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Synthesis, Stability, and Structure of Gadolinium(III) and Yttrium(III) Macrocyclic Poly(amino carboxylates)

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The ligand protonation constants of three macrocyclic poly(amino carboxylates), DO3A, HP-DO3A, and DOTA, and stability constants governing formation of their Gd(III) and Y(III) complexes have been determined by potentiometric and spectrophotometric methods, respectively, at 25.0 ± 0.1 °C and at a constant ionic strength of 0.1 M ((TMA)Cl). The first protonation constant of the ligands was lowered in the presence of Na^+ ions, indicating a preferred binding of the ligands to Na^+. Corroborating this finding, a crystal structure analysis of a complex of NaBr and of the tetra-*tert*-butyl ester of DOTA revealed that the Na^+ ion was chelated deep in the ligand cage. The thermodynamic stability constants of the Gd(III) and Y(III) complexes followed the order: DOTA > HP-DO3A > DTPA > DO3A > EDTA. Crystal structures of the *isostructural* Gd(III) and Y(III) complexes of HP-DO3A, the [Na(tBu-DOTA)] Br complex, and the H_2SO_4 salt of DO3A were determined. The nine-coordinated Gd(III) and Y(III) ions were eight-coordinated by the ligand, with a water molecule occupying the ninth (apical) position. The geometry of the eight-coordinate binding of Na^+ in the DOTA tetraester was similar to that in the (Gd/Y)HP-DO3A complexes, except that sodium was ~0.3 Å deeper in the ligand cavity. The metal-free DO3A ligand (protonated on the *sec* and *trans*annular nitrogens) was preorganized for metal coordination.

Introduction

The development of novel Gd(III) complexes as contrast agents in magnetic resonance imaging (MRI)[2,3] and ^{90}Y(III)-labeled monoclonal antibodies as radiotherapeutic agents[4-6] has stimulated interest in exceptionally inert lanthanide and yttrium chelates. The ionic radii, oxidation state, and coordination numbers of Y(III) and Gd(III) are generally similar. Consequently, the same chelating ligands are used in both applications. Knowledge of the dynamic and structural chemistry of new complexes is critical for understanding and controlling stability and dissociation inertia, factors which are essential to minimizing in vivo dissociation of Gd^{3+} and $^{90}Y^{3+}$ ions and ionized ligand, all of which are poorly tolerated relative to the chelates.

The thermodynamics of gadolinium(III) and yttrium(III) complexation with macrocyclic poly(amino carboxylates) depends on the cavity size, the rigidity, and the number and nature of the donor atoms. Sherry and co-workers[7] measured the stability constants of lanthanide (La–Lu) complexes of a 9-membered macrocyclic poly(amino carboxylate), NOTA (1,4,7-triazacyclononane-*N,N′N″*-triacetic acid, H_3L) and a 12-membered macrocyclic poly(amino carboxylate), DOTA (1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid, H_4L). They reported that metal–ligand stability increased with smaller ionic radii or higher charge density of the metal ion. However, there is poor agreement among the several previous measurements of the stability constants of Gd(DOTA)$^-$:[7-11] log K = 22–28. X-ray crystallographic structural studies of Gd(III), Y(III), and Eu(III) complexes of DOTA have also been reported.[12-14]

The goals of this work were as follows: (1) to reexamine the metal complex formation equilibria of Gd(DOTA)$^-$, (2) to compare the stability constants of Gd(III) and Y(III) complexes of a relatively homologous series of macrocyclic poly(amino carboxylates) with donor atoms of a variable number and nature, and (3) to understand the stability constants in terms of the three dimensional structures of the complexes. We report the ligand protonation constants and the conditional (pH 4.0 and 7.4) and the thermodynamic stability constants of Gd(III) and Y(III) complexes of DO3A (1,4,7,10-tetraazacyclododecane 1,4,7-triacetic acid, H_3L, **I**), HP-DO3A (10-(2-hydroxypropyl)-1,4,7,-10-tetraazacyclododecane 1,4,7-triacetic acid, H_3L, **II**), DOTA, EDTA, and DTPA. The crystal structures of Gd(III) and Y(III) complexes of HP-DO3A, the sodium bromide complex of the tetra-*tert*-butyl ester of DOTA, and the sulfate salt of the diprotonated DO3A ligand are also described.

Experimental Section

Materials. The acid form of the ligands, DO3A, HP-DO3A, and DOTA were prepared by published methods.[16-18] Elemental analysis and FAB mass spectra confirmed the composition of the products (calculated percentages are given in parentheses).

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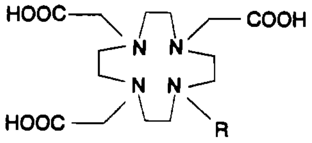

I	R = H	DO3A
II	R = $CH_2CHOHCH_3$	HP- DO3A

DO3A. Anal. Found (calcd) for $C_{14}H_{26}N_4O_6{\cdot}0.6H_2O$: C, 47.47 (47.10); H, 7.78 (7.67); N, 15.59 (15.69). MS: *m/e* at 347 for $(M + H)^+$.

HP-DO3A. Anal. Found (calcd) for $C_{17}H_{32}N_4O_7{\cdot}0.17H_2O$: C, 50.55 (50.29); H, 8.04 (7.99); N, 13.72 (13.80). MS: *m/e* at 405 for $(M + H)^+$ and for 427 $(M + Na)^+$.

DOTA. Anal. Found (calcd) for $C_{16}H_{28}N_4O_8{\cdot}0.2\,Na_2SO_4{\cdot}2H_2O$: C, 41.22 (40.99); H, 6.91 (6.83); N, 11.96 (11.96). MS: *m/e* at 405 $(M + H)^+$ and 427 $(M + Na)^+$.

Gd(HP-DO3A). The racemic chelate was synthesized and characterized by a literature procedure.[16,17] Anal. Found (calcd) for $C_{17}H_{29}N_4O_7Gd{\cdot}1.3H_2O$: C, 34.86 (35.07); H, 5.58 (5.48); N, 9.77 (9.63). MS: *m/e* at 560 $(M + H)^+$. Crystals for X-ray analysis were obtained from (1:1) aqueous DMF solution.

Y(HP-DO3A). The racemic chelate was prepared from the reaction of freshly prepared $Y(OH)_3$ and HP-DO3A. To a solution of 8.05 mL of YCl_3 (75.2 mM, 0.605 mmol) was added 1.85 mL of 1.0 N NaOH (1.85 mmol) to precipitate a white gelatinous solid. The solid $Y(OH)_3$ was washed three times with 10 mL of water. Then the solid was separated from the wash solutions by centrifugation. The white gel was added to a stirring solution of HP-DO3A (0.605 mmol) in 25.0 mL of water. The suspension was dissolved upon heating at 90 °C for 10 min. The solvent was removed by evaporating under reduced pressure to give a white solid. The sample was recrystallized from a mixture of methanol and acetone. The recrystallized material was washed with 2 mL of a methanol/acetone (1:4) mixture and was dried in vacuum for 2 h. Yield: 80 mg (21%). Anal. Found (calcd) for $C_{20}H_{29}N_4O_7Y{\cdot}C_3H_6O{\cdot}4H_2O$: C, 38.67 (38.71); H, 6.73 (6.98); N, 9.18 (9.02). MS: *m/e* at 491 $(M + H)^+$. Crystals for X-ray analysis were obtained from aqueous ethanol solution.

Na[Gd(DOTA)]. The gadolinium complex of DOTA was synthesized according to a published procedure.[18] Yield: 90%. Anal. Found (calcd) for $C_{16}H_{24}N_4O_8GdNa{\cdot}5.25H_2O$: C, 28.75 (28.45); H, 5.04 (5.11); N, 8.10 (8.30). MS: *m/e* at 560 $(M + 2H)^+$ and 582 $(M + H + Na)^+$.

Na[Y(DOTA)]. The yttrium chelate of DOTA was prepared by the method given elsewhere.[12] The elemental and FAB mass analysis confirmed the composition of the product. Anal. Found (calcd) for $C_{16}H_{24}N_4O_8YNa{\cdot}5H_2O$: C, 31.42 (31.90); H, 5.62 (5.69); N, 9.27 (9.30). MS: *m/e* at 513 $(M + Na + H)^+$ and 535 $(M + 2Na - H)^+$.

[Na(DOTA-tetrabutyl ester)]Br. *tert*-Butyl bromoacetate (75.7 g, 0.388 mol) was added over a period of 20 min with external cooling ($T < 30$ °C), to a solution of 1,4,7,10-tetraazacyclododecane (17.2 g, 0.10 mol) in 80 mL of DMF. Sodium carbonate (50 g, 0.47 mol) in 600 mL of water was then added, and the resulting biphasic mixture was stirred for 3.5 h at 30 °C. The mixture was transferred to a separatory funnel and washed with 340 mL of toluene. The solid which separated at the interface was collected by filtration, washed with toluene, and dried in vacuum. The dry solid (45.3) g was taken up in 200 mL of methylene chloride and washed with 25 mL of water to dissolve some insoluble residue. Separation of the phases and evaporation of the methylene chloride afforded 43 g of fine white crystals of the sodium bromide complex. An additional 7.5 g of larger crystals suitable for X-ray analysis were deposited overnight from the initial toluene/water mixture. Yield: 50.5 g (63.6%). Anal. Found (calcd) for $C_{32}H_{60}N_4O_8NaBr{\cdot}3.5H_2O$: C, 47.80 (47.81); H, 7.76 (8.53); N, 6.98 (6.97); Br, 10.49 (9.94); Na, 2.81 (2.86).

DO3A·H_2SO_4. The salt was prepared by neutralizing DO3A[17] (10 g, 0.0289 mol) in 40 mL of water with H_2SO_4 (1.54 mL, 0.0578 mol). The precipitate was suspended in water (7 mL/g) at 20–25 °C and an equivalent volume of acetone was added with stirring. The crystalline slurry was filtered, washed with acetone–water (85:15) and then acetone, and vacuum dried at 40–50 °C. Anal. Found (calcd) for $C_{14}H_{28}N_4O_{10}S{\cdot}1.5H_2O$: C, 35.80 (35.59); H, 6.70 (6.64); N, 11.65 (11.86); S, 6.64 (6.79). Crystals for diffraction studies were obtained by slow evaporation of aqueous acetonitrile solutions.

Solution Preparations. Standardization of tetramethylammonium hydroxide solution was carried out using dried potassium hydrogen phthalate (KHP) as the primary standard and phenolphthalein as the indicator. The strong base solution, tetramethyl ammonium hydroxide, was prepared by dissolving the solid material from Aldrich in boiled and nitrogen bubbled distilled deionized water. An ascarite tube was attached to the container to avoid absorption of carbon dioxide. The stock solutions of $GdCl_3$ and YCl_3 were prepared from solid samples (Research Chemicals, Inc.). Solutions of these metal salts were prepared and standardized by EDTA titration using xylenol orange as the indicator.[19] Arsenazo-III (Aldrich), sodium acetate, acetic acid (Fisher), and tetramethylammonium chloride (Aldrich) were used as received. The disodium salt of ethylenediaminetetraacetic acid (Na_2H_2EDTA) (Fisher) and diethylenetriaminepentaacetic acid (H_5DTPA) (Aldrich) were used as received. The concentrations of the ligand solutions, DO3A, HP-DO3A, and DOTA, were determined by complexometric titrations and by acid–base titrations using bromothymol blue as the indicator. These concentration values were within 0.5–0.8% of the values obtained from potentiometric titrations.

Methods. Solution pH values were measured with a Brinkmann combination glass electrode and a MetroOhm pH meter Model 605. Potentiometric titrations for the determination of the ligand protonation constants[20] were carried out at a constant ionic strength of 0.1 $(CH_3)_4NCl$. More than three titrations were carried out in each medium. An automatic titrator/pH meter (Brinkmann 670 Titroprocessor) was used. It has a precision of ±0.002 pH unit) and is thermostated (25.0 ± 0.1 °C) with a glass-jacketed titration cell fitted with a combination glass electrode and a MetroOhm piston buret with a capillary tip placed below the surface of the sample. This avoids absorption of CO_2 by the base solution. The pH meter–electrode system was calibrated with standard buffers. All pH values were converted to $-\log[H^+]$ or p[H] by using a correction factor to the measured pHs. The correction factor was established from a standard acid–base titration at 25.0 ± 0.1 °C and 0.1 (TMACl). The ligand concentration was 0.001–0.002 M. Precautions were taken to avoid CO_2 absorption by the base solution.

A direct potentiometric titration technique could not be used to determine the metal–ligand stability constants because the formation of Gd(III) and Y(III) complexes is extremely slow. Consequently, a spectrophotometric method using the indicator arsenazo-III was used.[7,21] All spectrophotometric measurements were made with an HP-8452 A diode-array spectrophotometer interfaced to an HP-310 data station. The conditional formation constants for the 1:1 (β_{LnAz}) and 1:2 (β_{LnAz_2}) complexes of the lanthanide with arsenazo-III at pH 4.0 ($[OAc]_T = 50$ mM) and $\mu = 0.1$ M ($(CH_3)_4NCl$) were determined by a literature procedure.[7] The extinction coefficients (ϵ, $M^{-1}\ cm^{-1}$) of 1:1 and 1:2 complexes of arsenazo-III were determined to be 38 000 and 50 000 for Gd(III) and 50 000 and 62 000 for Y(III), in agreement with previously reported values.[7,21] The stability constants (log *K*) of 1:1 and 1:2 complexes of arsenazo-III were 6.6 and 12.8 for Gd(III) and 7.07 and 13.01 for Y(III). Batch solutions of mixtures of Gd(III) and Y(III) and arsenazo-III and variable amounts of the ligand were prepared. Absorbance changes with ligand concentration were used to calculate the equilibrium constant of the reaction given in eq 1. Two to three experiments were carried out to determine the conditional stability constant of the chelate at pH 4.0.

$$MAz_n + L \leftrightarrow ML + nAz \qquad (1)$$

The pH-metric titration data were used to calculate[20] the stepwise ligand protonation constants defined in eq 2, where $n = 1, 2, 3,$ or 4,

$$K_n^{\ H} = ([H_nL]/[H_{n-1}L][H^+]) \qquad (2)$$

depending on the ligand. For the calculation of the ligand protonation constants, the program PKAS was used.[20] The conditional stability constants (K_f' at pH 4.0) were calculated from the absorbance data.[7,21] The programs ARSENAZO and COMPLETE[7,21] were used to calculate the stability constants of $GdAz_n$ and the conditional stability constants of GdL at pH 4.0, respectively. Dell-200 and Zenith Z-157 computers were used for all calculations. The conditional stability constants at pH 4.0 were converted to thermodynamic stability constants (K_f) using the ligand protonation constants at 0.1 (TMACl) and at 25.0 ± 0.1 °C. The accuracy of this technique was verified by measuring the thermodynamic stability constants for the lanthanides with the well-known ligands ethylenediaminetetraacetic acid (EDTA) and diethylenetriamine-

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Table 1. Crystallographic Data and Details of Refinement for Gd(HP-DO3A), Y(HP-DO3A), [Na(tBu-tetraester DOTA)]Br, and DO3A·H_2SO_4

	[Gd(H_2O)(HP-DO3A)]	[Y(H_2O)(HP-DO3A)]	[Na(tBu-DOTA)]Br	DO3A·H_2SO_4
a, Å	16.974(4)	16.958(2)	10.521(1)	25.813(3)
b, Å	25.45(1)	25.202(5)	26.240(2)	14.384(3)
c, Å	11.247(4)	11.257(2)	16.779(1)	11.426(1)
β, deg	90.0	90.0	106.51(1)	90.0
V, Å^3	4859(5)	4811(2)	4441(1)	4242(2)
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1/c$	$Pbca$
d_{obs}, g cm^{-3}	1.72	1.50	1.18	1.47
d_{calc}, g cm^{-3}				
for fully occupied solvent	1.70	1.52	1.20	1.50
for partially occupied solvent	1.66	1.49	1.19	
Formula	Gd(H_2O)$C_{17}H_{29}N_4O_7$	Y(H_2O)$C_{17}H_{29}N_4O_7$	$NaBrC_{32}H_{60}N_4O_8$	$C_{14}H_{28}N_4O_6SO_4$
fully occupied solvent	2.5 H_2O	2.5 H_2O	4.0 H_2O	2.0 H_2O
partially occupied solvent	1.75 H_2O	1.97 H_2O	3.6 H_2O	–
fw (no solvent/solvated)	576.7/621.7	508.35/553.4	731.7/803.8	444.46/480.49
Z	8	8	4	8
color	colorless	colorless	colorless	colorless
dimens, mm	0.3 × 0.35 × 0.2	0.3 × 0.18 × 0.2	0.2 × 0.2 × 0.15	0.32 × 0.08 × 0.13
μ, cm^{-1}	28.0	25.0	17.0	19.4
abs corr method	DIFABS	DIFABS	not applied	not applied
transm factors, min-max	0.9–1.07	0.43–1.32		
instrument	SYNTEX P2_1	CAD4	SYNTEX P2_1	CAD4
λ, Å	0.71069	0.71069	1.5418	1.5418
2θ (max), deg	50	54	140	140
N_{ref}[a]	4805	5829	8974	4516
N_{uni}[b]	4688	5794	7806	4015
N_{obs}[c]	3475	2276	4454	2487
N_{var}[d]	560	271	446	281
ERRWT[e]	1.4	1.8	2.6	1.8
SHIFT/ERR[f]	0.01	0.0	0.3	0.03
R	0.042	0.081	0.073	0.055
R_w	0.048	0.080	0.098	0.066
enantiomer	R	S		

[a] Total number of measured reflections within 2θ max. [b] Total number of symmetry-independent measured reflections. [c] Total number of "observed" reflections with $I \geq 3\sigma(I)$ used in least-squares refinements. [d] Number of variables in least-squares refinements. [e] Error in an observation of unit weight. [f] Maximum shift/error during the final cycle of refinement.

pentaacetic acid (DTPA). For the determination of pK_a values, more than three titrations were carried out in each medium.

Crystallographic Studies. Unit cell parameters and some details of data collection and refinement are summarized in Table 1. The general comments here apply to all analyses. Unit cell parameters were obtained through a least-squares analysis of at least 15 high angle reflections. Crystal densities were measured by flotation in hexane/carbon tetrachloride/bromoform mixtures. Reflections were measured diffractometrically at 23 °C with ω–2θ variable scan technique and were corrected for Lorentz–polarization factors and for absorption.[22] 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 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 hydrogens on heteroatoms were introduced in observed positions. All others were introduced in fixed idealized positions and assigned isotropic temperature factors.

For [Gd(HP-DO3A)], refined parameters were coordinates and anisotropic temperature factors of the non-hydrogen atoms of the complex, coordinates, population factors (O1′, 0.7; O2′, 0.7; O3′, 0.6; O4′, 0.6; O5′, 0.9), and isotropic temperature factors of the lattice waters.

For [Y(HP-DO3A)], refined variables were coordinates of all non-hydrogen atoms, anisotropic temperature factors of yttrium atoms, isotropic temperature factors of all other non-hydrogen atoms, and population factors (O99, 0.64; O98, 0.89; O97, 0.74; O96, 0.79; O95, 0.88) of the lattice waters of hydration.

For [Na(*tert*-butyl tetraester DOTA)]Br, refined parameters were coordinates and anisotropic temperature factors of the non-hydrogen atoms of the complex and the fully occupied water sites (O98 and O99), and coordinates only of the partially occupied (O95, 0.4; O96, 0.4; O97, 0.6) lattice water sites. O94 (0.2) is another possible water site.

For [DO3A·H_2SO_4], refined parameters were coordinates and anisotropic temperature factors of all non-hydrogen atoms.

All calculations utilized the SDP software package with minor local modifications.[23] Least-squares weights $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2 = \epsilon^2 + (\rho I)^2$, 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 $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

Results

Protonation and Stability Constants. Acid–base titrations of the acid forms of DO3A, HP-DO3A, and DOTA were carried out in three different media, tetramethylammonium chloride (TMACl), NaCl, and KCl (0.1 M). Excess hydrochloric acid was added to the ligand solutions to determine the lower protonation constants. The pK_a values calculated from the titration data in three different media, (TMA)Cl, NaCl, and KCl, are tabulated in Table 2. The protonation constants for Cyclen (1,4,7,10 tetraazacyclododecane) are also listed for comparison.[24]

From the spectrophotometric titration data, the equilibrium constants were determined for reaction 1 for Gd(III) and Y(III) (Table 3). Using the stability constants of the Arsenazo-III complexes, the calculations of the conditional stability constants of the complexes at pH 4.0 were made. Table 3 lists the conditional formation constants of Gd(III) and Y(III) complexes of several linear and macrocyclic aminopolycarboxylates at pH 4.0. By using eq 3, the thermodynamic stability constants (K_f) (Table 3) for GdL and YL were calculated from the conditional formation constants and the stepwise ligand protonation constants.

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Table 2. Protonation Equilibrium Constants of Some Linear and Macrocyclic Poly(amino carboxylates) in Different Media (μ = 0.1; 25.0 ± 0.1 °C)

protonation equilibrium	0.1 M TMACl	0.1 M NaCl	0.1 M KCl
Cyclen[a]			
log K_1		10.6	
log K_2		9.6	
log K_3		1.5	
log K_4		0.7	
DO3A			
log K_1	11.59 ± 0.03	10.51 ± 0.01	11.55 ± 0.08
log K_2	9.24 ± 0.03	9.08 ± 0.09	9.15 ± 0.09
log K_3	4.43 ± 0.07	4.36 ± 0.13	4.48 ± 0.2
log K_4	3.48 ± 0.01		
HP-DO3A			
log K_1	11.96 ± 0.02	9.24 ± 0.05	11.87 ± 0.047
log K_2	9.43 ± 0.01	9.27 ± 0.02	9.43 ± 0.03
log K_3	4.30 ± 0.04	4.45 ± 0.11	4.44 ± 0.11
log K_4	3.26 ± 0.01		
DOTA			
log K_1	11.73 ± 0.03	9.37 ± 0.05	11.14 ± 0.07
log K_2	9.40 ± 0.02	9.14 ± 0.08	9.50 ± 0.01
log K_3	4.50 ± 0.04	4.63 ± 0.12	4.61 ± 0.09
log K_4	4.19 ± 0.06	3.91 ± 0.07	4.30 ± 0.09
DTPA			
log K_1	10.41 ± 0.02	9.45 ± 0.03	10.10 ± 0.04
log K_2	8.37 ± 0.03	8.21 ± 0.09	8.34 ± 0.03
log K_3	4.09 ± 0.05	4.09 ± 0.09	4.21 ± 0.05
log K_4	2.51 ± 0.03	2.49 ± 0.07	2.48 ± 0.01
log K_5	2.04 ± 0.02	1.87 ± 0.11	1.58 ± 0.01
EDTA			
log K_1	10.11 ± 0.04	9.42 ± 0.05	10.08 ± 0.04
log K_2	6.19 ± 0.04	6.22 ± 0.07	6.42 ± 0.05
log K_3	2.87 ± 0.04	2.88 ± 0.04	3.11 ± 0.05
log K_4	2.26 ± 0.04	2.19 ± 0.04	2.33 ± 0.04

[a] Reference 24.

Table 3. Thermodynamic (K_f) and Conditional (K_f') Formation Constants of Gd(III) and Y(III) Complexes of Linear and Macrocyclic Polyamino Polycarboxylates[a]

chelate	log K_f'		log K_f[a]
	pH 4.0	pH 7.4	
Gd(EDTA)$^-$	9.24 ± 0.09	14.8	17.7 (17.37 ± 0.04)[b]
Y(EDTA)$^-$	10.08	15.6	18.5 (18.09 ± 0.04)[b]
Gd(DTPA)$^{2-}$	10.5 ± 0.1	17.8	22.2 (22.4)[c]
Y(DTPA)$^{2-}$	10.8 ± 0.5	18.1	22.5 (22.1)[c]
Gd(DO3A)	7.2 ± 0.2	14.5	21.0
Y(DO3A)	7.30 ± 0.3	14.6	21.1
Gd(HP-DO3A)	9.9 ± 0.1	17.1	23.8
Y(HP-DO3A)	8.3 ± 0.3	15.6	22.2
Gd(DOTA)$^-$	11.2 ± 0.6	18.6	25.3[d] (24.6)[e] (24.0)[f]
Y(DOTA)$^-$	10.2 ± 0.5	17.6	24.3[d] (25.9)[g]

[a] This work at 25.0 ± 0.1 °C, μ = 0.1, ± 1 standard deviation. [b] Reference 47. [c] Reference 46. [d] Using pK_a values from ref 33. [e] Reference 7. [f] Reference 29. [g] Reference 6.

$$K_{\mathrm{ML(Therm)}} = K_{\mathrm{ML(Cond)}}(1 + K_1[\mathrm{H}^+] + K_1K_2[\mathrm{H}^+]^2 + \ldots + K_n[\mathrm{H}^+]^n) \quad (3)$$

Here K_1, K_2, K_3, ..., K_n are the stepwise protonation constants of the ligand.

A knowledge of the conditional formation constants of Gd(III) and Y(III) complexes under physiological conditions (pH 7.4) is useful in the context of biological studies.[25] To provide data for such studies the values of the stability constants were calculated at pH 7.4 using eq 3 and are tabulated in Table 3. Under physiologic conditions there is a significant proton competition with the metals which differs among the ligands.

Crystal Structure Studies of Isostructural Gd(HP-DO3A) and Y(HP-DO3A). Although the crystals for this study were obtained by crystallization of racemic complexes, the crystal structure is chiral ($P2_12_12_1$), and only one stereoisomer of the chiral 2-hydroxypropyl arm is present in a single crystal. Crystallization therefore occurred with "spontaneous resolution" resulting in a conglomerate mixture containing equal amounts of *R* and *S* crystals. The asymmetric unit contains two crystallographically independent molecules of the *ennea*-coordinate complex and several partially occupied water sites. Fractional atomic coordinates are given in Tables 4 and 5.

The macrocycle in Gd(HP-DO3A) and Y(HP-DO3A) has a quadrangular [3333][15] conformation in which the four nitrogen and four oxygen atoms (one from each arm) are coordinated to the embedded Gd/Y atom. The ninth, apical, coordination site is occupied by a water molecule in the capped square antiprism arrangement. The nitrogen atoms are coplanar within experimental error, while the coordinated oxygen atoms define another plane. The Gd/Y is sandwiched between these two nearly parallel planes (Figure 1). For Gd(HP-DO3A), the Gd lies d_N = 1.61 Å above the nitrogen plane (1.68 Å in the other independent complex) and d_O = 0.75 (0.78) Å below the oxygen plane; for Y(HP-DO3A), d_N = 1.58 (1.69) Å and d_O = 0.75 (0.77) Å. The ninth ligand of Gd(HP-DO3A) lies 1.72 (1.76) Å above the oxygen plane (1.68 (1.75) Å for Y(HP-DO3A)). It is of interest that the two independent complexes in the asymmetric unit have diastereomeric conformations.[26] Thus, all of the coordinating arms are twisted in the *same sense*, with average Gd–N–C–C (O) and N–C–C–O torsional angles of 38 and –28°, respectively, for one Gd complex, and 49 and –28° for the other. However, the quadrangular conformations of the tetraazacyclododecane macrocycle are enantiomeric for the two independent complexes: average macrocyclic N–C–C–N, C–C–N–C, and C–N–C–C– torsional angles are 58, 80, and –163° in one complex and –55, –82, and 160° in the other Gd complex. Corresponding values for all of the above torsional angles in the two independent Y complexes are 37, –26, 48, –30, 57, 82, –164, –61, –76, and 161° respectively.

Tables 6 and 7 summarize interatomic distances and angles about the metal. The variation among M–N and/or M–O(three carboxylate) distances is similar for the Gd and Y complexes. For example, metal–ligand bond lengths fall in the ranges Gd–N = 2.64–2.65 Å, Y–N = 2.58–2.63 Å, and M–O (carboxylate) = 2.31–2.38 and 2.27–2.35 Å for Gd and Y complexes, respectively. M–O(hydroxypropyl) distances are comparable to M–O(carboxylate), distances and are significantly shorter than M–OH_2 bond distances (2.50 Å for Gd and 2.49 Å for Y). These bond distances, and indeed the entire structures, are very similar to those of the *isostructural* Gd(DOTA)$^-$, Y(DOTA)$^-$, and Eu(DOTA)$^-$ complexes reported previously.[12-14] A least-squares fit of all non-hydrogen atoms except C–CH_3 of the Gd(HP-DO3A) complex and the corresponding atoms of Gd(DOTA)$^-$ has an rms deviation of 0.06 Å (28 atoms). As expected from the ionic nature of the bonds in the chelates, M–N bonds are longer than M–O bonds.

The crystal structures are hydrates with an ideal asymmetric unit composition of $[\mathrm{M(H_2O)(HP\text{-}DO3A)}]_2\cdot5\mathrm{H_2O}$. Refinement of the site occupancy factors suggest that each of the five sites for lattice waters was only partially occupied (70–90%) under the conditions of the measurements. The two sites for the water molecules directly coordinated to the metals, as the ninth ligand, are fully occupied.

Crystal Structure Study of [Na(*tert*-butyl ester DOTA)]Br. The solid-state structure of the nearly C_4 symmetric NaBr complex of the esterified DOTA ligand is shown in Figure 2; atomic

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[25] Wedeking, P.; Kumar, K.; Tweedle, M. F. *Magn. Reson. Imaging* **1992**, *10*, 641.

[26] Similar distereomeric conformations are also present in the crystal structure of homochiral Gd(DO3MA). Kang, S.; Ranganathan, R.; Emswiler, J.; Kumar, K.; Gougoutas, J.; Tweedle, M. F. *Inorg. Chem.* **1993**, *32*, 2912.

Table 4. Atomic Fractional Coordinates for the Non-Hydrogen Atoms of Gd(HP-DO3A)

atom	*x*	*y*	*z*	atom	*x*	*y*	*z*
Gd1	0.34026(4)	0.26000(2)	0.49467(6)	Gd21	0.49426(4)	0.47691(2)	0.52428(5)
N1	0.1984(7)	0.2891(5)	0.4250(9)	N21	0.3863(6)	0.5217(5)	0.668(1)
N2	0.3182(7)	0.2417(5)	0.2653(9)	N22	0.5423(7)	0.4871(4)	0.7446(9)
N3	0.3491(7)	0.1587(4)	0.4415(9)	N23	0.6150(7)	0.5403(5)	0.550(1)
N4	0.2286(8)	0.2058(4)	0.6052(9)	N24	0.4574(7)	0.5777(4)	0.466(1)
O1	0.3363(6)	0.3447(3)	0.4044(8)	O21	0.3959(5)	0.4211(3)	0.6099(8)
O3	0.4565(6)	0.2494(4)	0.3897(8)	O23	0.5815(6)	0.4130(4)	0.5938(8)
O5	0.4060(6)	0.2106(4)	0.6399(8)	O25	0.5778(6)	0.4834(4)	0.3628(8)
O7	0.2818(6)	0.3045(4)	0.6605(8)	O27	0.3928(6)	0.4915(4)	0.3736(9)
O9	0.4435(6)	0.3169(4)	0.5887(8)	O29	0.4768(6)	0.3968(4)	0.3989(8)
C1	0.178(1)	0.2694(6)	0.303(1)	C21	0.409(1)	0.5116(6)	0.798(1)
C2	0.2476(9)	0.2751(6)	0.221(1)	C22	0.492(1)	0.5190(5)	0.823(1)
C3	0.302(1)	0.1857(6)	0.244(1)	C23	0.623(1)	0.5091(6)	0.754(1)
C4	0.358(1)	0.1494(6)	0.316(1)	C24	0.635(1)	0.5521(8)	0.674(1)
C5	0.2775(8)	0.1315(5)	0.486(2)	C25	0.600(1)	0.5913(6)	0.484(2)
C6	0.2467(9)	0.1492(6)	0.606(1)	C26	0.5192(9)	0.6149(5)	0.496(1)
C7	0.1500(9)	0.2128(6)	0.550(1)	C27	0.383(1)	0.5955(6)	0.524(1)
C8	0.1361(8)	0.2703(5)	0.504(1)	C28	0.379(1)	0.5815(6)	0.650(1)
C9	0.2757(9)	0.3736(6)	0.392(1)	C29	0.3285(9)	0.4346(5)	0.643(1)
C10	0.1965(9)	0.3472(6)	0.422(1)	C30	0.3132(8)	0.4941(6)	0.639(1)
C11	0.4636(9)	0.2459(7)	0.277(1)	C31	0.586(1)	0.3989(5)	0.699(1)
C12	0.393(1)	0.2600(7)	0.205(1)	C32	0.544(1)	0.4316(6)	0.789(1)
C13	0.441(1)	0.1677(6)	0.621(1)	C33	0.6502(9)	0.4928(7)	0.369(2)
C14	0.4213(9)	0.1394(5)	0.503(1)	C34	0.6779(8)	0.5149(5)	0.491(1)
C15	0.231(1)	0.2811(6)	0.750(1)	C35	0.3893(9)	0.5340(6)	0.294(1)
C16	0.231(1)	0.2240(6)	0.732(1)	C36	0.447(1)	0.5755(7)	0.335(1)
C17	0.259(1)	0.2943(8)	0.872(1)	C37	0.404(1)	0.5199(8)	0.166(1)
O2	0.2766(7)	0.4196(4)	0.357(1)	O22	0.2731(7)	0.4057(4)	0.673(1)
O4	0.5260(6)	0.2345(6)	0.2251(9)	O24	0.6216(8)	0.3593(4)	0.736(1)
O6	0.4894(7)	0.1484(4)	0.6859(9)	O26	0.6988(7)	0.4875(6)	0.287(1)
				O1′	0.588(1)	0.2519(9)	0.005(2)
				O2′	0.674(1)	0.3509(7)	−0.021(2)
				O3′	0.620(2)	0.445(1)	0.085(2)
				O4′	0.506(2)	0.391(1)	0.149(2)
				O5′	0.486(1)	0.2663(7)	0.824(1)

Table 5. Atomic Fractional Coordinates for the Non-Hydrogen Atoms of Y(HP-DO3A)

atom	*x*	*y*	*z*	atom	*x*	*y*	*z*
Y1	0.6606(1)	0.74062(7)	0.5034(2)	Y21	0.5068(1)	0.52273(8)	0.4741(2)
N1	0.801(1)	0.7106(6)	0.573(1)	N21	0.614(1)	0.4774(7)	0.334(1)
N2	0.6829(9)	0.7577(7)	0.734(1)	N22	0.466(1)	0.5131(7)	0.250(2)
N3	0.6497(9)	0.8402(6)	0.555(1)	N23	0.3866(9)	0.4581(6)	0.446(1)
N4	0.769(1)	0.7949(7)	0.394(2)	N24	0.5419(9)	0.4203(6)	0.536(2)
O1	0.6651(8)	0.6559(5)	0.589(1)	O21	0.6031(8)	0.5790(5)	0.392(1)
O3	0.5445(8)	0.7503(6)	0.602(1)	O23	0.4184(8)	0.5853(5)	0.410(1)
O5	0.5953(8)	0.7878(5)	0.364(1)	O25	0.4263(8)	0.5171(5)	0.634(1)
O7	0.7158(8)	0.6969(5)	0.340(1)	O27	0.6068(8)	0.5089(5)	0.620(1)
O9	0.5568(8)	0.6825(6)	0.412(1)	O29	0.5233(8)	0.6023(6)	0.598(1)
O2	0.7237(9)	0.5814(6)	0.638(1)	O22	0.7236(9)	0.5933(6)	0.324(1)
O4	0.473(1)	0.7632(7)	0.769(2)	O24	0.379(1)	0.6420(7)	0.265(2)
O6	0.508(1)	0.8498(6)	0.316(1)	O26	0.307(1)	0.5114(7)	0.706(2)
C1	0.823(1)	0.7294(9)	0.693(2)	C21	0.592(1)	0.489(1)	0.201(2)
C2	0.751(1)	0.7268(9)	0.777(2)	C22	0.510(2)	0.480(1)	0.173(2)
C3	0.694(1)	0.8116(9)	0.757(2)	C23	0.378(1)	0.4880(9)	0.251(2)
C4	0.640(1)	0.8499(9)	0.686(2)	C24	0.366(2)	0.443(1)	0.327(3)
C5	0.719(1)	0.8717(9)	0.514(2)	C25	0.403(1)	0.4076(9)	0.514(2)
C6	0.749(1)	0.8541(9)	0.400(2)	C26	0.477(1)	0.3845(9)	0.498(2)
C7	0.848(1)	0.7877(8)	0.452(2)	C27	0.615(1)	0.4041(8)	0.473(2)
C8	0.866(1)	0.7323(7)	0.494(2)	C28	0.625(2)	0.419(1)	0.363(3)
C9	0.725(1)	0.6280(9)	0.601(2)	C29	0.670(1)	0.5649(9)	0.359(2)
C10	0.804(1)	0.6530(8)	0.564(2)	C30	0.688(1)	0.5051(9)	0.362(2)
C11	0.535(1)	0.7510(9)	0.716(2)	C31	0.416(1)	0.600(1)	0.306(2)
C12	0.606(1)	0.7379(9)	0.789(2)	C32	0.456(1)	0.5656(9)	0.209(2)
C13	0.560(1)	0.8342(9)	0.383(2)	C33	0.355(1)	0.5068(9)	0.623(2)
C14	0.578(1)	0.8606(8)	0.495(2)	C34	0.325(1)	0.4855(8)	0.507(2)
C15	0.765(1)	0.720(1)	0.250(2)	C35	0.608(1)	0.4632(9)	0.701(2)
C16	0.771(1)	0.7782(8)	0.271(2)	C36	0.549(1)	0.4235(9)	0.661(2)
C17	0.740(2)	0.706(1)	0.132(3)	C37	0.599(2)	0.481(1)	0.828(3)
				O99	0.416(2)	0.743(1)	0.987(3)
				O98	0.323(1)	0.6444(7)	1.027(2)
				O97	0.379(1)	0.5457(9)	0.919(2)
				O96	0.494(2)	0.613(1)	0.851(2)
				O95	0.513(1)	0.7362(8)	0.170(2)

coordinates are given in Table 8. Even though this DOTA complex has four equivalent neutral ester arms instead of the hydroxypropyl and three ionized carboxylate arms of the (Gd/Y)HP-DO3A complexes, the structures of the two types of complexes are very

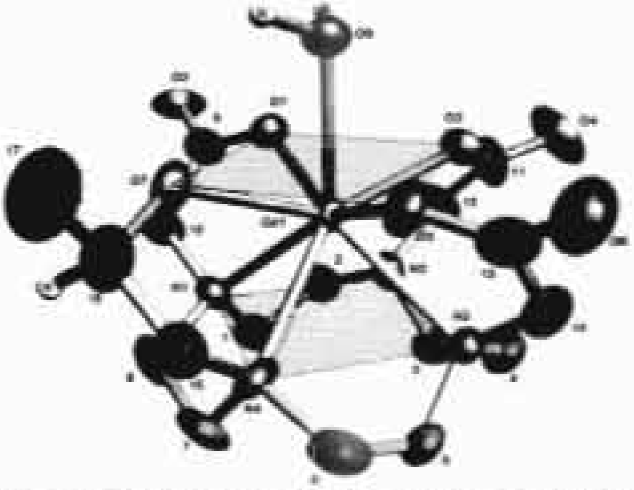

Figure 1. Perspective drawing of one of the conformationally diastereomeric (Gd/Y)HP-DO3A complexes. Most hydrogens have been omitted. Thermal ellipsoids are shown at 50% probability level.

Table 6. Bond Distances (Å) and Angles (deg) for Gd(HP-DO3A)

Gd1–N1	2.638(11)	Gd21–N21	2.696(11)
Gd1–N2	2.653(12)	Gd21–N22	2.720(11)
Gd1–N3	2.650(10)	Gd21–N23	2.625(11)
Gd1–N4	2.648(10)	Gd21–N24	2.631(11)
Gd1–O1	2.383(8)	Gd21–O21	2.395(9)
Gd1–O3	2.397(10)	Gd21–O23	2.444(10)
Gd1–O5	2.344(10)	Gd21–O25	2.309(9)
Gd1–O7	2.315(9)	Gd21–O27	2.335(10)
Gd1–O9	2.507(10)	Gd21–O29	2.497(10)
N1–Gd1–N2	68.5(4)	N21–Gd21–N23	101.8(3)
N1–Gd1–N3	104.9(4)	N21–Gd21–N24	66.6(3)
N1–Gd1–N4	68.4(4)	N21–Gd21–O21	62.4(2)
N1–Gd1–O1	66.0(3)	N21–Gd21–O23	82.7(2)
N1–Gd1–O3	73.8(3)	N21–Gd21–O25	149.1(3)
N1–Gd1–O5	142.4(3)	N21–Gd21–O27	121.7(2)
N1–Gd1–O7	131.2(3)	N21–Gd21–O29	127.1(2)
N1–Gd1–O9	126.9(3)	N22–Gd21–N23	68.1(4)
N2–Gd1–N3	68.9(3)	N22–Gd21–N24	101.9(4)
N2–Gd1–N4	105.3(3)	N22–Gd21–O21	119.7(3)
N2–Gd1–O1	130.5(3)	N22–Gd21–O23	61.9(4)
N2–Gd1–O3	65.5(3)	N22–Gd21–O25	83.4(4)
N2–Gd1–O5	74.6(4)	N22–Gd21–O27	152.1(4)
N2–Gd1–O7	141.9(3)	N22–Gd21–O29	127.4(3)
N2–Gd1–O9	127.0(3)	N23–Gd21–N24	65.9(4)
N3–Gd1–N4	67.5(3)	N22–Gd21–O29	127.4(3)
N3–Gd1–O1	141.7(3)	N23–Gd21–O21	149.8(3)
N3–Gd1–O3	131.2(3)	N23–Gd21–O23	122.3(4)
N3–Gd1–O5	66.9(3)	N23–Gd21–O25	64.2(4)
N3–Gd1–O7	73.9(4)	N23–Gd21–O27	84.0(4)
N3–Gd1–O9	128.1(3)	N23–Gd21–O29	131.1(3)
N4–Gd1–O1	74.9(3)	N24–Gd21–O21	84.0(3)
N4–Gd1–O3	141.5(4)	N24–Gd21–O23	149.3(4)
N4–Gd1–O5	130.6(3)	N24–Gd21–O25	123.0(4)
N4–Gd1–O7	66.6(3)	N24–Gd21–O27	63.6(3)
N4–Gd1–O9	127.7(3)	N24–Gd21–O29	130.6(3)
O1–Gd1–O3	83.8(3)	O21–Gd21–O23	83.0(3)
O1–Gd1–O5	142.7(3)	O21–Gd21–O25	141.9(3)
O1–Gd1–O7	85.0(3)	O21–Gd21–O23	83.0(3)
O1–Gd1–O9	71.2(3)	O21–Gd21–O29	70.1(3)
O3–Gd1–O5	84.8(3)	O23–Gd21–O25	82.9(3)
O3–Gd1–O7	143.6(4)	O23–Gd21–O27	141.7(3)
O3–Gd1–O9	71.8(3)	O23–Gd21–O29	69.4(3)
O5–Gd1–O7	83.3(3)	O25–Gd21–O27	85.6(3)
O5–Gd1–O9	71.6(3)	O25–Gd21–O29	71.8(4)
O7–Gd1–O9	71.8(3)	O27–Gd21–O29	72.3(3)
N21–Gd21–N22	65.7(3)		

Table 7. Bond Distances (Å) and Angles (deg) for Y(HP-DO3A)[a]

Y1–N1	2.63(2)	Y21–N21	2.66(2)
Y1–N2	2.66(2)	Y21–N22	2.63(2)
Y1–N3	2.58(2)	Y21–N23	2.63(2)
Y1–N4	2.61(2)	Y21–O21	2.351(14)
Y1–O1	2.345(13)	Y21–O23	2.294(13)
Y1–O3	2.274(14)	Y21–O25	2.262(13)
Y1–O5	2.260(13)	Y21–O27	2.384(14)
Y1–O7	2.336(14)	Y21–O29	2.458(14)
Y1–O9	2.511(14)		
N1–Y1–N2	68.0(5)	O3–Y1–O9	69.9(5)
N1–Y1–N3	106.1(5)	O5–Y1–O7	84.3(5)
N1–Y1–N4	69.4(5)	O5–Y1–O9	71.3(5)
N1–Y1–O1	65.5(5)	O7–Y1–O9	71.3(5)
N1–Y1–O3	132.3(5)	N21–Y21–N22	64.7(5)
N1–Y1–O5	143.6(5)	N21–Y21–N23	101.1(5)
N1–Y1–O7	74.6(5)	N21–Y21–O21	63.4(5)
N1–Y1–O9	126.3(5)	N21–Y21–O23	123.7(5)
N2–Y1–N3	68.4(5)	N21–Y21–O25	148.8(5)
N2–Y1–N4	106.0(5)	N21–Y21–O27	81.8(5)
N2–Y1–O1	73.0(5)	N21–Y21–O29	127.4(5)
N2–Y1–O3	68.2(5)	N22–Y21–N23	67.8(5)
N2–Y1–O5	131.5(5)	N22–Y21–O21	82.1(5)
N2–Y1–O7	141.9(5)	N22–Y21–O23	65.7(5)
N2–Y1–O9	126.5(5)	N22–Y21–O25	126.8(5)
N3–Y1–N4	69.4(5)	N22–Y21–O27	146.5(5)
N3–Y1–O1	142.5(5)	N22–Y21–O29	130.5(5)
N3–Y1–O3	73.9(5)	N23–Y21–O21	149.9(5)
N3–Y1–O5	67.1(5)	N23–Y21–O23	83.2(5)
N3–Y1–O7	131.6(5)	N23–Y21–O25	65.7(5)
N3–Y1–O9	127.6(5)	N23–Y21–O27	122.9(5)
N4–Y1–O1	130.5(5)	N23–Y21–O29	131.5(5)
N4–Y1–O3	142.0(5)	O21–Y21–O23	85.2(5)
N4–Y1–O5	73.0(5)	O21–Y21–O25	140.3(5)
N4–Y1–O7	65.9(5)	O21–Y21–O27	82.2(5)
N4–Y1–O9	127.4(5)	O21–Y21–O29	69.6(5)
O1–Y1–O3	85.7(5)	O23–Y21–O25	84.2(5)
O1–Y1–O5	141.4(5)	O23–Y21–O27	141.5(5)
O1–Y1–O7	83.2(5)	O23–Y21–O29	72.0(5)
O1–Y1–O9	70.1(5)	O25–Y21–O27	82.7(5)
O3–Y1–O5	81.9(5)	O25–Y21–O29	70.7(5)
O3–Y1–O7	141.4(5)	O27–Y21–O29	69.4(5)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

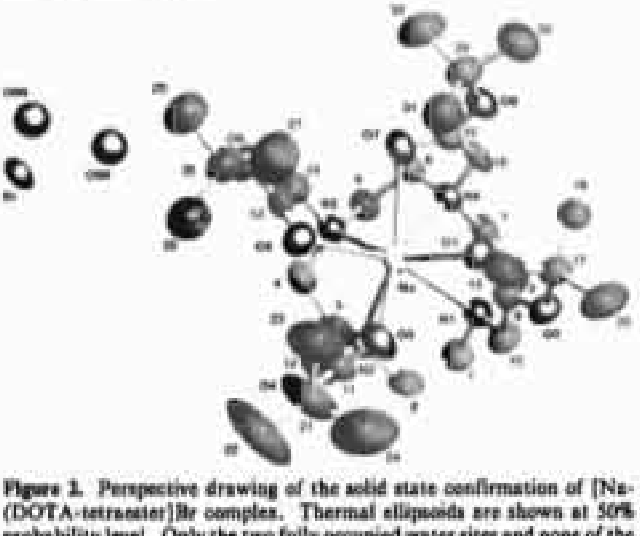

Figure 2. Perspective drawing of the solid state confirmation of [Na-(DOTA-tetraester)]Br complex. Thermal ellipsoids are shown at 50% probability level. Only the two fully occupied water sites and none of the hydrogen atoms are shown.

similar (only one of the two types of distereomeric (Gd/Y)HP-DO3A macrocyclic conformations is present in the NaBr complex). The four –CN(C)C– groups and four coordinated oxygens of the two complexes can be superimposed with an rms deviation of 0.08 Å (Figure 3, top). The eight-coordinate sodium ion is embedded deep within the esterified DOTA ligand; the *tert*-butyl groups of the esters extend well above the ninth apical water site of Gd/Y complexes. The Na–N distances are ~0.1 Å shorter and Na–O distances 0.2 Å longer than the corresponding distances in the (Gd/Y)HP-DO3A complexes. Accordingly, the sodium lies ~0.3 Å deeper than Gd/Y ions in the ligand cavity (d_N = 1.43 Å and d_O = 1.13 Å). Bond distances and angles involving the sodium ion are given in Table 9. The crystal structure appears to accommodate a maximum of four water molecules.

Table 8. Atomic Fractional Coordinates for the Non-Hydrogen Atoms of NaBr(*tert*-butyl ester DOTA)

atom	*x*	*y*	*z*
N1	0.4443(5)	0.5789(2)	0.2138(3)
C1	0.4136(7)	0.5857(3)	0.1232(4)
C2	0.4169(7)	0.6408(3)	0.0988(4)
N2	0.5459(5)	0.6658(2)	0.1342(3)
C3	0.6423(6)	0.6511(3)	0.0903(3)
C4	0.7832(6)	0.6616(3)	0.1389(3)
N3	0.8252(5)	0.6351(2)	0.2195(3)
C5	0.8581(6)	0.5811(2)	0.2096(4)
C6	0.8532(7)	0.5490(2)	0.2839(4)
N4	0.7232(5)	0.5497(2)	0.3008(3)
C7	0.6304(7)	0.5164(2)	0.2424(4)
C8	0.4872(7)	0.5262(3)	0.2384(4)
C9	0.3840(6)	0.6036(2)	0.3370(4)
C10	0.3332(6)	0.5934(3)	0.2452(4)
O1	0.4962(4)	0.6124(2)	0.3740(2)
O2	0.2846(4)	0.6017(2)	0.3725(2)
O3	0.4580(5)	0.7085(2)	0.2587(3)
O4	0.4471(5)	0.7860(2)	0.2016(3)
O5	0.7740(4)	0.7165(2)	0.3081(3)
O6	0.9915(4)	0.7301(2)	0.3681(3)
O7	0.8176(4)	0.6183(2)	0.4333(2)
O8	0.7819(5)	0.5603(2)	0.5237(2)
C11	0.4717(7)	0.7366(2)	0.2055(4)
C12	0.5294(7)	0.7212(3)	0.1369(4)
C13	0.8886(6)	0.7060(2)	0.3189(4)
C14	0.9352(6)	0.6614(3)	0.2767(4)
C15	0.7837(6)	0.5772(2)	0.4485(4)
C16	0.7380(7)	0.5348(2)	0.3864(4)
C17	0.3139(6)	0.6094(3)	0.4637(4)
C18	0.3612(8)	0.6626(3)	0.4841(4)
C19	0.4066(7)	0.5693(3)	0.5082(4)
C20	0.1783(7)	0.6022(4)	0.4780(4)
C21	0.3873(8)	0.8117(3)	0.2617(4)
C22	0.382(1)	0.8660(4)	0.2330(6)
C23	0.473(1)	0.8057(4)	0.3482(5)
C24	0.255(1)	0.7902(5)	0.2537(6)
C25	0.9726(8)	0.7736(3)	0.4193(5)
C26	1.1134(9)	0.7869(3)	0.4672(6)
C27	0.8945(9)	0.7560(4)	0.4771(5)
C28	0.911(1)	0.8176(3)	0.3623(7)
C29	0.8271(7)	0.5907(3)	0.6006(4)
C30	0.8006(9)	0.5555(4)	0.6653(5)
C31	0.7483(8)	0.6396(4)	0.5927(5)
C32	0.9722(8)	0.6007(4)	0.6206(5)
Na	0.6318(2)	0.63958(8)	0.2854(1)
Br	0.8277(1)	0.43045(4)	0.11760(6)
O94	0.292(2)	0.4635(9)	0.012(1)
O95	0.245(1)	0.4292(5)	0.0649(7)
O96	0.218(1)	0.4585(5)	0.0200(8)
O97	0.502(1)	0.4553(4)	0.0504(6)
O98	0.0297(6)	0.5884(2)	0.0387(3)
O99	0.1016(6)	0.5007(2)	0.1378(3)

Two of the water sites (O98 and O99) are fully occupied, while site O97 and the mutually exclusive sites O95 and O96 are partially occupied. Interatomic distances about the sodium are given in Table 9.

Crystal Structure Study of DO3A·H_2SO_4. The crystal structure of this salt is a dihydrate (Figure 4) in which both water sites are fully occupied; fractional atomic coordinates are given in Table 10. The molecular structure of the ligand is considered below.

Discussion

The pattern of the protonation constants of the ligands is very similar to that of the parent macrocyclic amine, cyclen (1,4,7,10-tetraazacyclododecane).[24] The first two protonations are therefore reasonably assigned to two nitrogens. It has previously been postulated that *trans*annular nitrogens are protonated to reduce electrostatic repulsion.[27-30] This postulate is supported by the crystal structure study of the transannularly diprotonated DO3A·H_2SO_4 ligand (*vide infra*, Figure 4), where it further appears that the protonation of adjacent nitrogens is sterically unfavorable. Sherry and Desreux[7,27] have proposed that, in the case of NOTA and DOTA, each protonated nitrogen is cyclically hydrogen bonded to the charged carboxylate oxygen of the pendent arm. Further support for the stability of this structure was offered by Kasprzyk and Wilkins.[30] They studied the formation kinetics of DOTA complexes and demonstrated that the diprotonated form of the ligands $(H_2L)^{2-}$ was 4–5 orders of magnitude less reactive than the monoprotonated form of the ligand, HL^{3-}. The third and fourth protonation constants are assigned to the protonation of the two carboxylate oxygens attached to the unprotonated nitrogens. This is reasonable in light of the facts that the protonation constant values are higher than those of the third and fourth protonation constants of cyclen and close to those of acetic acid (log K = 4.6). The protonation scheme of the macrocyclic poly(amino carboxylate) ligands differs from that of the common linear poly(amino carboxylates)[31] such as EDTA and higher homologues like DTPA, where all nitrogens are protonated before any of the carboxylate groups.

Table 9. Bond Distances (Å) and Angles (deg) for NaBr(*tert*-butyl ester DOTA)

Na–N1	2.554(5)	Na–O1	2.441(5)
Na–N2	2.534(5)	Na–O3	2.520(5)
Na–N3	2.580(6)	Na–O5	2.476(5)
Na–N4	2.532(5)	Na–O7	2.745(4)
N1–Na–N2	72.0(2)	N3–Na–O1	156.3(2)
N1–Na–N3	111.6(2)	N3–Na–O3	125.3(2)
N1–Na–N4	71.8(2)	N3–Na–O5	65.6(2)
N1–Na–O1	66.2(2)	N3–Na–O7	86.1(2)
N1–Na–O3	86.6(2)	N4–Na–O1	86.3(2)
N1–Na–O5	158.9(2)	N4–Na–O3	157.2(2)
N1–Na–O7	123.7(2)	N4–Na–O5	123.2(2)
N2–Na–N3	71.6(2)	N4–Na–O7	64.3(1)
N2–Na–N4	111.8(2)	O1–Na–O3	78.4(2)
N2–Na–O1	125.8(2)	O1–Na–O5	125.2(2)
N2–Na–O3	66.0(2)	O1–Na–O7	77.2(1)
N2–Na–O5	87.8(2)	O3–Na–O5	79.5(2)
N2–Na–O7	156.9(2)	O3–Na–O7	126.9(2)
N3–Na–N4	71.2(2)	O5–Na–O7	77.5(1)

The fact that the first nitrogen in the deprotonated macrocyclic poly(amino carboxylates) is more basic than the nitrogen in the parent macrocyclic amine (Table 2)[24] is readily rationalized. The substitution of ionized acetate groups on the nitrogen atoms would be expected to increase the basicity of the nitrogen through an electrostatic effect. Surprisingly, however, acetate substitution seems to have very little effect on the second protonation constant of macrocyclic poly(amino carboxylates). The effect could represent a balance in opposing electrostatic forces, one from the negative carboxylate on the nitrogen to be protonated and the other from the first proton held jointly by the transnnular nitrogen and carboxylate.

A comparison of the values of the first protonation constants of DO3A, HP-DO3A, and DOTA is in order. Although enhancement of the basicity of DOTA nitrogens relative to those of DO3A can be explained in terms of a charge effect, the increase in the value of log K_1 of HP-DO3A cannot. It might be due the presence of an electron donating methyl group on the arm, making the nitrogen more basic. A similar difference was observed in the case of the first pK_a of EDTA and *t*-Bu-EDTA.[32]

Preorganization of the metal-free DO3A ligand is apparent; the 12 atoms of the macrocycles of H_2DO3A^{2+} and (Gd/Y)-HP-DO3A are essentially superimposable (rms = 0.14 Å, Figure 3, bottom). In H_2DO3A^{2+} the secondary nitrogen N4 and its

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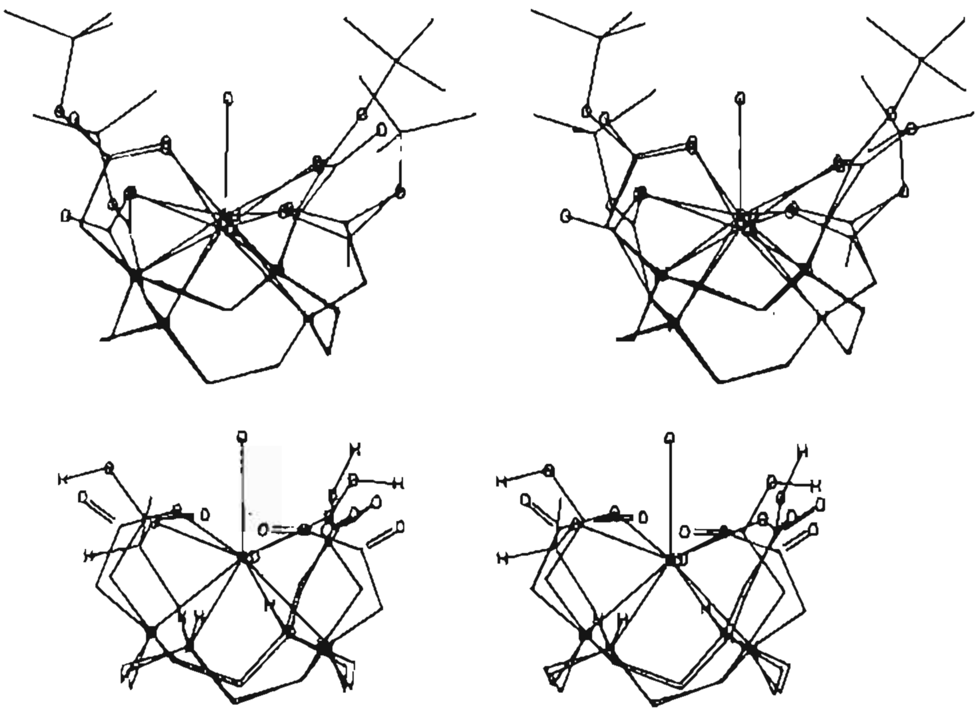

Figure 3. (Top) Stereoscopic superposition of the Gd(HP-DO3A) and Na[DOTA-tetraester]B complexes. (Bottom) Stereoscopic superposition of the Gd(HP-DO3A) complex and the preorganized metal-free ligand $H_3(DO3A)^{2+}$.

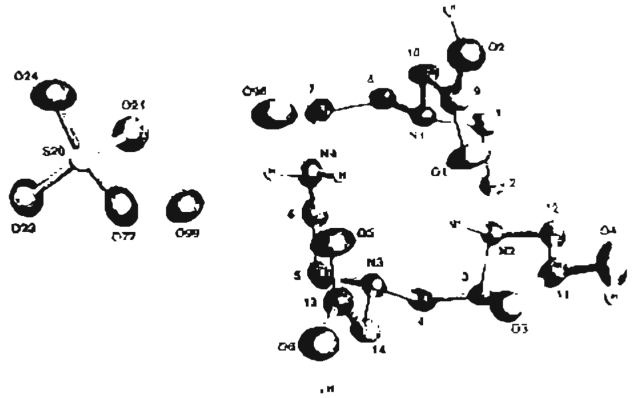

Figure 4. Perspective drawing of the conformation in the dihydrate crystal structure of $H_3(DO3A)SO_4$. Most hydrogens have been omitted. Thermal ellipsoids are shown at the 50% probability level.

*trans*annular tertiary nitrogen N2 are protonated, as are each of the three carboxyl groups, resulting in an overall +2 charge for the ligand. One of the N4–H bonds and the N2–H bond are internally directed toward toward the potential binding site of a metal. The carbonyl oxygen atoms of the three carboxylic acids are located over the macrocycle, at distances of only 0.5, 0.9, and 1.1 Å from the positions of carboxylate ligand oxygens in the (Gd/Y)HP-DO3A complexes. One of the lattice water molecules, O98, is 0.8 Å from the fourth coordination site of the HP-DO3A ligand, and hydrogen bonded to O5 (O—O distance = 2.901 Å). The *intra*molecular N4---O5 and N2---O1 distances, 2.90 and 3.03 Å, suggest some interactions, but the N–H---O angles (~125°) are not optimal. The other proton on N4 is hydrogen bonded to water O99.

Sodium and Potassium Binding. The first protonation constant of the ligands (log K_1) is highly dependent on the selection of the electrolyte for the ionic strength control (Table 2). As suggested previously in the case of linear and macrocyclic poly(amino carboxylates),[32-38] it is probably a result of the complexation of Na⁺ or K⁺ with fully deprotonated ligands. The crystal structure of the sodium bromide complex of the tetra *tert*-butyl ester of DOTA (*vide infra*) now demonstrates the complexation of Na⁺ in a macrocyclic ligand with no formal charge.

Table 10. Table of Positional Parameters and Their Estimated Standard Deviations for $DO3A{\cdot}H_2SO_4{\cdot}2H_2O$

atom	*x*	*y*	*z*
N1	0.7012(1)	0.4557(2)	0.2136(3)
C1	0.7072(2)	0.3989(3)	0.1071(4)
C2	0.6563(2)	0.3840(3)	0.0453(3)
N2	0.6186(1)	0.3284(2)	0.1191(3)
C3	0.5636(2)	0.3394(3)	0.0755(4)
C4	0.5416(2)	0.4344(3)	0.0981(4)
N3	0.5489(1)	0.4660(2)	0.2194(3)
C5	0.5409(2)	0.5664(3)	0.2304(4)
C6	0.5908(2)	0.6183(3)	0.2119(4)
N4	0.6286(1)	0.5890(3)	0.3029(3)
C7	0.6833(2)	0.6173(3)	0.2791(4)
C8	0.7073(2)	0.5551(3)	0.1867(4)
C9	0.7218(2)	0.3342(3)	0.3588(4)
C10	0.7370(2)	0.4258(3)	0.3058(4)
O1	0.6809(1)	0.2961(2)	0.3403(3)
O2	0.7565(1)	0.2967(2)	0.4308(3)
C11	0.6091(2)	0.1744(3)	0.2185(4)
C12	0.6338(2)	0.2284(3)	0.1192(4)
O3	0.5764(1)	0.2047(2)	0.2833(3)
O4	0.6289(1)	0.0905(2)	0.2222(3)
C13	0.5436(2)	0.4088(3)	0.4208(4)
C14	0.5176(2)	0.4144(3)	0.3027(4)
O5	0.5878(1)	0.4343(3)	0.4373(3)
O6	0.5161(1)	0.3740(3)	0.5067(3)
S20	0.61362(4)	0.62340(7)	0.85047(9)
O21	0.6350(1)	0.6437(2)	0.7346(3)
O22	0.5908(1)	0.5293(2)	0.8517(3)
O23	0.5731(1)	0.6893(2)	0.8802(3)
O24	0.6554(1)	0.6259(3)	0.9386(3)
O98	0.6755(1)	0.5305(3)	0.5398(3)
O99	0.5801(1)	0.6699(2)	0.5243(3)

The large differences among the values of first protonation

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constants of DOTA reported by several investigators[27,29,33,39] are probably due both to variable binding of ions in the media and to uncertainty associated with the large magnitude of the value. Our values of the first two protonation constants of DOTA measured in (TMA)Cl are 0.37 and 0.28 log units lower than those of Delgado and DaSilva[33] in (TMA)NO_3. A slightly lower value of the first protonation constant of DOTA observed in our work may be due to the presence of some Na^+ ions in our sample of DOTA. It is worth reiterating that the use of noncoordinating ions such as tetramethylammonium chloride for ionic strength control is essential for the determination of protonation constants of linear and macrocyclic poly(amino carboxylates).[33–38] For the calculation of the stability constant of the DOTA complexes, the literature values[33] of the ligand protonation constants of DOTA were used.

The effect of sodium ion on the first protonation constant is much greater than the effect of potassium, which suggests that sodium binds the ligands with greater affinity. Excluding HP-DO3A, for which inseparable first and second protonation constants were observed, the effect of sodium ion on the first protonation constant followed the order DOTA($^{4-}$) > DO3A($^{3-}$) > DTPA($^{5-}$) > EDTA($^{4-}$); the effect of potassium was less in magnitude and in the order DOTA($^{4-}$) > DTPA($^{5-}$) with no effect on the other ligands. The implication is that the K^+ ion is too large for an optimal fit to the binding cavities. (Our survey of the Cambridge Structural Data base indicated that K–O and K–N bonds generally are 0.2–0.4 Å longer than the corresponding Na–O and Na–N bonds.[40]) The affinity of both ions appears to be greater for the macrocyclic ligands than for the linear ones, consistent with the preorganized structures in the former and with the behavior of the lanthanide ions. The stability constants of NaL^{1-n} were determined from the potentiometric titration of the NaCl mixture to be (log K) 3.18 for Na(DO3A)$^{2-}$ and 4.06 for Na(HP-DO3A)$^{2-}$, the latter being comparable to the value[33] of 4.38 reported for Na(DOTA)$^{3-}$.

Gadolinium and Yttrium Binding. For the Gd(III) complexes, the relative stability follows the order M(DOTA)$^-$ > M(HP-DO3A) > M(DO3A) for the macrocycles and M(DTPA)$^{2-}$ > M(EDTA)$^-$ for the linear ligands. The order is the same for M = Gd(III) or Y(III) within the ligand types, but a linear ligand, e.g. EDTA, prefers Y(III) to Gd(III) by 0.8 log units, while the heptadentate and octadentate linear and macrocyclic ligands DOTA and HP-DO3A do not show significant differences in Y(III) and Gd(III) stability constants. We note that the complexes of Y(III) and Gd(III) are frequently nine-coordinate where crystal structures are known: Gd/Y(DOTA)$^-$,[12] Gd(DTPA)$^{2-}$,[41] Gd(DO3A),[12] Gd/Y(HP-DO3A) (this work), Gd(DO3MA),[26] and Gd(DTPA-BEA).[42]

It is generally observed that, for linear, multidentate poly(amino carboxylate) ligands such as EDTA and DTPA, the stabilities of the heavy lanthanide complexes are greater than for the lighter lanthanides. The smaller ionic radii of the heavier ions[43] creates greater ionic potential and thus stronger attraction for the charged ligands.[44] The ionic radius of the Y(III) (1.019 Å) ion is similar to that of the Ho(III) ion (1.015 Å).[43] Therefore one might expect Y(III) to behave more like a heavy lanthanide ion and have greater stability constants than Gd(III). However, the charge density (nuclear charge) on Y(III) is substantially less than Gd(III) as the atomic number of Y(III) is 39 compared to 64 for Gd(III). Consequently the Y chelates could be less stable. The Y(DTPA) was previously reported[45] to be less stable than Gd(DTPA). However, in the present work most of the chelates were found to be equally stable. Y(III) complexes are known to show unpredictable results.[46] The reported results for Y(EDTA) and Gd(EDTA) demonstrated the stability order Y(EDTA) > Gd(EDTA).[47] This trend in the stability order can be rationalized in terms of simple ion-size considerations.

The solid-state structures of Gd- and Y(HP-DO3A) are consistent with the solution stability studies and with solution hydration and relaxivity studies[26] which indicates that the HP-DO3A and DOTA complexes are also nine-coordinate in dispersed phases. Aime suggested that two isomeric forms of Ln(DOTA)$^-$ existed in solution, based on an NMR study.[48] However, the structural results present no clear basis for further refining our understanding of the 100-fold difference in the stabilities of the complexes of HP-DO3A and DOTA.

Conclusions

The solid-state and solution structural and dynamic studies to date are consistent with a highly preorganized structure for poly(amino carboxylate) ligands based on the tetraazacyclododecane macrocycle known as cyclen. The preorganization is primarily encouraged by the stability of the [3333] conformation of the macrocycle and hence is present for both hepta- and octadentate variants. The binding cavities in these ligands are rigid and have a well-defined size. The rigidity creates exceptionally stable and kinetically inert metal complexes, including much stronger complexes with alkali metals than is the case for linear ligands. Complexation with sodium persists even when the charged oxygen atoms are rendered neutral esters.

Acknowledgment. We thank Drs. A. D. Sherry and R. J. Motekaitis for providing the computer programs and assistance in computation of stability constants and protonation constants, respectively, and Dr. E. Delaney and Mr. W. Schmidt for the [Na(tBu-tetraester DOTA)]Br sample.

Supplementary Material Available: Tables listing all bond distances, bond angles, anisotropic temperature factors, and hydrogen positional parameters for the crystal structures of Gd(HP-DO3A), Y(HP-DO3A), NaBr(tBu ester DOTA), and DO3A·H_2SO_4 (25 pages). Ordering information is given on any current masthead page.

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