

Complex Formation of 1-Hydroxyethylidene-1,1-diphosphonic Acid with Gadolinium(III) and Calcium(II) in the Aqueous Solutions

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Abstract—The complex formation constant have been determined for the reactions of 1-hydroxyethylidene-diphosphonic acid (H_4L) with $Ca(II)$ and $Gd(III)$. The solubility constant has been estimated for the products differing in the ligand deprotonation state. In the cases of both cations, four complex types are common: $Me(H_2L)_2$, MeH_3L_2 , Me_2L , and $Me_2(HL)_2$. The $Gd(H_2L)_2$ and GdH_3L_2 complexes are much more stable than the respective calcium complexes. It has been demonstrated that, on the contrary to the commonly accepted practice, gadolinium ion cannot model the behavior of calcium ions.

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1-Hydroxyethylidene-1,1-diphosphonic acid H_4L , a representative of the biphosphonates class, is known for many medical applications in the forms of mixed sodium-potassium (Xydiphone) or disodium (Ethydrone) salts preventing excessive calcium erosion from osseous tissue, soft tissues calcification, and calcium salts crystallization in urea.

Due to high affinity towards phosphates, lanthanides are efficiently bound to hydroxyapatites (major component of the osseous tissue) without breaking the mineral structure [1]. Lanthanides suppress the growth of osteoclasts, agents of bone resorption. Due to the ability of lanthanide ions to mimic the functions of calcium ions [2, 3], lanthanides can be used in the model studies as well as in therapy of osseous diseases [4].

The similarity of the physico-chemical behavior of calcium and gadolinium ions can be explained in view of the combined parameter $P\alpha$ (with P for polarization strength and α for polarizability), a measure of interaction strength between the cation and surrounding species, provided the interaction is majorly ionic [5–7]. Using ionic radii and ionization potentials from [2, 8], we have calculated the values of $P\alpha$ ($eV \text{ \AA}^{5/2}$) for $Gd(III)$ and $Ca(II)$; they equaled, respectively, 2.62 and 2.75 (coordination number of 6), 3.07 and 3.13 (7), 3.49 and 3.52 (8), and 3.95 and 3.96 (9). Thus, the

coordination number and ligand surrounding being the same, the interaction energy of $Gd(III)$ and $Ca(II)$ ions should be close.

In order to extend the medical applications of 1-hydroxyethylidene-1,1-diphosphonic acid, detailed knowledge on its acid-base and complexing properties is required; however, this information has been contradictory and insufficient so far. We have demonstrated [9] that in the aqueous solutions of H_4L , along with commonly recognized forms (H_3L^- , H_2L^{2-} , HL^{3-} , and L^{4-}), the homoconjugates are formed: $\{H_3L^- \cdot H_3L^-\}$, $\{H_3L^- \cdot H_2L^{2-}\}$, $\{H_2L^{2-} \cdot H_2L^{2-}\}$, $\{H_2L^{2-} \cdot HL^{3-}\}$, and $\{HL^{3-} \cdot HL^{3-}\}$. Such conjugates have special acid base-properties, different from those of monomeric H_4L .

Due to paramagnetic properties of gadolinium ion, its complexing properties can be studied by proton magnetic relaxation in addition to commonly applied potentiometry. Gadolinium(III) is thus considered a paramagnetic probe to model calcium behavior in the presence and in the absence of biologically active 1-hydroxyethylidene-1,1-diphosphonic acid. The aim of this work was to support or reject this approach by comparison of stability and stoichiometry of the complexes forming between 1-hydroxyethylidene-1,1-diphosphonic acid and $Ca(II)$ or $Gd(III)$.

We intended to use the H_4L acid-base equilibrium constants from [9] to model the systems with the

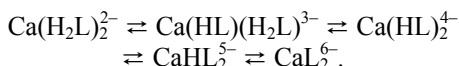
components concentrations of 5×10^{-3} to 2×10^{-1} mol/L. However, the data could only be unified at the high external ionic strength only, of about 5 mol/L; that would deliberately alter the complexes behavior. Thus, in this work the solutions ionic strength was not kept constant; instead, we took advantage of the 3rd generation CPESP software [10] that calculated the ionic strength and the ion activities at each titration point. Thus, the activities were used for modeling and the elaborated constants were thermodynamic ones.

Ca(II)–H₄L. Potentiometric titration of H₄L was performed in the presence of Ca(II) ions (Table 1, Fig. 1).

The mathematical model of the system was constructed basing on the matrix that included different forms of H₄L [9] and its complexes with potassium and calcium ions. As followed from the value of the Fisher criterion ($F = 0.101$), the system was adequately described ($F_{\text{crit}} \leq 1$ at $p = 0.05$ [11]). The data on stoichiometry and stability of the formed complexes is collected in Table 2.

To confirm the validity of the derived result, the precipitate formed at pH 5.50 and 7.70 at metal to ligand ratio of 2 : 1 was analyzed (Fig. 2); such conditions were selected in view of highest amount of precipitate to be isolated. The ratios of metal : ligand : water were found of 3 : 2 : 10.5 [$\text{Ca}_3(\text{HL})_2 \cdot 10.5\text{H}_2\text{O}$ at pH = 5.50] and of 2 : 1 : 4 ($\text{Ca}_2\text{L} \cdot 4\text{H}_2\text{O}$, pH = 7.70).

Basing on the experimental results, the following scheme of Ca^{2+} interaction with H₄L was suggested (valid at Ca:L of 2 : 1 to 1 : 5; at 5-fold excess of the ligand the complexes with Ca to ligand ratio of 1 : 2 are majorly formed).



The precipitates Ca_2L and $\text{Ca}_3\text{H}_2\text{L}_2$ were formed as well, thus the system was heterogeneous (opaque).

At considerably high concentration (Table 1, nos. 3–5) of the complexing metal ion and ligand the binuclear complexes $\text{Ca}_2\text{H}_5\text{L}_2^+$ and $\text{Ca}_2\text{H}_2\text{L}_2^{2-}$ were formed along with the 1 : 2 complexes (Figs. 2–4). At metal to ligand ratio of 1 : 1 the precipitate forms Ca_2L and $\text{Ca}_3\text{H}_2\text{L}_2$ were accumulated (Fig. 3).

In contrast to the previously reported data [12, 13], we observed the formation of binuclear complexes and bis-complexes $\text{Ca}(\text{H}_2\text{L})_2^{2-}$, $\text{Ca}(\text{HL})(\text{H}_2\text{L})^{3-}$, $\text{Ca}(\text{HL})_2^{4-}$, CaHL_2^{5-} , CaL_2^{6-} , $\text{Ca}_2\text{H}_5\text{L}_2^+$, and $\text{Ca}_2\text{H}_2\text{L}_2^{2-}$. The insoluble forms were Ca_2L (described in [11]) and $\text{Ca}_3\text{H}_2\text{L}_2$.

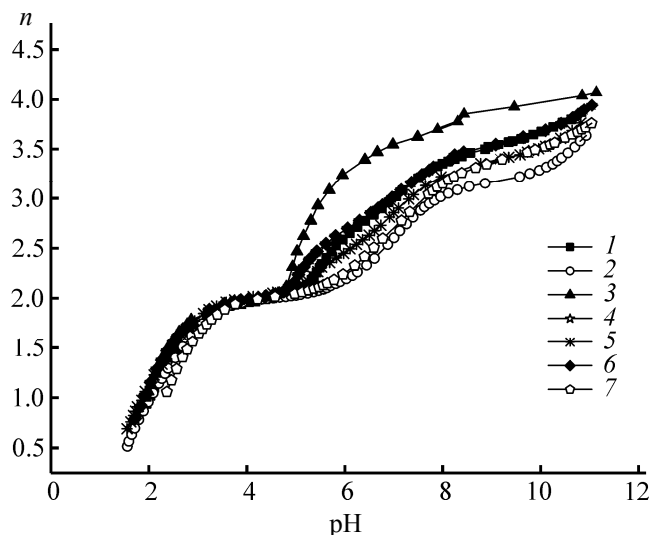
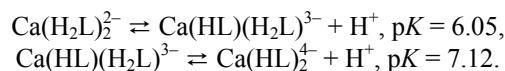


Fig. 1. Experimental (dots) and calculated (lines) Bjerrum function n . The studied concentrations are listed in Table 1.

The structure of the soluble complexes remained unclear; however, from the X-ray diffraction [14] and neutron scattering [13] data collected for $\text{CaH}_2\text{L} \cdot 2\text{H}_2\text{O}$, the studied diphosphonic acid acted as bi- or tridentate ligand upon complex formation with calcium in the crystal.

The suggested coordination type was in line with the acid-base properties of the bis-complexes: the dissociation constant of the third POH group was somewhat lower than in the isolated ligand ($\text{p}K_3 = 7.57$ [9]).



The same applied to the fourth deprotonation of the coordinated H₄L ($\text{p}K_4 = 11.50$ [9]).



Table 1. Titration of 1-hydroxyethylidene-1,1-diphosphonic acid (H₄L) in the presence of calcium ions ($V_{\text{start}} = 25$ mL, $25 \pm 0.2^\circ\text{C}$)

Run no.	Concentrations of titrated components, mol/L		Titrant (KOH) concentration, mol/L
	H ₄ L	Ca ²⁺	
1	0.01185	0.009500	0.03650
2	0.05330	0.009500	0.09133
3	0.01185	0.01900	0.04567
4	0.02369	0.01900	0.09133
5	0.04029	0.01900	0.09133
6	0.002361	0.001900	0.008560
7	0.004044	0.001900	0.01711

Table 2. Stoichiometry and stability of the complexes in the Ca^{2+} –1-hydroxyethylidene-1,1-diphosphonic acid

Run no.	H_4L l^a	Ca^{2+} m^a	$-\text{H}$ h^a	Form	n	$\log K_p$, $\delta \leq 0.15$	$\log \beta_{\text{stab}} \pm 0.2$ ($\log K_{\text{dissolv}} \pm 0.3$)
1	1	1	4	CaL^{2-}	4.0	–16.06	7.4
2	1	1	5	$\text{CaL}(\text{OH})^{3-}$	5.0	–27.73	10.0
3	2	1	4	$\text{Ca}(\text{H}_2\text{L})_2^{2-}$	2.0	–3.94	2.7
4	2	1	5	$\text{Ca}(\text{HL})(\text{H}_2\text{L})^3$	2.5	–9.99	6.9
5	2	1	6	$\text{Ca}(\text{HL})_2^{4-}$	3.0	–17.11	7.1
6	2	1	7	CaHL_2^{5-}	3.5	–25.78	10.1
7	2	1	8	CaL_2^{6-}	4.0	–37.76	9.6
8	2	2	3	$\text{Ca}_2\text{H}_5\text{L}_2^+$	1.5	0.15	6.6
9	2	2	6	$\text{Ca}_2(\text{HL})_2^{2-}$	3.0	–12.29	12.1
10	1	2	4	$\text{Ca}_2\text{L}\downarrow$	4.0	7.28 ^b	(–16.4)
11	2	3	6	$\text{Ca}_3(\text{HL})_2\downarrow$	3.0	5.76 ^b	(–18.6)

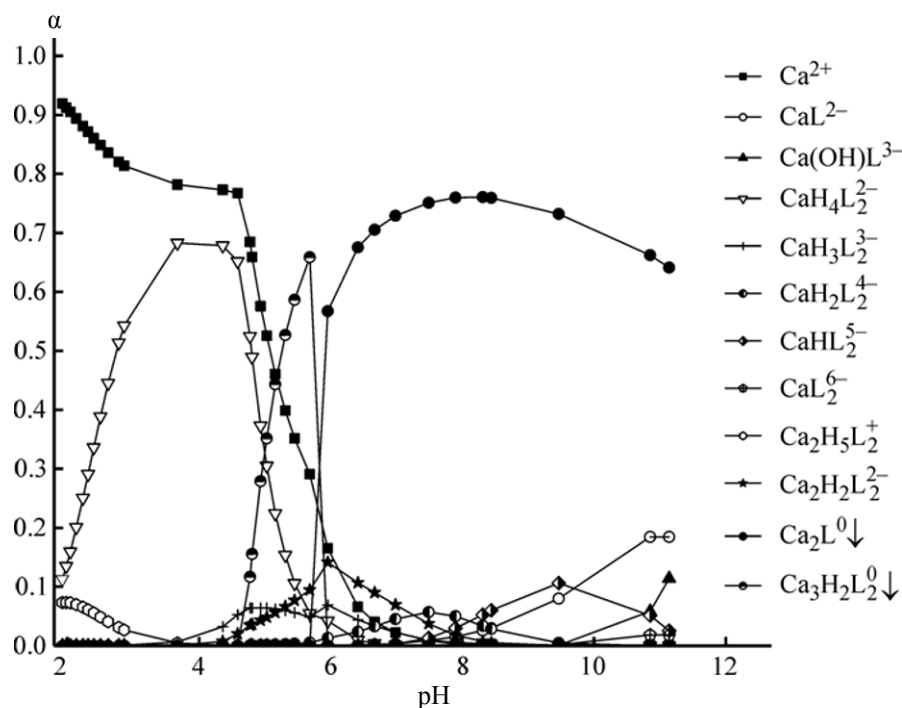
^a For $m\text{Ca}^{2+} + l\text{H}_4\text{L} \rightleftharpoons [\text{Ca}_m\text{H}_{4-h}\text{L}_l]^{2m-h} + h\text{H}^+$. ^b Precipitate dissolution constant $\text{Ca}_m\text{H}_{4-h}\text{L}_l\downarrow + h\text{H}^+ \rightleftharpoons m\text{Ca}^{2+} + l\text{H}_4\text{L}$.

Gd(III)– H_4L . The potentiometric titrations of H_4L were performed in the presence of Gd(III) at several components concentrations (Table 3, Fig. 5); usually, the equilibration time in the case of precipitation (pH of 1.5–11) did not exceed 5–10 min. Additionally, the magnetic relaxation data was obtained (Fig. 6).

The mathematical model of the system was constructed basing on the matrix that included different forms of H_4L [9] and its complexes with

gadolinium (including hydroxyl complexes and gadolinium hydroxide as precipitate). The Fisher criterion was of $F = 0.397$. The data on stoichiometry and stability of the formed complexes is collected in Table 4.

To confirm the validity of the derived result, the precipitate formed at pH 1.06 and 8.42 at metal to ligand ratio of 2 : 2 was analyzed. The ratios of metal: ligand:water were found of 2 : 3 : 4 [$\text{Gd}_2(\text{H}_2\text{L})_3 \cdot 4\text{H}_2\text{O}$

**Fig. 2.** Fractions of the complex forms at 0.01185 mol/L of 1-hydroxyethylidene-1,1-diphosphonic acid and 0.01900 mol/L of Ca^{2+} .

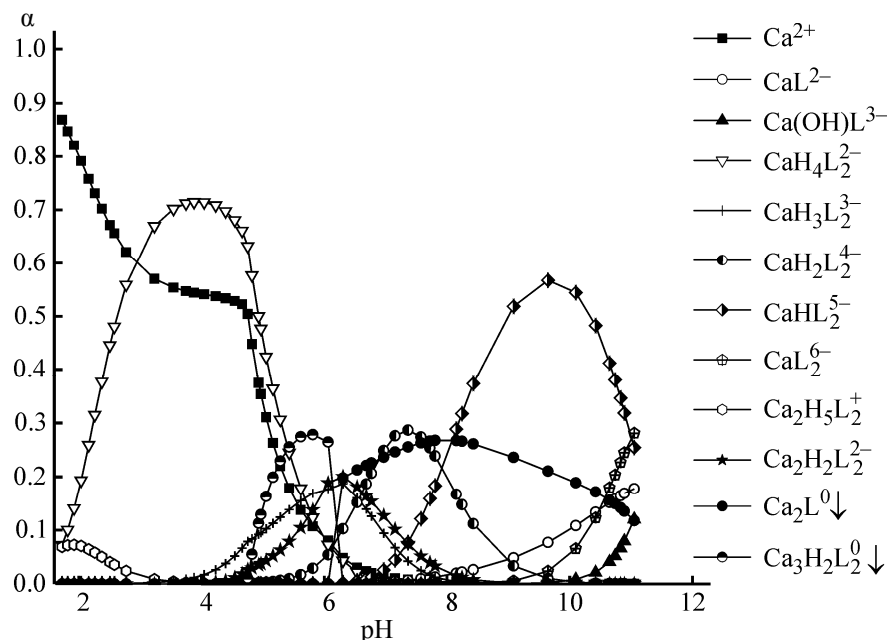


Fig. 3. Fractions of the complex forms at 0.02369 mol/L of 1-hydroxyethylidene-1,1-diphosphonic acid and 0.01900 mol/L of Ca^{2+} .

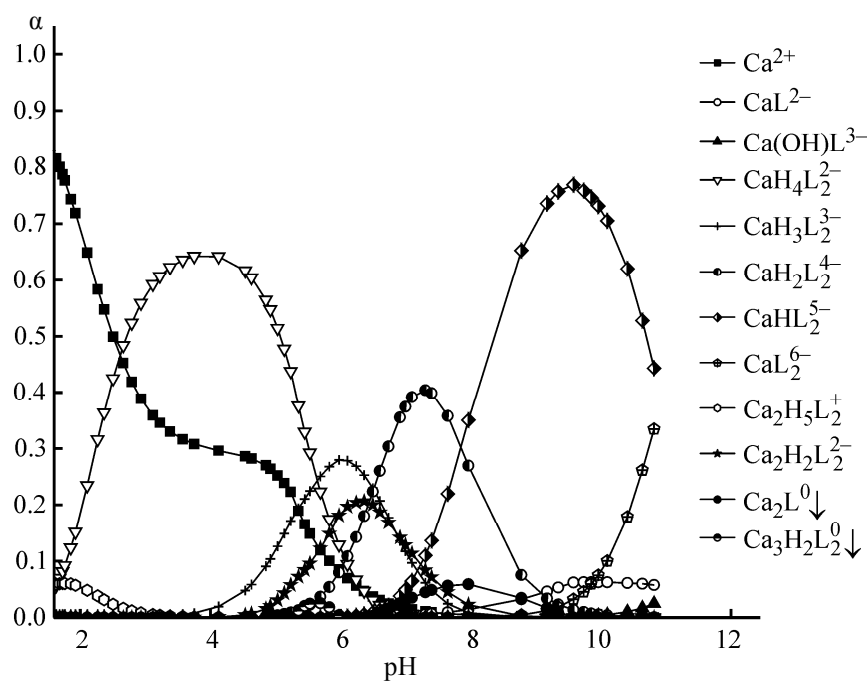


Fig. 4. Fractions of the complex forms at 0.04029 mol/L of 1-hydroxyethylidene-1,1-diphosphonic acid and 0.01900 mol/L of Ca^{2+} .

at $\text{pH} = 1.06$] and of 2 : 2 : 8 [$\text{K}_3\text{Gd}_2\text{L}_2(\text{OH}) \cdot 8\text{H}_2\text{O}$, $\text{pH} = 8.42$]. The precipitates analysis data thus confirmed the results reported in Table 4.

Comparison of the results (Tables 2 and 4) revealed significant differences in the compositions of calcium

and gadolinium complexes, likely due to different charge, coordination number, and radius of the ions. The charge determined the conditions of neutral precipitates formation, whereas the radius and the coordination number influenced the quantity of the bound electron-donor groups. It is commonly accepted

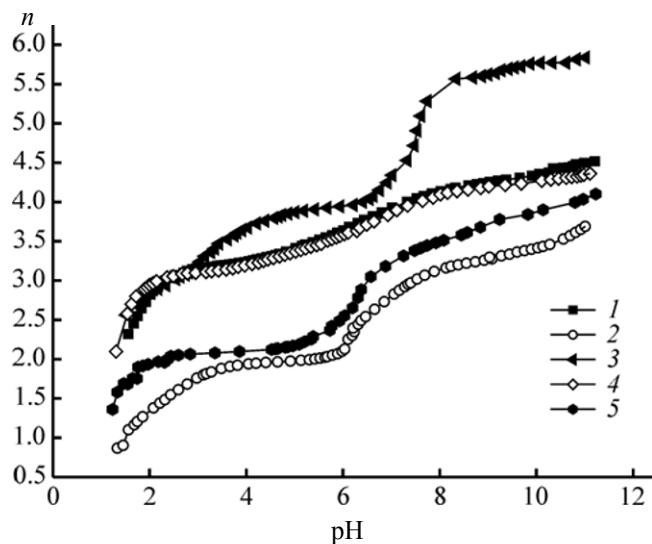


Fig. 5. Experimental (dots) and calculated (lines) Bjerrum function n . The studied concentrations are listed in Table 3.

that the denticity of H_4L in its complexes with lanthanide ions can reach 4 [15, 16].

Only four of the revealed complex forms were common for the both cations: $Me(H_2L)_2$, MeH_3L_2 , Me_2L , and $Me_2(HL)_2$. The two latter forms were precipitates, either in the case of $Ca(II)$ or $Gd(III)$. The two $Gd(III)$ complexes, $Me(H_2L)_2$ and MeH_3L_2 , were found to be much more stable than the corresponding $Ca(II)$ complexes (the difference in stability exceeded 25 orders of magnitude). The increase of stability on the case of Gd ion was due to larger ionic radius (and thus the higher coordination number) and the higher denticity of the ligand.

The higher thermal stability was also revealed for Gd complexes in the solid phase (see results of TGA/DSC/MS in Fig. 7); the both complexes contained the

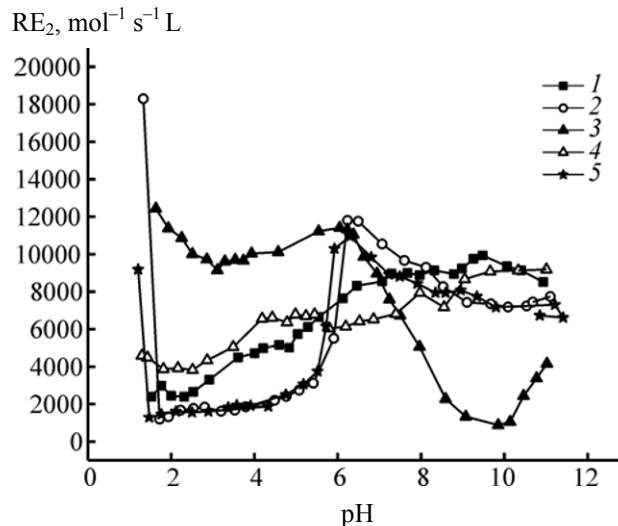


Fig. 6. Relaxation efficiency (RE) as function of pH. The components concentrations are listed in Table 3. $RE_2 = (BT_2)^{-1}$; B , $Gd(III)$ concentration; T_2 , proton spin-lattice relaxation time.

ligand in the form of HL^{3-} . Elimination of the crystal hydrate water was noticeable from the very start of heating; however, the highest dehydration rate was observed at 123.8°C (calcium complex) and at 148.3°C (gadolinium complex). The onset of the ligand decomposition was also different: 312.4°C (calcium complex) and 325.5°C (gadolinium complex).

The difference in the coordination ability of the cations was reflected also in the tendency of $Gd(III)$ to form binuclear compounds 2 : 1, including the soluble forms.

To conclude, comparison of the coordination behavior in the presence of 1-hydroxyethylidene-1,1-diphosphonic acid demonstrated that gadolinium(III) ions do not fully mimic the behavior of calcium(II) ions. Thus, $Gd(III)$ should be used as a model of $Ca(II)$ with extreme care.

EXPERIMENTAL

Gadolinium(III) nitrate, calcium(II) nitrate, 1-hydroxyethylidene-1,1-diphosphonic acid (all of special pure grade, Fluka) and potassium hydroxide (analytical pure grade) were used as received. Hydrogen ions activity was determined with Expert-001 potentiometer with the accuracy of ± 0.005 pH; the pH-meter was calibrated using the standard buffer solutions. The titration was performed under argon, at $25 \pm 0.2^\circ\text{C}$. The ligand concentration was determined by potentiometric titration with carbonate-free KOH.

Table 3. Titration of 1-hydroxyethylidene-1,1-diphosphonic acid (HL_4) in the presence of gadolinium ions ($V_{\text{start}} = 25$ mL, $25 \pm 0.2^\circ\text{C}$)

Run no.	Concentrations of titrated components, mol/L		Titrant (KOH) concentration, mol/L
	H_4L	Gd^{3+}	
1	0.01185	0.0109	0.04471
2	0.05332	0.0109	0.1571
3	0.01185	0.0218	0.05589
4	0.02369	0.0218	0.08942
5	0.04265	0.0218	0.07069

Table 4. Stoichiometry and stability of the complexes in the Gd^{3+} –1-hydroxyethylidene-1,1-diphosphonic acid

Run no.	H_4L l^a	Gd^{3+} m^a	$-\text{H}^+$ h^a	K^+ k^a	Form	n	$\log K_p$ $\delta \leq 0.19$	$\log \beta_{\text{stab}}$ ($\log K_{\text{dissolv}}$) $\delta \leq 0.4$	$\log \beta_{\text{stab}}$ ($\log K_{\text{dissolv}}$) for Ca^{2+}
1	1	1	2	0	GdH_2L^+	2.0	14.31	19.0	–
2	2	1	1	0	GdH_7L_2^+	0.5	22.58	24.3	–
3	2	1	3	0	GdH_5L_2^-	1.5	19.87	26.2	–
4	2	1	4	0	$\text{Gd}(\text{H}_2\text{L})_2^-$	2.0	19.03	28.4	2.7
5	2	1	5	0	$\text{GdH}_3\text{L}_2^{2-}$	2.5	12.87	29.8	6.9
6	2	2	8	0	$\text{Gd}_2\text{L}_2^{2-}$	4.0	20.17	67.6	–
7	2	2	9	0	$\text{Gd}_2\text{L}_2(\text{OH})^{3-}$	4.5	11.82	73.2	–
8	1	2	2	0	$\text{Gd}_2\text{H}_2\text{L}^{4+}$	2.0	17.12	21.8	–
9	1	2	3	0	$\text{Gd}_2\text{HL}^{3+}$	3.0	16.70	28.9	–
10	1	2	4	0	Gd_2L^{2+}	4.0	13.48	37.2	(–16.4)
11	1	2	5	0	$\text{Gd}_2\text{L}(\text{OH})^+$	5.0	6.38	44.1	–
12	1	2	6	0	$\text{Gd}_2\text{L}(\text{OH})_2\downarrow$	6.0	–1.60 ^b	(–50.1)	–
13	2	2	6	0	$\text{Gd}_2(\text{HL})_2\downarrow$	3.0	–30.20 ^b	(–54.6)	12.1
14	3	2	6	0	$\text{Gd}_2(\text{H}_2\text{L})_3\downarrow$	2.0	–42.61 ^b	(–56.5)	–
15	2	2	7	1	$\text{KGd}_2\text{HL}_2\downarrow$	3.5	–30.49 ^b	(–66.4)	–
16	2	2	9	3	$\text{K}_3\text{Gd}_2\text{L}_2(\text{OH})\downarrow$	4.5	–20.45 ^b	(–81.9)	–

^a For $m'\text{Gd}^{3+} + l\text{H}_4\text{L} \rightleftharpoons [\text{Gd}_{m'}\text{H}_{4l-h}\text{L}_l]^{3m'-h} + h\text{H}^+$. ^b Precipitate dissolution constant $\text{K}_k\text{Gd}_{m'}\text{H}_{4l-h}\text{L}_l\downarrow + h\text{H}^+ \rightleftharpoons k\text{K}^+ + m'\text{Gd}^{3+} + l\text{H}_4\text{L}$.

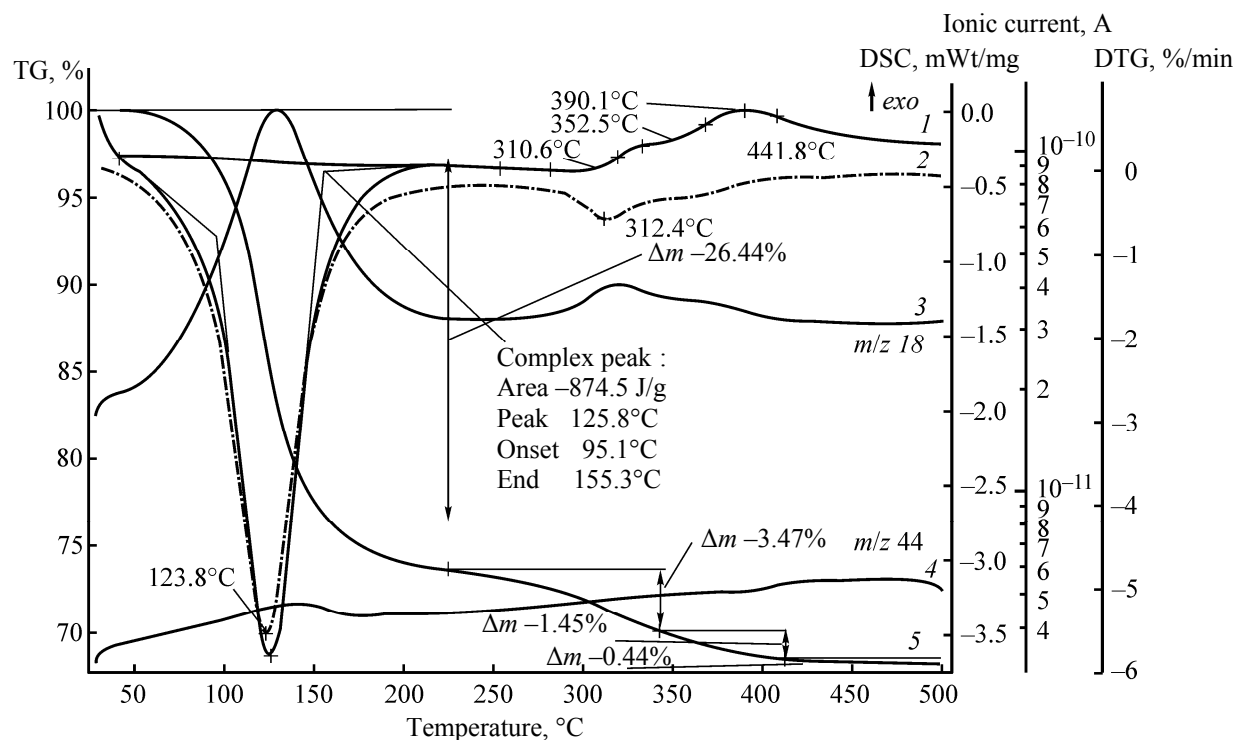


Fig. 7. TGA/DSC/MS curves of the $\text{Ca}_3(\text{HL})_2 \cdot 10.5\text{H}_2\text{O}$ complex (isolated at metal:ligand ratio 2:1 and pH 5.48). (1) DSC, (2) dif. TGA, (3) ionic thermogram of water, (4) ionic thermogram of CO_2 , (5) TGA.

The proton magnetic spin-lattice relaxation time was determined using Minispek mq20 (Bruker) relaxometer. Calcium content in the precipitate was determined by EDTA titration at pH > 11 with calcine indicator; the precipitate was thermally decomposed at 1200°C in air prior to the test [17, 18]. The concentration of gadolinium was determined by means of spin-lattice relaxation time measurement [19] after transformation of Gd(III) in the aquatic complex form by treatment with nitric acid (1 mol/L). The content of bound water in the precipitate was determined by means of combined TGA/DSC analysis with MS detection of the decay products. Potentiometry and magnetic relaxation data were analyzed using CPESP (Complex formation Parameters of Equilibria in Solutions with Solid Phases) software [10].

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