Chelator-Assisted High Performance Liquid Chromatographic Separation of Trivalent Lanthanides and Actinides

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Complete List of Authors:	M. Pallares, Roger; Lawrence Berkeley National Laboratory, Hebert, Solene; E O Lawrence Berkeley National Laboratory, Chemical Sciences Sturzbecher-Hoehne, Manuel; E O Lawrence Berkeley National Laboratory, Chemical Sciences Abergel, Rebecca; E O Lawrence Berkeley National Laboratory, Chemical Sciences

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Roger M. Pallares,[a] Solène Hébert,[a] Manuel Sturzbecher-Hoehne,[a] and Rebecca J. Abergel *[a,b]

While lanthanides and actinides are essential to many clean energy technologies, they are at high risk for supply chain disruption. As such, the development of recycling and recovery techniques for lanthanides and actinides is essential to avoid future shortages. Conventional reversed-phase chromatography cannot readily discriminate between the metals, making column modifications, such as adsorption of ion-pair agents, necessary to achieve element separation. In this work, we demonstrate that a siderophore-inspired synthetic derivative, 3,4,3-LI(1,2-HOPO), can be used as an in-situ chelating agent, promoting lanthanide and trivalent actinide separation in less than 15 min without column modification. By employing alternative chelating ligands, f-element separations are therefore achievable in chromatographic systems used in analytical laboratories around the world, creating new opportunities for the separation and recovery of these critical materials.

Clean energy technologies, such as those powered through photovoltaics and wind turbines, require metals at high risk of supply chain disruption.[1] Nine rare earth elements, including Y and eight lanthanides La, Ce, Pr, Nd, Sm, Eu, Tb, and Dy, have been identified by the U.S. Department of Energy (DOE) as critical materials for renewable energy applications.[2] The recovery and reuse of these elements has been proposed as a strategy to avoid future supply disruptions. However, the separation of these elements is challenging due to the consistency of lanthanide properties across the series, such as a preference for the +3 oxidation state and similar ionic sizes.[3] Moreover, lanthanides are often mixed with long-lived minor actinides in nuclear spent fuel, a source of f-elements that has not been exploited due to the low efficiency and high costs of current separation technologies.[4] Lanthanide separation from trivalent actinides, such as Am and Cm, is particularly challenging due to their chemical similarity. Therefore, relevant recovery processes must also isolate lanthanides from trivalent actinides.

Current industrial f-element separation processes rely on either solvent extraction, where hydrophobic molecules extract cations into an organic phase,[5-11] or liquid chromatography.[12-15] By enabling the rapid and precise separation of multi-element samples, providing detection capabilities, and offering low operating and instrumentation costs, high-performance liquid chromatography (HPLC) has emerged as one of the most reliable separation techniques for lanthanides and actinides.[16, 17] Ion pair is frequently preferred to isolate f-elements over other HPLC methods because it achieves relatively fast separation times (between 5 and 20 min).[18, 19] This technique employs reversed-phase columns treated with water-soluble surfactants, such as sodium *n*-octane sulfonate, creating a dynamic cation exchange surface. Hence, the separation is based on the coulombic interactions between metal complexes and the charged solid surface.[18] By complexing the metal with certain ligands, such as α-hydroxyisobutyric acid (α-HIBA)[20] and adjusting the solvent conditions, distinct retention times can be obtained for each cation.[16, 17] Ion pair chromatography is limited, however, by the slow surfactant adsorption to the column step before analysis, which can necessitate the use of up to 20 column volumes to achieve the desired mobile phase composition,[18] and the reproducibility of dynamic equilibria, as the surfactant adsorption on the column surface is dependent on a number of operational variables.[18] The surfactant adsorption step cannot be avoided, since most common chelating ligands used in HPLC yield highly polar lanthanide complexes that are not discriminated on conventional reversed-phase columns.[20] A chelator that yields water-soluble lanthanide and actinide complexes with different retention times in reversed-phase columns (without surfactant adsorption) would improve separation robustness and decrease overall experimental times, contributing to wide-spread f-block element separation and recovery applications

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[a] *Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, 94720, USA*
[b] *Department of Nuclear Engineering, University of California, Berkeley, CA, 94720, USA*

Corresponding authors: abergel@berkeley.edu

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Siderophores are biological molecules produced by bacteria, fungi, and some plants that transport iron across cellular membranes.[21] Siderophore-inspired synthetic analogues containing bidentate hydroxypyridinonate (HOPO) groups show high selectivity and affinity for lanthanides and actinides.[22-24] The octadentate ligand 3,4,3-LI(1,2-HOPO) (Fig. S1, ESI) displays HOPO subunits linked to a central spermine scaffold, and has been employed in decorporation[25-27] and therapeutic applications.[28, 29] Furthermore, HOPO functional groups also sensitize the luminescence of some f-elements,[30, 31] a property that has been exploited for analytical assay development.[32, 33] Our group has leveraged the high affinity of 3,4,3-LI(1,2-HOPO) for trivalent actinides relative to lanthanides to achieve their separation through solvent extraction.[34] Although 3,4,3-LI(1,2-HOPO) had never been used as a chelating ligand in HPLC, we hypothesized that the distinct physicochemical properties of its complexes with f-elements would allow for systematic lanthanide and trivalent actinide separations on reversed-phase columns.

Here we report a HPLC method that separates both lanthanides and trivalent actinides using 3,4,3-LI(1,2-HOPO) as a chelating vector. Leveraging the distinct behaviours of the 3,4,3-LI(1,2-HOPO)-metal complexes (**Fig. 1a**), separations were achieved in reversed-phase columns without functionalization in only 15 min. Separation resolutions higher than 1.0 and metal recoveries above 90% (with 99% chemical purity) were obtained for most of the tested metal pairs. Moreover, the HPLC method preserved its performance in three element samples. These results highlight that by employing alternative chelating agents, lanthanide and actinide separations can be achieved in chromatographic systems commonly used in analytical laboratories, creating new opportunities for the separation and recovery of f-elements.

Lanthanide stock solutions were mixed with equimolar concentrations of 3,4,3-LI(1,2-HOPO) (50 µM), and injected into the system. HPLC was performed using a gradient elution approach with water and acetonitrile as solvents, and their proportion being varied over time (Fig. S2, ESI). Formic acid (FA) was added to both solvents to improve resolution and to provide a suitable environment for ionization in the mass spectrometer used for species analysis. Various experimental conditions were optimized to improve the lanthanide retention behaviour and separation. pH did not significantly affect separation, as similar results were obtained at pH 2.5 and 7.4 (**Fig. 1b**), a finding consistent with 3,4,3-LI(1,2-HOPO)'s ability to complex various f-elements over a wide range of pH values.[30, 35] While a 10-fold decrease in metal complex concentration did not improve separation efficiency, increasing FA content in the solvents from 0.1% to 1% resulted in better separations of early lanthanides (Pr, Nd, and Sm). Therefore, the subsequent experiments were performed at pH 2.5 and 1% FA to maximize metal separations. Notably, these results confirmed that, unlike commonly used HPLC ligands such as α-HIBA,[20] 3,4,3-LI(1,2-HOPO) could be employed as a chelating vector to discriminate lanthanides in reversed-phase columns.

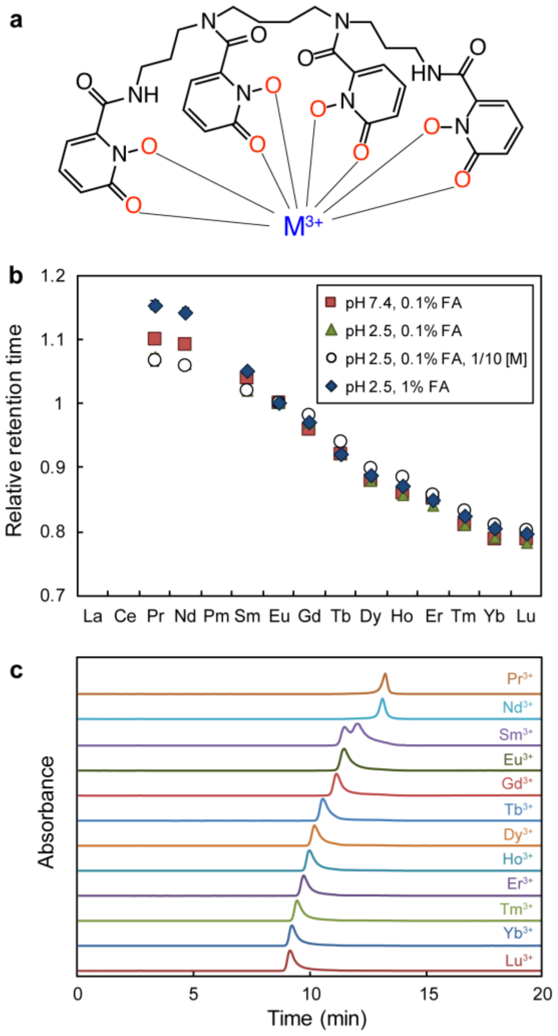

Fig. 1. (**a**) Scheme of M^{3+}– 3,4,3-LI(1,2-HOPO) complex. (**b**) Optimization of lanthanide retention times under different experimental conditions. The relative retention times were calculated by dividing the metal retention time by the Eu retention time. (**c**) Chromatograms of solutions containing 3,4,3-LI(1,2-HOPO), Eu^{3+}, and lanthanides, observed in negative ion mode at specific-complex masses. For clarity purposes, the chromatograms have been offset. Absorbance was recorded at 302 nm.

Next, we evaluated the elution behaviour of lanthanide mixtures. Solutions containing 100 µM 3,4,3-LI(1,2-HOPO), 50 µM of single lanthanide cations, and 50 µM of Eu^{3+} were injected to the HPLC system. Eu^{3+} was used as both internal standard and as a reference to compare separations because it was one of the essential rare earth elements highlighted by the DOE, and it is located in the middle of the lanthanide series. The retention times of the lanthanide complexes decreased along the series (**Fig. 1c**), likely due to ion contraction and increased Lewis acidity along the series.[3] For clarity purposes, the chromatograms are displayed under specific lanthanide-complex masses, where the absorbance at 302 nm is only reported by the system when the mass spectrometer detects the complex of interest (Table S1, ESI). The chromatogram of the Sm^{3+} sample showed two peaks because of the isotopic pattern, where the m/z ratios of Sm^{3+}-3,4,3-LI(1,2-HOPO) partially overlapped with those from Eu^{3+}-3,4,3-LI(1,2-HOPO) (Fig. S4, ESI). Therefore, the Sm^{3+} chromatogram reported the peaks of both Eu^{3+} and Sm^{3+} complexes. For a representative set of chromatograms displaying simultaneously the lanthanide and Eu^{3+} complex peaks, and their fitting, please refer to **Fig. 2a** and **2b,** and for all the chromatograms refer to Fig. S3 (ESI). The retention times, separation resolutions, and separation results (calculated as % of the first metal recovered before 1% elution of the second metal) are displayed in Table 1. All but two separation resolutions were above 1.0, highlighting the consistently high separation performance of our method. Moreover, all separations were carried out in less than 15 min, resulting in over 90% recovery with 99% purity of the first metal eluted after only one HPLC cycle for most of the metal pairs tested.

Table 1. Retention times, separation resolutions, and separation results of lanthanide samples

	Retention time (min)	*Separation resolution*	*Separation of first metal*
Pr^{3+}	13.25	3.1	95% Eu with 99% purity
Nd^{3+}	13.12	3.0	93% Eu with 99% purity
Sm^{3+}	12.06	0.7	49% Eu with 99% purity
Eu^{3+}	11.48		
Gd^{3+}	11.15	0.4	28% Gd with 99% purity
Tb^{3+}	10.57	1.3	81% Tb with 99% purity
Dy^{3+}	10.20	2.0	91% Dy with 99% purity
Ho^{3+}	9.99	1.1	93% Ho with 99% purity
Er^{3+}	9.74	2.4	95% Er with 99% purity
Tm^{3+}	9.45	3.0	96% Tm with 99% purity
Yb^{3+}	9.23	3.5	97% Yb with 99% purity
Lu^{3+}	9.15	3.7	97% Lu with 99% purity

Separation resolutions (R_s) were calculated based on the equation:[36] $R_s = 1.18 \cdot \frac{t_{R2}-t_{R1}}{W_{h1}+W_{h2}}$, where t_{R1} *and* t_{R2} are the retention times of complex 1 and 2, respectively, and W_{h1} and W_{h2} are the peak width at half height of complex 1 and 2, respectively.

We further assessed the robustness of our method by injecting a sample with three lanthanides (50 µM Eu^{3+}, 50 µM Dy^{3+}, 50 µM Yb^{3+}, and 150 µM 3,4,3-LI(1,2-HOPO)). The resulting chromatogram showed three sharp peaks (**Fig. 2c**) with the same metal complex retention times as compared to the two-metal samples, and separation resolutions of 1.4 and 1.5 (Table S2, ESI). These results further highlighted the potential of this chromatographic method for the separation of lanthanides in multi-element samples, such as in recovery and separation applications of spent nuclear fuel.

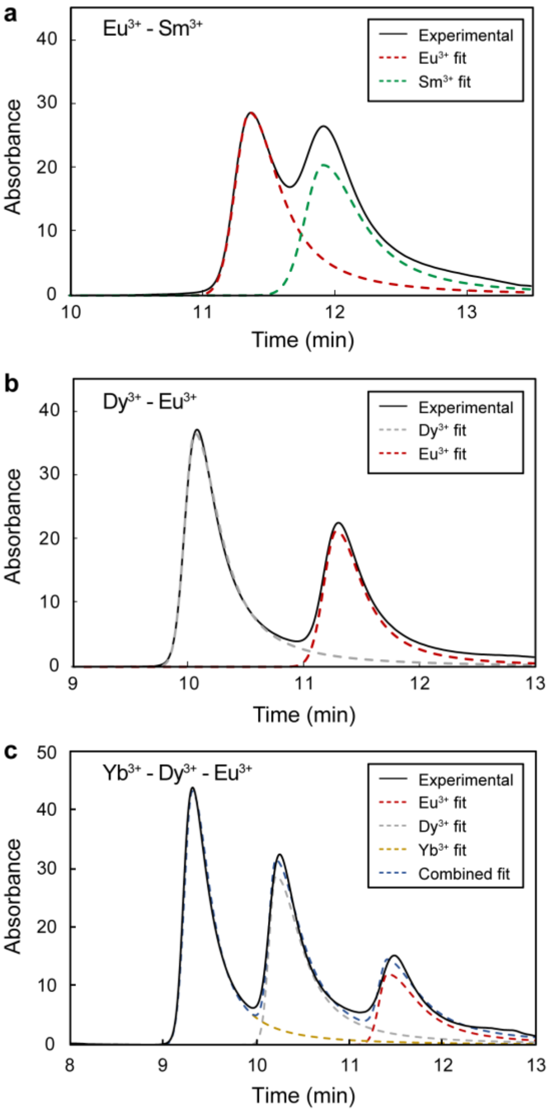

Fig. 2. Chromatograms of solutions containing (**a**) 50 µM Eu^{3+}, 50 µM Sm^{3+}, and 100 µM 3,4,3-LI(1,2-HOPO), (**b**) 50 µM Eu^{3+}, 50 µM Dy^{3+}, and 100 µM 3,4,3-LI(1,2-HOPO), and (**c**) 50 µM Eu^{3+}, 50 µM Dy^{3+}, 50 µM Yb^{3+}, and 150 µM 3,4,3-LI(1,2-HOPO). Absorbance was recorded at 302 nm. The fitting for each peak is also displayed.

Lastly, we explored whether the HPLC method could be used to separate Eu^{3+} from trivalent actinides, such as Am^{3+} and Cm^{3+}. Eu^{3+} was chosen not only for consistency with previous experiments but also because the electronic configuration of Eu^{3+} makes it a surrogate for Am^{3+}, rendering their separation more challenging than that of Am^{3+} with lighter or heavier lanthanides. Two solutions containing 100 µM 3,4,3-LI(1,2-HOPO), 50 µM of Am^{3+} or Cm^{3+}, and 50 µM of Eu^{3+} were injected into the HPLC system (**Fig. 3**) and the method described above was conducted. Separated samples containing 50 µM 3,4,3-LI(1,2-HOPO) and 50 µM of each metal were used as references. Eluting the f-elements as a mixture had no effect on their retention, since the metal complexes had the same retention times independent of whether they were injected into the system individually or in mixtures. Their elution peaks, however, became broader when samples were injected as mixtures. Nevertheless, both Am^{3+} and Cm^{3+} complexes formed with 3,4,3-LI(1,2-HOPO) were successfully separated from the Eu^{3+} complex (Table 2), with the former showing higher separation resolution and better overall separation (calculated as % of the first metal recovered before 1% elution of the second metal). These results were consistent with Cm^{3+} close resemblance to

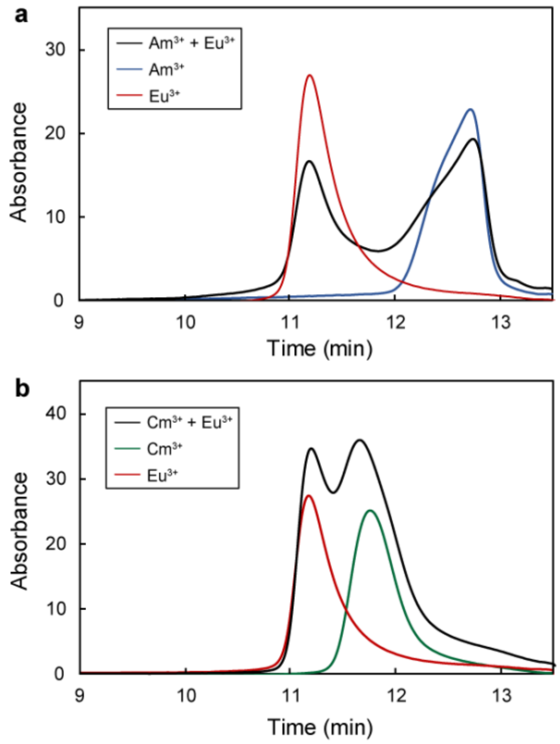

Fig. 3. Chromatograms of solution containing (**a**) 50 µM Eu^{3+}, 50 µM Am^{3+}, and 100 µM 3,4,3-LI(1,2-HOPO), and (**b**) 50 µM Eu^{3+}, 50 µM Cm^{3+}, and 100 µM 3,4,3-LI(1,2-HOPO). For comparison purposes, each figure also shows the individual metal complex chromatograms. Absorbance was recorded at 302 nm.

Eu^{3+} in ionic radius and Lewis acidity relative to Am^{3+},[37, 38] potentially resulting in similar retention times for Cm^{3+} and Eu^{3+}.

Table 2. Retention times, separation resolutions, and separation results of lanthanide and actinide samples

	Retention time (min)	*Separation resolution*	*Separation of first metal*
Am^{3+}	12.77	1.7	75% Eu with 99% purity
Cm^{3+}	11.77	0.7	27% Eu with 99% purity

In summary, we have developed an HPLC method to separate lanthanides and actinides in less than 15 min using reversed-phase HPLC columns. Although conventional chromatographic ligands cannot discriminate trivalent f-elements in hydrophobic columns, the use of 3,4,3-LI(1,2-HOPO) as a chelating ligand yielded separation resolutions above 1.0 for nearly all metal pairs tested. We obtained over 90% recovery with 99% purity of the first metal eluted after only one chromatographic cycle in eight of thirteen separations. Furthermore, separation performance was preserved when mixtures of three elements were run through the system. Because this chromatographic method is rapid, provides good separation performance of multi-element samples, and employs reversed-phase columns (the most common types of HPLC columns), we expect that this work will provide new opportunities in the field of lanthanide and actinide separation and recovery.

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Conflicts of interest

There are no conflicts to declare.

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