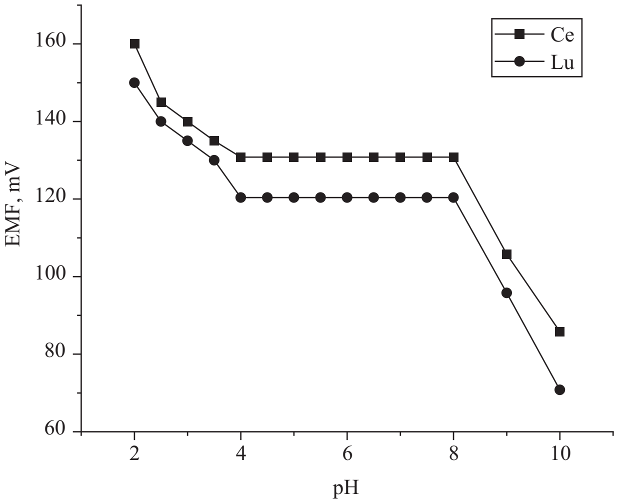

Fig. 4. Dependence of the electromotive force (EMF) of the cell with ISE on the pH of the cefazolin solution

determined by the mixed solution method. The electrode potential is shown to be independent of the acidity of the medium in the pH range of 4–8 at a cefazolin concentration of 0.1 *M*.

Figure 4 illustrates the dependence of the electromotive force (emf) of the created ISEs on the pH of the cefazolin solution. As can be seen from the figure, the ISE potential is independent of the pH of the solutions in the range of 4–8.

This indicates that the created ISEs have a fairly high stability. However, at pH ≤ 4 and pH ≥ 8, jumps in the electrode potential are observed, indicating a nonlinear change in the concentration of the antibiotic in an alkaline and acidic medium, which is typical for most ISEs [28].

CONCLUSIONS

The conducted studies confirm that ISEs in which the electrode-active substances are REE complexes with cefazolin are promising for use in determining antibiotics in microvolume samples. The created membrane electrodes demonstrate stability, have a concentration range of operation of pC 1–3, and can be used in the pH range of 4–8. Testing of the selectivity of the ISEs with respect to Na^+ and K^+ ions demonstrated that the electrodes are effective even when used in thousandfold excess. The performance of the electrodes was tested on model objects.

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Authors' contributions

T.V. Kryukov—experiments, collecting and processing the research materials.

M.A. Feofanova—idea, general guidance.

V.M. Nikol'skii—research concept, scientific editing.

A.I. Ivanova—performing experiments, selecting the optimal conditions for experiments.

I.A. Kaplunov—scientific consulting at all stages of work.

The authors declare no conflict of interest.

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