The formation stability, hydrolytic behavior, mass spectrometry, DFT study, and luminescence properties of trivalent lanthanide complexes of H$_2$ODO2A

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The trivalent lanthanide complex formation constants (log $K_1$) of the macrocyclic ligand H$_2$ODO2A (4,10-dicarboxymethyl-1-oxa-4,7,10-triazacyclododecane) have been determined by pH titration techniques to be in the range 10.84–12.62 which increase with increasing lanthanide atomic number, and are smaller than those of the corresponding H$_2$DO2A (1,7-dicarboxymethyl-1,4,7,10-tetraazaacyclododecane) complexes. The equilibrium formation of the dinuclear hydrolysis species, e.g. Ln$_2$(ODO2A)$_2$(μ-μOH)$^+$ and Ln$_2$(ODO2A)$_2$(μ-μOH)$_2$, dominates over the mononuclear species, e.g. LnODO2A(OH) and LnODO2A(OH)$_2^+$. Mass spectrometry confirmed the presence of [Eu(ODO2A)H]$^+$, [Eu(ODO2A)(OH)+H]$^+$, [Eu$_2$(ODO2A)$_2$(OH)$_2$]$^+$, [Eu(ODO2A)OH]$_2^+$ and [Eu(ODO2A)$_2$(OH)$_2$]$_2^+$ species at pH > 7. Density function theory (DFT) calculated structures of the EuODO2A(H$_2$O)$_3^+$ and EuODO2A(H$_2$O)$_5^+$ complexes indicate that three inner-sphere coordinated water molecules are arranged in a meridional configuration, i.e. the 3 water molecules are on the same plane perpendicular to that of the basal N$_2$O$_3$ or N$_3$O$_6$ atoms. However, luminescence lifetime studies reveal that the EuODO2A$^+$ and TbODO2A$^+$ complexes have 4.1 and 2.9 inner-sphere coordinated water molecules, respectively, indicating that other equilibrium species are also present for the EuODO2A$^+$ complex. The respective emission spectral intensities and lifetimes at 615 nm ($\lambda_{ex} = 395$ nm) and 544 nm ($\lambda_{ex} = 369$ nm) of the EuODO2A$^+$ and TbODO2A$^+$ complexes increase with increasing pH, consistent with the formation of μ-OH-bridged dinuclear species at higher pH. Additional DFT calculations show that each Y(III) ion is 8-coordinated in the three possible cis-[Y$_2$(ODO2A)$_2$(2μ-μOH)(H$_2$O)$_2$]$^+$, trans-[Y$_2$(ODO2A)$_2$(2μ-μOH)(H$_2$O)$_2$]$^+$ and [Y$_2$(ODO2A)$_2$(2μ-μOH)$_2$] dinuclear complex structures. The first and the second include 6-coordination by the ligand ODO2A$^{2-}$, one by the bridged μ-OH ion and one by a water molecule. The third includes 6-coordination by the ligand ODO2A$^{2-}$ and two by the bridged μ-OH ions. The two inner-sphere coordinated water molecules in the cis- and trans-[Y$_2$(ODO2A)$_2$(2μ-μOH)(H$_2$O)$_2$]$^+$ dinuclear complexes are in a staggered conformation with torsional angles of 82.21° and 148.54°, respectively.

Introduction

Trivalent lanthanide ions (Ln$^{3+}$) are hard Lewis acids and in aqueous solution they are usually 8–10 coordinated. When the Ln$^{3+}$ ion, particularly Gd$^{3+}$, is coordinated with multidentate ligands that allow usually one inner-sphere coordinated water molecule, the resulting stable complexes have been used as effective magnetic resonance imaging (MRI) contrast agents, e.g. Magnestiv, ProHance and Omniscan. If the coordinated ligand or inner-sphere coordinated water molecules on the Ln$^{3+}$ ion are able to be bio-activated (bio-responsive) or allow anion replacement, these systems could be used as molecular imaging agents or luminescent anion sensors. On the other hand, the coordinated water molecules could be hydrolyzed at relatively lower pH which makes them potentially good candidates as artificial nucleases, peptidases and hydrolases.

Early research works on the hydrolysis of trivalent lanthanide ions are summarized in an excellent monograph. Although a number of ligand-controlled self-assembly of polynuclear lanthanide-oxo/hydroxo complexes have been recently synthesized and characterized by crystallography, except for the first hydrolysis constants leading to the formation of the mononuclear Ln-OH$^{2-}$ species, the equilibrium constants for the formation of...
polynuclear species such as Ln₂(OH)₂⁴⁺, Ln₃(OH)₃⁴⁺ and Ln₃(OH)₆⁶⁺ could only be determined in high ionic strength media with limited accuracy, due to the complexity of various hydrolysis equilibria at high pH and easy hydroxide precipitation.

Formation of trivalent lanthanide complexes with multidentate ligands tends to reduce the number of the inner-coordinated water molecules and allow possibly better control of their hydrolysis behaviors. For example, the anionic EuEDTA⁻ (EDTA₄⁻ = ethylenediamine-₆N,N,N',N'-tetraacetic ion) and neutral EuHEDTA (HEDTA₃⁻ = N-hydroxyethyl(ethylenediamine)-₆N,N,N'-triacetic ion) complexes have the respective coordinated water hydrolysis constants of pH = 12.48⁸⁰ and pH = 10.1.⁸⁵ However, for applications as artificial nucleases, recent studies suggested the use of stable and positively charged dinuclear lanthanide complexes with at least two or more inner-sphere coordinated water molecules.⁹ In our laboratory, we have found that the EuDO₂A⁺ complex with 3 inner-sphere coordinated water molecules was able to promote phosphodiester bond hydrolysis with appreciable rates at pH 9–10 (DOD₂A₂⁻ is the deprotonated form of H₂DO₂A, i.e. 1,7-dicarboxymethyl-1,4,7,10-tetraazacyclododecane, Scheme 1).¹⁰ It was proposed that the mono-hydroxo-bridged Eu₂(DO₂A)₂(μ-OH)(OH)(H₂O)₃ and the di-hydroxy-bridged Eu₂(DO₂A)₂(μ-OH)₂(H₂O)₂ species were more reactive than the mononuclear species. However, due to the slow complex formation rates, the formation constants for these μ-OH bridged dinuclear species could not be determined directly and accurately to further confirm exactly which species was the more reactive.¹¹

Previously, we have found that the Ln(III) complex formation constants¹² of a number of oxaaza-macrocyclic diacetic acid ligands, i.e. H₃K₂1DA (dapda, 1,7-diaza-4,10,13-trioxacyclopentadecane-₆N₆-diacetic acid,¹²b Scheme 1) and H₃K₂2DA (dacda, 1,10-diaza-4,7,13,16-tetraoxaacyclooctadecane-₆N₆-diacetic acid,¹²a Scheme 1) could be conveniently determined by pH titration techniques. In order to understand the formation stability, hydrolysis behaviors, and structures of trivalent lanthanide complexes better, we have synthesized the oxaaza-macrocyclic ligand, 4,10-dicarboxymethyl-1-oxa-4,7,10-triaza-cyclododecane (H₂DO₂A, Scheme 1),¹³ and have determined their trivalent lanthanide complex stability constants and various formation constants involving hydroxide species. We have also studied mass spectrometry, solution luminescence properties¹⁴ and density function theoretical (DFT) predictions of their structures.¹⁵ The results are reported in this paper.

**Results and discussion**

**Synthesis and purification of H₂DO₂A**

The synthesis of the ligand H₂DO₂A has been reported previously and is rather straightforward.¹³ Protection of the middle secondary ring nitrogen atom from carboxymethylation can be done by controlling reaction solution pH because protonation of this more basic nitrogen atom occurs at high pH, i.e. the logarithmic first protonation constant of 1-oxa-4,7,10-triazacyclododecane is 10.11.¹⁶a Although the previously reported synthesis for the carboxymethylation reaction was performed at pH 8.5, in our hands we found that by keeping the pH to ca. 8.0 and using two equivalents of bromoacetate, the tris-carboxy-methylation by-product could be greatly reduced. This final purification of H₂DO₂A was performed by first passing the last reaction product solution through an anion exchange column, concentrating it, and then recrystallizing it in ethanolic HCl solution.

**Ligand protonation constants and protonation sites of H₂DO₂A**

The logarithmic protonation constants of H₂DO₂A determined by the potentiometric method are 11.08 ± 0.02, 5.96 ± 0.04, 2.85 ± 0.10, and 1.94 ± 0.10. These values are a little lower than those reported previously,¹³ i.e. 11.24, 6.02, 2.94. The previously reported NMR titration experiments at various pH solutions were also repeated by us and similar results were obtained (Fig. S1, ESI†). The data concerning the protonation sequence were best explained by first protonation at the secondary ring nitrogen and second protonation on the tertiary ring nitrogen atoms with simultaneous partial deprotonation of the secondary ring nitrogen atom.

**Stabilities of LnDO₂A⁺ complexes**

Fluorescence titration by the molar ratio method indicated that Eu⁺ and ODO₂A⁻ at pH 6.7 form a 1:1 complex (λₑₓ = 395 nm, λₑₘ = 615 nm; data not shown). Unlike those of DO₂A²⁻ complexes,¹¹ the kinetics are relatively faster for the formation reactions between the trivalent lanthanide ions and the ligand ODO₂A⁻ due to faster equilibrium pH establishment after each addition of standard base, and the stability constants could be conveniently determined by potentiometric pH titration techniques. The logarithmic formation constants of the LnDO₂A⁺ complexes (including YDO₂A⁺) and their hydrolysis species (vide infra) are listed in Table 1. Scheme S1† shows the definitions of formation reactions and constants for these hydrolysis species (ESI†, L = ODO₂A). For comparison purposes, the stability data of Ln₃⁺ complexes of three structural analogues of ODO₂A⁻, i.e. DO₂A⁻, K21DA⁻ and K22DA⁻ are listed in Table S1 (ESI†) and plotted in Fig. 1. Fig. S2 (ESI†) shows some selected pH titration curves of LnDO₂A⁺.

The formation constants of the LnDO₂A⁺ complexes are in the range log Kᵢ = 10.84–12.62 and increase with increasing
Table 1 Formation constants of the Ln(III)-ODO2A\(^2-\) complex systems, 25 °C, ionic strength 0.1\(^a,b\)

<table>
<thead>
<tr>
<th>Ln</th>
<th>(\log K_{10}(\log K_f))</th>
<th>(\log K_{11})</th>
<th>(\log K_{22-1})</th>
<th>(\log K_{22-2})</th>
<th>(\log K_{22-3})</th>
<th>(\log K_{22-4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>La</td>
<td>10.84 (0.02)</td>
<td>14.46 (0.41)</td>
<td>17.12 (0.09)</td>
<td>8.58 (0.10)</td>
<td>-0.10 (0.12)</td>
<td>-10.11 (0.08)</td>
</tr>
<tr>
<td>Ce</td>
<td>11.30 (0.01)</td>
<td>15.28 (0.06)</td>
<td>18.10 (0.08)</td>
<td>9.49 (0.08)</td>
<td>0.35 (0.08)</td>
<td>-9.52 (0.08)</td>
</tr>
<tr>
<td>Pr</td>
<td>11.98 (0.01)</td>
<td>15.28 (0.10)</td>
<td>19.66 (0.09)</td>
<td>11.21 (0.09)</td>
<td>0.82 (0.19)</td>
<td>-8.79 (0.09)</td>
</tr>
<tr>
<td>Nd</td>
<td>11.95 (0.01)</td>
<td>15.02 (0.22)</td>
<td>19.67 (0.08)</td>
<td>10.95 (0.11)</td>
<td>1.04 (0.11)</td>
<td>-8.94 (0.10)</td>
</tr>
<tr>
<td>Sm</td>
<td>12.41 (0.01)</td>
<td>16.01 (0.06)</td>
<td>20.50 (0.12)</td>
<td>12.38 (0.06)</td>
<td>1.90 (0.16)</td>
<td>-8.37 (0.10)</td>
</tr>
<tr>
<td>Eu</td>
<td>12.27 (0.01)</td>
<td>15.55 (0.13)</td>
<td>20.15 (0.17)</td>
<td>10.84 (0.25)</td>
<td>1.67 (0.16)</td>
<td>-9.15 (0.21)</td>
</tr>
<tr>
<td>Gd</td>
<td>12.00 (0.01)</td>
<td>—</td>
<td>19.38 (0.14)</td>
<td>9.85 (0.17)</td>
<td>-1.55 (0.58)</td>
<td>-11.97 (0.22)</td>
</tr>
<tr>
<td>Tb</td>
<td>12.13 (0.01)</td>
<td>—</td>
<td>19.87 (0.15)</td>
<td>12.06 (0.11)</td>
<td>2.23 (0.17)</td>
<td>-7.84 (0.12)</td>
</tr>
<tr>
<td>Dy</td>
<td>12.04 (0.01)</td>
<td>—</td>
<td>19.66 (0.14)</td>
<td>10.66 (0.16)</td>
<td>0.36 (0.18)</td>
<td>-10.85 (0.34)</td>
</tr>
<tr>
<td>Ho</td>
<td>12.04 (0.01)</td>
<td>—</td>
<td>19.82 (0.08)</td>
<td>11.66 (0.07)</td>
<td>1.55 (0.11)</td>
<td>-8.82 (0.09)</td>
</tr>
<tr>
<td>Er</td>
<td>12.04 (0.01)</td>
<td>—</td>
<td>19.93 (0.18)</td>
<td>11.76 (0.20)</td>
<td>2.03 (0.28)</td>
<td>-8.09 (0.25)</td>
</tr>
<tr>
<td>Tm</td>
<td>12.17 (0.01)</td>
<td>—</td>
<td>19.94 (0.22)</td>
<td>11.13 (0.25)</td>
<td>1.05 (0.27)</td>
<td>-9.59 (0.31)</td>
</tr>
<tr>
<td>Yb</td>
<td>12.62 (0.01)</td>
<td>—</td>
<td>20.90 (0.15)</td>
<td>13.23 (0.10)</td>
<td>4.05 (0.12)</td>
<td>-6.00 (0.12)</td>
</tr>
<tr>
<td>Lu</td>
<td>12.60 (0.01)</td>
<td>—</td>
<td>20.87 (0.12)</td>
<td>12.01 (0.24)</td>
<td>2.28 (0.25)</td>
<td>-7.49 (0.19)</td>
</tr>
<tr>
<td>Y</td>
<td>11.72 (0.02)</td>
<td>—</td>
<td>19.95 (0.20)</td>
<td>11.63 (0.18)</td>
<td>2.95 (0.18)</td>
<td>-7.59 (0.19)</td>
</tr>
</tbody>
</table>

\(^a\) The overall protonation constants for ODO2A\(^2-\) are: \(\log K_1, 11.08; \log K_2, 17.04; \log K_3, 19.89; \log K_4, 21.83.\)  
\(^b\) The formation constants were the averaged values of three to five determinations. Values in parentheses are the standard deviations of each formation constant. The averaged standard deviation values are as follows: \(\log K_2, 0.01; \log K_{11}, 0.16; \log K_{22-1}, 0.13; \log K_{22-2}, 0.14; \log K_{22-3}, 0.20; \log K_{22-4}, 0.17.\)

Among the ligands illustrated in this paper, the gadolinium break seems also apparent. The Ln(III)-ODO2A\(^+\) stability is usually smaller (i.e. up to 1.27 log \(K\) units) than that of the corresponding LnDO2A\(^+\). Thus, substituting one secondary nitrogen donor atom of the cyclen macrocycle of DO2A\(^2-\) by an ether donor atom to result in the ligand ODO2A\(^2-\) decreases the overall Ln(III) formation stability. At least three reasons are apparent. The first is that the basicity of ODO2A\(^2-\) as represented by the summation of the first three protonation constants (2log \(K\) = 19.89) is less than that of DO2A\(^2-\) (2log \(K\) = 24.34). Second, the rigidity of the macrocycle of ODO2A\(^2-\) is relatively less than that of DO2A\(^2-\) as manifested by the relatively faster Ln(III)-ODO2A\(^+\) formation and dissociation kinetics (to be reported elsewhere). Third, the Ln(III)-ODO2A\(^+\) complex is less symmetrical than the corresponding Ln(III)-DO2A\(^+\) and is more distorted and results in lower stabilization energy.

For macrocyclic ligands with ionizable coordinating pendant functional groups, the electrostatic interactions between the Ln(III) ions and the ligand are expected to increase as the charge density of the Ln(III) ion increases across the series due to lanthanide contraction. On the other hand, the match between the size of the macrocyclic cavity and the Ln(III) ion could tune the complex formation selectivity. A more careful examination of the stability trend of the lighter Ln(III)-ODO2A\(^2-\) complexes (i.e. La–Eu) indicates that it is similar to those of LnDO2A\(^+\) and LnK21DA\(^+\), as well as other macrocyclic aminopolycarboxylate complexes of DOTAC\(^+\) (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate ion), TETA\(^+\) (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetate ion), PEPAS\(^+\) (1,4,7,10,13-pentaazacyclo-pentadecane-N,N',N'',N''',N'''',N''''-pentaacetate ion) and HEHAD\(^+\) (1,4,7,10,13,16-hexaaza-cyclooctadecane-N,N',N'',N''',N''''',N'''',N''''''-hexaacetate ion),\(^17\) consistent with the notion that electrostatic interaction dominates the lighter Ln(III)-cyclen macrocyclic complex formation. The ODO2A\(^2-\) macrocycle is too small to exert a size effect towards the lighter and larger Ln(III) ions. However, for the heavier Ln(III)-ODO2A\(^2-\) complexes (i.e. Gd–Lu), the observed trend suggests factors such as better fit between metal ion radius and ligand cavity size may be important. As the number of the ether oxygen atoms is increased and the macrocycle ring becomes larger, the flexibility of the macrocycle ring is increased and so are the modulations of the size effect to Ln(III) ion selectivities. This probably could be shown by the Δlog \(K_f\) values (i.e. log \(K_{f,\text{highest}}\) − log \(K_{f,\text{lowest}}\)). Among the ligands illustrated in this paper, the Δlog \(K_f\) values are greater for lanthanide complexes with dominant ionic interactions (e.g. the respective Δlog \(K_f\) values for DO2A\(^2-\), TETA\(^+\), PEPAS\(^+\), and HEHAD\(^+\) are 2.37, 2.57, 3.14 and 5.16 with selectivities towards the heavier lanthanides) and smaller

![Fig. 1](image-url)
for those with more cavity size modulations (e.g. the respective \( \Delta \log K_{\text{range}} \) values for ODO2A\(^{2-}\), K21DA\(^{2-}\) and K22DA\(^{2-}\) are 1.78, 1.74, and 1.39 with selectivities varied from that for heavier, middle and lighter lanthanides, respectively). Note that an unprecedented selectivity for lighter lanthanides has been reported for a new macrocyclic ligand, \( N,N'\)-bis[6-carboxy-2-pyridyl]methyl]-4,13-diaza-18-crown-6 with a \( \Delta \log K_{\text{range}} \) of 6.86.\(^{18} \) For analogous cationic complexes of LnODO2A\(^{+}\), the stability trend is roughly LnK22DA\(^{+}\) > LnDO2A\(^{+}\) ≥ LnODO2A\(^{+}\) for the lighter La–Eu complexes, with a few exceptions of the LnK22DA\(^{+}\) and LnDO2A\(^{+}\) complexes (i.e. Ln = Nd and Eu). For the heavier Gd–Lu complexes, the trend is roughly LnDO2A\(^{+}\) > LnODO2A\(^{+}\) > LnK22DA\(^{+}\) presumably due to the larger ring size flexibilities of the K21DA/K22DA ligands and the interplay of the overall greater basicity and ring rigidity of the DO2A/ODO2A ligands. The protonation constants of the lanthanide complexes (log \( K_f \)) could be obtained by the differences between the corresponding \( \log \beta_{111} \) and \( \log K_f (\log \beta_{110}) \) values. Our titration data allow the calculations of these values only for six lighter LnODO2A\(^{+}\) (Ln = La–Eu) complexes and they are in the range 3.28–3.98. These values are similar to those of the LnDO2A\(^{+}\) complex, i.e. 3.20–3.98.\(^{19a} \) and the LnK21DA\(^{+}\) complex, i.e. 3.47–4.24.\(^{19b} \) determined from kinetic studies. These values are consistent with the proposition that protonation is on the carbonylate functional groups of these complexes.

Hydrolytic behaviors of the LnODO2A\(^{+}\) complexes in aqueous solution

It is also noted that the titration curves became much more complex after roughly 5 equivalents of base were added (Fig. S2, ESI†). Fitting these data to the equilibrium and hydrolysis model shown in Fig. 2 leads to much more interesting and significant results involving µ-OH bridged dinuclear Ln2L2-µ(OH)m (\( m,n = 1,2 \)) species formation with smaller deviations. Note that when mononuclear hydroxide species were included, the data fittings in most cases either wouldn’t converge or converged with larger deviations. To our knowledge, although seemingly straightforward, this general behavior has not been reported previously in a complete and systematic fashion. It is also noted that this scheme was not reported when transition metal (e.g. Cu(II) and Zn(II) oxatria complexes were studied because those complexes preferred simple stepwise mononuclear hydroxide species formation.\(^{16} \)

Depending on the ionic radius of the Ln\(^{3+}\) ion, the number of inner-sphere coordinated water molecules could be 2, 3, or 4 if the 6-coordinating ODO2A\(^{-}\) is already coordinated to the Ln\(^{3+}\) ion. For a smaller Ln(III) ion (e.g. Yb\(^{3+}\) and Lu\(^{3+}\)) and for the macrocyclic ligands which result in the formation of Ln(III) complexes with two inner-sphere coordinated water molecules (e.g. DO2A\(^{2-}\), ODO2A\(^{2-}\) and Ln-K21DA\(^{2-}\)), the number of major dinuclear µ-OH bridged species would be two, i.e. Ln2L2-µ(OH) and Ln2L2-µ(OH)2. More careful examinations of the speciation diagrams (e.g. Fig. 3) reveal that: (1) the µ-OH bridged Ln2L2-µ(OH) species is always formed before LnL(OH); (2) Ln2L2-µ(OH) is formed prior to Ln2L2-µ(OH)2, Ln2L2-µ(OH)2(OH)\(^{-}\), and Ln2L2-µ(OH)2(OH)2\(^{2-}\), and its stability gradually increases slightly with increasing atomic number, however; the relative species abundances are not always easily predictable; (3) the equilibrium formation of the mononuclear species (e.g. LnL(OH) and LnL(OH)\(^{-}\)) is less significant as compared to the dinuclear species; (4) the \( \log \beta_{22,3} \) and \( \log \beta_{22,4} \) values are subjected to larger uncertainties due to relatively larger measured errors at higher pH, and systematic trends are not obviously observed.

Fig. 3 shows the speciation diagrams of the La(III)-ODO2A\(^{2-}\), Eu(III)-ODO2A\(^{2-}\) and Yb(III)-ODO2A\(^{2-}\) complex systems. It is observed that although maximum EuODO2A\(^{2-}\) formation occurs at a lower pH (i.e. pH 5.5) than that of LaODO2A\(^{2-}\) (pH ≈ 6.0), the maximum formations of the µ-OH bridged dinuclear La2L2-µ(OH)m (\( m,n = 1,2 \)) species all occur at lower pH than the corresponding Eu2L2-µ(OH)m (\( m,n = 1,2 \)) species. On the other hand, 95% of YbODO2A\(^{2-}\) forms at pH 5.4 which is lower than those of LaODO2A\(^{2-}\) and EuODO2A\(^{+}\), the maximum formations of the µ-OH bridged dinuclear YbL2-µ(OH)m (\( m,n = 1,2 \)) species both occur at lower pH than the corresponding La2L2-µ(OH)m (\( m,n = 1,2 \)) species. Similar data have also been found for other macrocyclic ligand systems such as H3NO2A (4,7-dicarboxymethyl-1,4,7-triazacyclononane) and H3ONO2A (4,7-dicarboxymethyl-1-oxa,4,7-diazacyclononane) but could not be obtained with traditional linear ligands such as ethylenediamine-N,N’-diacetic acid (H\(_2\)EDDA) nor those with easy hydroxide precipitation. These results will be reported elsewhere.

Mass spectrometry

Both the positive and negative ESI-MS spectral data of the Eu(III)-ODO2A\(^{2-}\) complex system confirmed the presence of the hydrolytic, mono- and di-nuclear species. The ESI-MS(+) peaks for the [Eu(ODO2A)]\(^{+}\) species (\( m/z \) at 438, 440), [Eu(ODO2A)]- (OH) + H\(^{+}\) species (\( m/z \) at 456 and 458) and for the [Eu2-(ODO2A)2(OH)2]+ species (\( m/z \) at 911, 913 and 915) could be observed at pH 7.36 (Fig. 4). The ESI-MS(−) peaks for the [Eu(ODO2A)(OH)2]+ species (\( m/z \) at 472 and 474) and for the [Eu2(ODO2A)2(OH)3]− species (\( m/z \) at 927, 929 and 931) could be observed at pH 8.28 (Fig. S3, ESI†). It is noteworthy that, due to the distinct ionization energies of the mononuclear and dinuclear species, it is very likely that these ions in solution could not be quantitatively compared according to their signals in mass spectrometry.
Density function theory calculations

The density function theory (DFT) calculated lowest energy structures of the EuDO2A(H2O)3+ and EuODO2A(H2O)3+ complexes are shown in Fig. 5. The DFT calculation method used was similar to those published and established for many complex systems including those of trivalent lanthanide complexes.20 The selected bond lengths of the two complexes together with those of [Gd(ODO3A)(H2O)]+21 and [Gd(DO3A)]22 are listed in Table 2 for comparison. Note that B3LYP calculations in combination with large-core ECPs are known to overestimate Ln–N distances. For example, the average crystal and our DFT calculated (in parentheses) Eu–N and Eu–O(carboxylate) bond distances for the EuDO2A− complex are 2.68 Å (2.73 Å) and 2.38 Å (2.36 Å), respectively. An overestimation of the Eu–N bond distance by 0.05 Å and an underestimation of the Eu–O bond distance by 0.02 Å compared to crystal structural data have been observed in the present DFT study.

In the EuDO2A(H2O)3+ structure, the 3 inner-sphere coordinated water molecules are arranged in a meridional configuration,3−23 i.e. the 3 water molecules are on the same plane perpendicular to that of the basal N4 atoms. For the EuDO2A−(H2O)3+ complex, the position of the middle coordinated water molecule is slightly moved away from the plane perpendicular to that of the basal N2O atoms. However, the Eu(III)–O (apical H2O) bond distance is longer than the other two Eu(III)–O (side H2O) bond distances for each complex. Thus, dinuclear species formation could only result in the form of Ln2L2(μ-OH)2. The formation of tri-hydroxo-bridged dinuclear species is unlikely for the Ln(III)-DO2A2− and Ln(III)-ODO2A2− complex systems.

Owing to the slow convergence of the geometry optimizations for the dinuclear Eu(III)-ODO2A2− systems in aqueous solution as experienced by us and others15, for Y(III) ion was used as a substitute for the Eu(III) ion in these systems for DFT calculations. The ionic radii of Y(III) (1.019 Å) and Eu(III) (1.066 Å) ions are similar,24 and they both belong to the rare-earth element family due to chemical similarities, although the Y(III) ion has no 4f electrons. Thus, the configurations of YDO2A+, YODO2A+, EuDO2A+ and EuODO2A+ are expected to be similar, except that the Eu(III) complexes are 9-coordinated with three inner-sphere coordinated H2O molecules, the Y(III) complexes are 8-coordinated with two inner-sphere coordinated H2O molecules. Attempts to either add or reduce inner-sphere coordinated H2O molecules resulted in higher energies for both Eu(III) and Y(III) complexes. On the other hand, the lack of 4f electrons allows the DFT calculations of the Y(III) complexes to run faster than those for Ln(III) complexes.

The DFT calculated low-energy structures of the μ-OH bridged Y2(ODO2A)2(μ-OH) dinuclear species are shown in Fig. 6. Two structures are illustrated for the mono-μ-OH bridged dinuclear species: one with the lowest energy has one μ-OH bridge and a H2O–Y–Y–OH2 torsional angle of 82.21° (cis-[Y2(ODO2A)2(μ-OH)(H2O)2]2−, −2326.666586 a.u.; Fig. 6, upper-left). The other with higher energy has one μ-OH bridge and a H2O–Y–Y–OH2 torsional angle of 148.54° (trans-
Fig. 5 DFT calculated EuDO2A(H2O)3+ (left two structures, top- and side-views) and EuODO2A(H2O)3+ (right two structures, top- and side-views) structures.

Table 2 DFT calculated selected bond lengths (Å) in [EuDO2A(H2O)3]2+ and [EuODO2A(H2O)3]2+, as compared with those of [GdODO3A(H2O)3]3− and [GdDO3A]3Na2CO3 molecules.a,b,c

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<tbody>
<tr>
<td>Eu–Oa (H2O)</td>
<td>2.644</td>
<td>2.762</td>
<td>2.559</td>
<td>2.46c</td>
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<tr>
<td>Eu–O1 (H2O/COO−)</td>
<td>2.619</td>
<td>2.580</td>
<td>2.328</td>
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<tr>
<td>Eu–O2 (COO−)</td>
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<td>2.357</td>
<td>2.354</td>
<td>2.34</td>
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<tr>
<td>Eu–O3 (H2O/COO−)</td>
<td>2.619</td>
<td>2.351</td>
<td>2.352</td>
<td>2.35</td>
</tr>
<tr>
<td>Eu–O4 (COO−)</td>
<td>2.293</td>
<td>2.237</td>
<td>2.244</td>
<td>2.25</td>
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<tr>
<td>Eu–N5/O5</td>
<td>2.708</td>
<td>2.574</td>
<td>2.60</td>
<td>2.56</td>
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<tr>
<td>Eu–N6 (3°)</td>
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<td>2.574</td>
<td>2.60</td>
<td>2.63</td>
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<tr>
<td>Eu–N7 (2°)</td>
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<td>2.644</td>
<td>2.59</td>
<td>2.60</td>
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<tr>
<td>Eu–N8 (3°)</td>
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<td>2.674</td>
<td>2.59</td>
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<td>Eu–N4/N1O plane</td>
<td>1.650</td>
<td>1.70</td>
<td>1.633</td>
<td>1.55</td>
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<td>Eu–COO− plane</td>
<td>0.720</td>
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</table>

a For DO2A2− and ODO2A2−, Oa is the apical H2O molecule. O1 and O3 are the two side H2O molecules. O2 and O4 are the oxygen atoms of the two COO− groups. For DO3A3− (1,4,7,10-tetrazacyclododecane-1,4,7-triacetate ion) and ODO3A3− (also abbreviated as DOTRA, 1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetate ion), O3 is the oxygen atom of the middle COO− group. b [Gd[ODO3A]] data were obtained from crystal data, ref. 21. c Values are from reference crystallographic data, ref. 22. The bond distances are the two Eu–O bonds with the coordinated carbonate anions.

[Y2(ODO2A)3(μ-OH)2]2−, −2326.4103883 a.u.; Fig. 6, upper-right). A structure of a di-μ-OH bridged dinuclear species is also shown in Fig. 6 (lower-middle, [Y2(ODO2A)3(μ-OH)2]3−). It is observed that each Y(III) ion is 8-coordinated in the three complex structures shown in Fig. 6. The first and the second include 6-coordination by the ligand ODO2A2−, one by the bridged μ-OH ion and one by a water molecule. The third includes 6-coordination by the ligand ODO2A2− and two by the bridged μ-OH ions.

The two inner-sphere coordinated water molecules in the [Y2(ODO2A)3(μ-OH)(H2O)3]3− complex are in a staggered conformation with a torsional angle of 82.21° or 148.54°. It is possible that the structure with one additional inner-sphere coordinated water molecule on each Y(III) ion at the available coordinating space of the [Y(ODO2A)3(μ-OH)]22− dinuclear species is also present because both β2,3 and β2,4 values could be fitted from the Y(III)-ODO2A2− titration data. Selected average bond distances and angles of these four complexes are listed in Table S2 (ESI†).

Luminescence studies

Fig. S4 (ESI†) show the emission spectra of the EuODO2A2+ complex at pH 6.1 in H2O and D2O, respectively, at room temperature (λex = 395 nm). These spectra are very similar to those measured at pH 7.0 and pH 5.0. The lifetime data for the emission peak at 615 nm of the EuODO2A2+ complex in both
H₂O and D₂O solutions at pH 7.0 could be fitted to a single exponential luminescence decay kinetic equation. Similarly, the emission spectra (λ_ex = 369 nm, Fig. S5, ESI†) and the emission lifetime data at 544 nm of the TbOĐO₂A⁺ complex at pH 7.0 in H₂O and D₂O, respectively, have been obtained at room temperature. Table 3 lists the lifetime data and the numbers of inner-sphere coordinated water molecules (q) of the EuOĐO₂A⁻(H₂O)₉⁺ and the TbOĐO₂A(H₂O)₉⁺ complexes obtained using the lifetime data by employing different previously established empirical equations.²⁵ For comparison purposes, those of the EuOĐO₂A(H₂O)₉⁺ complex are also included.¹¹

The q values obtained for the EuOĐO₂A(H₂O)₉⁺ and EuOĐO₂A(H₂O)₉⁺ complexes from empirical equations q²⁴ were all greater than that from equation q³°. The early empirical equation q³ by Sudnick and Horrocks quoted an uncertainty value of ±0.5 for the q values obtained probably due to the lower number of experimental data points.²⁵ This has been refined by equation q³° with a standard error of ±0.1 in q-values.²⁵ For the derivation of the parameters for equation q³° by Beeby et al.,²⁵b no species with q values greater than 6 were employed and the results for q values tend to be on the higher side. For equations q³° and q³, it assumes that the quenching effects in D₂O are similar for all Eu³⁺ complexes and certainly provided only rough estimates of the q values.²⁵c,d It is noted that these five equations all assumed that the contributions from the alcoholic O–H, amine N–H, alkane C–H and amide carbonyl oscillators in the first coordination sphere of the Eu³⁺ complex were negligible which is certainly not always true.¹¹,²⁵e,f

Ideally, lifetime measurements should be carried out without deuterium exchange of NH groups, so that these oscillators would contribute to the same extent to quench lanthanide luminescence. It has been found that deuterium exchange is very slow for NH groups coordinated to lanthanide ions.²⁶ To check the effect of the H/D exchange in the D₂O solution without drying and redissolving, it was found that τ₁₂₂₀ (1.42 ms) was the same as that with drying and redissolving. This indicates that H/D exchange in the EuOĐO₂A⁺ complex at pH 7.0 is probably slow within the D₂O solution preparation time period and the lifetime result obtained in D₂O solution is valid for the estimation of q value.

The averaged q value for the EuOĐO₂A(H₂O)₉⁺ complex is 4.1 which is greater than that of the EuOĐO₂A(H₂O)₉⁺ complex (q = 3.0), indicating that the complex has structures with an average of four inner-sphere coordinated water molecules. Thus, although the DFT calculated structure has the lowest energy with q = 3 (vide supra), it might still be possible that this complex could have equilibrium structures accommodating four or more inner-sphere coordinating water molecules. This might be due to the fact that the 12-membered macrocyclic ring of OĐO₂A⁻ is smaller, less symmetrical, not pre-organized²⁶b and more rigid which may lead to more coordination space available for more inner-sphere coordinated water molecules on the Ln(III) ion. Similar results have been observed for other Eu(III) complexes of multidentate ligands with oxaaza backbones.¹⁴,²⁷,²⁸ Note that the DFT calculated EuOĐO₂A⁺ structure showed that the Eu–O₅ bond distance (2.55 Å) is shorter than the three Eu–N(6–8) bond distances (averaged 2.72 Å) leading to a less-symmetrical coordination environment as compared to that of the EuOĐO₂A⁺ complex. (Care should be exercised here to note that an overestimation of the Eu–N (e.g. 0.05 Å) bond distance and an under-estimation of the Eu–O bond distance (e.g. 0.02 Å) are known in the present DFT study (vide supra.) This could allow other complex conformations with similar or slightly higher energies to occur and with one more coordinated water molecule. In addition, it is also possible that the oxygen atom and the secondary nitrogen atom in the macrocycle may have additional unusual effects in helping the complex to relax from the excited state.

For comparison purposes, the number of inner-sphere coordinated water molecules of TbOĐO₂A⁺ has also been measured²⁵a,b,d to be 2.9 which is consistent with the expected q = 3 and previously reported values of several Tb(III) complexes of linear and macrocylic multidentate ligands.²⁸ For example, the average q value in the pH range 4–11 is 1.8 ± 0.2 for TbOĐA(ĐO₃A)⁻ (1,4,7,10-tetraazaacyclododecane-1,4,7-triacetate ion) because ĐO₃A⁻ is a 7-coordinating ligand and Tb(III) ion is 9-coordinated.²⁸b

An interesting pH-dependence effect is observed for the luminescence emission spectra of the EuOĐO₂A⁺ complex, i.e. the spectral band intensity at 615 nm increases with increasing pH (Fig. 7). The lifetimes (in ms) are roughly constant from pH 5 to pH 7 and increase with increasing pH afterwards: 0.218 (pH 4.0), 0.220 (pH 5.0), 0.220 (pH 6.1), 0.219 (pH 7.0), 0.232 (pH 8.0), 0.257 (pH 9.0), 0.283 (pH 10.0), and 0.291 (pH 11.0). The gradual increase with increasing pH of lifetimes after pH 7.0 is consistent with the fact that the number of O–H oscillators decreases with increasing pH due to µ-OH bridged dinuclear species as well as mono-coordinated-OH formations. Similar observations have been found for the TbOĐO₂A⁺ complex (data not shown).

Conclusions

The log Kₑ values of the LnOĐO₂A⁺ complexes increase roughly with increasing lanthanide atomic number which

<table>
<thead>
<tr>
<th>Species</th>
<th>τ₁₂₂₀ (ms)</th>
<th>τ₁₂₂₀ (ms)</th>
<th>q⁴</th>
<th>q⁵</th>
<th>q⁶</th>
<th>q⁷</th>
<th>qave (ms)</th>
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<tbody>
<tr>
<td>EuOĐO₂A(H₂O)₉⁺</td>
<td>0.219</td>
<td>1.42</td>
<td>4.0³°</td>
<td>4.3³°</td>
<td>4.1⁴°</td>
<td>4.3⁴°</td>
<td>3.9⁵</td>
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<tr>
<td>TbOĐO₂A(H₂O)₉⁺</td>
<td>0.980</td>
<td>2.93</td>
<td>2.7⁵</td>
<td>2.9⁴</td>
<td>3.1¹</td>
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<td>—</td>
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<tr>
<td>EuOĐO₂A(H₂O)₉⁺</td>
<td>0.280</td>
<td>1.34</td>
<td>3.0</td>
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<td>3.1</td>
<td>3.2</td>
<td>2.8</td>
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<tr>
<td>EuOĐO₂A(OH)(H₂O)₉⁺</td>
<td>0.313</td>
<td>1.46</td>
<td>2.6</td>
<td>2.7</td>
<td>2.7</td>
<td>2.8</td>
<td>2.4</td>
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</table>

* Empirical equations for EuOĐO₂A⁻: b q⁴ = 1.05(τ₁₂₂₀−1 − τ₁₂₂₀−1); c q⁵ = 1.2(τ₁₂₂₀−1 − τ₁₂₂₀−1 − 0.25); d q⁶ = (1.05τ₁₂₂₀−1 − 0.70); e q⁷ = (1.15τ₁₂₂₀−1 − 0.71); f q⁸ = 1.16(τ₁₂₂₀−1 − τ₁₂₂₀−1 − 0.31). For TbOĐO₂A⁺: g q⁶ = 5.0(τ₁₂₂₀−1 − τ₁₂₂₀−1 − B), B = 0.06 + 0.09pH, for OĐO₂A B = 0.06 + 0.09 = 0.15; h q⁷ = 4.20(τ₁₂₂₀−1 − τ₁₂₂₀−1); i q⁸ = (4.0τ₁₂₂₀−1 − 1.0).
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(CH₃)₄NCl. The (CH₃)₄NOH solution was delivered from a 10 mL automatic Brinkmann Metrohm Model 665 Dosimat buret with a reading accuracy of ±0.001 mL. Most of the titration reactions reached equilibrium rather quickly during the potentiometric titration process, and the titrations were completed within 18 000–40 000 s.

The pH-metric titration data were used to calculate the stepwise ligand protonation constants defined in eqn (1), where \( n = 1–4 \) for ODO2A (L):

\[
K_n = \frac{[\text{H}_n\text{L}]/([\text{H}_{n-1}\text{L}][\text{H}^+]])
\]

(1)

All equilibrium calculations were performed using the program Hyperquad2008 Version 5.2.15. The averaged values are presented together with the standard deviations calculated from valid data points. Speciation diagrams were generated using Hyss 2006 software.

Mass spectral measurements

Mass spectra of the Eu(III)-ODO2A²⁻ complex system at various pH were acquired by direct infusion (10 μL). ESI(+)MS experiments were carried out using a LTQ-Orbitrap hybrid tandem mass spectrometer (ThermoFisher, USA) equipped with an electrospray ionization (ESI) source operating in positive ion mode. The parameters of ESI(+) included 4.0 kV for ion spray voltage, 200 °C for capillary temperature, and 3–5 erb for sheath gas flow rate. The mass spectra were collected over the mass range of \( m/z \) 150–2000 at a resolving power of 30 000. The collected data were analyzed using Xcalibur software (ThermoFisher, USA). ESI(−)-MS measurements were performed using a micro-tandem quadrupole mass spectrometer equipped with an ESI source operating in negative ion mode. The conditions used for the ESI(−) interface included 500 (L h⁻¹) for desolvation gas, 52 (L h⁻¹) for cone gas, 3.2 kV for capillary voltage, 30 V for cone voltage and 250 °C for desolvation temperature.

NMR determinations of protonation sites

Solutions of ligand (0.1 mM) for \(^{1}H\) NMR titrations were prepared in D₂O solution, and pH was adjusted with DCl or carbonate-free NaOD. The apparent pD (pH) of the ligand solutions was determined with a microelectrode and the final pD value was obtained from the equation pD = pH + 0.40. All chemical shifts were referenced to the 3-(trimethylsilyl)propionic acid-d₄ sodium salt.

Luminescence measurements

Steady-state luminescence experiments were carried out on an Edinburgh Instruments FSP920 fluorescence system equipped with a 450 W xenon arc lamp as the illumination source. Emission light was collected into a TMS300 Czerny-Turner configuration double grating monochromator and detected by a Hamamatsu R928P photomultiplier tube in the visible wavelength range. Spectra were recorded by use of F900 Fluorescence spectrometer software. Luminescence lifetimes were recorded by use of a μF920H flashlamp (lamp frequency: 100 Hz) as the excitation source with the multiple-channel single photon counting mode (MCS). Data was fitted by a nonlinear least-squares iterative technique (Marquardt-Levenberg algorithm).

For the LnODO2A²⁻ systems (Ln = Eu or Tb), all solutions were prepared from stock solutions of Ln(NO₃)₃ (0.01 M) and H₂ODO2A (~0.01 M). The molar ratio of the H₂ODO2A and Ln⁺³ was ca. 1.00 : 0.99 to make sure that the ligand was in slight excess. All solutions were allowed to equilibrate for at least 12 h to ensure complete formation reaction prior to luminescence measurements. The sample solutions in D₂O were prepared by first evaporating the aqueous solutions in appropriate flasks to dryness using a high vacuum system. To each flask, D₂O was added to dissolve the solids, the solution was equilibrated for at least 1 h, dried again, and finally dissolved in D₂O to a cuvette for luminescence measurements. Freshly prepared complex solutions in D₂O without drying and redissolving were also prepared for comparative measurements. The corresponding numbers of inner-sphere coordinated water molecules were calculated using the lifetime data in H₂O and D₂O with established empirical equations. All data were checked at least twice carefully.

Density function theory (DFT) computations of lanthanide complex structures

All calculations were performed employing HF and hybrid DFT with the B3LYP exchange correlation functional and the Gaussian 09 package. Full geometry optimizations of the [Eu(DO2A)(H₂O)]⁺, [Eu(ADO2A)₂(H₂O)₃]⁺, cis-[Y₂(ADO2A)₂(µ-OH)(H₂O)₂]⁺, trans-[Y₂(ADO2A)₂(µ-OH)(H₂O)₃]⁺ and [Y₂(ADO2A)₂(µ-OH)₂] systems were obtained in vacuum by using the 3-21G and 6-31G* basis sets for carbon, hydrogen, nitrogen, and oxygen. For these complexes, for example, the lowest energy crystallographic structure of EuDOTA⁻ [square antiprismic, SAP, (Aδδδδ)] from Cambridge Structural Database (CSD) was used to construct the initial guessed structures of the EuDO2A⁻ complex by removing two opposite carboxylate groups. The initial guessed structures were refined by a lower level HF/3-21G method and then refined by DFT calculations using the B3LYP/6-31G* method to find the lowest energy complex structures. The quasi-relativistic effective core potential (ECP) of Stuttgart RSC 1997 ECP and the related [5s4p3d]-GTO valence basis set were applied to europium and yttrium atoms. This ECP treats [Kr]4d⁰⁰⁰⁰⁰⁰ as fixed core, while only the 5s5p6s5d6p shell is taken into account explicitly. The procedure involved initial HF/3-21G optimization of the molecular system and refinement by using B3LYP/6-31G* basis set, both in gas phase. The geometries of the complexes were then fully optimized by B3LYP/6-31G* and ECP in aqueous solutions by using a polarizable continuum model (PCM). Frequency calculations with zero-point corrections were also performed with the lowest-energy conformers of the LnL⁻ (Ln = Eu, Y; L = DO2A²⁻, ODO2A⁻) complexes.

Acknowledgements

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References


