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Complex of Ca(II) with Ceftriaxone: Synthesis, Structure, Spectral and Antibacterial Properties

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Abstract. The calcium complex of ceftriaxone was synthesized and characterized by elemental, atomic-emission analysis, TGA, IR spectroscopy and density functional theory calculations. The luminescence and antibacterial properties of the ceftriaxone disodium and calcium complex were investigated. Ca(II) complex was obtained in a crystalline form, cell parameters of the compound were determined. Ceftriaxone was coordinated to the calcium ion by the oxygen of the triazine cycle in the 6th position, the nitrogen of the amine group of the thiazole ring, and the oxygens of the lactam carbonyl and carboxylate groups. The complex of Ca(II) with ceftriaxone was screened for antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, and the results were compared with the activity of ceftriaxone disodium salt.

Keywords: ceftriaxone, calcium, DFT, IR spectroscopy, luminescence properties, antibacterial screening.

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Комплекс Ca(II) с цефтриаксоном: синтез, структура, спектральные и антибактериальные свойства

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Аннотация. Кальциевый комплекс цефтриаксона был синтезирован и охарактеризован с помощью элементного, атомно-эмиссионного анализа, ТГА, ИК-спектроскопии и расчетов теории функционала плотности. Исследованы люминесцентные и антибактериальные свойства динатриевой соли цефтриаксона и комплекса цефтриаксона с кальцием. Комплекс Ca(II) получен в кристаллическом виде, определены параметры кристаллической решетки соединения. Цефтриаксон координировался к иону кальция через атом кислорода триазинового цикла в 6-м положении, атом азота аминогруппы тиазольного кольца и атомами кислорода карбонильной и карбоксилатной групп. Комплекс Ca(II) с цефтриаксоном обладает антибактериальной активностью против *Staphylococcus aureus*, *Escherichia coli* и *Pseudomonas aeruginosa*, полученные результаты сравнивали с активностью динатриевой соли цефтриаксона.

Ключевые слова: цефтриаксон, кальций, теория функционала плотности, ИК-спектроскопия, люминесцентные свойства, антибактериальный скрининг.

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Introduction

Modern medicine needs drugs, the use of which would solve a wide range of problems associated with the intervention of bacteria in the organism [1]. Cephalosporins are a broad class of beta-lactam antibiotics meeting medical requirements. Ceftriaxone (H_2CefTria) (Fig. 1) is the III generation antibiotic of a wide action range against a number of Gram-positive and Gram-negative bacteria [2, 3]. Ceftriaxone's bactericidal activity is caused by its inhibition of the synthesis of the bacterial cell wall [4]. At the same time, the rats study example has shown, that ceftriaxone has an anticonvulsant effect [5]. One way to solve this problem is to develop new antibacterial drugs based on known antibiotics, for example, complex formation with metal ions.

Nowadays several metal complexes were synthesized with ceftriaxone. Anacona et al. obtained complexes of ceftriaxone with Mn(II), Co(II), Cu(II), Cd(II), Sn(II) and Fe(III) in the ratio of M: L=1:1 [6–8]. Fe(III) was bound with the antibiotic through the oxygen atoms of lactam, carboxyl and aminocarbonyl groups [8]. In other complexes ceftriaxone was coordinated to M(II) by oxygen of carboxylate, lactam carbonyl, amino groups and two atoms N, O, of triazine cycle except Sn(II) compound in which the oxygen atom of triazine cycle was not bond with tin(II) [6, 7]. However, other authors synthesized compounds of ceftriaxone with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II) in the ratio of M: L=1:1, in which the antibiotic had another way of binding to metal ions [9]. In these compounds, ceftriaxone was chelated to Co^{2+}, Cd^{2+}, Hg^{2+}, Mn^{2+} and Ni^{2+} through the oxygen atoms of the carboxyl and lactam groups. The antibiotic was coordinated to Zn^{2+} and Cu^{2+} by the oxygen atoms of lactam and carboxylate groups, and nitrogen of the amino group [9]. Only in the complex of Pb(II) with ceftriaxone was had, a similar type of coordination of ceftriaxone with our Ca(II) complex [10]. Moamen S. Refat et al obtained calcium complex with ceftriaxone. However, this complex has a different structure and luminescence and antibacterial properties were not study [11]. Many metal complexes of this antibiotic have toxicological and pharmacological properties but the problem is that some of them lose their antibacterial properties *in vivo* when they interact with protein or human plasma [12–14].

Calcium is biogenic metals contained in the bones and teeth of the human body. It is involved in blood clotting, contained in the cytoplasm, in some enzymes and hormones [15]. Thus, ceftriaxone

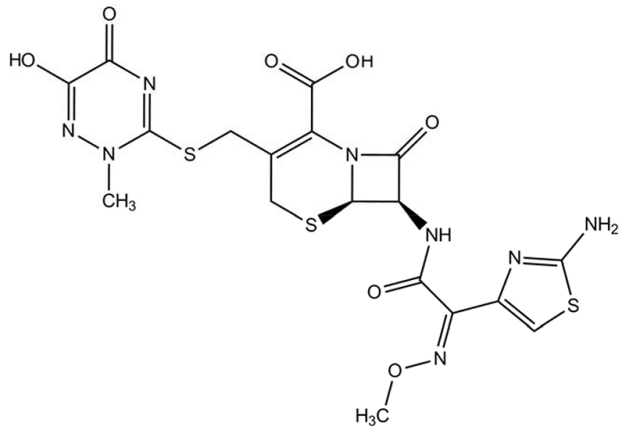

Fig. 1. Structure of ceftriaxone acid

binds with calcium ion in the organism of newborn children, which leads to cardiopulmonary, urolithiasis and renal injury [16, 17]. Simultaneous injection of calcium and ceftriaxone preparations into the body of patients results in sediments in blood plasma, lungs and kidneys and, as a consequence to the death of newborns [16–19].

Thus, a systematic study of metal ion complexation with antibiotics is crucial for better comprehension of metal–ceftriaxone binding mechanisms in living tissues and organisms. The synthesis of such metal–antibiotic complexes is an important area of pharmacology and medical chemistry [20–21].

This paper deals with the synthesis of the Ca(II) complex of ceftriaxone and a multicenter study including IR spectroscopy, TGA measurements, luminescent and antibacterial properties. DFT investigation of molecular structure and vibrational properties was carried out to obtain more information.

Experimental

Measurements

The content of sodium and calcium ions was performed by capillary electrophoresis instrument «KAPEL – 104T» with a UV photometric detector. The content of chloride ions was measured by argentometric titration using silver-silver chloride electrodes. The elemental analysis for C, N, H, S was performed out by Chromatographic analyzer HCNS-O EA1112 (Flash, USA). Thermogravimetric analysis (TGA) was carried out by simultaneously using Shimadzu XRD-7000 thermal analyzer with coupled IR attachment Nikolet 380 (USA) in the argon atmosphere within 300–580 K at the scan rate of 10 K/min. The IR spectra of ceftriaxone disodium salt and complex were obtained from a KBr pellet within 4000–400 cm^{-1} with a Nicolet 6700 spectrometer and spectra were processed in the Omnic program. The CuK-edge X-ray adsorption spectra were collected with a "X'Pert Pro" (PANanalytical) diffractometer. Cell parameters were calculated using EXPO 2014 [22]. The luminescence spectra were obtained by the scanning spectrofluorimeter «Cary Eclipse» (Varian, Australia).

Synthesis

All chemicals were obtained in pure form, no further purification was performed: $CaSO_4 \cdot 2H_2O$ (Aldrich), ceftriaxone disodium salt (hemi)heptahydrate (Qilu Antibiotics Pharmaceutical Co., Ltd).

Synthesis of calcium complex

The ceftriaxone disodium salt (hemi)heptahydrate (0.5 g, $7.6 \cdot 10^{-4}$mole) was dissolved in 8 ml water-ethanol medium (1:1) and consequently mixed with $CaSO_4 \cdot 2H_2O$ ($1.5 \cdot 10^{-4}$mole), pH=6.5. The milky precipitates were formed in 1h at room temperature 25 °C. Then, the reaction mixtures of complex of Ca(II) was filtered, washed with H_2O, Et_2O and dried in a sealed vessel with granulated $CaCl_2$. Elemental Anal. Calcd for $C_{18}H_{24}N_8O_{11}S_3Ca$ (%): C, 32.5; H, 3.6; N, 16.9; S, 14.5; Ca, 6.0. Found: C, 32.1; H, 3.8; N, 16.9; S, 14.3; Ca, 6.0.

IR ($C_{18}H_{24}N_8O_{11}S_3Ca$): 3404 (b), 3269 (b), 2932 (vw), 2890 (vw), 1754 (vs), 1661 (s), 1576 (vs), 1536 (s), 1497 (s), 1434 (s), 1401 (s), 1362 (s), 1286 (w), 1207 (w), 1134 (s), 1108 (s), 1039 (s), 884 (w), 799 (w), 670 (w), 601 (w), 515 (w), 472 (w).

IR ($C_{18}H_{34}N_8O_{10.5}S_3Na_2$): 3427 (b), 3266 (b), 3114 (vw), 2930 (vw), 1741 (vs), 1648 (vs), 1602 (vs), 1533 (s), 1497 (s), 1395 (s), 1365 (s), 1283 (w), 1181 (w), 1154 (w), 1098 (w), 1032 (s), 802 (w), 726 (w), 601 (w), 497 (w).

Computational methods

The geometry optimization and harmonic vibrational frequency calculations of the most stable conformers were performed with B3LYP [23] density functional in combination with SBKJC(p, d) basis set [24, 25] augmented with s diffuse functions, as implemented in the GAMESS suite of electronic structure programs [26, 27]. The relativistic effective core potential (ECP) was used for Ca atom. The applicability of this basis set and ECP to such complexes was demonstrated earlier [28, 29]. The Grimme's D3 dispersion correction of ceftriaxone with Ca(II) was used in all DFT calculations [30]. The partial atomic charges were obtained from Mulliken population analysis. All molecular structures were visualized by the Chemcraft program.

Antibacterial activity

The complex were screened *in vitro* for antibacterial activity against Gram-positive bacteria *Staphylococcus aureus* 25923 and Gram-negative bacteria *Escherichia coli* 25922 and *Pseudomonas aeruginosa* 13883. The effects of disodium ceftriaxone and complex on the bacteria were investigated using the paper disk diffusion method [31]. The method included the following steps: (1) preparation of the Mueller–Hinton growth medium; (2) preparation of the micro-organism suspensions of a 0.5 McFarland standard (final concentration final concentration 1×10^8 CFU mL^{-1}); (3) inoculation; (4) pouring the nutrient agar onto a plate and its solidification; (5) drop wise addition of the test substance to a 5 mm diameter filter paper disk placed at the center of each agar plate followed by incubation; and (6) measuring the diameters of the inhibition zones. The bacteria were cultured in an incubator for 18–24 h at 36 °C. Standard disks were impregnated with the solutions of the compounds in phosphate buffer (pH 6).

Results and discussion

The results of chemical and elemental analysis showed that the ratio of the M: L=1:1. The chemical analysis gave no evidence of sodium ions presence in the complex. Hence, the compounds have the chemical composition of [CaCefTria]·$4H_2O$. Compound is soluble in water and insoluble in EtOH and acetone. The complex is obtained in crystalline form. Cell parameters were determined for the [CaCefTria]·$4H_2O$ is: a =16.436, b = 15.820, c =10.957, α =108.186, β = 98.864, γ =105.858, V = 2512.69$Å^3$, space group symbol: P-1. A single crystal failed to grow because its destruction in an aqueous solution after 8 hours and at heating above 35 °C.

Thermal analysis

The thermal analysis of the compound [CaCefTria]·$4H_2O$ showed that the mass of compound decreased by 10.9 % (Calc. 9.8 %) from 302 to 394K, which was equivalent to four molecules of crystallization water (Fig. 2). A considerable loss of mass exceeding 394K was caused by ligand decomposition. Thermal decomposition evolved by emission of NH_3, CO_2 and HNCO. The mass loss at 394K and 560K was followed by exoeffect and at 372K – by endoeffect.

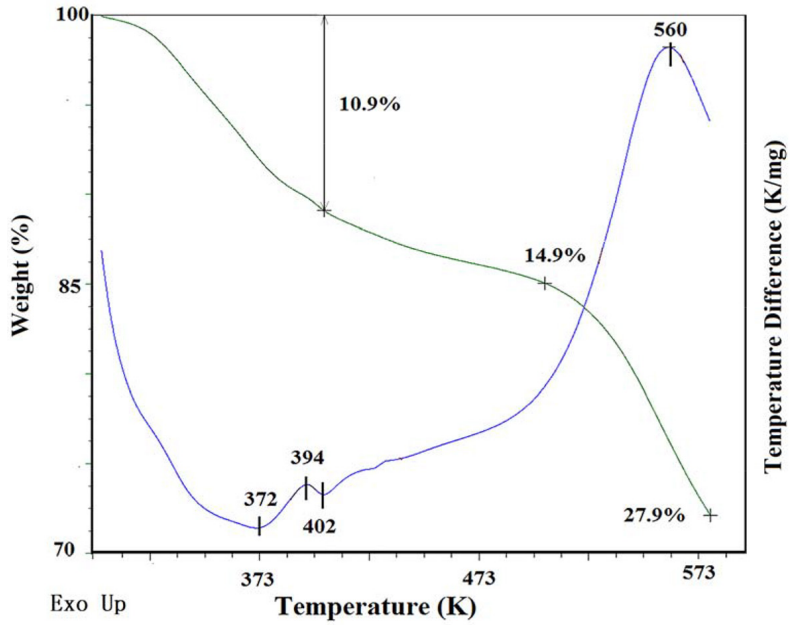

Fig. 2. Differential scanning calorimetry of [CaCefTria]·4H_2O in temperature range of 300–580K in inert atmosphere

Fluorescence

The presence of aromatic rings in the molecules of cephalosporins suggests that they can have luminescent properties. When the compound of calcium complex was irradiated with ultraviolet light, intense blue-green luminescence arose, the characteristics of which were close to the characteristics of disodium ceftriaxone luminescence. The absorption and emission spectra in the UV range of frequencies was due to the presence of a π-conjugated electron system of bonding and antibonding molecular orbitals with electronic transition energies. Disodium ceftriaxone exhibited luminescent properties. The excitation spectra were recorded in the range of 300–425 nm, the luminescence spectra were recorded in the range of 400–650 nm (Fig. 4). Excitation and luminescence maximum of complex was shifted relative to the maximum excitation and luminescence of Na_2CefTria·3.5H_2O. The complex [CaCefTria]·4H_2O in the near-UV demonstrated excitation spectra in the range of 300–400 nm and had the intractable maximum at λ_{max} = 341 nm. The luminescence spectrum range was a Gaussian curve at λ_{max} = 495 nm, which corresponded to the transition of the π→π* in the ring 8-oxo-5-thio-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (Fig. 3). Duration of an afterglow of the complex did not exceed 10^{-6}, which suggests it may relate to fluorescence.

IR spectroscopy

The FT-IR spectra of disodium ceftriaxone and [CaCefTria]·4H_2O were analyzed to establish the type of coordination of ceftriaxone to metal ions. A ceftriaxone has several donor atoms: a nitrogen atom of amino group, oxygen atoms of carboxylate, lactam, and amide carbonyl group and oxygen of thiazole cycle. In the IR spectrum of the complex

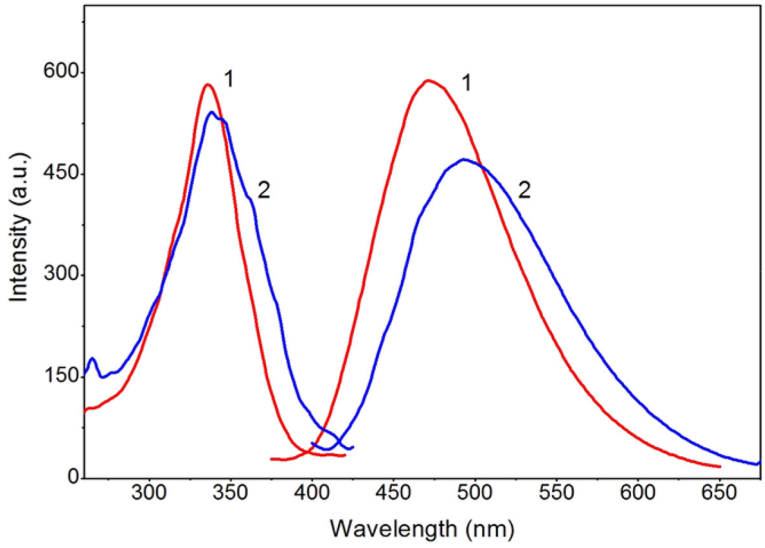

Fig. 3. Excitation spectra of compounds ($Na_2CefTria{\cdot}3.5H_2O$ – 1, $[CaCefTria]{\cdot}4H_2O$ – 2, λ_{max} = 341 nm) at left and luminescence spectra of compounds ($Na_2CefTria{\cdot}3.5H_2O$ – 1, $[CaCefTria]{\cdot}4H_2O$ – 2, λ_{max} =495 nm) at right

Table 1. Experimental IR frequencies and calculated B3LYP vibrational frequencies of Ca(II) with ceftriaxone, cm^{-1}

	Ca(II)	
Exp. IR freq.	Calc. IR freq.	Functional group
1754	1744	ν(COO^-) + ν(C=O) oxo group + ν(C-O)-triazine + ν(C=O) lactam
1661	1670	ν(C–C) cephem + r(CH_2) cephem
1576	1561	ν(C–C) aminothiazole + ν(C=N) triazine + ν(C-O)-triazine
1536	1526	ν(C=N) aminothiazole + ν(C=N) triazine + ω(NH_2) aminothiazole
1497	1504	ν(C=N) aminothiazole + ν(C=N) triazine + δ(CH_3) triazine + δ(NH_2) aminothiazole
1434	1432	δ(CH_3)
1401	1412	δ(CH_3) triazine + δ(CH_2) cephem
1362	1363	ν(COO^-) + ν(C-O)-triazine + ν(C=N) triazine
1286	1275	ν(C-N) cephem + δ(CH) lactam
1207	1210	ω(CH_2) cephem + δ(CH) lactam
1134	1135	τ(CH_3) triazine
1108	1103	ν(C=N) lactam + r(CH_2) + ν(C–C) lactam

ν(C=O-lactam)=1754 cm^{-1} vibration is shifted in the spectrum of the complex relative to spectrum of disodium ceftriaxone ν(C=O-lactam)=1741 cm^{-1} (Table 1, Fig. S1 and Fig. S2, Supplementary File: http://journal.sfu-kras.ru/article/144180#applications). This indicates that the oxygen of the lactam group is bound to the metal ion. The IR spectra show that the wavenumbers of the ν(C=O)-triazine=1648 cm^{-1} ($Na_2CefTria{\cdot}3.5H_2O$) is shifted after ceftriaxone coordination to metal ion ν(C=O)-triazine=1661 cm^{-1} ($[CaCefTria]{\cdot}4H_2O$). The shift of the ν(C=O)-lactam and ν(C=O)-

triazine groups vibrational wavenumbers leads to the formation of chelate complex. Symmetric and asymmetric stretching vibrations of COO^- group belong to the bands in the 1300–1700 cm^{-1} spectral region with C=O absorption bands observed in the 1600–1700 cm^{-1} range ($Na_2CefTria{\cdot}3.5H_2O$: $\nu_{as}(COO^-)$=1602 cm^{-1} and $\nu_s(COO^-)$=1395 cm^{-1}) [32–34]. In the experimental IR spectrum of the complex $\nu_{as}(COO^-)$=1576 cm^{-1} and $\nu_s(COO^-)$=1362 cm^{-1}. These shifts indicate that the carboxylate group (COO^-), the lactam carbonyl group (C=O), and the oxo group of the triazine ring are involved in the formation of a bond with metal ions. The broad banding of the complex spectrum from 1700 to 1600 cm^{-1} has high intensity and low resolution due to the overlap of several vibrational modes, including ν(C=O)-amide, ν(C=O)-triazine, $\nu_{as}(COO^-)$, ν(C=C), and ν(C=N). This analysis is in agreement with previous studies where ceftriaxone is described as a polydentate ligand [35, 36].

Computational studies

A single crystal of complex failed to grow, thus quantum chemical calculations were performed. Full conformation analysis was carried out earlier [10] using CONFLEX 6.0 program with MMFF94s molecular mechanics force field and Newton–Raphson method for geometry optimization [37, 38]. The results showed the two $CefTria^{2-}$ dianions in the most stable conformations. This investigation indicated that the s-cys–s-cys conformer is more energetically favorable than the s-trans–s-cys conformer [37]. The more energetically favorable s-cys–s-cys conformer geometry was used as a ceftriaxone dianion involved in the complex formation. The geometry of the $CefTria^{2-}$ dianion in that conformation was optimized with B3LYP density functional theory as in an earlier study [32].

According to the B3LYP calculations, the coordination of I is 15.7 kcal M^{-1} lower in energy than the coordination of II for the Ca(II) compound. This correspondence indicates that complex has I coordination because of more favourable energy values (Fig. 4).

Table 1 summarizes the comparison of experimental and calculated vibrational frequencies of the compounds of calcium and magnesium with ceftriaxone. The average deviations of the B3LYP frequencies from the experimental values are 6.7 cm^{-1} for Ca(II). The maximum absolute deviations are 14.6 cm^{-1}. It was found that all calculated vibrational frequencies were in good agreement with the experimental IR frequencies.

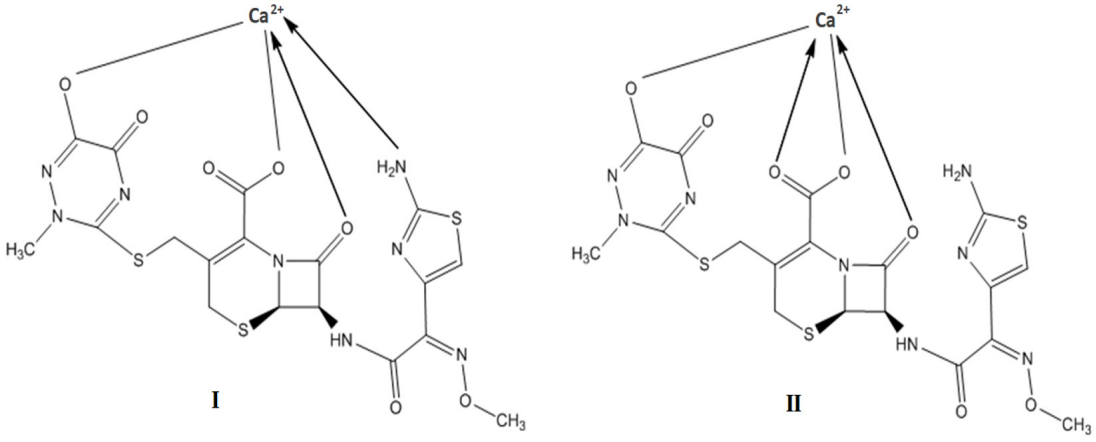

Fig. 4. Possible structures of ceftriaxone complex with Ca(II)

Microbiological screening

The cephalosporins are the antibiotics of broad-spectrum coverage. Antibacterial properties of complex salts can be increased or decreased in relation to disodium ceftriaxone. The biological activities of disodium ceftriaxone and complex were studied against Gram-positive and Gram-negative bacteria in the concentrations of 0.4, 0.6 mg mL^{-1}. The effects of compounds on the growth of such bacterial strains as *E. coli*, *S. aureus* and *Pseudomonas aeruginosa* are summarized in Table 2. The increase of antibacterial activity of [CaCefTria]·$4H_2O$ (50–63 %) relative to the biological activity of Na_2CefTria against *Staphylococcus aureus* may be explained by the formation of a chelate through the oxygen atom of lactam group and the simultaneous effect of the complex. The biological activity of the calcium complex of ceftriaxone slightly changed relative to the biological activity of Na_2CefTria against *Escherichia coli* in the concentrations of 0.4 and 0.6 mL^{-1}. Table 2 shows that the [CaCefTria]·$4H_2O$ did not have antibacterial activity against *Pseudomonas aeruginosa* and we observed the growth of bacteria. The increase of antibacterial activity of metal complex of ceftriaxone may play an important role in the inhibition of bacterial growth [39].

Table 2. Antibacterial activity of ceftriaxone disodium salt and calcium complex

Compound	Concentration, mg mL^{-1}	Zone of inhibition (mm)		
		Staphylococcus aureus	*Escherichia coli*	*Pseudomonas aeruginosa*
[CaCefTria]·$4H_2O$	0.4	40	45	growth
	0.6	50	47	growth
Na_2CefTria	0.4	20	46	38
	0.6	there is no growth	46	42

Conclusion

The compound [CaCefTria]·$4H_2O$ was synthesized by the reaction of ceftriaxone disodium salt (hemi)heptahydrate with metal salt in water–ethanol medium. The structure of the complex was studied using elemental, atomic-emission analysis, TGA, IR spectroscopy and DFT calculations. TGA indicated the existence of four crystallization water molecules in the complex. The combination of research methods established that ceftriaxone is coordinated to calcium ion by the oxygen of the triazine cycle in the 6th position, the nitrogen of the amine group of the thiazole ring, and the oxygens of the lactam carbonyl and carboxylate groups. The ceftriaxone disodium and calcium complex have luminescence properties, in particular fluorescence. The [CaCefTria]·$4H_2O$ had antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, and no growth was revealed for a single colony of *Staphylococcus aureus* at the concentration of 0.6 mg mL^{-1}. Antibacterial properties of calcium complex were higher than ceftriaxone disodium against *Staphylococcus aureus.*

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