Published in final edited form as:

Eur J Inorg Chem. 2018 April 17; 2018(14): 1556–1562. doi:10.1002/ejic.201701398.

Crystallographic Characterization and Non-Innocent Redox Activity of the Glycine Modified DOTA Scaffold and Its Impact on Eu^{III} Electrochemistry

Marianne E. Burnett^[a], Bukola Adebesein^[b], S. James Ratnakar^[b], and Kayla N. Green^[a]

^[a]Department of Chemistry and Biochemistry, Texas Christian University, 2950 W. Bowie, Fort Worth, TX, 76129, USA, kayla.green@tcu.edu, <http://chemistry.tcu.edu/staff/kayla-green/>

^[b]Advanced Imaging Research Center, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75930, USA, James.Ratnakar@UTSouthwestern.edu, <http://www.utsouthwestern.edu/education/medical-school/departments/airc/>

Abstract

EuDOTA-glycine derivatives have been explored as alternatives to typical gadolinium-containing complexes for MRI agents used in diagnostic imaging. Different imaging modalities can be accessed (T_1 or PARACEST) dependent on the oxidation state of the europium ion. Throughout the past 30 years, there have been significant manipulations and additions made to the DOTA scaffold; yet, characterizations related to electrochemistry and structure determined through XRD analysis have not been fully analyzed. In this work, electrochemical analysis using cyclic voltammetry was carried out on EuDOTA derivatives, including the free ligand DOTAGly₄ (**4**) and the complexes. Effects of glycinate substitution on the DOTA scaffold, specifically, ligand interactions with the glassy carbon electrode were observed. A range of electrochemical investigations were carried out to show that increased glycinate substitution led to increased interaction with the electrode surface, thus implicating a new factor to consider when evaluating the electrochemistry of glycinate substituted ligands. In addition, the solid-state structure of EuDOTAGly₄ (**Eu4**) was determined by X-ray diffraction and a brief analysis is presented compared to known Ln³⁺ structures found within literature. The **Eu4** complex crystallizes in a rare polymer type arrangement via bridging side-arms between adjacent complexes.

Keywords

Imaging agents; DOTA; Europium; Cyclic voltammetry; Ligand effects

Introduction

Magnetic resonance imaging (MRI) is a non-invasive diagnostic tool that can be used to monitor physiological changes.^[1,2] A three-dimensional signal intensity map of the proton signals from water molecules in a given voxel produces an image in the MRI. The contrast is

achieved by the difference in both the longitudinal and transverse relaxation rates of the protons. Lanthanide complexes capable of producing a metal–water interaction can be administered to achieve contrast enhancement. The transfer of the longitudinal relaxation effect of the lanthanide ion through the exchange process of the metal bound water with the bulk water in vivo gives rise to enhanced T_1 weighted contrast.^[3] The majority of contrast agents for T_1 weighted imaging in MRI incorporate the paramagnetic Gd^{3+} ion, with an electronic configuration of $S = 7/2$. The ligand that chelates the metal ion plays a strong role in modulating the interaction of water with the paramagnetic metal ion but also reduces metal toxicity, thus making the complex relatively inert by the control of complex thermodynamic stability.^[3,4] Therefore, ligand design has been a significant area of interest in the field of MRI contrast.^[5–12]

A tetraaza tetraacetic macrocycle, more commonly referred to as DOTA (1,4,7,10-tetraazacyclododecane- N,N',N'',N''' -tetra-acetic acid) and denoted as **1** herein, was one of the earliest reported ligand systems investigated as a MRI agent.^[13,14] Desreux discussed two important advantages of this ligand-set as a result of the pendant arms: (1) selectivity of metal ions due to steric effects and (2) pH-sensitive complexation.^[13] In addition, it was reported that the ligand system complexed with Gd^{3+} resulted in a large stability constant ($\log K_{ML} = 28.2$ – 29.2) but was kinetically slow in terms of formation, a common theme observed for other metal ions with macrocyclic scaffolds.^[13,15,16] This eight-coordinate ligand would provide the ideal scaffold to stabilize Ln^{3+} ions allowing for the ninth coordination site to be occupied by water within the inner-sphere, contributing to the desired proton relaxivity as a result of proton exchange.^[10]

In addition to traditional T_1 -weighted imaging agents, CEST (Chemical Exchange Saturation Transfer) imaging has been investigated as a technique to provide chemical structures that can be modulated by the environment to provide a chemical response suitable for MRI measurements.^[17] The signal alteration is achieved by a process of decreasing the overall signal intensity by transferring the magnetization saturation from one proton pool to another by means of chemical exchange, particularly from the metal bound water protons to the bulk water.^[4] This technique takes advantage of the residence lifetime of exchangeable protons in response to the radiofrequency correlating to the Larmor frequency of the paramagnetically shifted water signal.^[4,17,18] Recently, europium containing complexes have been investigated as T_1 and/or PARACEST (PARA = paramagnetic) agents.^[4,19–22] The Eu^{2+} ion, isoelectronic to the Gd^{3+} ion, provides an alternative for T_1 imaging; however, the redox stability of the Eu^{2+} ion is highly dependent on the ligand scaffold.^[23] Additionally, the Eu^{3+} ion is thermodynamically stable and, when combined with appropriate water exchange kinetics, typical DOTAglycinate-derivatives^[11,21,22] can be used as PARACEST agents.^[4] The development of an agent that can access both Eu^{2+} or Eu^{3+} within biological conditions is key to achieve the dual modality, but is only possible if the ligand scaffold can provide the appropriate thermodynamic and kinetic stability for both the oxidation states.^[21,22]

As previously mentioned, ligands based on **1** have been widely used for MRI contrast agents due to increased stability and slow metal-ligand dissociation.^[6] Specifically, a derivative of DOTAGly4 [acetic acid(glycine) amide], herein referred to as **4**, has been investigated as the

scaffold for multiple PARACEST agents due to the availability of a necessary water exchange kinetics upon metalation with a lanthanide ion, specifically Eu^{3+} .^[24,25] We initially set-out to analyze the impact of glycine substitution of **1** on the metal center of the europium complexes of **Eu1**, EuDO3A1Gly (**Eu2**), EuDO2A2Gly (**Eu3**), and EuDOTAGly4 (**Eu4**) (Figure 1) under typical electrochemical parameters (1 mM analyte, 1 M KCl, glassy carbon working electrode). However, results from electrochemical analysis indicate that the glycinated ligand, DOTAGly4 (**4**), is non-innocent in nature under the experimental conditions used. We were able to modify the experimental setup to circumvent this reactivity and focus on the $\text{Eu}^{2+/3+}$ alone; the results of that work are described in a separate report which correlates the basicity of the ligand environment to the metal redox chemistry.^[23] In addition and described herein, the redox activity of the ligands and europium complexes is highly dependent on exposure time with the electrode and solution pH. Synthetic preparative methods and salt content are also contributors to redox activity but will not be the focus of this discussion, but are noted in depth by others for europium salts.^[26,27] Herein, the role of the glycinate pendant arm in the electrochemical behavior of the ligand and europium mixed ligand complexes with a glassy carbon electrode will be described. In addition and a compliment to the study of Eu^{3+} complexes, the solid-state structure of **Eu4** determined by X-ray diffraction will also be presented and compared to other relevant lanthanide-DOTA complexes.

Results and Discussion

Electrochemical Analysis

In many metal complexes, the ligand–metal interaction stabilizes and tunes the redox potential of the metal ion. However, some ligands themselves are redox active or interact with the electrode surface.^[28–31] While studying the redox activity of DOTA and the DOTAglycinate congeners using cyclic voltammetry methods, it was observed that the glycinate ligand of cyclen was non-innocent in nature under the experimental conditions described herein. The individual cyclic voltammograms from these experiments are detailed in Figures S1–S53. The following discussion will focus on the methods and analysis used to understand this behavior by comparing the ligand and Eu^{3+} complex sets outlined in Figure 1.

The redox behavior of **Eu4** was explored at pH values of 3.5, 4.0, and 7.0 due to the known pH sensitivity of the ligand backbone.^[19,32,33] A three electrode setup was used and consisted of a glassy carbon working electrode, Ag/AgCl reference electrode, and platinum wire auxiliary electrode in KCl (aq) solution. Under these conditions and at a pH of 3.5, one reduction event is observed at -1188 mV (vs. Ag/AgCl, 100 mV/s) upon addition of the working electrode to a nitrogen purged solution of **Eu4** (1 mM) and KCl (1 M) (0 min). The scan window of 0.0 to -1.5 V was based on the solvent window of the experimental conditions. When the electrode setup remains in contact with the analyte solution and under a nitrogen purge, changes to the cyclic voltammograms over time are observed (Figure 2).

Two consecutive reductions are measured at -845 mV and -1038 mV (vs. Ag/AgCl, 100 mV/s, 20 min). The corresponding data is outlined in Table 1. An increase in scan rate results in a shift of the observed reduction events to more negative potentials with the

resolution of each reduction wave becoming less defined with increasing time (for pH 3.5: Figure S16). This behavior is congruent with a slow electron transfer process associated with reducing the europium metal center from the +3 to +2 oxidation state. The two reduction events observed suggest two independent species; most likely due to destabilization of the metal ion from the complex itself as a result of acidic pH. This theory is supported by the pK values known for the ligand, **4**.^[24] At a pH of 4.0, only a single reduction is measured for the **Eu4** complex at -729 mV (vs. Ag/AgCl, 100 mV/s), which shifts to more negative values over time (20 min, -1062 mV vs. Ag/AgCl, 100 mV/s, Figure S20). The presence of an oxidation event begins to appear at -833 mV (vs. Ag/AgCl) after 15 minutes of the electrode setup being in contact with the analyte solution. Finally, at a pH of 7.0, both a reduction (-1014 mV vs. Ag/AgCl, 20 min, 100 mV/s) and oxidation wave (-931 mV vs. Ag/AgCl, 20 min, 100 mV/s) are observed for the **Eu4** complex (Figure S24). The E of the coupled potentials decreases by 62 mV (Table 2) after 20 minutes. A comparison of the changes in redox potential measured for **Eu4** over the 20-minute window of interrogation at pH values of both 3.5 and 7.0 is shown in Figure 4A. The shift in the position of the redox events indicates that the changes in potential are more drastic at more acidic pH values. A plot of the square root of the scan rate ($v^{1/2}$) vs. the reduction current (I_{pc}) (Figure S28) did support a diffusion-controlled process at a pH of 7.0. However, the overall depletion of the current overtime (before polishing the electrode) suggested that the complex was interacting with the electrode surface as the electrode remained in solution between scans over the course of the 20-minute period.

To further investigate the hypothesis that the **Eu4** complex formed an interaction with the electrode surface, cyclic voltammetry experiments at pH values of 3.5, 4.0, and 7.0 were carried out using **4** with no metal ion present (Figure 3). At a pH of 3.5, a reduction event was observed at -1304 mV (vs. Ag/AgCl, 100 mV/s). Overtime, the reduction shifted to a more positive potential, -1023 mV (vs. Ag/AgCl, 100 mV/s, Figure S3). The position of this redox activity paralleled the second, more negative, reduction event observed for the **Eu4** complex at pH 3.5. The corresponding current decreased over the 20-minute period presumably due to the ligand interacting with the electrode based on the results described above (Figure 4B, Table 2). This was confirmed by polishing the electrode after the 20-minute increment, resulting in reconstitution of the original signal first observed at minute 0. This behavior was also observed at a pH of 4.0. However, the reduction only occurred during the initial sweep and was no longer present in the consecutive sweeps that occurred within a multi-scan sequence (Figure S8, Figure S10). A reduction event at more positive potential (-1363 to -947 mV vs. Ag/AgCl, 100 mV/s) was repeatedly obtained upon stirring the solution under nitrogen between multi-scan experiments carried out over a 20-minute time interval. A plot of the shifts in potential over time showed a drastic shift (> 250 mV) to more positive potentials, which plateaued after approximately 10 minutes (Figure 4B). At a pH of 7.0, no reduction or oxidative activity was observed. Altogether, these experiments show that **4** is redox active, or non-innocent in nature, and that the ligand interacts with the glassy carbon electrode surface.

To understand the unexpected redox behavior observed with **4**, cyclic voltammetry experiments were completed using DOTA, which contain acetate arms in place of glycinate.

The results of these studies showed no redox behavior at pH 7.0 (Figure S1). These results indicate that the activity observed with **4** is not due to the macrocyclic backbone but the presence of the glycine pendant arms.

The redox activity observed with **4** shows that the activity of **Eu4** is not simply a result of the $\text{Eu}^{3+/2+}$ couple at pH 3.5 and 4. As an additional comparison, cyclic voltammetry experiments were carried out for the Eu^{3+} complexes containing mixed pendant arms with different degrees of glycine and acetate substitution. Specifically, the complexes investigated were **Eu2** and **Eu3** for comparison to **4** (Figure S53) as well as **1**, which has been previously reported in the literature.^[23,34]

Ligand **2** is the mono-substituted derivative of **1**, while **3** is the di-substituted glycine congener (Figure 1). The cyclic voltammetry measurements of **Eu2** and **Eu3** carried out at pH 3.5 and 4.0 show a reduction whose position is pH and time dependent (due to analyte interaction with electrode surface), similar to that of **Eu4** described above. For all complexes, shifts in potential were observed as well as an increase in the current output over the 20-minute time interval of the experiment. This is consistent with the glycine arms of the ligand complex interacting with the electrode surface, thus resulting in an increase in current output associated with the close proximity of the europium center to the electrode surface. For comparison, cyclic voltammetry on the glycinate-free **Eu1** complex has been studied and reported in the literature; the $E_{1/2}$ value of the $\text{Eu}^{3+/2+}$ couple was reported at -1135 mV (vs. Ag/AgCl).^[34] The chelation of the europium metal by **1** stabilizes the europium redox activity based on the comparison to the EuCl_3 metal salt. Under our experimental conditions, EuCl_3 was found to have an $E_{1/2}$ value of -624 mV (vs. Ag/AgCl, 100 mV/s, Table S1), which is comparable to that reported in literature (-585 mV vs. Ag/AgCl).^[34]

As shown in Figure 5, the addition of four glycinate pendant arms results in a shift to more positive potentials as well as an increase in current output that equilibrates after 5 min. Moreover, the time at which the shifts in potential occur increase with increasing number of glycinate arms. This trend is observed for **Eu2** and **Eu3**; however, the degree to which the shifts occur are much smaller but consistent with the decreasing number of glycine pendant arms present. Additionally, as a heterogeneous system, the analyte is dependent on diffusion to reach the electrode surface. Although analysis of the cyclic voltammograms of each complex at different scan rates was not consistent with a diffusion-controlled process with the exception of **Eu4**, current output and shifts in potential correlate to the compound moving towards the electrode surface and interacting slowly over time.

Crystallographic Analysis of Eu4

Lanthanide-based complexes can be more challenging to obtain materials suitable for solid-state determination of the structure. However, crystalline material suitable for X-ray diffraction analysis were obtained by slow evaporation of an aqueous solution of **Eu4** at room temperature. Analysis of the sample resulted in the structure shown in Figure 6.

The asymmetric unit of **Eu4** shows the expected eight-coordinate ligand system with four N atoms from the cyclen ring bound and four O-atoms from the amide bond interacting with the Eu^{3+} ion. The ninth coordination site of lanthanide complexes is typically occupied by

inner-coordination sphere water.^[3,10,18,34] However, upon symmetry generation, the ninth coordination site of **Eu4** is occupied by a neighboring O-atom from the carboxylic acid group on one of the pendant arms (Figure 7). This packing arrangement is indeed unusual but not unprecedented and was proposed by Tóth and co-workers for a $\text{Eu}^{2+}(\text{ODDA})$ complex in addition to a similar arrangement being observed for $\text{Sr}(\text{ODDA})$.^[9,10,34]

With the addition of the glycinate pendant arms, the bond lengths observed between the O-atoms and the Eu metal center have decreased in comparison with a typical DOTA (**1**) scaffold. For europium-DOTA complexes reported previously, the $\text{Eu-O}_{\text{carboxylate}}$ bond length was larger, 2.58–2.62 Å.^[34,35] However, we observe $\text{Eu-O}_{\text{carboxylate}}$ bond lengths to be closer to 2.380 Å which is comparable to lengths obtained for GdDOTA species^[36,37] (2.366 Å) as well as an $\text{Yb}(\text{DOTA} \text{tetraacetoamide})$ complex^[38] (2.301 Å) and EuDOTAGlyOEt_4 (2.380 Å).^[39] This decrease in bond length is most likely a result of increased flexibility within the pendant arms. The mean Eu–N bond lengths measured (2.682 Å) are consistent with other lanthanide based DOTA complexes (Table 3).

Additionally, the crystal structure of the **Eu4** complex adopts a square antiprism (SAP) geometry, which is consistent with ^1H NMR characterization of the complex. The angles observed in this complex (Table S14) are comparable to angles for GdDOTA and EuDOTA previously published that also adopt a SAP geometry.^[37] In addition, the N4/O4 twist angle was measured to be 38.2° which is consistent with the 39° twist angle that defines the SAP geometry.^[4] The SAP geometry is reported to provide slower water exchange rates that are ideal for PARACEST imaging methods.^[39,40] The independent planes formed by the N-atoms of the cyclen ring and the coordinating O-atoms of the ligand arms are co-planar and separated by 2.320 Å, which is also consistent with other SAP structures in the literature.^[39,40] The europium ion contained within **Eu4** is only 0.667 Å from the O4 plane (Figure 8). This distance is slightly shorter than that reported (0.778 Å) for the EuDOTAGlyOEt_4 congener.^[39] The result of the short distance between the europium ion and the O4 plane is a slightly lengthened distance (1.653 Å) between the europium and the N4 cyclen plane.

Conclusions

Europium is an important lanthanide alternative to gadolinium to investigate for diagnostic imaging, specifically as a T_1 -weighted agent and PARACEST agent. Despite the characterization of the complexes to date, an intensive electrochemical analysis focusing on the ligand environment by cyclic voltammetry had not been completed. **Eu1**, **Eu2**, **Eu3**, and **Eu4** were investigated to look at the effects of the addition of a glycine to the pendant arms. Most importantly, **4** was shown to be non-innocent in nature. The position of the redox activity associated with the glycinated-ligands and the corresponding complexes was both pH sensitive as well as time dependent. The shifts observed in the potential and current were also dependent on the number of glycinated pendant arms within the scaffold **1** present in the europium complexes. In addition, a solid-state structure was obtained showing a unique solid-state polymerization. The site traditionally occupied by water for diagnostic purposes was occupied instead by an O-atom of a neighboring complex within the crystal lattice. Bond lengths observed are within the typical limits of europium complexes. However, large overlaps are observed for bond lengths associated with GdDOTA and EuDOTAGlyOEt_4 .

The results obtained through electrochemistry and crystallography show how the ligand environment imparts changes to the Eu^{3+} ion.

Experimental Section

Synthesis: Complexes were synthesized according to methods previously reported in literature^[11,13,23] with the exception of **Eu4**, which was purchased from Macrocyclics.

Cyclic Voltammetry

Cyclic voltammograms were obtained in a nitrogen atmosphere at 22 °C using a BASi EC Epsilon potentiostat equipped with a 3.0 mm glassy carbon working electrode (BASi MF-2012), a platinum wire auxiliary electrode (BASi MF-2013), and quasi silver/silver chloride reference electrode (BASi, MF-2052). Diamond polish purchased from BASi was used to polish the electrode surface (BASi MF-2051, MF-2059, MF-2054). Measurements were performed in water (molecular reagent grade purchased from Sigma) solution with 1 M KCl as supporting electrolyte. The pH of solutions was adjusted using 0.1 M NaOH or 0.1 M HCl. All electrochemical experiments for each compound were completed using the same experimental parameters described below.

A stock solution of water was adjusted to pH 7.0 and served as the solvent for all cyclic voltammetry experiments. Approximately 10 mL of the pH adjusted water was added to the electrochemical cell with 1 M KCl and allowed to stir and purge under nitrogen for at least 30 min. The three electrodes were properly placed within the cell before completing the background scan. The background scan was completed using a scan window from 0 to –1500, scanning at a rate of 100 mV/s, completing three sweeps within this window. The working electrode was removed from the cell, polished, and placed aside while 1 mM (final concentration) of the compound of interest was added and stirred in solution. The solution remained under a nitrogen purge. The working electrode was not placed immediately back into the electrochemical cell and only added back to the cell immediately before the next experimental scan ($t = 0$ min). The scan window remained from 0 to –1500 mV, scanned at a rate of 500 mV/s, completing three sweeps within this scan window. Upon experiment completion, the working electrode remained in solution and the previous parameters were completed every 5 min for 20 min. At the end of this 20-minute window, the working electrode was polished once again and placed back into solution immediately before starting the next set of scans. The next set of scans were completed within the scan window of 0 to –1500 mV, scanned at a rate of 100 mV/s, completing three sweeps within this scan window. Again, the working electrode was left in solution and these parameters were repeated every 5 min for 20 min. The working electrode was removed once more, polished, and set aside while the parameters for the next scan rate were adjusted. The electrode was placed into the cell immediately before the next experiments were completed. The scan window was 0 to –1500 mV, scanned at a rate of 500 mV/s, completing 10 sweeps. The electrode remained in solution and these scan parameters were completed every 5 min for 20 min. Upon completion, the working electrode was removed, polished, and set aside. The electrode would not be placed in solution until immediately before the next scan set. The scan window

was once again 0 to –1500 mV, scanned at 100 mV/s, completing 10 sweeps within this window. These parameters were completed every 5 min for 20 min.

X-ray Data Collection and Structure Solutions

The single crystals of **Eu4** were grown from aqueous solution by slow evaporation at room temperature. A single crystal of **Eu4**, from available crystals, was mounted on the goniometer using Paratone-N oil (cryoprotectant) on the tip of MiTeGen MicroLoops LD™, 45 mm away from the detector and was cooled to a temperature of 100(1) K under the flow of liquid nitrogen using Oxford Cryo-system.^[41] X-ray intensity data were collected with a Bruker D8 Quest diffractometer equipped with a Photon 100 CMOS detector and generator operating at 50 kV and 30 A. The indexing of Bragg intensities was carried out with APEX2 package.^[42] Data reduction and absorption corrections were performed with the SAINT^[43] and SADABS^[44] software packages, respectively. Structures were solved by the direct method using the SHELXL-97 software and refined using SHELXL in the WinGX package. OLEX2 software was used to prepare material and graphics for publication.^[45]

CCDC 1563863 (for **Eu4**) contains the supplementary crystallo-graphic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful for generous financial support from the TCU Andrews Institute of Mathematics & Science Education, the TCU Research and Creativity Activity Grant, the TCU Invests in Scholarship, and the INFOR Moncrief Foundation Support. We would also like to thank Bruce Noll for his expertise with crystal structure refinement related to **Eu4**. The UTSW AIRC is grateful for funding from the NIH (R01-CA115531 and P41-EB015908).

References

- [1]. Caki N, Gündüz S, Rengarasu R, Angelovski G, Tetrahedron Lett 2015, 56, 759–765.
- [2]. Scherzinger AL, Hendee WR, Western J Med 1985, 143, 782–792.
- [3]. Caravan P, Ellison JJ, McMurry TJ, Lauffer RB, Chem. Rev 1999, 99, 2293–2352. [PubMed: 11749483]
- [4]. Viswanathan S, Kovacs Z, Green KN, Ratnakar SJ, Sherry AD, Chem. Rev 2010, 110, 2960–3018. [PubMed: 20397688]
- [5]. Tircsó G, Regueiro-Figueroa M, Nagy V, Garda Z, Garai T, Kalman FK, Esteban-Gomez D, Toth E, Platas-Iglesias C, Chem. Eur. J 2016, 22, 896–901. [PubMed: 26583317]
- [6]. Sherry AD, Caravan P, Lenkinski RE, J. Magn. Reson. Imaging 2009, 30, 1240–1248. [PubMed: 19938036]
- [7]. Sink RM, Buster DC, Sherry AD, Inorg. Chem 1990, 29, 3645–3649.
- [8]. Gupta RJ, Gupta P, J. Magn. Reson 1982, 47, 344–350.
- [9]. Burai L, Tóth E, Seibig S, Scopelliti R, Merbach AE, Chem. Eur. J 2000, 6, 3761–3770. [PubMed: 11073247]
- [10]. Tóth E, Burai L, Merbach AE, Coord. Chem. Rev 2001, 216–217, 363–382.

- [11]. Green KN, Viswanathan S, Rojas-Quijano FA, Kovacs Z, Sherry AD, *Inorg. Chem* 2011, 50, 1648–1655. [PubMed: 21306137]
- [12]. Ratnakar SJ, Woods M, Lubag AJM, Kovács Z, Sherry AD, *J. Am. Chem. Soc* 2008, 130, 6–7. [PubMed: 18067296]
- [13]. Desreux JF, *Inorg. Chem* 1980, 19, 1319–1324.
- [14]. Stetter H, Frank W, *Angew. Chem. Int. Ed. Engl* 1976, 15, 686; *Angew. Chem.* 1976, 88, 760.
- [15]. Kasprzyk SP, Wilkins RG, *Inorg. Chem* 1982, 21, 3349–3352.
- [16]. Loncin MF, Desreux JF, Merciny E, *Inorg. Chem* 1986, 25, 2646–2648.
- [17]. Sherry AD, Woods M, *Annu. Rev. Biomed. Eng* 2008, 10, 391–411. [PubMed: 18647117]
- [18]. Zhang S, Merritt M, Woessner DE, Lenkinski RE, Sherry AD, *Acc. Chem. Res* 2003, 36, 783–790. [PubMed: 14567712]
- [19]. Ratnakar SJ, Viswanathan S, Kovacs Z, Jindal AK, Green KN, Sherry AD, *J. Am. Chem. Soc* 2012, 134, 5798–5800. [PubMed: 22420507]
- [20]. Han G, Deng Y, Sun J, Ling J, Shen Z, *Exp. Ther. Med* 2015, 9, 1561–1566. [PubMed: 26136858]
- [21]. Funk AM, Clavijo Jordan V, Sherry AD, Ratnakar SJ, Kovacs Z, *Angew. Chem. Int. Ed* 2016, 55, 5024–5027; *Angew. Chem.* 2016, 128, 5108.
- [22]. Ekanger LA, Mills DR, Ali MM, Polin LA, Shen Y, Haacke EM, Allen MJ, *Inorg. Chem* 2016, 55, 9981–9988. [PubMed: 27244124]
- [23]. Burnett ME, Ratnakar JS, Adebesein B, Funk AM, Kovács Z, Sherry AD, Ekanger LA, Allen MJ, Green KN, *Eur. J. Inorg. Chem* 2017, 5001–5005. [PubMed: 29403330]
- [24]. Pasha A, Tircsó G, Benyó ET, Brücher E, Sherry AD, *Eur. J. Inorg. Chem* 2007, 4340–4349. [PubMed: 19802361]
- [25]. Stasiuk GJ, Long NJ, *Chem. Commun* 2013, 49, 2732–2746.
- [26]. Morss LR, Haug HO, *J. Chem. Thermodyn* 1973, 5, 513–524.
- [27]. Zeli M, *Croat. Chem. Acta* 2003, 76, 241–248.
- [28]. Berben LA, de Bruin B, Heyduk AF, *Chem. Commun* 2015, 51, 1553–1554.
- [29]. van der Meer M, Rechkemmer Y, Peremykin I, Hohloch S, van Slageren J, Sarkar B, *Chem. Commun* 2014, 50, 11104–11106.
- [30]. Lewis RA, MacLeod KC, Mercado BQ, Holland PL, *Chem. Commun* 2014, 50, 11114–11117.
- [31]. Marangoni DG, Smith RS, Roscoe SG, *Can. J. Chem* 1989, 67, 921–926.
- [32]. Sheth VR, Liu G, Li Y, Pagel MD, *Contrast Media Mol. Imaging* 2012, 7, 26–34. [PubMed: 22344877]
- [33]. Zhang S, Wu K, Sherry AD, *Angew. Chem. Int. Ed* 1999, 38, 3192–3194; *Angew. Chem.* 1999, 111, 3382.
- [34]. Burai L, Tóth E, Moreau G, Sour A, Scopelliti R, Merback AE, *Chem. Eur. J* 2003, 9, 1394–1404. [PubMed: 12645029]
- [35]. Spirlet M, Rebizant J, Desreux JF, Loncin MF, *Inorg. Chem* 1984, 23, 359–363.
- [36]. Dubost JP, Leger JM, Langlois MH, Meyer D, Schaefer M, C. R. l' Academie Sci., Ser. II 1991, 312, 349–354.
- [37]. Chang CA, Francesconi LC, Malley MF, Kumar K, Gougoutas JZ, Tweedle MF, *Inorg. Chem* 1993, 32, 3501–3508.
- [38]. Zhang S, Michaudet L, Burgess S, Sherry AD, *Angew. Chem. Int. Ed* 2002, 41, 1919–1921; *Angew. Chem.* 2002, 114, 1999.
- [39]. Zhang S, Wu K, Biewer MC, Sherry AD, *Inorg. Chem* 2001, 40, 4284–4290. [PubMed: 11487334]
- [40]. Aime S, Barge A, Bruce JI, Botta M, Howard JAK, Moloney JM, Parker D, de Sousa AS, Woods M, *J. Am. Chem. Soc* 1999, 121, 5762–5771.
- [41]. Cosier J, Glazer AM, *J. Appl. Crystallogr* 1986, 19, 105–107.
- [42]. APEX3, 2016.9–0 ed, Bruker-AXS, Madison, Wisconsin, USA, 2016.
- [43]. SAINT, Siemens Analytical X-ray Instrument Inc., Madison, Wisconsin, USA, 1996.

- [44]. SADABS Correction, Siemens Industrial Automation, Inc, Madison, Wisconsin, USA, 1996.
- [45]. Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JAK, Puschmann H.J. Appl. Crystallogr 2009, 42, 339–341.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.
Ligand set and the corresponding europium containing complexes.

Figure 2.

Cyclic voltammogram overlay of **Eu4** measured over the course of 20 min at a pH 3.5 (1 M KCl in water, 100 mV/s).

Figure 3.

Cyclic voltammogram of **4** comparing data scanned at 100 mV/s after 20 min completed at pH values of 3.5, 4.0, and 7.0.

Figure 4.

A. Plot of the shifts in potential over time for **Eu4** at pH values 3.5 and 7.0. **B.** Plot of the shifts in potential over time for **4** at pH 3.5 and 4.0. At pH 4.0, reductions were only observed on initial sweeps.

Figure 5.

A. Comparison of glycine-containing complexes (**Eu2**, **Eu3**, **Eu4**) and how the potential [mV] shifts over time [min] at pH 3.5 scanning at a rate of 100 mV/s. **B.** Comparison of glycine-containing complexes (**Eu2**, **Eu3**, **Eu4**) and how the current output [μ A] shifts over time (min) at pH 3.5 scanning at a rate of 100 mV/s.

Eur J Inorg Chem. Author manuscript; available in PMC 2019 April 17.

Figure 7.
Symmetry generation of **Eu4** with the ninth coordination site occupied by neighboring O-atom.

Figure 8.

A. Parameters of interest for **Eu4** related to the Eu^{3+} coordination sphere. **B.** **Eu4** structure oriented to visualize the N4/O4 twist angle of 38.2°.

Table 1.

Electrochemical data for **Eu4** measured over 20 min at a pH 3.5 (1 M KCl in water, 100 mV/s).

100 mV/s	0 min	5 min	10 min	15 min	20 min
E_{pc} (mV)	-1188	-893	-868	-820	-845
			-1047	-1040	-1038
I_{pc} (μA)	3.4028	12.1523	12.8539	11.7464	12.4849
			–	4.2664	3.3234

Table 2.

Electrochemical data measured for **4** at a pH 3.5 and 4.0 (1 M KCl in water, 100 mV/s). (* At pH 4.0, reduction only visualized on the initial sweep).

Time (min)	0	5	10	15	20
pH 3.5					
E_{pc} (mV)	−1304	−1080	−1050	−1035	−1023
I_{pc} (μA)	11.2276	10.8888	10.2419	8.6275	7.3335
pH 4.0 ^[a]					
E_{pc} (mV)	−1363	−955	−956	−951	−947
I_{pc} (μA)	0.2594	6.1707	8.6732	8.1849	8.8716

^[a] At pH 4.0, reductions were only observed on initial sweeps.

Table 3.Comparison of the *mean* bond lengths measured for DOTA derivatives and **Eu4**.

Complex	M–O _{carboxylate}	M–N	M–O _{water}	Ref.
[GdDOTA·H ₂ O] ^[a]	2.366	2.663	2.458	[36,37]
[EuDOTA·H ₂ O] ^[a]	2.379	2.709	2.480	[35]
[YbDOTA tetraacetoamide·H ₂ O] ^{3+,[a]}	2.301	2.608	2.335	[38]
[Eu4] ^{3,[a]}	2.380	2.682	2.365 ^[b]	this work
[EuDOTAGlyOEt ₄] ^{3+,[a]}	2.335	2.627	2.414	[39]

^[a] Square antiprism geometry.^[b] M–O_{water} coordination actually occupied by the O atom from carboxylic acid of the neighboring complex.