2846 *Inorg. Chem.* **1998,** *37,* 2846−2847

External Coordination of Europium(III) Prior to Its Encapsulation within a Cyclen-Based Pendant Donor Macrocycle

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Received January 6, 1998

The gadolinium(III) magnetic resonance imaging reagents and the luminescent europium(III) and terbium(III) complexes now being used as probes for biochemical processes are focusing considerable attention on lanthanide(III) chemistry.[1] Much effort has been expended in identifying ligands that maximize the thermodynamic and kinetic stability of the complexes that are used for these purposes owing to the necessity of the complex retaining its integrity during the time span of the application, and because of the toxicity of the metal ion.[2,3]

The ligands most consistently chosen for these applications are cyclen-based ligands to which pendant oxygen donor groups have been attached (cyclen = 1,4,7,10-tetraazacyclododecane).[1] Some attention has been paid to the kinetics associated with the formation of the complexes,[2] but little is known of the detailed mechanism by which the metal ion enters the macrocyclic cavity. Once within the cavity, X-ray crystallography has shown, in numerous instances, that with four pendant donors present the metal ion is sandwiched between N_4 and O_4 planes of donor atoms which define opposite faces of a distorted square antiprism.[4] To achieve this position the metal ion must penetrate the periphery of the ligand, and so it is possible that, en route, it may be trapped in a stable intermediate complex by a group of donor atoms which is smaller in number than the final group of eight. Structural information concerning such an intermediate would provide knowledge relating to the progression of the metal ion from the solvated state to the fully encapsulated state. In the past, others[5−9] and we ourselves[10−14] have suggested that pre-encapsulation of the metal ion by the pendant donor groups may be responsible for kinetically assisting the metal ion into and out of the macrocyclic cavity, but no intermediate complex, which would substantiate this theory, has been reported.

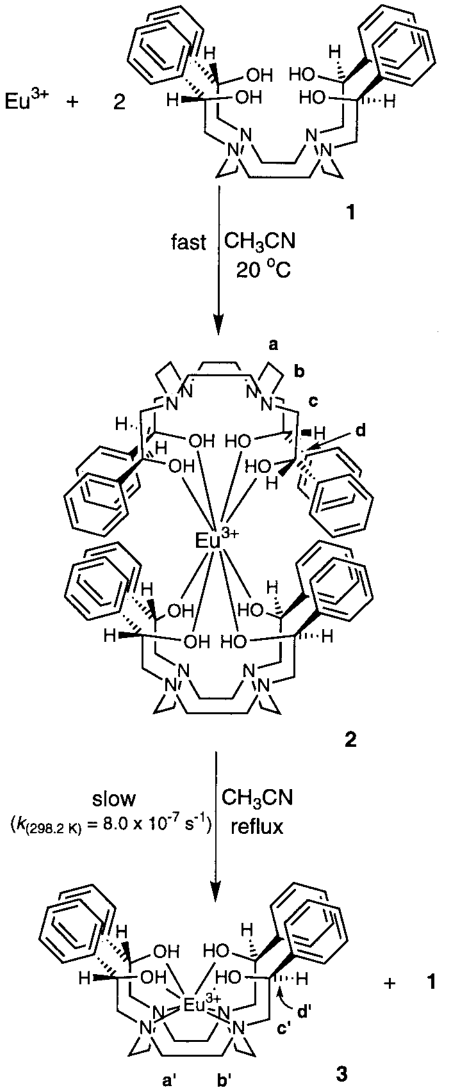

Figure 1. Proposed mechanism for Eu(III) incorporation into Δ*R*-thpec12, **1**.

We have recently described the synthesis and the structure in solution of the pendant donor cyclen derivative Δ-1,4,7,10-tetrakis((*R*)-2-hydroxy-2-phenylethyl)-1,4,7,10-tetraazacyclododecane (Δ*R*-thpec12), **1**,[15] and have subsequently begun an investigation of its lanthanide(III) coordination chemistry. In the course of reacting this ligand with europium(III) triflate in acetonitrile we have found that, when the reaction is conducted at ca. 293 K, an unusual 2:1 ligand:metal complex can be isolated which slowly

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converts to a 1:1 complex if returned to solution. From the data presented below it appears that this 2:1 complex is the first example of the elusive intermediate complex, referred to above.

The 2:1 complex (Anal. Calcd for $C_{83}H_{104}EuF_9N_8O_{17}S_3$: C, 52.3; H, 5.5; N, 5.9. Found: C, 52.4; H, 5.9; N, 5.7) can be precipitated in quantitative yield by combining europium(III) triflate with Δ*R*-thpec12, both in dry acetonitrile, at room temperature for a few minutes, and then adding diethyl ether. This dimer is characterized by high lability with respect to ligand interchange, which is evident from the coalescence of corresponding ^{13}C NMR (75.46 MHz) resonances associated with the free ligand and complex, that is observed when the two are combined at room temperature or above, and by a tendency to slowly convert to a 1:1 ligand:metal complex. If the formation reaction is prolonged and carried out in refluxing dry acetonitrile using a 1:1 ratio of ligand to metal salt, the monomer (Anal. Calcd for $C_{43}H_{52}N_4EuF_9O_{13}S_3$: C, 41.3; H, 4.2; N, 4.5. Found: C, 41.7; H, 4.2; N, 4.5) can be isolated as the sole reaction product in 90% yield. ^{13}C NMR analysis of the monomer shows that the rate of ligand interchange has slowed to the point at which ligand and complex show separate sets of ^{13}C NMR resonances at temperatures up to 348.2 K. Furthermore, the resonances associated with the nonaromatic carbon atoms of the complex (δ 93.9, 85.7, 84.1, 83.0) exhibit a lanthanide-induced shift of ca. 30 ppm downfield with respect to the corresponding resonance positions of either the dimer (δ 67.2, 59.9, 49.8, 47.6) or Δ*R*-thpec12 (δ 68.6, 63.0, 50.2 (8C)).[16]

These facts all point to the sequence of events shown in Figure 1 as the mechanism by which Eu(III) becomes fully encapsulated within the structure of Δ*R*-thpec12: The structure proposed for the dimer, **2**, accounts both for its lability, through the absence of either a chelate or a macrocyclic effect, and for the lack of significant lanthanide-induced NMR shifts, through the remoteness of the paramagnetic ion from the ligand. The structure shown for the monomer, **3**, is that normally found for a complex of this type[4] and is one which accounts for its relative nonlability as well as the significant lanthanide-induced NMR shifts that would be expected to arise from the closer association, both through-space and through-bond between the Eu(III) ion and the carbon atoms of the ligand.[17]

The rate of formation of **3** from **2**, in d_3-acetonitrile, was monitored by following the increase over time in the area enclosed by the four emerging ^{13}C NMR resonances, arising from carbon atoms **a′**, **b′**, **c′**, and **d′** (refer to Figure 1) of **3**, as shown in Figure 2, and was found to follow first-order kinetics. An Eyring plot of data obtained in the temperature range 333.2−313.2 K gave the following parameters for this process: $\Delta H^{\ddagger} = 118.2 \pm 0.9$ kJ mol^{-1}, $\Delta S^{\ddagger} = 232.1 \pm 2.8$ J mol^{-1} K^{-1}, and k (298.2 K) = $8.0 \pm 0.3 \times 10^{-7}$ s^{-1}.

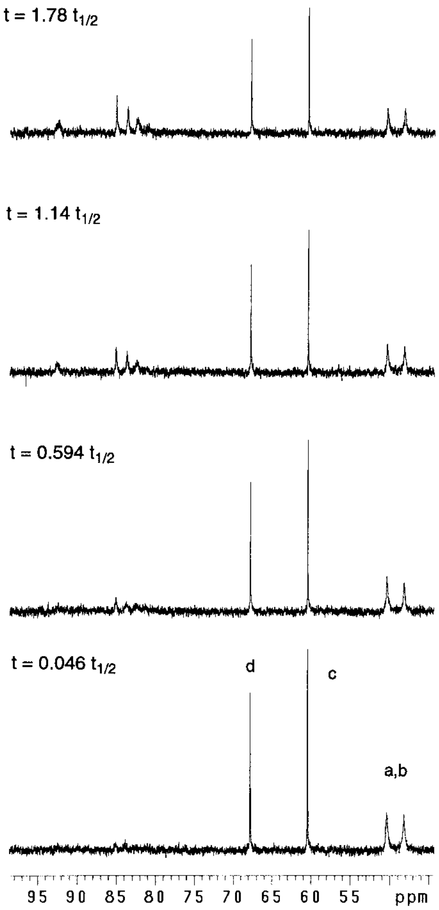

Figure 2. ^{13}C NMR (75.46 MHz) spectra of a 1:1 mixture of Eu-(CF_3SO_3)$_3$ and Δ*R*-thpec12 in d_3-acetonitrile held at 323.2 K. Each spectrum was recorded at an elapsed time which is shown as a multiple of $t_{1/2}$, where $t_{1/2} = 3.52 \times 10^4$ s (5.49 h) at 323.2 K. The four downfield resonances are associated with carbon atoms **a′**, **b′**, **c′**, and **d′** of the monomer, but are not labeled because they cannot be unambiguously assigned. Resonances **a**, **b**, **c** and **d** arise from the corresponding carbon atoms of the dimer.

Acknowledgment. Financial support from the Australian Research Council is gratefully acknowledged.

IC980012+

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[16] ^{13}C NMR chemical shift values quoted are those measured in d_3-acetonitrile at 295 K referenced to the nitrile resonance of d_3-acetonitrile taken as δ 116.55.

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