Solution Structure and Dynamics of Lanthanide Complexes of the Macrocyclic Polyamino Carboxylate DTPA-dien. NMR Study and Crystal Structures of the Lanthanum(III) and Europium(III) Complexes

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An 18-membered macrocyclic DTPA-bis(amide) ligand (DTPA = diethylenetriaminepentaacetic acid) containing a heteroatom in the amide link has been prepared *via* the condensation of DTPA-dianhydride and diethylenetriamine. The solution structures of the two isomeric pairs present in the Ln(III) complexes of DTPA-dien have been investigated by ^{1}H NMR. One enantiomeric pair exhibits slow exchange on the NMR time scale at low temperatures (0−25 °C) and "dynamic" behavior at higher temperatures. The other isomeric pair exhibits an unusual "static" behavior; exchange remains slow even at 95 °C. Peak assignments for the Eu(DTPA-dien) spectra are given based on deuteration studies, 2D COSY spectroscopy, and 2D EXSY spectroscopy. 2D EXSY spectroscopy at several temperatures and mixing times showed that $\Delta G^{\ddagger}_{299}$ for the "dynamic" isomerization is 57.5 ± 0.3 kJ/mol, and that the "dynamic" isomer is an intermediate for the "static" isomerization, which occurs with a change in backbone amine chirality. The structures of the lanthanum(III) and europium(III) DTPA-dien complexes have been determined by X-ray analysis. $[La(DTPA\text{-}dienH^+)H_2O]_2(CF_3SO_3^-)_2{\cdot}18H_2O$ (**I**) crystallizes as a carboxylate-bridged dimer about a center of inversion in the orthorhombic space group *Pbca* with $a = 12.626(2)$ Å, $b = 21.405(3)$ Å, $c = 26.422(9)$ Å, and $Z = 8$. Each lanthanum ion is 11-coordinate with octadentate ligand coordination, an η^2 bridging carboxylate, and one water. $[Eu(DTPA\text{-}dienH^+)]_4(CF_3SO_3^-)_4{\cdot}6NaCF_3SO_3{\cdot}20H_2O$ (**II**) crystallizes as a carboxylate-bridged tetramer with two crystallographically independent Eu(III) positions ($Z = 8$ for each) in the monoclinic space group *C2/c*: $a = 30.94(1)$ Å, $b = 23.456(3)$ Å, $c = 22.611(4)$ Å, $\beta = 105.78(2)°$. The coordination geometries about Eu1 and Eu2 are nearly identical and are described as a nine-coordinate tricapped trigonal prism with octadentate ligand coordination plus an η^1 bridging carboxylate. The tendency to oligomerize is attributed to the constraints imposed by the macrocycle and the hydrogen bonding available with the link heteroatom. The structrual differences between the two complexes are attributed to a difference in La(III) and Eu(III) ionic size. The solution structure of the "dynamic" isomer is found to be the same as the monomer unit of the crystal structures, and the "static" isomer is similar, save for a change in one terminal backbone nitrogens' chirality.

Introduction

Over the past two decades Magnetic Resonance Imaging (MRI) has become a very powerful tool of diagnostic medicine. The use of paramagnetic metal complexes as image enhancement agents allows imaging that, for several important applications, is otherwise unobtainable.[1,2] Since the Gd(III) ion, with a 4f^7 electronic configuration has a $S = {}^7/_2$ ground state, it is particularly attractive as an imaging agent. However, the free metal ion, which is similar in size to Ca(II) and binds tightly to calcium binding sites,[1,3] is toxic and so must be sequestered in a metal complex.[1,4] The first such agent in wide use has been $[Gd\ (DTPA)]^{2-}$,[5] but the negative charge of this complex adversely affects tissue distribution for many applications. Additionally, the high osmolality of formulations containing this complex make administration by injection painful.[1,2]

Recently, particular effort has focused on derivitizing DTPA to give neutral lanthanide complexes, thus decreasing the possibility of osmotic cell damage. Although there are several avenues to approach this problem, including esterification[6] and covalent modification of the backbone,[7] one particularly elegant and simple method is the formation of the bis(amide) derivative of DTPA *via* amine addition to DTPA-dianhydride.[8] This method, employed by Nycomed/Salutar Corp. for the synthesis of the contrast agent Gd(DTPA-bis(methylamide) (BMA)),[8] allows the relatively straightforward synthesis of a range of DTPA-bis(amide) complexes.

Since the mechanism for proton relaxation by these complexes relies on proton (water) exchange and hence on isomerization reactions,[1,2] the structures of the complex species in solution and their possible interchange are significant. The aqueous proton NMR spectra of $[Ln(DTPA)]^{2-}$ (Ln = La, Pr, Eu, Yb, Lu) complexes have been studied in some detail,[9−12] although

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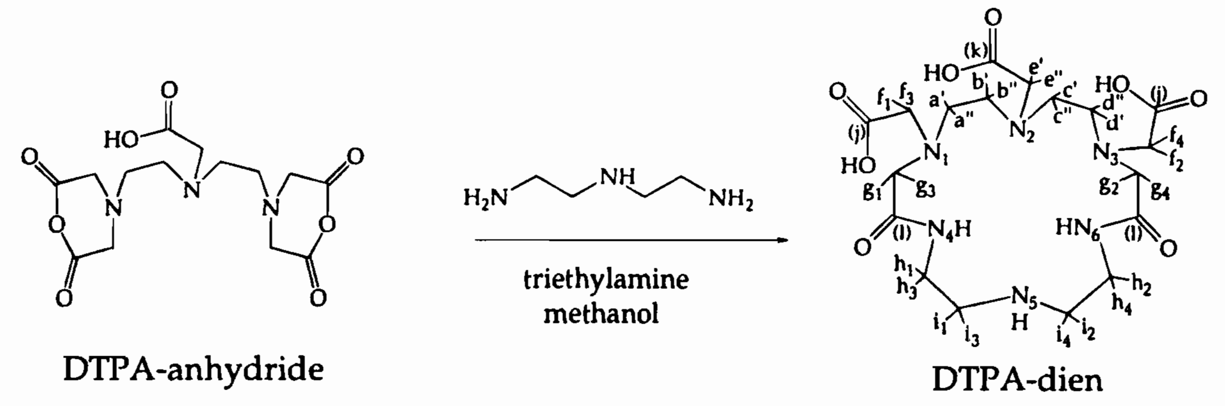
Scheme 1



later work came to different assignments for the structures and interchange mechanisms.[11,12] Neutral complexes of Gd(III) with DTPA derivatives have been shown to have properties somewhat different from the parent ionic complex. Preliminary studies of the bis(amide) ligands, which have a lower effective symmetry for the ligand, showed the spectra are highly complex and rapidly interconverting.[13,14] The constraint of tethering the two amide groups together substantially diminishes both the number of isomers and the pathways for interconversion. Hence macrocyclic bis(amide) complexes were prepared for study.

We report here the synthesis of DTPA-dien, a new macrocyclic bis(amide) ligand, and the crystal structures of its La(III) and Eu(III) complexes (Scheme 1). This hexaazacyclen derivative, synthesized *via* the condensation of DTPA-dianhydride and diethylenetriamine (dien), contains a heteroatom (N) within the bis(amide) link. We have found that these alterations cause significant changes in the aqueous solution structure and dynamics of the lanthanide complexes relative to both $[Ln(DTPA)]^{2-}$ and linear Ln(DTPA-bis(amide)) complexes, and even relative to macrocycles with simple carbon chain links.[15] Additionally, we report the solution structures of these lanthanide macrocycles as determined by a systematic NMR study; these are then compared with the solid state structures.

Experimental Section

Syntheses. General Information. Diethylenetriamine (dien) and triethylamine were obtained from Aldrich and distilled from Na. Methanol was distilled from CaH_2. Thin-layer chromatography (tlc) of the ligands was performed with 8:1 methanol:HCl (0.1 M) eluant on silica plates, using I_2 for visualization. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley, CA. Fast atom bombardment (FAB+) mass spectra were obtained at the Mass Spectrometry Laboratory at University of California, Berkeley.

DTPA-dien. Diethylenetriamine (1.10 mL, 10 mmol) and triethylamine (2.80 mL, 20 mmol) were added via syringe to 500 mL of methanol. DTPA-dianhydride (4.65 g, 10 mmol)[16] was placed in a solid addition funnel and gradually added to the stirring solution. All solid was allowed to dissolve prior to each addition of anhydride. The resulting pale yellow, clear solution was stirred at room temperature overnight. Solvent was removed by rotary evaporation to give a pale yellow glass. In order to remove triethylamine, the glass was redissolved in 50 mL of 0.1 M NaOH and the solvent removed by rotary evaporation three times. The resultant glass was taken up in 10 mL of methanol and purified by SiO_2 chromatography. Fractions (6–8 mL) were eluted with an 8:1 methanol:HCl_{aq} (0.1 M) mixture and followed by tlc. The fractions including the highest R_f spot ($R_f = 0.15$) were combined and solvent removed by rotary evaporation to give a colorless, hygroscopic glass. This solid was dissolved in methanol to yield a clear, colorless solution from which a white fluffy powder immediately precipitated. The solid was filtered, dried, and characterized. Yield = 1.701 g (37.0%). ^1H-NMR (D_2O, assignments as in Scheme 1): δ 3.08 (br t, 4 H, *i*), 3.15 (br t, 4 H, *bc*), 3.20 (br t, 4 H, *h*), 3.25 (s, 4 H, *g*), 3.38 (s, 4 H, *f*), 3.45 (br t, 4 H, *ad*), 3.60 (s, 2 H, *e*). ^{13}C-NMR (D_2O): δ 35.7 (*h*), 46.9 (*i*), 50.1 (*g*), 53.4 (*f*), 53.9 (*e*), 57.5 (*bc*), 58.4 (*ad*), 170.8 (*k*), 173.2 (*j*), 177.5 (*l*). MS: *m*/*e* = 461.4 (MH^+). Anal. Calcd (found) for $C_{18}H_{32}N_6O_8{\cdot}H_2O$: C, 45.18 (45.33); H, 7.16 (7.28); N, 17.56 (17.04).

Ln^{III}(DTPA-dien) Complexes. The lanthanide trifluoromethanesulfonate (triflate) salts of La, Sm, Eu, Ho, Yb, and Lu were made from the lanthanide oxides (Apache Co., 99.9% pure) following published procedure.[17] DTPA-dien complexes of these ions were made as above by adding stoichiometric amounts of $Ln(trif)_3$ and DTPA-dien to D_2O at room temperature and stirring for 2–3 h. Solvent was removed under vacuum and the resulting powder redissolved in D_2O prior to recording the NMR spectra (pH = 2, uncorrected for deuterium isotope effect).

The DTPA-dien complexes of Ce and Dy were made from the $LnCl_3$ salts (Ce, March Co.; Dy, Orion Co.) in an analogous fashion (pH = 2). The DTPA-dien complexes of Nd, Tb, Er, and Tm were made directly from the oxides (Apache Co., except Er_2O_3 from Orion Co.) by heating a small excess of the lanthanide oxide with DTPA-dien in 0.1 M HCl at 50 °C for 2 days. Any remaining undissolved oxide was removed by filtration, the solution brought to pH = 2 with NaOH, and solvent removed under vacuum. The solids were redissolved in D_2O prior to recording the NMR spectra.

Vapor Pressure Osmometry. Solution molecular weight was measured on a Knauer vapor pressure osmometer in H_2O at 45 °C (head temperature = 51 °C). Sucrose was used as a standard over a 0.2–0.5 M concentration gradient to yield a machine constant of 492 units/(mol/L). The samples were measured over an estimated concentration gradient of 0.1–0.5 M (7–32 mg/mL).

The $[Eu(DTPA\text{-}dien(OH^-))]Na^+$ complex for vapor pressure osmometry was made by adding stoichiometric amounts of DTPA-dien (monosodium salt) and Eu_2O_3 in H_2O without added acid and stirring at room temperature for 4 days. Solvent was removed from the clear solution to yield a colorless glass; pH of a 0.5 M solution = 9. Anal. Calcd (found) for $C_{18}H_{29}N_6O_8Eu{\cdot}3H_2O{\cdot}NaOH$: C, 30.73 (30.75); H, 5.16 (5.63); N, 11.95 (11.49). The $[Eu(DTPA\text{-}dienH^+)]OAc^-$ complex was made by heating an excess of Eu_2O_3 with DTPA-dien (protonated)

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at 50 °C for 4 days, followed by the addition of acetic acid (pH from 8 to 5.5) and heating for an additional day. Excess oxide was removed by filtration, the solvent was removed from the filtrate, and the complex purified on a Sephadex G-25 column in H_2O. pH of a 0.5 M solution = 6. Anal. Calcd (found) for $C_{18}H_{29}N_6O_8Eu\cdot 3H_2O\cdot HOAc$: C, 33.20 (33.25); H, 5.43 (5.02); N, 11.62 (11.21).

Synthesis of Eu(DTPA-dien) for X-ray Analysis. DTPA-dien (100 mg, 0.20 mmol) and $Eu(trif)_3$ (120 mg, 0.20 mmol) were dissolved in 5.0 mL of H_2O and allowed to stir at room temperature for 1 h (pH = 1.6). The clear, colorless solution was neutralized with NaOH(aq) (pH = 8.6), and solvent was removed *via* rotary evaporation. The resulting white solid was redissolved in 1 mL of D_2O (pH = 6.8) and ^1H-NMR spectra were recorded. Crystals suitable for diffration were eventually isolated from this solution. MS: *m*/*e* = 611.2 (75%), [Eu(DTPA-dienH$^+$)], *m*/*e* = 761.0 (35%), H^+[Eu(DTPA-dienH$^+$)]($CF_3SO_3^-$), *m*/*e* = 1219.2 (25%), H^+[Eu(DTPA-dien)]$_2$. **La(DTPA-dien)** crystals suitable for diffration were prepared in an analogous fashion, with final pH = 7.2. MS: *m*/*e* = 597.2 (100%), [La(DTPA-dienH$^+$)], *m*/*e* = 747.1 (48%), H^+[La(DTPA-dienH$^+$)]($CF_3SO_3^-$).

NMR. General Information. Unless noted otherwise, NMR spectra were collected in D_2O between pH = 2 and 6 and at concentrations of 0.01−0.03 M on either a Bruker AM 400 or AM 500 at the University of California at Berkeley, College of Chemistry NMR Facility. Chemical shifts are reported with respect to the water signal. The complexes are fully formed over the pH range studied; spectra at pH 2 show little to no free ligand, and peaks attributied to the protonated metal complexes do not change in peak shape or position between pH = 2 and 6. Chemical exchange processes were studied using the standard NOESY 2D pulse sequence[18] $90°-t_1-90°-t_m-90°$ where t_1 is the evolution time (frequency labeling) and t_m is the mixing time (magnetization exchange). Since paramagnetic relaxation is the dominant mechanism and exchange is fast, nuclear Overhauser effects are negligable for these compounds, and only exchange effects are observed in these spectra.[19] The 2D NOESY experiments described here will thus be referred to as EXSY spectra.[11] Pure absorption spectra were obtained by using time-proportional phase incrementation (TPPI).[20] Longitudinal relaxation times (T_1) were measured by the standard inversion-recovery technique.

2D EXSY spectra of Eu(DTPA-dien) (100−150 mg/mL, pH = 2) were recorded at several temperatures. For the experiment at 0 °C (General Electric GN-500), a t_m of 25 ms was employed. Data were collected with 1200 points in F_2 (8 scans over 80 ppm) and 580 points in F_1 with presaturation of the HOD peak. The final data matrix was zero-filled to 2K(complex) × 4K(real). Data were processed using a skewed, 60° shifted sine^2 bell functon in F_2 and F_1. The assigned spectrum is available with the supplementary material.

The 2D EXSY experiment at 500 MHz and 26.0 °C employed a t_m of 600 μs. Data were collected with 1024 points in F_2 (32 scans over 71 ppm) and 512 points in F_1. The final data matrix was 512 × 512 points, and data were processed by using a $\pi/2$ phase shifted sine^2 bell window in both dimensions. Under conditions where the mixing time is such that the observed magnetization exchange is small, the rate constant for the exchange can be found by integrating selected on- and off-diagonal peaks.[21] For two-site isomerization exchange of spins A and B, the relationship between exchange rate and intensities of diagonal peaks ($I_{AA} = I_{BB}$) and cross peaks ($I_{AB} = I_{BA}$) is given by

$$k = \frac{1(r+1)}{t_{\mathrm{m}}(r-1)}$$

$r = (I_{AA} + I_{BB})/(I_{AB} + I_{BA})$.[21] From this exchange rate and the temperature, $K^{\ddagger}$ and $\Delta G^{\ddagger}{}_T$ can be calculated.[22]

Several 2D EXSY experiments were run at 95 °C, varying the mixing time from 2 to 100 ms. For each of eight experiments, data were collected with 1024 points in F_2 (8 scans over 45 ppm) and 256 points in F_1. The final data matrices were zero-filled to 512 × 512 points, and data were processed using a $\pi/2$ phase-shifted sine^2 bell window. The evolution of cross peaks in successive experiments allowed the determination of relative exchange rates between isomers. No quantitative information can be obtained from the slow exchange processes observed at 95 °C, as the exchange rates are a significant fraction of most of the protons' T_1 values (T_1 range: 30−200 ms).

A 2D homonuclear correlation spectrum (COSY) of Eu(DTPA-dien) was obtained at 500 MHz and 92.8 °C, conditions under which the "dynamic" isomer pair exhibits average signals. Data were collected with 4K points in F_2 (16 scans over 60 ppm) and 1K points in F_1. Data were processed as a 2K × 4K matrix and the spectrum symmetrized about the diagonal. The assigned spectrum is available with the supplementary material.

Peak Assignments. Peak assignments for ^1H NMR of Eu(DTPA-dien) at 5 °C and 95 °C are given in Figure 7. Acetate methylene protons (*f* and *e*) were assigned by deuteration studies (DTPA-dien was stirred at reflux in D_2O at pH ≥ 12 (NaOD) for 18 h); ^1H NMR of the ligand indicated complete deuteration of the acetates, but no deuteration of the amide methylenes. Metal complexes were made and studied at several temperatures to assign these six peaks of both isomers.

The 2D COSY at 95 °C allowed the assignment of groups of protons of the "static" isomer, as the nitrogens partition the complex into four groups of four protons and five groups of two protons. Amide methylene protons (g_1g_2 and g_3g_4) were assigned from the latter pairs by the process of elimination. Backbone protons ($a''a'b'b''$ and $c''c'd'd''$) were assigned based on the positions of a pair of furthest-shifted protons (downfield shift for Eu and Yb, upfield for Pr) which appear in all paramagnetic DTPA and DTPA-analog complexes studied to date.[11−13,23] As in the [Ln DTPA]$^{2-}$ complexes,[11] these peaks for both isomers have been assigned to the c'' and a'' protons, which, based on CAChe modeling studies and the crystal structures presented herein, are relatively close to the metal and approximately along the highest pseudosymmetry axis of the complex (the Ln−H_2O vector). With the assignments of c'' and a'' and a Karplus curve estimate[24] of vicinal coupling constant from the CAChe model, the backbone of the "static" isomer could be fully assigned.

The 2D EXSY spectrum at 0 °C with all the "dynamic" isomer peaks well resolved allowed the assignments of pairs of protons (amide methylene g_1g_3, for example) exchanging through a pseudomirror plane intermediate. A few COSY peaks (dispersive rather than all positive) could be distinguished for the "static" isomer as well. The 2D EXSY spectrum at 95 °C allowed the assignments of groups of similar protons in the "static" isomer, and the synthesis of the above information about both isomer pairs.

At high temperatures, the six "static" acetate protons were distinguishable as four *f* protons (exchanging with two coalesced "dynamic" peaks) and two *e* protons. Backbone proton sets ($a'a''d'd''$ and $b'b''c'c''$) complimented the COSY assignments and the low temperature EXSY assignments. Groups of link protons (*h* and *i*) can be unambiguously assigned as sets, but individual protons cannot be distinguished within these sets, and computer modeling of the system was not completely successful.

X-ray Crystallography. $[La(DTPA\text{-}dienH^+)H_2O]_2(CF_3SO_3^-)_2\cdot 18H_2O$ (I). Crystal data and collection parameters for the colorless, plate-like crystals of La(DTPA-dien) are summarized in Table 1. An absorption correction was applied using DIFABS[25] (min. correction = 0.91, max. correction = 1.20) after removing 5343 systematically absent and "bad" data from the structure factor calculations (data were flagged "bad" based on apparent peak overlap and poor averaging statistics of symmetry equivalent reflections). Redundant data were averaged

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Table 1. Crystal Data and Data Collection Parameters for [La(DTPA-dienH$^+$)·H$_2$O]$_2$(CF$_3$SO$_3$$^-$)$_2$·18H$_2$O (**I**) and [Eu(DTPA-dienH$^+$)]$_4$(CF$_3$SO$_3$$^-$)$_4$·6NaCF$_3SO_3$·20H$_2$O (**II**)

	I	**II**
formula	LaSF$_3$O$_{21}$N$_6$C$_{19}$H$_{50}$	Eu$_2$S$_5$Na$_3$F$_{15}$O$_{41}$N$_{12}$C$_{41}$H$_{80}$
fw	926.61	2215.34
temp (°C)	−105	−119
space group (No.)	*Pbca* (61)	*C*2/*c* (15)
cell constants^a		
a (Å)	12.626(2)	30.94(1)
b (Å)	21.405(3)	23.456(3)
c (Å)	26.422(9)	22.611(4)
α (deg)	90	90
β (deg)	90	105.78(2)
γ (deg)	90	90
V (Å^3)	7141(4)	15792(11)
Z	8	8 (Eu1), 8 (Eu2)
abs coeff, μ_{calc} (cm^{-1})	13.56	18.48
d_{calc} (g/mL)	1.724	1.863
F(000)	3792	8896
crystal dimens (mm^3)	0.50 × 0.45 × 0.20	0.35 × 0.33 × 0.31
radiation	Mo Kα (λ = 0.710 73 Å)	Mo Kα (λ = 0.710 73 Å)
diffractometer	Enraf-Nonius CAD-4	Enraf-Nonius CAD-4
h, *k*, *l* range collected	0→8, 0→30, −37→+37 8→17, 0→30, 0→37	−33→33, 0→25, 0→+24
2θ range (deg)	3.0−60.0	3.0−45.0
scan type	$\omega-2\theta$	ω
scan speed (θ°/min)	5.49	5.49
no. of reflns collected	20 448	11 835
no. of unique reflns	9491	10602
no. of reflns with ($F_o^2 > 3\sigma(F_o^2)$)	6020	7641
no. of params	467	1022
data/param ratio	12.9	7.5
$R = [\Sigma\lvert\Delta F\rvert/\Sigma\lvert F_o\rvert]$	0.074	0.061
$R_w = [\Sigma w(\Delta F)^2/\Sigma wF_o^2]$	0.087	0.069
GOF	2.983	2.748
final diff $\varrho_{max}^+/\varrho_{max}^-$ (e/Å^3)	+1.744^b/−2.987^c	+1.086^d/−0.161^e

^{a} Unit cell parameters and their esd's were derived by least-squares fittings of the setting angles of 24 reflections in the ranges 27.90° ≤ 2θ ≤ 29.22° (**I**) and 27.772° ≤ 2θ ≤ 28.672° (**II**). Difference peaks located near ^{b}La1, ^{c}O6, ^{d}O115′, and ^{e}C17. For **I**, Intensity standards[36] indicated no significant decomposition occurred during 92.6 h of exposure. The crystal was reoriented[36] 17 times during data collection, including manual recentering once. Approximately 75 reflections were recollected on either side of four reorientations for which data collection had stopped due to ice buildup and intensity fading. For **II**, Intensity standards indicated a small amount of decomposition during the 48.5 h of exposure. A linear decay correction was applied according to the following slopes: 0 h = 100%, 48.5 h = 91.70% (min. correction = 1.00, max. correction = 1.04, average correction = 1.02). Crystal orientation was redetermined three times during data collection.

following the absorption correction to yield 9491 unique reflections, of which 22 more reflections were weighted to zero.

The structure was solved in space group *Pbca* (No. 61) by heavy atom procedures. The complex co-crystallizes with a triflate counterion and nine water molecules. The anion and solvent are disordered, and modeled by refining the multiplicities of disordered atoms while constraining their isotropic thermal parameters to be equal. Selected inter- and intramolecular distances are listed in Table 2.

[Eu(DTPA-dienH$^+$)]$_4$(CF$_3$SO$_3$$^-$)$_4$·6NaCF$_3SO_3$·20H$_2$O (II). The crystals of Eu(DTPA-dien) were colorless, tetragonally elongated octahedral prisms from which the tip of a thick needle-like crystal was cut and mounted in Paratone oil. Data were collected as described above, with crystal data and collection parameters summarized in Table 1. In the range *l* = 0→1 all reflections were collected and the centering condition $h + k = 2n$ confirmed. For the range *l* = 1→24 the systematically absent reflections ($h + k = 2n + 1$) were not collected. An empirical absorption correction (EAC) was applied based on azimuthal scans; min.(unique) absorbance = 93.79% and min.(average) absorbance = 95.13%. Systematically absent data for the space group *C*2/*c* along with 40 redundant reflections were removed to give 10 602 unique reflections.

The space group was confirmed and the structure solved by Patterson map, with two unique Eu positions in the asymmetric unit. The protonated complex crystallizes as the triflate salt. An additional 2.5−3 molecules of Na(CF$_3$SO$_3$) and 10 water molecules co-crystallized with the complex. The water molecules and four out of five triflate anions exhibited substantial to severe disorder, which was resolved as above by constraining the isotropic thermal parameters (B11) of groups of atoms to be equal while refining peak multiplicity. The triflate about S5 could not be completely resolved, and was modeled as 0.5 S5 among 10 oxygen atoms whose multiplicities refined between 0.406 and 0.728 oxygen. A dampening factor of 0.70 was used during refinements. Selected inter- and intramolecular distances are given in Table 2.

Results and Discussion

Stereochemistry. The ligand [DTPA]$^{5-}$ is itself achiral. However, chelating a lanthanide ion results in a pair of enantiomeric, chiral isomers of the complex. This can be understood by considering a "points on a sphere" model, in which the ligand is an octadentate chelator (Figure 1a). The central amine chirality (*R* or *S*), and therefore the chirality of the complex, arises from the relative proximity of carboxylate C$_2$ to either C$_1$ or C$_3$. The lack of any effective ligand field for the coordination geometry of Ln(III) ions makes rotation on the spherical metal surface very facile,[3] as long as the constraints of atom linkages within the ligand are maintained.

Once two of the DTPA carboxylate arms are functionalized, additional chirality arises since, once bound, the terminal backbone nitrogens (N$_1$ and N$_3$) of the DTPA-bis(amides) are chiral. There are then four possible configurations these ligands can take about a sphere, assuming octadentate coordination (Figure 1b). Two may contain mirror symmetry (*RS*, *SR*), although none contain C_2 symmetry. No amount of rearrangement about the sphere can change any of the nitrogen configurations, even in the two cases (*R*R*R*, *S*S*S*) in which the central backbone nitrogen is also chiral. Again, the chirality of N$_2$ arises from the relative proximity of a terminal amide *vs*

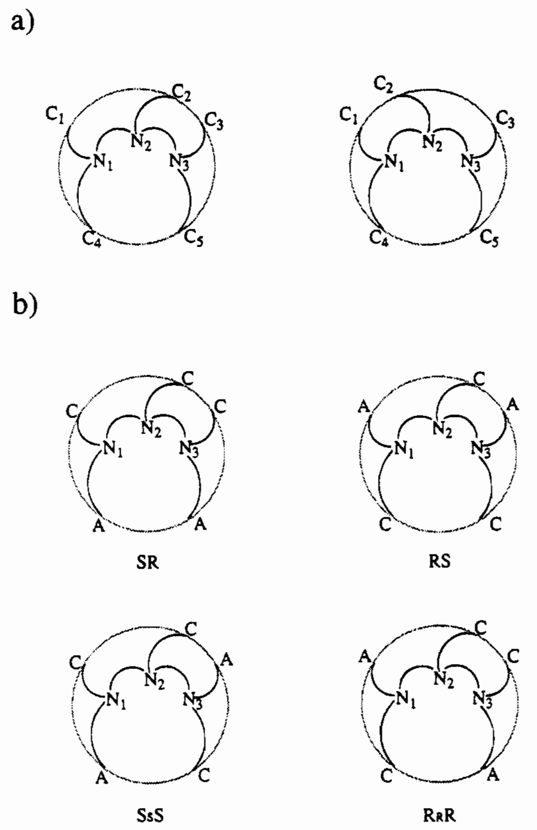

Figure 1. (a) Points-on-a-sphere model of the two enantiomeric DTPA conformations about a lanthanide. (b) Points-on-a-sphere model of the four octadentate DTPA-bis(amide) configurations about a lanthanide (shown without enantiomers).

Table 2. Selected Bond Lengths for La(DTPA-dien) and Eu(DTPA-dien) [Distances around Eu2 in Brackets]

		$Ln-O_{carboxylate}$	
La−O1	2.582(6)	Eu1−O1	2.407(8) [2.407(7)]
La−O1	2.650(5)	Eu1−O3	2.361(8) [2.374(8)]
La−O2	2.862(7)	Eu1−O5	2.382(8) [2.348(7)]
La−O3	2.555(6)	Eu1−O9′	2.376(7) [2.376(7)]
La−O5	2.570(6)		
		$Ln-O_{amide}$	
La−O7	2.615(5)	Eu1−O7	2.408(7) [2.389(8)]
La−O8	2.689(5)	Eu1−O8	2.440(8) [2.438(7)]
		Ln−N	
La−N1	2.889(6)	Eu1−N1	2.816(8) [2.767(9)]
La−N2	2.796(7)	Eu1−N2	2.615(10) [2.633(9)]
La−N3	2.826(6)	Eu1−N3	2.646(9) [2.675(8)]
		Ln−Ln and $Ln-H_2O$	
La−La	4.560(1)	Eu1−Eu2	6.609(1)
		Eu1−Eu2	6.688(1)
La−O9	2.586(6)		
		Briding $C-O_{carboxylate}$	
O1−C14	1.290(8)	O1−C14	1.274(12) [1.254(12)]
O2−C14	1.253(9)	O2−C14	1.255(12) [1.240(12)]
		$C-O_{carboxylate}$	
O3−C16	1.271(10)	O3−C16	1.257(15) [1.300(15)]
O4−C16	1.238(9)	O4−C16	1.224(15) [1.219(16)]
O5−C18	1.268(9)	O5−C18	1.270(14) [1.268(12)]
O6−C18	1.229(9)	O6−C18	1.252(14) [1.256(12)]

carboxylate, which is constant through any rotation. However, since the ligand wraps about the metal in an asymmetric conformation, in the absence of rapid rotation about the sphere, more than one lanthanide environment can be present for each of the four N_1N_3 configurations (Figure 1b).

Linear DTPA-bis(amide) ligands such as DTPA-BMA, DTPA-bis(ethylamide) (BEA),[26] and DTPA-bis(propylamide) (BPA)[13] with their simple, primary alkylamide functionalities were originally designed to test the viability of a trianionic (presumed hexadentate) ligand as a lanthanide chelator. The solid state structures of Gd(DTPA-BEA)[26] and of Dy(DTPA-BMA)[27] show the neutral complex to have, in fact, octadentate coordination, with both amide oxygens bound, and one water molecule in the ninth coordination site. The ligands DTPA-BPA[13] and DTPA-BMA[14] have been shown to be octadentate chelators in ligand solution, as well. These structures, then, are analogous to the DTPA structure,[28] as described in Figure 1b. Cyclizing these ligands by linking the amide moieties generates macrocycles which are stereochemically constrained, limiting the degrees of freedom available to the complex, and further changing the possible coordination isomers present.

As shown in Figure 2, eight tricapped trigonal prismatic isomers can then be generated for this bis(amide) system based on the following criteria: (1) the ligand is octadentate, including both amide oxygens; (2) the weaker ligands, with longer bond lengths, prefer to sit on the face caps; (3) bond strength order, from weakest to strongest, is amine **N** < H_2**O** < NC=**O** < OC=O. Since all three amines cannot simultaneously cap the prism, the central amine (N_2) sits on an edge, and water occupies the third cap. Once bound to the metal, the terminal amines of the backbone are chiral. The eight possible isomers are designated **d** or **l** below each pictogram on Figure 2 by the "chirality" of the metal (named for the "handedness" of the carboxylates when viewed down the H_2O-Ln bond, in analogy to the IUPAC Δ, Λ nomenclature for chiral coordination complexes),[29] and of the two chiral nitrogens. The four pairs of **d**, **l** enantiomers have been numbered (1−4) arbitrarily.

X-ray Crystallography. Many attempts to grow X-ray quality crystals of Ln(DTPA-dien) complexes were made. The complexes are soluble in H_2O and sparingly so in methanol and dimethylformamide (DMF). The habit of Ln^{III}(DTPA-dien) crystals grown from H_2O/acetonitrile, H_2O/diglyme, H_2O/monoglyme, slow evaporation from methanol/dichloromethane, and from H_2O/DMF was always very fine needles. However, very slow evaporation of D_2O (which often results in a glass) produced colorless plate-like blocks of the La(III) complex and thick needles of the Eu(III) complex which were of sufficient quality and size for study by X-ray diffraction.

The most notable distinction between the structures of La(DTPA-dien) and Eu(DTPA-dien) and the structures of $[Gd(DTPA)]^{2-}$,[28] Gd(DTPA-BEA),[26] and Dy(DTPA-BMA)[27] is the macrocycles' tendency to oligomerize by the formation of two different types of carboxylate bridges. The La(DTPA-dien) complex crystallizes as a M_2L_2 dimer about a point of inversion (Figure 3). The lanthanum ions sit on general positions (1 symmetry, $Z = 8$), with the closest La−La distance being 4.56 Å. Each ion is chelated by three amines, two amide oxygens, and three carboxylate oxygens of its own ligand, plus asymmetric bidentate chelation from one carboxylate moiety of the inversion-related ligand (O1 and O2; O1 bridges both metals). One molecule of water per metal completes the coordination sphere, making lanthanum 11-coordinate. The presence of the counterion (which is also seen in the mass spectrum) indicates that the complex is protonated, presumably at the central amine of the linking moiety (LH $pK_a = 10.02(4)$).[30]

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(26) Konings, M. S.; Dow, W. C.; Love, D. B.; Raymond, K. N.; Quay, S. C.; Rocklage, S. M. *Inorg. Chem.* **1990**, *29*, 1488−1491.

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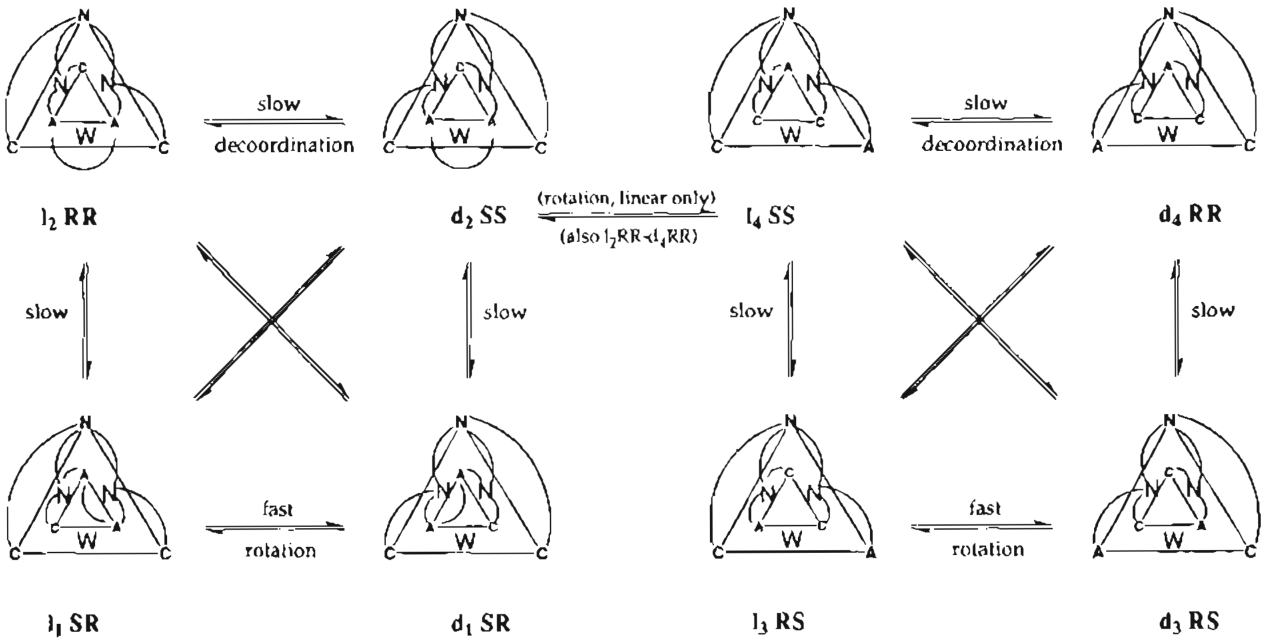

Figure 2. Possible isomers for [Ln(DTPA-bis(amide))·H_2O], assuming octadentate chelation and tricapped trigonal prismatic geometry. Only l_1**SR**, d_1**SR**, l_2**RR**, and d_2**SS** are available to the macrocycles. Weaker ligands sit on face caps (from weakest to strongest: N < H_2O < C−O). The backbone amines cannot span the three face caps, so the central amine (N_2) must sit on a vertex with the terminal amines (N_1 and N_3) on two of the caps. The water caps the third face. Nomenclature: A = amide oxygen, C = carboxylate oxygen, W = water oxygen. Isomers are designated by chirality at the metal center and at N_1 and N_3.

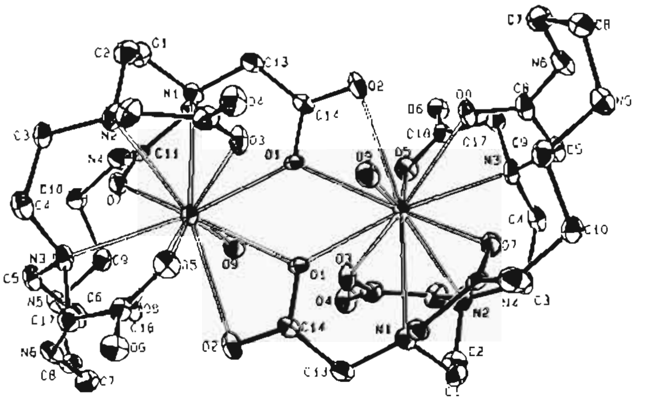

Figure 3. ORTEP diagram of [La(DTPA-dienH$^+$)]$_2$ dimer (**I**). Solvating water molecules and triflate counterions are not shown for clarity.

The Eu(DTPA-dien) complex crystallizes as a M_4L_4 tetramer about a 2-fold axis with two crystallographically independent but geometrically nearly identical Eu(DTPA-dien) units (Figure 4). The minimized rms deviation between monomer units is 0.117 Å (Chem3D). Eu atoms sit on general positions (1 symmetry, $Z = 8$), with the closest Eu−Eu distance being 6.61 Å. Each metal is 9-coordinate, with octadentate chelation from its own DTPA-dien ligand, plus a bridging carboxylate from the neighboring complex (O9′ and O2, respectively) completing the coordination sphere (Figure 5). The central cavity of the tetramer is occupied by water molecules O205 (0.5 multiplicity) and O209, and peripherally by O207 and O210. Na1 is within bonding distance (2.33(1) Å) of O6, and Na2 is within bonding distance (2.42(1) Å) of O12′.

The tendency of these amide/amino carboxylate complexes to oligomerize at very high concentrations (including crystalline solids) can be attributed to the relatively exposed metal face imposed by constraining the two amide arms to be on the same side of the metal ion. In contrast, the linear bis-amide structures[26,27] have the amide arms on opposite sides of the metal, with the amide substituents sterically hindering an approach to the exposed face (H_2O site) of the metal. Oligomers are thus more difficult to form.

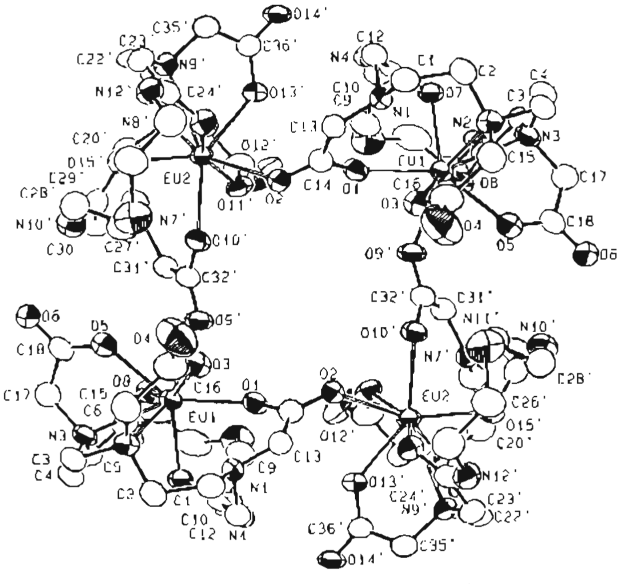

Figure 4. ORTEP diagram of [Eu(DTPA-dienH$^+$)]$_4$ tetramer (**II**) viewed down the 2-fold axis. Solvating water, Na(CF_3SO_3), and $CF_3SO_3^-$ counterions have been omitted for clarity.

Since it is known from luminescence lifetime studies[30] that Eu(DTPA-dien) has one coordinated water molecule in solution ($q = 1.3 \pm 0.5$), it is likely that this compound exists as an oligomer only in the solid state. This assumption was confirmed by vapor pressure osmometry of Eu(DTPA-dien) isolated under both acidic and basic conditions. Under conditions in which the complex is monoanionic (due to a bound hydroxide rather than water), the expected solution molecular weight is 325 g/mol (the average of the hydroxide complex (627 g/mol) and the Na$^+$ counterion (23 g/mol)). If the complex were oligomeric, the expected weight would be 433 g/mol for a dimer, and 520 g/mol

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(30) Wu, S. L.; Horrocks, W. DeW.; Franklin, S. J.; Raymond, K. N. Manuscript in preparation.

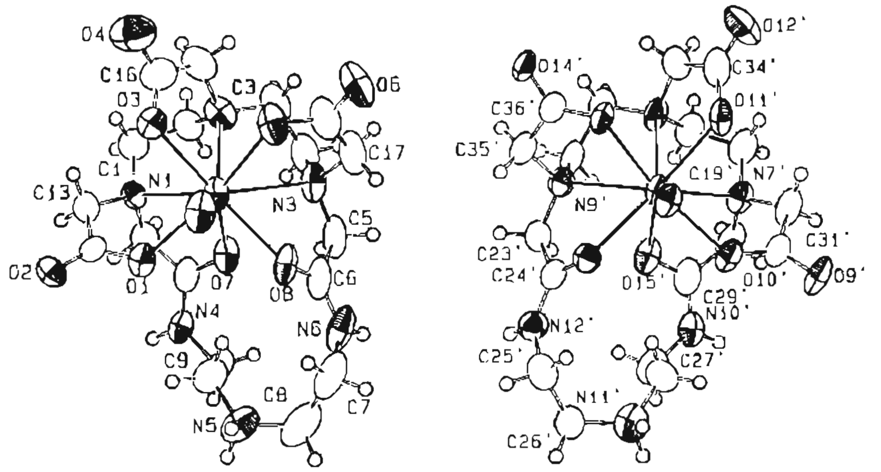

Figure 5. ORTEP view of both unique ML monomers (**II**) in the asymmetric unit showing labeling schemes. Bridging carboxylate oxygens (O2 and O9′) are shown as bare oxygens projecting toward the viewer.

for a tetrameric species. The experimental result of 311 ± 20 g/mol clearly supports the conclusion that the complex is monomeric under these conditions. Similarly, the solution molecular weight of the monoprotonated complex (as the acetate salt) was found to be 361 ± 20 g/mol, consistent with the expected monomer molecular weight of 344 g/mol (dimer = 458 g/mol, tetramer = 550 g/mol). The latter result is particularly relevant, as the complex is monoprotonated under the conditions in which the crystals were grown and the NMR spectra were recorded (as both the acetate and triflate salts).

In the crystal structure, the substantial hydrogen bonding network among amide protons [N4, N10′] and neighboring carboxylate moieties [O14′ and O6, respectively], as well as the favorable electrostatics of the bridging carboxylates compensate for the entropic loss in oligomer formation in low H_2O environments. It seems likely that intermolecular hydrogen-bonding and the relative size of the macrocyclic cavity to Ln(III) ion dictate the oligomers formed, since the ligands described here are still octadentate, but differ in their carboxylate bridging mode. This is unlike the recently reported M_2L_2 structure of the Gd(DTPA-ethylenediamine (en))[31] in which the smaller macrocycle is a binuclear chelator (five bonds and three bonds, respectively). The crystal structure of the macrocyclic complex Gd(DTPA-propanediamine (pn)) shows the ligand is large enough to maintain octadentate chelation, but lacks the link heteroatom which further stabilized oligomerization; this compound is monomeric as a solid.[31]

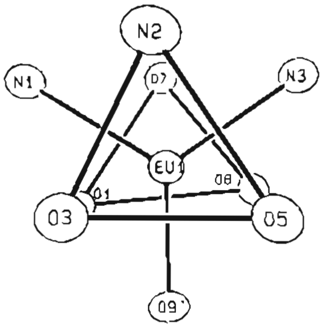

Figure 6. View down the "3-fold" axis of one l_1**SR** tricapped trigonal prism. An oxygen from the bridging carboxylate (O9′) replaces water in the solid state.

Table 3. Polyhedral Angles (deg) for [Eu(DTPA-dienH$^+$)]$_4$ (**II**)

face 1[a]	face 2[a]	idealized[b] angle, D_{3h}	Eu1[c]	Eu2[d]	Gd-(DTPA-BEA)[e]
O1,O7,O8	O3,N2,O5	180.0	174.2	175.0	175.9
O1,O7,O8	N1,O9′,N3	180.0	171.8	172.4	171.1
N1,O9′,N3	O3,N2,O5	180.0	175.5	174.4	173.8
N1,N2,O7	O5,O9′,O8	146.4	139.3	138.7	139.2
N3,N2,O7	O1,O9′,O3	146.4	142.0	142.9	146.6
N3,O5,O8	N1,O3,O1	146.4	143.6	143.1	141.9
N1,N2,O7	N3,N2,O7	26.4	15.0	15.7	19.8
N3,O5,O8	O5,O9′,O8	26.4	26.2	24.1	20.5
O1,O9′,O3	N1,O3,O1	26.4	24.5	25.9	29.2
O3,O5,O1,O8	O3,N2,O7,O1	60.0	57.5	57.3	56.9
O3,O5,O1,O8	N2,O5,O8,O7	60.0	55.3	56.2	58.6
O3,N2,O7,O1	N2,O5,O8,O7	60.0	67.3	66.6	64.7

[a] Faces are designated by the coordination sphere about Eu1 in the structure of Eu(DTPA-dien) tetramer. The analogous faces were used in the angle comparisons with the other structures. [b] For the tricapped trigonal prism; from ref 32. [c] Angles from the coordination sphere about Eu1; this work. [d] Angles from the coordination sphere about Eu2; this work. [e] Angles from the coordination sphere about Gd; from ref 26.

The coordination sphere about Eu(III) in the Eu(DTPA-dien) tetramer is very close to an idealized tricapped trigonal prism, with N1, N3, and O9′ [N7′, N9′, and O2] as the rectangular face caps (Figure 6). As shown in Table 3, the dihedral angles between faces compare as favorably with the idealized D_{3h} angles[32] as do the dihedral angles of the linear bis-amide Gd-(DTPA-BEA).[26] The coordination sphere about Eu(III) is apparently unstrained by the macrocycle, although marginally by the oligomerization. Because the ligand is wrapped around the metal with the central amine on the trigonal prism and the terminal backbone amines on the face caps (as generalized in Figure 2), both terminal amines are expected to be further from the metal than is the central amine. This trend is seen in the Gd(DTPA-BEA) structure, and in a comparison of Eu1−N3 and Eu1−N2 in this structure [Eu2−N9′ and Eu2−N8′]. However, the Eu1−N1 bond length (2.816(8) Å) [Eu2−N7′ = 2.767(9) Å] is longer than that of Eu1−N3 (2.646(9) Å) [Eu2−N9′ = 2.657(8) Å]. This discrepancy is attributed to the bridging carboxylate arm being stretched away from its chelated metal in order to coordinate the next metal. The same trend is seen in Eu1−O1 [Eu2−O10′] distances.

The coordination spheres of both Gd(DTPA-BEA) and Dy-(DTPA-BMA) are d_3**RS**, l_3**RS** isomers (Figure 2) which, along with l_4**SS**, d_4**RR**, are not available to the macrocyclic compounds with their tethered amides sterically required to be on the same prismatic face. As shown in Figure 5, one water molecule bound in place of the bridging carboxylate results in

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the same type of coordination sphere for Eu(DTPA-dien) as exhibited by Gd(DTPA-BEA), Dy(DTPA-BMA), and Gd(DTPA-pn) and generalized in Figure 2. This monomer unit crystallizes in the form $\mathbf{l_1SR}$, $\mathbf{d_1SR}$, as does Gd(DTPA-pn). Assuming an expanded hydrated face, the solid state structure of the La(DTPA-dien) monomer unit is of the general form $\mathbf{l_1SR}$, $\mathbf{d_1SR}$ as well.

Variable Temperature NMR. Several studies of various lanthanide polyamino carboxylate complexes' solution behavior by variable temperature ^{1}H NMR have been presented in the literature. The spectra of the DTPA complexes of La, Pr, Eu, and Yb in D_2O[11,12] all show signal coalescence as the temperature is raised. For the paramagnetic complexes at 0 °C, 18 peaks are observed, corresponding to the 18 non-exchangeable protons. These peaks shift and broaden with temperature until coalescing to 9 signals at 95 °C. At high temperatures, the two enantiomeric, chiral isomers (Figure 1a) exchange rapidly in solution, giving averaged signals for pairs of protons.

This same variable temperature behavior is seen in the somewhat more complicated spectra of the Ln^{III}(DTPA-bis(propylamides))[13] and Ln^{III}(DTPA-bis(methylamides).[14] Four pairs of isomers can be resolved in the ^{13}C VT NMR, all undergoing rapid exchange at high temperature. Even the lanthanide complexes of the macrocyclic ligand DOTA show this coalescence behavior above about 45 °C in D_2O.[33] Here, two isomeric pairs are observed which have been assigned to antiprismatic and prismatic ligand arrangement about the metal. Each isomer, in ratios dependent on the metal ions, exhibits six peaks at 0 °C which coalesce to six peaks of equal intesity by about 45 °C, and then further to three peaks at higher temperatures.

In all these cases, this dynamic behavior (the second isomerization in the case of $[\mathrm{Ln\ DOTA}]^-$ complexes) has been attributed to a rotation about the metal ion involving a "shuffling" of coordinated acetates, along with a backbone "ethylenic flip"[11] or "wagging" motion.[13] Nitrogen chirality does not change with the rotation, although an overall complex chirality change (from **d** to **l**) occurs without ligand decoordination.

The ligand DTPA-dien, named for the diethylenetriamine linking moiety, is a macrocyclic analog of ligands such as DTPA-BPA, and might be expected to behave similarly. However, the macrocyclization and introduction of a secondary amine heteroatom into the link results in substantially different Ln(III) complex NMR behavior. The ^{1}H NMR spectra of most of the DTPA-dien Ln(III) complexes have been recorded, and in all cases, two pairs of isomers are present. Peak assignments for the Eu(III) complex are shown in Figure 7. The NMR spectrum of Eu(DTPA-dien) as a function of temperature (VT) is given in Figure 8 (minor isomer marked with •). At low temperatures, 26 peaks are resolvable for both the major and minor isomers. As the temperature is raised, the peaks of the minor isomer broaden and recoalesce to half that number, while the major isomer peaks remain essentially unchanged. The slight peak sharpening has been attributed to a paramagnetic temperature effect.[34] The particularly striking feature of the Ln(DTPA-dien) complexes' VT NMR spectra is that one of the pair is an unusual "static" isomer; enantiomeric isomerization is slow on the NMR time scale, even at 97 °C. This behavior is unique to the macrocycle.

The low temperature limiting spectra of several Ln(DTPA-dien) complexes are shown in Figure 8 (Ln = Eu) and Figure 9 (Ln = Pr and Yb), and a summary of the isomeric ratios for a series of lanthanide complexes is available with the supplementary material. These ratios were determined by integration of the ^{1}H NMR spectra at low pH (pH = 1.3–3.5) and, whenever possible, at low temperature (1–3 °C). In the case of the Ce, Pr, and Yb complexes, the coalescence temperature for the dynamic isomerization is near 0 °C, and ratios were determined from integrations of averaged signals at higher temperatures. The error in these numbers is estimated to be ±10%, as careful integration of peaks which in some cases are several ppm wide and quite dependent on pH is difficult. Integrations of the Sm and Er complexes were particularly difficult because a few peaks that by integration appear to be the major (static) isomer seem to exhibit fluxional behavior at 0 °C (the peaks are very broad).

There is a distinct trend toward the static isomer across the lanthanide series, with the dynamic isomer comprising merely 5% of the Yb(DTPA-dien) solution structure, while the Eu(DTPA-dien) is present as about 20% of the dynamic isomer at 5 °C, and is well resolved to 26 sharp peaks at this temperature. The dynamic isomer of Pr(DTPA-dien), however, is both more abundant (50%) and more fluctional at this temperature. Several of the dynamic peaks remain poorly resolved in the low temperature limiting spectrum. As might be expected, the coalesced Pr(DTPA-dien) dynamic peaks are well resolved at 95 °C, whereas only 10 of the 13 dynamic peaks of Eu(DTPA-dien) are distinguishable. This evidence suggests that the shape and size of the cavity available for metal binding in the static isomer favors the smaller, late lanthanides.

Two-Dimensional NMR. The 2D EXSY spectra at 0 and 26 °C are taken under conditions where there is no detectable exchange involving the static isomer. The dynamic isomer, however, undergoes rapid exchange at these temperatures, from which pairs of exchanging protons can be readily distinguished. As well as contributing to peak assignments, the single cross peak for a given signal indicates that only one exchange process occurs between dynamic isomers, and they must therefore be enantiomers. This is in keeping with the solution behavior of $[\mathrm{Ln(DTPA)}]^{2-}$ and Ln(DTPA-bis(linear amide)) complexes.[11–14]

At room temperature, a significant amount of isomerization occurs before T_1 decay decreases on-diagonal signal intensity. It was therefore possible to calculate a rate constant of 555 ± 70 s^{-1} for the dynamic process at 26.0 °C, which translates to a $\Delta G^{\ddagger}_{299}$ of 57.5 ± 0.3 kJ/mol.[21,22] This free energy is comparable to that found for the $[\mathrm{Ln(DTPA)}]^{2-}$ complexes,[11] Nd(DTPA-BPA),[13b] and the second isomerization process for $[\mathrm{La(DOTA)}]^-$ [35] (Table 4). This is evidence that the exchange processes involve the same mechanism, namely an "ethylenic flip",[11] or rotation, about the metal without decoordination.

At 95.0 °C and pH = 2, the "static" isomer clearly isn't static, undergoing exchange which is rapid enough to be detectable by exchange spectroscopy (Figure 10). However, it is too slow to be useful for kinetic studies, as k_{ex} is a significant fraction of all but a few of the T_1 values. As evidenced by a similar 2D EXSY spectrum of Yb(DTPA-dien) at 97 °C and pH = 2.3, attaining kinetic data for any static exchange processes is further complicated by the large pH dependence of the rate; at neutral pH, T_1 values remain essentially unchanged, but no static isomer exchange is detectable even at these temperatures. Hence the static isomerization appears to be acid catalyzed.

Unlike the dynamic isomerization which involves the exchange of pairs of protons, the static isomer exchange process

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(36) General data collection and reduction procedures can be found in: Eigenbrot, C. W.; Raymond, K. N. *Inorg. Chem.* **1982**, *21*, 2653–2660.

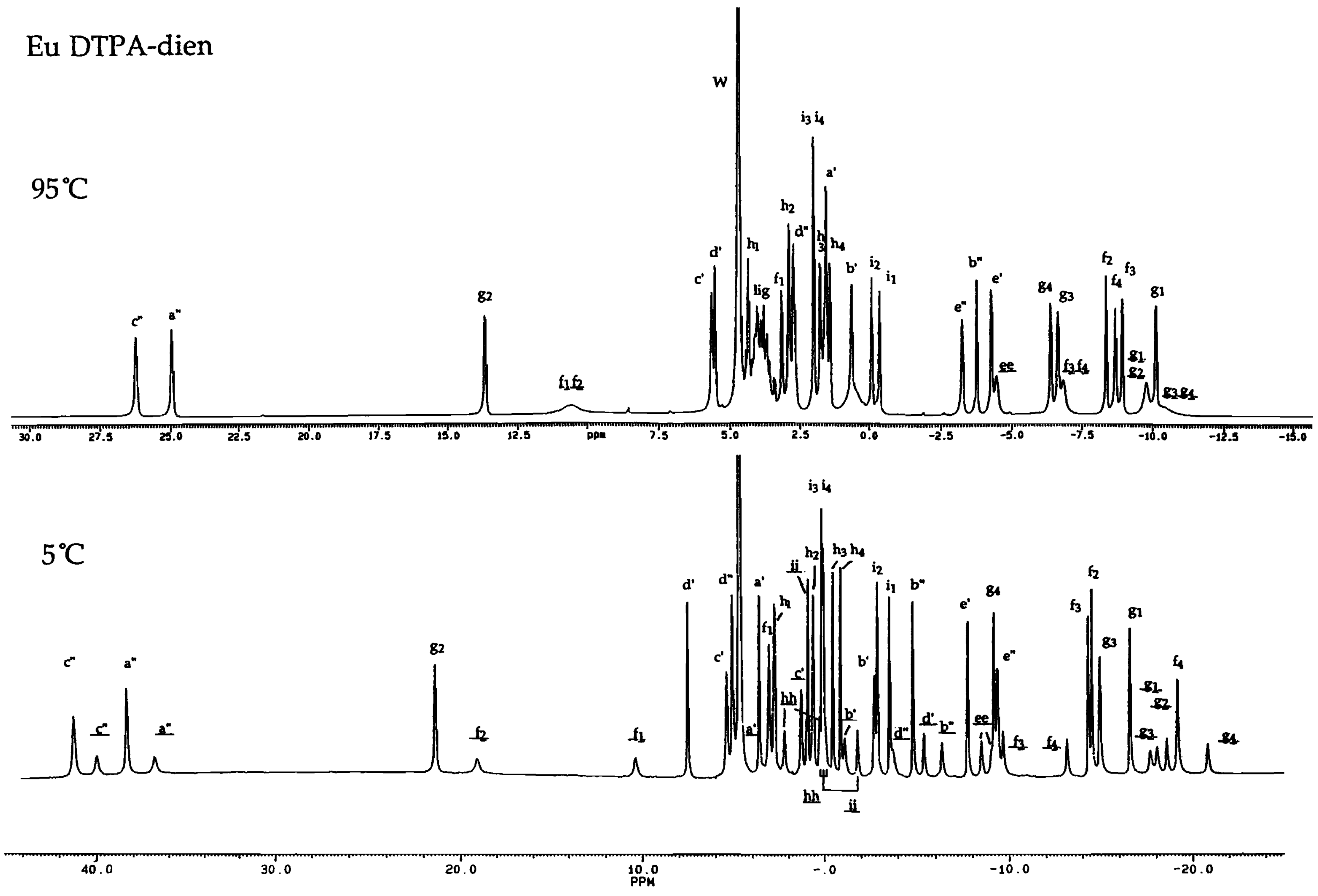

Figure 7. Eu(DTPA-dien) ^1H NMR peak assignments at 5 and 95 °C in D_2O. The labeling scheme is as in Scheme 1; dynamic isomer peak labels are underlined.

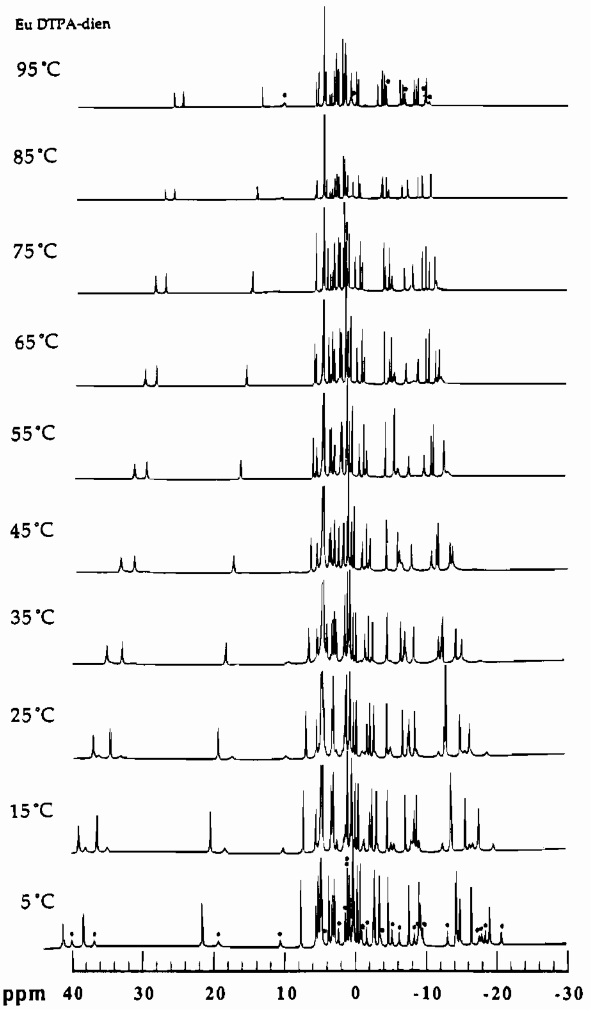

Figure 8. Variable temperature ^{1}H NMR spectra of Eu(DTPA-dien) in D_2O. Dynamic peaks are designated by a dot (•).

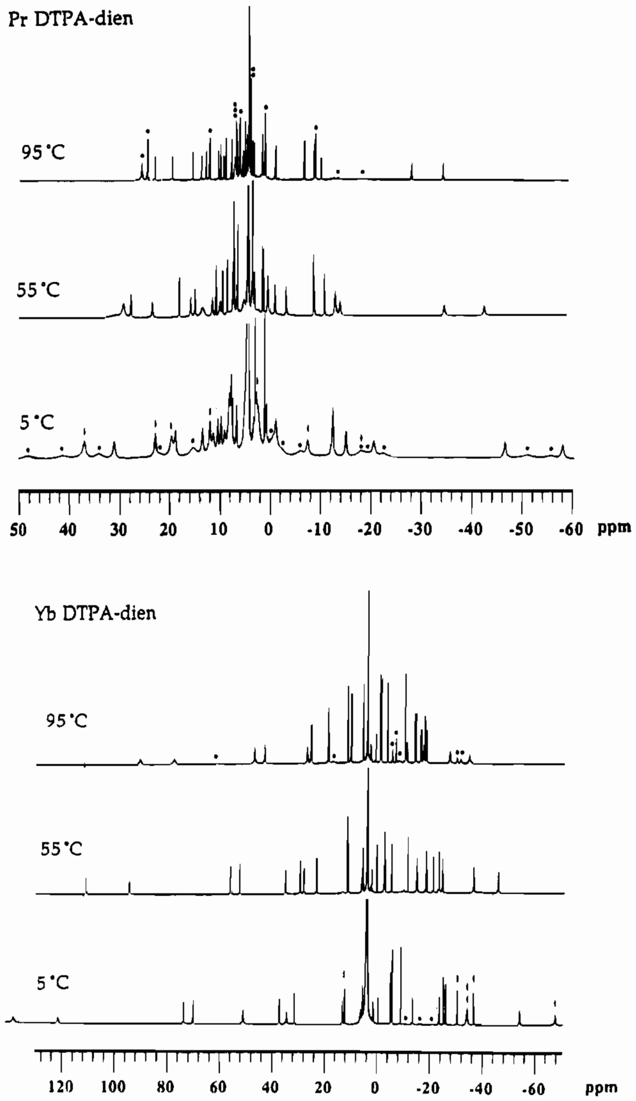

Figure 9. Variable temperature ^{1}H NMR spectra of Pr(DTPA-dien) and Yb(DTPA-dien) in D_2O. Dynamic peaks are designated by a dot (•), and acetate protons (*f* and *e*) are indicated by a |.

is much more complicated. With time, each peak develops several cross peaks, whose relative time of incidence was determined by studying the exchange at various mixing times. This is illustrated for static backbone protons c'' and a'' in Figure 11, in which the cross peaks are numbered in order of appearance. The initial exchange is assigned to a partial decoordination of the ligand, as complete dissociation would result in all subsequent cross peaks evolving simultaneously. The complicated envelope of peaks between 2 and 4 ppm may also obscure coalesced dynamic backbone peaks ($a'd''$ and $b''c'$), whose chronology is lost. The second peaks observed are the dynamic peaks $c''b'$ and $a''d'$, indicating static and dynamic exchange. With longer mixing times, magnetization eventually develops at b'' and d'', then b' and d', and finally c' and a'. This is evidence that the mechanism for slow static isomer exchange involves the dynamic isomer as an intermediate, and results in scrambling of geminal backbone protons. This clearly suggests a decoordination mechanism, with consequent inversion of the chirality of N_1 and N_3.

A pseudorotation through a mirror plane without changing the chirality of the nitrogens has been proposed for the relatively low energy dynamic process observed in the NMR of [LnDTPA]$^{2-}$ complexes[11,12] and Ln(DTPA-bis(propylamides)).[13] For interconversion between enantiomeric pairs (**d_n**, **l_n**), this mechanism is only available between **d_1SR**, **l_1SR** and **d_3RS**, **l_3RS** isomers (Figure 2). The rotations between diastereomers **d_2SS↔l_4SS** and **d_4RR↔l_2RR**, which are not available to the macrocycles, are observed in the NMR of the Ln(DTPA-bis(propylamides)) as well. For these compounds, any of the eight possible isomers given in Figure 2 have a rotational isomerization pathway available, thus assuring "dynamic" behavior for any isomer.

Assuming this type of octadentate coordination, the Ln(DTPA-dien) complexes' dynamic behavior must be due to a rotation mechanism affecting the enantiomeric isomerization between **d_1SR** and **l_1SR** isomers. The crystal structures presented here provide good models for the macrocycles' octadentate solution structure. Assuming a water in place of the bridging carboxylate, Eu(DTPA-dien) crystallizes as the **d_1SR, l_1SR** enantiomer pair, as does Gd(DTPA-pn). La(DTPA-dien) also crystallized in the general form of the **d_1SR, l_1SR** enantiomeric pair, with the bidentate bridging carboxylate observed in solid state presumably occupied by two or three waters in solution.

However, the other isomeric forms available to these macrocycles (**d_2SS, l_2RR**) are incapable of rotational isomerization. The only mechanism for entiomeric isomerization involves successive decoordination and subsequent change in backbone amine chirality (N_1 and N_3). This mechanism would involve a much higher barrier to isomerization than mere rotation, which would be reflected in a relatively slower rate of exchange. The decoordinative change in chirality, unlike the

Table 4. Free Energies of Activation for Rotational Isomerization of Several Ln(III) Polyamino Carboxylate Complexes

complex	$\Delta G^{\ddagger}_T$ (kJ/mol)	T (K)	complex	$\Delta G^{\ddagger}_T$ (kJ/mol)	T (K)
[Eu(DTPA-dienH$^+$)]	57.5 ± 0.3	299	[Yb(DTPA)]$^{2-}$	49.4 ± 10.0[a]	298
[Pr(DTPA)]$^{2-}$	56.5 ± 3.6[a]	298	Nd(DTPA-BPA)	53[b]	283
[Eu(DTPA)]$^{2-}$	55.4 ± 4.6[a]	298	[La(DOTA)]$^-$	60.7 ± 1.2[c]	298

[a] From ref 11. [b] From ref 13b. [c] From ref 35.

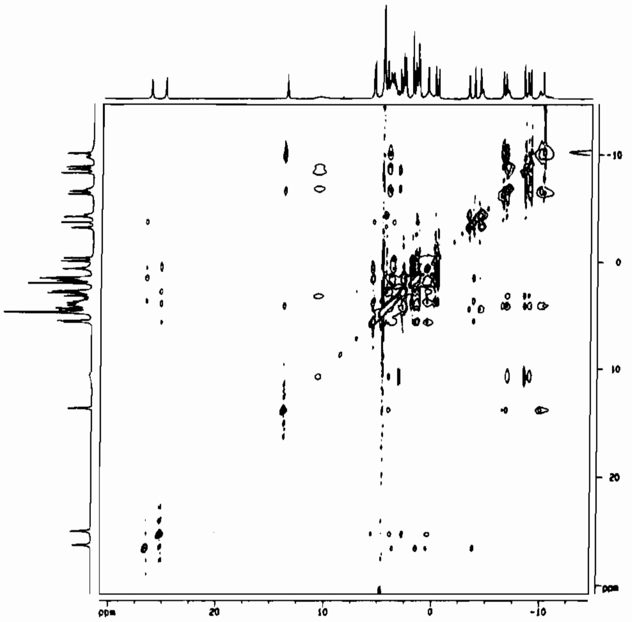

Figure 10. 2D EXSY spectrum of Eu(DTPA-dien) at 95 °C in D_2O with t_m = 60 ms.

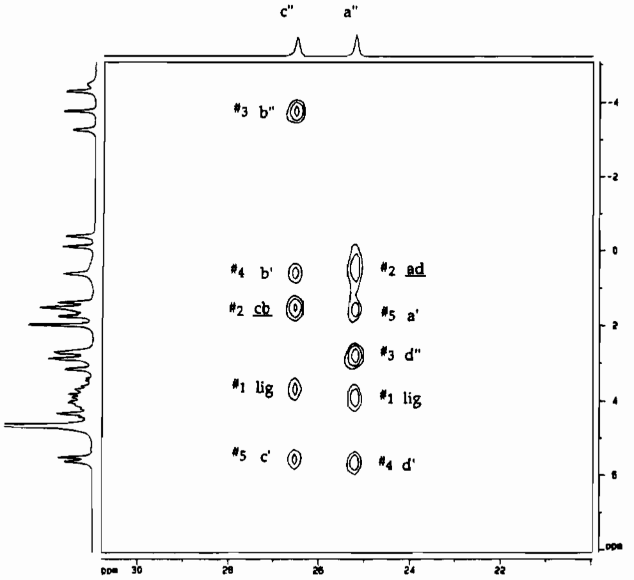

Figure 11. Expanded region of 2D EXSY spectrum of Eu(DTPA-dien) at 95 °C in D_2O with t_m = 100 ms. Cross peaks are labeled in order of appearance based on several EXSY experiments in which the mixing time was varied from 2 to 100 ms.

rotational process, would result in the scrambling of geminal protons, would be acid catalyzed, and would involve the $\mathbf{d_1SR}$, $\mathbf{l_1SR}$ pair as an intermediate.

As it is precisely this type of behavior observed for the unusual static isomer, the $\mathbf{d_2SS}$, $\mathbf{l_2RR}$ enantiomeric pair is its proposed solution structure (Figure 2), while the $\mathbf{d_1SR}$, $\mathbf{l_1SR}$ enantiomeric conformations described by the crystal structures are the proposed structures for the dynamic isomer pair interconverting *via* rotation, with a variable number of facial water molecules depending on the size of the lanthanide ion. The DTPA-dien macrocycle stabilizes the $\mathbf{d_2SS}$, $\mathbf{l_2RR}$ pair relative to the linear DTPA-bis(amide) complexes, particularly for the smaller, late lanthanides ions.

Summary

Macrocyclic bis(amide) derivatives of diethylenetriaminepentaacetic acid (DTPA) have been studied with regard to their lanthanide coordination chemistry, in both aqueous solution and the solid state. These compounds are similar to the parent [Gd(DTPA)]$^{2-}$ complex and the bis(methylamide) complex [Gd(DTPA-BMA)], both of which are commercial magnetic resonance image enhancement agents. The additional steric constraints that result from linking the two amide group together in the macrocycle alter the possible coordination isomers but also substantially slow some exchange processes as seen in the NMR spectra. For the ligand DTPA-dien (in which the two terminal nitrogens of a bridging diethylenetriamine form the amide groups) the Eu(III) and La(III) complexes have the central, secondary amine of the bridge protonated at neutral pH. The lanthanum complex is 11-coordinate in the solid state, with eight donor groups from the ligand, an η^2 carboxylate bridge, and one water. The Eu(III) complex is 9-coordinate (in concert with its smaller size) and has no coordinate water as a solid; a bridging carboxylate group replaces the water which is present in the ninth coordination site in solution.

The DTPA(amide)$_2$ ligands in principle are composed of two symmetry-equivalent halves. In the metal complex the end nitrogens of the DTPA ligand fragment are chiral, with four different substituents (including coordination to the metal ion). For interchange of *R* with *R* and *S* with *S* the process requires only interchange of coordinating groups on the metal ion surface. Hence the meso isomers ($SR \leftrightarrow SR$) show rapid averaging of the NMR resonances of the two ends of the molecule as the metal environment changes from **d** to **l** with simple rotation. For the interchange of *R* with *S*, decoordination of the nitrogen is required so as to allow racemization. For these isomers ($RR \leftrightarrow SS$) the exchange between **d** and **l** is slow and acid catalyzed. These two different types of exchange almost certainly parallel the corresponding exchange processes of the lanthanide complexes of the bis(amide) ligands such as DTPA-BPA,[13b] as well as those of the complexes of DTPA itself.[11,12] In each case it can be expected that interchange of groups on the metal surface will be a rapid process, while a partial decoordination of the ligand will be much slower.

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Supplementary Material Available: Tables of anisotropic thermal parameters, atomic positional parameters, intramolecular distances, and intra- and intermolecular angles for La(DTPA-dien) and figures showing isomeric ratios for various Ln^{III}(DTPA-dien) complexes in D_2O from NMR integrations, the assigned 2D EXSY spectrum of Eu(DTPA-dien) at 0 °C, and the assigned 2D COSY spectrum of Eu(DTPA-dien) at 95 °C (12 pages). Ordering information is given on any current masthead page.