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Deferasirox Derivatives: New Ligands for the Lanthanide Series

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ABSTRACT: Deferasirox is an FDA-approved iron chelator used in the treatment of iron toxicity. In this work, we report the use of several deferasirox derivatives as lanthanide chelators. Solid state structural studies of three representative trivalent lanthanide cations, La(III), Eu(III), and Lu(III), revealed the formation of 2:2 complexes in the solid state. A 1:1 stoichiometry dominates in DMSO solution with K_a values of 472 ± 14 M⁻¹, 477 ± 11 M⁻¹, and 496 ± 15 M⁻¹ being obtained in the case of these three cations, respectively. Under conditions of competitive precipitation in the presence of triethylamine, high selectivity (up to 80%) for lutetium(III) was observed in competition with La(III), Ce(III), and Eu(III). Theoretical calculations provide support for the observed selective crystallization.

Introduction

Lanthanides are some of the most critical resources in the modern world. They play essential roles in many high-tech commodities including inter alia TVs, cell phones, electric cars, and satellites.^{1, 2} Additionally, lanthanide alloys based on neodymium are found in permanent magnets used in renewable energy technologies such as wind turbines.³¹ While demand for these elements continues to rise, the purification of lanthanide ions remains challenging.³ Purification is exacerbated by difficulties associated with separating individual lanthanides from one another. This difficulty reflects in part the similarity of the trivalent lanthanide cations in terms of both their chemical and physical properties. The small changes in the ionic radii that occur across the lanthanide series (lanthanide contraction) continue to be exploited to prepare extractants that can drive separations.⁴ Nevertheless, new ligand systems that allow for the complexation of lanthanides could provide the basis for alternative separation strategies yielding potential benefits in both initial lanthanide isolation and post-consumer recycling.

While nearly every stable lanthanide and actinide is of technological importance, lutetium is currently seeing use in applications running the gamut from hydrocarbon cracking, cancer treatments using the medicinal isotope ¹⁷⁷Lu, optical lenses, scintillators and X-ray phosphors.14-16 Most commercial lutetium ion separation processes rely largely on multi-stage counter-current liquid-liquid extractions where lutetium is separated in the later stages.^{32,33} Selective precipitation of lanthanide salts is increasing in popularity as a possible purification alternative owing to its relatively low energy demand. However, this technique has mainly focused on group lanthanide recovery, rather than specific cation isolation.³⁴⁻³⁹ Moreover, precipitation-based separations have proved most effective in targeting light lanthanide cations with, for example, La(III)/Ln(III) separation factors of up to 248 having been reported.³⁹ Reversing this selectivity to favor the heavier lanthanides thus constitutes an allbut-unmet challenge. More broadly, improved lutetium separation processes may make its isolation more cost effective, increase its availability, or support research leading to new opportunities. The present study, describing deferasirox complexation and precipitation-based selective isolation of a lutetium complex, may advance these efforts.

Deferasirox is an FDA-approved agent that is used in the treatment of iron overload disease.5-7 It is an O, N, O chelator that forms stable complexes with Fe(III) and which has attracted attention as a potential chemotherapeutic, antifungal, and antimicrobial agent.^{12,13} Our group has recently reported on the photophysical, chemotherapeutic, antimicrobial, and diagnostic abilities of several deferasirox derivatives (cf. Figure 1).^{8, 9} These derivatives, like the parent deferasirox system, comprise a triazole core flanked by two phenolic arms. The similarities in the coordination chemistry of Fe(III) and Ln(III), namely their preference for strong oxygen donor ligands and high Lewis acidity,^{28,29} led us to postulate that deferasirox derivatives might act as effective receptors for the trivalent lanthanide cations. Support for this suggestion comes from previous work by Pidcock and coworkers who revealed through ligand screening that several, low denticity chelators stabilize lanthanide ion complexes with varying coordination numbers. These studies revealed differences in low dentate ligand binding between divalent cations, such as calcium, which was not facile, compared to trivalent lanthanide ions, which occurred much more readily.²⁷ Additionally, Griffiths and co-workers reported mono- and bi-dentate ligand binding of lanthanide cations in biological systems.³⁰ To date, deferasirox, and several of its analogues, have been used to stabilize complexes with numerous bio-relevant metals, including Ca(II), Mg(II), Cu(II), Zn(II), Pt(II), and Al(III).¹⁰ Recently Buglyo and coworkers reported the coordination of deferasirox analogues to Ru(III), Os(VI), Co(III), and Ga(III).¹¹ Bertrand and coworkers reported the formation of a bimetallic Pt(II) deferasirox analogue complex that displayed promising antiproliferative properties.¹² Separately, Maurya and coworkers reported that a deferasirox-vanadium complex possessed antiamoebic activity.13 While deferasirox has been studied extensively as a chelator for transition metal cations, to our knowledge, few published reports have appeared detailing efforts to extend these studies to include the *f*-block elements. We are aware of only a single study wherein terbium sensitization was used to quantify deferasirox concentrations in biological samples.²⁶ No crystallographically characterized deferasirox complexes of *f*-block elements were found in a CSD query. Nor, to our knowledge, has deferasirox or its derivatives been applied to the problem of lanthanide separations. We have carried out solution phase complexation and solid-state X-ray diffraction-based structural studies in an effort to address this knowledge gap.



 $R = -CF_3$ (9), $-SO_3H$ (10), $-NMe_2$ (11)

Figure 1. Chemical structures of the deferasirox derivatives (referred to as ExR) considered in this study.

Results and Discussion

The chemical structures of the two pro-ligands explored in this study, ExPh (1) and ExBT (2) are shown in Figure 1, as well as the synthesis of their corresponding lanthanide complexes 3 - 8 (Scheme 1). Derivatives 9-11 were also studied in an effort to explore the effect of deferasirox derivative structure on lanthanide complexation. These derivatives were prepared via previously reported synthetic methods.^{9,17,18}

Scheme 1. Reaction scheme for lanthanide complexation.



As a first test of whether the deferasirox scaffold would support lanthanide complexation, ExPh (1) was added to La(NO₃)₃ in basic THF media and allowed to react, as shown in Scheme 1. This resulted in the formation of a tan precipitate. ¹H NMR spectroscopic analysis of the precipitate dissolved in DMSO- d_6 (trimethoxybenzene internal standard), revealed features consistent with the formation of a lanthanum(III) complex.^{11,19} The formation of a La(III) complex was further supported by mass spectrometric studies, which revealed a peak corresponding to $[ExPhLa][DMSO]_2^+$.

To investigate the binding stoichiometry between ExPh (1) and La(III) nitrate under solution phase conditions, we employed the method of continuous variation (Job plot analysis) using ¹H NMR spectroscopy in DMSO- d_6 in the presence of triethylamine (2 molar equivalents).²⁰ A representative plot of complex formation against the mole fraction of ExPh added is shown in Figure S9 in the Supporting Information. The complex concentration was found to be maximal at a mole ratio of 0.5. Although we are aware of the limitations associated with Job plot analyses,²¹ such a finding is as expected for an empirical 1:1 ligand-to-metal binding stoichiometry.²⁰ Similar results were obtained when the Job plot analysis was performed for the putative complexes formed from ExPh (1) with the corresponding Eu(III) and Lu(III) nitrate salts (SI, Figure S10-11).

Diffraction grade single crystals of the lanthanide complexes 5, 6, and 7 were obtained via the slow evaporation of a mixed THF DMSO (20:1, v/v) solution or through vapor diffusion of hexanes into a solution of THF and DMSO (20:1, v/v). The resulting X-ray diffraction analyses revealed the formation of dimeric $[ExR-Ln(DMSO)_2(NO_3)]_2$ complexes (Ln = La, Eu, Lu; R = benzothiazole or phenyl) as shown in Figure 2. In the case of the La-ExBT, complex 6, the La(III) ions were found coordinated to an ExBT ligand with two solvent DMSO molecules and a single nitrate anion (Figure 2). The La(III) center in complex 6 was bound in a hepta-coordinate ligand environment characterized by a capped trigonal prism geometry and c_{2v} -symmetry. The ExBT ligand acts as an (O, N, O) chelator with cation coordination occurring through the triazole nitrogen (La-N_{triazole}, 2.650(4) Å) and two phenolate oxygen atoms, one of which is bound through a κ_1 terminal bond (La-O2, 2.284(3) Å), while the other binds to both La(III) metal cations via a μ_2 bridge (La1-O1, 2.422(3) Å) that is slightly distorted (La2-O1, 2.492(3) Å). The phenolate anionic center bound in a κ_1 fashion is coplanar to the triazole ring. The phenolate ring belonging to the bridging O is tilted off the mean ligand plane giving rise to a torsion angle of 44.2(7)°. The La(1)-La(2) distance is 4.0436(5) Å. The DMSO-La bonding distances vary from 2.455(4) to 2.545(8) Å.

The Eu(III) complex **7** exists as a dimeric structure (SI, Figure S16). As observed in the case of complex **6**, the Eu(III) cations are bound to the ExBT ligand via the triazole nitrogen and phenolic arms. The Eu-N_{triazole} distance is 2.537(3) Å, corresponding to a slightly shorter bond than observed in complex **6** (La-N_{triazole} = 2.650(4) Å; vide supra). The Eu-O terminal phenolate bond distance is 2.213(2) Å, while the Eu-O bond distance is 2.331(2) Å in the case of the bridging phenolate. The Eu-Eu distance is 3.8866(3) Å. The torsion angle of the bridging phenolate is 37.4(5)°. As in complex **6**, the terminal bonding phenolate is coplanar with the triazole ring. All metal-ligand bonds for the Eu complex were slightly shorter than for the corresponding La(III) complex **6**. This is as expected given the smaller ionic radius of Eu(III) (1.087 Å) relative to La(III) (1.172 Å).²²

X-ray diffraction quality crystals of a Lu-ExPh complex **5** were obtained from a THF DMSO (20:1, v/v) solution. The resulting analysis revealed a dimeric complex, [ExPh-Lu(DMSO)₂(NO₃)]₂ (**5**) (Figure 3) that was structurally similar to that of complexes **6** and **7**.



Figure 2. View of La(III) ExBT complex **6** showing the heteroatom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The methyl group hydrogen atoms and lower occupancy atoms of the disordered DMSO groups are omitted for clarity.



Figure 3. View of the Lu(III) ExPh complex **5** showing the heteroatom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The methyl group hydrogen atoms and the lower occupancy atoms of the disordered DMSO solvent molecules are omitted for clarity.

The Lu-N_{triazole} bond distance in complex **5** was found to be 2.442(3) Å, corresponding to a shorter bond than observed in the ExBT-La and ExBT-Eu complexes **6** and **7**. The κ_1 Lu-O bond distance is 2.153(3) Å. The bridging phenolate Lu1-O distance is 2.308(3) Å, and the Lu2-O distance is 2.234(3) Å. A distortion similar to what was observed in complexes **6** and **7** was also seen. The torsion angle within the bridging phenolate is 36.0(6)°, while the other terminal coordinating phenolate was coplanar with the triazole ring. The Lu1-Lu2 distance of 3.7230(4) Å seen in **5** is significantly shorter than the Ln1-Ln2 separation observed in complexes **6** (4.0436(5) Å) and **7** (3.8866(3) Å).

¹H NMR Spectroscopy

To explore the solution formation of the putative Ln(III) complexes in greater detail, ¹H NMR spectroscopic studies of complexes **3-5** were carried out in DMSO- d_6 in the presence of base (Supporting Information, Figures S6-S8). The spectral changes observed upon adding additional quantities of the nitrate salts of La(III), Eu(III), and Lu(III) to ExPh were consistent with an equilibrium process that was slow on the NMR time scale in that the resonances for both the starting ligand and putative complex were seen.

An effort was made to fit the spectral changes as a function of added salt to a 1:1 binding profile. A local analysis method was employed that involved monitoring two, single proton signals corresponding to the formation of the complex and disappearance of the ligand at 7.85 ppm and 8.01 ppm, respectively. The free ligand with triethylamine (TEA; 2.2 equiv) (i.e., prior to the addition of Lu(NO₃)₃) is shown as the lower trace in Figure 4. The addition of the metal salt in increments of 0.1 molar equivalents resulted in the appearance and sequential increase in the intensity of the signal at 7.85 ppm corresponding to the presumed 1:1 complex with a commensurate reduction in the intensity of the resonance for the free ligand at 8.01 ppm. On this basis, we conclude that complex formation is slow on the NMR time scale. Using equations S1-S3 (cf. Supporting Information) and the 1:1 stoichiometry inferred from the Job plot analyses, the equilibrium concentrations of free ligand, free metal, and complex were calculated. Under the conditions used for titration, i.e., room temperature and mM concentrations in DMSO- d_6 , the reaction equilibrium was established on the order of seconds. This conclusion was supported by collecting several NMR spectra after a single addition with no changes in the ligand or complex peak signals being observed over longer timescales. Efforts to fit the data to other putative binding stoichiometries (e.g., 1:2 or 2:1) failed to give reasonable fits.

Equilibrium binding constants in DMSO- d_6 were calculated based on a 1:1 ligand-to-metal binding stoichiometry with the formation of a single complex using the BindFit software.^{21,23} The binding constants for complexes 3, 4, and 5 were calculated to be $472 \pm 14 \text{ M}^{-1}$, $477 \pm 11 \text{ M}^{-1}$, and $496 \pm 15 \text{ M}^{-1}$. The errors reported are the curve fit errors. The titrations were repeated 3 times and concordant results were obtained. The binding constants corresponding to the formation of the La(III) (3) and Eu(III) (4) complexes were similar with that of the Lu(III) complex 5, although 5 exhibited a slightly larger value than for 3 or 4. The use of other derivatives, such as ExBT, or varying amounts of TEA, or different bases did not lead to discernible differences in the relative La(III), Eu(III), and Lu(III) binding affinities. On the other hand, the Lu(III) complex was found qualitatively to be less soluble as manifest by the formation of a precipitate over time in the NMR tubes.

Selectivity Measurements

To explore whether the inferred solubility differences in the deferasirox complexes could provide the basis for a selective separation between the Ln(III) cations, competition experiments were carried out. In these studies, four test lanthanide(III) nitrate salts spanning the lanthanide series (viz. La, Ce, Eu, Lu) were allowed to react (1 molar equivalent of each metal nitrate salt) with a single equivalent of a given deferasirox derivative in the presence of 2 equivalents of TEA in THF (Scheme 2). Once precipitation was complete, the reaction mixture was filtered, and the collected solid residue was washed with water. After drying under vacuum at room temperature, the resulting solid was dissolved in concentrated nitric acid, and the metal ion concentrations determined via inductively coupled plasmaoptical emission spectroscopy (ICP-OES). The emissions for each metal were measured at a wavelength that caused the least interference between the other ions (La at 333.749 nm, Ce at

ExPh Lu	u 13						MM	1.2 eq	uiv. Lu(N	O ₃) ₃
ExPh Lu	u 12						M			
ExPh Lu	u 11						M			
ExPh Lu	u 10						MM			
ExPh Lu	ı 9						\sim			
ExPh Lu	18						\sim			Z
ExPh Lu	ı 7						\sim			sing
ExPh Lu	ı 6			~~			\sim	0.5 eq	uiv. Lu(N	O ₃) ₃
ExPh Lu	ı 5									I
ExPh Lu	J 4			M						
ExPh Lu	ı 3			MM						
ExPh Lu	ı 2		M					0.1 eq	uiv. Lu(N	O ₃) ₃
ExPh Lu	ı 1		M			ExPh (0 equiv. Lu(NO ₃) ₃				
,										
.2	8.2	8.1	8.0	8.0 Cher	7.9 nical shift (p	7.9 pm)	7.8	7.8	7.8	7

Figure 4. ¹H NMR spectra of ExPh (1) (bottom) in DMSO-d₆ recorded upon the iterative addition of Lu(NO₃)₃.

418.659 nm, Eu at 412.972 nm, and Lu at 261.541 nm). Reference to standards were made and both the standard and sample measurements were carried out in triplicate. Calibration curves for each metal were developed using ICP-OES standard solutions purchased commercially, and the resulting calibration curves were found to have an R² value greater than 0.998 for all metals (SI, Figure S19). A relative ratio of 1:1.5:5.7:33.8 for La:Ce:Eu:Lu was obtained for the ExBT derivative, corresponding to an 83% Lu(III) selectivity. The error estimate for this value is \leq 4%.

Scheme 2. Reaction scheme for the competitive lanthanide complexation experiments of this study.



R = H (1), benzothiazole (2), CF₃ (9), SO₃H (10), NMe₂ (11)

To understand the influence of modifying the ligand backbone, $ExNMe_2$ (11), ExPh (1), $ExCF_3$ (9), and $ExSO_3H$ (10) were tested under identical reaction conditions. All derivatives displayed Lu selectivity, with the $ExSO_3H$ showing the lowest selectivity at 69 ± 2% and ExPh the greatest at 84 ± 3%. Ligands ExPh, ExBT, and $ExSO_3H$ displayed a similar Lu>Eu>Ce>La selectivity trend. In contrast, a Lu>Ce>Eu>La selectivity trend

was seen for $ExNMe_2$ and $ExCF_3$ with the Ce(III) cation outcompeting Eu(III) and La(III), but not Lu(III). These results provide support for the conclusion that modulating the ligand scaffold affects selectivity, although not to the point of reversing the preference for Lu(III).

Using ExBT, different bases were then screened to assess their effect on selectivity. The use of triethylamine provided the greatest selectivity at $83 \pm 4\%$. Pyridine, NaOMe, and NaOH decreased the relative selectivity for Lu(III) to 73 ± 2 , 71 ± 2 , and $69 \pm 3\%$, respectively. KOH and *t*BuOK further decreased the relative selectivity to 59 and 49% with errors of 4 and 2%, respectively. Adding more than 2.5 base equivalents further reduced the relative Lu(III) selectivity.

The apparent contradiction between the similarity in the calculated binding constants for the La(III), Eu(III), and Lu(III) complexes in DMSO under equilibrium conditions and the above preference for Lu(III) in the precipitation studies is taken as evidence that the relative affinities under solution phase equilibrium conditions do not recapitulate fully the precipitation from THF. We thus suggest that the observed Lu(III) selectivity may be the result of selective crystallization under competitive equilibrium conditions. In this system, Lu(III) out-competes the other lanthanide cations in ligand binding. Although a crystal suitable for XRD was not obtained through traditional recrystallization techniques, slow evaporation of the complexation mixture containing Lu(III) and the ExBT ligand (2) resulted in a crystal that could be partially refined following X-ray diffraction analysis. The resulting structure provided support for the formation of the ExBT-Lu(III) complex 8, which exists as an oxo cluster containing seven Lu(III) ions surrounded by six ExBT ligands (Figure 5).

The crystals used for the above analysis were not subject to any further recrystallization prior to study. As such, this solid state result provides insight into the formation of a precipitate enriched in Lu(III); presumably, the cluster is the dominate species formed under the conditions of slow evaporation. In our hands the evolution of such a relatively insoluble cluster was only seen in the case of Lu(III), a finding that may help rationalize the experimental finding that addition of lutetium nitrate to the deferasirox derivatives of this study results in a greater level of precipitation as compared to the other lanthanide(III) nitrate salts.

This work utilizing simple-chelates for precipitation of lanthanide ions could provide a stepping stone for the selective precipitation of later-lanthanide cations, which is poorly developed in the literature.³⁴⁻³⁹ Unfortunately, efforts to achieve selectivity under conditions where Lu(III) was the minor species designed to mimic the low relative composition of lutetium found in, e.g., bastnaesite ore ($\leq 0.1\%$) proved unsuccessful. See the Supporting Information for further details.



Figure 5. Partially refined view of the single crystal X-ray diffraction structure of the Lu(III)-ExBT cluster (8). Displacement ellipsoids are scaled to the 30% probability level.

Computational Analyses

In an effort to obtain further insights into the lutetium(III) selectivity when precipitation was carried out using a 1:1:1:1 mixture of trivalent La, Ce, Eu, Lu nitrate salts, gas phase DFT calculations were carried out on complexes **3-5**. Geometries were first optimized using the B3LYP functional with the def2-tzvp effective core potential for the lanthanide cations, and 6-311+G* basis set for the H, C, O, N, and S atoms.^{24, 25} As starting points, the complexes were optimized using the SC-XRD derived geometries. Gaussian 16 basis set superposition errors (BSSE) were used to calculate complexation energies. The energies for both the formation of the monomeric complex as well as the formation of a dimeric complex as observed in the solidstate X-ray crystal structures were evaluated.

The La(III) complex **3** had the lowest complexation energy (-475.91 kcal/mol), followed by Eu(III) complex **4** (-490.24 kcal/mol). Conversely, the Lu(III) complex **5** had the highest

binding energy within this representative set (-501.95 kcal/mol). As noted above, the SC-XRD analysis revealed the formation of a dimer in the solid state. We thus calculated the BSSE corrected energies of dimerization, where monomeric complexes of ExPh-Ln(DMSO)2(NO3) were allowed to dimerize to form [ExPh-Ln(DMSO)₂(NO₃)]₂. They were found to be -48.44, -59.46, and -128.01 kcal/mol for complexes 3-5, respectively. The complexation energy for the Lu(III) complex 5 is significantly greater than for the europium and lanthanum complexes. These results lead us to suggest that while formation of monomeric and dimeric complexes is energetically favored in the case of all three lanthanide(III) cations in the gas phase, dimerization leads to a stable complex in the case of Lu(III). This finding could provide a possible explanation for the selectivity observed for the Lu(III) complexes in that formation of a dimeric (or higher order) complex could promote precipitation.

Conclusion

Deferasirox, long recognized for its strong Fe(III) binding ability, has received attention as a metal chelator for various transition metal cations. Here, we show that deferasirox derivatives are effective ligands for representative *f*-elements. Specifically, we were able to coordinate various deferasirox derivatives (ExPh (1), ExBT (2), ExCF₃(9), ExNMe₂ (11), and ExSO₃ (10)) to selected trivalent metal cations spanning the lanthanide series. Solution based ¹H NMR spectroscopic studies carried out in DMSO-d₆ revealed that Lu(III), Eu(III), and La(III) were complexed with similar binding affinities. However, competition experiments carried out under conditions favoring precipitation (THF containing a base) revealed selectivity for Lu(III). Judicious choice of base was important to achieve an optimal Lu(III) selectivity, with TEA giving the best results. Theoretical analyses were performed to probe the energetics of the complexes. Gas phase DFT calculations revealed that a model Lu(III) complex displayed the highest complexation energy within the series consisting of La(III), Eu(III), and Lu(III). The determination of a partially refined Lu(III) cluster structure from crystals grown via direct evaporation, as opposed to recrystallization, provides further support for the selective precipitation of the Lu(III) complexes of this study.

The finding that deferasirox derivatives display selectivity towards lutetium(III) over the other test lanthanide cations under conditions of selective precipitation leads us to propose that they could prove helpful in the separation of lutetium from other lanthanide ions. We note in this context that the precipitate formed in the case of the lutetium(III) complex is easily separated from the mother liquor, allowing for facile isolation of the complex. The structural variability of the deferasirox platform and its straightforward synthesis will encourage further optimization of the observed selectivity or, alternatively, tuning it towards other members of the lanthanide series.

ASSOCIATED CONTENT

This supporting information is available free of charge via the Internet at <u>http://pubs.acs.org</u>. Materials and methods, synthetic procedures, experimental details, crystallographic data, and NMR titration and spectra for all compounds (PDF) Accession Codes

CCDC 2222840–2222842 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road,

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Author Contributions

‡Equal contribution. J.L.S., A.C.S. and D.N.M. conceived of the project. G.J.J., D.N.M., and A.S. prepared the compounds. All authors analyzed the data and contributed to the preparation of the manuscript, to which all authors have given approval in its final form.

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