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Synthesis and Solution Properties of Lanthanum(III), Europium(III), and Lutetium(III) THP Complexes and an X-ray Diffraction Study of a Crystal Containing Four Stereoisomers of a Europium(III) THP Complex (THP = 1,4,7,10-Tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane). Methyl Groups Impart Rigidity to *S,S,S,S*-THP Macrocyclic Complexes

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The macrocycle 1,4,7,10-tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane (THP) prepared from racemic propylene oxide and cyclen (1,4,7,10-tetraazacyclododecane) consists of a mixture of stereoisomers that arise from the chiral α-carbons of the hydroxypropyl groups. ^{13}C NMR studies suggest that five different diastereomers are formed. Lanthanum(III), europium(III), and lutetium(III) THP complexes are synthesized from the mixture of THP stereoisomers. Europium(III) THP complexes containing *R,R,R,S* and *S,S,S,R* configurations at the α-carbons of the hydroxypropyl groups cocrystallize from solution. The complex $[Eu(THP)(H_2O)]_2(CF_3SO_3)_6\cdot 2EtOH\cdot H_2O$ crystallizes in the centrosymetric monoclinic space group $P2_1/c$ (No. 14) with $a = 22.5019(60)$ Å, $b = 20.1684(33)$ Å, $c = 19.8962(39)$ Å, $\beta = 105.923(17)°$, $V = 8683(3)$ Å^3, and $Z = 4$. Four stereoisomers (two enantiomeric pairs) of the complex appear in the crystal. Each asymmetric unit consists of two different diastereomers of the europium(III) cation, six triflate anions, two ethanol molecules, and one water molecule of solvation. The structure was solved and refined to $R = 5.54\%$ and $R_w = 5.72\%$ for those 3351 reflections with $|F_o| > 6\sigma|F_o|$. The nine-coordinate Eu^{3+} ion of each cation is partially encapsulated by an octadentate macrocyclic ligand (the four donor N atoms form a plane and are staggered by only about 19.0–24.2° from the orientations of the four donor O atoms) and has a water molecule capping the metal atom above the O_4 plane of the coordination sphere. The coordination sphere is thus a 4:4:1 arrangement, midway between a capped cube and a capped square antiprism. In addition, synthesis of the THP stereoisomer with all hydroxypropyl groups containing the *S*-configuration (*S*-THP) is accomplished by use of *S*-propylene oxide. The synthesis of lanthanum(III), europium(III), and lutetium(III) complexes of *S*-THP is reported; ^{1}H and ^{13}C NMR spectra of the lanthanum and lutetium complexes indicate that only one diastereomer is present in solution. Complexes of lanthanum(III), europium(III), and lutetium(III) are remarkably robust in water with half-lives of 73, 100, and 53 days, respectively, at 37 °C and pH 6.0.

Introduction

Work is underway in our laboratory[1] to harness the remarkable ability of trivalent lanthanide ions to promote rapid cleavage of RNA.[2] First-generation lanthanide complex catalysts were hexadentate Schiff-base macrocyclic complexes. New lanthanide(III) macrocyclic complexes were synthesized recently in our laboratories[3] in order to counteract a few undesirable characteristics of the first-generation catalysts. For example, the hexadentate Schiff-base complexes eventually hydrolyze at the imine bonds of the macrocycle and are not readily modified without sacrificing the robust nature of the macrocycle.[4] In order for lanthanide complexes to be useful in applications utilizing these compounds as artificial ribonucleases, the complexes must have a high degree of stability and/or inertness to dissociation under physiological conditions. In addition, open coordination sites for catalysis and an overall positive charge on the complex appear to be necessary in the construction of efficient catalysts.[1,5]

Lanthanide complexes of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate (DOTA) are among the most thermodynamically stable and kinetically inert lanthanide(III) complexes known to date.[6] However, negatively charged polyamino carboxylate complexes of the lanthanides are not effective catalysts for RNA cleavage.[5] Fortunately, macrocycles that are related to DOTA are readily synthesized by varying the pendent groups on the cyclen ring. Furthermore, one of the advantages of using DOTA-related macrocyclic ligands is the large number of pendent groups to choose from.[7] Several new ligands have been constructed[8,9] on the basis of our prediction that the four acetate groups can be replaced with other functional groups and retain much of the robust nature of the lanthanide DOTA complexes. Initial studies with these DOTA-related ligands have centered on the use of four neutral pendent groups to form a lanthanide complex with an overall +3 charge. Thus far, these neutral octadentate ligands appear to be attractive choices for constructing robust, positively charged complexes of the trivalent lanthanides. Rapid phosphate ester transesterification is catalyzed[10] by some of these lanthanide complexes, and studies are underway to delineate the properties of these complexes that are important in catalysis.

The THED (THED = 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane) ligand forms complexes with

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lanthanum(III) and europium(III) that are inert toward dissociation in water.[3] However, only the europium derivative appears sufficiently resistant for practical use. In an attempt to synthesize similar complexes that are more resistant to dissociation, we have investigated the use of the THP ligand (THP = 1,4,7,10-tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane). Our studies of the solution properties of lanthanide complexes of THED led us to believe that the addition of a methyl group to the four pendent groups of the macrocycle would yield a more conformationally rigid ligand that would not readily release the lanthanide ion. In this study, we report the synthesis of lanthanum(III), europium(III), and lutetium(III) derivatives of THP and an X-ray diffraction study of four stereoisomers of a europium(III) THP complex. A single stereoisomer of THP that has all four pendent hydroxypropyl groups with the *S* configuration at the α-carbon of the hydroxypropyl group, *S*-THP, has been synthesized. Studies of the dissociation of lanthanide(III) complexes indicate that this ligand forms exceptionally inert complexes with early, middle, and late lanthanides. This will enable us to exploit the multitude of interesting spectroscopic, electrochemical, and radiopharmaceutical properties of the lanthanide elements.[11]

Experimental Section

An Orion Research 510 digital ion analyzer equipped with a temperature compensation probe was used for all pH measurements. The pD was calculated as pH + 0.4.[12] A Hewlett-Packard diode array 8452A spectrophotometer with a thermostated cell compartment was employed for UV–vis spectra and for kinetic measurements. All ^{1}H NMR and ^{13}C NMR spectra were recorded by use of a Varian 400 XL spectrophotometer and are reported as parts per million downfield of $SiMe_4$. NMR sample temperatures were measured by use of a thermocouple located near the probe. Elemental analyses were performed by E & R Microanalytical Laboratories. A VG-SE fast atom bombardment mass spectrometer was utilized.

Cyclen (1,4,7,10-tetraazacyclododecane) in the free-base form was generated by passing the tetrahydrochloride salt (Parish Chemicals) through a Dowex 1X8-200 anion exchange column (30 cm × 2.5 cm, hydroxide form). $La(CF_3SO_3)_3$, $Eu(CF_3SO_3)_3$, and $Lu(CF_3SO_3)_3$ were obtained by treating the respective lanthanide oxides with concentrated trifluoromethanesulfonic acid as reported previously.[13] The lutetium oxide/trifluoromethanesulfonic acid slurry was heated to almost 100 °C to achieve a nearly neutral (6–7) pH. All reagents used were analytical grade. Acetonitrile was dried over CaH_2. Milli-Q purified water was used for all kinetic experiments.

1,4,7,10-Tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane (THP) was prepared as reported previously by treating cyclen with a 50% excess of propylene oxide in absolute ethanol at room temperature for 2 days.[14] The ethanol was removed in vacuo to yield a sticky white solid. The solid was dissolved in boiling hexane, and white crystals of the product were obtained from the filtered hexane solution in 40% yield. FAB MS, *m/z*: 405. ^{13}C NMR (D_2O, 18 °C) gave a spectrum with four sets of resonances: 19.9, 20.4, 20.5, 20.9; 50.6, 50.8, 51.0, 51.5, 51.7; 62.7, 63.0, 63.1, 63.3; 64.6, 65.0, 65.3, 65.6, 65.7. *S*-THP was prepared by a procedure similar to that used for THP by utilizing *S*-propylene oxide. FAB MS, *m/z*: 405. ^{1}H NMR (D_2O, 18 °C): 0.95 (d, 12 H, CH_3), 2.20–2.30 (16 H, NCH_2CH_2N), 2.85 (d, 8 H, $\mathrm{C}\mathit{H}_2\mathrm{CH(OH)(CH_3)}$), 3.85 (m, 4 H, $\mathrm{C}\mathit{H}\mathrm{(OH)(CH_3)}$). ^{13}C NMR ($D_2O$, 18 °C): 20.0 ($CH_3$), 50.5 ($NCH_2CH_2N$), 62.5 ($\mathit{C}\mathrm{H_2CH(OH)(CH_3)}$), 65.0 ($\mathit{C}\mathrm{H(OH)(CH_3)}$).

La(THP)(H₂O)(CF₃SO₃)₃. The lanthanum complex was prepared by the following method. Typically, $La(CF_3SO_3)_3$ (1.24×10^{-3} mol) was refluxed under nitrogen in a mixture of 100 mL of dry acetonitrile and 12.1 mL of trimethyl orthoformate for 1 h. THP (1.24×10^{-3} mol) dissolved in dry acetonitrile was added to the solution containing the lanthanum salt, and the mixture was refluxed for 1 h. The acetonitrile was concentrated in vacuo and a (1:1) mixture of methylene chloride and anhydrous ether was added. The white microcrystalline product was obtained in 85% yield. Anal. Calcd for $C_{23}H_{44}N_4O_{13}F_9S_3La$: C, 27.88; H, 4.44; N, 5.65. Found: C, 27.63; H, 4.55; N, 5.78. ^{1}H NMR (D_2O, 18 °C) gave a spectrum with two doublets (1.10 and 1.25) and very broad multiplets (2.25, 2.85, 3.40, and 4.40). ^{13}C NMR (methanol-d_4, 18 °C) gave a total of 26 peaks.

La(*S*-THP)(CF₃SO₃)₃. The lanthanum *S*-THP complex was prepared by a procedure similar to that for the lanthanum THP complex. *S*-THP and $La(CF_3SO_3)_3$ (3.7×10^{-4} mol each) and 3.60 mL of trimethyl orthoformate in 50 mL of acetonitrile were used. The white microcrystalline product was isolated in 87% yield. Anal. Calcd for $C_{23}H_{44}NO_{413}F_9S_3La$: C, 27.88; H, 4.44; N, 5.65. Found: C, 27.51; H, 4.46; N, 5.70. ^{1}H NMR (methanol-d_4, 18 °C): 1.40 (d, 12 H, CH_3), 2.35 (d, 4 H, equatorial ring protons), 2.45 (m, 8 H, equatorial ring protons and $\mathrm{C}\mathit{H}_2\mathrm{CH(OH)(CH_3)}$), 3.15 (t, 4 H, $\mathrm{C}\mathit{H}_2\mathrm{CH(OH)(CH_3)}$), 3.60 (t, 4 H, axial ring protons), 3.75 (t, 4 H, axial ring protons), 4.70 (m, 4H, $\mathrm{C}\mathit{H}\mathrm{(OH)(CH_3)}$). ^{13}C NMR (methanol-$d_4$, 18 °C): 20.75 ($CH_3$), 50.4 and 52.7 ($NCH_2CH_2N$), 60.8 ($\mathit{C}\mathrm{H_2CH(OH)(CH_3)}$), 69.2 ($\mathit{C}\mathrm{H(OH)(CH_3)}$).

Eu(THP)(CF₃SO₃)₃. The europium THP complex was prepared by a method similar to that described above for the lanthanum THP complex. The white microcrystalline product was isolated in 90% yield. Anal. Calcd for $C_{23}H_{44}N_4O_{13}F_9S_3Eu$: C, 27.52; H, 4.39; N, 5.58; Eu, 14.89. Found: C, 27.30; H, 4.55; N, 5.61; Eu, 14.88.

Eu(*S*-THP)(CF₃SO₃)₃. The europium complex was prepared by a method similar to that described above for the lanthanum *S*-THP complex. The white microcrystalline product was obtained in 84% yield. Anal. Calcd for $C_{23}H_{44}N_4O_{13}F_9S_3Eu$: C, 27.52; H, 4.39; N, 5.58. Found: C, 27.33; H, 4.38; N, 5.33. ^{1}H NMR (methanol-d_4 18 °C): −14.0 (4 H), −10.2 (4 H), −9.8 (4 H), 0.6 (12 H), 1.6 (4 H), 2.8 (4 H), 3.3 (4 H), 4.5 (4 H). ^{13}C NMR (methanol-d_4, 18 °C): 13.8 (CH_3), 81.0, 82.2, 84.0 (NCH_2CH_2N and $\mathit{C}\mathrm{H_2CH(OH)(CH_3)}$), 97.2 ($\mathit{C}\mathrm{H(OH)(CH_3)}$).

Lu(THP)(CF₃SO₃)₃. The lutetium THP complex was prepared by a method similar to that described above for the lanthanum THP complex. The white microcrystalline product was obtained in 70% yield. Anal. Calcd for $C_{23}H_{44}N_4O_{13}F_9S_3Lu$: C, 26.90; H, 4.29; N. 5.45. Found: C, 26.67; H, 4.27; N, 5.59. FAB MS, *m/z*: 876 ($Lu(THP)(CF_3SO_3)_3 - (CF_3SO_3)$). ^{1}H NMR ($D_2O$, 18 °C) gave a spectrum with two doublets (1.20 and 1.40) and very broad multiplets (2.60, 2.95, 3.15, 3.40, and 4.45). ^{13}C NMR (methanol-d_4, 18 °C) gave a total of 36 peaks.

Lu(*S*-THP)(CF₃SO₃)₃. The lutetium *S*-THP complex was prepared by a method similar to that described above for the lanthanum *S*-THP complex. The white microcrystalline product was obtained in 60% yield. Anal. Calcd for $C_{23}H_{44}N_4O_{13}F_9S_3Lu$: C, 26.90; H, 4.29; N, 5.45. Found: C, 26.92; H, 4.25; N, 5.22. ^{1}H NMR (methanol-d_4, 18 °C): 1.40 (d, 12 H, CH_3), 2.6 (m, 12 H, 8 H for equatorial ring protons and 4 H for equatorial $\mathrm{C}\mathit{H}_2\mathrm{CH(OH)(CH_3)}$), 3.15 (t, 4 H for $\mathrm{C}\mathit{H}_2\mathrm{CH(OH)(CH_3)}$), 3.60 (d, 8 H for axial ring protons, resolves into a quintet in D_2O), 4.70 (m, 4H, $\mathrm{C}\mathit{H}\mathrm{(OH)(CH_3)}$). ^{13}C NMR (methanol-$d_4$, 18 °C): 19.35 (q, $J_{C-H} = 126$ Hz, CH_3), 51.2 and 52.3 (both are t, $J_{C-H} = 140$ Hz, NCH_2CH_2N), 60.7 (t, $J_{C-H} = 130$ Hz, $\mathit{C}\mathrm{H_2CH(OH)(CH_3)}$), 69.0 (d, $J_{C-H} = 152$ Hz, $\mathit{C}\mathrm{H(OH)(CH_3)}$).

^{1}H NMR was used to monitor the dissociation of La(*S*-THP)$(CF_3SO_3)_3$ and Lu(*S*-THP)$(CF_3SO_3)_3$ in both the absence and the presence of a 2-fold excess of DTPA (diethylenetriaminepentaacetic acid) in D_2O at pD 7.3 and 25 °C. Typically, solutions contained 3.2 mM complex and 6.3 mM DTPA. The pD varied by 0.1 pD unit or less over the course of the experiment. Formation of the lutetium and lanthanum complexes was monitored in D_2O at pD 7.3 and 37 °C. For these experiments, the $Ln(CF_3SO_3)_3$ concentration was 43 mM and the concentration of THP was 10 mM.

Kinetics. The rates of dissociation of La^{3+}, Eu^{3+}, and Lu^{3+} from the THP and *S*-THP complexes were monitored by following the increase in absorbance at 314 nm. Beer's law plots with varying concentrations of the Cu(II) THP complex (0.100–1.00 mM) gave extinction coefficients at 314 nm of 6150 M^{-1} cm^{-1} at pH 6.0 and 37 °C, 6190 M^{-1} cm^{-1} at pH 6.0 and 60 °C, and 4520 M^{-1} cm^{-1} at pH 3.0 and 60 °C. Solutions for reactions at pH 6.0 were prepared either with or without 0.01 M Mes buffer; the addition of buffer did not affect the rate of the reaction. The pH was found to have changed by less than 0.1 pH unit during the duration of the reaction. Solutions at pH 3.0 contained no buffer, but the pH changed by less than 0.1 pH unit during the reaction.

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Table 1. Structure Determination Summary

Crystal Data	
empirical formula	$C_{50}H_{102}Eu_2F_{18}N_8O_{31}S_6$
crystal size	0.267 × 0.233 × 0.200 mm^3
crystal system	monoclinic
space group	$P2_1/c$
unit cell dimens	a = 22.5019(60) Å b = 20.1684(33) Å c = 19.8962(39) Å β = 105.923(17)°
V	8682.98(309) Å^3
Z	4
fw	2127.5
d(calcd)	1.627 Mg/m^3
abs coeff	1.683 mm^{-1}
F(000)	4272
Data Collection	
diffractometer	Siemens $P2_1$/P3
radiation	Mo Kα (λ = 0.710 73 Å)
T	298 K
monochromator	highly oriented graphite crystal
2θ range	5.0–40.0°
scan type	ω
scan speed	Constant; 2.00°/min in ω
scan range (ω)	0.60°
bkgd measmt	stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
std reflns	3 measd every 97 reflns
index ranges	$-20 \le h + 21, -19 \le k \le 0, -19 \le l \le 0$
no. of reflns collected	8914
no. of indep reflns	8138 (R_{int} = 3.58%)
no. of obsd reflns ($F < 3.0\sigma(F)$)	4540
no. of obsd reflns ($F > 6.0\sigma(F)$)	3351
abs cor	Semiempirical
min/max transm	0.4361/0.4844
Solution and Refinement	
system used	Siemens SHELXTL PLUS (VMS)
solution	direct methods
refinement method	full-matrix least-squares
quantity minimized	$\sum w(F_o - F_c)^2$
extinction cor	χ = 0.000 015(12), where $F^* = F[1 + 0.002\chi F^2/\sin(2\theta)]^{-1/4}$
hydrogen atoms	riding model, fixed isotropic U
weighting scheme	$w^{-1} = \sigma^2(F) + 0.0007F^2$
no. of params refined	823
final R indices (6σ data)	R = 5.54%, R_w = 5.72%
final R indices (3σ data)	R = 8.32%, R_w = 6.68%
goodness-of-fit	1.37
largest and mean Δ/σ (Eu^{3+} cation)	0.047, 0.002
largest and mean Δ/σ (triflate)	0.073, 0.004
data-to-param ratio	4.1:1
largest diff peak	0.67 e Å^{-3}
largest diff hole	−0.66 e Å^{-3}

The initial rates of the reaction for dissociation of the lanthanum and lutetium complexes were independent of Cu^{2+} for copper concentrations in the range 0.20–1.00 mM. The dissociation of the lanthanide complexes of *S*-THP was followed by monitoring the reaction over a period of several weeks. The first-order rate constants were calculated by using the first-order rate equation $\ln(1 - B/A_0) = -kt$, where B is the concentration of the Cu(II) *S*-THP complex, A_0 is the initial concentration of the lanthanide complex, and t is the time in seconds. Correlation coefficients were 0.96 or greater.

Collection of X-ray Diffraction Data for [Eu(THP)(H$_2$O)]$_2$(CF$_3$SO$_3$)$_6$·2EtOH·H$_2$O. A colorless single crystal (dimensions = 0.27 mm × 0.23 mm × 0.20 mm) of $[Eu(THP)(H_2O)]_2(CF_3SO_3)_6 \cdot 2EtOH \cdot H_2O$ was selected for the X-ray diffraction study. The air-stable crystal was sealed into a 0.30 mm diameter thin-walled capillary under atmospheric conditions. It was then mounted and aligned on an upgraded Siemens $P2_1$/P3 diffractometer. Data were collected through the use of the ω-scan technique. Details of the data collection appear in Table 1. Only a single form of data was collected (Mo Kα, λ = 0.710 73 Å, 2θ = 5.0–40.0°) due to the large volume of the unit cell. A total of 8914 reflections were collected and were merged into a unique set of 8138 reflections (R_{int} = 3.58%). All data were corrected for Lorentz and polarization effects and for absorption. The systematic absences $h0l$ for $l = 2n + 1$ and $0k0$ for $k = 2n + 1$ show unequivocally the crystal belongs to the monoclinic centrosymmetric space group $P2_1/c$ (C_{2h}^5; No. 14).

Solution and Refinement of the Crystal Structure of [Eu(THP)(H$_2$O)]$_2$(CF$_3$SO$_3$)$_6$·2EtOH·H$_2$O. All crystallographic calculations were carried out with the use of the Siemens SHELXTL PLUS[15] program package. The analytical scattering factors for neutral atoms were corrected for both the $\Delta f'$ and the $i\Delta f''$ components of anomalous dispersion.[16] The structure was solved by the use of direct methods. Refinement of parameters was achieved through the minimization of the function $w(|F_o| - |F_c|)^2$. Those 4540 data with $|F_o| > 3\sigma|F_o|$ were used in the refinement process. The asymmetric unit of the unit cell contains 115 non-hydrogen atoms described by 823 parameters. The asymmetric unit was divided into two sets of atoms that were alternately refined to convergence. The first set contained both of the europium complexes, and the second set contained the six triflate molecules, two ethanol molecules, and the water molecule. This procedure allowed the refinement of more parameters than the program set can normally handle in a single cycle. The final data-to-parameter ratio was only 4.1:1, indicating a weak data set; nevertheless, refinement proceeded smoothly to convergence. A secondary extinction parameter (χ) was refined to a value of 0.000 015(12) (see Table 1). Positional parameters and anisotropic thermal parameters for the europium atoms, oxygen atoms, and nitrogen atoms of the europium complex plus all triflate anions (except for one triflate anion which suffered from rotational disorder) and all solvent molecules (ethanol and water) were refined. The carbon atoms of the europium complex and of the rotationally disordered triflate anion were refined using isotropic thermal parameters. All hydrogen atoms bonded to carbon atoms were placed in calculated positions with d(C–H) = 0.96 Å and with the appropriate staggered tetrahedral geometry.[17] The isotropic thermal parameter of each hydrogen atom was defined as equal to the U_{eq} of the atom to which it was bonded. The hydrogen atoms of the alcohol groups were not located and were omitted from the analysis. Refinement of the model converged with R = 8.32% and R_w = 6.68% for 823 parameters refined against those 4540 reflections with $|F_o| > 3\sigma|F_o|$ and R = 5.54% and R_w = 5.72% for those reflections with $|F_o| > 6\sigma|F_o|$. The extreme features left on the difference-Fourier map were a peak of height 0.67 e Å^{-3} and a negative feature of −0.66 e Å^{-3}. Atomic coordinates appear in Table 2.

Results and Discussion

THP was prepared from racemic propylene oxide and cyclen as reported by Hancock and co-workers (THP = 1,4,7,10-tetrakis-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane).[14] Four chiral centers are introduced into the macrocycle in this synthesis. Various combinations of *R* and *S* configurations at the α-carbon of the pendent hydroxypropyl groups give rise to six possible stereoisomers (*R,R,R,R*; *R,R,R,S*; *R,R,S,S*; *R,S,R,S*; *R,S,S,S*; *S,S,S,S*) with one enantiomeric pair (*R,R,R,R* and *S,S,S,S*). A parent ion peak (THP + H$^+$) was found in the mass spectrum of the product with no peaks for other cyclen-containing species. In the ^{13}C NMR spectrum of the recrystallized ligand, there are four sets of resonances corresponding to four different types of carbons (see Experimental Section for assignments). Each set of resonances consists of four or five peaks, suggesting that all possible diastereomers are present in solution. Hancock and co-workers obtained the *R,R,R,R*-THP and *S,S,S,S*-THP enantiomeric pair from a hexane recrystallization. This assignment was based on the ^{1}H NMR spectrum of the product and an X-ray crystallographic study which showed the presence of two Pb(II) macrocycles (*S,S,S,S*-THP and *R,R,R,R*-THP). The crystalline product that we obtained from hexane recrystallization routinely contained a mixture of several stereoisomers. However,

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Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($Å^2 \times 10^3$)

	x	*y*	*z*	*U*(eq)[a]		*x*	*y*	*z*	*U*(eq)[a]
Eu(1)	4345(1)	9374(1)	2311(1)	55(1)	O(1a)	8813(7)	2388(8)	3315(8)	84(8)
O(1)	4988(8)	9376(10)	3516(9)	116(10)	O(2a)	8146(7)	2872(8)	3938(10)	95(9)
O(2)	4194(7)	10503(7)	2593(9)	86(8)	O(3a)	7796(7)	2809(9)	2681(9)	90(8)
O(3)	4341(8)	9886(9)	1207(9)	106(9)	C(1a)	7836(15)	1731(15)	3333(20)	87(17)
O(4)	5172(7)	8772(8)	2057(10)	102(9)	F(1a)	7829(8)	1358(9)	2801(11)	127(10)
O(5)	5285(6)	10086(7)	2435(7)	66(7)	F(2a)	7253(8)	1801(8)	3368(10)	128(10)
N(1)	4165(9)	8418(9)	3151(12)	83(11)	F(3a)	8145(8)	1388(8)	3906(9)	123(9)
N(4)	3365(8)	9602(9)	2812(11)	73(10)	S(1b)	3065(5)	2282(6)	1445(6)	112(5)
N(7)	3245(8)	9399(11)	1323(9)	70(9)	O(1b)	3701(9)	2393(11)	1522(12)	151(13)
N(10)	4058(9)	8223(8)	1633(10)	68(9)	O(2b)	2902(11)	1600(11)	1495(13)	168(15)
C(2)	3696(12)	8614(13)	3508(14)	97(9)	O(3b)	2821(22)	2744(12)	1813(13)	169(16)
C(3)	3203(13)	9029(14)	3169(15)	119(11)	C(1b)	2685(21)	2530(19)	517(28)	142(28)
C(5)	2813(12)	9793(12)	2216(13)	90(9)	F(1b)	2901(17)	2147(17)	177(14)	252(23)
C(6)	2710(12)	9451(13)	1590(13)	97(9)	F(2b)	2108(12)	2434(14)	429(15)	244(18)
C(8)	3192(12)	8830(13)	871(14)	105(10)	F(3b)	2816(10)	3137(12)	455(12)	191(13)
C(9)	3442(14)	8228(14)	1185(16)	122(11)	S(1c)	884(4)	4002(5)	3717(5)	89(5)
C(11)	4126(11)	7662(13)	2167(13)	99(9)	O(1c)	789(9)	3348(9)	3896(10)	121(11)
C(12)	3902(12)	7815(14)	2752(14)	106(10)	O(2c)	565(9)	4479(9)	3990(11)	120(11)
C(13)	4769(14)	8247(15)	3610(16)	126(12)	O(3c)	833(9)	4094(9)	2998(12)	117(11)
C(14)	5095(17)	8802(19)	3972(20)	160(15)	C(1c)	1708(21)	4182(26)	4179(21)	126(26)
C(15)	5682(13)	8731(14)	4382(15)	136(12)	F(1c)	1747(11)	4126(13)	4825(13)	209(16)
C(16)	3542(12)	10180(12)	3303(13)	87(9)	F(2c)	1842(9)	4787(10)	4031(15)	202(16)
C(17)	3803(13)	10729(14)	3040(15)	102(10)	F(3c)	2045(10)	3799(13)	3952(15)	191(16)
C(18)	4117(12)	11214(13)	3587(13)	117(10)	S(1d)	4320(4)	5927(5)	4082(5)	84(4)
C(19)	3256(12)	9987(13)	861(14)	95(9)	O(1d)	4291(8)	5903(10)	4808(11)	121(11)
C(20)	3805(15)	10201(16)	751(17)	126(12)	O(2d)	4604(8)	6467(10)	3800(12)	133(12)
C(21)	3865(12)	10729(13)	297(13)	117(10)	O(3d)	4391(8)	5285(9)	3800(9)	96(9)
C(22)	4507(13)	8110(14)	1207(15)	115(11)	C(1d)	3499(15)	6111(28)	3718(27)	128(25)
C(23)	5137(13)	8210(15)	1588(15)	106(10)	F(1d)	3154(8)	5666(11)	3930(11)	159(12)
C(24)	5559(12)	8277(14)	1132(14)	132(12)	F(2d)	3352(10)	6657(12)	3959(16)	200(18)
Eu(1′)	9858(1)	2375(1)	1597(1)	54(1)	F(3d)	3352(10)	6092(16)	3054(13)	210(15)
O(1′)	9777(8)	1314(8)	2168(8)	99(9)	S(1e)	4045(5)	5883(5)	732(5)	111(5)
O(2′)	9423(8)	2994(8)	2428(9)	108(9)	O(1e)	4422(16)	5396(17)	615(21)	120(14)
O(3′)	10535(9)	3338(9)	1814(9)	122(11)	O(2e)	4236(17)	6493(19)	408(20)	149(17)
O(4′)	10829(8)	1886(9)	1639(10)	120(10)	O(3e)	4121(15)	6012(18)	1483(21)	146(17)
O(5′)	10546(6)	2361(7)	2821(7)	71(7)	O(1e′)	4239(31)	5616(36)	91(43)	145(31)
N(1′)	8759(10)	1732(10)	1132(11)	90(11)	O(2e′)	3895(28)	6515(30)	771(31)	101(25)
N(4′)	8891(9)	3187(10)	1029(11)	82(10)	O(3e′)	4204(23)	5367(28)	1224(29)	90(24)
N(7′)	9959(10)	2988(10)	428(12)	96(11)	C(1e)	3089(33)	5678(27)	449(24)	202(35)
N(10′)	9826(10)	1529(11)	542(12)	100(12)	F(1e)	3176(18)	5110(23)	688(27)	191(18)
C(2′)	8239(12)	2229(13)	996(14)	103(10)	F(2e)	3199(17)	5400(24)	−200(24)	178(17)
C(3′)	8354(12)	2825(13)	664(14)	105(10)	F(3e)	2995(27)	6161(30)	300(38)	279(32)
C(5′)	9086(12)	3625(13)	521(14)	101(10)	F(1e′)	3152(22)	4869(29)	171(34)	120(24)
C(6′)	9445(13)	3335(14)	98(15)	110(11)	F(2e′)	2997(26)	5878(37)	−247(36)	132(25)
C(8′)	10146(12)	2471(13)	−26(14)	98(10)	F(3e′)	2884(22)	5596(30)	889(32)	98(21)
C(9′)	9750(13)	1844(13)	−82(16)	104(10)	S(1f)	851(5)	708(7)	3729(8)	155(7)
C(11′)	9290(13)	1040(13)	453(15)	110(10)	O(1f)	726(22)	1354(16)	3940(20)	339(34)
C(12′)	8734(12)	1369(13)	525(14)	98(10)	O(2f)	876(14)	754(17)	3053(13)	220(20)
C(13′)	8724(11)	1324(12)	1759(13)	85(9)	O(3f)	633(15)	142(18)	3928(23)	334(31)
C(14′)	9228(13)	929(15)	2101(15)	108(10)	C(1f)	1668	571	4100	200
C(15′)	9186(10)	710(12)	2799(12)	88(8)	F(1f)	1972(16)	1112(15)	4187(28)	392(32)
C(16′)	8734(11)	3577(13)	1582(14)	91(9)	F(2f)	1678(17)	571(28)	4764(14)	347(31)
C(17′)	9194(12)	3632(13)	2235(14)	88(9)	F(3f)	1878(12)	221(16)	3828(25)	363(33)
C(18′)	9051(11)	4030(12)	2782(12)	97(9)	O(1s)	1895(10)	2356(15)	2424(14)	165(14)
C(19′)	10462(17)	3466(19)	644(19)	166(16)	C(2s)	2102(20)	2319(34)	3065(23)	246(35)
C(20′)	10746(21)	3624(24)	1241(26)	205(20)	C(3s)	2760(19)	2309(23)	3489(19)	206(25)
C(21′)	11336(12)	4034(12)	1553(14)	117(10)	O(4s)	3634(10)	3890(12)	2236(12)	136(13)
C(22′)	10383(14)	1111(14)	770(16)	126(11)	C(5s)	3191(22)	4404(37)	2240(40)	244(45)
C(23′)	10914(17)	1360(19)	1193(20)	157(14)	C(6s)	2865(26)	4491(42)	2528(54)	354(62)
C(24′)	11453(11)	874(12)	1534(13)	110(10)	O(7s)	4638(7)	1554(8)	2101(9)	96(9)
S(1a)	8183(3)	2533(4)	3317(5)	76(4)					

[a] Equivalent isotropic *U* defined as one-third of the trace of the orthogonalized $\mathbf{U}_{ij}$ tensor.

a single stereoisomer with the *S*-configuration at all α-carbons, *S*,*S*,*S*,*S*-THP (abbreviated *S*-THP), was readily synthesized from cyclen and *S*-propylene oxide in good yield.

The synthesis of lanthanum(III), europium(III), and lutetium(III) THP and *S*-THP complexes is best carried out under anhydrous conditions to minimize formation of lanthanide hydroxide precipitates. Conditions are similar to those for the synthesis of lanthanum(III) and europium(III) THED complexes (THED = 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane).[3] The use of lanthanide(III) triflate ($Ln(CF_3SO_3)_3$) enabled us to isolate analytically pure samples of the lanthanide complexes of THP or *S*-THP in good yield. Although all products were initially microcrystalline or formed single crystals, crystallinity was rapidly lost once all solvent was removed. Similar difficulties were encountered in obtaining single crystals of lanthanide THED complexes out of acetonitrile.[3] Recrystallization of the europium(III) THP complex from wet ethanol and hexanes gave fine white needles that were suitable for a single-crystal X-ray diffraction study.

Structure of Europium(III) THP Complex. Single crystals of a europium complex were obtained from a synthesis using the mixture of THP stereoisomers. The asymmetric unit of the unit cell consists of two discrete $[Eu(THP)(H_2O)]^{3+}$ cations, six triflate counteranions, two ethanol molecules, and one uncoordinated

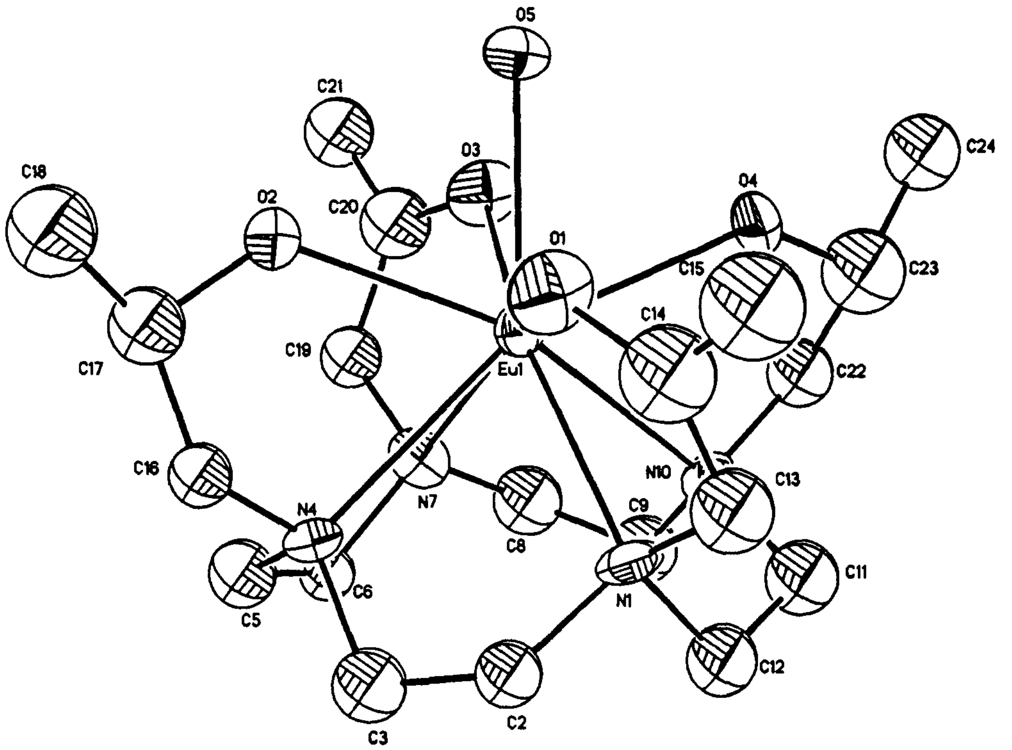

Figure 1. General view of the structure of one $[Eu(THP)(H_2O)]^{3+}$ cation (molecule 1).

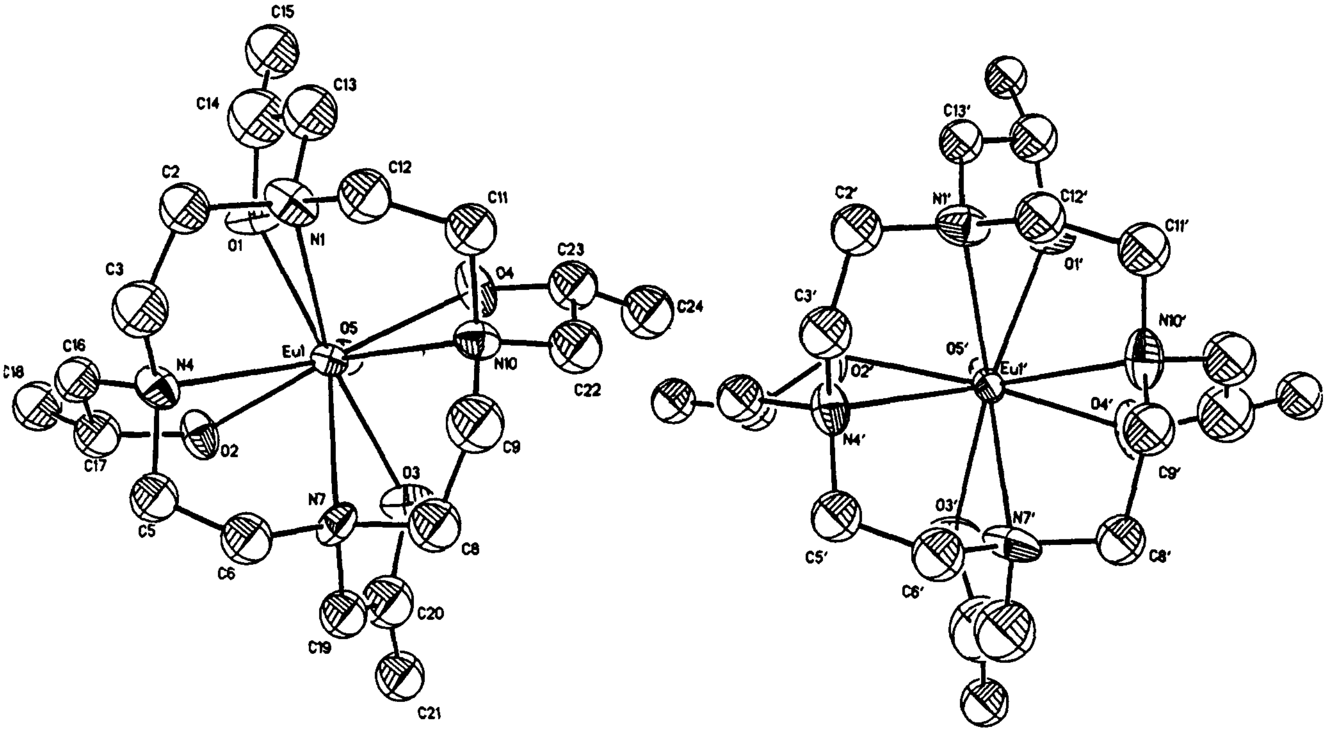

Figure 2. Side-by-side comparison of the two europium(III) cations which define the asymmetric unit.

water molecule of solvation. The essential atomic labeling scheme for the cations is given in Figure 1. Each Eu^{3+} cation is shown in Figure 2, projected onto the plane of the four nitrogen atoms in the macrocyclic ring.

The two crystallographically independent cations are diastereomers of one another. Two different diastereomers are also present in the structure of uncoordinated (2*R*,5*R*,8*R*,11*R*)-2,5,8,11-tetraethyl-1,4,7,10-tetraazacyclododecane.[18] This type of isomerization occurs because the molecule has two independent structural features that influence its chirality. The pendent hydroxypropyl groups are orientated around the europium(III) ion in a propeller-like manner in either a clockwise or a counterclockwise direction. Secondly, the macrocyclic ring can adopt two different conformations when it is coordinated to the metal cation. These two conformations are related by an inversion center. Coupled together, these two structural features give rise to a total of four possible isomers in the crystal structure: the two diastereomers which are present in the defined asymmetric unit and their enantiomeric equivalents (related to the former by symmetry operations of the second kind—i.e., inversion center and *c*-glides). The diastereomeric relationship between molecules in the asymmetric unit can be observed by superimposing the two different molecules of the europium(III) complex as shown in Figure 3. The macrocyclic rings of the two molecules overlap

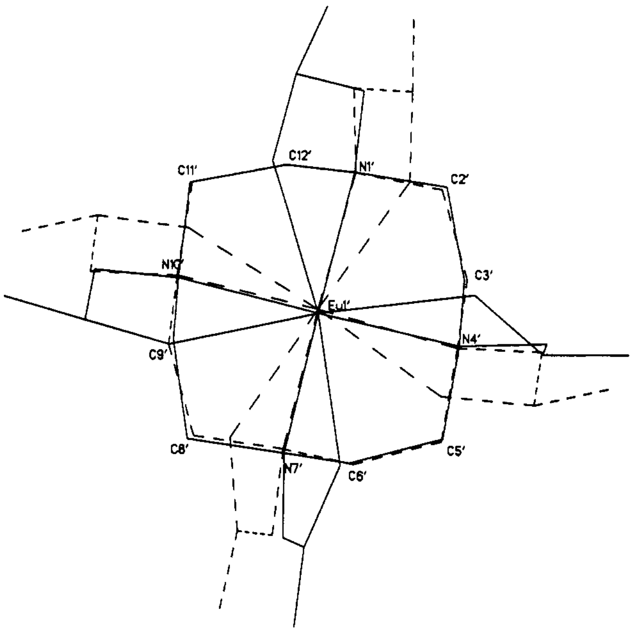

Figure 3. Overlap of the macrocyclic rings of the two cations in the asymmetric unit. Note the different chiralities of the pendent groups.

Table 3. Oxygen–Oxygen Intermolecular Interactions <3 Å

molecule 1		molecule 2	
O(1)–O(1e)	2.781	O(1′)–O(2f)	2.846
O(1)–O(3e′)	2.656		
O(2)–O(7s)	2.642	O(2′)–O(1a)	2.797
O(3)–O(3d)	2.969	O(3′)–O(3c)	2.730
O(4)–O(4s)	2.680	O(4′)–O(1s)	2.654

Table 4. Comparison of Selected Interatomic Distances of the Primary Coordination Sphere (Å)

molecule 1		molecule 2	
Eu(1)–N(1)	2.654(22)	Eu(1′)–N(1′)	2.720(21)
Eu(1)–N(4)	2.697(21)	Eu(1′)–N(4′)	2.711(14)
Eu(1)–N(7)	2.707(15)	Eu(1′)–N(7′)	2.698(24)
Eu(1)–N(10)	2.674(17)	Eu(1′)–N(10′)	2.691(24)
Eu(1)–O(1)	2.435(15)	Eu(1′)–O(1′)	2.452(17)
Eu(1)–O(2)	2.390(15)	Eu(1′)–O(2′)	2.478(19)
Eu(1)–O(3)	2.426(18)	Eu(1′)–O(3′)	2.433(19)
Eu(1)–O(4)	2.390(18)	Eu(1′)–O(4′)	2.377(19)
Eu(1)–O(5)	2.512(14)	Eu(1′)–O(5′)	2.502(12)

very closely (average deviation = 0.072 Å), but the pendent hydroxypropyl groups are arranged around the metal cation with opposite chiralities. The remaining two isomers can be generated by inversion of the two isomers in the defined asymmetric unit. In summary, each crystal of $[Eu(THP)(H_2O)]_2(CF_3SO_3)_6{\cdot}2EtOH{\cdot}H_2O$ contains four different isomers of the Eu(III)-containing cation.

Table 3 lists all intermolecular oxygen–oxygen interactions <3 Å. Corresponding oxygen atoms of the alcohol groups of the two molecules have similar intermolecular interactions (except those involving O(2) and O(2′)). Oxygen atom O(2) is associated with the water solvent molecule O(7s) at a distance of 2.642 Å, while oxygen atom O(2′) is associated with atom O(1a) from a triflate anion at a distance of 2.797 Å.

Each nine-coordinate cation consists of a europium(III) ion partially encapsulated by the octadentate THP macrocycle with an additional water molecule capping the O_4 face of the primary coordination sphere. Selected bond distances and angles are given in Tables 4 and 5. The primary coordination polyhedron of the molecular core is best described as a capped distorted square prism. The nitrogen atoms form a square pyramid with the europium ion forming the apex; this can be shown by the angle of intercept of the planes N(1)–Eu(1)–N(7) and N(4)–Eu(1)–N(10) which is 90.1° (89.7° in molecule 2). The four oxygen atoms of the alcohol groups are involved in a similar, but flattened, square pyramid (due to the short length of the hydrocarbon chain of the isopropyl groups). The angle of intercept of the planes O(1)–Eu(1)–O(3) and O(2)–Eu(1)–O(4) is 91.5° (95.1° in molecule 2). The increased angle of intercept in molecule 2 could be a consequence of the different intermolecular interactions of O(2) and O(2′). These two square pyramids have a staggered conformation with a rotational angle of 19.0° from an idealized square prismatic geometry. The second molecule is rotated slightly further from the idealized square prismatic geometry with a rotation angle of 24.2°. (The conformations are almost midway between prismatic (0°) and antiprismatic (45°).) The oxygen atoms of the alcohol groups and the nitrogen atoms of the macrocyclic ligand lie in two planes, the average displacement of these atoms from their respective planes being 0.026 and 0.011 Å, respectively (0.004 and 0.018 Å, respectively, for the second molecule). These planes are almost parallel, with a dihedral angle of only 1.6° (2.4° for molecule 2). The interatomic distances associated with the molecular cores of both molecules are compared in Table 4 and have the following average Eu-N and Eu-O values: Eu-N = 2.683 (±0.029) Å, $Eu\text{-}O_{alcohol}$ = 2.410 (±0.028) Å, Eu′-N′ = 2.705 (±0.014) Å and $Eu'\text{-}O'_{alcohol}$ = 2.435 (±0.058) Å. The Eu-N bond distances are in agreement with values determined for the structure of the $Eu(DOTA)(H_2O)$ complex[19] (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate), which has the average values $Eu\text{-}O_{carboxyl}$ = 2.393 Å and Eu-N = 2.680 Å. The primary coordination sphere bond distances with the largest variations between the two molecules are Eu(1)–O(2) = 2.390(15) Å and Eu(1′)–O(2′) = 2.478(19) Å. This difference is probably due to the difference in the intermolecular interactions of these two atoms as described above. Notice that the Eu-N bond lengths are greater than the sum of their Pauling covalent radii ($r_{Eu} + r_N$ = 2.60 Å), while the $Eu\text{-}O_{alcohol}$ distances are smaller than the sum of the covalent radii ($r_{Eu} + r_O$ = 2.58 Å). The europium–oxygen bonds associated with the water molecules O(5) and O(5′) are also slightly shorter than the sum of their covalent radii. This can be explained by the fact that the macrocyclic nitrogen atoms are located in the semirigid macrocycle. This reduces the ability of the nitrogen atoms to adopt a perfect coordination geometry. The oxygen atoms of the pendent hydroxypropyl groups are on flexible hydrocarbon chains. This places them in a less rigid environment than the nitrogen atoms of the macrocyclic ring, and therefore, they are more able to rearrange and adopt a favorable coordination geometry. The average distance between trans nitrogen atoms of the macrocyclic ligand is 4.181 Å (4.212 Å for the second molecule). These distances define a cavity that is too small to be occupied by an "in-plane" europium(III) ion. The europium(III) ion lies above the center of the macrocyclic ring and is linked also to four 2-hydroxypropyl ligand arms which fold over it (trans distances within the O_4 sphere of the alcohols average 4.475 Å (4.552 Å for molecule 2)). Due to the small length of the pendent ligand arms, the oxygen atoms of the 2-hydroxypropyl groups cannot completely encapsulate the europium(III) ion. A gap is left in the coordination sphere that is sufficiently large to allow the coordination of a water molecule. The displacements of the europium(III) ion from the centroids of the rings O(1)–O(2)–O(3)–O(4) and N(1)–N(4)–N(7)–N(10) are 0.894 and

Table 5. Comparison of Selected Bond Angles (deg)

molecule 1		molecule 2	
O(1)–Eu(1)–O(3)	139.1(7)	O(1′)–Eu(1′)–O(3′)	138.4(6)
O(2)–Eu(1)–O(4)	136.2(6)	O(2′)–Eu(1′)–O(4′)	136.3(6)
N(1)–Eu(1)–N(7)	103.2(8)	N(1′)–Eu(1′)–N(7′)	102.0(8)
N(4)–Eu(1)–N(10)	102.1(8)	N(4′)–Eu(1′)–N(10′)	103.1(8)

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Table 6. Comparison of the Trans O–M^{3+}–O and N–M^{3+}–N Bond Angles (deg) for Selected Compounds (M = Eu, La, Gd)

	O–M^{3+}–O	N–M^{3+}–N	ref
[Eu(THP)(H$_2$O)]$^{3+}$	137.0	102.5	
[Eu(DOTA)(H$_2$O)]$^-$	145.5	103.9	19
[La(TCEC)]$^{3+}$	119.0	106.6	8
Gd(L)(H$_2$O)^a	146.2	103.9	20

^{a} L = 10-[2-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-1-[(phenylmethoxy)methyl]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.

Table 7. Comparison of the Torsion Angles Associated with the Isopropyl Ligand Groups

molecule 1		molecule 2	
Eu(1)–N(1)–C(13)–C(14)	54.2	Eu(1′)–N(1′)–C(13′)–C(14′)	–49.9
N(1)–C(13)–C(14)–O(1)	–38.0	N(1′)–C(13′)–C(14′)–O(1′)	43.4
Eu(1)–O(1)–C(14)–C(13)	–0.1	Eu(1′)–O(1′)–C(14′)–C(13′)	–11.2
Eu(1)–N(4)–C(16)–C(17)	47.9	Eu(1′)–N(4′)–C(16′)–C(17′)	19.1
N(4)–C(16)–C(17)–O(2)	–35.9	N(4′)–C(16′)–C(17′)–O(2′)	–47.7
Eu(1)–O(2)–C(17)–C(16)	2.0	Eu(1′)–O(2′)–C(17′)–C(16′)	56.6
Eu(1)–N(7)–C(19)–C(20)	30.8	Eu(1′)–N(7′)–C(19′)–C(20′)	–7.5
N(7)–C(19)–C(20)–O(3)	–10.2	N(7′)–C(19′)–C(20′)–O(3′)	–4.6
Eu(1)–O(3)–C(20)–C(19)	–21.9	Eu(1′)–O(3′)–C(20′)–C(19′)	16.7
Eu(1)–N(10)–C(22)–C(23)	48.0	Eu(1′)–N(10′)–C(22′)–C(23′)	–32.7
N(10)–C(22)–C(23)–O(4)	–38.1	N(10′)–C(22′)–C(23′)–O(4′)	27.9
Eu(1)–O(4)–C(23)–C(22)	7.9	Eu(1′)–O(4′)–C(23′)–C(22′)	–5.5

Table 8. Comparison of Selected Interatomic Distances (Å) of the Isopropyl Ligand Groups

molecule 1		molecule 2	
N(1)–C(13)	1.457(33)	N(1′)–C(13′)	1.513(35)
N(4)–C(16)	1.502(30)	N(4′)–C(16′)	1.471(36)
N(7)–C(19)	1.504(34)	N(7′)–C(19′)	1.459(43)
N(10)–C(22)	1.505(40)	N(10′)–C(22′)	1.476(36)
O(1)–C(14)	1.450(43)	O(1′)–C(14′)	1.434(42)
O(2)–C(17)	1.486(37)	O(2′)–C(17′)	1.405(35)
O(3)–C(20)	1.442(34)	O(3′)–C(20′)	1.435(57)
O(4)–C(23)	1.505(40)	O(4′)–C(23′)	1.440(53)
C(13)–C(14)	1.424(48)	C(13′)–C(14′)	1.425(45)
C(16)–C(17)	1.415(49)	C(16′)–C(17′)	1.419(39)
C(19)–C(20)	1.395(52)	C(19′)–C(20′)	1.270(58)
C(22)–C(23)	1.452(62)	C(22′)–C(23′)	1.316(51)

1.682 Å, respectively (0.894 and 1.700 Å, respectively, for the second molecule). Some interesting bond angles associated with these cavities are provided in Table 5. The average trans N–Eu–N bond angles are 102.4° for the first molecule and 102.5° for the second molecule. These do not leave a cavity sufficiently large to accommodate the coordination of a water molecule above the N$_4$ face. However, the average trans O–Eu–O bond angles are much larger with values of 136.4° for the first molecule and 137.6° for the second molecule, leaving a cavity that is now sufficiently large to allow the coordination of a water molecule. Table 6 compares the bite angle of some selected lanthanide complexes. The complexes which have coordinated water molecules occupying the ninth coordination site on the lanthanide ion have angles which are at least 10° greater than the bite angles of complexes that do not contain water molecules. The macrocyclic ligands with pendent arms that can form five-membered chelate rings allow the coordination of a water molecule,[19,20] while the La^{3+} complex, which has pendent groups forming a six-membered chelate ring, does not.[8]

The hydroxypropyl pendent groups are arranged in a propeller-like conformation with all the blades arranged in either a clockwise or a counterclockwise configuration around the europium(III) cation. Selected torsion angles of the hydroxypropyl groups are given in Table 7. All of the C–N and C–O bond distances are equivalent within the limits of experimental error. The average C–N bond distance is 1.492 (±0.035) Å and the average C–O bond distance is 1.459 (±0.017) Å (1.480 (±0.033) and 1.433 (±0.036) Å, respectively, for molecule 2). All hydroxypropyl ligand bond distances in the two molecules are statistically equivalent and are given in Table 8. Carbon atoms C(14), C(17), C(20), and C(23) are chiral. The first molecule has three chiral carbon atoms in the *R* conformation (C(14), C(17), and C(23)), while the fourth carbon atom (C(20)) is in the opposite *S* conformation. In the second molecule the trend is the opposite, three carbon atoms in the *S* conformation (C(14′), C(20′), and C(23′)) and one carbon atom (C(17′)) in the *R* conformation. The 12-membered macrocyclic ring adopts a typical 3333 square conformation that places all four nitrogen atoms on the same side of the ring as described by Dale.[21] This allows coordination of all four nitrogen atoms with the europium(III) ion. The average values of the torsion angles around the macrocyclic ring are similar in the molecules: C–N–C–C = –85.4 (±5.3)°, N–C–C–N = –50.0 (±5.2)°, and C–C–N–C = 154.6 (±2.7)° for molecule 1 and –81.0 (±1.5), –57.3 (±6.5), and 159.1 (±5.6)°, respectively, for molecule 2. These torsion angles are similar to those reported for a 1,4,7,10-tetraazacyclododecane derivative.[18] All of the C–C and C–N bond distances of the macrocyclic ring are statistically equivalent with C–N = 1.472 (±0.045) Å and C–C = 1.407 (±0.021) Å.

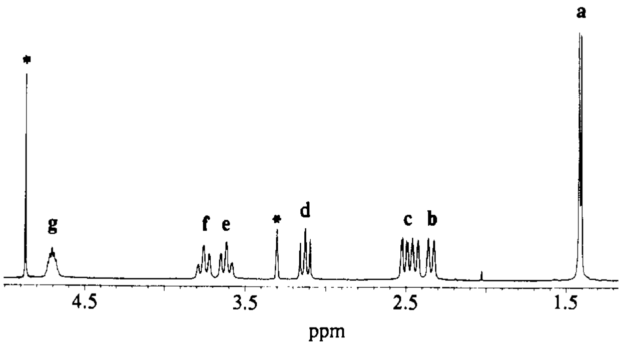

Figure 4. ^{1}H NMR spectrum of La(*S*-THP)(CF$_3$SO$_3$)$_3$ in methanol-*d*$_4$ at 18 °C.

Solution NMR Properties. Interpretation of ^{13}C and ^{1}H NMR spectra of lanthanide(III) complexes synthesized from the mixture of THP stereoisomers is complicated by the large number of overlapping peaks. In addition, some of the peaks are broadened, probably due to dynamic processes. For a given lanthanide complex, there are potentially five different THP complexes that would have distinct NMR resonances. In addition, each complex may have more than one conformation in solution (as described below), giving rise to a more complicated set of resonances. We did not attempt to assign resonances in the NMR spectra of these complexes. Lanthanide complexes of the *S*-THP macrocycles gave much simpler ^{1}H and ^{13}C NMR spectra that are readily assigned and support a solution structure that has some features in common with the solid-state structure of the europium(III) THP complex.

The ^{1}H NMR spectrum of La(*S*-THP)(CF$_3$SO$_3$)$_3$ in methanol-*d*$_4$ at 18 °C is shown in Figure 4. (A similar ^{1}H NMR spectrum is observed in D$_2$O with the two triplets in the 3.5–4.0 ppm region appearing as a quintet.) The assignments of the resonances are made partially through the use of 2D COSY NMR experiments. Resonances attributed to the pendent hydroxypropyl groups appear as a doublet (a) for the methyl group, a pseudoquintet (g) for C*H*(OH)(Me), and two triplets (resonance d and overlapping resonance c) for the ethylene protons. ^{1}H resonances are readily assigned to axial and equatorial protons in the ring. Small gauche coupling constants and large trans-axial and geminal coupling constants give rise to doublets for the equatorial protons and

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(20) Aime, S.; Anelli, P. L.; Botta, M.; Fedeli, F.; Grandi, M.; Paoli, P.; Uggeri, F. *Inorg. Chem.* **1992**, *31*, 2422–2428.

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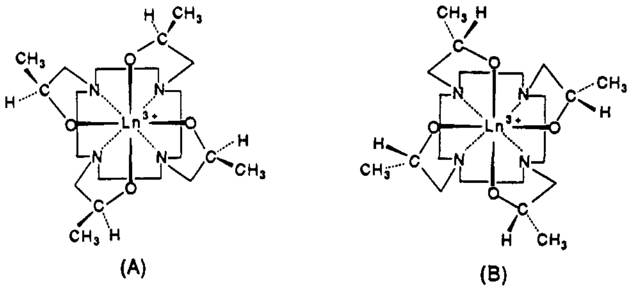
triplets for the axial protons, as observed for similar complexes.[22] Cyclen ring protons in equatorial positions appear as two doublets (resonance b and overlapping resonance c), and axial protons appear as two triplets (e, f). The geminal coupling constant for the ring protons is 12.1 Hz and that for the protons of the CH_2 group of the propyl arm is 13.0 Hz. 2D COSY experiments indicate that equatorial proton b is geminal to axial proton e and equatorial proton c is geminal to axial proton f. A similar ^1H NMR spectrum is observed for the lutetium complex; assignments are given in the Experimental Section. Eight ^1H NMR resonances are observed for the europium complex at 18 °C in methanol-d_4. (A similar ^1H NMR spectrum is observed in D_2O.) All resonances are broad, and no coupling could be resolved. However, this spectrum is consistent with what we observe for the lanthanum and lutetium complexes in that there are eight different ^1H resonances arising from eight chemically inequivalent protons.

Five resonances are observed in the ^{13}C NMR spectra of all Ln(*S*-THP)$(CF_3SO_3)_3$ complexes. For the lanthanum complex, the resonance at 20.8 ppm is assigned to the carbon of the methyl group and the two peaks at 50.4 and 52.7 ppm are attributed to the carbons of the cyclen ring. The CH_2 of the pendent group gives rise to a ^{13}C resonance at 60.8 ppm, and the carbon of C(H)(Me)(OH) gives rise to a resonance at 69.2 ppm. Assignments are made similarly for the lutetium complex (see Experimental Section). These assignments are confirmed by use of ^1H-coupled ^{13}C NMR experiments. The ^{13}C NMR spectrum of the europium complex has a resonance at 13.8 ppm assigned to the methyl group of the propyl arm. Resonances at 81.0, 82.2, and 84.0 ppm are assigned to the ring carbons and the CH_2 carbon of the propyl group. The resonance at 97.2 ppm is tentatively assigned to the CH(OH) carbon of the propyl arm. These assignments are based partially on comparison to the ^{13}C NMR spectrum of the $Eu(THED)^{3+}$ complex, where assignment of the cyclen ring carbons was made on the basis of the temperature-dependent behavior of the different resonances.[3]

The most interesting feature of the NMR spectral properties of lanthanide *S*-THP complexes as compared to DOTA and THED derivatives is the apparent absence of dynamic processes on the NMR time scale. (Little change in the ^1H NMR spectrum of the lanthanum complex is observed over the temperature range 18–100 °C.) Lanthanum(III) DOTA and THED complexes are fluxional at room temperature on the NMR time scale.[3,22] This fluxionality is best described as rotation of the cyclen ethylene groups about the C–C bond in concert with movement of the pendent groups.[22b] These motions interconvert enantiomeric pairs. (These are formed by changing the conformation of the cyclen ethylene groups in concert with having the pendent groups swirl clockwise or counterclockwise.) The *S*-THP complexes are different in that the additional methyl group on the α-carbon adds four chiral centers. Instead of an enantiomeric pair, two different diastereomers are possible. However, ^1H and ^{13}C NMR studies indicate the presence of only one of the two possible diastereomers, suggesting that one diastereomer is energetically favored. If we assume that in solution the donor atoms of THP are found in a square antiprismatic arrangement about the lanthanide (in the structure of the europium THP complex they are midway between a square antiprism and a square prismatic arrangement), then the two diastereomers for the *S*-THP lanthanide(III) complexes may be represented as shown in Chart 1, where the pendent groups may be arranged clockwise or counterclockwise. (Note that, even for a square prismatic arrangement, two diasteromers would arise because of the four chiral pendent groups and the two possible conformations of the macrocycle ring as described in the description of the structure of the europium complex.) The solid-state structure of the europium THP diastereomer that contains *S,S,S,R*-THP corresponds to A in Chart 1 (with one hydroxypropyl converted from *S* to *R*). Molecular models suggest that isomer A may be favored from steric considerations and is probably the same one observed in solution for the lanthanum and lutetium complexes. Thus, the effect of the methyl groups of lanthanum and lutetium *S*-THP complexes is to dictate the arrangement of the pendent groups and to favor a particular conformation of the cyclen ethylene groups. This may increase macrocycle rigidity and has a profound effect on the resistance of the macrocyclic complex to dissociation as shown below. Enhanced kinetic inertness arising from macrocycle rigidity was recently reported for lanthanide(III) DOTA derivatives containing asymmetric carbons bearing α-methyl groups (*all-R* configuration) in the pendent carboxylic groups.[23]

Chart 1



(A) (B)

Kinetics of Dissociation. Because of our interest in synthesizing lanthanide complexes that are kinetically inert to metal ion release under physiological conditions, we have studied the resistance of these complexes to dissociation at various pHs and temperatures and in the presence of chelating agents such as DTPA. Most of our kinetic studies of the dissociation of Ln(THP)$(CF_3SO_3)_3$ or Ln(*S*-THP)$(CF_3SO_3)_3$ complexes use excess Cu^{2+} as a trapping agent and monitor the appearance of a UV–vis absorbance peak at 314 nm attributed to the Cu(II) THP complexes. These studies are usually done at pH 6.0 because absorbance bands of free Cu^{2+} at a concentration of 1 mM mask the 314-nm absorbance of the $Cu(THP)^{2+}$ complex at more basic pH values. Variation of the Cu^{2+} concentration has no effect on the reaction rate; hence dissociation of the lanthanide macrocyclic complexes is not assisted by Cu^{2+}.

The dissociation of the lanthanide complexes synthesized from the mixture of THP stereoisomers was followed over a period of days. Each stereoisomer of the lanthanide complex may dissociate at a different rate. With the exception of the lutetium isomer, this gives rise to a dependence of absorbance versus time which does not fit a simple first-order kinetic expression. (For $Lu(THP)^{3+}$, a first-order rate constant of 7 (±1) × 10^{-6} s^{-1} is obtained.) The proportion of each stereoisomer in these mixtures is unknown and may be different from that in the free ligand. Thus, the exact extinction coefficient for the Cu(II) THP complexes is not known. Assuming that the extinction coefficient varies only slightly for Cu(II) complexes of the various isomers, we estimate that approximately 76%, 83%, and 93% of the europium(III), lanthanum(III), and lutetium(III), respectively, has dissociated after 10 days. Qualitatively, these data would indicate that the europium and lanthanum THP complexes are similar to the europium and lanthanum THED complexes (half-lives of 270 and 21 h, respectively). The fact that the absorbance for the Cu(II) THP complexes levels off at less than 100% over a period of 10 days is consistent with a proportion of the THP complexes containing the more robust *S*-THP (or *R*) isomer, as discussed below. Kinetic studies of the dissociation of the analogous *S*-THP complexes yield first-order rate constants at

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Table 9. First-Order Rate Constants for Dissociation of Lanthanide *S*-THP Complexes in Water[a]

complex	temp, °C	pH	k, s^{-1}	half-life, days
La(*S*-THP)(CF$_3$SO$_3$)$_3$	37	6.0	$(1.1\ (\pm 0.4)) \times 10^{-7}$	73
Eu(*S*-THP)(CF$_3$SO$_3$)$_3$	37	6.0	$(8.0\ (\pm 0.2)) \times 10^{-8}$	100
Lu(*S*-THP)(CF$_3$SO$_3$)$_3$	37	6.0	$(1.5\ (\pm 0.5)) \times 10^{-7}$	53
La(*S*-THP)(CF$_3$SO$_3$)$_3$	60	6.0	$(7.5\ (\pm 0.5)) \times 10^{-7}$	11
Eu(*S*-THP)(CF$_3$SO$_3$)$_3$	60	6.0	$(3.0\ (\pm 0.3)) \times 10^{-7}$	27
Lu(*S*-THP)(CF$_3$SO$_3$)$_3$	60	6.0	$(5.0\ (\pm 0.5)) \times 10^{-7}$	16
La(*S*-THP)(CF$_3$SO$_3$)$_3$	60	3.0	$(2.0\ (\pm 0.5)) \times 10^{-6}$	4.0
Eu(*S*-THP)(CF$_3$SO$_3$)$_3$	60	3.0	$(6.3\ (\pm 0.3)) \times 10^{-7}$	13
Lu(*S*-THP)(CF$_3$SO$_3$)$_3$	60	3.0	$(2.0\ (\pm 0.5)) \times 10^{-6}$	4.0

[a] Determined from measurement of Cu(II) THP absorbance; 0.1 mM Ln(THP)(CF$_3$SO$_3$)$_3$ and 1.0 mM Cu^{2+}.

pH 6.0 and 37 and 60 °C and at pH 3.0 and 60 °C (Table 9). Half-lives for dissociation of the *S*-THP complexes indicate that they are much more resistant to dissociation than are the complexes synthesized from the mixture of THP stereoisomers.

The lanthanide THP complexes are a mixture of complexes formed from different stereoisomers of THP. The stereoisomers of THP differ in the number and relative positions of *R* and *S* chiral centers of the α-carbon of the hydroxypropyl group. With the exception of complexes of the *S,S,S,S* and *R,R,R,R* stereoisomers, the macrocyclic compounds contain ligands with mixed pendent groups of *S* and *R* configuration. As discussed above, the methyl groups of *S*-THP may serve to enhance macrocycle rigidity. With mixed *R* and *S* groups one might expect that this effect would be lost. Examination of molecular models suggests that there may be steric problems associated with placing a pendent group with an *R* configuration adjacent to a pendent group with an *S* configuration. The dissociation data in Table 9 and the NMR data for lanthanum and lutetium complexes described below suggest that this is indeed the case. All three lanthanide *S*-THP complexes were found to be considerably more resistant to dissociation than the lanthanide THP and THED complexes at pH 6.0 and 37 °C. The lanthanum and europium *S*-THP complexes are approximately 80-fold and 9-fold more inert to dissociation than their respective THED complexes. The lutetium *S*-THP complex is 60-fold more resistant to dissociation than the mixture of lutetium THP stereoisomers. The europium(III) *S*-THP complex is again the most resistant to dissociation compared to early and late lanthanides; however, both lanthanum and lutetium complexes are also resistant to dissociation. In fact, there is remarkably little difference between the lanthanide complexes. In other systems, such as the hexadentate Schiff-base complexes,[24] a much greater variation in lability of the lanthanum complex compared to the lutetium complex is observed.[1] Most macrocyclic ligands have an optimal metal ion radius with a certain degree of flexibility for binding. The Schiff-base macrocyclic ligand L^1 is apparently more sensitive to ionic radius than is *S*-THP. The decreasing ionic radius of the lanthanide ions as one progresses from La^{3+} to Lu^{3+} may also result in a different coordination number and geometry of the complexes in water.[11] Thus, it is surprising that differences in dissociation rates are so minor for *S*-THP complexes of early, middle, and late lanthanides.

Under more rigorous conditions, the lanthanide(III) *S*-THP complexes dissociate in water. Dissociation is accelerated at higher temperatures. At 60 °C and pH 6.0 the half-life of the europium *S*-THP complex is shortened to 27 days. More rapid dissociation is observed at pH 3.0 and 60 °C, as would be anticipated if there were an acid-catalyzed dissociation pathway.[6a] Under all conditions, the europium complex is the most robust.

Our studies suggest that dissociation is not markedly accelerated by DTPA, a good ligand for the trivalent lanthanides. The dissociations of the lanthanum and lutetium *S*-THP complexes are readily monitored by ^{1}H NMR in D$_2$O at pD 7.3 and 25 °C in the presence and absence of a 2-fold excess of DTPA. Dissociation of the europium complex was not studied by use of ^{1}H NMR because the broad resonances of the complex mask most other peaks. No decomposition of the lanthanum complex is observed after 1 day. A trace of free ligand is observed for the lutetium complex both in the presence (1% dissociation) and in the absence (<1%) of a 2-fold excess of DTPA. After 3 weeks, approximately 7.0 (±2%) of the lanthanum complex is dissociated, and after 6 weeks in the presence of DTPA 6 (±2)% is dissociated. In the presence and absence of DTPA 20 (±2)% and 10 (±1)% of the lutetium complex, respectively, are dissociated after 3 weeks.

Because of our interest in the conjugation of lanthanide THP complexes to oligonucleotides, coordination of Lu^{3+} and La^{3+} by *S*-THP was studied in D$_2$O at pD 7.5 and 37 °C by use of ^{1}H NMR. After 1 day, 10% of the lanthanum *S*-THP complex was formed. The percentage of complex formed remained at 10% after 3 days. Only a trace of the lutetium complex was formed under these conditions (<1%) after 3 or more days. That little of the *S*-THP lanthanum or lutetium complexes form in water stands in contrast to lanthanide DOTA complexes, where formation constants are large and the europium and gadolinium complexes form completely even at acidic pHs.[6a] In this respect, the *S*-THP complexes resemble lanthanide(III) complexes of [2.2.1]-cryptates[25] and THED in that the complexes are inert to dissociation in water but do not have large formation constants. However, the La(*S*-THP)$^{3+}$ complex forms to a greater extent than does the La(THED)$^{3+}$ complex (0%) under similar conditions.[3] Hence, the formation constant for the La(*S*-THP)$^{3+}$ complex is probably larger than that for the La(THED)$^{3+}$ complex.

Conclusion. The *S*-THP ligand is an excellent ligand for the trivalent lanthanides; *S*-THP complexes of lanthanum(III), europium(III), and lutetium(III) are highly resistant to dissociation in water. Further studies are needed to probe whether these complexes remain intact in blood serum and in vivo. Fortunately, the ability of complexes to remain intact in serum frequently correlates well to the kinetic inertness of the complex to dissociation. There are many examples from the fields of radiopharmaceuticals or magnetic resonance imaging agents where metal complexes that contain macrocyclic ligands[26] are shown to remain intact better in serum than do linear chelates despite the high formation constants of the latter.

With the *S*-THP complexes, we have in hand complexes of early, middle, and late lanthanides that are resistant to dissociation. Because properties of the lanthanides such as ionic radius, Lewis acidity, and coordination number change in the lanthanide series, it will be interesting to examine the effect that these changes may have on lanthanide ion promoted RNA cleavage.

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Supplementary Material Available: Complete tables of bond lengths, bond angles, anisotropic thermal parameters, and calculated positions of hydrogen atoms (9 pages). Ordering information is given on any current masthead page.

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