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**The solution structures and relative stability constants of lanthanide-EDTA complexes  
predicted from computation**

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## ABSTRACT

Ligand selectivity to specific lanthanide (Ln) ions is key to the separation of rare earth elements from each other. Ligand selectivity can be quantified with relative stability constants (measured experimentally) or relative binding energies (calculated computationally). The relative stability constants of EDTA (ethylenediaminetetraacetic acid) with  $\text{La}^{3+}$ ,  $\text{Eu}^{3+}$ ,  $\text{Gd}^{3+}$ , and  $\text{Lu}^{3+}$  were predicted from relative binding energies, which were quantified using electronic structure calculations with relativistic effects and based on the molecular structures of Ln-EDTA complexes in solution from density functional theory molecular dynamics simulations. The protonation state of an EDTA amine group was varied to study pH  $\sim 7$  and  $\sim 11$  conditions. Further, simulations at 25 °C and 90 °C were performed to elucidate how structural variations of Ln-EDTA complexes with temperature are related to complex stabilities at different pH conditions. Relative stability trends are predicted from computation for varying  $\text{Ln}^{3+}$  ions (La, Eu, Gd, Lu) with a single ligand (EDTA at pH  $\sim 11$ ), as well as for a single  $\text{Ln}^{3+}$  ion (La) with varying ligands (EDTA at pH  $\sim 7$  and  $\sim 11$ ). Changing the protonation state of an EDTA amine site significantly changes the solution structure of the Ln-EDTA complex resulting in a reduction of the complex stability. Increased Ln-ligand complex stability is correlated to reduced structural variations in solution upon an increase in temperature.

## 1. Introduction

The stability of lanthanide (Ln) ligand complexes in solution is relevant to purifying rare earth elements since complexation is needed to separate  $\text{Ln}^{3+}$  ions from each other in solution. The selectivity of a ligand to a particular  $\text{Ln}^{3+}$  ion compared to other  $\text{Ln}^{3+}$  ions determines the viability of Ln-Ln solvent extraction,<sup>1,2</sup> and it can be quantified by comparing the relative stability of a ligand to different  $\text{Ln}^{3+}$  ions. Ln-ligand complex stability can be determined experimentally with stability constants measurements,<sup>3</sup> or computationally with binding energy calculations.<sup>4-7</sup> Relative binding energies can be compared to relative stability constants and be used to predict ligand selectivity to a particular  $\text{Ln}^{3+}$  ion.

Changes in solution pH are used in rare earth separations to drive Ln extraction. For example, after the solvent extraction process, which transfers the desired  $\text{Ln}^{3+}$  ion to the organic phase as a  $\text{Ln}^{3+}$ -ligand complex, the  $\text{Ln}^{3+}$  ion is stripped to recycle the ligand that remains in the organic phase and concentrate the  $\text{Ln}^{3+}$  ion in the new aqueous phase.<sup>8,9</sup> The stripping process usually involves the addition of acid to unbind of the  $\text{Ln}^{3+}$ -ligand complex. The Ln-ligand unbinding behavior in acidic conditions with protic ligands is well characterized at the process level; however, much remains to be resolved at molecular scale regarding how solution pH affects Ln-ligand complex stability, and ultimately how solution pH affects ligand selectivity to particular  $\text{Ln}^{3+}$  ions.

Ethylenediaminetetraacetic acid (EDTA) is an ion chelator with six Brønsted acidic sites (four carboxylate, two amine) that change protonation state according to the solution pH. The stability constants of EDTA to most  $\text{Ln}^{3+}$  ions are known, and for some  $\text{Ln}^{3+}$  at different protonation states.<sup>3</sup> Therefore,  $\text{Ln}^{3+}$ -EDTA complexes are ideally suited to develop a computational protocol that calculates relative Ln-ligand binding energies and identify how pH affects the structure of Ln-ligand complexes in solution and their relative binding energies.

In order to calculate the relative binding energies of a ligand to  $\text{Ln}^{3+}$  ions, the molecular structures of  $\text{Ln}^{3+}$ -ligand complexes must be resolved. In solution, this is challenging due to the high number of degrees of freedom and conformations of a Ln/ligand/anion/solvent system.<sup>10</sup> In our previous work, we reported a computational protocol, based on density functional theory (DFT) ab initio molecular dynamics (AIMD) simulations that predicted the solution structure of the  $\text{Eu}^{3+}$ -EDTA complex within 0.05 Å of experimental measurements, including the number water molecules coordinated to the  $\text{Eu}^{3+}$  ion and ion coordination number.<sup>11</sup> In this work, we

applied the same DFT AIMD protocol to determine the 25 °C solution structures of  $\text{La}^{3+}$ ,  $\text{Gd}^{3+}$ , and  $\text{Lu}^{3+}$  complexes with EDTA at a protonation state corresponding to  $\text{pH} \sim 11$ , and that of  $\text{La}^{3+}$  complexed with EDTA at a protonation state corresponding to  $\text{pH} \sim 7$ . Relative binding energies, which were calculated based on the resolved complex structures in solution, were compared to experimental stability constants to identify a computational approach that can predict the selectivity of a ligand to a particular  $\text{Ln}^{3+}$  ion. In addition, AIMD simulations of the La-EDTA complexes at both pH values, and the Lu-EDTA complex, were performed at 90 °C to determine how Ln-ligand structural variation with temperature and pH relate to Ln-ligand complex stability.

## 2. Computational Methods

Electronic structure calculations with relativistic effects (Section 2.1) were used to calculate binding energies based on the solution structures of Ln-ligand complexes that were resolved with DFT AIMD simulations (Section 2.2).

Ln-ligand binding energies ( $BE$ ) were calculated using two thermodynamic integration schemes: i) for a given ligand and varying  $\text{Ln}^{3+}$  ions, and ii) for a given  $\text{Ln}^{3+}$  ion and varying ligands. Equation 1 shows the thermodynamic integration to calculate *Ln-ligand binding energies for a given ligand* and varying the  $\text{Ln}^{3+}$  ion:

$$BE_{[\text{Ln} - \text{ligand} \cdot (\text{H}_2\text{O})_n]^p} = E_{[\text{Ln} - \text{ligand} \cdot (\text{H}_2\text{O})_n]^p} - E_{\text{Ln}^{3+}} - E_{[\text{ligand}]^{(p-3)}} - n \cdot E_{\text{water}} \quad (\text{Eq. 1})$$

where  $n$  is the number of water molecules coordinated to the  $\text{Ln}^{3+}$  ion in the Ln-ligand complex and  $p$  is the charge of the Ln-ligand complex. At  $\text{pH} \sim 11$  EDTA is completely unprotonated ( $\text{EDTA}^{4-}$ ) while at  $\text{pH} \sim 7$  EDTA has one proton ( $\text{HEDTA}^{3-}$ ), resulting in Ln-EDTA complexes with an overall charge of -1 and 0, respectively. In this work the Ln ions are always in the +III oxidation state ( $\text{Ln}^{3+}$ ), their most common state in solution. Equation 2 shows the thermodynamic integration to calculate *Ln-ligand binding energies for a given  $\text{Ln}^{3+}$  ion* and varying the ligand:

$$BE_{[\text{Ln} - \text{ligand} \cdot (\text{H}_2\text{O})_n]^p} = E_{[\text{Ln} - \text{ligand} \cdot (\text{H}_2\text{O})_n]^p} - E_{[\text{Ln} \cdot (\text{H}_2\text{O})_m]^{3+}} - E_{[\text{ligand}]^{(p-3)}} - (m - n) \cdot E_{\text{water}} \quad (\text{Eq. 2})$$

where  $m$  is the number of water molecules in the  $\text{Ln}^{3+}$  aqua ion without a ligand.

The main difference between the two thermodynamic integration schemes is that in Equation 1 the energy of the  $\text{Ln}^{3+}$  ion is calculated without any explicit solvent molecules, while in Equation 2 the energy of the  $\text{Ln}^{3+}$  ion is calculated as that of the  $\text{Ln}^{3+}$  aqua ion with coordinated water molecules. It was observed that using two different thermodynamic integration schemes rather than a single thermodynamic integration scheme provides better predictions for their respective cases - a given ligand (varying  $\text{Ln}^{3+}$  ion) and a given  $\text{Ln}^{3+}$  ion (varying ligand); see additional discussion in the Supplementary Information (SI), which also includes discussion regarding the use of relative binding energies instead of relative free binding energies.

The free energies of binding ( $\Delta G^{\text{bind}}$ ) from experiment were calculated from the measured stability constants ( $\log(K)$ ) as shown in equation 3:

$$\log(K) = \frac{\Delta G^{\text{bind}}}{\ln(10)RT} \quad (\text{Eq. 3})$$

where  $R$  is the gas constant and  $T$  is the temperature. Relative experimental free energies of binding were compared to relative calculated binding energies ( $BE$ ), with the energies of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_n]^-$  complex as a reference point. Equation 4 shows how the absolute error ( $\varepsilon_{\text{exp} - \text{comp}}$ ) between experiment and computation:

$$\varepsilon_{\text{exp} - \text{comp}} = \left| \frac{\Delta G_{[\text{Ln} - \text{ligand} \cdot (\text{H}_2\text{O})_n]^p}^{\text{bind}}}{\Delta G_{[\text{La}^{3+} - \text{EDTA}^{4-} \cdot (\text{H}_2\text{O})_n]^-}^{\text{bind}}} - \frac{BE_{[\text{Ln} - \text{ligand} \cdot (\text{H}_2\text{O})_n]^p}^{\text{bind}}}{BE_{[\text{La}^{3+} - \text{EDTA}^{4-} \cdot (\text{H}_2\text{O})_n]^-}^{\text{bind}}} \right| * 100 \quad (\text{Eq. 4})$$

The binding energies (experiment, computation) of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_n]^-$  complex were chosen as the reference point to reduce underestimating the relative error between experiment and computation. Since relative values are being compared, the magnitude of the absolute value of the reference changes the relative energies, i.e., if the reference point has the smallest magnitude, then the errors are larger, whereas if the reference point has the largest magnitude, then the errors are artificially smaller. La appears at the start of the Ln series and has the smallest magnitude in binding energy values for a given ligand, so it is the most appropriate reference point to not underestimate the error between experiment and computation.

## 2.1. Binding energies from electronic structure calculations with relativistic effects

The energies of each species in equations 1 and 2 were calculated with all-electron single-point energy calculations, as performed in our previous work, where we calculated the acidity constants of Ln aqua ions.<sup>12</sup> All energy calculations were done with the M06 functional, a relativistic second order Douglas–Kroll–Hess (DKH2) Hamiltonian,<sup>13,14</sup> segmented all-electron relativistically contracted (SARC) basis set<sup>15</sup> for the Ln atoms, and the minimally augmented<sup>16</sup> ma-def2-TZVPP basis set<sup>17,18</sup> for ligand and water atoms. Studies demonstrate that the M06 functional is a reliable choice for the calculations of thermodynamic properties in broad variety of chemical systems,<sup>19</sup> including the Ln-containing molecules and Ln complexes.<sup>20,21</sup> Relativistic effects are required for accurate calculations with Ln elements.<sup>22</sup> Thus, the DKH and SARC basis set have been used with lanthanides.<sup>23–25</sup> Another study demonstrated that the ma-def2-TZVP basis set containing diffuse functions improved the prediction of Ln-ligand binding energies when compared to smaller 6-31+G\* basis set.<sup>5</sup>

The ligand and water molecules were separately optimized with the M06 functional<sup>26</sup> and the cc-pVTZ basis set<sup>27</sup> to obtain the molecular coordinates for the energy calculation in the thermodynamic integration. The molecular coordinates of the Ln-ligand complexes were obtained from AIMD simulations (Section 2.2).

In all calculations, an implicit water solvent model (conductor-like polarizable continuum model) was used.<sup>28</sup> All electronic structure calculations were done with ORCA<sup>29</sup> using the resolution of identity chain of sphere (RIJCOSX)<sup>30</sup> to improve the calculations efficiency by using “Grid7” and “GridX7” grids.

## 2.2. Solution structures from *ab initio* molecular dynamics simulations

In our previous work, an  $[\text{Eu}^{3+}\text{-EDTA}^{4-}]$  complex structure was placed in the center of a  $17.5 \text{ \AA} \times 17.5 \text{ \AA} \times 17.5 \text{ \AA}$  periodic box and solvated with explicit water molecules and a  $\text{Na}^+$  ion to neutralize the charge. An AIMD protocol that includes high temperature MD and simulated annealing to identify a minimum of complex solution structure in a large conformational space was followed. From that, the solution structure of the complex was identified as  $[\text{Eu}^{3+}\text{-EDTA}^{4-} \cdot (\text{H}_2\text{O})_3]^-$ , with three water molecules directly coordinating on the  $\text{Eu}^{3+}$  ion, the four carboxylate groups binding in a monodentate fashion, and both amine nitrogen atoms coordinating to the  $\text{Eu}^{3+}$  ion, the same solution structure previously resolved from experiment.<sup>31,32</sup>

Using the optimized structure of the  $[\text{Eu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complex in basic conditions in solution from our previous work,<sup>11</sup> we replaced the  $\text{Eu}^{3+}$  ion with a  $\text{La}^{3+}$ ,  $\text{Gd}^{3+}$ , and  $\text{Lu}^{3+}$  ion in independent simulation boxes, and performed AIMD simulations of the periodic box with explicit water molecules to resolve the solution structures of the Ln-EDTA (La, Eu, Gd, Lu) complexes at  $\text{pH}\sim 11$ . In addition, the structure of the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_n]^0$  complex at  $\text{pH}\sim 7$  was determined by adding a proton to an amine group in the equilibrated structure of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complex. As the solvent conformations were already equilibrated, in this work the focus of the AIMD simulations were to refine the ligand conformation, characterize  $\text{Ln}^{3+}\text{-O}_{\text{WATER}}$ ,  $\text{Ln}^{3+}\text{-O}_{\text{EDTA}}$ , and  $\text{Ln}^{3+}\text{-N}_{\text{EDTA}}$  coordination bonds, determine the number of water molecules that remain directly coordinated to the  $\text{Ln}^{3+}$  ion, and sample equilibrium configurations of the complexes in solution at 25 °C and 90 °C.

AIMD simulations in this work were performed in the NVT ensemble (constant volume and temperature), with a 1.0 fs time step, at 25 °C or 90 °C, for at least 10 ps of equilibrated trajectory. The AIMD simulations at 90 °C were performed as in our previous work,<sup>33</sup> by taking an equilibrated frame at 25 °C and performing an NVT simulation at 90 °C until at least  $\sim 10$  ps of equilibrated trajectory is sampled. The analysis of radial distribution functions (RDFs), coordination numbers (CNs), and root mean square deviations (RMSDs, see SI) to ideal geometries of the studied systems was done for equilibrated parts of the trajectories that corresponded to at least  $\sim 10$  ps. Plots of the potential energies of the AIMD trajectories appear in the SI. DFT AIMD simulations were performed within the PBE/LnPP1 GTH level of theory,<sup>34,35</sup> as implemented in the CP2K package.<sup>36</sup> Core electrons were modeled with norm-conserving GTH pseudopotentials, while valence electrons were treated with polarizable double-zeta quality basis sets.<sup>37</sup> We used our LnPP1 pseudopotentials and basis sets for the lanthanides, which include the *f* electrons in the valence shell.<sup>35</sup> The long-range electrostatics terms were calculated with an additional plane wave basis set, with a 500 Ry cutoff for La, Eu, and Gd, and a 1000 Ry cutoff of Lu. Grimme's dispersion correction (DFT-D3)<sup>38</sup> was used to account for van der Waals interactions with a 6.0 Å radius. All systems containing  $\text{La}^{3+}$  and  $\text{Lu}^{3+}$  had singlet multiplicity,  $\text{Eu}^{3+}$  had septet multiplicity, and  $\text{Gd}^{3+}$  had an octet multiplicity. This DFT and AIMD protocol was previously shown to result in structures of the Ln aqua ions, and the  $[\text{Eu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complex, with Ln-O and Eu-N distances within 0.05 Å of those measured with extended X-ray absorption fine structure spectroscopy.<sup>11,39</sup>



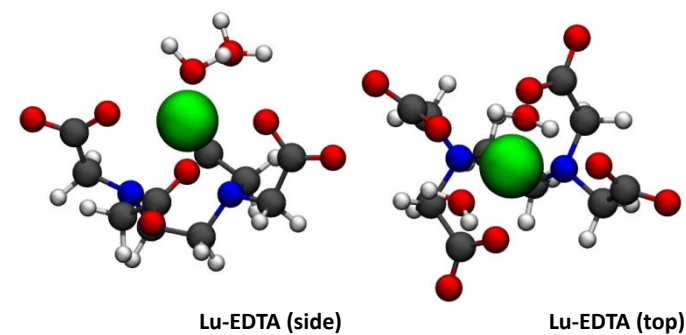
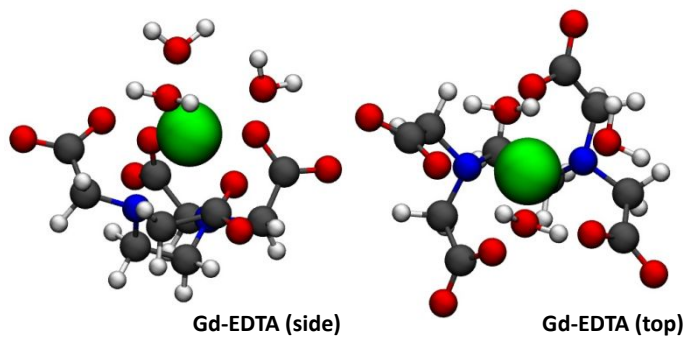
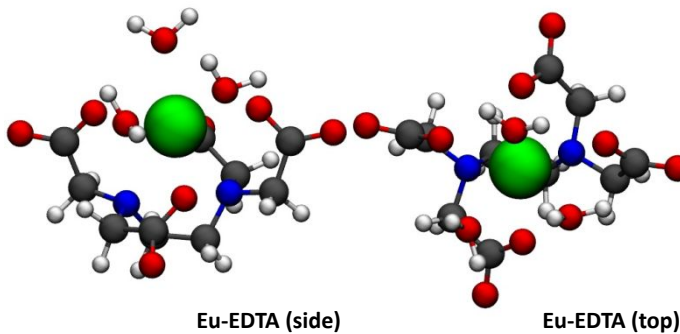
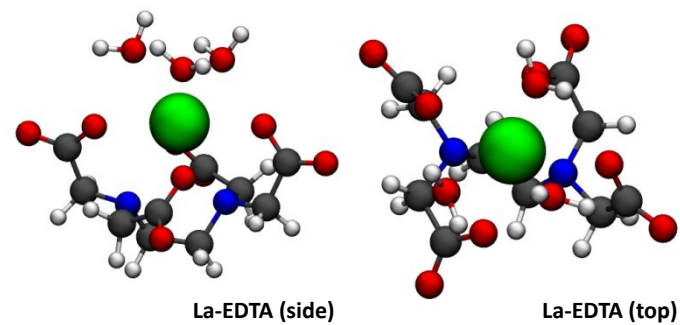
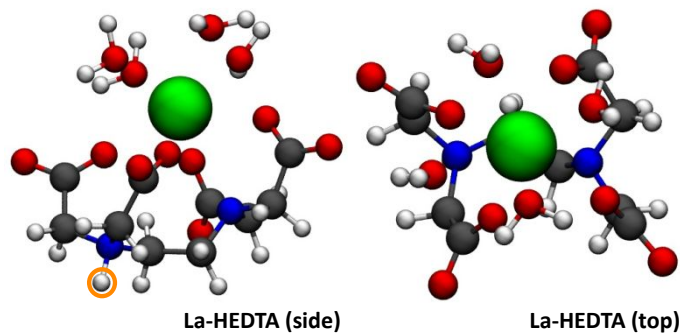
The Ln-ligand complex coordinates for binding energy calculations (Section 2.1) were optimized in the solution phase by the following protocol in the full explicit solvent simulation box: starting from an AIMD equilibrated frame at 25 °C, a simulated annealing to ~0 K was performed (typically ~2,000 MD steps), followed by a final geometry optimization.

### 3. Results and Discussion

#### 3.1. Solution structures of Ln-EDTA complexes

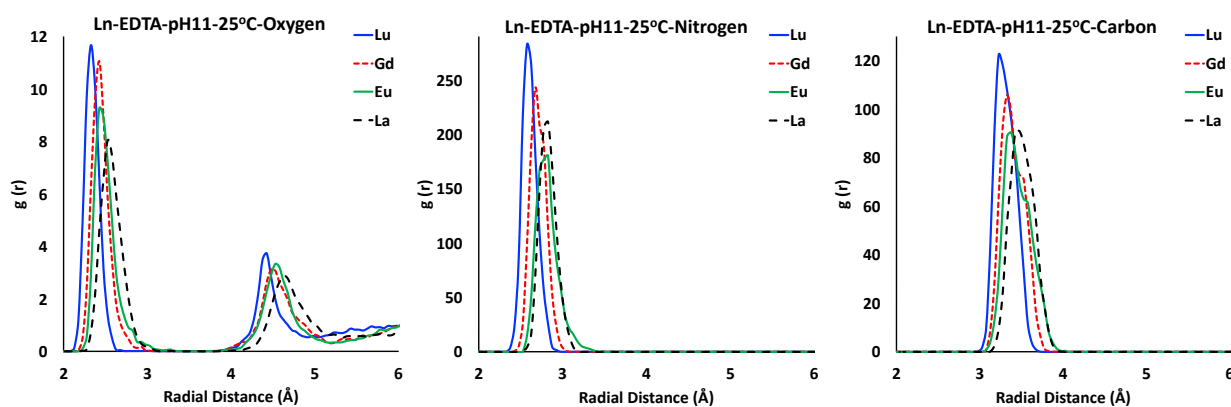
Figure 1 shows the resolved solution structures of  $\text{La}^{3+}$ ,  $\text{Eu}^{3+}$ ,  $\text{Gd}^{3+}$ , and  $\text{Lu}^{3+}$  complexed with  $\text{EDTA}^{4-}$ , the protonation state of EDTA at pH ~11. The structure of the  $[\text{Eu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complex was resolved in our previous work,<sup>11</sup> but is discussed here for comparison. The structures of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  and  $[\text{Gd}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complexes are very similar to that of the  $[\text{Eu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complex such that the four carboxylates bound in a monodentate fashion, both nitrogen atoms buckled in to form coordination bonds with the  $\text{Ln}^{3+}$  ion, and has three coordinated water molecules to give a total coordination number of 9. The  $[\text{Lu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_2]^-$  complex had the same ligand conformation, except that two water molecules remained coordinated to the  $\text{Lu}^{3+}$  ion instead of three, resulting in a total coordination number of 8. These findings are in agreement with results from a classical molecular dynamics study examining the chelation of  $\text{EDTA}^{4-}$  with  $\text{La}^{3+}$ ,  $\text{Eu}^{3+}$ , and  $\text{Lu}^{3+}$ .<sup>40</sup>

Figure 1 illustrates the structure of the  $\text{La}^{3+}$  ion complexed with the protonated HEDTA<sup>3-</sup> molecule. Unlike the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  structure, in the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  complex the nitrogen of the protonated amine group did not coordinate with the  $\text{La}^{3+}$  ion, and instead, an additional fourth water molecule bound to the  $\text{La}^{3+}$  ion to maintain a 9-coordinate structure. Therefore, solution pH and subsequent change in EDTA protonation state changes the coordination structure of Ln-EDTA complexes.



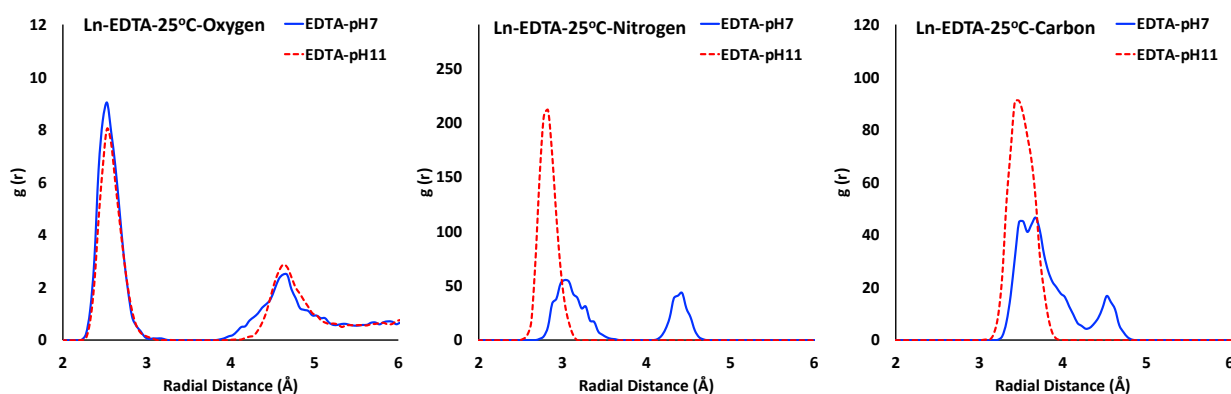
**Figure 1:** Side views (left) and top views (right) of the optimized solution structures of the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$ ,  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ ,  $[\text{Eu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ ,  $[\text{Gd}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ , and  $[\text{Lu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_2]^-$  complexes, in descending order. Only molecules coordinated to the  $\text{Ln}^{3+}$  ion are shown for clarity; however, all structures are in solution and were determined in a periodic box with explicit water molecules.  $\text{Ln}^{3+}$  ions in green, carbon atoms in gray, oxygen atoms in red, nitrogen atoms in blue, and hydrogen atoms in white. An orange circle highlights the protonation state difference between  $\text{HEDTA}^{3-}$  and  $\text{EDTA}^{4-}$ , which correspond to  $\text{pH}\sim 7$  and  $\text{pH}\sim 11$ , respectively.

Radial distribution functions (RDFs) were computed for each complex to illustrate the frequency of carbon, nitrogen, and oxygen atom distances from the  $\text{Ln}^{3+}$  ion. The RDFs for the different  $\text{Ln}^{3+}$  ions bound to the same ligand ( $\text{EDTA}^{4-}$ ), at  $25\text{ }^\circ\text{C}$ , are plotted together in Figure 2 to compare how distances change across the Ln series. As expected, due to the Ln ionic radius contraction, Ln-O and Ln-N distances become smaller as the  $\text{Ln}^{3+}$  ion becomes heavier. Interestingly, the Ln-C distances follow the same trend, indicating that the whole  $\text{EDTA}^{4-}$  ligand comes closer to the  $\text{Ln}^{3+}$  ion along the Ln series. Moreover, only a single Ln-C peak is observed, even though there are two types of carbon atoms: carboxylate and tertiary amine. This is also confirmed by the second peak in the Ln-O RDF, which corresponds to the unbound O atom in the monodentate-bound carboxylate groups.



**Figure 2:** Radial distribution functions of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ ,  $[\text{Eu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ ,  $[\text{Gd}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ , and  $[\text{Lu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_2]^-$  complexes at  $25\text{ }^\circ\text{C}$ . Left, center, and right figures show the Ln-O, Ln-N, and Ln-C pair distribution functions, respectively.

To describe how varying ligand ( $\text{EDTA}^{4-}$ ,  $\text{HEDTA}^{3-}$ ) affects the solution structure of Ln-ligand complexes, the La-O, La-N, and La-C RDFs of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  and  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  complexes at 25 °C are plotted in Figure 3. While the La-O RDF was not significantly affected, the Ln-N RDF changed from a single peak ( $\text{EDTA}^{4-}$ ) to two peaks ( $\text{HEDTA}^{3-}$ ) as a result of the La-coordinated and uncoordinated N atoms. The La-C RDF also changed with the increased flexibility of the uncoordinated  $\text{HEDTA}^{3+}$  amine yielding a broader distribution compared to  $\text{EDTA}^{4-}$ , and two peaks observed as expected for the different (carboxylate or amine) carbon types.



**Figure 3:** Radial distribution functions of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ , and  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  complexes at 25 °C. Left, center, and right figures show the La-O, La-N, and La-C pair distribution functions, respectively.

### 3.2. Relative binding energies of Ln-EDTA complexes

For a given ligand ( $\text{EDTA}^{4-}$ ), Table 1 demonstrates that the experimental relative binding energies follow a trend of increasing binding strength for heavier lanthanides. Using Eq. 1 the binding energies of  $\text{Eu}^{3+}$ ,  $\text{Gd}^{3+}$ , and  $\text{Lu}^{3+}$  with  $\text{EDTA}^{4-}$  were computed and compared to that of  $\text{La}^{3+}$  with  $\text{EDTA}^{4-}$ . The results (Table 1) followed this qualitative trend with errors between experiment and computation (Eq. 4) of 10%, 12%, and 13%, respectively. For a given  $\text{Ln}^{3+}$  ion ( $\text{La}^{3+}$ ), using Eq. 2, the binding energy of  $\text{HEDTA}^{3-}$  to  $\text{La}^{3+}$  was compared to that of  $\text{EDTA}^{4-}$  with  $\text{La}^{3+}$ , and a 2% error was found between experiment and computation (Table 1).

**Table 1:** Stability constants from experiment and calculated binding energies

Complex	Experimental stability constants*	Relative free energy of binding from experiment**	Relative binding energy from computation***	$\epsilon_{\text{exp}} - \text{comp}$
$[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$	2.24	0.14	0.12	2%
$[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$	15.46	1 (reference)	1 (reference)	-
$[\text{Eu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$	17.32	1.12	1.22	10%
$[\text{Gd}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$	17.35	1.12	1.25	13%
$[\text{Lu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_2]^-$	19.80	1.28	1.40	12%

\* $\log(K)$  values at 25 °C, from A.E. Martell and Robert M. Smith, "Critical Stability Constants", 1974, Plenum Press, New York.

\*\*The free energies of binding were calculated from the stability constants with Eq.3.

\*\*\*The binding energy for  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  was obtained with the thermodynamic integration in Eq. 2, while the remaining binding energies with Eq. 1.

While it is known that  $\text{Ln}^{3+}$  ions bind with EDTA much stronger at pH ~11 than at pH ~7, and that for EDTA<sup>4-</sup> slightly stronger binding is observed along the Ln series, in this work the same trends were predicted solely from computation, without fitting parameters. By comparing the RDFs with the binding behavior, observations can be made on how changes in the solution structure result in different binding energies. From Figure 2, for a given ligand, complexes with slightly stronger binding energies are observed to have Ln-O, Ln-N, and Ln-C peaks at smaller radial distances. As with the  $\text{Ln}^{3+}$  aqua ions, the coordination number of Ln-ligand complexes changes from 9 to 8 as the  $\text{Ln}^{3+}$  ion becomes smaller. However, the bound ligand allows  $\text{Eu}^{3+}$  and  $\text{Gd}^{3+}$  to remain 9-coordinate at 25 °C, while for their aqua ions the 8-coordinate state is more likely.<sup>39</sup>

By comparing the solution structures of the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  and  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  complexes, and RDFs in Figure 3, it was found that lower complex stability correlates with increased ligand/solvent disorder in the Ln-ligand complex. The much stronger binding energy with EDTA<sup>4-</sup>, evidenced by a more rigid ligand structure (sharper Ln-O, Ln-N, and Ln-C peaks), is coupled with the chelate effect of having both nitrogen atoms bound resulting in less coordinating water molecules. The weaker binding to HEDTA<sup>3-</sup>, shown by broader Ln-O, Ln-N, and Ln-C peaks, comes with a more disordered bound ligand in the complex with an additional coordinated water molecule. Aside from the fact that the  $\text{La}^{3+}$  first sphere changed from an N-coordination site from the ligand (in the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complex) to an O-coordination site from the solvent (in the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  complex), the geometry of the first coordination sphere does not change much when going from pH ~11 to pH ~7. This is seen in: i)

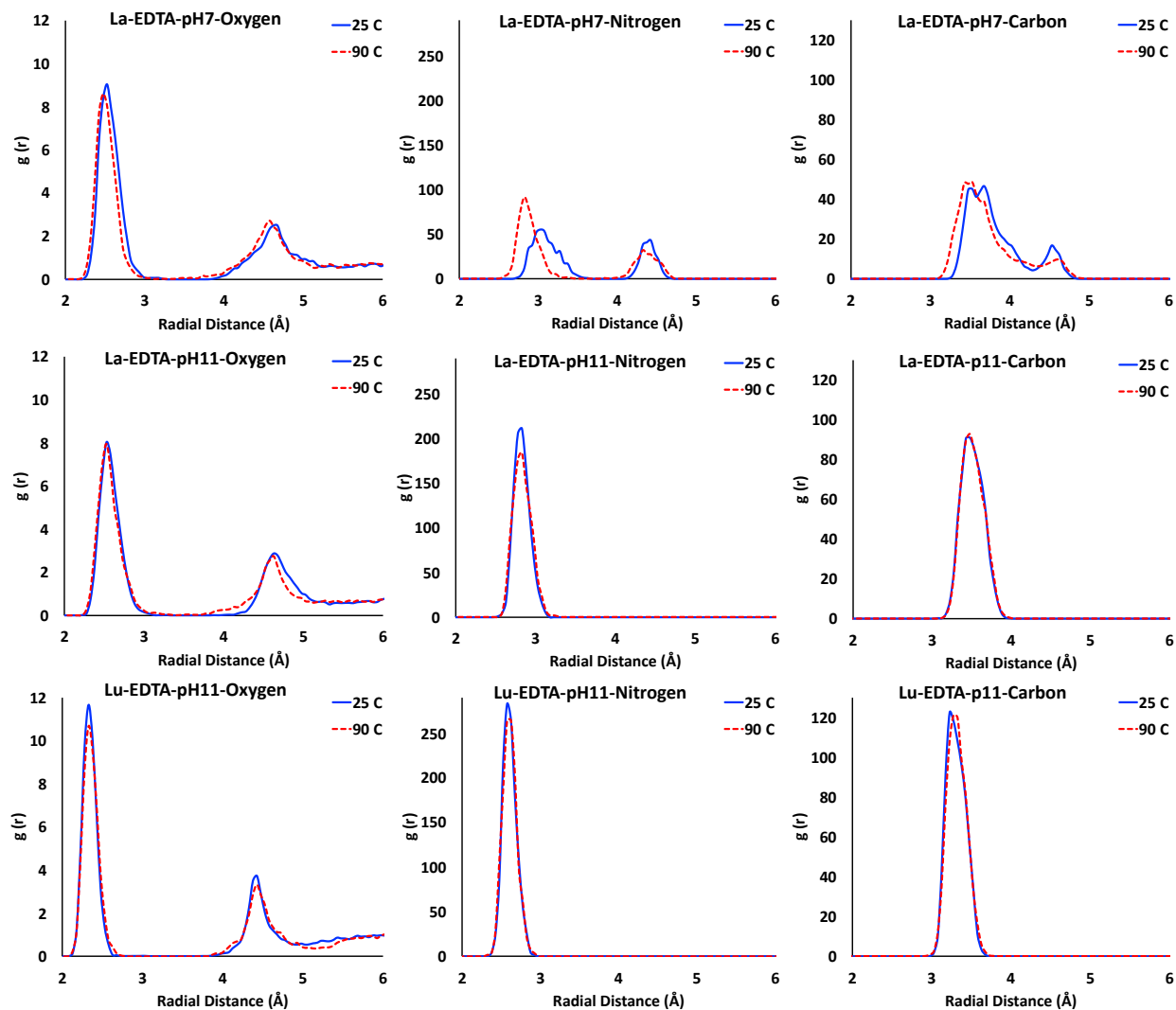
very similar La-O RDFs in Figure 3, ii) in both complexes  $\text{La}^{3+}$  is 9-coordinate, and iii) RMSD values to ideal geometries are within the standard deviations, with  $0.53 \pm 0.8 \text{ \AA}$  and  $0.58 \pm 0.8 \text{ \AA}$  to an ideal tricapped trigonal prism geometry, and  $0.47 \pm 0.8 \text{ \AA}$  and  $0.57 \pm 0.8 \text{ \AA}$  to an ideal capped square antiprism geometry, for the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  and  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  complexes respectively. Therefore, the significant change in binding energy between the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  and  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_4]^0$  complexes, evidenced by bound-ligand rigidity in the solution structure, comes from an additional ligand N-binding site coupled with the chelate effect, whose binding behavior can be altered with solution pH.

### 3.3. Effect of temperature on Ln-EDTA complex structure in solution

Simulations were performed at 90 °C of the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_n]^0$  complex (pH ~7), as well as the  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$  and  $[\text{Lu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_2]^-$  complexes (pH ~11), to determine how temperature affects the solution structure of Ln-ligand complexes with different stabilities. Most notably, the weaker binding  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_n]^0$  complex changed coordination number from 9 to 8 because a water molecule left the first coordination sphere at the higher temperature ( $n=4$  at 25 °C and  $n=3$  at 90 °C), while the coordination number did not change for the complexes at pH ~11 with stronger binding. Therefore, ligand binding strength affects the temperature-induced disorder of the first coordination sphere, as well as the binding strength of coordinated solvent molecules in Ln-EDTA complexes.

The Ln-O, Ln-N, and Ln-C RDFs at 25 °C and 90 °C are plotted on the same graph for each complex in Figure 4 to illustrate how each Ln-EDTA complex changed with temperature in solution. The complexes with greater stability constants appear to have minuscule changes in their RDFs between 25 °C and 90 °C, while the RDFs of the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_n]^0$  complex with weaker binding changed more with temperature, especially the Ln-N and Ln-C RDFs. This shows that bound ligands in complexes with greater stability remain rigid in solution when the temperature increases, however, weaker bound ligands are more susceptible to change their conformation in solution with higher temperatures. Notably, the Ln-N RDFs at 25 °C and 90 °C of the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_n]^0$  complex (Figure 4, top row) appear counterintuitive in that the peak is sharper at the higher temperature; this behavior is explained by the fact that the coordination number of the complex changed from 9 (25 °C) to 8 (90 °C).

Ln-O RDFs exhibit very small change with temperature (Figure 4), even for the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_n]^0$  complex where the small change is the result of the coordination number change between 90 °C and 25 °C, as was observed with the Ln aqua ions where the temperature-induced disorder decreased along the Ln series.<sup>33</sup> In the  $\text{Ln}^{3+}$  aqua ions, increasing from 25 °C to 90 °C resulted in a change in coordination number of the earlier Ln elements ( $\text{Ce}^{3+}$ ,  $\text{Sm}^{3+}$ ) but not in the  $\text{Lu}^{3+}$  aqua ion; a similar behavior is observed in  $\text{La}^{3+}$  with a weakly-bound ligand ( $\text{HEDTA}^{3-}$ ) but not in  $\text{La}^{3+}$  with a stronger-binding ligand ( $\text{EDTA}^{4-}$ ) that stabilizes the entire complex keeping coordinated water molecules in the first shell of the Ln-ligand complex. For the  $\text{Lu}^{3+}$  ion, both the aqua ion and complex with  $\text{EDTA}^{4-}$  remained 8-coordinate and retained their first coordination sphere geometry, as shown with RMSD values to ideal geometries between the two temperatures that are within their standard deviation:  $0.39\pm 0.06$  Å and  $0.40\pm 0.05$  Å for the bicapped trigonal prismatic geometry;  $0.41\pm 0.08$  Å and  $0.39\pm 0.07$  Å for the square antiprism; and  $0.29\pm 0.04$  Å and  $0.33\pm 0.07$  Å for the dodecahedral geometry; at 25 °C and 90 °C respectively. Although the  $\text{Lu}^{3+}$  aqua ion favors the square antiprism geometry at 25 °C,<sup>41</sup> and the dodecahedral geometry at 90 °C,<sup>33</sup> the  $\text{Lu}^{3+}$  ion favors the dodecahedral geometry at both temperatures in complex with  $\text{EDTA}^{4-}$ .



**Figure 4:** Radial distribution functions of the  $[\text{La}^{3+}\text{-HEDTA}^{3-}\cdot(\text{H}_2\text{O})_n]^0$ ,  $[\text{La}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_3]^-$ , and  $[\text{Lu}^{3+}\text{-EDTA}^{4-}\cdot(\text{H}_2\text{O})_2]^-$  complexes, shown in descending order, at 25 °C and 90 °C. Left, center, and right figures show the Ln-O, Ln-N, and Ln-C pair distribution functions, respectively.

#### 4. Conclusions

AIMD simulations were used to characterize the solution structures of EDTA complexed with  $\text{Ln}^{3+}$  ions in two different pH conditions and temperatures. Radial pair distributions for the  $\text{Ln}^{3+}$ -EDTA<sup>4-</sup> complexes, corresponding to pH ~11, confirm that as the  $\text{Ln}^{3+}$  ionic radius decreases,  $\text{Ln}^{3+}$ -O/N bonds shorten and the number of coordinated water molecules decreases from three (for the  $\text{La}^{3+}$ ,  $\text{Eu}^{3+}$ ,  $\text{Gd}^{3+}$  ions) to two (for the  $\text{Lu}^{3+}$  ion). The trend in thermodynamic stability for  $\text{Ln}^{3+}$ -EDTA<sup>4-</sup> was reproduced in the relative binding energies computed with electronic structure



calculations. Protonating an amine nitrogen atom of EDTA<sup>4-</sup> to form HEDTA<sup>3-</sup>, as a result of changing from pH ~11 to pH ~7, prevented Ln-nitrogen coordination without significant effect on the coordinated carboxylate groups; instead, an additional water molecule coordinated to the complex to maintain the same coordination number. Nevertheless, the thermodynamic stability of the La<sup>3+</sup>-HEDTA<sup>3-</sup> complex, corresponding to pH ~7, was greatly reduced compared to that of the La<sup>3+</sup>-EDTA<sup>4-</sup> complex, corresponding to pH ~11. This relative difference was reproduced by calculating relative binding energies. The reported Ln<sup>3+</sup>-EDTA<sup>4-</sup> structures agree with previous studies, and the reported structure of the La<sup>3+</sup>-HEDTA<sup>3-</sup> complex shows the structural basis of how solution pH can change complex stability constants. Regarding temperature, while the solution structures of Ln<sup>3+</sup>-EDTA<sup>4-</sup> complexes did not change significantly upon increasing from 25 °C to 90 °C, a water from La<sup>3+</sup>-HEDTA<sup>3-</sup> detached and the complex changed from 9- to 8-coordinate, similar to what has been previously observed for lanthanide aqua complexes. Furthermore, this work provides an avenue for predicting relative lanthanide-ligand stabilities in the absence of experimental data.

**Supplementary Information:** Discussion on binding energy calculations; Energies of species used in binding energy calculations; Root mean square distance analysis; Plots of energy vs simulation frame

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