Synthesis, Stability, and Crystal Structure Studies of Some Ca^{2+}, Cu^{2+}, and Zn^{2+} Complexes of Macrocyclic Polyamino Carboxylates

Krishan Kumar,*,[†] M. F. Tweedle,[†] M. F. Malley,[‡] and J. Z. Gougoutas[‡]

Bracco Research USA, P.O. Box 5225, Princeton, New Jersey 08543-5225, and Solid State Chemistry Department, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000

The stability constants of the complexes of three ligands, DO3A (1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid), HP-DO3A (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid), and DO3MA (1R,4R,7R)-α,α′,α″-trimethyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid), with Ca^{2+}, Cu^{2+}, and Zn^{2+} were measured at 25.0 ± 0.1 °C and $\mu = 0.1$ (TMACl). Calcium and gadolinium complexes which have five-membered chelate rings follow linear log K_{ML} vs ΣpK_a and log K_{GdL} vs log K_{CaL} correlations, suggesting Ca^{2+} and Gd^{3+} have similar coordination behavior. A linear correlation between log K_{ML} and Z/r (charge density on the metal ion) for HP-DO3A complexes is consistent with the lower stability constant of the Ca^{2+} vs Gd^{3+} complex. The overall selectivity constants for Gd^{3+} over other metal ions were calculated. The crystal structures of three hydrated forms of $Ca[Ca(HP\text{-}DO3A)]_2$ were determined by X-ray single-crystal analysis: a C_2 symmetric trinuclear structure, $Ca(H_2O)_4[Ca(HP\text{-}DO3A)]_2\cdot10H_2O$, a centrosymmetric hexanuclear structure, $\{Ca(H_2O)_3[Ca(HP\text{-}DO3A)]_2\cdot3H_2O\}_2$, and a C_2 symmetric trinuclear structure, $Ca(H_2O)_4[Ca(HP\text{-}DO3A)]_2\cdot2H_2O$, which is formed through topotactic dehydration of the first structure at 22 °C. The conformations of the macrocyclic ligands, [3333], and their coordination to the embedded calcium ions are virtually identical in all forms. The embedded calcium is sandwiched between two nearly parallel planes of four nitrogens and oxygens. The macrocyclic ring in the crystal structure of HCu(DO3A) adopts a quadrangular [2334] conformation in which the four nitrogens and two opposite carboxylate arms are coordinated to the Cu(II) atom.

Introduction

Lanthanide complexes of linear and macrocyclic polyamino carboxylates have been the subject of many investigations in recent years. The interest in this class of complexes is due to their coordination chemistry,[1,2] analytical application as metal ion selective reagents,[3] and medical applications[4−6] such as Gd^{3+} complexes in magnetic resonance imaging[4,5] and ^{90}Y-labeled antibodies for radiotherapy.[6] Four such complexes, GdL (where L = DTPA, diethylenetriaminepentaacetic acid, DTPA-BMA = the bis(methyl amide) of DTPA, HP-DO3A = 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, and DOTA = 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid), are being used clinically.[5]

The evaluation of any new gadolinium complex as a potential MRI contrast agent must focus on stability and kinetic behavior[7−23] because in their uncomplexed states, both Gd^{3+}

and the ligands are highly toxic. The release of free Gd^{3+} from the chelate in vivo is a function of multiple equilibria.[24,25] The complex may undergo transmetalation, ligand displacement, base hydrolysis, and acid-catalyzed dissociation due to the presence of such endogenously available ions as Ca^{2+}, Cu^{2+}, Zn^{2+}, PO_4^{3-}, CO_3^{2-}, OH^-, and H^+. The competition of these ions with Gd^{3+} or ligand depends on the relative affinity of the ligand for these metal ions (stability constants) and H^+ (ligand protonation constants). The low-solubility products of $Gd(PO_4)$ and $Gd(OH)_3$ are sufficient to precipitate Gd^{3+} from chelates with

---

[†] Bracco Research USA.
[‡] Bristol-Myers Squibb Pharmaceutical Research Institute.
[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1995.
(1) Choppin, G. R. *J. Less-Common Met.* **1985**, *112*, 193.
(2) Margerum, D. W.; Cayley, G. A.; Weatherburn, D. C.; Pagenkopf, G. K. In *Coordination Chemistry;* Martell, A. E., Ed.; ACS Monograph 174; American Chemical Society: Washington, DC, 1978; Vol. 2, p 1.
(3) Marcus, Y.; Kertes, A. S. *Ion-Exchange and Solvent Extraction of Metal Chelates*; Wiley-Intersciences: London, 1969.
(4) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901.
(5) Kumar, K.; Tweedle, M. F. *Pure Appl. Chem.* **1992**, *65*, 515.
(6) Parker, D. *Chem. Soc. Rev.* **1990**, *19*, 271.
(7) Kumar, K.; Chang, C. A.; Tweedle, M. F. *Inorg. Chem.* **1993**, *32*, 587.
(8) Kumar, K.; Tweedle, M. F. *Inorg. Chem.* **1993**, *32*, 4193.
(9) Kumar, K.; Jin, T.; Wang, X.; Desreux, J. F.; Tweedle, M. F *Inorg. Chem.* **1994**, *33*, 3567.
(10) Kumar, K.; Chang, C. A.; Francesconi, L. F.; Dischino, D.; Malley, M.; Gougoutas, J. Z.; Tweedle, M. F. *Inorg. Chem.* **1994**, *33*, 3567.

(11) Kang, S. I.; Ranganathan, R. S.; Emswiler, J. E.; Kumar, K.; Gougoutas, J. Z.; Malley, M.; Tweedle, M. F. *Inorg. Chem.* **1993**, *32*, 2912.
(12) Cacheris, W. P.; Nickel, S. K.; Sherry, A. D. *Inorg. Chem.* **1987**, *26*, 958.
(13) Brucher, E.; Sherry, A. D. *Inorg. Chem.* **1990**, *29*, 1555.
(14) Brucher, E.; Cortes, S.; Chavez, F.; Sherry, A. D. *Inorg. Chem.* **1991**, *30*, 2092.
(15) Wang, X.; Tianzhu, J.; Comblin, V.; Lopez-Mut, A.; Merciny, E.; Desreux, J. F. *Inorg. Chem.* **1992**, *31*, 1095.
(16) Chang, C. A.; Ochaya, V. O.; Chandra Sekhar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 1724.
(17) Chandra Sekhar, V.; Chang, C. A. *Inorg. Chem.* **1986**, *25*, 2061.
(18) Kodama, M.; Koike, T.; Mahatma, A. B.; Kimura, E. *Inorg. Chem.* **1991**, *30*, 1270.
(19) Aime, S.; Anelli, P. L.; Botta, M.; Fedeli, F.; Grandi, M.; Paoli, P.; Uggeri, F. *Inorg. Chem.* **1992**, *31*, 2422.
(20) Carvalho, J. F.; Kim, S.-H.; Chang, C. A. *Inorg. Chem.* **1992**, *31*, 4065.
(21) Delgado, R.; Sun, Y.; Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1993**, *32*, 3320.
(22) Clarke, E. T.; Martell, A. E. *Inorg. Chim. Acta* **1991**, *181*, 273.
(23) Rizkalla, E. N.; Choppin, G. R.; Cacheris, W. P. *Inorg. Chem.* **1993**, *32*, 582.
(24) Rubin, M.; Martell, A. E.; Gohil, R.; Penhos, J. C.; Weiss, P.; Motekaitis, R. J. *ACS Symp. Ser.* **1980**, 279.
(25) Cacheris, W. P.; Quay, S. C.; Rocklage, S. M. *Magn. Reson. Imaging* **1990**, *8*, 467.

relatively low stability constants and kinetic inertia.[26] A knowledge of the ligand protonation and stability constants of Ca^{2+}, Cu^{2+}, Zn^{2+}, and Gd^{3+} is essential to an understanding of the physiological tolerance of gadolinium chelates.

The relative stabilities of various Gd^{3+} complexes may be expressed in three different ways: (1) the conditional stability constant, $K_{ML(cond)}$ (the stability constant at pH 7.4; it is smaller than the overall stability constant due to the competition between H^+ and Gd^{3+} for the ligand at this pH), (2) the selectivity constant,[24,25] K_{sel} (the difference between the stability constant (log K value) of the Gd^{3+} complex and the stability constant of the complex of endogenously available metal ions; higher selectivity toward Gd^{3+} indicates that endogenously available metal ions are less able to displace Gd^{3+} in the chelate), and (3) the modified selectivity constant, K_{sel}' (the stability constant corrected for the competition between the endogenously available metal ions and H^+).

The objectives of this work were as follows: (1) to determine stability constants of some divalent metal ions with a series of macrocyclic polyamino carboxylates and to compare them with the stability constants of mono- and trivalent metal complexes, (2) to determine the effects of basicity, number of donor atoms, size of the macrocyclic cavity, and conformation on the stability of calcium complexes, (3) to compare the stability constants of calcium and gadolinium complexes of linear and macrocyclic polyamino carboxylates (both form complexes with predominantly ionic binding), and (4) to determine the selectivity of the macrocyclic polyamino carboxylate ligands for gadolinium over endogenously available metal ions.

We report herein the stability constants of Ca^{2+}, Cu^{2+}, and Zn^{2+} complexes of a series of macrocyclic polyamino carboxylate ligands: DO3A (**I**; 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid), HP-DO3A (**II**) and DO3MA (**III**; 1R,4R,7R-α,α',α''-trimethyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid). These data are compared with published data on the metal complexes of other macrocyclic polyamino carboxylates: NOTA (**IV**; 1,4,7-triazacyclononane-*N,N',N''*-triacetic acid) and DOTA (**V**).

Multidentate ligands such as EDTA and DOTA are known to utilize all of the donor atoms in gadolinium and calcium complexes.[10,27,28] In contrast, DOTA and TETA (1,4,8,11-tetraazacyclotetradecane-*N,N',N'',N'''*-tetraacetic acid) do not utilize all ligand donor atoms in their Cu^{2+} and Ni^{2+} complexes.[29-31] We also report here the solid-state structures of several forms of the calcium salt of Ca(HP-DO3A)⁻ and the structure of HCu(DO3A).

I, DO3A   II, HP-DO3A   III, DO3MA
IV, NOTA   V, DOTA
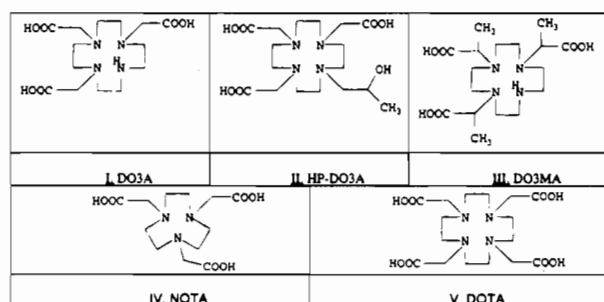
Experimental Section

Materials. The acid forms of the free ligands, DO3A, HP-DO3A, and DO3MA, were synthesized and characterized by the literature procedures.[11,32] The syntheses of the calcium complex of HP-DO3A and the copper complex of DO3A were accomplished as follows:

Ca[Ca(HP-DO3A)]₂. The ligand, HP-DO3A, (0.518 g, 1.24 mmol) was dissolved in 10 mL of water at room temperature to give a clear, colorless solution. Solid $CaCO_3$ (Fisher) (0.204 g, 2.03 mmol, 7% molar excess) was added to the stirred HP-DO3A solution in two portions. All of the $CaCO_3$ added in the first portion (0.132 g) dissolved, and effervescence was noted. Most of the second portion (0.072 g) was dissolved (effervescence again was noted) to give a cloudy solution. The cloudy solution was heated at 90 °C for 2.5 h. The resulting reaction mixture consisted of a white solid suspended in a clear solution of pH 7.95.

The suspension was centrifuged to separate the solid from the clear solution. The solution was evaporated under vacuum to dryness to give 0.56 g of white solid (yield = 48.6%). The β hydrate, $Ca(H_2O)_4$-[Ca(HP-DO3A)]₂·$10H_2O$, is obtained when the crude material is crystallized from aqueous acetone; it readily undergoes partial dehydration to the γ hydrate, $Ca(H_2O)_4$[Ca(HP-DO3A)]₂·$2H_2O$. For material dried in vacuo at room temperature for 3 h: Anal. Found (calcd) for $C_{34}H_{58}N_8O_{14}Ca_3$·$6.1H_2O$: C, 39.66 (39.50); H, 6.83 (6.85); N, 10.76 (10.84); Ca, 11.25 (11.63). FAB MS: *m/e* 923 (m + H)⁺, 921 (M − H)⁻. IR: 1600 cm⁻¹, characteristic of metal complexes of carboxylates. Crystallization from aqueous DMF usually gives the α hydrate $Ca(H_2O)_3$[Ca(HP-DO3A)]₂·$3H_2O$.

HCu(DO3A). The ligand, DO3A, (1.178 g, 3.2 mmol) was dissolved in 10 mL of water. A solution of copper acetate (Alfa) (0.6388 g, 3.2 mmol, in 15 mL) was added to the ligand solution. The reaction mixture was stirred at room temperature for 2.5 h, and the volume of the reaction mixture was made up to 30 mL. The pH of the reaction mixture was adjusted to ~4 with 1 N NaOH. The volume of the reaction mixture was reduced to 15 mL. Addition of 15 mL of acetone to the concentrated reaction mixture produced an oil. The oil was triturated with 30 mL of acetone followed by an addition of ethanol. A blue solid powder, produced by addition of ethanol, was removed by filtration. The solid was dissolved in a hot ethanol/water mixture. The solution was filtered while hot, cooled slowly to room temperature, and left at 4 °C overnight. Blue crystals suitable for X-ray analysis were separated by filtration and washed twice with 10 mL of ethanol. The composition of the solid material was confirmed by elemental analysis. Anal. Found (calcd) for $C_{14}H_{24}N_4O_6Cu$·$0.2H_2O$: C, 40.93 (40.89); H, 5.96 (5.97); N, 13.43 (13.63).

Solution Preparations. The solutions of the free ligands were prepared and standardized by complexometric and potentiometric titrations. The strong base solution, tetramethylammonium hydroxide, was prepared by dissolving the solid material from Aldrich in boiled and nitrogen-bubbled water. Standardization of tetramethylammonium hydroxide solution (0.1023 M) was carried out using dried potassium hydrogen phthalate (KHP) as the primary standard and phenolphthalein as the indicator. Tetramethylammonium chloride (Aldrich) was used for ionic strength control. The metal salt solutions, $CaCl_2$, $CuCl_2$, and $Zn(NO_3)_2$ (Fisher Scientific), were prepared, and the concentrations were determined by EDTA titrations using murexide or Xylenol Orange as the indicators. The disodium salt of ethylenediaminetetraacetic acid (Na_2H_2EDTA) (Fisher) was used as received.

Potentiometric Measurements. Solution pH values were measured with an Orion combination glass electrode and an Orion meter model 605. Potentiometric titrations for the determination of the stability constants were carried out at a constant ionic strength of 0.1 ((CH_3)₄-NCl). An automatic titrator/pH meter (Brinkmann 670 Titroprocessor,

(26) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum Press: New York, 1975, 1976, 1977; Vols. 1–4.
(27) Barnett, B. L.; Uctman, V. A. *Inorg. Chem.* **1979**, *18*, 2674.
(28) Anderson, O. P.; Reibenspies, J. H. Abstract of the Annual Meeting of the American Crystallographic Association, Philadelphia, PA, June 1988, p 76. We thank Dr. Anderson for supplying the atomic coordinates of Ca(DOTA)²⁻.
(29) Riesen, A.; Zehnder, M.; Kaden, T. A *Helv. Chim. Acta* **1986**, *69*, 2067.
(30) Riesen, A.; Zehnder, M.; Kaden, T. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1336.
(31) Riesen, A.; Zehnder, M.; Kaden, T. A. *Helv. Chim. Acta* **1986**, *69*, 2074.
(32) Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. A.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, *30*, 1265.

Table 1. Ligand Protonation Constants of Some Macrocyclic Polyamino Carboxylates[a]

ligand	$\log K_1$	$\log K_2$	$\log K_3$	$\log K_4$
DO3A	11.59	9.24	4.43	3.48
HP-DO3A	11.96	9.43	4.30	3.26
DO3MA	13.38[b]	9.15[b]	5.24[b]	4.07[b]
DOTA	12.09[c]	9.68[c]	4.55[c]	4.13[c]
NOTA	11.61[d]	5.87[d]	3.41[d]	

[a] At 25.0 ± 0.1 °C and $\mu = 0.1$ (TMACl), ref 10. [b] Reference 11. [c] Delgado, R.; Frausto Da Silva, J. J. R. *Talanta* **1982**, *29*, 815. [d] At 25.0 ± 0.1 °C and $\mu = 0.1$ (TMACl), Kumar, K. Unpublished Work.

precision ± 0.002 pH unit), equipped with a thermostated (25 ± 0.1 °C) glass-jacketed titration cell fitted with a combination glass electrode and a MetroOhm piston buret, was used. 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 pH's. 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 in the titrations. Precautions were taken to avoid CO_2 absorption by the base solution. All solutions were prepared in boiled and nitrogen-purged water. An ascarite tube was attached to the base-containing bottle. During each titration the capillary tip of the automatic buret was always under the solution, which was never exposed to air.

The rate of complexation and equilibration of DOTA with Ca^{2+}, Cu^{2+}, and Zn^{2+} is on the order of milliseconds.[33] Preliminary species distribution calculations[34] on $Ca(DOTA)^{2-}$ suggested >50% free ligand and the free calcium in the beginning of the titrations for complexation. Sufficient amounts of the free metal and the free ligands were present in other experiments also. This information allowed us to use direct potentiometric titration methods to determine stability constants of Ca^{2+}, Cu^{2+}, and Zn^{2+} complexes of DO3A, HP-DO3A, and DO3MA. The base, tetramethylammonium hydroxide, was added slowly to allow additional time for equilibration. Published values of the ligand protonation constants (Table 1)[10,11] were used to calculate the stability constants of the metal complexes. For these titrations a mixture of metal and ligand (the ligand being in slight excess, i.e. <1%) was titrated against standard tetramethylammonium hydroxide. The ionic strength of these determinations was maintained at 0.1 (TMACl), and the temperature, at 25.0 ± 0.1 °C. For each determination of the stability constant at least three to four runs were made. The stability constants of Na^+, Y^{3+}, Ce^{3+}, and Gd^{3+} were determined previously.[10-12]

Computational Methods. The overall stability constants of the various species formed in aqueous solution were obtained from the experimental data with the use of the program BEST.[34] The stability (eq 1) and protonation (eqs 2 and 3) constants of the metal complexes and the stability constants of the protonated metal complexes (eqs 4 and 5) were calculated using the overall stability constants and the ligand protonation constants.[10,11]

$$K_{ML} = [ML]/[M][L] \tag{1}$$

$$K_{MHL} = [MHL]/[ML][H] \tag{2}$$

$$K_{MH_2L} = [MH_2L]/[MHL][H] \tag{3}$$

$$K_{MHL}' = [MHL]/[M][HL] \tag{4}$$

$$K_{MH_2L}' = [MH_2L]/[M][H_2L] \tag{5}$$

For these determinations $50-100$ data points were collected. The program compares p[H]$_{cal}$ and p[H]$_{obsd}$ over the entire pH titration curve. The range of deviation between observed and calculated pH was $0.001-0.01$. In exceptional cases the difference was somewhat higher in the basic region. At least triplicate titrations were performed, and the

(33) Kasprzyk, S. P.; Wilkins, R. G. *Inorg. Chem.* **1982**, *21*, 3349.
(34) Martell, A. E.; Motekaitis, R. J. *The Determination and Use of Stability Constants*; VCH Publishers, Inc.: New York, 1988.

reported values are an average of these measurements. The value of $K_w = [H^+][OH^-]$ used in the computation was $10^{-13.78}$. Calculations were performed on an IBM AT or a Dell 486 DX computer.

The conditional stability constants ($K_{ML(cond)}$ at pH 7.4) were calculated from the overall stability constants and the ligand protonation constants using eq 6.

$$K_{ML(therm)} = K_{ML(cond)}(1 + K_1[H^+] + \\ K_1K_2[H^+]^2 + ... + K_n[H^+]^n) \tag{6}$$

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

Crystallographic Studies. Unit cell parameters and some details of X-ray diffraction data collection and refinement are summarized in Table 2. The general comments here apply to all analyses. Unit cell parameters were obtained through a least-squares analysis of at least fifteen high-angle reflections. Crystal densities were measured by flotation in hexane/carbon tetrachloride/bromoform mixtures. Reflections were measured diffractometrically with Cu Kα ($\lambda = 1.5418$ Å) radiation at 23 °C with the $\omega - 2\theta$ variable scan technique and were corrected for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half the time of the scan. Except for the γ form of Ca[Ca(HP-DO3A)]$_2$, two standard reflections were monitored for decay; no decrease of intensity was observed during the course of the measurements. Structures were solved by direct methods 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 the waters and those on the heteroatoms were introduced in observed positions. All other hydrogens were introduced in idealized positions and assigned isotropic temperature factors.

X-ray diffraction studies of polycrystalline samples (~ 100 mg) of Ca(HP-DO3A)$^-$ which were exposed for ~ 2 weeks to a controlled relative humidity demonstrate the existence and *solid-state interconversion* of at least three different crystal structures: form β predominates in samples stored at 52% or greater relative humidity, form γ in samples stored at 31% relative humidity, and form δ in samples stored at 6% or less relative humidity. Storage at intermediate humidities gave mixtures during this time period. A fourth form, α, and the highly hydrated β form have been obtained as single crystals by crystallization from aqueous DMF or aqueous acetone solutions. The α form is relatively stable and was not observed to interconvert with any of the other forms in the solid state. To date, a single crystal of the γ form has been obtained only through solid-state transformation of a single crystal of the β form. Form δ was not investigated further.

The solid-state $\beta \rightarrow \gamma$ transformation was shown through Weissenberg photography and diffractometric studies to occur topotactically with a reproducible alignment of the parent and daughter lattices (typical mosaic spread of ~ 4°).[35] Complete transformation of an unprotected single crystal of the β phase usually required several hours of exposure to ambient laboratory conditions. In a typical experiment, the unit cell vectors of the β lattice, and their orientation relative to a fixed coordinate system of the diffractometer, were measured within 1 h after isolation of the single crystal from solvents. Disappearance of the parent intensities and concomitant appearance of noncoincident, single-crystal intensities of the γ phase were monitored continuously. After several hours, the unit cell vectors of the daughter γ lattice were measured relative to the fixed coordinate system, and a complete set of intensities was measured out to $2\theta = 120$°.

The structure of the γ phase was determined by heavy methods. Its topotactic orientation relative to the parent β structure was derived by appropriate multiplications of the two orientation matrices.

For α form of Ca[Ca(HP-DO3A)]$_2$: Refined parameters were the coordinates and anisotropic temperature factors of the non-hydrogen atoms of the complex and the population parameters of the lattice waters (O96, 70%; O98, 80%).

(35) Gougoutas, J. Z. *Isr. J. Chem.* **1972**, *10*, 395.

Table 2. Crystallographic Data and Details of Refinement for Three Crystalline Forms of Hydrated Ca[Ca(HP-DO3A)]$_2$ and for HCu(DO3A)

	form α	form β	form γ	HCu(DO3A)
a, Å	16.304(5)	33.623(3)	33.575(20)	7.448(3)
b, Å	18.811(2)	9.516(1)	9.373(4)	15.821(4)
c, Å	16.727(3)	20.949(1)	20.207(10)	13.929(6)
β, deg	112.13(2)	125.35(1)	131.62(5)	97.98(3)
V, Å^3	4752(3)	5467(2)	4754(11)	1625(2)
crystal system	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$C2/c$	$C2/c$	$P2_1/n$
formula (ideal)	Ca$_3$C$_{34}$H$_{70}$N$_8$O$_{20}$	Ca$_3$C$_{34}$H$_{86}$N$_8$O$_{28}$	Ca$_3$C$_{34}$H$_{70}$N$_8$O$_{20}$	CuC$_{14}$H$_{24}$N$_4$O$_6$
fw (ideal)	1031.2	1175.4	1031.2	407.91
d_{obs}, g cm^{-3}	1.42	1.43	1.44	1.65
d_{calc}, g cm^{-3} fully occupied solvent	1.441	1.428	1.441	1.667
d_{calc}, g cm^{-3} partially occupied solvent	1.429		1.428	
Z	4	4	4	4
color	colorless	colorless	colorless	blue
habit	mutifaceted prisms	rectangular prisms	rectangular prisms	plates
dimen, mm	0.35 × 0.17 × 0.22	0.35 × 0.4 × 0.2	0.3 × 0.4 × 0.2	0.25 × 0.2 × 0.15
instrument	CAD4	CAD4	CAD4	Syntex P2$_1$
$2\theta_{max}$, deg	140	140	120	140
N_{ref}^a	9513	5601	3887	2535
N_{uni}^b	8878	5102	3535	2134
N_{obs}^c	5943	4086	1077	1493
N_{var}^d	587	331	139	226
ERRWT^e	1.68	1.71	2.79	1.49
SHIFT/ERR^f	0.06	0.03	0.01	0.00
R	0.051	0.040	0.106	0.041
R_w	0.062	0.054	0.115	0.050

^{a} Total number of measured reflections within $2\theta_{max}$. ^{b} Total number of symmetry-independent measured reflections. ^{c} Total number of "observed" reflections with $I > 3\sigma(I)$ 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.

For β form of Ca[Ca(HP-DO3A)]$_2$ and for HCu(DO3A): Refined parameters were the coordinates and anisotropic temperature factors of the non-hydrogen atoms.

For γ form of Ca[Ca(HP-DO3A)]$_2$: Refined variables were the coordinates of all non-hydrogen atoms, the anisotropic temperature factors of the calcium atoms, the isotropic temperature factors of all other non-hydrogen atoms, and the population factors of the lattice water (O98, 74%).

All calculations utilized the SDP software package with minor local modifications.[36] Least-squares weights, $\omega = \sigma^{-2}(F_o)$ 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 $\Sigma w(|F_o| - |F_c|)^2$. R is defined as $\Sigma||F_o| - |F_c||/\Sigma|F_o|$ while $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.

Results and Discussion

Complexation of the Ligands with Ca^{2+}. When CaCl$_2$ and the ligand, DO3A, HP-DO3A, or DO3MA, were mixed in equivalent amounts, the initial pH of the solution was the same as that of the solution of the free ligand. This suggested no immediate formation of the protonated or unprotonated complex of Ca^{2+}. An inflection point was observed in all cases when three equivalents of the base had been added. The titration data were fitted for the formation of CaL. However, in the case of DO3MA, a better fit between p[H]$_{obsd}$ and p[H]$_{calc}$ was observed when the existence of MHL and ML species was considered. For example sigma pH fit values were 0.023 and 0.108 for calculations with and without protonated species, respectively. Calculated values of the stability constants of ML and MHL and the protonation constants of ML are given in Table 3.

The stability constants of the complexes follow the order: Ca(DOTA)$^{2-}$ > Ca(HP-DO3A)$^-$ > Ca(DO3MA)$^-$ > Ca(DO3A)$^-$ > Ca(NOTA)$^-$, which is the order of basicity of the ligands. A good linear correlation exists between log K_{CaL}

(36) Bohemia, N. Y. SDP Structure Determination Package, ENRAF NONIUS. 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 2.2 A and 2.3.1.

and ΣpK_a (log $K_{CaL} = (0.51 \pm 0.02)\Sigma pK_a$, $r^2 = 0.99$) for the ligands which form five-membered chelate rings (Figure 1). This correlation is similar to the correlation for Gd^{3+} complexes given in Figure 1 (log $K_{GdL} = (0.85 \pm 0.02)\Sigma pK_a$, $r^2 = 0.99$). This reflects the ionic nature of calcium and lanthanide complexes. The ionic radii of Ca^{2+} (1.00 Å)[37] and lanthanides (0.977–1.144 Å)[38] are comparable.

An excellent linear correlation was also observed between the stability constants of Gd^{3+} and Ca^{2+} complexes (log $K_{GdL} = (1.4 \pm 0.1)$log $K_{CaL} + (2.5 \pm 1.2)$, $r^2 = 0.95$) with five- and six-membered chelate rings (Figure 2). This observation suggests that any differences in stability introduced by five- vs six-membered chelate rings for gadolinium chelates are the same for calcium chelates. We suggest that the stability constants of Gd^{3+} complexes can be predicted from the observed correlation and the known stability constant of a calcium complex. Traditionally, the stability constants of gadolinium complexes of macrocyclic polyamino carboxylates are difficult and tedious to measure and require indirect spectrophotometric methods due to their slow formation and equilibration. In contrast, the stability constants of calcium complexes of macrocyclic polyamino carboxylates can be determined by direct potentiometry.

In Figure 2, DTPA, DTPA-BMA, EGTA, and TTHA do not fall in this correlation but define another line with similar slope. Greater charge neutralization in the case of Gd^{3+} than Ca^{2+} is not responsible for this difference, as DTPA-BMA (3-), EGTA (4-), DTPA (5-), and TTHA (5-) fall on the same line. Alternately, we propose that Ca^{2+} does not take advantage of all donor atoms in the case of linear polyamino carboxylates due to their flexible nature. This is supported by the fact that the stability constant of Ca(EDTA)$^{2-}$ (10.61) is comparable to that of Ca(DTPA)$^{3-}$ (10.75). The coordination number of calcium in the crystal structure of Ca(EDTA)$^{2-}$ is eight, six donor atoms from EDTA and two coordinated waters.[27] Since the stabilities of DTPA and EDTA complexes of calcium are similar, it appears that the coordination behavior of DTPA type

Table 3. Stability Constants of Ca^{2+}, Cu^{2+}, Zn^{2+}, Na^+, Gd^{3+}, Y^{3+}, and Ce^{3+} Complexes of Some Macrocyclic Polyamino Carboxylates[a]

equilibrium	DO3A	HP-DO3A	DO3MA	DOTA	NOTA
[CaL]/[Ca][L]	11.74 ± 0.02	14.83 ± 0.09	13.82 ± 0.09	17.23^b	8.92^c
[CaHL]/[CaL][H]			5.76 ± 0.08	3.54^d	
[CaHL]/[Ca][HL]			6.2 ± 0.1	8.68^b	
log K_{CaL}' (pH 7.4)	5.71^e	8.24^e	6.09^e	10.26^e	4.70^e
[CuL]/[Cu][L]	22.87 ± 0.03	22.84 ± 0.07	22.7 ± 0.2	22.63^b	21.63^c
[CuHL]/[CuL][H]	3.2 ± 0.2	3.72 ± 0.08	4.2 ± 0.1	4.30^d	2.74^c
[CuHL]/[Cu][HL]	14.5 ± 0.1	14.6 ± 0.1	13.5 ± 0.2	14.42^b	12.96^d
[CuH$_2$L]/[CuHL][H}	2.8 ± 0.1	2.3 ± 0.3	2.3 ± 0.3	3.58^d	
[CuH$_2$L]/[Cu][H$_2$L]	8.02 ± 0.08	7.4 ± 0.2	6.7 ± 0.3	8.32^b	
log K_{CuL}' (pH 7.4)	16.84^e	16.25^e	15.17^e	15.66^e	17.41^e
[ZnL]/[Zn][L]	19.26 ± 0.05	19.37 ± 0.24	20.3 ± 0.5	21.05^b	18.3^f
[ZnHL]/[ZnL][H]	3.77 ± 0.09	3.7 ± 0.2	4.2 ± 0.5	4.19^d	
[ZnHL]/[Zn][HL]	11.45 ± 0.09	11.1 ± 0.3	11.1 ± 0.1	13.15^b	
[ZnH$_2$L]/[ZnHL][H]				3.54^d	
[ZnH$_2$L]/[Zn][H$_2$L]				7.01^b	
log K_{ZnL}' (pH 7.4)	13.23^e	12.78^e	12.58^e	14.08^e	14.03^e
[NaL]/[Na$^+$][L]	3.18^g	4.06^g		4.38^b	
log K_{NaL}' (pH 7.4)	-2.85^e	-2.53^e		-2.59^e	
[GdL]/[Gd][L]	21.0^g	23.8^g	25.3^i	25.3^g	13.7^h
log K_{GdL}' (pH 7.4)	14.97^e	17.21^e	17.57^e	18.33^e	9.48^e
[YL]/[Y][L]	21.1^g	22.2^g	25.2^i	24.3^g	
log K_{YL}' (pH 7.4)	15.07^e	15.61^e	17.47^e	17.33^e	
[CeL]/[Ce][L]	19.7^j	21.2^j		23.0^j	13.3^k
log K_{CeL}' (pH 7.4)	13.67^e	14.61^e		16.03^e	9.08^e

[a] At 25.0 ± 0.1 °C and $\mu = 0.1$ (TMACl). [b] Delgado, R.; Frausto Da Silva, J. J. R. *Talanta* **1982**, *29*, 815. [c] Bevilacqua, A.; Gelb, R. I.; Hebard, W. B.; Zompa, L. J. *Inorg. Chem.* **1987**, *26*, 2699. [d] Calculated from the stability constant for ML and MHL. [e] Calculated conditional stability constant at pH 7.4 with the use of eq 6. [f] Hama, H.; Takamoto, S. *Nippon Kagaku Kaishi* **1975**, 1182 (quoted in: Cortes, S.; Brucher, E.; Geraldes, C. F. G. C. Sherry, A. D. *Inorg. Chem.* **1990**, *29*, 5). [g] Reference 10. [h] Reference 14. [i] Reference 11. [j] Reference 7. [k] Estimated from a figure in ref 12.
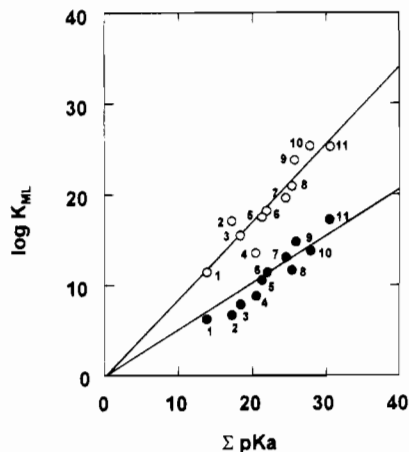

Figure 1. Plot of log K_{CaL} (●) and log K_{GdL} (○) vs the sum of the pK_a's of the ligands. The ligands used for these correlations are (1) NTA, (2) DTPA-BMA, (3) HEEDTA, (4) NOTA, (5) EDTA, (6) 1,2-PDTA, (7) CDTA, (8) DO3A, (9) HP-DO3A, (10) DO3MA, and (11) DOTA.

ligands is similar to that of EDTA, i.e., hexacoordination. Choppin and co-workers[23] also proposed hexacoordination of Ca^{2+} with EDTA, DTPA, and DTPA-BMA.

The crystal structure of Ca(DOTA)$^{2-}$ was reported by Anderson et al.[28] All of the donor atoms of DOTA are coordinated to the embedded octadentate calcium. The ligand is preorganized, and the macrocyclic ring in the complex is in the [3333] conformation, which explains the unusually high stability of the chelate, Ca(DOTA)$^{2-}$. Similarly, the X-ray crystal structure studies of Ca(HP-DO3A)$^-$ (vide infra) (also having a high log K value) suggested coordination of all donor atoms. The lower stability of Ca(HP-DO3A)$^-$ vs Ca(DOTA)$^{2-}$ is reflected in the lower basicity of the former ligand.

The size of Ca^{2+} is comparable to that of sodium and lanthanide ions; consequently, the coordination behavior of the Ca^{2+} metal ion is very similar to that of lanthanide ions. A
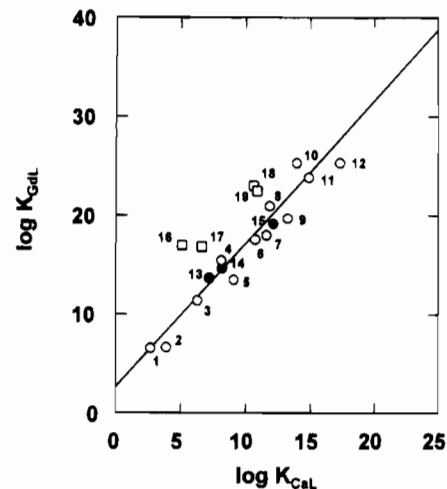

Figure 2. Correlation of log K_{GdL} with log K_{CaL} for some linear and macrocyclic polyamino carboxylates. The ligands which form the five-membered chelate ring (represented by open circles) are (1) IDA, (2) MIDA, (3) NTA, (4) HEEDTA, (5) NOTA, (6) EDTA, (7) 1,2 PDTA, (8) DO3A, (9) CDTA, (10) DO3MA, (11) HP-DO3A, and (12) DOTA. The ligands which form the five- and six-membered chelate rings (shown by solid circles) are (13) 1,3 PDTA, (14) TETA, and (15) TRITA. The DTPA type ligands (shown by squares) are (16) EGTA, (17) DTPA-BMA, (18) TTHA, and (19) DTPA.

plot of log K_{ML} (where L = HP-DO3A) vs Z/r, for several metal ions with variable charge density (Na^+, Ca^{2+}, Ce^{3+}, Y^{3+}, and Gd^{3+}), supported the preferred ionic binding of Na^+, Ca^{2+}, and Ln^{3+}. Data on Na^+ and Ln^{3+} complexes are taken from our previous work.[7,10] The ionic radii (Å) used were 1.02 for Na^+, and 1.00 for Ca^{2+}.[37] For lanthanide ions, the Shannon radii[38] were used for coordination numbers of nine or eight: 1.196 (Ce^{3+}), 1.075 (Y^{3+}), and 1.053 (Gd^{3+}). An excellent correlation

(37) Cotton, F. A.; Wilkinson, G. A. *Advanced Inorganic Chemistry*; John Wiley and Sons: New York, 1988.
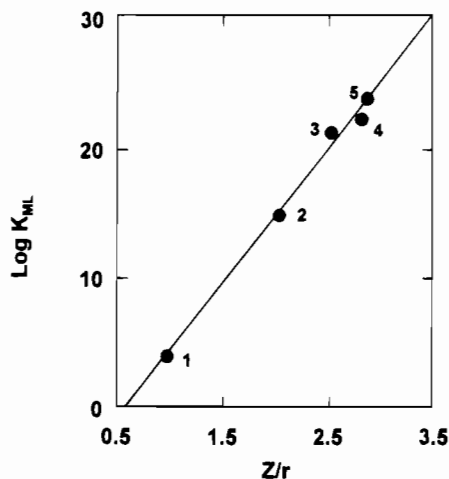(38) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

Figure 3. Plot of stability constants of some metal complexes of HP-DO3A vs the charge density of the metal, Z/r. The metals used are (1) Na^+, (2) Ca^{2+}, (3) Ce^{3+}, (4) Y^{3+}, and Gd^{3+}.

($\log K_{ML} = (10.5 \pm 0.5)Z/r - (6.1 \pm 1.3)$ with $r^2 = 0.99$) was seen, which was suggestive of the similar coordination behavior of these metal ions.

Complexation of Cu^{2+} and Zn^{2+} with the Ligands. Less than 0.2 equiv of protons was released upon mixing a 1:1 ratio of $CuCl_2$ and the ligands. These experiments suggested the probable formation of an equilibrium mixture of MH_2L, MHL, and ML species. The calculated values of the overall stability constants of the species and the protonation constants of the complexes are given in Table 3. Similarly, in the case of ZnL systems, the formation of ML and MHL was observed. Data were fitted for the possible formation of MH_2L type species. However, either the fit of pH_{obsd} and pH_{cal} did not improve or the protonation constant of MHL was <2 with large uncertainty. The formation of binuclear species, M_2L, in the solid state was demonstrated by Kaden and co-workers.[31] However, the formation of such species in solution is negligible under the conditions of our experiments. In agreement with the Irving–Williams series,[39] for a ligand, the $\log K$ value of the Cu^{2+} complex was higher than that of the Zn^{2+} complex.

The stability constants of Ca^{2+} complexes of the macrocyclic polyamino carboxylates in the present work vary by 8 orders of magnitude, e.g., 8.92 for $Ca(NOTA)^-$ vs 17.23 for $Ca(DOTA)^{2-}$. The stability constants of Cu^{2+} and Zn^{2+} complexes with different macrocyclic polyamino carboxylates are similar and of the same order of magnitude as those of the linear polyamino carboxylates, suggesting that not all donor atoms are coordinated to the metal. The crystal structures[29-31] of $H_2Cu(DOTA)^{2-}$ and $H_2Cu(TETA)^{2-}$, and our analysis of $HCu(DO3A)$ (*vide infra*) support this suggestion.

A comparison of the protonation constants of CaL and transition metal ion complexes is of interest. The protonation of DO3MA complexes is much higher than that of the complexes of DO3A and HP-DO3A, presumably due to the presence of more basic free carboxylate in the complex. A direct comparison of the protonation constants of $Ca(DOTA)^{2-}$ and DOTA complexes of transition metal ions can also be made. The protonation constants of smaller transition metal ion complexes are generally higher than the protonation constant of $Ca(DOTA)^-$. This again is consistent with the lower coordination number of transition metals vs calcium or lanthanides.

The stability constants of the protonated species MHL and MH_2L were calculated from the stability constants of the

chelates and the protonation constants of the chelates and the ligand (Tables 1 and 3). It is proposed that the ligands in MHL are pentadentate, as the stability constants of CaHL, CuHL, and ZnHL are larger than those of corresponding $M(EDDA)$ complexes and smaller than those of $M(EDTA)^{2-}$ complexes.

Conditional Stability Constants of Gd^{3+} Complexes and Selectivity of the Ligands for Gd^{3+}. A knowledge of the conditional stability constants of the metal chelates under physiological conditions (pH 7.4) is useful in the context of biological studies[40] and in terms of understanding relative stability. The conditional stability constant can be calculated by using eq 6. Under physiological conditions there is a significant proton competition depending on the basicity of the ligand, which differs among the ligands. For example the DOTA and DO3MA complexes of Gd^{3+} are equally stable; however, at pH 7.4, the DO3MA complex is an order of magnitude less stable than the DOTA complex. Similarly, Gd-(NOTA) is 11.6 orders of magnitude less stable than $Gd(DOTA)^-$; however, at pH 7.4 the NOTA complex is only 9 orders of magnitude less stable. The conditional stability constants of the gadolinium chelates at pH 7.4 are given in Table 3.

The logarithmic selectivity constant, $\log K_{sel}$, of the ligands for Gd^{3+} over other metal ions is the difference between the $\log K_{GdL}$ and the stability constant of the metal complex, $\log K_{ML}$ (where $M = Ca^{2+}$, Cu^{2+}, and Zn^{2+}), individually. The calculated $\log K_{sel}$ values for Gd^{3+} over individual metal ions for DO3A, HP-DO3A, DO3MA, DOTA, and NOTA are 9.26, 8.97, 11.48, 8.07, 4.78 (for Gd^{3+} over Ca^{2+}), -1.87, 0.96, 2.40, 2.67, -7.93 (for Gd^{3+} over Cu^{2+}), and 1.74, 4.43, 4.99, 4.25, -4.60 (for Gd^{3+} over Zn^{2+}), respectively.

Although $\log K_{sel}$ for Gd^{3+} against other metal ions gives some idea of displacement of Gd^{3+} in the chelate by other endogenously available ions, the thermodynamic stability constant, K_{ML}, can be used to calculate a modified selectivity constant, K_{sel}', with the use of eq 7.[24]

$$K_{sel}' = K_{ML}(\alpha_H^{-1} + \alpha_{CaL}^{-1} + \alpha_{CuL}^{-1} + \alpha_{ZnL}^{-1})^{-1} \quad (7)$$

where α's are the side reaction coefficients which are defined below (eqs 8–11):

$$\alpha_H^{-1} = 1 + K_1[H^+] + K_1K_2[H^+]^2 + K_1K_2K_3[H]^3 + ... \quad (8)$$

K_1, K_2, and K_3 are the consecutive ligand protonation constants (Table 1).

$$\alpha_{CaL}^{-1} = 1 + K_{CaL}[Ca^{2+}] \quad (9)$$

$$\alpha_{CuL}^{-1} = 1 + K_{CuL}[Cu^{2+}] \quad (10)$$

$$\alpha_{ZnL}^{-1} = 1 + K_{ZnL}[Zn^{2+}] \quad (11)$$

The in vivo concentrations of Ca, Cu, and Zn in plasma are taken from the literature[25] as 2.5 mM, 1 μM, and 50 μM. The stability constants of the corresponding chelates are given in Table 3. The calculated $\log K_{sel}'$ (given in parentheses) values at pH 7.4 for the Gd(III) complexes follow the order $Gd(DOTA)^-$ (8.3) ~ Gd(DO3MA) (8.3) > Gd(HP-DO3A) (6.95) > Gd-(DO3A) (4.13) > Gd(NOTA) (-1.94), suggesting that NOTA has lowest selectivity for Gd^{3+} in vivo. The ligands DOTA, DO3MA, and HP-DO3A appear to have comparable selectivity and should have comparable toxicity due to metal ion displacement reactions in vivo. However, the observed tolerance for

(39) Irving, H.; Williams, R. J. P. *Nature* **1948**, *162*, 746.

(40) Wedeking, P.; Kumar, K.; Tweedle, M. F. *Magn. Reson. Imaging* **1992**, *10*, 641.
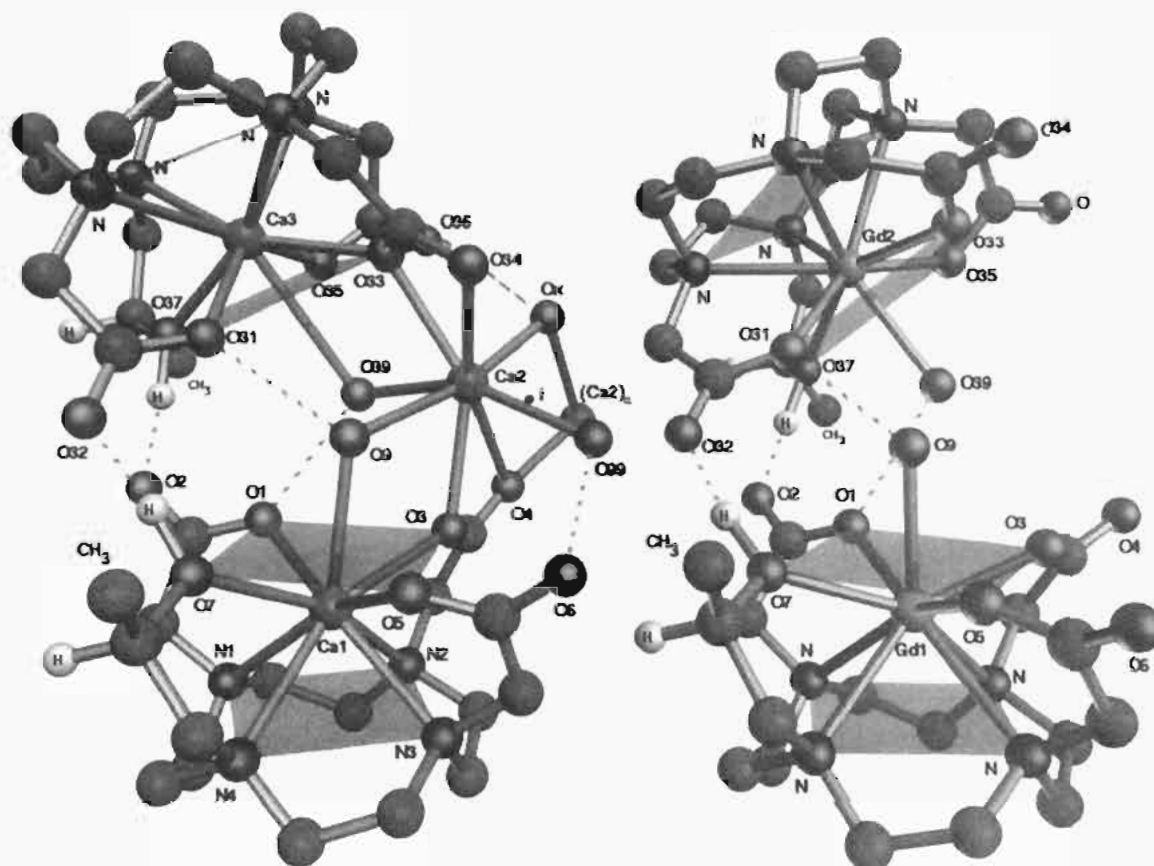
Figure 4. Solid-state structures of the trinuclear complexes of Ca[Ca(HP-DO3A)]₂ (left) and Gd(HP-DO3A) (right).[10] The inversion center and atom (Ca2)ₙ are present only in the α structure, in which case Ox is the invert of O4. A crystallographic twofold axis (horizontal) passes through Ca2 in the β and γ structures and Ox is equivalent to O99.

Gd^{3+} complexes (in terms of intravenous LD_{50} in mice) is DOTA ~ HP-DO3A > DO3A.[41] Tolerance data on Gd(NOTA) are not known. It is proposed that the relative tolerance of macrocyclic polyamino carboxylate complexes of Gd^{3+} cannot be explained by selectivity constants but by kinetic inertia, acid-assisted dissociation, and metal-exchange rates.

Crystal Structure Studies of Ca[Ca(HP-DO3A)]₂. The racemic complex Ca[Ca(HP-DO3A)]₂ crystallizes in several hydrated structures, three of which have been obtained and studied as single crystals: form α, a centrosymmetric hexa-nuclear structure {Ca(H₂O)₃[Ca(HP-DO3A)]₂·3H₂O}₂; form β, a trinuclear structure Ca(H₂O)₄[Ca(HP-DO3A)]₂·10H₂O; form γ, a trinuclear structure Ca(H₂O)₄[Ca(HP-DO3A)]₂·2H₂O which results from a topotactic single crystal → single crystal transformation when form β partially dehydrates during exposure to ambient laboratory conditions (22 °C, 35% relative humidity) over a period of ~6−20 h. The β and γ forms differ structurally only though the number and arrangement of "lattice" water molecules (those not directly coordinated to any calcium ion).

The molecular structures and conformations of the anionic complexes Ca(HP-DO3A)⁻ are virtually identical in all three crystal structures (Figure 4). Moreover, in each structure, two anions are joined through a water molecule (O9 and O39) and a multidentate carboxyl group (O3,O4 and O33, O34) to an octacoordinated calcium cation, Ca2, so as to form essentially the same C2 symmetric trinuclear unit (C2 axis through Ca2;

Ca2−O9 = 2.45(2) Å,[42] Ca2−O3 = 2.43(1) Å, Ca2−O4 = 2.63(2) Å). The twofold symmetry is crystallographically imposed in the β and γ forms, which further have two water molecules (O99 and its symmetry equivalent Ox) coordinated to the bridging calcium (Ca2−O99 = 2.39(2) Å). In the α form the twofold symmetry of the trinuclear unit is noncrystallo-graphic; however, the unit is further dimerized to form a centrosymmetric hexanuclear structure in which the symmetry equivalent oxygen Ox = O4 is substituted for one of the waters coordinated to Ca2 (Ca2−Ox = 2.314 Å) in the β and γ forms. The two anionic complexes of each trinuclear unit are further associated at the other end through two hydrogen bonds involving the secondary hydroxyl groups (O7 and O37) and carboxyl oxygens O32 and O2 (O- - -O distance = 2.68(4) Å).

One of the waters (O9 or O39) of each hydrated cation lies directly above the embedded calcium (Ca1 or Ca3), *in a position entirely analogous to the ninth (water) ligand of gadolinium* in the corresponding complex Gd(H₂O)(HP-DO3A)[10] (Figure 4; Gd1−O9 = 2.502 Å; Ca1−O9 = 2.792 and 2.722 Å in forms β and γ and 2.698 and 3.231 Å in form α). The striking structural similarity between the Gd and Ca complexes is further evident from a superposition of O9 and the twenty-eight C, N, and O atoms of the macrocyclic ligand in Gd(H₂O)(HP-DO3A) and Ca(H₂O)(HP-DO3A)⁻ (form β), root mean square deviation = 0.246 Å. Moreover, a comparable fit (root mean square deviation = 0.282 Å) results when O39, O31, O33, O35, and O37 from the associated complex are included in the superposi-

(41) The reported values are as follows: 11 for Gd(DOTA)⁻ (Meyer, D.; Schaefer, M.; Daucet, D. *Invest. Radiol.* **1990**, *25*, 553), 12 for Gd(HP-DO3A) (Runge, V. M.; Gelblum, D. Y.; Jacobson, S. *Magn. Reson. Imaging* **1991**, *9*, 79), and 7−9 for Gd(DO3A) (Unpublished work).

(42) All distances are given in angstroms. Except where noted, distances for Ca[Ca(HP-DO3A)]₂ are averages over all three crystal forms. Numbers in parentheses are average deviations for the least significant figures.

Table 4. Comparison of Some Crystal Structure Parameters for Some Calcium and Gadolinium Complexes

complex	ring conf	d_N, Å	d_O, Å	d_{M-N}[a]	d_{M-O}[a]	d_{H_2O}[a]
Ca[Ca(HP-DO3A)]$_2$	[3333]	1.63(4)	0.92(4)	2.66(4)	2.41(2)	2.86(18)
Ca(DOTA)[b]	[3333]	1.53(2)	1.08(1)	2.59(2)	2.42(3)	
Gd(HP-DO3A)[c]	[3333]	1.65(3)	0.76(1)	2.66(3)	2.37(4)	2.502(5)
Gd(DOTA)[d]	[3333]	1.632	0.715	2.66(1)	2.368(8)	2.463
Y(HP-DO3A)[c]	[3333]	1.63(5)	0.80(3)	2.65(3)	2.32(4)	2.488(4)
Y(DOTA)[d]	[3333]	1.616	0.718	2.6591)	2.323(3)	2.437

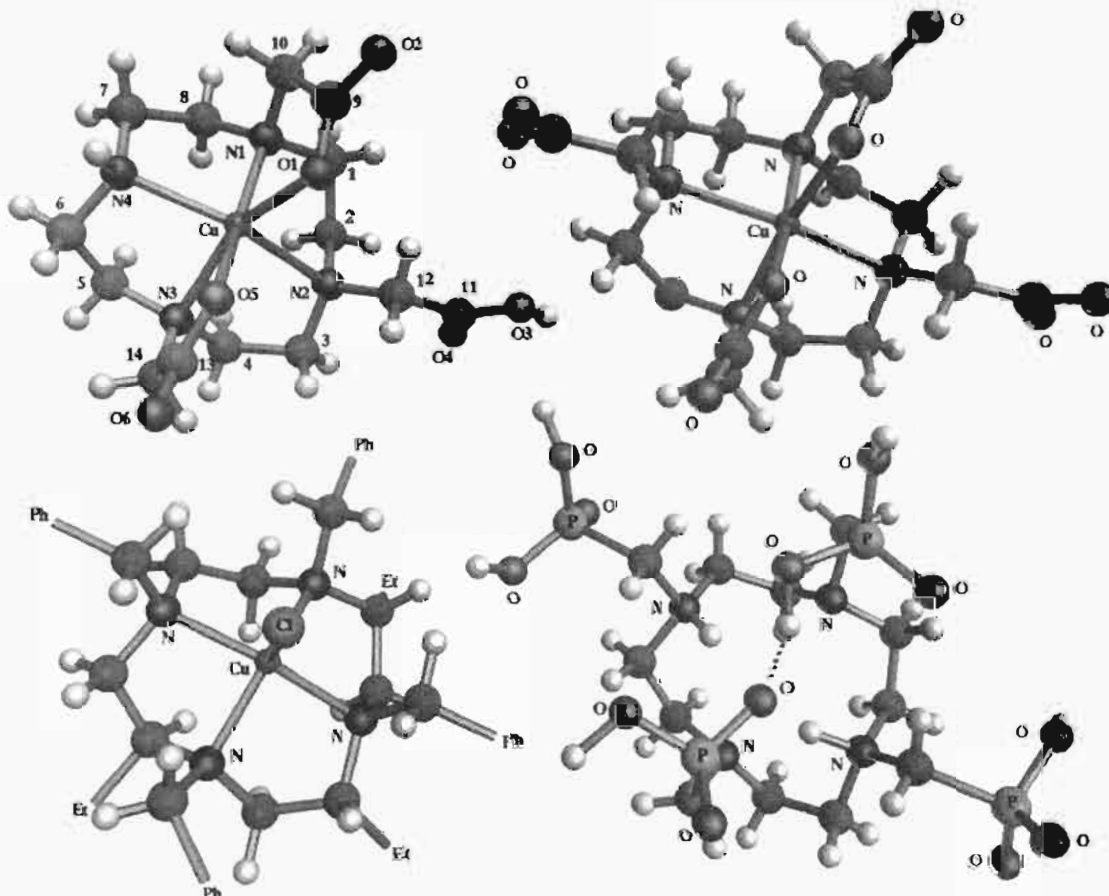[a] Average distance (one deviation) to metal. [b] Reference 28. [c] Reference 10. [d] Reference 48.

Figure 5. Perspective drawing of the conformation in the crystal structures of copper complexes of DO3A (top left), DOTA (top right),[29-31] tetrabenzyltetraethyl[12]ane N$_4$[46] (bottom left) ligands, and the free ligand, DOTP (bottom right).[47]

tion, despite the absence of a bridging cation and the presence of a diastereomeric macrocyclic conformation in the associated Gd structure.

As in the structure of the α form, the crystal structure of CaDOTA^{2-} also contains similar trinuclear units which are further linked through centrosymmetric water bridges between Ca2 type cations. The higher molecular symmetry of the CaDOTA^{2-} ligand and anionic complex is crystallographically imposed on the trinuclear unit (crystallographic C2 axis through Ca1 and Ca3), which accordingly is linked at both ends through centrosymmetric Ca2 water bridges, resulting in a polymeric association of cationic and anionic nuclei. In this arrangement, the "9th" water (O9 and O39) lies much further (4.09 Å) from the embedded calciums, Ca1 and Ca3.

The embedded metal of each anion lies between the least-squares plane of the four coordinating nitrogen atoms and the nearly parallel plane of the four coordinating oxygen atoms of the macrocyclic ligand. Displacements of the metal from these planes, d_N and d_O, as well as average metal−oxygen and metal−nitrogen distances are presented in Table 4 together with

corresponding data for other related complexes. In all cases, the macrocyclic ligand adopts a quadrangular [3333] conformation.[43]

Crystal Structure Studies of HCu(DO3A). As in the previously reported crystal structures of the Cu^{2+} complexes with DOTA$^{29-31}$ (and the isostructural Ni^{2+} and Zn^{2+} complexes^{29,44}), the Cu^{2+} in Cu(DO3A) is octahedrally coordinated to the four nitrogens and two (opposite) carboxylate arms, while the other protonated carboxyl group(s) is turned away from the Cu atom (Figure 5; Cu−O = 1.923(4) and 2.077(4) Å in Cu-(DO3A) and 1.965(5) Å in Cu(DOTA)$^{29-31}$). However, the DOTA and DO3A macrocycles have different conformations: the C_{2v} symmetric [2424] DOTA conformation has a short (3.343 Å) and a long (4.505 Å) transannular N−N distance (Cu−N distances are 2.107(5) and 2.318(6) Å), while in the [2334] conformation of Cu(DO3A) the transannular distances are intermediate (3.742 and 4.277(6) Å; Cu−N distances for N1−N4 are 2.028, 2.390, 2.391, and 2.183(6) Å, respectively).

(43) Dale, J. *Isr. J. Chem.* **1980**, *20*, 3.
(44) Riesen, A.; Zehnder, M.; Kaden, T. A. *Acta Crystallogr.* **1991**, *C47*, 531.

Bond angles involving the metal in Cu(DO3A) are given in the supporting information. Although similar [2334] conformations have been previously observed in the pentacoordinated copper complexes of pentaazabicyclo[7.5.5]nonadecane and tetrabenzyltetraethyl[12]ane N_4 ligands[45,46] and in the free ligand DOTP,[47] the DO3A macrocycle has previously been found only in the square [3333] conformation.[48,49] We note that in contrast with Cu, the Fe complexes of both DO3A and DOTA adopt the same [3333] macrocyclic conformation.

Topotactic Dehydration of Ca[Ca(HP-DO3A)]₂. Spontaneous decomposition of a single crystal of the β form results in a moderately well-ordered single crystal of the γ form, despite the remarkable loss of thirty-two lattice water molecules from the unit cell and the corresponding decrease of 713 Å³ (13%) in unit cell volume. The space group, unique direction of monoclinic symmetry, b, and $C2$ crystallographic symmetry of the trinuclear unit (TNU) are spatially preserved in the transformation, and there is no twinning of the γ daughter phase.[35] In addition to the alignment of $+b$ axes (9.516 and 9.373 Å for the β and γ structures, respectively), the topotaxy is characterized by a parallel alignment of the ($\overline{2}$01) planes ($d_{(\overline{2}01)}$ =16.21 and 16.39 Å for β and γ structures).

The transformation only involves the loss of lattice waters (not directly coordinated to calcium). Four nonlattice water molecules coordinated to one (O99 and Ox; see Figure 4) or two (O9 and O39) calcium atoms of the TNU are retained during transformation. In addition to an intranuclear hydrogen bond (O99, Ox- - -O6, O36 = 2.859 and 2.78 Å in the β and γ

structures, respectively), O99 and Ox form strong internuclear hydrogen bonds between translationally related TNUs along the conserved b axes (O99, Ox- - -O2, O32 = 2.784 and 2.70 Å for β and γ). The five symmetry-independent lattice waters of the β structure are hydrogen bonded to each other and oxygens of neighboring TNUs to form infinite molecular layers parallel to (001), but they are not retained during transformation. The sole lattice water O98 (and O98′) of the γ structure is hydrogen bonded to two carbonyl oxygens of one TNU (O98- - -O6 = 2.91 and O10- - -O36 = 3.02 Å). Accordingly, only the infinite b-translational chains of hydrogen-bonded TNUs are conserved during dehydration. The lattice waters presumably escape along the tubular solvent channels which extend parallel to b throughout a single crystal of the β hydrate.

Conclusions

The solid-state and solution studies suggest that Ca^{2+}, like Gd^{3+}, prefers ionic binding. A good correlation between log K_{GdL} and log K_{CaL} is observed, which is useful in predicting stability constants of unknown Gd^{3+} complexes of macrocyclic polyamino carboxylates. The relative tolerance of Gd^{3+} complexes of macrocyclic polyamino carboxylates cannot be explained by the selectivity constants but can be explained by kinetic inertia.

Supporting Information Available: Tables listing details of data collection, fractional atomic coordinates, hydrogen positional parameters, bond distances, bond angles, and anisotropic temperature factors, for the crystal structures of three forms of Ca[Ca(HP-DO3A)]₂ and HCu(DO3A), a figure depicting the molecular rearrangement in the topotactic conversion of Ca[Ca(HP-DO3A)]₂, and tables listing raw titration data and curves (51 pages). Ordering information is given on any current masthead page.

IC950765L

(45) Ciampolini, M.; Micheloni, M.; Vizza, F.; Zanobini, F.; Chimichi, S.; Dapporto, P. *J. Chem. Soc., Dalton Trans.* **1986**, 505.
(46) Tsuboyama, S.; Kobayashi, K.; Sakurai, T.; Tsuboyama, K. *Acta Crystallogr., Sect. C* **1984**, 1178.
(47) Lazar, I.; Hrncir, D. C.; Won-Dae, K.; Kiefer, G. E.; Sherry, A. D. *Inorg. Chem.* **1992**, *31*, 4422.
(48) Chang, C. A.; Francesconi, L. F.; Malley, M. F.; Kumar, K.; Gougoutas, J. Z.; Tweedle, M. F.; Lee, D. W.; Wilson, L. F. *Inorg. Chem.* **1993**, *32*, 3501.
(49) Riesen, A.; Kaden, T. A.; Ritter, W.; Maecke, M. R. *J. Chem. Soc., Chem. Commun.* **1989**, 460.