Study of homo- and heteronuclear complex formation in 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP)—erbium(III) and HEDP—erbium(III)—calcium(II) systems in an aqueous solution*

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Erbium(III)—HEDP and erbium(III)—calcium(II)—HEDP systems (HEDP is 1-hydroxy-ethylidene-1,1-diphosphonic acid) have been studied using potentiometry method in association with mathematical modelling. In the erbium(III)—HEDP system the formation of compexes having various degree of deprotonation of a ligand, 1 : 1 and 2 : 1 mono- and dinuclear complexes, as well as mononuclear bis-complexes has been shown. It was found, that heteronuclear complexes generated in erbium(III)—calcium(II)—HEDP system, do not coincide neither with calcium nor with erbium forms in composition .

Key words: diphosphonates, 1-hydroxyethylidene-1,1-diphosphonic acid, complex formation, rare-earth elements.

Due to a similarity between the molecules of pyrophosphoric acid and diphosphonates, the latter selectively bind calcium ions and concentrate in bone tissues. Diphosphonates retard the process of bone degradation by osteoclasts inhibiting their apoptosis.[1] Therefore, they have found wide application in oncology, particularly in treatment of metastatic bone lesions.[2]

1-Hydroxyethylidene-1,1-diphosphonic acid (HEDP) — diphosphonate — is used in medicine in the form of potassium sodium salt (xydifon) and disodium salt (etidronate), presents a bone resorption inhibitor,[3] prevents an excessive bone decalcification, pathological calcification of soft tissues, crystal formation, growth and aggregation of calcium oxalate and calcium phosphate crystals in urine.[4]

Medical use of HEDP provides for a study of acid-base properties as well as compex formation of HEDP with various metal cations, mainly with calcium and magnesium ions.

According to the literature data,[5] lanthanoid ions inhibit the development of cells (osteoclasts) responsible for bone tissue resorption. The ability of lanthanoid ions to mimic calcium ion function[6,7] permits not only to simulate the behaviour ot the latter using lanthanoid ions (rareearth probes), but also to use lanthanoids actually as components in therapy of bone tissue disorders.[8]

From the physico-chemical viewpoint, the similarity in the behaviour of calcium and erbium ion correlates with an idea of a combined parameter $P\alpha$ (P is a polarization force, α is a polarizability) as a measure of an interaction force between cations and an environment at a predominantly ion bonding, which idea was first presented in a study,[9] and later found the further development.[10,11] $P\alpha$ values calculated by us (in eV $Å^{5/2}$) for the coordination numbers (CN) 6, 7, 8, 9 for Ca^{II} and Er^{III} are 2.75, 3.13, 3.52, 3.96 and 2.52, 2.93, 3.42, 3.92, correspondingly (r_{ion} values[7,12] and ionization potentials[12] were taken from the literature). Thus, CNs for the same ligand environment being equal, the energies of chemical bonding for Er^{III} and Ca^{II} should be similar.

Earlier we have deduced constants for the protolytic equilibria of HEDP (see Ref. 13) and complex formation between Ca^{II} and HEDP.[14] The constants obtained were proposed to be used to describe Er^{III}—HEDP and Er^{III}—Ca^{II}—HEDP systems in the concentration range of $(1—5) \cdot 10^{-2}$ mol L^{-1}.

At such concentrations, the correct integration of all the data requires the creation of an ionic strength of ≥ 2 mol L^{-1}, which inevitably results in the additional ion-ion interactions. As an alternative, the third-generation CPESSP programme[15] was applied in the data processing, allowing one to calculate the ionic strength according to the Davies—Vasiliev equation[16] as well as activity coefficients at each titration point. Thus, in the course of the mathematical modelling, the activities of the forms were used, and the constants obtained should be recognized as thermodynamical.

As cations of the ittrium group lanthanoids(III) are considered to be "paramagnetic probes" simulating the behav-

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iour of calcium in biosystems in general and in the presence of HEDP in particular, it was of particular interest to compare the behaviour of these ions, to reveal the general and peculiar features in the chemistry (stoichiometry and stability) of the complex formation with of HEDP.

Experimental

The activity of protons was measured using a potentiometer «Expert-001» to an accuracy of 0.005 pH units; pH-meter was calibrated with standartized aqueous buffer solutions. All measurements were performed at 25 ± 0.1 °C.

Concentration of a resulting HEDP solution was found by the pH-metric titration with KOH solution, the concentration was determined by titration with a fixanal solution (0.1 M HCl) in the presence of an acid-base phenolphtalein indicator under argon atmosphere.

As a complex-forming metal ion, erbium(III) was used as erbium nitrate 8-hydrate («chemically pure»). To find the accurate concentration of the solution, erbium nitrate was titrated with the EDTA solution at pH 5.6 (acetate buffer[17] with Xylenol orange), while to determine an accurate Ca^{II} concentration, the calcium chloride solution («reagent grade») was titrated with EDTA solution at pH 10 in ammonia chloride buffer.[18] The equivalence point was found using the eriochrome black indicator.

Er^III—HEDP system. The present study gives a pH-metric titration of the Er^III—HEDP system (Fig. 1) at different concentrations given in Table 1. An equilibrium time in the precipitate zone nearly throughout the total examined range of pH 1.5—11 usually did not exceed 5—10 min.

Modelling of the data (see Fig. 1) on the basis of only protolytic equilibria for HEDP gives the F-test $F_{cr} = 120$ (the model is considered to be adequate if $F_{cr} \leq 1$).[16] The further approximation to the adequate description of the systems was based on fixing the constants obtained for HEDP and introducing the soluble complex forms of a ligand of various composition and protonicity with erbium ions(III). Complex forms having 1 : 1, 2 : 2, 2 : 1 and 1 : 2 metal:ligand ratio and various protonation degree were introduced into a matrix. This enabled to reduce F_{cr} down to 3.4. Then precipitate forms of erbium complexes with HEDP were introduced into the matrix, enabling to reduce the

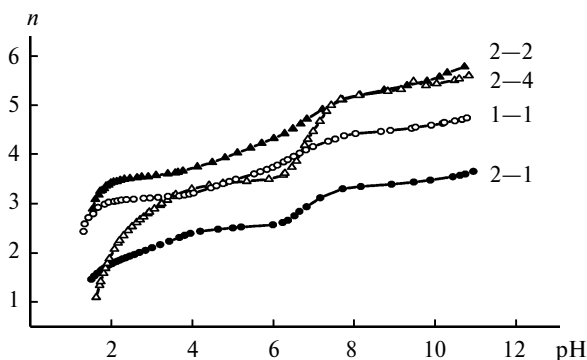**Fig. 1.** pH-dependence of Bjorrum functions (n) for the Er^III—HEDP system at the ratios given in Table 1.

Table 1. Titration conditions for the Er^III—HEDP system ($V_0 = 25$ mL, $T = 25$ °C)

Concentration/mol L^{-1}			Legend of Er^III—HEDP system
HEDP (KOH)	Er^III	Titrant	
0.01219	0.02130	0.0489	2—1
0.02194	0.01988	0.1100	2—2
0.03550	0.02164	0.2201	2—4
0.01219	0.00994	0.0489	1—1

Table 2. Stoichiometry matrix for an equilibrium m Er^III + l H$_4$L $\rightleftharpoons$ [Er$_m$H$_{4l-h}$L$_l$]$^{3m-h}$ + h H$^+$ and formation constants for various forms in the Er^III—HEDP system

l	m	k	h	n	Complex form	log$K$ ($\delta \leq 0.12$)
1	1	0	2	2.0	ErH$_2$L$^+$	10.06
2	1	0	1	0.5	ErH$_7$L$_2^{2+}$	23.86
2	1	0	3	1.5	ErH$_5$L$_2^{2-}$	19.47
2	1	0	4	2.0	Er(H$_2$L)$^{2-}$	15.43
2	1	0	5	2.5	ErH$_3$L$_2^{2-}$	8.64
2	2	0	8	4.0	Er$_2$L$_2^{2-}$	7.30
2	2	0	9	4.5	Er$_2$L$_2$(OH)$^{3-}$	−13.24
1	2	0	2	2.0	Er$_2$H$_2$L^{4+}	12.85
1	2	0	3	3.0	Er$_2$HL^{3+}	11.08
1	2	0	4	4.0	Er$_2$L^{2+}	10.04
1	2	0	5	5.0	Er$_2$L(OH)$^+$	6.41
1	2	0	6	6.0	Er$_2$L(OH)$_2\downarrow$	−2.42*
2	2	0	6	3.0	Er$_2$(HL)$_2\downarrow$	−23.96*
3	2	0	6	2.0	Er$_2$(H$_2$L)$_3\downarrow$	−4.99*
2	2	1	7	3.5	KEr$_2$HL$_2\downarrow$	−4.00*
2	2	3	9	4.5	K$_3$Er$_2$L$_2$(OH)$\downarrow$	−18.03*

* Solubility constant of a precipitate: K$_k$Er$_m$H$_{4l-h}$L$_l\downarrow$ + h H$^+$ $\rightleftharpoons$ k K$^+$ + m Er^III + l H$_4$L.

F-test down to 0.84. The final matrix is given in Table 2. Distribution of the forms depending on medium acidity and concentration conditions is shown in Figures 2—5.

Elemental analysis of precipitates was performed on a microwave plasma-atomic emission spectrometer «Agilent 4100» with a preliminary dissolution of the precipitate in 1 M nitric acid. The precipitates were isolated at a constant pH in the region of maximal accumulation of the forms (see, *e.g.*, Fig. 3: pH 8—11 for Er$_2$L(OH)$_2$; Fig. 4: pH 2—6 for Er$_2$(H$_2$L)$_3$). Analysis of the precipitates showed that they are in accordance with the forms given in the stoichiometry matrix (see Table 2).

The Er^III—Ca^II—HEDP system. We performed the pH-metric titration of Er^III—Ca^II—HEDP system at various concentrations given in Table 3. Equilibrium time in the precipitate zone nearly throughout the total examined range of pH 1.5—11 usually did not exceed 5—10 min.

In result of mathematical modelling, the final stoichiometry matrix was obtained (Table 4), illustrating only the actually ($\geq5\%$)
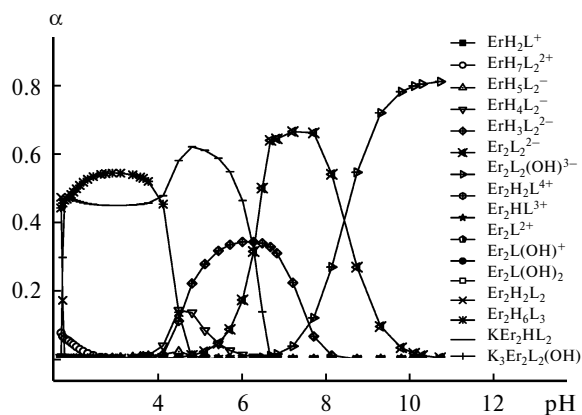
Fig. 2. pH-dependence for portions of different form accumulation for the Er^{III}—HEDP (1 : 1) system.
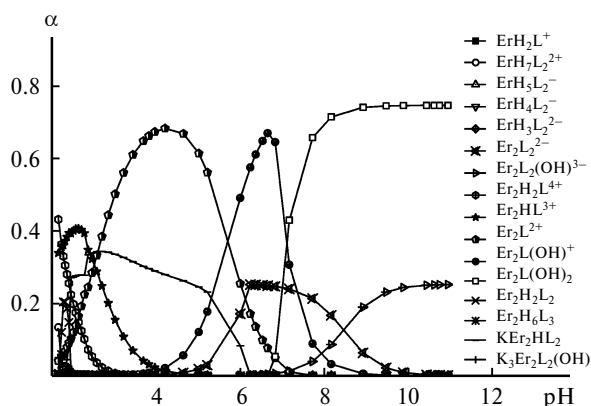

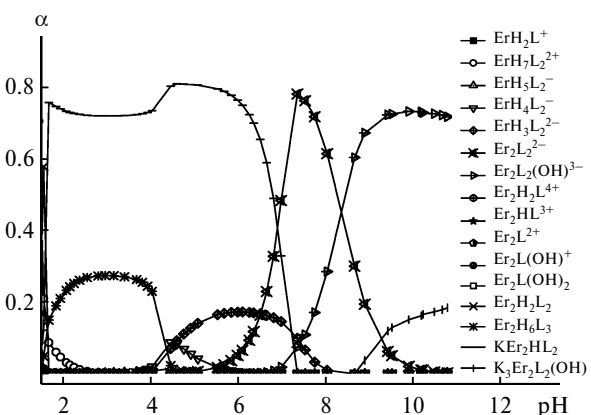**Fig. 3.** pH-dependence for portions of different form accumulation for the Er^{III}—HEDP (2 : 1) system.

Fig. 4. pH-dependence for portions of different form accumulation for the Er^{III}—HEDP (2 : 2) system.
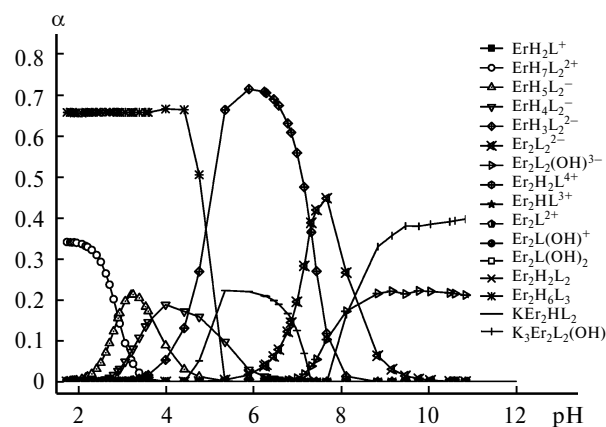

Fig. 5. pH-dependence for portions of different form accumulation for the Er^{III}—HEDP (2 : 4) system.

Table 3. Titration conditions for the Er^{III}—Ca^{II}—HEDP system (V_0 = 25 mL, T = 25 °C)

Concentration/mol L^{-1}				Legend for the system Er^{III}—Ca^{II}—HEDP
HEDP	Er^{III}	Ca^{II}	KOH	
0.02527	0.01447	0.01038	0.044	1—1—2
0.2246	0.02172	0.02076	0.704	2—2—22
0.0449	0.02172	0.02076	0.1716	2—2—4

Table 4. Final stoichiometry matrix for an equilibrium $m\ Er^{III} + m'\ Ca^{II} + l\ H_4L \rightleftharpoons [Er_mCa_{m'}H_{4l-h}L_l]^{3m'+2m'-h} + h\ H^+$ and formation constants for different forms in the Er^{III}—Ca^{II}—HEDP system

l	m	m'	h	n	Complex form	logK ($\delta \le 0.16$)
2	1	0	1	0.5	$ErH_7L_2^{2+}$	23.86
2	1	0	3	1.5	$ErH_5L_2^-$	19.47
2	1	0	4	2.0	$ErH_4L_2^-$	15.43
2	1	0	5	2.5	$ErH_3L_2^{2-}$	8.64
1	1	1	2	2.0	$ErCaH_2L^{3+}$	26.10
1	1	1	4	4.0	$ErCaL^+$	23.08
1	1	1	5	5.0	$ErCaL(OH)\downarrow$	16.37
2	1	1	5	2.5	$ErCaH_3L_2\downarrow$	−27.46*
2	2	1	8	4.0	$Er_2CaL_2\downarrow$	−35.01*

* Solubility constant of a precipitate: $K_kEr_mCa_{m'}H_{4l-h}L_l\downarrow + h\ H^+ \rightleftharpoons k\ K^+ + m'\ Er^{3+} + m'\ Ca^{2+} + l\ H_4L$.

accumulated forms, which were only nine, the five of them being heteronuclear while the others were erbium ones. F-test was

0.92. Distribution of forms depending on medium acidity is shown in Figures 7—9.
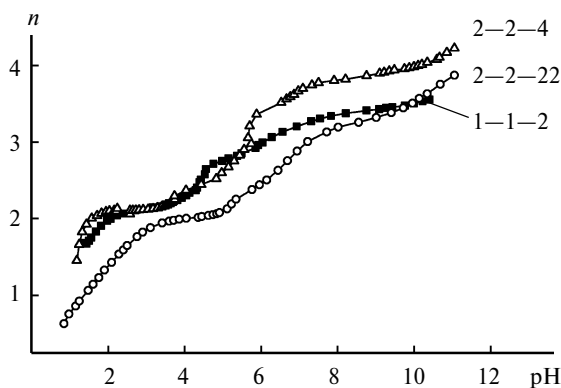
Fig. 6. pH-dependences of Bjorrum functions (n) for the Er^{III}—Ca^{II}—HEDP system at the ratios given in Table 3.

Fig. 9. pH-dependence for portions of different form accumulation for the Er^{III}—Ca^{II}—HEDP (2 : 2 : 4) system.
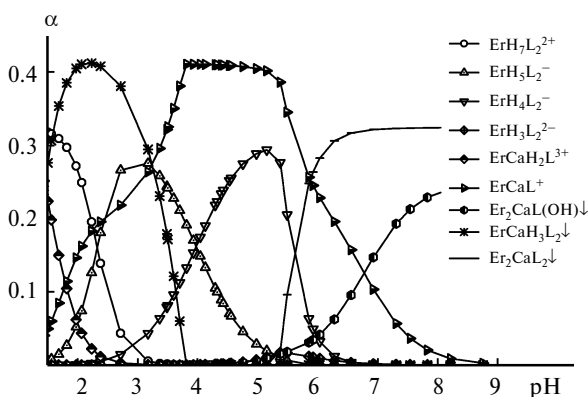
Fig. 7. pH-dependence for portions of different form accumulation for the Er^{III}—Ca^{II}—HEDP (1 : 1 : 2) system.

mulated in a solution. Note, that over the whole range of pH (2—11), soluble forms are accompanied by the $Er_2L(OH)_2$, $Er_2(HL)_2$, $Er_2(H_2L)_3$, KEr_2HL_2, and $K_3Er_2L_2(OH)$ precipitate forms.

Study of the Ca^{II}—Er^{III}—HEDP heteronuclear system testifies the prevalence of heteronuclear forms in parallel with retaining a part of some erbium forms and the absence of calcium compexes.

From the physico-chemical viewpoint, a difference in behaviour of erbium and calcium ions[14] may be explained by the following factors (Table 5): a) different values of $P\alpha$ parameter, responsible for the interaction energy of an ion with the electron-donor groups, b) difference in the ion radii at the same CN, determining the coordination polyhedron and a ligand denticity through the ion—ion, ion—dipole and dipole—dipole interactions in the first coordination sphere.

As noted above, consideration of the Ca^{II}—Er^{III}—HEDP heteronuclear system testifies the prevalence of heteronuclear forms in parallel with retaining a part of erbium forms, but with the absence of calcium compelex.

Fig. 8. pH-dependence for portions of different form accumulation for the Er^{III}—Ca^{II}—HEDP (2 : 2 : 22) system.

Results and Discussion

Analysis of dependence distribution of erbium complexes forms upon medium acidity relationship suggests that mostly mono- and binuclear bis-complexes are accu-
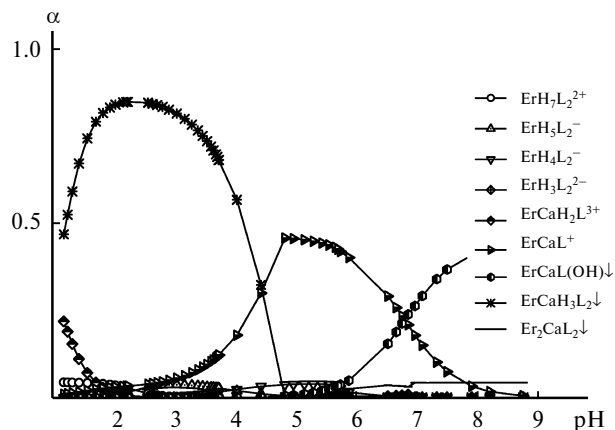
Table 5. Interrelation between the CN, ionic radius (r_{ion}) and $P\alpha$* parameter

Ion	CN	r_{ion}/nm[7,12]	$P\alpha$/eV Å$^{5/2}$
Er^{III}	6	89.0	2.52
	7	94.5	2.93
	8	100.4	3.42
	9	106.2	3.92
Ca^{II}	6	114	2.75
	7	120	3.13
	8	126	3.52
	9	132	3.96

* $P = (z/r_{ion})/S_{eff}$, where $S_{eff} = (5z^{1.27})/(r_{ion}^{1/2}I_z)$; $\alpha(\text{Å}^3) = r_{ion}^3$ (see Refs 9—11).

Table 6. pH ranges of fractional accumulation of heteronuclear complex forms for the Er^{III}—Ca^{II}—HEDP system and homonuclear forms for the Er^{III}—HEDP and Ca^{II}—HEDP systems

Area	Er^{III}—Ca^{II}—HEDP	pH range of accumulation	Er^{III}—HEDP	pH range of accumulation	Ca^{II}—HEDP (see Ref. 14)	pH range of accumulation
1	$ErCaL^+$	1.5—8	$ErH_4L_2^-$	3—8	$Ca_2H_2L_2^{2-}$	4—6
			$Er_2H_2L_2$	1.5—7	$CaH_3L_2^{3-}$	4—8
			Er_2L^{2+}	1.5—5	Ca_2L	6—11
					$Ca_3H_2L_2$	5—6
2	$ErCaH_2L^{3+}$	1.5—3	$ErH_7L_2^{2+}$	1.5—3	$CaH_4L_2^{2-}$	2—6
	$ErCaH_3L_2$	1.5—3	$ErH_5L_2^-$	1.5—3	$Ca_2H_5L_2^+$	2—3
3	$ErCaL(OH)$	5—9	$Er_2L_2^{2-}$	6—11	$CaHL_2^{5-}$	5—11
	Er_2CaL_2	6—9	$ErH_3L_2^{2-}$	5—9	CaL^{2-}	7—11
					$Ca_2H_2L_2^{2-}$	6—10
					$CaH_2L_2^{4-}$	5—9
					Ca_2L	6—11

The latter are initially less stable[14] compared to lanthanoid complexes. According to the $P\alpha$-concept this is apparently due (see Table 5) to the fact that the coordination configuration of a ligand (position of the donor groups) requires the realization of a lesser ionic radius (and, consequently, of the CN) for the calcium atom, resulting in a lesser $P\alpha$ value and hence, to a lesser energy of interaction.

Note also, that heteronuclear complexes do not coincide in composition neither with calcium nor with erbium forms. Obviously, variability of CN (and, consequently, of the ionic radius) for the both ions and sufficient flexibility of a ligand result in novel combinations (forms) being more stable compared to the parent complexes.

As for the chemistry of the heteronuclear complex form generation, in the pH range wherein accumulation of heteronuclear forms occur (Table 6), several erbium and calcium complexes exist, which different combinations may afford one or another heteronuclear form.

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