

# Spectroscopic Characterization of Eu(III) Complexes with New Monophosphorus Acid Derivatives of H<sub>4</sub>dota

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The luminescence lifetimes of europium(III) complexes with new monophosphorus acid derivatives of H<sub>4</sub>dota were measured by means of time-resolved laser-induced luminescence spectroscopy in H<sub>2</sub>O and D<sub>2</sub>O. The hydration numbers of these complexes were estimated using different empirical equations [Horrocks and Sudnick (1979) *J. Am. Chem. Soc.* **101** (1979) 334; Choppin and Barthelemy(1989) *Inorg. Chem.* **28**, 3354–3357; Choppin and Bünzli *Lanthanide probes in life, chemical and earth sciences. Theory and practice* (1989); Kimura and Kato *J. Alloys Comp.* **275–277** (1998) 806; Parker (1999) *J. Chem. Soc., Perkin Trans. 2*, 493–503; Supkowski and Horrocks (2002) *Inorg. Chim. Acta.* **340**, 44–48]. It was shown that all the relationships gave similar results with a satisfactory precision. The hydration numbers of complexes of H<sub>3</sub>do3a and H<sub>4</sub>dota agreed with the literature values. One water molecule is coordinated in complexes of the new ligands. The results showed that the Choppin formula based on measurements only in H<sub>2</sub>O can be satisfactorily used for estimation of the hydration numbers.

**KEY WORDS:** Macrocyclic DOTA-like ligands; phosphonate and phosphinate Eu(III) complexes; hydration number; time-resolved laser-induced fluorescence spectroscopy (TRLIFS).

## INTRODUCTION

Lanthanide(III) complexes of H<sub>4</sub>dota and its derivatives have been used in many areas of medicinal chemistry. Ligands binding metal radioisotopes (<sup>90</sup>Y, <sup>153</sup>Sm, <sup>166</sup>Ho, <sup>177</sup>Lu) are utilized as carriers in nuclear medicine [1]. Most contrast agents in magnetic resonance imaging (MRI) are based on gadolinium(III) complexes of such ligands [2,3]. Some lanthanide(III) ions (e.g. Eu<sup>3+</sup>/Tb<sup>3+</sup> emitting in VIS and Yb<sup>3+</sup>/Nd<sup>3+</sup> emitting in NIR regions, respectively) bound in complexes of the

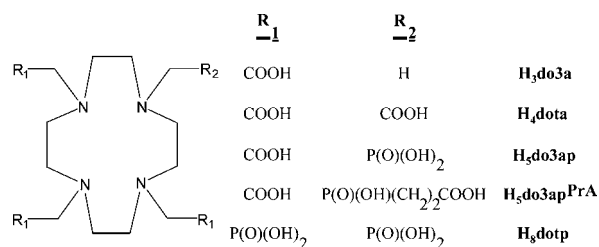
ligands change to enhance the luminescence intensity due to the alternation of their coordination environment in presence of light harvesting units [4–9] and, therefore, they can be used as luminescent probes. If the complexes are attached to bioactive molecules responsible for a desired distribution in organism (e.g. monoclonal antibodies, small peptides, hormones, sugars, etc.) they may serve as fluorescent labels for immunoassays (Eu<sup>3+</sup>, Tb<sup>3+</sup>) [4–8]. The so-called bifunctional chelates (BFC) are necessary for such conjugation. They should sequester lanthanide(III) ions with a high thermodynamic stability and the complexes formed should exhibit a high kinetic inertness under physiological conditions [1]. In the case of luminescent probes especially, the number of water molecules directly coordinated to the central ion should be as low as possible due to quenching effect of proximal O–H oscillators. These properties are strongly influenced by type of derivatization of a ligand skeleton (the ligands are mostly based on acyclic H<sub>5</sub>dtpa or macrocyclic

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Scheme 1.

$\text{H}_4\text{dota}$ ). It was demonstrated that the  $\text{H}_4\text{dota}$  derivatives with phosphorus acid pendant arms have some similarities to the acetic parent compound due to their acid character of the groups but the other properties (bulkiness, basicity, hydrogen bond formation ability) are different [10].

In this contribution, europium(III) complexes of cyclen derivatives containing acetic and phosphonic/phosphinic acid pendant groups were investigated (Scheme 1). The hydration numbers of the complexes,  $q$ , were determined by means of the measurement of luminescence lifetime of the excited state of the Eu(III) ion. The data concerning the hydration numbers of the complexes are important for possible applications of these complexes *in vivo*.

## MATERIALS AND METHODS

A stock solution of europium(III) perchlorate ( $0.01 \text{ mol dm}^{-3}$ ) was obtained by dissolving of  $\text{Eu}_2\text{O}_3$  (spectroscopically pure, prepared in the Department of Rare Earths, Faculty of Chemistry, Adam Mickiewicz University, Poznań) in perchloric acid solution (Analar grade, Fluka). The  $\text{H}_3\text{do3a}\cdot\text{H}_2\text{SO}_4$  was a kind gift of Bracco SpA (Italy). The other ligands were prepared as described elsewhere:  $\text{H}_4\text{dota}$  [11],  $\text{H}_5\text{do3ap}$  [12],  $\text{H}_5\text{do3ap}^{\text{PrA}}$  [13] and  $\text{H}_8\text{dotp}$  [14]. Stock solutions of the ligands were prepared by dissolving of a weighed amount in bidistilled water. Most of the samples for luminescence measurements were prepared by mixing of appropriate volumes of aqueous solutions of europium(III) perchlorate, the ligand and the buffer (2-(*N*-morpholinoyl)ethanesulfonic acid, MES). In some cases, the influence of MES on luminescence properties of Eu(III) complexes was followed, and therefore, the buffering properties of the complexes themselves were utilized. Luminescence intensities and lifetimes were measured after complete complex formation with ligand excess (20% molar excess) to eliminate any effect of other equilibria, e.g. dissociation of metal complex. Samples for measurements in  $\text{D}_2\text{O}$  (99.9% D, Radioisotope Production and Distribution Centre, Świerk, Poland) were prepared after full deuterium exchange (three times evaporation of the samples with fresh  $\text{D}_2\text{O}$ ).

Frozen samples for luminescence-lifetime measurements were prepared by immersing the aqueous solution of studied complexes in a 4 mm quartz cell into liquid nitrogen quickly. The samples were placed in a special quartz Dewar vessel during the measurements. The corrected luminescence spectra were recorded on a Perkin Elmer MPF-3 or Aminco Bowman AB2 spectrofluorimeters in 1 cm quartz cells ( $\lambda_{\text{exc}} = 394 \text{ nm}$ ). The luminescence-lifetime measurements were carried out using the detection system, consisting of a nitrogen laser pumping a tuneable dye laser, as described earlier ( $\lambda_{\text{exc}} = 394 \text{ nm}$ ) [15]. The hydration numbers of the complexes,  $q$ , were determined from the differences between luminescence decay rates measured in  $\text{H}_2\text{O}$ ,  $\tau_{\text{H}}^{-1}$ , and  $\text{D}_2\text{O}$ ,  $\tau_{\text{D}}^{-1}$ . The calculations were done using the different equations [15–23]. The most often used relationship is Eq. (1) derived by Horrocks *et al.* [16,17]

$$q_{\text{H1}} = 1.05 \times (\tau_{\text{H}}^{-1} - \tau_{\text{D}}^{-1}) \quad (1)$$

Choppin *et al.* [18] simplified this equation as follows:

$$q_{\text{B}} = 1.05 \times \tau_{\text{H}}^{-1} - 0.7 \quad (2)$$

It has advantage that there is no necessity of any measurements in  $\text{D}_2\text{O}$ . Both the equations give  $q$  with precision  $\pm 0.5$ . The Eq. (2) was verified by Kimura and Kato by measurements of luminescent decays of lanthanide(III) complexes with acyclic polyaminocarboxylates [19] and they suggested similar Eq. (3)

$$q_{\text{K}} = 1.05 \times \tau_{\text{H}}^{-1} - 0.44 \quad (3)$$

In order to involve the effect of the second hydration sphere and the influence of other proximal functional groups (mostly containing N–H and C–H oscillators) to the quenching, the improved version of Eq. (1) was introduced by Parker *et al.* [20] (Eq. (4) with correction factor  $k_{\text{XH}}$  for the presence of mentioned oscillators and outer sphere water molecules)

$$q_{\text{P}} = 1.20 \times (\tau_{\text{H}}^{-1} - \tau_{\text{D}}^{-1} - k_{\text{XH}}) \quad (4)$$

Horrocks pointed out that the Eq. (4) does not give reliable results for Eu(III) complexes with a higher hydration number [21,22] and, therefore, he modified Eq. (4) to Eq. (5):

$$q_{\text{H2}} = 1.11 \times (\tau_{\text{H}}^{-1} - \tau_{\text{D}}^{-1} - k_{\text{XH}}) \quad (5)$$

$$k_{\text{XH}} = 0.31 + 0.45 n_{\text{OH}} + 0.99 n_{\text{NH}} + 0.075 n_{\text{O}=\text{CNH}} \quad (6)$$

where  $k_{\text{XH}}$  is defined by Eq. (6) ( $n$  is number of particular oscillators in a molecule). Equation (5) can be simplified if only O–H oscillators present in complex as water

molecule(s) are responsible for the quenching (Eq. (7))

$$q_{H_2} = 1.11 \times (\tau_H^{-1} - \tau_D^{-1} - 0.31) \quad (7)$$

The authors declared the precision of  $q$  to be  $\pm 0.1$  for determination of hydration number of complexes [22].

Kimura [23] introduced equations for determination of  $q$  values, in frozen aqueous solutions at liquid nitrogen temperature, for several Ln<sup>3+</sup> ions. In the case of Eu(III) ion and its complexes the following equation was used (Eq. (8)):

$$q_{K2} = 1.02 \times \tau_H^{-1} - 0.17 \quad (8)$$

## DISCUSSION

Excitation and emission spectra of the concerning Eu(do3ap)<sup>2-</sup> complex, as examples, are shown in Figs. 1 and 2.

The luminescence lifetimes of Eu(III) aqua ion and its complexes with H<sub>3</sub>do3a, H<sub>4</sub>dota, H<sub>5</sub>do3ap, H<sub>5</sub>do3ap<sup>PrA</sup> and H<sub>8</sub>dotp (Scheme 1) were measured in H<sub>2</sub>O and in some cases in D<sub>2</sub>O as well. To verify the following measurements, the first step was the determination of coordinated water molecules in [Eu(H<sub>2</sub>O)<sub>*n*</sub>]<sup>3+</sup> complex using the Eq. (2) or (3). The obtained values of luminescence decays are in an agreement with those given in literature (for H<sub>2</sub>O, 0.110 ms [19], 0.115–0.120 ms [22], 0.1106 ms [24] and 0.111 ms [25]). Considering all facts about hydration numbers of lanthanides obtained by X-ray and neutron diffraction, fluorescence, Raman and visible spectroscopy, Rizkalla and Choppin concluded that the light lanthanide ions (La<sup>3+</sup>–Nd<sup>3+</sup>) are present in aqueous solution as nona-aqua complexes whereas heavier lanthanide ions (Tb<sup>3+</sup>–Lu<sup>3+</sup>) form octa-aqua species and for middle-series lanthanide ions (Nd<sup>3+</sup>–Tb<sup>3+</sup>) there is

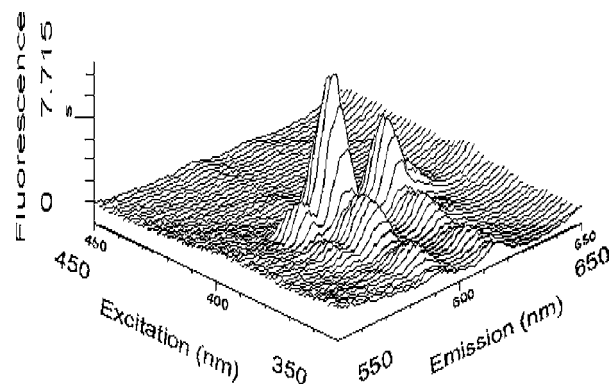


Fig 1. Excitation vs. emission spectra of Eu(do3ap)<sup>2-</sup> complex ( $c_{ML} = 1 \times 10^{-3} \text{ mol L}^{-1}$ , pH = 5.0).

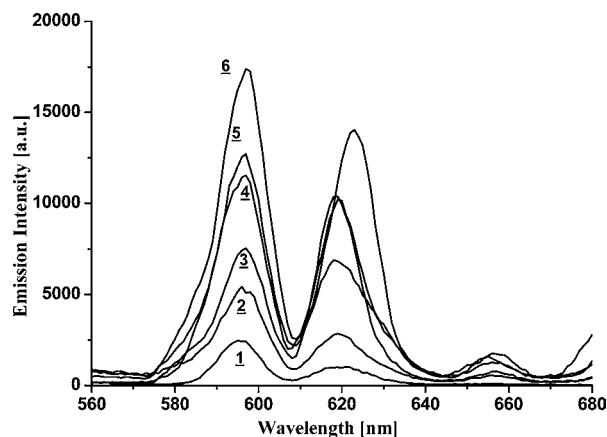


Fig 2. Luminescent spectra of aqueous solutions of europium(III) perchlorate (1) and europium(III) complexes with ligands studied (do3ap<sup>PrA</sup>(2), do3a (3), dotp(4), do3ap(5), dota(6)). The concentrations of complexes: do3ap<sup>PrA</sup>, 0.007 mol L<sup>-1</sup>, do3ap, 0.014 mol L<sup>-1</sup>, others, 0.015 mol L<sup>-1</sup>. The pH values of solutions are given in Table I.

a rapid equilibrium between both the species [26]. As it was pointed out [22], the luminescence spectroscopy is not a suitable method for determination of number of bound water molecules in Eu(III) aqua ion because of low sensitivity for distinguishing between these aqua species. Therefore, an arbitrary value of 9 for hydration number of Eu(III) aqua ion could be used [19,23,27]. It is in a good agreement with the value obtained by us (Table I).

Other critical factors are experimental conditions under which the luminescent properties of complexes are measured. We tested influence of molar ratio of ligand to metal ion, absence/presence of buffer and pH of solution on decay of luminescence (Fig. 3). As it can be noticed from Table I, there is no influence of the above parameters. These facts can be used as an indirect proof that Eu(III) forms very stable metal complexes with M:L = 1:1 stoichiometry with all macrocyclic ligands in the region close to physiological pH. The buffer has no quenching effect on luminescence decay probably due to a low overall hydration number of the complexes.

Hydration numbers of the Eu(III) complexes were calculated using Eqs. (1)–(8) and the results of the calculations are given in Table I. Except for H<sub>3</sub>do3a, all equations gave almost the same values within the precision given by the original papers. Values of  $q$  found for the H<sub>3</sub>do3a and H<sub>4</sub>dota complexes are in an agreement with values commonly accepted [7,28,29]. It can be seen that the hydration numbers of the complexes of new ligands (H<sub>5</sub>do3ap and H<sub>5</sub>do3ap<sup>PrA</sup>) are equal to 1. In case of H<sub>5</sub>do3ap, this hydration number is in agreement with

**Table I.** Spectroscopic Data and Number of Coordinated Water Molecules for Eu<sup>3+</sup>-DOTA Derivative Complexes

Species	pH	$\tau$ (H <sub>2</sub> O) (ms)		$\tau$ (D <sub>2</sub> O) (ms) pD	298 K	$n(\text{H}_2\text{O})^g$				$n(\text{H}_2\text{O})^h$	$\eta$ ( $I_{615}/I_{594}$ )	
		298 K	77 K			$q_{H1}$	$q_B$	$q_{H2}$	$q_K$			
Eu <sup>3+</sup>	2.2 <sup>a</sup>	0.1082	0.1208									
Eu(do3a)	5.6 <sup>b</sup>	0.375 <sup>e</sup>										
	5.6 <sup>b</sup>	0.371 <sup>f</sup>										
Eu(do3a)	7.4 <sup>c</sup>	0.290 <sup>e</sup>		7.4 <sup>c</sup>	2.2 <sup>c</sup>	3.1 <sup>d</sup>	2.9 <sup>d</sup>	1.9 <sup>c</sup>	3.2 <sup>d</sup>			1.69
Eu(dota) <sup>-</sup>	5.6 <sup>b</sup>	0.6765										
	7.4 <sup>c</sup>	0.640 <sup>e</sup>		7.4 <sup>c</sup>	2.4 <sup>c</sup>	1.2 <sup>d</sup>	0.9 <sup>d</sup>	0.94 <sup>c</sup>	1.2 <sup>d</sup>			
Eu(dota) <sup>-</sup>	7.5 <sup>a</sup>	0.6606	0.8002									
Eu(do3ap) <sup>2-</sup>	5.6 <sup>a</sup>	0.671										
Eu(do3ap) <sup>2-</sup>	5.6 <sup>b</sup>	0.692										
Eu(do3ap) <sup>2-</sup>	6.8 <sup>a</sup>	0.6673	0.8140									
Eu(do3ap) <sup>2-</sup>	7.4 <sup>a</sup>	0.676		7.4 <sup>a</sup>	2.380	0.8	1.1	0.9	1.1			0.66
Eu(do3ap <sup>PrA</sup> ) <sup>2-</sup>	5.8 <sup>b</sup>	0.674										
Eu(do3ap <sup>PrA</sup> ) <sup>2-</sup>	7.2 <sup>a</sup>	0.6701	0.9083									
Eu(do3ap <sup>PrA</sup> ) <sup>2-</sup>	7.4 <sup>a</sup>	0.682		7.4 <sup>a</sup>	2.031	0.8	1.0	0.8	1.1			0.65
Eu(dotp) <sup>5-</sup>	7.8 <sup>a</sup>	1.2139	1.3195									
							0.2		0.4	0.6		1.60

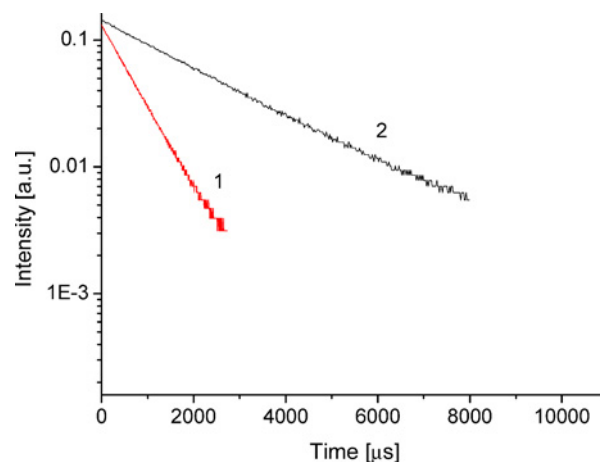
<sup>a</sup>No buffer used.<sup>b</sup>MES used as buffer.<sup>c</sup>Ref. [16,17].<sup>d</sup>Calculated in this work.<sup>e</sup> $c(\text{Eu}) = 0.005 \text{ mol L}^{-1}$ ,  $c(\text{L}) = 0.006 \text{ mol L}^{-1}$ .<sup>f</sup> $c(\text{Eu}) = 0.005 \text{ mol L}^{-1}$ ,  $c(\text{L}) = 0.010 \text{ mol L}^{-1}$ .<sup>g</sup> $n(\text{H}_2\text{O})$  calculated at 298 K.<sup>h</sup> $n(\text{H}_2\text{O})$  calculated at 77 K.

X-ray crystal structure of [Nd(H<sub>2</sub>O)(Hdo3ap)]<sup>-</sup> complex where the ligand is octadentate (4N + 4O donor set) with one water molecule in apical position [12]. According to literature [30], no water molecule in the first coordination sphere is supposed for the gadolinium(III) complex of H<sub>8</sub>dotp.

In frozen state, vibrations other than OH can be neglected [31]. The hydration numbers determined from Kimura equation (Eq. (8)) [23] for samples in frozen state are similar to those obtained in solution at room temperature. We observed that the values of Eu(III) lifetimes measured for the complexes studied in low temperature (77 K) are about 9–35% longer, due to less effective deactivation processes.

In case of symmetrical emission bands of Eu(III) complexes with macrocyclic ligands, their intensities at wavelength 615 and 594 nm were analysed to determine the ratio  $\eta = I_{615}/I_{594}$  (Table I). The knowledge of  $\eta$  value provides information on the geometry of the complex [32]. In the aqua complex, the water molecules are arranged symmetrically around the metal ion and the value  $\eta$  is low (0.39). Removal of six or nine bound water molecules from the inner coordination sphere of Eu(III) ion in the do3a and dotp complexes reduces more the symmetry of complexes than removal eight water molecules (DOTA,

DO3AP, DO3AP<sup>PrA</sup>). From the correlation of coordination number of Eu(III) in its complexes and  $\eta$  parameter, it can be suggested that its inter-spherical coordination mode which is characteristic for Eu(III) chelates with high coordination number and low value of  $\eta$  parameter [27].



**Fig 3.** Decay curves of luminescence from Eu(III) (<sup>5</sup>D<sub>0</sub>) of Eu(do3ap)<sup>2-</sup> complex ( $c_M = 5.0 \times 10^{-3} \text{ mol L}^{-1}$ ,  $c_L = 5.2 \times 10^{-3} \text{ mol L}^{-1}$ ). (1) in H<sub>2</sub>O, pH = 7.4, (2) in D<sub>2</sub>O, pD = 7.4.

## CONCLUSIONS

We determined hydration numbers of several Eu(III) complexes with macrocyclic ligands. Our measurement confirmed values of  $q$  for complexes of known ligands. Complexes of new monophosphorus acid derivatives of H<sub>4</sub>dota have one water molecule in the first coordination sphere. We tested several empirical equations for determination of hydration number on Eu(III) complexes. Relations working with emission lifetimes in H<sub>2</sub>O proved to be satisfactory for determination of  $q$ . Such approach is more simple and fast as there is no requirement for using D<sub>2</sub>O.

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