Inorg. Chem. **1993,** *32,* 3501–3508

Synthesis, Characterization, and Crystal Structures of M(DO3A) (M = Fe, Gd) and Na[M(DOTA)] (M = Fe, Y, Gd)

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Received November 17, 1992

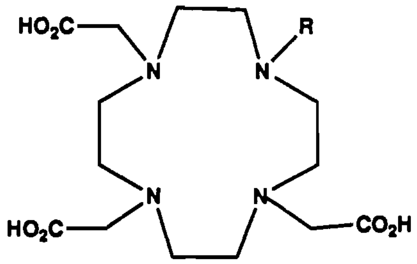
Macrocyclic amino carboxylate (DOTA and DO3A, where DOTA is 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecane and DO3A is 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane) complexes of Gd(III) and Fe(III) have been synthesized, characterized, and evaluated for use as potential contrast agents for magnetic resonance imaging (MRI). X-ray single-crystal analyses reveal four nitrogens and three oxygens coordinated to the iron in both Na[Fe(DOTA)]·5H_2O and Fe(DO3A)·3H_2O. None of the waters are coordinated to iron atoms; the former iron complex has an uncoordinated carboxylate arm. Magnetic susceptibility and Mössbauer data confirm that both of the Fe(III) complexes are high spin ($S = 5/2$) compounds. *Ennea*coordination about the metal in the *crystallographically isostructural* series Na[M(DOTA)(H_2O)]·4H_2O (M = Gd, Y, Eu) involves the four nitrogen atoms, an oxygen from each carboxyl arm, and one water molecule. Gd(DO3A) has been crystallized as a novel hydrated complex [{Gd(DO3A)}$_3$·Na_2CO_3]·17H_2O in which each *ennea*coordinate Gd atom is coordinated to the four nitrogens and an oxygen from each carboxyl arm of the ligand, as well as two oxygens of the carbonate ion. No water molecule is coordinated to the Gd atoms in the crystal structure. The Gd(DO3A) and Gd(DOTA)$^-$ species are more effective water proton relaxation agents than the Fe(III) chelates.

Introduction

The development of magnetic resonance imaging (MRI) as a clinical diagnostic modality has created the need for a new class of pharmaceuticals called MRI contrast agents. These pharmaceuticals are paramagnetic substances which function to provide contrast between diseased and normal tissue and/or show the status of organ function and blood flow.

The first example of a paramagnetic substance used for tissue discrimination in MRI was provided by Lauterbur, Mendoca-Dias, and Rudin.[1] Since then, a variety of paramagnetic contrast agents have been examined. At present, two ionic, i.e. $(NMG)_2$[Gd(DTPA)][2] and (NMG)[Gd(DOTA)],[3] and two nonionic, i.e. Gd(HP-DO3A)[4] and Gd(DTPA-BMA),[5] complexes are used in humans (NMG is *N*-methylglucamine, DTPA is diethylenetriaminepentaacetate, DTPA-BMA is the bis(methylamide) derivative of DTPA, DOTA is 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecanate, and HP-DO3A is 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate).

The criteria for a paramagnetic contrast agent suitable for clinical use are as follows:[6,7] The molecules must be effective catalysts for relaxation of protons in the bulk water; i.e., a high "relaxivity" ($^{20}r_1$, *vide infra*) is required. For metal chelates of ordinary mass (≤1000 amu), the relaxivity is dependent on the electronic ground state of the metal ion, the effective magnetic moment of the metal ion, and the number (q) of water molecules in the inner coordination sphere. Potential MRI contrast agents should also have high water solubility on the order of 0.5 M and an inner-sphere water exchange rate constant, k_{ex}, of $>10^6$ s^{-1}. In this study, we have examined Gd(III) and Fe(III) complexes of the macrocyclic amino carboxylate DO3A (1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane) and Fe(III), Y(III), and Gd(III) complexes of DOTA (Figure 1).



R	Abbreviation
H	H_3DO3A
CH_2COOH	H_4DOTA

Figure 1. Structure of chelating agents.

The aim was to further our understanding of this interesting and useful structural type, with the long-term goal of increasing

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0020-1669/93/1332-3501$04.00/0

Table I. Crystallographic Data

	Fe(DO3A)	Na[Fe(DOTA)]	$[Gd(DO3A)]_3 \cdot Na_2CO_3$	$Na[Y(H_2O)(DOTA)]$	$Na[Gd(H_2O)(DOTA)]$
a, Å	17.405(7)	8.764(2)	12.428(3)	8.752(2)	8.711(1)
b, Å	16.794(5)	18.618(4)	12.459(2)	9.097(2)	9.111(1)
c, Å	13.416(4)	14.382(2)	24.272(4)	15.625(2)	15.711(2)
α, deg			82.07(2)	82.94(1)	82.86(1)
β, deg			87.39(2)	85.88(1)	85.47(1)
γ, deg			71.20(2)	81.61(1)	81.50(1)
V, Å^3	3922(4)	2347(1)	3523(2)	1219.5(7)	1221.3(4)
space group	$Pbca$	$Pna2_1$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
D_{obs}, g cm^{-3}	1.54	1.58	NA	1.63	1.83
D_{calc}, g cm^{-3}	1.53	1.61	1.82	1.64	1.82
formula	$FeC_{14}H_{23}N_4O_6 \cdot 3H_2O$	$FeNaC_{16}H_{24}N_4O_8 \cdot 5H_2O$	$(GdC_{14}H_{23}N_4O_6)_3 \cdot Na_2CO_3 \cdot 17H_2O$	$YNaC_{16}H_{26}N_4O_9 \cdot 4H_2O$	$GdNaC_{16}H_{28}N_4O_9 \cdot 4H_2O$
fw	453.3	569.3	1932.1	602.4	670.7
Z	8	4	2	2	2
μ, cm^{-1}	8.2	7.3	29.2	24.9	28.1
transm factor	0.93–1.00	0.85–1.1	0.8–1.45	0.71–1.16	0.93–1
temp, °C	22	22	−30	22	22
N_{uni}[a]	3458	2819	12363	4483	4482
N_{obs}[b]	1879	1375	6918	2870	3721
N_{var}[c]	254	315	406	316	316
R	0.041	0.045	0.071	0.042	0.026
R_w	0.046	0.045	0.079	0.045	0.031

[a] Total number of symmetry-independent measured reflections. [b] Total number of "observed" reflections with $I \geq 3\sigma(I)$ used for refinements. [c] Number of variables in least-squares refinements.

Table II. FAB-MS, Mössbauer, Magnetic Susceptibility, Hydration Number, and Relaxivity Data

	Fe(DO3A)	Na[Fe(DOTA)][b]	Gd(DO3A)	Na[Gd(DOTA)]
FAB-MS, positive ion[a]	401 (M + 2H)	481 (M + 2H + Na) 459 (M + 3H)	502 (M + H)	582 (M + H + Na) 560 (M + 2H)
FAB-MS, negative ion[a]	399 (M) 397 (M − 2H)	479 (M + Na) 457 (M + H)	500 (M − H)	580 (M − H) + Na 558 (M)
μ_{eff}, μ_B at 84 K	6.3	6.2	7.94[c]	7.94[c]
isomer shift[d] δ, mm s^{-1} at 80 K	0.37	0.61	NA	NA
E_Q, mm s^{-1}	0.60	1.07	NA	NA
q	0[e]	0[e]	1.8[f,14]	1.0[f,14]
$^{20}r_1$, mM^{-1} s^{-1}	0.5	0.4	4.8[14]	3.5[14]

[a] The FAB-MS data are reported for ^{56}Fe (isotope abundance 91.66%) and ^{158}Gd(isotope abundance 24.87%). The mass spectra correspond well to the metal ion isotope distribution. [b] The $Fe(DOTA)^-$ ion was reduced during the mass spectrometry experiment. A proposed process, for example, could be as follows: $M^- + e^- + H^+ \rightarrow (M + H)^-$; $(M + H)^- + H^+ + Na^+ \rightarrow (M + 2H + Na)^+$; $(M + H)^- + 2H^+ \rightarrow (M + 3H)^+$, $(M + H)^- + Na^+ \rightarrow (M + Na)^- + H^+$. [c] Calculated spin-only value. [d] Reported relative to iron foil; estimated error: 0.03 mm s^{-1}. [e] Solid state. [f] Solution state.

the relaxivity of metal chelates through control of electronic and structural features.

Experimental Section

Materials. Many of the reagents used for the preparation of compounds were purchased from commercial sources and used as received: $FeCl_3 \cdot 6H_2O$ (Alfa), Gd_2O_3 (99.99%, Molycorp), and the disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, Fisher), 1,4,7,10-Tetrakis-(carboxymethyl)-1,4,7,10-tetraazacyclododecane (H_4DOTA) was purchased from Parrish Chemical Co. and purified by adsorbing it onto a cation exchange AG50WX8 column in the protonated form and eluting with NH_4OH. The eluate was adsorbed onto an anion exchange resin, AG1, washed with water, and eluted with 0.5 M formic acid. The final solution was reduced to dryness under vacuum, the resulting solid dissolved in hot ethanol, and the solution cooled to 0 °C to give crystalline H_4-DOTA. The ligand H_3DO3A was prepared by a published method.[8] Water was deionized by passage through a Millipore "Super Q" purification system.

Techniques, Apparatus, and Methods. Elemental analysis was performed by the Analytical Department at the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ. Fast atom bombardment (FAB) mass spectra of samples dissolved in glycol matrix were recorded with a VG-ZAB-2F mass spectrometer. Infrared spectra were obtained from KBr pellets on a Sirius 100 spectrophotometer in the range 4000–500 cm^{-1}.

Magnetic susceptibilities were obtained for solid samples of Fe(DO3A) and Na[Fe(DOTA)] by the Faraday method, using a Cahn Model 6600-1 research magnetic susceptibility system equipped with a continuous-flow liquid coolant cryostat. The cryogenic apparatus consisted of an Air Products Interface Model DMX-19 vacuum shroud, an LT-3-110 B Helitran system, and a Scientific Instruments Model 3800 temperature indicator/controller equipped with an LFE Model 4427 voltmeter monitoring a Scientific Instruments model Si-400 silicon diode sensor. Diamagnetic corrections in cgsu/mol were calculated from Pascal's constants.

Mössbauer spectra were obtained for Fe(DO3A) and Na[Fe(DOTA)] using a Ranger Scientific Model MS-900 Mössbauer spectrometer system interfaced to an exchange gas cryostat. The cryogenic apparatus consisted of a Cryo Industries Model 8CC variable-temperature optical cryostat with temperature controlled and monitored by a TRI Research Model T-2000 Cryo Controller. The spectrometer was interfaced to an NEC APC-3 computer system for data storage, deconvolution, and curve fitting using the Ranger Scientific Software package. Sodium nitroprusside, at room temperature, was used as a reference standard for the isomer shift parameter.

Preparative HPLC was run for the purification of Gd(DO3A) using 25 cm Rainin Dynamax C18 columns (diameter 2.14 or 4.14 cm) eluted with 98% water/2% CH_3CN (flow rates 10 or 20 mL/min, respectively). A 5-cm-long guard column of the same diameter and packing material was also used. Peak detection was performed by a Perkin-Elmer PE 650-15 fluorescence spectrophotometer (excitation at 280 nm; emission at 315 nm).

Analytical HPLC to assay for free Gd(III) employed a Nucleosil C-18 column (25 cm) and a mobile phase consisting of 2% CH_3CN and 98% buffer (50 mM Na_2EDTA, 10 mM Tris acetate, pH 7.4) at a flow rate of 1 mL/min. Gd(III)-containing compounds were detected by their fluorescence (excitation at 280 nm, emission at 316 nm). With this system, free Gd(III) forms $[Gd(EDTA)]^-$ in the buffer and elutes at ca. 2.1 min, $[Gd(DOTA)]^-$ at 3.8 min, and [Gd(DO3A)] at 5.4 min. The details of this method have been reported previously.[9] Free Gd(III) is reported in mole percentages relative to [Gd(DO3A)].

Unit cell parameters and some details of x-ray diffraction data collection and refinement are summarized in Table I. In general: Unit cell parameters were obtained through a least-squares analysis of at least 15 high-angle reflections. Crystal densities were measured by flotation in

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(8) Dischino, D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. T.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, *30*, 1265.

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Table III. Positional Parameters and Estimated Standard Deviations for Fe(DO3A)·$3H_2O$

atom	*x*	*y*	*z*
Fe	0.48211(4)	0.82562(4)	0.8347(2)
N1	0.6067(2)	0.8347(2)	0.3688(3)
N2	0.5024(2)	0.7066(2)	0.3216(3)
N3	0.3822(2)	0.8142(2)	0.3035(3)
N4	0.4834(2)	0.9392(2)	0.3348(3)
O1	0.5280(2)	0.9017(2)	0.5203(2)
O2	0.6320(2)	0.9363(2)	0.6050(2)
O3	0.5147(2)	0.7438(2)	0.5151(2)
O4	0.5557(2)	0.6241(2)	0.5598(3)
O5	0.3876(2)	0.8429(2)	0.4958(2)
O6	0.2643(2)	0.8148(2)	0.5207(3)
C1	0.6343(3)	0.7573(3)	0.3289(4)
C2	0.5738(3)	0.7199(3)	0.2641(4)
C3	0.4381(3)	0.6872(3)	0.2518(4)
C4	0.4002(3)	0.7622(3)	0.2172(4)
C5	0.3626(3)	0.8955(3)	0.2687(4)
C6	0.4349(3)	0.9406(3)	0.2444(4)
C7	0.5626(3)	0.9675(3)	0.3171(4)
C8	0.6132(3)	0.8970(3)	0.2915(4)
C9	0.6001(3)	0.9020(3)	0.5341(3)
C10	0.6494(3)	0.8574(3)	0.4611(4)
C11	0.5312(3)	0.6709(3)	0.4975(3)
C12	0.5136(4)	0.6410(3)	0.3942(4)
C13	0.3221(3)	0.8163(3)	0.4684(4)
C14	0.3180(3)	0.7828(3)	0.3643(4)
O11	0.7796(2)	0.9271(3)	0.6636(3)
O21	0.8681(3)	0.9837(3)	0.5071(3)
O31	0.7631(3)	1.0477(3)	0.3628(4)

hexane/carbon tetrachloride/bromoform mixtures. Reflections [Mo Kα radiation ($\lambda = 0.710\ 69$ Å)] were measured diffractometrically using the θ–2θ variable scan technique and were corrected for Lorentz–polarization factors and for absorption. Background counts were collected at the extremes of the scan for half the time of the scan. Two standard reflections were monitored for decay; no decrease of intensity was observed during the course of the measurements. The highly hydrated $[Gd(DO3A)]_3 \cdot Na_2CO_3$ crystals decomposed through the loss of water and became opaque within a few seconds after exposure to ambient temperature and humidity. The crystal for data collection was transferred with some mother liquor to a capillary which was sealed and kept at −30 °C during all measurements. Structures were solved by heavy atom techniques and refined on the basis of "observed" reflections with $I \geq 3\sigma(I)$. Although most hydrogen positions were evident in difference maps during the latter stages of refinement, only the observed hydrogens on oxygen and nitrogen atoms were retained in observed positions. All other hydrogens were introduced in idealized positions and assigned isotropic temperature factors. The coordinates and anisotropic temperature factors of all atoms except hydrogen were refined (for $[Gd(DO3A)]_3 \cdot Na_2CO_3$, only Gd and Na atoms were refined anisotropically; the C, N, and O atoms were refined isotropically). All calculations utilized the SDP software package with minor local modifications.[10] Least-squares weights, $w = \sigma^{-2}(F_o)$, were calculated with the assumption that $\sigma^2 = \epsilon^2 + (pI)^2$, where ϵ is the statistical counting error and $\rho = 0.04$. The function minimized in the least-squares refinements was $\sum w(|F_o| - |F_c|)^2$. R is defined as $\sum||F_o| - |F_c||/\sum|F_o|$ while $R_w = [\sum w(|F_o| - |F_c| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

Relaxivity measurements were made on a Bruker PC/20 Multispec relaxometer operating at a radio frequency of 20 MHz with a 4.7-kG permanent magnet maintained at 40 ● 1 °C. T_1 measurements were made using the inversion–recovery method described elsewhere.[11] Samples for the relaxivity measurements were dissolved in Bis–Tris buffer at pH 7.0. Deionized distilled water was used for all solution preparations. The T_1 relaxivity, ${}^{20}r_1$ (*vide infra*), for each complex was obtained as the least-squares slope of the plot of $1/T$ vs [complex].

Preparation of Complexes. [Fe(DO3A)]·$3H_2O$. A slurry of 1.9 mmol of $Fe(OH)_3$ (prepared by reacting 0.516 g (1.92 mmol) of $FeCl_3 \cdot H_2O$ with 0.249 g (6.2 mmol) of NaOH) was reacted with 0.731 g (1.90 mmol) of H_3DO3A in water. The resulting suspension was stirred and heated at 90 °C for 1 h. The resulting clear yellow solution was evaporated under reduced pressure to give a yellow-green solid. The compound was crystallized by dissolving the solid in 35 mL of boiling ethanol containing 1% water and cooling the solution slowly to 0 °C. Yellow crystals formed after 3 h. The crystals were collected, washed with 5 mL of ethanol, followed by 5 mL of acetone. These crystals were used for the diffraction studies. Samples for elemental analysis were dried *in vacuo* over P_2O_5 for 10 h. Yield: 0.20 g, 40% based on $FeCl_3 \cdot H_2O$. Anal. Calcd for $FeC_{14}H_{23}O_6N_4 \cdot 3H_2O$: C, 40.79; H, 5.98; N, 13.59. Found: C, 40.89; H, 5.97; N, 13.49.

Table IV. Positional Parameters and Estimated Standard Deviations for Na[Fe(DOTA)]·$5H_2O$

atom	*x*	*y*	*z*
Fe	0.8398(1)	0.44624(6)	0.271
N1	0.6282(8)	0.4046(4)	0.2081(5)
N2	0.6672(8)	0.5413(3)	0.2958(4)
N3	0.9595(8)	0.5479(3)	0.2239(5)
N4	0.9333(8)	0.4143(4)	0.1303(5)
O1	0.8622(6)	0.3370(3)	0.2893(4)
O2	0.7356(8)	0.2355(3)	0.3169(5)
O3	0.7590(8)	0.4329(3)	0.4039(5)
O4	0.6116(8)	0.4598(4)	0.5231(5)
O5	1.0492(7)	0.4426(3)	0.3338(4)
O6	1.2481(7)	0.5030(4)	0.3901(5)
O7	1.0951(7)	0.3481(3)	−0.0237(4)
O8	1.2931(8)	0.3218(4)	0.0654(5)
C1	0.495(1)	0.4506(5)	0.2287(6)
C2	0.540(1)	0.5285(5)	0.2288(7)
C3	0.7343(9)	0.6128(4)	0.2791(8)
C4	0.853(1)	0.6079(4)	0.2038(6)
C5	1.053(1)	0.5319(5)	0.1387(7)
C6	0.967(1)	0.4808(5)	0.0775(6)
C7	0.811(1)	0.3721(5)	0.0833(6)
C8	0.658(1)	0.4033(5)	0.1051(6)
C9	0.742(1)	0.2978(4)	0.2865(6)
C10	0.600(1)	0.3318(5)	0.2435(6)
C11	0.663(1)	0.4719(5)	0.4453(6)
C12	0.608(1)	0.5382(4)	0.3936(6)
C13	1.1294(9)	0.5000(5)	0.3443(6)
C14	1.063(1)	0.5669(4)	0.3016(6)
C15	1.160(1)	0.3450(4)	0.0520(6)
C16	1.076(1)	0.3694(5)	0.1407(7)
Na	1.0562(5)	0.3274(2)	0.4007(3)
O11	0.9038(8)	0.2437(4)	0.9060(5)
O21	0.6597(8)	0.2983(4)	0.7976(5)
O31	0.6760(9)	0.3193(4)	0.6067(5)
O41	1.2665(9)	0.3704(4)	0.4887(5)
O51	0.9433(9)	0.2629(4)	0.5211(5)

Na[Fe(DOTA)]·$5H_2O$. Freshly precipitated $Fe(OH)_3$ was prepared by reacting 0.542 g (2.01 mmol) of $FeCl_3 \cdot 6H_2O$ with 6.5 mL of 1 N NaOH (6.03 mmol). A red-orange solid precipitated immediately. The solid was washed four times, each time with 40 mL of water, to remove NaCl. A slurry of the solid was added to a 10 mL of a solution of H_4-DOTA (2 M, 2.0 mmol). The resulting suspension was stirred and heated at 90 °C. After 15 min, the solid dissolved to give a red solution. The solution was heated for a total of 2.5 h and then cooled to room temperature. NaOH (1N, 2 mL) was added to adjust the pH to 9. The solution was evaporated to dryness under reduced pressure to yield a red-orange solid. The solid was recrystallized by dissolving it in 35 mL of a hot water–ethanol mixture (2:5), cooling to 25 °C and adding dropwise 10 mL of acetone. Crystals started to form after 1 h of further cooling at 0 °C. The crystals were collected and washed with 3 mL of ethanol, followed by 3 mL of acetone. These crystals were used for the diffraction studies. Samples for elemental analysis were dried *in vacuo* over P_2O_5 for 10 h. Anal. Calcd for $FeC_{16}H_{24}O_8N_4 \cdot 5H_2O$: C, 33.61; H, 6.04; N, 9.80. Found: 33.79; H, 5.62; N, 9.62.

Gd(DO3A). This compound was prepared by a method similar to the published one.[8] A mixture of 15.6 g of H_3DO3A (42.3 mmol, corrected for 6% water) and 8.16 g of Gd_2O_3 (45.1 mmol) in 100 mL of water was heated to 100 °C for 4 h. Over that time, most of the solid oxide dissolved and the pH of the mixture increased from 3.5 to 7.2. The undissolved solid was removed by centrifugation. The resulting solution was purified by preparative HPLC. Yield: 70–90%. Analytical HPLC indicated that <0.05% of free Gd(III) was present in Gd(DO3A). Anal. Calcd. for $GdC_{14}H_{23}N_4O_6 \cdot 3H_2O$: C, 30.31; H, 5.27; N, 10.10. Found: C, 30.25; H, 5.48; N, 9.97. The purified Gd(DO3A) is amorphous and very hygroscopic. The crystallization of Gd(DO3A) of varying degrees of purity has been attempted many times in these and other laboratories during the past several years. Numerous combinations of solvents and

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(10) SDP, Structure Determination Package, Enraf-Nonius, Bohemia, NY. Scattering factors, including *f* ′, and *f* ′, in the SDP software were taken from: *International Tables for Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Tables 2.2A and 2.3.1.

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Table V. Positional Parameters and Estimated Standard Deviations for $[Gd(DO3A)]_3{\cdot}Na_2CO_3{\cdot}17H_2O$

atom	*x*	*y*	*z*	atom	*x*	*y*	*z*
Gd1	0.69443(7)	0.11774(7)	0.30164(4)	O26	1.168(1)	0.058(1)	0.1864(6)
N1	0.509(1)	0.149(1)	0.3634(6)	Gd3	0.79787(7)	–0.13845(7)	0.15837(4)
N2	0.625(1)	0.325(1)	0.3298(6)	N41	0.702(1)	–0.285(1)	0.1357(7)
N3	0.642(1)	0.265(1)	0.2130(5)	N42	0.755(1)	–0.113(1)	0.0532(6)
N4	0.528(1)	0.103(1)	0.2476(6)	N43	0.986(1)	–0.167(1)	0.1013(6)
O1	0.6708(9)	–0.0533(9)	0.3456(5)	N44	0.936(1)	–0.343(1)	0.1788(6)
O3	0.7550(9)	0.1218(9)	0.3911(5)	O41	0.721(1)	–0.220(1)	0.2366(5)
O5	0.8337(9)	0.2060(9)	0.2750(5)	O43	0.6082(9)	–0.033(1)	0.1393(5)
C1	0.492(1)	0.250(1)	0.3932(8)	O45	0.830(1)	0.0329(9)	0.1183(5)
C2	0.504(2)	0.349(2)	0.3521(8)	C41	0.648(2)	–0.251(2)	0.0781(9)
C3	0.623(1)	0.407(1)	0.2804(7)	C42	0.730(2)	–0.216(2)	0.036(1)
C4	0.573(1)	0.380(1)	0.2294(8)	C43	0.851(2)	–0.095(2)	0.0187(8)
C5	0.575(2)	0.234(2)	0.1720(8)	C44	0.968(2)	–0.180(2)	0.0422(8)
C6	0.483(1)	0.195(1)	0.2041(8)	C45	1.078(2)	–0.274(2)	0.1269(8)
C7	0.435(2)	0.081(2)	0.2849(8)	C46	1.033(2)	–0.375(2)	0.1404(9)
C8	0.405(2)	0.165(1)	0.3282(8)	C47	0.873(2)	–0.430(2)	0.1844(9)
C9	0.600(1)	–0.060(1)	0.3830(7)	C48	0.785(2)	–0.403(2)	0.137(1)
C10	0.526(2)	0.047(2)	0.4064(8)	C49	0.648(2)	–0.274(2)	0.2351(8)
C11	0.763(1)	0.212(1)	0.4058(7)	C50	0.613(2)	–0.289(2)	0.1775(9)
C12	0.703(1)	0.330(1)	0.3720(7)	C51	0.575(2)	0.007(2)	0.0912(9)
C13	0.842(1)	0.256(1)	0.2260(7)	C52	0.656(2)	–0.005(2)	0.0411(9)
C14	0.749(1)	0.269(1)	0.1860(7)	C53	0.925(1)	0.040(1)	0.1041(8)
O2	0.592(1)	–0.156(1)	0.4047(6)	C54	1.025(2)	–0.069(2)	0.1023(8)
O4	0.827(1)	0.215(1)	0.4429(5)	O42	0.604(1)	–0.314(1)	0.2764(6)
O6	0.925(1)	0.286(1)	0.2095(5)	O44	0.473(1)	0.071(1)	0.0800(6)
Gd2	1.06300(7)	–0.18766(7)	0.31014(4)	O46	0.945(1)	0.132(1)	0.0912(5)
N21	1.137(1)	–0.357(1)	0.3910(6)	Na71	1.0407(7)	0.2362(7)	0.1316(3)
N22	1.282(1)	–0.251(1)	0.3184(5)	Na81	0.7253(6)	–0.2550(6)	0.3345(3)
N23	1.128(1)	–0.021(1)	0.3323(6)	C61	0.859(1)	–0.060(1)	0.2531(7)
N24	0.992(1)	–0.128(1)	0.4063(6)	O62	0.8849(9)	–0.0316(9)	0.2990(5)
O21	0.9282(9)	–0.2833(9)	0.3398(5)	O63	0.7639(9)	–0.0049(9)	0.2293(5)
O23	1.152(1)	–0.349(1)	0.2662(5)	O64	0.9273(9)	–0.1454(9)	0.2324(5)
O25	1.1278(9)	–0.0906(9)	0.2331(5)	O83	0.467(3)	0.554(3)	–0.051(2)
C21	1.260(1)	–0.417(1)	0.3831(7)	O84	0.601(2)	0.439(2)	–0.123(1)
C22	1.323(2)	–0.329(2)	0.3691(8)	O85	0.652(2)	0.670(2)	–0.070(1)
C23	1.327(1)	–0.151(1)	0.3171(7)	O86	0.970(1)	0.343(1)	0.4093(5)
C24	1.248(1)	–0.069(1)	0.3550(7)	O87	0.682(2)	0.046(2)	–0.1112(9)
C25	1.052(1)	0.041(1)	0.3765(7)	O88	0.667(2)	0.228(2)	–0.0558(8)
C26	1.037(1)	–0.042(1)	0.4258(7)	O89	0.755(1)	0.296(1)	0.0316(7)
C27	1.002(1)	–0.225(1)	0.4504(8)	O90	0.825(2)	0.485(2)	–0.0113(9)
C28	1.117(2)	–0.317(2)	0.4461(8)	O91	1.013(1)	0.384(1)	0.0587(8)
C29	0.951(1)	–0.378(1)	0.3710(7)	O92	0.258(2)	0.371(2)	0.5144(9)
C30	1.073(2)	–0.440(2)	0.3874(8)	O93	1.198(2)	0.281(2)	0.1522(8)
C31	1.254(1)	–0.375(1)	0.2516(8)	O94	1.216(1)	0.366(1)	0.2468(7)
C32	1.382(2)	–0.310(2)	0.2672(8)	O95	0.469(1)	0.407(1)	0.4923(7)
C33	1.145(1)	0.001(1)	0.2303(7)	O96	1.006(1)	0.373(1)	0.2925(7)
C34	1.117(1)	0.063(1)	0.2824(7)	O97	0.591(1)	0.190(1)	0.5353(6)
O22	0.875(1)	–0.421(1)	0.3895(5)	O98	1.200(1)	0.234(1)	0.4469(7)
O24	1.299(1)	–0.457(1)	0.2236(6)	O99	0.748(1)	–0.008(1)	0.5012(6)

conditions have been explored; most solutions failed to crystallize. A few attempts gave small amounts of minute, highly unstable crystals, but in general, the conditions for crystallization were not reproducible. Two of the aqueous methanolic solutions to which a drop of saturated aqueous sodium chloride had been added eventually deposited some crystals which, by single-crystal X-ray analysis, were shown to be a (3:1) complex of Gd(DO3A) and Na_2CO_3 (carbonate is a known contaminant of Gd_2O_3). Subsequent attempts to prepare larger quantities of the crystals from (3:1) mixtures of purified Gd(DO3A) and Na_2CO_3 in aqueous solvents gave mixtures of amorphous and crystalline material. Another form of Gd(DO3A) eventually crystallized from a methanolic solution of Gd(DO3A) which had been allowed to stand at ambient temperature in an atmosphere of acetone. All crystals of this unstable trigonal form (apparent lattice parameters $a = 13.479(3)$ Å, $\alpha = 98.3°$, $V = 2365(2)$ Å^3; probable space group *R*3) which were examined were twinned.

[NaY(DOTA)(H₂O)]·4H₂O. The chelate was prepared from the reaction of freshly prepared $Y(OH)_3$ and H_4DOTA. A 1 N NaOH solution (1.85 mL) was added to a solution of YCl_3 (0.605 mmol) to precipitate a white gelatinous solid. Additional NaOH was used to raise the pH of the reaction mixture to 8.5–9.0. The solid gelatinous $Y(OH)_3$ was washed three times with 10 mL of water and was separated for the wash solutions by centrifugation. The gel was added to a stirred solution of H_4DOTA (0.605 mmol) in 25.0 mL of water. The suspension dissolved upon heating at 90 °C for 10 min. Evaporation of the reaction mixture to dryness gave a white solid (0.84 g) (100% based on Y); 0.42 g of this solid was suspended in 25 mL of ethanol. The suspension was heated to boiling and 10 mL of water was added to dissolve the solid. Acetone was added dropwise (2 mL) to the cooled solution until an additional drop gave an initial cloudiness which disappeared on swirling. The solution was cooled further to 0 °C. White crystals formed within 1 h and were collected by filtration, washed with 5 mL of acetone–water (3:1) and with acetone, and dried *in vacuo*. Yield: 140 mg (30%). Anal. Calcd for $C_{16}H_{26}N_4O_8YNa{\cdot}5H_2O$: C, 31.90; H, 5.69; N, 9.30. Found: C, 31.42; H, 5.62; N, 9.27.

Na[Gd(DOTA)H₂O]·4H₂O. The compound was prepared by reacting Gd_2O_3 with the ligand according to a published method.[12] Yield: 80–90%. Anal. Calcd. for $GdNaC_{16}H_{26}N_4O_8{\cdot}5H_2O$: C, 28.46; H, 5.15; N, 8.30. Found: C, 28.75; H, 5.04; N, 8.10. Crystals for diffraction studies were grown from water.

Results and Discussion

Synthesis and General Characterizations. The use of freshly precipitated $Fe(OH)_3$ in the preparation of the Fe(III) complexes circumvented problems often encountered using other ferric reagents such as the formation of hydrated ferric oxides when the pH was raised during the reaction or workup. This technique has been used in the preparation of $[Fe(EDTA){\cdot}H_2O]$.[13] The reaction between the ligand and $Fe(OH)_3$ occurs quickly (*ca.* 15

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Table VI. Positional Parameters and Estimated Standard Deviations for $Na[Y(DOTA)(H_2O)]\cdot 4H_2O$

atom	*x*	*y*	*z*
Y	0.59463(6)	0.25190(6)	0.30645(3)
N1	0.8479(5)	0.0559(4)	0.3031(2)
N2	0.6463(5)	0.1370(5)	0.1564(2)
N3	0.6380(5)	0.4569(4)	0.1761(2)
N4	0.8433(5)	0.3789(4)	0.3223(3)
O1	0.6827(4)	0.1651(4)	0.4430(2)
O3	0.5110(4)	0.0201(4)	0.3100(2)
O5	0.3771(4)	0.3271(4)	0.2274(2)
O7	0.5405(4)	0.4802(4)	0.3624(2)
O9	0.3684(4)	0.2555(4)	0.4069(2)
C1	0.8476(6)	−0.0413(6)	0.2333(3)
C2	0.8025(6)	0.0483(6)	0.1491(3)
C3	0.6312(6)	0.2560(6)	0.0817(3)
C4	0.7066(6)	0.3878(6)	0.0980(3)
C5	0.7413(6)	0.5603(6)	0.1989(3)
C6	0.8825(6)	0.4761(6)	0.2425(3)
C7	0.9787(6)	0.2642(6)	0.3424(3)
C8	0.9876(6)	0.0439(5)	0.4613(3)
C9	0.7732(6)	0.0439(5)	0.4613(3)
C10	0.8504(6)	−0.0377(6)	0.3876(3)
C11	0.4711(6)	−0.0290(6)	0.2435(3)
C12	0.5256(6)	0.0388(6)	0.1552(3)
C13	0.3578(6)	0.4394(6)	0.1715(3)
C14	0.4823(6)	0.5400(6)	0.1583(3)
C15	0.6365(6)	0.5460(6)	0.3947(3)
C16	0.8032(6)	0.4718(6)	0.3939(3)
O2	0.7971(4)	−0.0135(4)	0.5369(2)
O4	0.3885(5)	−0.1289(4)	0.2463(2)
O6	0.2431(4)	0.4725(4)	0.1266(2)
O8	0.6027(4)	0.6654(4)	0.4282(2)
Na	0.3733(3)	0.8204(3)	0.4008(1)
O21	0.2023(5)	−0.0667(5)	0.1005(3)
O31	0.0329(5)	0.7203(5)	0.0768(3)
O41	0.1407(6)	0.2346(6)	0.0638(4)
O51	0.2234(5)	0.6230(5)	0.3758(3)

min.) at 90 °C. The use of pure Gd_2O_3 for the preparation of complexes offers a similar advantage.

Where possible, the Fe(III) and Gd(III) amino carboxylate complexes were characterized by elemental analysis, infrared spectroscopy, fast atom bombardment (FAB) mass spectrometry, Mössbauer spectroscopy, variable-temperature magnetic susceptibility measurements, inner-sphere hydration number determinations, and relaxivity measurements (Table II).

The bands in the IR spectra are characteristic of metal amino carboxylate complexes. In particular, all the ligand carboxylate stretching frequencies shift to lower wavenumbers between 1600 and 1650 cm^{-1} on complexation with a metal ion. FAB-MS experiments show the appropriate m/z values for all complexes.

The ^{57}Fe Mossbauer isomer shift and quadrupole splitting parameters for both Fe(DO3A) and Na[Fe(DOTA)] at 80 K are consistent with a high-spin ($S = {}^5/_2$) ferric ion. The variable-temperature (84–290 K) magnetic susceptibility data are also consistent with $S = {}^5/_2$ Fe(III). For both Fe(DO3A) and Na[Fe(DOTA)], the Curie–Weiss law is obeyed, and the magnetic moments of *ca.* 6.0 μ_B approximate the $S = 5/2$ spin-only value.

X-ray Structural Results. Atomic coordinates and drawings depicting the atom numbering schemes for $Fe(DO3A)\cdot 3H_2O$, $Na[Fe(DOTA)]\cdot 5H_2O$, $[Gd(DO3A)]_3\cdot Na_2CO_3\cdot 17H_2O$, and $Na[Y(DOTA)H_2O]\cdot 4H_2O$ are presented in Tables III–VI and Figures 2–5 (the numbering scheme for Gd(DO3A) is analogous to that of Fe(DO3A). Bond distances and angles about the metals are given in Table VII.

The molecular structure of the neutral Fe(DO3A) (Figure 2) is virtually identical to the previously described heptacoordinate face-capped trigonal prismatic structure of In(DO3A)[15] in which all four nitrogens and an oxygen from each of the three carboxylate arms are coordinated to the central metal. The anionic complex $Fe(DOTA)^-$ in $Na[Fe(DOTA)]\cdot 5H_2O$ is also a seven-coordinate species and has a very similar structure, despite the presence of an addditional carboxylate arm in the DOTA ligand (Figure 3). The latter, uncoordinated, arm is turned away from the central Fe atom and is the acceptor of two hydrogen bonds from water molecules in the crystal structure. As in the structure of In(DO3A), the shortest metal–N distance in Fe(DO3A) (2.190(4) Å) involves the (secondary) nitrogen atom, N4, which is not further linked to the metal through a carboxyl arm. However, the corresponding Fe–N4 bond in $Fe(DOTA)^-$ (2.269(7) Å) is not compressed, apparently because of steric interactions between the methylene hydrogens of the "turned" acetate arm C16 and the coordinated oxygens O1 and O5 of the flanking carboxyl groups.

In the remarkable crystal structure of $[Gd(DO3A)]_3\cdot Na_2CO_3$, the three crystallographically independent Gd(DO3A) units have essentially the same structure, conformation, and chirality. As in Fe(DO3A) and In(DO3A), the four nitrogens and an oxygen from each of the three carboxylate arms bind the ligand to the metal (average Gd–N = 2.60 Å, Gd–O = 2.35 Å). Although 17 water sites have been identified in the asymmetric unit, no water is coordinated to a gadolinium atom. Instead, the eight and ninth coordination sites for *all three Gd(DO3A) units are filled by a single carbonate* ion: pairwise bidentate combinations of the three carbonate oxygens (average Gd–O = 2.46 Å) join the three Gd(DO3A) units to form a nearly C_3 symmetric arrangement in which the bridging carbonate dianion is completely encapsulated (Figure 4). The trimeric arrangement appears to gain some additional stability from the interaction of each secondary N–H group with a carboxylate oxygen from another Gd(DO3A) unit in the trimer (average N–O distance = 3.42 Å). The two sodium ions cap the trimer at opposite ends through coordination to carboxylate oxygens. The sodium ion at one end lies within the trimer, surrounded by six oxygens (a carboxyl group from each Gd(DO3A) unit serves as a bidentate ligand, average Na81–O = 2.45 Å; the distance from the carbonate carbon to the sodium is Na81–C61 = 3.69 Å) while, at the other end, the other sodium ion lies outside the complex and is coordinated to one exposed oxygen from each of the three Gd(DO3A) units (average Na71–O = 2.40 Å; Na71–C61 = 5.40 Å) and two water molecules. The latter sodium is also coordinated to two oxygens of lattice water molecules (average Na71–O = 2.31 Å) and therefore has a C_3 symmetric environment only with regard to the trimer.

Not surprisingly, the complexes $Na[M(DOTA)(H_2O)]\cdot 4H_2O$, with M = Y, Eu,[16] and Gd,[17] are *crystallographically isostructural* and have similar geometries. The *ennea*coordinate metal in the C_4 symmetric anions is coordinated to the four nitrogens and an oxygen atom from each of the four carboxylate arms of the octadentate ligand. The ninth coordination site is occupied by a water molecule which caps the square antiprismatic arrangement of the other eight ligating atoms (Figure 5). The conformation of the macrocycle and the geometry of *ennea*coordination (Tables

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(17) We reported the structure of the Na[Gd(DOTA)] complex at the 196th National Meeting of the American Chemical Society, Los Angeles CA, Sept 1988. Subsequent independent reports on the same structure have appeared: (a) Dubost, J. P.; Meyer, D.; Schaefer, M.; Langlois, M. H.; Legar, J. M. Crystallographic Structure of DOTA–Gadolinium. Presented at the XVth Congress and General Assembly International Union of Crystallography, Bordeaux, France, July 28, 1990; MS-06.01.03. (b) Dubost, J. P.; Legar, J. M.; Langlois, M. H., Meyer, D.; Schaefer, M. *C. R. Acad. Sci. Paris, Ser. 2* **1991**, *312*, 349–354.

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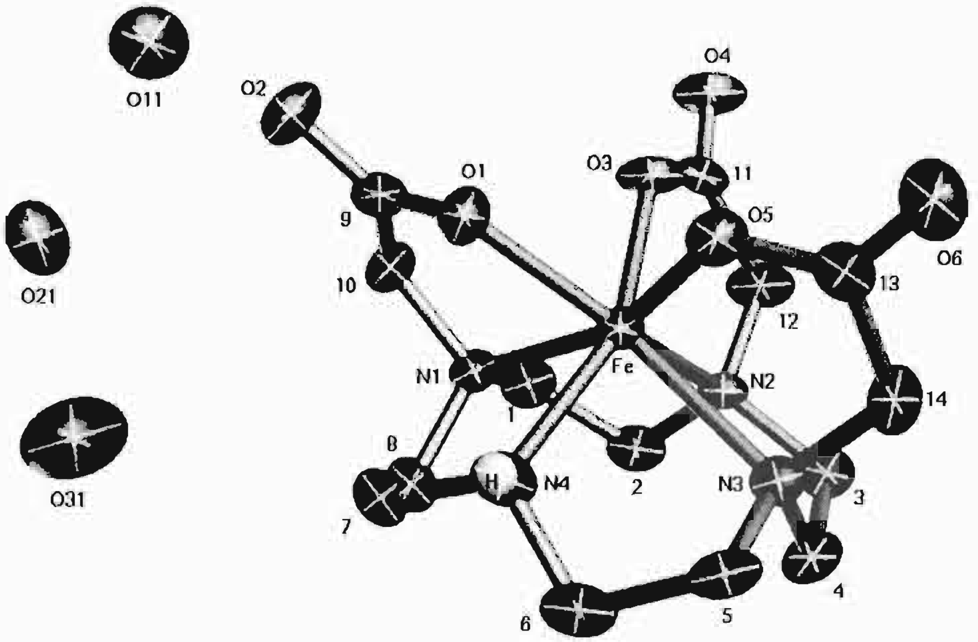

Figure 2. Solid state conformation of the Fe(DO3A)·$3H_2O$ complex. All non-hydrogen atoms are represented by (50% probability) ellipsoids consistent with refined anisotropic thermal parameters. The hydrogen atom on N4 has been assigned an arbitrary radius.

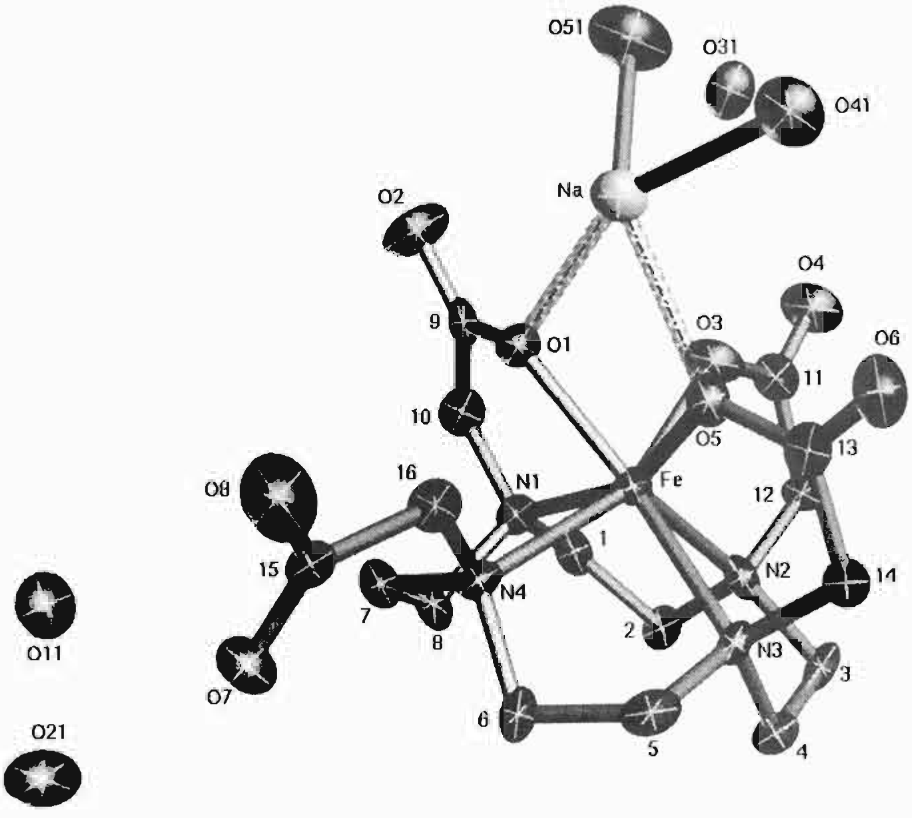

Figure 3. Solid-state conformation of the NaFe(DOTA)·$5H_2O$ complex. All atoms are represented by (50% probability) ellipsoids consistent with refined anisotropic thermal parameters.

VIII and IX) are in fact very similar to those in the cations, (12-crown-4-*O,O',O'',O'''*)pentaaqua-M^{3+} for the reported[21,22] *isostructural* series of complexes (M = Ce, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Y). This structural similarity is particularly interesting since, in contrast to the DOTA complexes, the macrocyclic (crown ether) ligand is not covalently linked to any of the other five oxygen (H_2O) ligands. For all of the above complexes, the macrocyclic ligands adopt nearly the same quadrangular [3333] conformation with carbon atoms at the corner positions.[23]

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(23) The macrocyclic conformation is [4242] in the isostructural hexacoordinate octahedral complexes Cu(DOTAH_2) and Ni(DOTAH_2) (Reisen, A.; Zehnder, M.; Kaden, T. *Helv. Chim. Acta.* **1986**, *69*, 2067–2073). All nitrogens and the carboxyl arms N1 and N3 are coordinated to the metals. As in Fe(DOTA)$^-$, the uncoordinated carboxyl arms (N2 and N4) are turned away from the metal and distances from the metal to N2 and N4 are 0.06 Å (Ni) and 0.11 Å (Cu) longer than metal–N1,N3 distances.

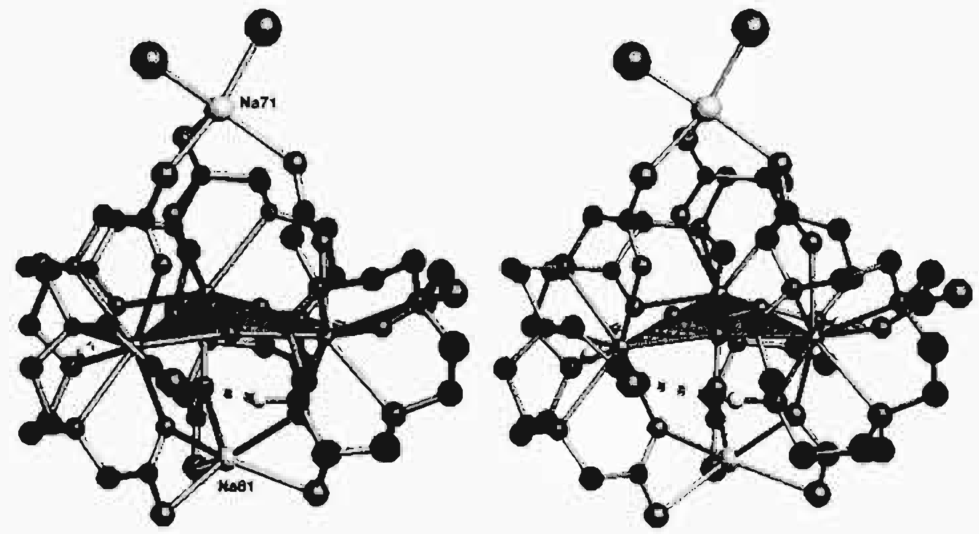

Figure 4. Stereoscopic drawing of the $[Gd(DO3A)]_3 \cdot Na_2CO_3$ complex. Only the two water molecules associated with the "external" sodium ion (top) are shown. Atoms are represented by (50% probability) surfaces consistent with refined thermal parameters.

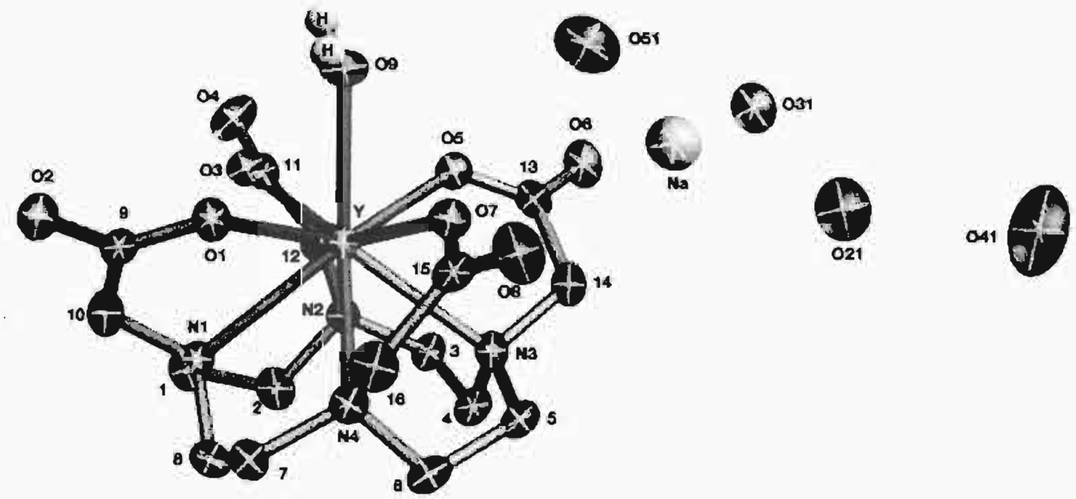

Figure 5. Solid-state conformation of the $Na[Y(DOTA)] \cdot 5H_2O$ complex. All non-hydrogen atoms are represented by (50% probability) ellipsoids consistent with refined anisotropic thermal parameters. The hydrogens of the apical water O9 have been assigned an arbitrary radius.

Idealized displacements D of the metals from the planes of n *symmetrically* coordinated O or N atoms in the above ligands

$$D = R\{[\cos Q - \cos (2\pi/n)]/[1 - \cos (2\pi/n)]\}^{1/2}$$

are compared to the experimentally observed displacements in an appendix included in the supplementary material.

Relaxivity. For a given paramagnetic species, there are two contributions to the longitudinal relaxivity, i.e. inner sphere and outer sphere.[11] Outer-sphere relaxivity involves noncoordinated water. The inner-sphere relaxivity requires inner-sphere coordinated water molecule(s) and depends on various parameters (eq 1 or, more formally, by the Solomon–Bloembergen–Morgan equation[6]):

$${}^{f}r_1 \propto q(\mu_{\mathrm{eff}})^2 \tau_c / r^6$$

where f is the measurement frequency (subscript 1 denotes a T_1 effect), q is the hydration number of the metal ion, μ_{eff} is the effective magnetic moment of the metal ion (which is near spin only for ions with spherically symmetric ground states), τ_c is the correlation time (the time during which the proton nucleus experiences a constant magnetic field from the paramagnetic species), and r is the metal–water proton distance. $Mn(EDTA)(H_2O)^{2-}$ and $Fe(EDTA)(H_2O)^-$ have relaxivities of ${}^{20}r_1 = 2.0–2.5$ and 1.8 $mM^{-1}\ s^{-1}$, respectively at 35–40 °C.[7,24,25] Probable outer-sphere examples are $Mn(NH_2Et)_2[15]pydieneN_5^{2+}$, ${}^{20}r_1 \simeq 0.7\ mM^{-1}\ s^{-1}$,[26] and $Fe(EHPG)^-$, ${}^{20}r_1 = 0.95\ mM^{-1}\ s^{-1}$.[6] For Fe(DO3A) and $Fe(DOTA)^-$, the ${}^{20}r_1$ values $\leq 0.5\ mM^{-1}\ s^{-1}$ (Table II) and crystal structures both indicate heptacoordinate Fe complexes which lack inner-sphere water. The relaxivity of these complexes is clearly outer-sphere.

On the other hand, both inner- and outer-sphere relaxivities are present for the Gd(DO3A) and $Gd(DOTA)^-$ complexes. In a separate study, the outer-sphere relaxivity (40 °C) for Gd(III) aminocarboxylate complexes was estimated to be 2.0 $mM^{-1}\ s^{-1}$,[11] which allowed the calculation of 2.9 and 1.5 $mM^{-1}\ s^{-1}$ for the respective inner-sphere relaxivities for $Gd(DO3A)(H_2O)_{1.8}$ and $Gd(DOTA)^-(H_2O)_{1.0}$, where the hydration numbers were determined for Tb^{3+} complexes of the same ligands.[14] In general, these outer-sphere relaxivities for the Gd(III) complexes are much greater than those for most 3d transition metal complexes[6] roughly in proportion to the ratio of their squared magnetic moments. The $4f^7$ Gd(III) complexes with relatively higher inner- and outer-sphere relaxivities are, in general, more effective T_1 relaxation agents in MRI than the structurally similar $3d^5$ Fe(III) transition metal complexes.

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Table VII. Bond Distances and Angles about the Metals

	Fe(DO3A)	Na[Fe(DOTA)]	$[\text{Gd(DO3A)}]_3\cdot\text{Na}_2\text{CO}_3$	$\text{Na}[\text{Y(H}_2\text{O)(DOTA)}]$	$\text{Na}[\text{Gd(H}_2\text{O)(DOTA)}]$
			Bond Distances		
M–N1	2.260(4)	2.207(7)	2.63(2)	2.635(4)	2.656(3)
M–N2	2.387(4)	2.353(7)	2.60	2.666(4)	2.688(3)
M–N3	2.303(4)	2.270(7)	2.59	2.633(4)	2.645(3)
M–N4	2.190(4)	2.269(7)	2.56	2.649(4)	2.661(4)
M–O1	2.065(3)	2.059(5)	2.35	2.327(3)	2.379(3)
M–O3	2.003(3)	2.047(7)	2.34	2.324(3)	2.362(3)
M–O5	1.991(3)	2.044(7)	2.35	2.316(3)	2.359(3)
M–O7				2.324(3)	2.370(3)
M–O9				2.435(3)	2.463(3)
			Bond Angles		
N1–M–N2	76.7(1)	77.6(3)	69.1	67.6(1)	67.5(1)
N1–M–N3	123.4(1)	123.8(3)	107.9	104.7(1)	104.3(1)
N1–M–N4	78.2(1)	80.9(3)	68.4	68.8(1)	68.5(1)
N1–M–O1	77.0(1)	77.6(2)	66.4	66.7(1)	65.9(1)
N1–M–O3	87.6(1)	92.9(3)	74.8	74.3(1)	74.4(1)
N1–M–O5	158.8(1)	157.5(3)	111.4	138.6(1)	138.7(1)
N1–M–O7				131.6(1)	131.1(1)
N1–M–O9				129.6(1)	129.5(1)
N2–M–N3	72.5(1)	73.4(2)	70.1	67.8(1)	67.7(1)
N2–M–N4	118.0(1)	124.2(2)	104.3	104.6(1)	104.4(1)
N2–M–O1	145.2(1)	141.7(2)	137.7	131.4(1)	130.5(1)
N2–M–O3	74.7(1)	74.4(2)	68.1	66.8(1)	66.0(1)
N2–M–O5	122.0(1)	122.5(2)	72.5	72.1(1)	72.1(1)
N2–M–O7				141.2(1)	141.5(1)
N2–M–O9				129.5(1)	129.7(1)
N3–M–N4	76.1(1)	77.4(2)	67.6	68.2(1)	68.0(1)
N3–M–O1	142.0(1)	144.8(2)	139.1	140.5(1)	140.5(1)
N3–M–O3	126.3(1)	122.8(3)	133.6	130.7(1)	130.0(1)
N3–M–O5	75.0(1)	75.2(2)	65.7	67.0(1)	66.7(1)
N3–M–O7				74.1(1)	74.4(1)
N3–M–O9				125.7(1)	126.1(1)
N4–M–O1	78.1(1)	79.5(2)	75.7	73.0(1)	73.0(1)
N4–M–O3	157.5(1)	157.8(3)	142.4	142.3(1)	142.3(1)

Table VIII. Distances and Planes[a]

structure	n	D_m	D_e	R_m	R_e	PHI	R_9	RMS_m	RMS_e
In(DO3A)[15]	7	1.18	1.39	2.36(4)	2.18(2)	3.2		0.02	0
Fe(DOTA)^-	7	1.06	1.36	2.29(5)	2.049(6)	5.1		0.01	0
Fe(DO3A)	7	1.13	1.28	2.29(6)	2.02(3)	5.8		0.05	0
Ca(DOTA)^{-2}[18]	8	1.529	1.082	2.59(2)	2.42(2)	0		0	
$[\text{Gd(DO3A)}]_{\text{ave.}}$	9	1.55	0.75	2.60(3)	2.35(3)	2.6		0.02	0.01
In(DOTA)^-[19]	8	1.279	1.127	2.423(9)	2.226(2)	0.2		0.004	0.001
Y(DOTA)^-	9	1.616	0.718	2.65(1)	2.323(3)	0.5	2.435(3)	0.004	0.01
Gd(DOTA)^-	9	1.632	0.72	2.66(1)	2.368(5)	0.3	2.463(3)	0.007	0.02
Eu(DOTA)^-[16]	9	1.640	0.71	2.68(11)	2.39(8)	0.2	2.480(3)	0.007	0.02
Gd(EDTA)[20]	9		0.51	2.651(4)	2.399(4)		2.472(4)		

[a] All distances and angles are given in Å and deg. n is the coordination number. D_m and D_e are metal-to-plane (P_m or P_e) distances. R_m is the average (average deviation) metal–N distance. R_e is the average (average deviation) metal–carboxyl oxygen coordination distance. R_9 is the metal–apical oxygen distance. PHI is the dihedral angle between P_m and P_e. RMS_m and RMS_e are rms deviations of the defining atoms from planes P_m and P_e.

Table IX. Average Angles[a]

structure	n	Q_m	Q_{meb}	Q_{me}	Q_e	Q_9
In(DO3A)	7	75.4(4)	74(2)		84(2)	
Fe(DOTA)^-	7	77(2)	76(1)		81(2)	
Fe(DO3A)	7	77(2)	75(1)		82(2)	
Gd(DO3A)	9	68.8(9)	66.7(9)	74(1)	83(1)	72(2)
Ca(DOTA)^{-2}	8	69.2(2)	66.3(4)	89(2)	78(2)	
In(DOTA)^-	8	73.8(1)	73.1(1)	78.0(1)	75.2(1)	
Y(DOTA)^-	9	68.1(4)	66.7(2)	73.4(6)	84(2)	72(1)
Gd(DOTA)^-	9	67.9(3)	66.2(3)	73.5(9)	85(2)	72(2)
Eu(DOTA)^-	9	68(2)	66(4)	73(3)	85(4)	73(2)

[a] Q_m is the N–metal–(adjacent-N) angle. Q_e is the O–metal–(adjacent O) angle. Q_{meb} is the N–metal–O bite angle for coordinated arms. Q_{me} is the other acute N–metal–O angle. Q_9 is the (apical oxygen)–metal–(equatorial O) angle.

Acknowledgment is made to S. C. Taylor and A. Krumwiede for technical assistance. At Rice University, this work was partially supported by Grant C-627 from the Robert A. Welch Foundation.

Supplementary Material Available: An appendix examining the systematic variation in coordination geometry about the embedded metals in the isostructural series of complexes, Tables SI–XXI, listing details of crystallographic data collection and refinement, fractional atomic coordinates for $\text{Na}[\text{Gd(DOTA)(H}_2\text{O)}]\cdot 4\text{H}_2\text{O}$, calculated hydrogen atom coordinates, observed thermal parameters, bond distances, and bond angles for $\text{Fe(DO3A)}\cdot 3\text{H}_2\text{O}$, $\text{Na}[\text{Fe(DOTA)}]\cdot 5\text{H}_2\text{O}$, $\text{Na}[\text{Y(DOTA)(H}_2\text{O)}]\cdot 4\text{H}_2\text{O}$, and $\text{Na}[\text{Gd(DOTA)(H}_2\text{O)}]\cdot 4\text{H}_2\text{O}$, and observed thermal parameters, bond distances, and bond angles for $[\text{Gd(DO3A)}]_3\cdot\text{Na}_2\text{CO}_3\cdot 17\text{H}_2\text{O}$ and tabular (Tables SXXII and SXXIII) and graphical data (Figures SXXIV–SXXVII) giving magnetic susceptibility and effective magnetic moments of Fe(DOTA) and Fe(DO3A) (36 pages). Ordering information is given on any current masthead page.