Biomimetic ligands: metal ion specificity and encapsulation

Kenneth N. Raymond* and Paul H. Smith

Department of Chemistry, University of California, Berkeley, CA 94720

Abstract – Ligands to complex Fe(III) and the related (but 8-coordinate) actinide(IV) ions have been developed using a biomimetic approach founded on the ligand structures of naturally occurring iron(III) sequestering agents called siderophores. The present study emphasizes the encapsulation aspects of such metal ion binding. A series of macrocyclic lanthanide amine complexes has been prepared by the addition of bis(dimethylamino)methane to one equivalent of lanthanide ion and two equivalents of triaminotriethylamine in acetonitrile. These compounds have been structurally characterized, and the electrochemical potential of a ytterbium complex in acetonitrile suggests a large stabilization of the +3 state. Two related lanthanide amine complexes have been prepared and structurally characterized and are evaluated as potential encapsulation precursors.

INTRODUCTION

Highly specific sequestering agents for iron(III) [siderophores] are produced by micro-organisms, and ligands to complex Fe(III) and the related (but 8-coordinate) actinide(IV) ions have been developed using a biomimetic approach founded on the ligand structures of these siderophores. While nature has no need to complex lanthanide(III) ions, there are several potential applications for the development of exchange inert complexes of these usually very labile ions, and thus the present study emphasizes the encapsulation aspects of such metal ion binding. Aside from its novelty, such a complex would be an interesting candidate for a Magnetic Resonance Imaging (MRI) agent and could have unusual electro-chemical properties. Since amines have three covalent bonds in addition to their lone-pair metal binding site, their topology is ideal for the synthesis of complex polycyclic ligands. The lanthanide complexes of the tetradentate amine, tren $[N(CH_2CH_2NH_2)_3]$, are well suited precursors for encapsulation reactions due to the proximity of the six coordinated primary amines.[1] We have recently reported the synthesis and structural characterization of the first such complexes.[2] This paper will describe the recent progress toward the goal of a kinetically inert, encapsulated lanthanide amine complex.

The synthesis by Sargeson and co-workers of cobalt cage complexes, the "sepulchrates," from $[Co(en)_3]Cl_3$, formaldehyde and ammonia[3] is a spectacular example of the template approach using a transition metal ion and suggests the use of formaldehyde as a general amine coupling reagent. Using a lanthanide ion as a template, one of several possible schemes would be to start with a lanthanide amine complex and couple the individual coordinated ligands to form a macrocyclic complex. Lanthanides have been shown to be effective template ions in the formation of macrocyclic Schiff's base complexes.[4,5] The use of formaldehyde itself in the cross linking of lanthanide amines is precluded by the production of water in the reaction. However the formaldehyde derivative bis(dimethylamino)methane, $CH_2[N(CH_3)_2]_2$, is equivalent and we have developed a procedure for bridging NH groups of coordinated lanthanide amines. The advantages of using this particular formaldehyde derivative as a coupling reagent are fourfold: 1) The reaction of this compound with an amine produces dimethyl amine which is volatile and eventually leaves the reaction mixture as a gas, thereby driving the reaction towards the desired product; 2) The reaction does not produce water, which in the presence of lanthanide amines reacts to form insoluble lanthanide hydroxides; 3) The reaction is reversible, which allows it to proceed to the thermodynamically stable product, thereby decreasing the number of possible isomers or alternative products; 4) The small bite angle of the $N-CH_2-N$ moiety favors high coordination numbers around the metal.

PREPARATION OF PARTIALLY ENCAPSULATED LANTHANIDE IONS[2]

Complexes of the composition $Ln(L)(trif)_3 \cdot CH_3CN$ [Ln = La, Yb; L = 1,9-bis(2-aminoethyl)1,4, 6,9,12,14-hexaazacyclohexadecane; trif = triflate = $CF_3SO_3^-$] have been prepared by the reaction of $Ln(trif)_3$ with two equivalents of tren in the presence of three equivalents of

the formaldehyde derivative, bis(dimethylamino)methane, thus producing the partially encapsulated lanthanide complexes in which four of the primary amines are attached with two methylene bridges. The lanthanum complex (78% yield) prepared by this procedure is ten-coordinate with eight nitrogens from the macrocycle and two oxygens from two triflate anions (Figure 1).
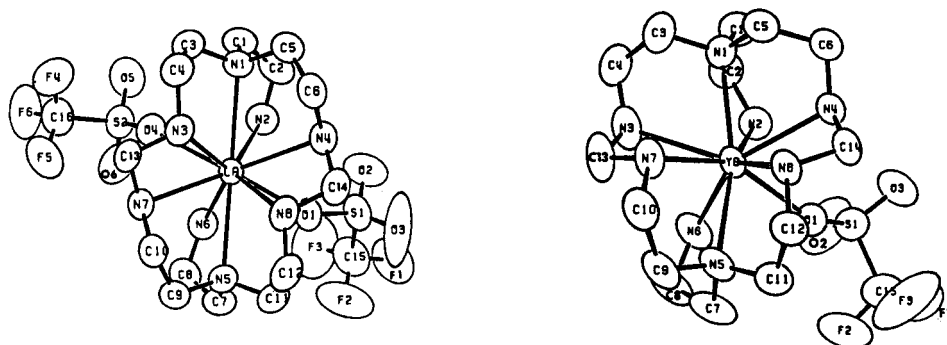

Figure 1. ORTEP drawings of [La(L)(trif)$_2$]$^+$ and [Yb(L)(trif)]$^{2+}$.

The complex has an approximate C$_2$ axis passing through the lanthanum ion and bisecting the O1-La-O4 angle. The average N-N distances for the ethylene and methylene bridged nitrogens are 2.92 and 2.36 Å, respectively. The closest non-bridged N-N distances are N2-N6 and N3-N8 at 3.29 and 3.27 Å, respectively. The analogous ytterbium complex (65% yield) is nine-coordinate with one triflate oxygen and eight nitrogens from the macrocycle (Figure 1). The average N-N distances for the ethylene- and methylene-bridged nitrogens are 2.85 and 2.35 Å, respectively. The closest non-bridged N-N distances are N2-N6 (3.051(4) Å) N3-N6 (3.085(6) Å) and N7-N8 (3.042(4) Å).

It is interesting to note the relative conformations of the hexaazamacrocycles in these two complexes. In the lanthanum species the macrocycle is somewhat "closed" in comparison to the "open" conformation of the macrocycle in the ytterbium species. This difference is illustrated by the difference in the N1-Ln-N5 angles of 162.4° and 148.8° for the La and Yb species, respectively. In the ytterbium species it appears that if the conformation of the macrocycle were to adopt the conformation seen in the lanthanum species, the formation of a third methylene bridge would be facilitated. This difference in macrocycle conformation may be due to the change in coordination number around the metal.

ELECTROCHEMISTRY OF THE PARTIALLY ENCAPSULATED YTTERBIUM ION

A normal pulse polarogram observed with 2mM Yb^{3+}(L) in acetonitrile solution (0.3 M sodium triflate) using a dropping mercury electrode (DME) as the working electrode is illustrated in Figure 2.
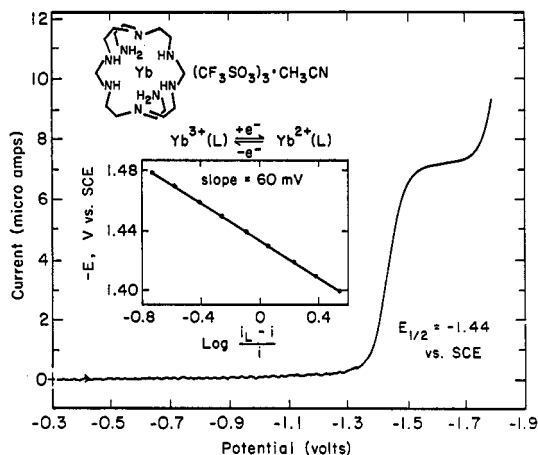

Figure 2. Normal pulse polarogram of Yb^{3+}(L) in 0.3 M sodium triflate acetonitrile solution. Negative potentials (V vs SCE) are plotted to the right and reduction currents are plotted upward. The inset shows a plot of -E vs log (i$_L$-i/i) for the normal pulse polarogram.

The log plot shown in the inset is linear with a slope of 60 mV, indicating that the electrode reaction is a Nernstian one-electron process. The half-wave potential is -1.44V vs SCE. This measured reduction potential is directly related to the stabilities, K_{III} and K_{II}, of the Yb(III) and Yb(II) with the macrocyclic ligand by the relationship,[6]

$$E_C^\circ - E_S^\circ = 0.059 \log (K_{II}/K_{III})$$

where E_C° and E_S° are the standard reduction potentials of the Yb(III,II) redox couple with and without being encapsulated by the ligand in acetonitrile. Since the standard reduction potentials can be approximately identified with half-wave potentials, using the half-wave potential of -0.6 V vs SCE for the Yb(III,II) couple in the absence of coordinating ligands in acetonitrile,[7] K_{III}/K_{II} is calculated to be 10^{14}. A part of the explanation for the observed remarkably larger stabilities for Yb(III) vs Yb(II) cryptates may be found in the significantly smaller size of the Yb(III) ionic radius compared to Yb(II),[8] yielding a better fit within the cryptate cavity. The advantages associated with the smaller size of the central metal ion in forming a stable conformation of these macrocylces have been demonstrated by the singly crystal X-ray structural studies of the La(III) and Yb(III) complexes for our macrocyclic ligand.[2] Another important factor may originate from the low solvation energy in acetonitrile[9], suggesting that there is not a considerably greater desolvation energy for encryptation of the Yb(III) ion in acetonitrile.

PREPARATION OF A COMPLETELY ENCAPSULATED YTTERBIUM ION

A similar encapsulation reaction with ytterbium ion under somewhat more forcing conditions produces a minor product which appears to be the completely encapsulated ytterbium complex, i.e., a ytterbium bis(tren) complex with three methylene bridges. Yb(trif)3, two equivalents of tren, and ten equivalents of bis(dimethylamino)methane were refluxed in acetonitrile for 25 h. Yb(L)(trif)3 [see above] was isolated as a crystalline solid (11% yield) from an acetonitrile/toluene mixture. The completely encapsulated complex was isolated from the mother liquors upon standing at room temperature for ≅ 2 months. The proposed structure of this complex is illustrated in Figure 3.
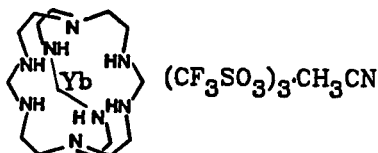

$(CF_3SO_3)_3 \cdot CH_3CN$

Figure 3. A schematic drawing of the proposed structure of the completely encapsulated ytterbium complex.

This complex appears to be relatively hydrolytically stable, whereas the dibridged complexes appear to decompose in the presence of water.

STRUCTURES OF POTENTIAL ENCAPSULATION PRECURSORS

The lanthanum tetrakis(ethylenediamine) complex[2] [La(en)4(trif)3·CH3CN] is nine-coordinate with four bidentate ethylenediamines and one oxygen from a triflate anion (Figure 4).
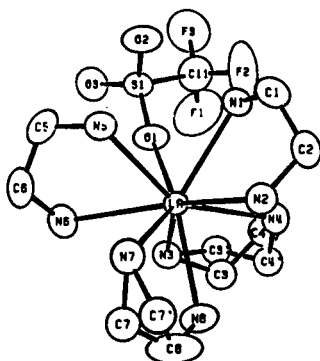

Figure 4. ORTEP drawing of $[La(en)_4(trif)]^{2+}$.

(Two of the ethylene diamine ligands have a conformational disorder (δ to λ) in the ethylene bridge.) The intra-ligand N-N distances range from 2.842(3) to 2.881(3) Å with an average of 2.860 Å. The shortest inter-ligand N-N distances are between 3.15 and 3.41 Å, giving some indication of the preferred ligand-ligand distances for 9-coordinate lanthanum. The first example of a mixed ligand lanthanide amine complex [Pr(trien)(tren)(trif)$_3$] has been prepared by the reaction of Pr(trif)$_3$ with technical grade triethylenetetramine (trien, the linear isomer of tren). The solubility of this complex is such that it crystallizes preferentially from an acetonitrile/toluene mixture, even in the presence of a large excess of trien over tren (the approximate ratio of trien:tren is at least 10:1). Thus, the mixed ligand complex consists of a coordinated tren and a coordinated trien, each bound in a tetradentate fashion. The structure (Figure 5) suggests the possibility of connecting four of the primary amines with methylene units, thus producing an isomer of the previously described dibridged bis(tren) complexes.
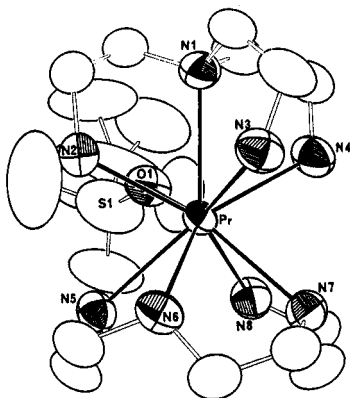

Figure 5.   ORTEP drawing of [Pr(trien)(tren)(trif)]$^{2+}$.

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