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Europium complex of 2,2′-bipyridine-6,6′-dicarboxylic acid bis[di(phosphonomethyl)amide] as a new efficient water-soluble luminescent dye

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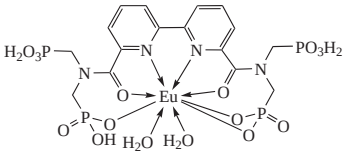
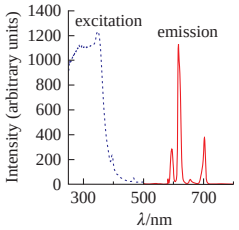
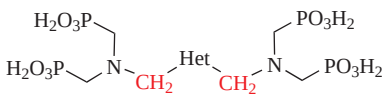
A new water-soluble luminescent complex of europium with an organic ligand bearing di(phosphonomethyl)amide moiety has been synthesized and characterized by NMR spectroscopy and HRMS-ESI analysis. Its luminescence quantum yield is 4.7 and 1.2%, and luminescence lifetime is 0.7 and 0.5 ms in methanol and water solutions, respectively. This type of complex can be used as biochemical luminescent probe.





Water-soluble complexes of lanthanides are of importance due to their application as biomedical luminescent probes.[1,2] Recent advance in the design of these complexes comprises incorporation of methylphosphonic acid moieties into various heterocyclic scaffolds as in structure **1**.[3–7] Thus, the combination of phosphonomethyl groups with pyridine-type heterocycles allowed one to create a new type of Cu-based PET imaging agents[3] and Gd-based MRI contrast agents.[4] A disadvantage of these compounds is the existence of C–H bonds both in phosphonomethyl moiety and in the methylene group, which links the phosphorus-containing part with the heterocyclic part, the latter in close proximity to the coordinated lanthanide ion position. This arrangement may result in quenching the lanthanide ion luminescence by high-energy C–H vibrational manifolds. To avoid this undesirable quenching, we have proposed a new type of ligand, namely hetarenecarboxylic acid di(phosphonomethyl)amide, instead of ligands with the less rigid di(phosphonomethyl)aminomethyl moiety.[6] In this new ligand type the CH_2–N bonds between the heterocyclic and the methylphosphonic acid parts as in structure **1** are replaced with C(O)–N ones as in structure **2**.

The aim of this work was the synthesis of europium complex with {2,2′-bipyridine-6,6′-diylbis[carbonylnitrilodi(methylene)]}-tetrakis(phosphonic acid) and investigation of its luminescence.



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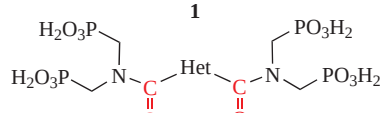

2

The water-soluble ligand **4** was prepared according to Scheme 1.† The reaction of compound **4** with europium(III) nitrate afforded complex **5** in 85% yield, which was characterized by HRMS, NMR, UV-VIS absorbance and luminescence spectroscopy. From the data obtained it was concluded that the ligand-to-metal ratio in it was 1 : 1.

Complex **5** exhibits bright luminescence [Figure 1(*a*)] and reveals pH-dependent water solubility of ~1×10^{-3} mol dm^{-3}. It is also soluble in polar organic solvents such as methanol or acetonitrile. The complex shows the main absorption band with

† *Octaethyl {2,2'-bipyridine-6,6'-diylbis[carbonylnitrilodi(methylene)]}-tetrakis(phosphonate)* **3**. 2,2′-Bipyridine-6,6′-dicarboxylic acid (0.37 g, 1.5 mmol) in mixture of thionyl chloride (10 ml) and DMF (0.3 ml) was refluxed for 2.5 h. Then thionyl chloride was removed, the solid residue was dissolved in absolute THF (15 ml) and the resulting solution was added portionwise to a solution of tetraethyl [iminodi(methylene)]bis(phosphonate) (1 g, 3.15 mmol) and Et_3N (1 ml) in absolute THF (10 ml). The mixture was stirred at room temperature for 16 h. Then water (5 ml) was added and the organic layer was separated, washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated to leave dark oil. Then diethyl ether (5 ml) was added to the oil and the mixture was ground until precipitate formation. The precipitate was filtered off, washed with cold diethyl ether and dried in air to afford product **3** as white powder. Yield 1 g (79%), mp 116–118 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.19 (t, 12H, CH_2*Me*, ^3J 7.0 Hz), 1.36 (t, 12H, CH_2*Me*, ^3J 7.0 Hz), 3.94–4.01 (m, 8H, C*H*$_2$Me), 4.20–4.27 (m, 8H, C*H*$_2$Me), 4.39 (d, 4H, 2CH_2P, ^2J 11.1 Hz), 4.76 (d, 4H, 2CH_2P, ^2J 11.2 Hz), 7.85 (d, 2H, 3,3′-CH, ^3J 7.5 Hz), 7.97 (t, 2H, 4,4′-CH, ^3J 7.7 Hz), 8.50 (d, 2H, 5,5′-CH, ^3J 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2 (d, *J* 5.1 Hz), 16.3 (d, *J* 5.0 Hz), 41.3 (d, *J* 155.9 Hz), 44.5 (d, *J* 154.7 Hz), 62.2 (d, *J* 6.0 Hz), 62.6 (d, *J* 5.7 Hz), 122.1, 125.4, 138.2, 152.5, 153.1, 167.5. ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.64, 21.65. MS (MALDI-TOF), *m*/*z*: 881 $[M+K]^+$. Found (%): C, 45.72; H, 6.51; N, 14.78. Calc. for $C_{32}H_{54}N_4O_{14}P_4$ (%): C, 45.61; H, 6.46; N, 14.70.

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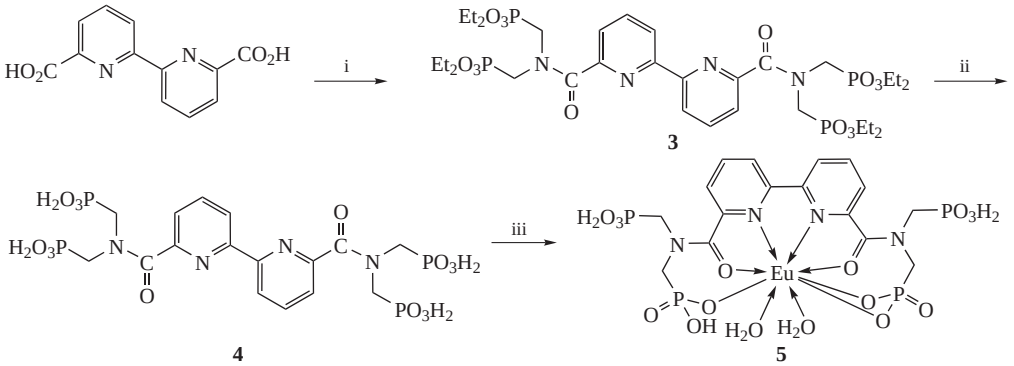

Scheme 1 *Reagents and conditions*: i, $SOCl_2$, DMF, reflux, 2.5 h, then $NH(CH_2PO_3Et_2)_2$, Et_3N, THF, room temperature, 16 h; ii, NaI, Me_3SiCl, MeCN, room temperature, 4 h, then H_2O; iii, $Eu(NO_3)_3 \cdot 6H_2O$, H_2O, 5 min.

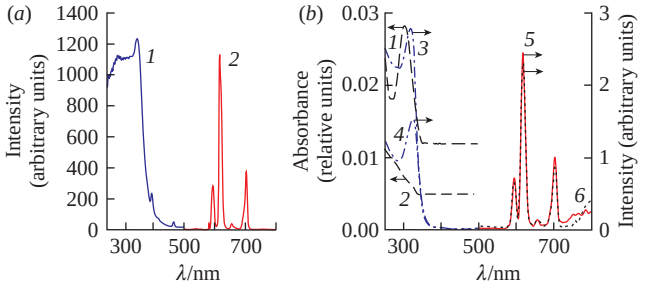

Figure 1 (*a*) Luminescence spectra of complex **5** in solid state: (*1*) excitation at λ_{em} 615 nm, (*2*) emission at λ_{ex} 320 nm; (*b*) spectra of complex **5** solutions at 1×10^{-5} mol dm^{-3} concentration: (*1*) absorption spectrum in H_2O, (*2*) absorption spectrum in D_2O, (*3*) luminescence excitation spectrum in H_2O at λ_{em} 615 nm, (*4*) luminescence excitation spectrum in D_2O at λ_{em} 615 nm, (*5*) luminescence emission spectrum in H_2O at λ_{ex} 320 nm, (*6*) luminescence emission spectrum in D_2O at λ_{ex} 320 nm.

a maximum at 299 nm in water and heavy water solutions [Figure 1(*b*)].‡ Its excitation spectra are in agreement with the ground-state absorption spectra. In the emission spectra, the typical europium(III) bands are observed, which corresponds to $^5D_0 \rightarrow {}^7F_J$ (J is 0, 1, 2, 3 and 4) transitions at 582, 594, 615, 653 and 700 nm, respectively.[8] The asymmetry ratio, *i.e.*, the coefficient determining the degree of symmetry distortion of the coordination sphere, was calculated using integrated luminescence intensities.[9]

$$R = I(^5D_0 \rightarrow {}^7F_2)/I(^5D_0 \rightarrow {}^7F_1),$$

where $I(^5D_0 \rightarrow {}^7F_2)$ and $I(^5D_0 \rightarrow {}^7F_1)$ are integrated luminescence intensities of the corresponding transition bands.

The calculated asymmetry ratio is 3.6 in aqueous solution and ~4.2 in solid state (Table 1), which indicates the poor influence of solvent water molecules on the symmetry distortion around the europium(III) ion.

The radiative luminescence lifetime for complex **5** was also calculated. We found the ratio of the total integrated luminescence intensity I_{tot} to the area of the peak corresponding to the magnetic dipole transition $I(^5D_0 \rightarrow {}^7F_1)$, as the most robust under experimental conditions, and then calculated the radiative lifetime using the following formula.[10]

$$1/\tau_{rad} = A_{MD,0} n^3 I_{tot}/I(^5D_0 \rightarrow {}^7F_1),$$

where n is the medium refractive index (1.33 for water, 1.328 for heavy water, 1.3288 for methanol and 1.55 in the solid state) and $A_{MD,0}$ is the probability of the spontaneous emission of magnetic dipole transition $I(^5D_0 \rightarrow {}^7F_1)$ taken as 14.65 s^{-1}.[11]

Luminescence decay curves for lanthanides are described by the following monoexponential equation.

$$I(t) = I(t_0)\exp(-t/\tau_{obs}),$$

where τ_{obs} is the observed luminescence lifetime. Calculated luminescence lifetime of complex **5** is given in Table 1. Water molecules in the first coordination sphere of europium atom lead to the decrease in luminescence lifetime, so the number of inner-sphere water molecules can be calculated using the following equation.[12]

$$q(H_2O) = 1.11(1/\tau_{H_2O} - 1/\tau_{D_2O} - 0.31),$$

where τ_{H_2O} and τ_{D_2O} are observed luminescence lifetimes of the complex solutions in water and heavy water, respectively. Using

Table 1 Luminescence characteristics of complex **5**.

Solvent	R	τ_{rad}/ms	τ_{obs}/ms	Q_{Ln}(%)	Q_L(%)	η (%)
H_2O	3.6	4.3	0.5	10	1.2[a]/0.3[b]	11[a]
D_2O	3.7	4.2	1.9	46	1.5[a]/1.0[b]	3.3[a]
MeOH	4.1	4.2	0.7	16	4.7[a]	29[a]
Solid state	4.2	2.7	0.5	18		

[a] Calculated using rhodamine B as reference dye. [b] Calculated using quinine sulfate as reference dye.

{2,2′-Bipyridine-6,6′-diylbis[carbonylnitrilodi(methylene)]}tetrakis(phosphonic acid) **4**. Dry sodium iodide (0.15 g, 1 mmol) was added to a solution of compound **3** (0.1 g, 0.1 mmol) in dry acetonitrile (3 ml) and the mixture was stirred until dissolution completed. Then chlorotrimethylsilane (0.11 g, 1 mmol) was added dropwise and the mixture was stirred at room temperature for 4 h. The precipitate was filtered off and the solvent was evaporated *in vacuo* without heating to afford a solid residue. Deionized water was added to the residue and the solution was evaporated to dryness *in vacuo* again. Isopropanol was added to the residue and the mixture was milled until crystallization of acid **4** as white powder. Yield 0.04 g (65%), mp > 250 °C. ^{1}H NMR (600 MHz, D_2O) δ: 3.88 (d, 4H, 2CH_2P, ^2J 10.7 Hz), 4.04 (d, 4H, 2CH_2P, ^2J 11.8 Hz,), 7.81 (d, 2H, 3,3′-CH, ^3J 7.7 Hz), 8.20 (t, 2H, 4,4′-CH, ^3J 7.9 Hz), 8.29 (d, 2H, 5,5′-CH, ^3J 8.1 Hz). ^{13}C NMR (100 MHz, D_2O) δ: 43.9 (d, J 146.7 Hz), 46.8 (d, J 145.4 Hz), 124.5, 125.2, 141.6, 150.7, 150.7, 167.7. ^{31}P NMR (162 MHz, D_2O) δ: 15.49, 16.97. Found (%): C, 31.19; H, 3.65; N, 9.14. Calc. for $C_{16}H_{22}N_4O_{14}P_4$ (%): C, 31.08; H, 3.59; N, 9.06.

{2,2′-Bipyridine-6,6′-diylbis[carbonylnitrilodi(methylene)]}tetrakis(phosphonato) diaqua europium(III) **5**. A solution of $Eu(NO_3)_3 \cdot 6H_2O$ (0.013 g) in distilled water (0.5 ml) was added to a solution of acid **4** (0.02 g, 0.03 mmol) in distilled water (2 ml) with stirring. The mixture was stirred for 5 min and the precipitate was filtered off to afford complex **5** as white powder. Yield 0.02 g (85%), mp > 250 °C. ^{1}H NMR (600 MHz, D_2O) δ: 3.55–3.60 (m, 4H, 2CH_2), 3.74–3.80 (m, 4H, 2CH_2), 7.51–7.60 (m, 2H, 2H_{Ar}), 8.03–8.17 (m, 2H, 2H_{Ar}), 8.46–8.55 (m, 2H, 2H_{Ar}). HRMS (ESI), m/z: 764.8969 [LEu – 4H]$^-$ (calc. for $C_{16}H_{18}EuN_4O_{14}P_4$, m/z: 764.8968).

‡ The UV-VIS spectra were measured on a Hitachi U-1900 spectrophotometer using a quartz cuvette with optical path length 10 mm, the baseline was corrected relative to water or heavy water. Excitation and emission luminescence spectra were recorded using a Hitachi F-7000 spectrophotometer, with solutions placed in a standard quartz cuvette with an optical path length 1 cm. The solid state luminescence spectra were recorded at room temperature with 90° geometry.

this equation, the value of 1.3 was obtained, thus it was established that complex **5** had one or two inner-sphere water molecules.

The external luminescence quantum yield of complex **5** was determined by the reference dye method[13] using rhodamine B and quinine sulfate (Table 1).[14–16] The difference in the obtained values between the reference dyes results from positions of their emission bands. Since rhodamine B emits in the same spectral range as europium(III), we used it for further measurements. The different luminescence quantum yields for H_2O and D_2O are due to high sensitivity of europium(III) emission to the quenching by O–H vibrations,[17] the probability of this quenching is lower after replacing ^1H atom with deuterium.[18]

Using radiative and observed luminescence lifetime values we calculated the internal luminescence quantum yield and then the sensibilization efficiency η in accordance with the following formula.[11]

$$\eta = Q_L/Q_{Ln} = Q_L\tau_{rad}/\tau_{obs},$$

where Q_L is external luminescence quantum yield and Q_{Ln} is internal luminescence quantum yield. The resulting values (Table 1) illustrate some effect of water molecule in the first coordination sphere on the luminescence sensibilization.

The obtained luminescence characteristics of complex **5** are in good agreement with published data: the luminescence lifetimes are close to those for other hydrated mononuclear L_1Eu_1 complexes[19] and the luminescence quantum yield is slightly less than those for the reported water-soluble binuclear europium helicates bearing the phosphonic acid moiety (4.6 or 6%).[20]

In summary, it has been shown that the new water-soluble europium complex with di(phosphonomethyl)amide moiety-bearing organic ligand luminesces well both in D_2O and in H_2O. From the kinetics of luminescence decay, the number of water molecules in the first coordination sphere was estimated to be 1.3. The complex can potentially be used as a luminescent probe, as a reagent for immunofluorescence analysis, as pH detector and in other biomedical areas since its luminescence lifetimes are significantly higher than the autofluorescence lifetimes of living tissues.

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