

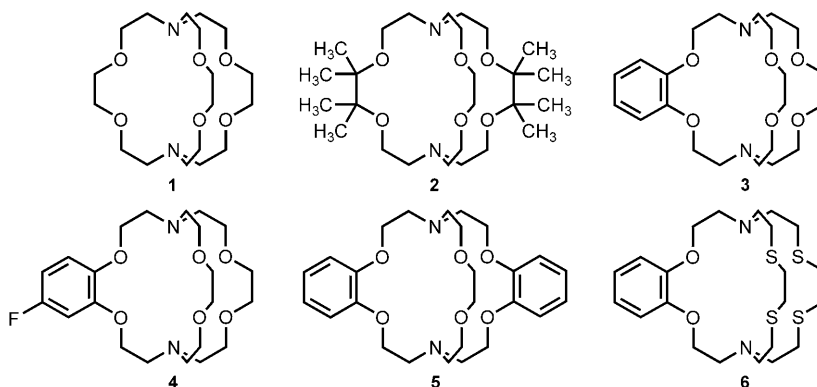
Oxidatively Stable, Aqueous Europium(II) Complexes through Steric and Electronic Manipulation of Cryptand Coordination Chemistry**

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The magnetic and optical properties of the divalent state of europium make this ion extremely attractive for use in materials,^[1] catalysis,^[2] luminescence,^[3] magnetic,^[4] and diagnostic-medical^[5] applications. A major hindrance to the use of Eu^{II} in many of these applications is the extreme propensity of the ion to oxidize to Eu^{III} , especially in aqueous solution. Research efforts aimed at increasing the stability of aqueous Eu^{II} have yielded little success:^[6,7] even the most stable aqueous Eu^{II} complex reported (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane europium(II), **1**-Eu) is not stable enough in aqueous solution for practical use.^[8,9] Our research group has generated Eu^{II} complexes in aqueous solution, and here we report the most oxidatively-stable aqueous Eu^{II} complexes known.

Our strategy for favoring Eu^{II} over Eu^{III} in aqueous solution involves the synthesis and use of ligands that would preferentially coordinate to large, soft, electron-rich metals like Eu^{II} . The template for our ligand design was cryptand **1** because **1**-Eu is the most oxidatively-stable, aqueous Eu^{II} complex previously reported.^[8] The stability of **1**-Eu is partially due to the better size match of the cavity of cryptand **1** (1.4 Å) to the Eu^{II} ion (1.25 Å) relative to the Eu^{III} ion (1.07 Å).^[10] We hypothesized that further oxidative stabilization could be achieved by modifying the structure of cryptand **1** using four principles of coordination chemistry to stabilize electron-rich metals.^[6,11] Specifically, our goals were 1) to increase the steric bulk surrounding cryptand **1** to minimize interactions between Eu^{II} and its environment; 2) to reduce the Lewis basicity of cryptand **1** to favor the electron-rich Eu^{II} over Eu^{III} ; 3) to change the cavity size of the cryptand to match the size of the Eu^{II} ion preferentially; and 4) to modify the hard-soft, acid-base (HSAB) properties of

cryptand **1** to coordinate Eu^{II} over Eu^{III} . To implement these strategies, we studied cryptands **1–6** (Scheme 1).



Scheme 1. Ligands used to observe trends in oxidative stability of aqueous Eu^{II} .

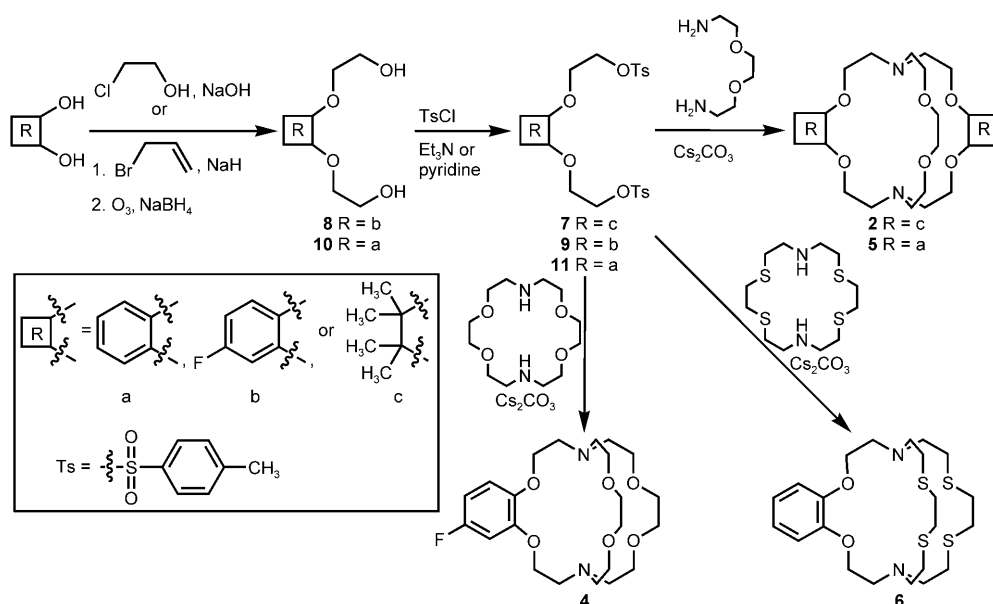
To increase the steric bulk of **1**, methyl groups were added to the ethylene carbon atoms between the oxygen atoms resulting in ligand **2**. This methyl substitution pattern was chosen because metal–environment interactions occur between the unmodified ethylene groups.^[8] Furthermore, to examine the influence of Lewis basicity on oxidative stability, phenyl rings were introduced to decrease the electron-donating ability of the adjacent oxygen atoms of ligands **3–5** by a resonance withdrawing effect.^[12] The extent of electron withdrawal was modulated by varying the electron density of the phenyl ring through the addition of a fluorine atom (**4**) or by increasing the number of rings (**5**). Phenyl-ring-containing cryptands **3–5** also have an influence on cavity size because each phenyl ring decreases the cavity size of the cryptand. We expected the seemingly minor influence of the phenyl rings on cavity size to have a noticeable effect on the oxidative stability of Eu^{II} because of selectivity studies with Group 2 cations using cryptands **1**, **3**, and **5**.^[13] Finally, relatively soft sulfur-atom donors were introduced in cryptand **6** in place of oxygen-atom donors to explore the HSAB preferences for the softer Eu^{II} ion relative to the harder Eu^{III} ion.

To synthesize the diverse set of cryptands **1–6**, a three-step procedure was devised that involved common intermediates **7**, **9**, and **11** (Scheme 2).^[14] Briefly, the synthesis involved the conversion of the appropriate ethylenediols or catechols into the corresponding ditosylates (**7**, **9**, and **11**) and subsequent ring closure with 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, 2,2'-(ethylenedioxy)bis(ethylamine), or 1,4,10,13-tetra-

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Scheme 2. Synthetic route to cryptands **2** and **4–6** using common intermediates **7**, **9**, and **11**.

thia-7,16-diazacyclooctadecane. Metal complexation was achieved in situ by mixing $\text{Eu}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ and the desired cryptand (**1–6**) in aqueous solution under an Ar atmosphere. The resulting solution was placed in a standard three-electrode cell (glassy-carbon working electrode, platinum-wire auxiliary electrode, and Ag/AgCl (1.0 M KCl) reference electrode). The potential at the carbon electrode was held at -0.8 V (vs. Ag/AgCl) while stirring to produce Eu^{II} in situ for metalation.^[7] After metalation, cyclic voltammograms were obtained for each complex in solution with ferrocene as an internal standard.^[9,15] A new anodic peak was observed for each complex at a more positive potential than the peak corresponding to oxidation of the aqueous Eu^{II} (Table 1). These data indicate that each cryptand imparted additional stability to Eu^{II} as hypothesized.

Table 1: Anodic peak potentials (E_{pa}) with respect to ferrocene/ferrocenium (Fc/Fc^+).

Sample	E_{pa} (V vs. Fc/Fc^+) ^[a]	Sample	E_{pa} (V vs. Fc/Fc^+) ^[a]
1 $\text{Eu}(\text{NO}_3)_3$	-0.701 ± 0.030	5 2-Eu	-0.169 ± 0.006
2 1-Eu	-0.336 ± 0.016	6 4-Eu	-0.079 ± 0.007
3 5-Eu	-0.211 ± 0.004	7 hemoglobin	-0.070 ± 0.003
4 3-Eu	-0.208 ± 0.009	8 6-Eu	-0.035 ± 0.010

[a] Potentials are listed as mean \pm standard error.

The cyclic voltammetric data of europium-containing solutions of **1** and **2** demonstrate that the increased steric bulk in cryptand **2** leads to increased oxidative stability over unmodified cryptand **1**. Furthermore, a more targeted examination of the influence of Lewis basicity on oxidative stability was achieved by examining the impact of ligands **3–5**. We observed that one phenyl ring on cryptand **3** was sufficient to stabilize Eu^{II} oxidatively by 128 mV with respect to the unmodified cryptand **1-Eu**. This stabilization is likely due to a combination of the decrease in Lewis basicity of the adjacent

oxygen atoms (better for electron-rich metals) and the reduction in cavity size caused by the phenyl ring (better match for the size of the Eu^{II} ion). However, the addition of a second phenyl ring (**5**) caused no difference in the anodic peak potential compared to the monophenyl cryptand **3** ($p = 0.76$). This effect is likely due to reduction of the cavity size counteracting the decreased basicity of the ligand, thus suggesting that a minimum cavity size for Eu^{II} stabilization was achieved with cryptand **3**. Further decrease in Lewis basicity through the addition of a fluorine substituent to the phenyl ring

(**4**) led to 129 mV greater stability than what was observed with unsubstituted monophenyl cryptand **3**. In addition, the oxidative stability of **4-Eu** is not different from that of Fe^{II} in hemoglobin ($p = 0.45$).

Finally, replacement of the harder oxygen atoms with softer sulfur atoms (**6**) produced the most dramatic stabilization effect of our cryptand series. This modification increased the oxidative stability of Eu^{II} by 173 mV compared to the structurally similar cryptand **3**. The cavity size of cryptand **6** increases slightly because of the increased bond length of C–S compared to C–O, thus suggesting that a decrease in stability should be observed based on the difference between cryptands **1** and **3**. However, the effect of cavity size is small relative to the influence of HSAB matching between Eu^{II} and sulfur. Cryptand **6** with Eu^{II} produces an oxidative potential that is 666 mV more positive than the aqueous Eu^{II} and 35 mV more positive than Fe^{II} in hemoglobin. To the best of our knowledge, this oxidative stability of Eu^{II} is the highest reported in aqueous solution and indicates the potential for the use of Eu^{II} in vivo.

We observed dramatic oxidative stabilization of Eu^{II} using modified cryptands. These trends in stability suggest that further stabilization of aqueous Eu^{II} and other lanthanide ions is possible. We are currently pursuing these avenues of research in addition to measuring the thermodynamic stability of the Eu^{II} complexes reported here. Finally, our most stable complex, with an oxidation potential indicative of biological oxidative stability, opens the door for the use of the magnetic and spectroscopic properties of Eu^{II} in vivo.

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