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Synthesis, Structure, and Dynamic Properties of the Lanthanum(III) Complex of 1,4,7,10-tetrakis(2-carbamoylethyl)-1,4,7,10-tetraazacyclododecane

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The synthesis, structure and dynamic properties of the lanthanum(III) complex of macrocycle **1** (**1** = 1,4,7,10-tetrakis(2-carbamoylethyl)-1,4,7,10-tetraazacyclododecane) are reported. $[La(\mathbf{1})^{3+}][CF_3SO_3^-]_3\cdot MeCN$ crystallizes with the complex lanthanum cation, three triflate counteranions, and one acetonitrile solvent molecule in the noncentrosymmetric orthorhombic space group $P2_12_12_1$ (No. 19) with a = 10.6937(13) Å, b = 17.6299(26) Å, c = 22.3554(36) Å, V = 4214.7(11) Å^3, and Z = 4. The structure was solved and refined to R = 5.39% and R_w = 4.56% for all 5538 independent reflections and R = 3.37% and R_w = 3.32% for those 4130 reflections with $|F_o| > 6\sigma|F_o|$. The eight-coordinate La^{3+} cation is encapsulated by the macrocyclic ligand and has a distorted square antiprismatic coordination geometry. The macrocyclic ligand coordinates strongly with the four oxygen atoms of the amide groups (average distance = 2.423 ± 0.032 Å) and weakly with the four nitrogen atoms within the macrocyclic ring (average distance = 2.718 ± 0.009 Å). The hydrogen atoms of the amide groups form a hydrogen-bonded system with the triflate counteranions. In acetonitrile or methanol solutions, ^{13}C NMR resonances for the amide C(O) carbons in the complex are shifted by greater than 2 ppm from those of **1**, suggesting that the amide groups are coordinated in these solvents. At low temperatures (0 °C) the ethylenic groups of the 12-membered tetraazamacrocycle are rigid on the NMR time scale. Variable-temperature ^{13}C NMR studies suggest that rigidity of the macrocycle is lost at higher temperatures. A dynamic process involving conformational changes about the cyclen ethylenic groups is consistent with ^{13}C NMR data, and an activation barrier of 58.9 ± 0.3 kJ mol^{-1} is calculated for this process. A second dynamic process that averages protons on the amide nitrogens may involve free rotation about the amide C–N bond. An activation barrier of 69.8 ± 0.5 kJ mol^{-1} is calculated for this process for the lanthanum complex in dimethyl-d_6 sulfoxide. The activation barrier calculated for the free ligand **1** is 70.5 ± 0.5 kJ mol^{-1}. The close correspondence of these values in conjunction with ^{13}C NMR data for the amide C(O) resonance suggests that, in dimethyl sulfoxide solution, the amide groups of the complex are not bound. The complex dissociates rapidly in water at neutral pH and 37 °C.

Introduction

Octadentate ligands for large metal ions may be constructed from tetraazamacrocycles that are N-alkylated with four pendent arms containing ligating groups. For example DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetic acid) and THP-12aneN$_4$ (1,4,7,10-tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane) coordinate strongly to lanthanides(III)[1,2] or lead(II)[3] through four nitrogen donors and four oxygen donors, essentially encapsulating these large metal ions. Our interest in the development of new lanthanide(III) complexes for use as artificial ribonucleases[4] has prompted us to investigate new ligands for the lanthanides. Tetraazamacrocycles with pendent groups are attractive as potential ligands for the lanthanides because of the variety of pendent groups to choose from.[5] The pendent groups will undoubtedly have an effect on the kinetic inertness of the lanthanide(III) complex as well as its ability to catalyze the hydrolysis of biopolymers. We are in the process of varying the pendent groups on tetraazamacrocycles and studying the coordination of these ligands to the trivalent lanthanides. Our work uses neutral pendent groups in order to maintain a positive charge on the complex for the creation of a more efficient artificial ribonuclease. Our preliminary studies have indicated that lanthanide complexes with an overall positive charge are efficient RNA transesterification catalysts while anionic or neutral lanthanide poly(amino carboxylate) complexes are not catalysts.[4] Initially, macrocyclic complexes with an overall +3 charge have been synthesized because of the ease of adding four identical pendent groups to a tetraazamacrocycle. The synthesis of macrocyclic complexes that are less highly charged may be accomplished by the addition of mixed neutral and anionic pendent groups; these macrocycles will be the subject of future studies.

The ligand DOTA is an exceptionally strong chelate for the lanthanides(III).[6] There is much interest in the development of highly stable Gd(III) complexes for use as magnetic resonance imaging (MRI) agents;[7] the exceptional thermodynamic stability and inertness to dissociation of Gd(DOTA)$^-$ and its derivatives make these complexes attractive as new MRI agents. A neutral amide group is a reasonable choice for replacement of the negatively charged acetate group. Similar to carboxylate, an amide coordinated through the oxygen of the carbonyl group is a sterically efficient donor group because the oxygen donor atom is connected to a carbon atom that bears no hydrogens.[8] Chelates containing amide groups have been used to form stable complexes of the trivalent lanthanides. For example, a single neutral amide

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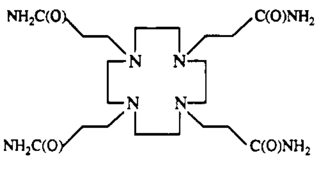
group has been used in conjunction with three acetate groups to impart a neutral charge on a gadolinium(III) complex.[7d–f] Linear polyamino ligands with amide and acetate pendent groups coordinate strongly to trivalent lanthanides.[7b] Coordination is through the oxygen atom of the amide.[7b,f]

The synthesis of a lanthanide(III) complex with a positive charge of three necessitates the replacement of all four acetate groups on DOTA with amide groups. Previous work on the synthesis of tetraamide macrocyclic complexes includes a Ni(II) complex of (1,4,8,11-tetrakis(2-carbamoylethyl)-1,4,8,11-tetraazacyclotetradecane);[9] this complex features coordination of Ni(II) to the macrocycle ring nitrogens alone. Other reports[10,11] suggest that Cu(II) coordinates amide ligands in tetraazamacrocycles bearing a single amide pendent group. Here we report the synthesis of a tetraazamacrocycle with four pendent amide groups, 1,4,7,10-tetrakis(2-carbamoylethyl)-1,4,7,10-tetraazacyclododecane (**1**), and its coordination to lanthanum(III). The solid state structure and variable temperature solution NMR studies of a salt of the cationic lanthanum(III) complex $\mathbf{2}^{3+}$ are reported.



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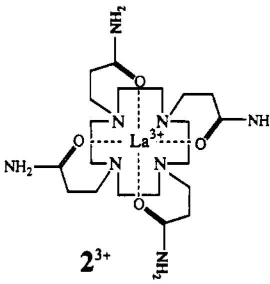

$\mathbf{2}^{3+}$

Experimental Section

The free base form of cyclen (1,4,7,10-tetraazacyclododecane) was generated by passing the tetrahydrochloride salt (Parish Chemicals or Strem Chemicals) through a Dowex 1X8-200 anion exchange column (30 cm × 2.5 cm, hydroxide form). $La(CF_3SO_3)_3$ was obtained by treating lanthanum oxide with concentrated trifluoromethane sulfonic acid as reported previously.[12] All other chemicals used were of analytical grade. Acetonitrile was dried over CaH_2. Reagent grade absolute methanol was used. Milli-Q purified water was used for kinetic experiments.

An Orion Research digital ion analyzer, Model 510, equipped with a temperature compensation probe was used for all pH measurements. A Hewlett-Packard diode array Model 8452A spectrophotometer with a thermostatted cell compartment was employed for UV–vis spectra and for kinetic measurements. All ^1H and ^{13}C NMR spectra were recorded by use of a Varian 400 XL spectrophotometer. ^1H and ^{13}C chemical shifts 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 and R Microanalytical Laboratories. A VG 70-SE mass spectrometer with fast atom bombardment was utilized.

1,4,7,10-Tetrakis(2-carbamoylethyl)-1,4,7,10-tetraazacyclododecane (1). Cyclen (0.200 g, 1.16 mmol) and acrylamide (0.397 g, 5.58 mmol) were dissolved in methanol (2 mL), and the solution was heated under a nitrogen atmosphere in an oil bath maintained at 75 °C for 50 h. A few drops of methanol were added periodically to redissolve the gelatinous mixture over the course of the reaction. The solution was cooled, and the gelatinous solid was dissolved in 1 mL of methanol. One mL of diethylether was added dropwise. A crystalline solid formed after several hours at room temperature. The solid was collected by filtration, washed with chloroform, and dried in vacuo at 50 °C. Yield: 87%. Mp: 174–177 °C. FABMS, *m/e*: 457 (ligand + H). ^1H NMR (D_2O): 2.27 (t, 8H, NCH_2), 2.53 (s, 16H, ring CH_2), 2.60 (t, 8H, $CH_2C(O)NH_2$).

La(1,4,7,10-tetrakis(2-carbamoylethyl)-1,4,7,10-tetraazacyclododecane)(CF_3SO_3)$_3$·CH_3CN, ($\mathbf{2}^{3+}(CF_3SO_3^-)_3 \cdot CH_3CN$). $La(SO_3CF_3)_3$ (0.323 g, 0.55 mmol) was refluxed under nitrogen in a mixture of 60 mL of dry acetonitrile and 6.5 mL of trimethyl orthoformate. Upon dissolution of the salt, **1** (0.250 g, 0.55 mmol) was added in a minimum amount of methanol. The mixture was refluxed for 3.5 h. The solution was concentrated in vacuo and methylene chloride was added until cloudiness was observed. Crystals formed from the solution overnight. Yield: 35%. Mp: 245–248 °C dec. Anal. Calcd for $C_{25}H_{43}N_9O_{13}F_9S_3La$: C, 27.70; H 4.00; N, 11.63. Found C, 27.57; H, 4.12; N, 11.64. FABMS, *m/e*: 893 (**2** – CF_3SO_3). ^{13}C NMR (acetonitrile-d_4, 17 °C): 30.8 (NCH_2), 52.4, 54.0 (NCH_2 ring), 55.3, ($CH_2C(O)NH_2$), 180.6 ($C(O)NH_2$).

Kinetics. ^1H NMR experiments to monitor dissociation of the lanthanum complex in water were carried out at 7 or 37 °C with solutions 0.02 *m* in complex. The extent dissociation at 37 °C was analyzed by cooling the sample from 37 to 0 °C and integrating the ^1H resonances of the free ligand and complex compared to ethanol as the internal standard. Analysis at 0 °C was necessary to resolve resonances of the complex and free ligand.

Collection of X-ray Diffraction Data. A colorless single crystal (dimensions = 0.30 mm × 0.30 mm × 0.20 mm) of $La[(CH_2CH_2(CO)NH_2)NCH_2CH_2]_4(CF_3SO_3)_3 \cdot CH_3CN$ was selected for the X-ray diffraction study. The crystal was air stable and was sealed into a 0.30 mm thin-walled capillary under atmospheric conditions. It was then mounted and aligned on an upgraded Siemens $P2_1$/P3 diffractometer. Details of the data collection appear in Table I. Data were collected with Mo Kα radiation (λ = 0.710 73 Å) for the 2θ range of 5.0–45.0°. No correction for crystal decay was necessary. A total of 6121 reflections were collected and were merged into a unique set of 5538 reflections (R_{int} = 1.24%). All data were corrected for Lorentz and polarization effects and for absorption. The intensity statistics of the data collected favored a noncentrosymmetric space group. It was determined that the crystal belonged to the orthorhombic crystal system. The noncentrosymmetric space group $P2_12_12_1$ (D_2^4; No. 14) is unequivocally determined from the systematic absences $h00$ for $h = 2n+1$, $0k0$ for $k = 2n+1$ and $00l$ for $l = 2n+1$. ($P2_12_12_1$ is one of the most commonly occurring noncentrosymmetric space groups.)

Solution and Refinement of the Crystal Structure. All crystallographic calculations were carried out with the use of the Siemens SHELXTL PLUS[13] 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.[14] The structure was solved by the use of a Patterson synthesis. Refinement of parameters was achieved through the minimization of the function $\sum w(|F_o| - |F_c|)^2$. The chirality of the crystal and the absolute configuration of the complex were determined through the use of η-refinement.[13] A secondary extinction parameter (χ) was refined to a value of 0.00008(3). (See Table I.) Positional and anisotropic thermal parameters for all nonhydrogen atoms were refined. The exact orientations of the hydrogen atoms on the amide groups were determined with some difficulty. The most probable position for one hydrogen atom on each amide group was determined by examination of the difference-Fourier map after heavily weighing the reflections of low 2θ. Two extra hydrogen atoms were placed on each amide nitrogen atom at calculated positions to form a tetrahedral configuration. The isotropic thermal parameters of the two new "hydrogen atoms" were fixed and the occupancy factors of both atoms on each amide group were coupled together as x and $1 - x$. After refinement, the occupancy factor of the atom in the correct position should approach unity, while the incorrect position should approach zero. Following refinement, the position with the larger occupancy was, in each case, chosen as the site for the second amide hydrogen atom. The positions of these hydrogen atoms were optimized by fixing them along the N–H vector at a distance of 0.87 Å.[15] All other hydrogen atoms were placed at calculated positions with d(C–H) = 0.96 Å[15] and with the appropriate staggered tetrahedral geometry. The isotropic thermal parameter of each hydrogen atom was defined as equal to the U_{eq} value of the atom to which it was bonded. Following refinement, the extreme features left on the difference-Fourier map were a peak of height 0.86 e Å^{-3} and a negative feature of –0.84 e Å^{-3}. Refinement of the model converged with R = 3.37% and R_w = 3.32% for 547 parameters refined against those 4130 reflections with $|F_o| > 6\sigma|F_o|$ and R = 5.39% for all data. Atomic coordinates appear in Table II.

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Table I. Experimental Details for the X-ray Diffraction Study

	Crystal Data
empirical formula	$(C_{20}H_{40}O_4N_8La^{3+})(CF_3SO_3^-)_3 \cdot MeCN$
cryst size, mm	0.30 × 0.30 × 0.20
cryst syst	orthorhombic
space group	$P2_12_12_1$
unit cell dimens	
a, Å	10.6937(13)
b, Å	17.6299(26)
c, Å	22.3554(36)
vol, $Å^3$	4214.72(105)
Z	4
fw	1083.8
d(calc), Mg/m^3	1.708
abs coeff, mm^{-1}	1.262
F(000)	2184
	Data Collection
diffractometer used	Siemens $P2_1/P3$
radiation	Mo Kα (λ = 0.710 73 Å)
temp, K	298
monochromator	Highly oriented graphite crystal
2θ range, deg	5.0–45.0
scan type	ω
scan speed, deg/min	Constant; 2.00 in ω
scan range (ω), deg	0.64
bkgd meas	stationary cryst and stationary counter at beginning and end of scan, each for 25.0% of total scan time
std reflcns	3 measd every 97 reflcns
index ranges	$-11 \leq h \leq 0, -19 \leq k \leq 0, -24 \leq l \leq 24$
no. of reflcns collcd	6121
no. of indep reflcns	5538 (R_{int} = 1.24%)
no. of obsd reflcns	4130 ($F > 6.0\sigma(F)$)
abs cor	semiempirical
min./max. transm	0.5541/0.6022
	Solution and Refinement
syst used	Siemens SHELXTL PLUS (VMS)
solution	Patterson synthesis
refinement method	full-matrix least-squares
quantity minimized	$\sum w(F_o - F_c)^2$
absolute struct	$\eta = 0.99(4)$
extinction cor	$\chi = 0.00008(3)$, where $F^* = F[1 + 0.002\chi F^2/(\sin 2\theta)]^{-1/4}$
hydrogen atoms	riding model, fixed isotropic *U*
weighting scheme	$w^{-1} = \sigma^2(F) + 0.0010F^2$
no. of params refined	547
final *R* indices (obsd data)	*R* = 5.39%; R_w = 4.56%
R indices (6σ data)	*R* = 3.37%; R_w = 3.32%
goodness-of-fit	0.87
largest and mean Δ/σ	0.001, 0.000
data-to-param ratio	10.1:1
largest diff peak, e $Å^{-3}$	0.86
largest diff hole, e $Å^{-3}$	–0.84

Results and Discussion

The ligand **1** was prepared in good yield from the free base form of cyclen (1,4,7,10-tetraazacyclododecane) and acrylamide. Similar procedures have been used to prepare macrocycles containing a single amide pendent group.[10,11] Alternate syntheses for attachment of amide groups have relied on metal ion promoted hydrolysis of nitrile functionalities[9] or the use of chloroacetamide.[7d] In the course of studying **1**, we noted that the ligand decomposed in basic aqueous solutions. Acrylamide was identified as a decomposition product by use of ^1H NMR. New ^1H NMR resonances indicated the formation of new macrocycle products. These observation are consistent with loss of acrylamide by a retro-Michael addition as has been observed previously.[11] The ligand appeared to be stable at neutral pH and in aprotic organic solvents. However, at elevated temperatures in methanol/acetonitrile mixtures, some ligand decomposition was detected by use of ^1H NMR. Ligand decomposition during the synthesis of the complex may lead to the reduced yields observed (35%).

Table II. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($Å^2 \times 10^3$) for $[La(1)^{3+}][CF_3SO_3^-]_3 \cdot MeCN$

	x	*y*	*z*	*U*(eq)[a]
La(1)	3201(1)	2885(1)	7787(1)	28(1)
O(11)	5261(5)	2432(3)	7575(2)	38(2)
O(21)	3936(5)	2324(3)	8717(2)	39(2)
O(31)	2905(5)	3878(3)	8514(2)	42(2)
O(41)	4371(5)	3964(3)	7376(2)	38(2)
N(1)	3019(6)	1461(3)	7318(3)	36(2)
N(2)	1292(5)	2104(4)	8295(3)	40(2)
N(3)	992(6)	3580(4)	7558(3)	41(2)
N(4)	2724(6)	2934(4)	6590(3)	39(2)
N(11)	6793(8)	1912(4)	8122(3)	56(3)
N(21)	4183(7)	2845(5)	9618(3)	56(3)
N(31)	3472(7)	5075(4)	8657(3)	60(3)
N(41)	6389(7)	4042(4)	7092(3)	61(3)
C(1)	2182(7)	1007(4)	7720(4)	44(3)
C(2)	1027(8)	1411(5)	7921(4)	44(3)
C(3)	181(7)	2617(5)	8294(4)	47(3)
C(4)	–27(7)	3027(5)	7706(4)	47(3)
C(5)	962(9)	3770(5)	6904(4)	46(3)
C(6)	1403(8)	3134(5)	6508(4)	43(3)
C(7)	2964(9)	2164(5)	6337(3)	49(3)
C(8)	2431(8)	1520(5)	6711(4)	43(3)
C(11)	5756(7)	1863(4)	7807(4)	35(3)
C(12)	5146(7)	1100(4)	7754(4)	45(3)
C(13)	4237(7)	1054(4)	7239(4)	46(3)
C(21)	3466(8)	2529(4)	9209(4)	43(3)
C(22)	2133(8)	2404(4)	9339(4)	46(3)
C(23)	1521(8)	1840(4)	8919(3)	46(3)
C(31)	2763(8)	4566(5)	8407(4)	44(3)
C(32)	1828(9)	4832(4)	7956(4)	51(3)
C(33)	722(8)	4296(4)	7898(4)	48(3)
C(41)	5215(9)	3856(5)	6996(4)	41(3)
C(42)	4905(8)	3499(5)	6400(4)	49(3)
C(43)	3497(8)	3501(5)	6261(4)	50(3)
S(1A)	6961(3)	4069(2)	8891(1)	58(1)
O(1A)	6675(10)	3333(5)	9061(5)	134(5)
O(2A)	7453(8)	4160(7)	8316(3)	132(5)
O(3A)	6047(7)	4623(5)	9022(4)	101(4)
C(1A)	8208(11)	4316(5)	9379(4)	56(3)
F(1A)	9187(6)	3840(5)	9317(3)	114(3)
F(2A)	8666(8)	4980(5)	9284(5)	155(5)
F(3A)	7922(7)	4284(4)	9938(3)	109(3)
S(1B)	7926(2)	540(1)	9216(1)	55(1)
O(1B)	8478(8)	1257(4)	9327(3)	90(3)
O(2B)	8513(7)	–106(4)	9466(3)	93(3)
O(3B)	7566(7)	452(3)	8601(3)	69(3)
C(1B)	6450(10)	599(6)	9613(5)	66(4)
F(1B)	5787(7)	1191(4)	9433(3)	108(3)
F(2B)	5772(6)	–19(4)	9542(3)	107(3)
F(3B)	6615(7)	675(4)	10193(3)	99(3)
S(1C)	8018(2)	2056(1)	6362(1)	46(1)
O(1C)	9019(7)	1671(4)	6663(3)	78(3)
O(2C)	6838(7)	1704(3)	6454(3)	63(2)
O(3C)	8044(6)	2867(3)	6403(3)	67(2)
C(1C)	8342(17)	1874(7)	5585(6)	102(6)
F(1C)	9422(10)	2144(6)	5418(4)	156(4)
F(2C)	7487(11)	2209(8)	5241(3)	171(6)
F(3C)	8326(11)	1147(4)	5463(3)	155(5)
N(1S)	1790(15)	–227(6)	8856(5)	120(6)
C(1S)	1478(10)	–509(6)	9263(5)	68(4)
C(2S)	1040(12)	–893(7)	9808(5)	87(5)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

The complex $2^{3+}(CF_3SO_3^-)_3 \cdot CH_3CN$ was prepared in acetonitrile under anhydrous conditions by treatment of $La(CF_3SO_3)_3$ with the free base form of **1**. The drying agent, trimethyl orthoformate, helped to dissolve $La(CF_3SO_3)_3$. Similar procedures have been used to prepare cryptate complexes of the trivalent lanthanides[16] where anhydrous conditions are also necessary. Crystals were grown from a mixture of acetonitrile and methylene chloride.

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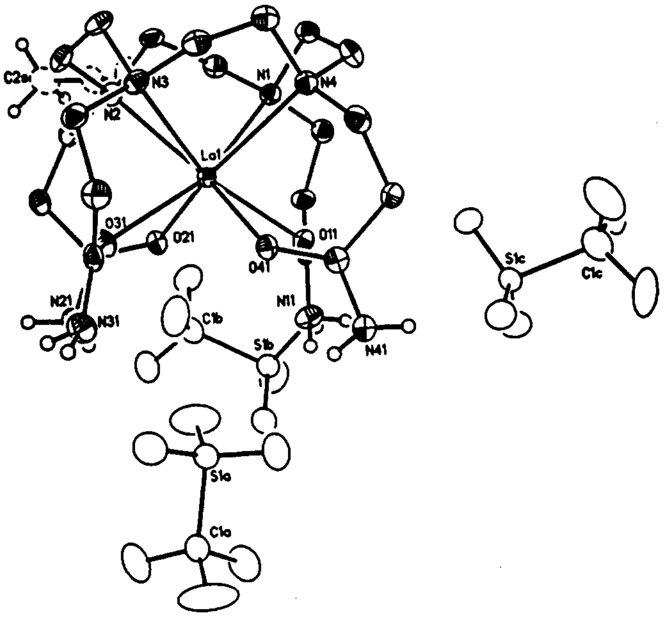

Figure 1. Overall structure of $[La(1)^{3+}][CF_3SO_3^-]_3 \cdot MeCN$.

Table III. Selected Bond Lengths (Å)

La(1)–O(11)	2.390(5)	La(1)–O(21)	2.434(5)
La(1)–O(31)	2.411(5)	La(1)–O(41)	2.455(5)
La(1)–N(1)	2.727(6)	La(1)–N(2)	2.711(6)
La(1)–N(3)	2.710(7)	La(1)–N(4)	2.724(6)
O(11)–C(11)	1.248(9)	O(21)–C(21)	1.260(10)
O(31)–C(31)	1.246(10)	O(41)–C(41)	1.255(10)
N(1)–C(1)	1.500(10)	N(1)–C(8)	1.499(10)
N(1)–C(13)	1.497(10)	N(2)–C(2)	1.506(11)
N(2)–C(3)	1.494(10)	N(2)–C(23)	1.492(10)
N(3)–C(4)	1.498(10)	N(3)–C(5)	1.502(11)
N(3)–C(33)	1.503(11)	N(4)–C(6)	1.468(10)
N(4)–C(7)	1.494(11)	N(4)–C(43)	1.491(11)
N(11)–C(11)	1.316(11)	N(21)–C(21)	1.318(11)
N(31)–C(31)	1.301(11)	N(41)–C(41)	1.316(12)
C(1)–C(2)	1.496(11)	C(3)–C(4)	1.517(13)
C(5)–C(6)	1.504(12)	C(7)–C(8)	1.521(11)
C(11)–C(12)	1.500(10)	C(12)–C(13)	1.509(12)
C(21)–C(22)	1.472(12)	C(22)–C(23)	1.515(11)
C(31)–C(32)	1.495(12)	C(32)–C(33)	1.519(12)
C(41)–C(42)	1.510(12)	C(42)–C(43)	1.537(12)

Table IV. Selected Bond Angles (deg)

O(11)–La(1)–O(21)	74.7(2)	O(11)–La(1)–O(31)	119.8(2)
O(21)–La(1)–O(31)	76.1(2)	O(11)–La(1)–O(41)	73.4(2)
O(21)–La(1)–O(41)	118.0(2)	O(31)–La(1)–O(41)	75.9(2)
O(11)–La(1)–N(1)	71.5(2)	O(21)–La(1)–N(1)	88.7(2)
O(31)–La(1)–N(1)	156.7(2)	O(41)–La(1)–N(1)	127.3(2)
O(11)–La(1)–N(2)	127.4(2)	O(21)–La(1)–N(2)	71.3(2)
O(31)–La(1)–N(2)	89.3(2)	O(41)–La(1)–N(2)	159.0(2)
N(1)–La(1)–N(2)	68.9(2)	O(11)–La(1)–N(3)	156.5(2)
O(21)–La(1)–N(3)	128.8(2)	O(31)–La(1)–N(3)	71.6(2)
O(41)–La(1)–N(3)	91.3(2)	N(1)–La(1)–N(3)	106.4(2)
N(2)–La(1)–N(3)	69.6(2)	O(11)–La(1)–N(4)	89.4(2)
O(21)–La(1)–N(4)	155.9(2)	O(31)–La(1)–N(4)	127.9(2)
O(41)–La(1)–N(4)	72.7(2)	N(1)–La(1)–N(4)	68.8(2)
N(2)–La(1)–N(4)	106.7(2)	N(3)–La(1)–N(4)	68.7(2)
La(1)–O(11)–C(11)	125.2(5)	La(1)–O(21)–C(21)	120.0(5)
La(1)–O(31)–C(31)	126.4(5)	La(1)–O(41)–C(41)	120.2(5)
La(1)–N(1)–C(1)	107.7(4)	La(1)–N(1)–C(8)	108.3(4)
C(1)–N(1)–C(8)	109.2(6)	La(1)–N(1)–C(13)	115.1(4)
C(1)–N(1)–C(13)	109.6(6)	C(8)–N(1)–C(13)	106.9(6)
La(1)–N(2)–C(2)	108.8(4)	La(1)–N(2)–C(3)	106.9(5)
C(2)–N(2)–C(3)	109.9(6)	La(1)–N(2)–C(23)	115.3(4)
C(2)–N(2)–C(23)	107.3(6)	C(3)–N(2)–C(23)	108.6(6)
La(1)–N(3)–C(4)	107.4(4)	La(1)–N(3)–C(5)	107.7(5)
C(4)–N(3)–C(5)	110.1(6)	La(1)–N(3)–C(33)	116.9(5)
C(4)–N(3)–C(33)	107.2(6)	C(5)–N(3)–C(33)	107.5(6)
La(1)–N(4)–C(6)	108.1(5)	La(1)–N(4)–C(7)	108.1(4)
C(6)–N(4)–C(7)	109.6(6)	La(1)–N(4)–C(43)	113.7(5)
C(6)–N(4)–C(43)	108.1(6)	C(7)–N(4)–C(43)	109.1(6)
N(1)–C(1)–C(2)	114.8(6)	N(2)–C(2)–C(1)	113.4(6)
N(2)–C(3)–C(4)	113.9(7)	N(3)–C(4)–C(3)	113.2(6)
N(3)–C(5)–C(6)	113.5(7)	N(4)–C(6)–C(5)	114.0(7)
N(4)–C(7)–C(8)	114.0(6)	N(1)–C(8)–C(7)	113.0(7)
O(11)–C(11)–N(11)	121.9(7)	O(11)–C(11)–C(12)	120.2(7)
N(11)–C(11)–C(12)	117.9(7)	C(11)–C(12)–C(13)	112.9(7)
N(1)–C(13)–C(12)	116.4(7)	O(21)–C(21)–N(21)	119.6(8)
O(21)–C(21)–C(22)	121.1(7)	N(21)–C(21)–C(22)	119.3(7)
C(21)–C(22)–C(23)	113.2(7)	N(2)–C(23)–C(22)	116.5(6)
O(31)–C(31)–N(31)	121.2(8)	O(31)–C(31)–C(32)	121.1(7)
N(31)–C(31)–C(32)	117.6(7)	C(31)–C(32)–C(33)	112.6(7)
N(3)–C(33)–C(32)	114.6(7)	O(41)–C(41)–N(41)	122.5(8)
O(41)–C(41)–C(42)	120.2(8)	N(41)–C(41)–C(42)	117.3(8)
C(41)–C(42)–C(43)	113.1(7)	N(4)–C(43)–C(42)	116.2(7)

The structure of the product is illustrated in Figure 1. Interatomic distances and angles are provided in Tables III and IV. The asymmetric unit contains one **2**$^{3+}$ cation, three triflate counteranions and one acetonitrile molecule of solvation. The three triflate molecules all reside on the oxygen-coordinated side of the primary coordination sphere of the lanthanum ion. The asymmetric unit is shown in Figure 1. There is hydrogen bonding between hydrogen atoms of the amide groups and the oxygen atoms of the triflate counteranions. The following values <3 Å were observed for nitrogen···oxygen distances; intermolecular hydrogen–oxygen interactions are given in parentheses: N(31)···O(2c) = 2.901 Å (H(31a)–O(2c) = 2.052 Å), N(11)···O(3b) = 2.907 Å (H(11b)–O(3b) = 2.528 Å), N(21)···(1b) = 2.939 Å (H(21a)–O(1b) = 2.185 Å), N(41)···O(2a) = 2.970 Å (H(41a)–O(2a) = 2.162 Å) and N(31)···O(3a) = 2.981 Å (H(31b)–O(3a) = 2.844 Å). The hydrogen-bonding scheme and crystal packing are shown in Figure 2. The hydrogen atoms of the acetonitrile molecule also have some interaction with the triflate oxygen atoms with a distance of O(3a)···H(sb) = 2.488 Å.

The cation consists of an encapsulated eight coordinate lanthanum(III) ion. The labeling of the atoms is shown in Figure 3. The primary coordination polyhedron of the molecular core can be described as a distorted square antiprism Figure 4. The amide substituents are arranged in a clockwise fashion around the lanthanum ion. [Note that the cation has C_4 symmetry and is chiral; the crystal selected for the X-ray study contains molecules of only one hand. Any other crystal has a 50% chance of having the same chirality and a 50% chance of having the opposite chirality.] The angle of interception of the planes N(1)–La(1)–N(3) and N(2)–La(1)–N(4) is 90.3°, while the O(11)–La(1)–O(31) and O(21)–La(1)–O(41) planes intercept at 89.7°. These angles show how closely the nitrogen atoms in the macrocyclic ring and the oxygen atoms of the amide groups occupy the equatorial vertices of two independent square pyramids. (The fifth vertex is the lanthanum ion). These square pyramids reside on opposite sides of the lanthanum cation and adopt a staggered conformation with a rotational angle of 26.5° relative to each other. The nitrogen atoms and oxygen atoms involved in the primary coordination sphere lie in two planes, with the average displacement of these atoms from their respective planes being 0.0031 and 0.0273 Å, respectively. These planes are almost parallel with a dihedral angle of 1.3°. The four nitrogen atoms of the amide groups also define a plane, which is parallel to the other two. These atoms have an average deviation of 0.0288 Å from this plane. The molecular core is associated with the following bond distances: La(1)–N(1) = 2.727(6) Å, La(1)–N(2) = 2.711(6) Å, La(1)–N(3) = 2.710(7) Å, La(1)–N(4) = 2.724(6) Å, La(1)–O(11) = 2.390(5) Å, La(1)–O(21) = 2.434(5) Å, La(1)–O(31) = 2.411(5) Å, and La(1)–O(41) = 2.455(5) Å (average La–N = 2.718(±0.009) Å, La–O = 2.423(±0.032) Å). The statistical variation among the sets of La–N and La–O bond lengths is insignificant. Both the La–N and the La–O bond lengths are much longer than would be predicted from their ionic radii.[17]

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[17] Shannon, R. D. *Acta Crystallogr., Sect. A* **1976**, *32*, 751. (Based upon $r(La^{3+}$, 8-coordinate) = 1.160 Å.)

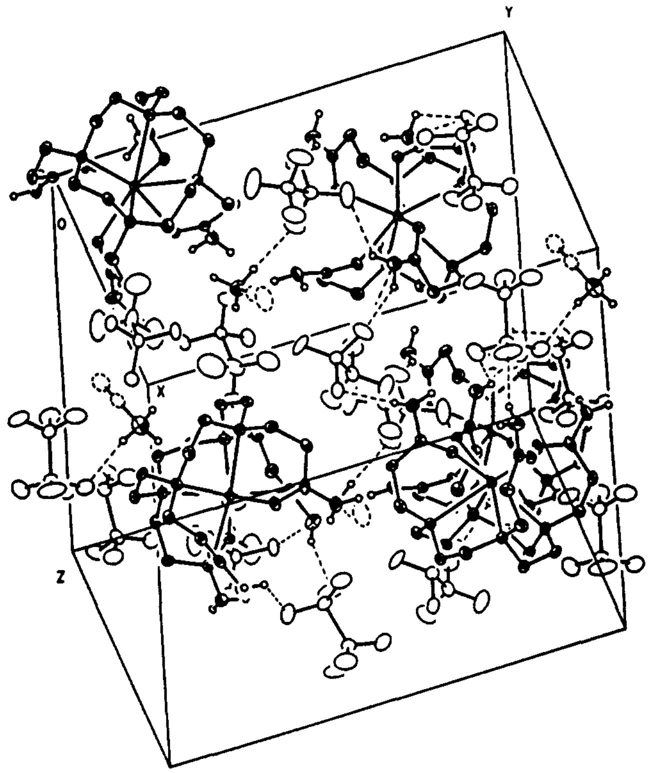

Figure 2. Unit cell contents for $[La(1)^{3+}][CF_3SO_3^-]_3 \cdot MeCN$, showing hydrogen bonding.

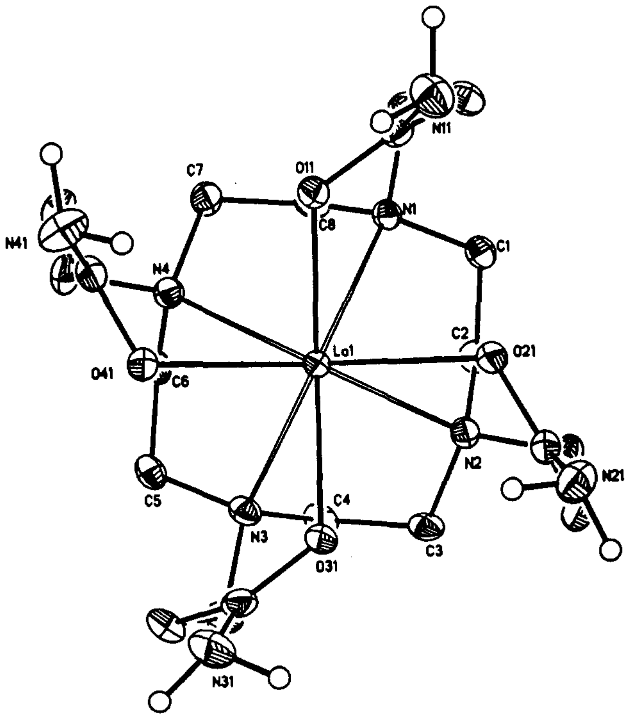

Figure 3. $[La(1)^{3+}]$ cation viewed down its C_4 axis.

The trend of short La–O bond distances and long La–N bond distances is also found in a number of other structures of macrocyclic poly(aminocarboxylate) complexes of lanthanum, europium, and gadolinium.[7f,18] The coordinated macrocycle has a cavity distance (trans N to N) of 4.356(±0.003) Å, which is far too small to contain a La^{3+} cation. This forces the lanthanum(III) ion to lay above the cavity with the amide substituents folding over and encapsulating the lanthanum ion.

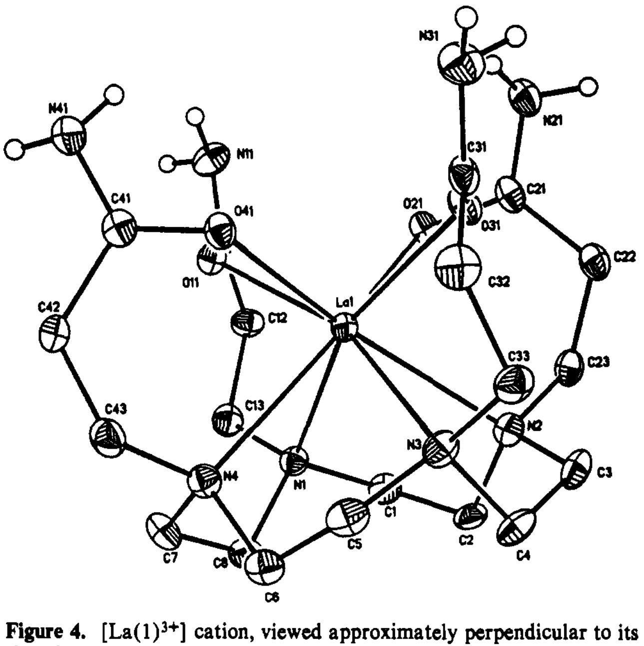

Figure 4. $[La(1)^{3+}]$ cation, viewed approximately perpendicular to its C_4 axis.

Some important angles associated with the coordination environment of the nitrogen atoms in the macrocyclic ring are N(1)–La(1)–N(3) = 106.4(2)° and N(2)–La(1)–N(4) = 106.7(2)° (average = 106.55°), while those associated with the amide oxygen atom cap are as follows: O(11)–La(1)–O(31) = 119.8(2)° and O(21)–La(1)–O(41) = 118.0(2)° (average = 118.9°). The N–La–N angles in the macrocyclic ring are similar to those found in other macrocyclic lanthanide complexes. For example, a macrocyclic complex of europium with pendent acetate groups[18] had N–Eu–N angles of 107.56(9) and 100.3(1)°. However, O–Eu–O angles of 147.51(9) and 143.4(1)° are observed in this structure where the primary coordination sphere of the europium(III) ion is a nine-coordinate distorted capped square antiprism, with a water molecule occupying the ninth site.

The C–C bonds in the octadentate macrocyclic ligand have three different types of environments with the following range of bond distances: *d*((amide sp^2)C–sp^3 C) = 1.472(12)–1.515(11) Å (four bonds, average = 1.494(±0.020) Å), *d*((amide sp^3)C–sp^3 C) = 1.509(12)–1.537(12) Å (four bonds, average = 1.520(±0.017) Å), *d*(amine C–C) = 1.496(11)–1.521(11) Å (four bonds, average = 1.509(±0.013) Å).

There are also three different environments for C–N bonds, with the following ranges of bond distances: *d*(N–C in macrocycle) = 1.468(10)–1.506(11) Å (eight bonds, average = 1.495(±0.027) Å), *d*(amine N–amide sp^3 C) = 1.491(10)–1.503(11) Å (four bonds, average = 1.496(±0.007) Å, and d(amide N–sp^2 C) = 1.301(11)–1.318(11) Å (four bonds, average = 1.313(±0.012) Å). The C–N bonds in the macrocycle have bond lengths identical to the sp^3 C–N bond lengths of the amide groups, while the sp^2 C–N(amide) bond distances are significantly shorter.

^1H and ^{13}C NMR studies of $\mathbf{2}^{3+}(CF_3SO_3^-)_3 \cdot CH_3CN$ in acetonitrile-d_3 indicate that the $\mathbf{2}^{3+}$ cation retains in solution many of the same structural features found in the solid state. ^1H and ^{13}C NMR spectra of the $\mathbf{2}^{3+}$ cation are reminiscent of the lanthanide(III) DOTA complexes in several respects.[1,19] Many of the characteristic NMR spectral properties of lanthanide(III) DOTA complexes arise from the unusually high degree of ligand rigidity in these complexes. The cation $\mathbf{2}^{3+}$ exhibits a similarly high degree of ligand rigidity as examined by use of ^{13}C and ^1H NMR. The ^{13}C resonances of the cyclen ethylenic groups are identified by their behavior in variable temperature studies as

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(18) Spirlet, M.-R.; Rebizant, J.; Desreux, J. F.; Loncin, M.-F. *Inorg. Chem.* **1984**, *23*, 359–363.

(19) Aime, S.; Botta, M.; Ermondi, G. *Inorg. Chem.* **1992**, *31*, 4291–4299.

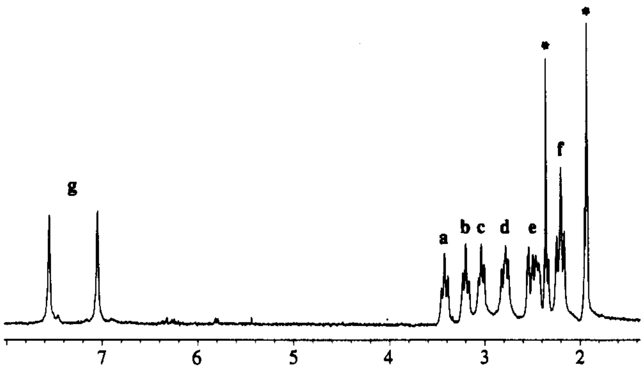

Figure 5. ^{1}H NMR spectrum of **2** in acetonitrile-d_3 at 0 °C. Asterisks denote peaks attributed to solvent.

described below. At 0 °C the ethylenic carbons of the cyclen ring are locked into a conformation described as a [3333] square[20] making the two carbons in an ethylene groups inequivalent (52.4 and 54.0 ppm). That there are two ^{13}C resonances for carbons in the cyclen ring at low temperatures indicates that all ethylenic groups in the cyclen ring are in the same conformation and that there is a C_4 axis of symmetry. Similar conformational rigidity of the ethylene groups of cyclen is observed for lanthanide DOTA complexes[1,19] and for lanthanide crown ether complexes.[21] For **2**$^{3+}$, macrocycle rigidity gives rise to five signals in the ^{13}C NMR spectrum of the complexes at low temperature, two for cyclen ring carbons and three for the carbamoylethyl groups. At low temperatures as noted above, the macrocycle ethylenic groups are locked into a staggered conformation, and one would expect eight unique protons for the **2**$^{3+}$ cation giving rise to eight resonances in the ^{1}H NMR spectrum (two resonances are overlapping, Figure 5). In the cyclen ring there are two types of axial protons and two types of equatorial protons. From comparison to the ^{1}H NMR spectrum of La(DOTA)$^-$and by use of 2-D COSY experiments, we assign the overlapping resonances at 2.20 ppm (f) to the equatorial protons of the cyclen ring and resonances at 3.43 (a) and 3.20 ppm (b) to axial protons of the ring. The four ethylenic protons in a carbamoylethyl group are all inequivalent at low temperature and appear as triplets at 3.04 (c, d) and 2.78 ppm and as two overlapping resonances at 2.50 ppm (e). That four ^{1}H resonances for the ethylene protons of the amide arm are observed is consistent with an asymmetric environment about each nitrogen with the nitrogen bound to the metal, a carbamoylethyl group, and carbons of two different cyclen ethylenic groups. All four carbamoylethyl groups are equivalent. The amide nitrogen ^{1}H resonances appear as two singlets (g), consistent with restricted rotation about the C–N bond. No coupling between the amide protons is observed.

Does **1** behave as an octadentate ligand in solution? ^{13}C NMR data and the activation barriers to rotation about the C–N bond for the complex and for the free ligand (as discussed below) indicate that the amide groups are displaced by strongly coordinating solvents. The ^{13}C chemical shift of the amide C(O) in **2**$^{3+}$ is highly dependent on solvent. In weakly coordinating solvents such as acetonitrile-d_3 or methanol-d_4, the amide C(O) ^{13}C resonance of the complex (180.6 and 180.2 ppm, respectively) is shifted downfield from that of the free ligand (177.9 and 178.1 ppm, respectively). In the more strongly coordinating solvent dimethyl-d_6 sulfoxide, the ^{13}C chemical shift of the amide C(O) is nearly identical to that of the free ligand (173.5 and 173.6 ppm, respectively). In comparison, the C(O) ^{13}C resonances of cobalt(III) pentaamine complexes of oxygen-bound dimethylformamide or dimethylurea shift downfield by approximately 5 and 2 ppm, respectively,[22] from those in the free ligands. Thus, the amide groups of **1** bind to the lanthanum ion when the complex is in acetonitrile or in methanol, but solvents that coordinate strongly to lanthanide ions such as dimethyl sulfoxide and probably water (as discussed below) appear to displace the amide groups as ligands.

For lanthanide(III) DOTA complexes a dynamic process interconverts cyclen ethylenic carbons through changes in conformation of the ethylenic groups.[1,19] This process also averages protons of the acetate groups because the quaternary nitrogen loses its asymmetry. A similar dynamic process is consistent with our results here. Carbon atoms in the cyclen ring of the **2**$^{3+}$ cation undergo an exchange process as observed by ^{13}C NMR spectroscopy. An activation barrier of 58.9 ± 0.3 kJ mol^{-1} is calculated at the coalescence temperature[23] (29°C) from the expression $k_{ex} = \pi(\Delta\nu_{AB})/(2)^{1/2}$. Comparison to the activation energy for La(DOTA)$^-$ (60.7 ± 1.2 kJ mol^{-1}) indicates that complex **2**$^{3+}$ cation has a similar degree of ligand rigidity to that found in La(DOTA)$^-$. It is surprising that similar activation barriers are observed for the two different macrocyclic complexes. Different pendent groups might be expected to modify ligand rigidity. For example, the six-membered ring formed by chelation of the pendent groups in the **2**$^{3+}$ cation may yield a more crowded and less flexible chelate. For a similar lanthanum(III) macrocyclic complex containing pendent hydroxyethyl groups that form a five-membered ring, we have calculated energy barriers for a similar dynamic process that are much lower than those for the **2**$^{3+}$ cation.[2] However, the water molecule bound as a ninth ligand[19] to La(DOTA) may very well affect complex dynamics.

A second dynamic process is observed for the **2**$^{3+}$ cation by use of ^{1}H NMR. Variable-temperature experiments in dimethyl-d_6 sulfoxide indicated a fluxional process that averaged ^{1}H resonances of the amide NH$_2$ groups in the **2**$^{3+}$ cation. An activation barrier of 69.8 ± 0.5 kJ mol^{-1} is calculated at coalescence (92°C). A dynamic process that interconverts amide protons through free rotation about the amide bond is consistent with these observations. In comparison, the activation energy for rotation about the C–N bond of the amide in the free ligand **1** calculated at coalescence (97 °C) is 70.5 ± 0.5 kJ mol^{-1}. The closeness of these values would indicate that in dimethyl sulfoxide coordination of the amide groups is very weak or nonexistent. This corroborates ^{13}C NMR data where little change in the ^{13}C resonance of the amide C(O) is observed in dimethyl-d_6 sulfoxide solution.

In D$_2$O at pH 6.5, the ^{1}H NMR spectrum of **2**$^{3+}$ closely resembles its spectrum in acetonitrile-d_3, suggesting that the solution structure in water has features similar to those in acetonitrile. However, water also coordinates strongly to lanthanide ions and, like dimethyl sulfoxide, water may coordinate to **2**$^{3+}$ and displace the amide groups. Indeed in water the complex dissociates readily. (In dimethyl sulfoxide, complete dissociation of the complex is not observed even upon heating the complex to 95 °C.) At 7 °C, no change in the spectrum of the complex over 1 h was observed. However at 37 °C at an initial pH of 6.5, dissociation of the complex was rapid; resonances of the free ligand were observed by use of ^{1}H NMR. Approximately 21% and 30% of the complex was dissociated after 10 and 20 min, respectively. After 70 min, 64% of the complex had dissociated. After 2 h at 37 °C, the ^{1}H NMR spectrum was essentially that of the free ligand. Precipitates were observed in D$_2$O solutions of (**2**$^{3+}$)(CF$_3$SO$_3$)$_3$·CH$_3$CN when left for a few hours at room temperature. Thus, the lability of the complex in water would suggest that the pendent amide groups are not tightly bound.

The tetraamide complex cation **2**$^{3+}$ is much more labile than the analogous DOTA complexes. The half-life for Gd(DOTA)$^-$ is approximately 200 days at pH 5.0.[6] This would suggest that

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[20] Dale, J. *Isr. J. Chem.* **1980**, *20*, 3–11.

[21] Desreux, J. F.; Duyckaerts, G. *Inorg. Chim. Acta* **1979**, *35*, L313–L315.

[22] Dixon, N. E.; Fairlie, D. P.; Jackson, W. G.; Sargeson, A. M. *Inorg. Chem.* **1983**, 22, 4038–4046.

[23] Faller, J. W. *Adv. Organomet. Chem.* **1977**, *16*, 211.

the 2-carbamoylethyl groups do not form kinetically inert complexes with the lanthanides in water. Ligand **1** contains six-membered rings whereas the optimal chelate size for most metal ions is a five-membered ring. Larger metal ions especially appear to favor the smaller ring size.[8] Work is underway to synthesize analogous tetraamide ligands that will form five-membered chelate rings.[24] Further work will examine the effect that various pendent groups have on the inertness of a complex to metal ion release and on the ability of these complexes to catalyze the hydrolysis of small molecules and biopolymers.

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Supplementary Material Available: Complete tables of bond lengths, bond angles, anisotropic thermal parameters and hydrogen parameters for $[La(1)^{3+}][CF_3SO_3^-]_3 \cdot MeCN$ values (5 pages). Ordering information is given on any current masthead page.

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(24) For a report on an analogous ligand see: Kataky, R.; Matthes, K. E.; Nicholson, P. E.; Parker, D.; Buschmann, H.-J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1425–1432.