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Correlation of Relaxivity with Coordination Number in Six-, Seven-, and Eight-Coordinate Mn(II) Complexes of Pendant-Arm Cyclen Derivatives

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Abstract

The syntheses and characterization of several complexes of Mn(II) with cyclen derivatives having variable numbers of pendant *N*-acetic acid or *N*-acetamide arms are reported. X-ray crystallographic results are presented for Mn(DOTAM)Cl₂·2H₂O (monoclinic *C*2/*c*, *a*=18.5798(15), *b*=13.6006(11), *c*=10.5800(8) Å, β=110.490(1)°, *Z*=4), [Mn(DO3AM)][MnCl₄]·EtOH (monoclinic *P*2₁/*n*, *a*=8.366(8), *b*=19.483(2), *c*=16.3627(16) Å, β=99.254(2)°, *Z*=4), and Mn(H₂DOTA) (monoclinic *C*2/*c*, *a*=16.374(3), *b*=6.6559(13), *c*=16.750(3) Å, β=98.381(3)°, *Z*=4), which exhibit 8-, 7-, and 6-coordinate Mn(II), respectively. ¹H relaxivity data in water at 20 MHz and 37°C is presented and interpreted in terms of a mechanism involving transient binding of water in an associative intermediate. Relaxivity studies in mixed water/methanol solvents are consistent with this interpretation.

INTRODUCTION

Manganese(II) complexes are attractive as potential MRI contrast agents since they have relatively high electronic spins (5/2), fast water exchange rates, and Mn²⁺(aq) has a lower intrinsic toxicity than many other paramagnetic metal ions, such as Gd³⁺.^{1–5} While recent advances have been made in the search for water soluble manganese-based small molecule contrast agents,^{6–12} only two Mn²⁺-containing contrast agents have been approved for clinical use. [Mn(dipyridoxyldiphosphate)]^{4–} is the paramagnetic component of Teslascan®, a liver imaging agent^{13,14} while LumenHance®, which contains MnCl₂, is employed in GI imaging.¹⁵

Since Mn²⁺ is substitutionally labile, chelating ligands are required in order to ensure the thermodynamic and kinetic stability of the complexes. Cyclic polyamine ligands are attractive candidates, but Mn²⁺ complexes of cyclen (1,4,7,10-tetraazacyclododecane) and related ligands are known to oxidize readily in air to give dimers or insoluble polymers.^{16–23} This is unfortunate since ligands such as cyclen and its derivatives have a rich aqueous chemistry with other metal ions.^{24–26} Attaching pendant arms (generally via the nitrogen atoms of the ring) that can also coordinate the metal leads to higher denticity of binding and has proved to be a useful strategy for further stabilizing labile complexes.^{27,28}

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Supporting Information **Available:** Details of the crystallographic analyses (including data collection and refinement details, atomic coordinates and isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, and analysis of hydrogen bonding), fits of relaxation data in mixed MeOH:H₂O solvent, and summary of electrochemical data (28 pgs). This material is available free of charge via the Internet at <http://pubs.acs.org>.

Given the potential of Mn^{2+} complexes as MRI contrast agents, we have developed an interest in more fully understanding the chemical features of these complexes that influence their relaxivities. In this context, it is instructive to explore structure/relaxivity correlations in a series of chemically and structurally related complexes. We report herein on the synthesis, X-ray crystal structures, and solution characterization of several complexes of Mn(II) with the pendant-arm cyclen derivatives shown in Scheme 1. Structural analyses demonstrate that in the solid state the coordination numbers range from 6 to 8. Evidence outlined below suggests that the mechanism of water ^1H relaxivity in the 6- and 7-coordinate cases involves transient binding of water to the metal ion in an associative process. This pathway is not available to the 8-coordinate complex $[\text{Mn}(\text{DOTAM})]^{2+}$. The most pronounced correlation appears to be that of higher coordination number with lower relaxivity. The results are also of interest since they suggest that metal complexes without bound water molecules may still dynamically interact with bulk water and exhibit significant relaxivities.

EXPERIMENTAL

Manganese salts were obtained from Strem Chemicals, Inc. 1,4,7,10-tetraazacyclododecane (cyclen) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (H_4DOTA) were obtained from Macrocyclics. All other starting materials were obtained from Sigma-Aldrich and used as received. 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetamide (DOTAM),²⁹⁻³¹ 1,4,7,10-tetraazacyclododecane-1,7-diacetic acid ($\text{H}_2\text{DO}_2\text{A}$),³² and 1,4,7,10-tetraazacyclododecane-1-(2-hydroxylcyclohexyl) (cyclen-CyOH)³³ were synthesized by published methods. All the complexes are air-stable and no precautions to exclude oxygen were necessary during the syntheses.

Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Mass spectra were obtained using a Waters 2795 HPLC system with ZQ single quadrupole MS and an electrospray ionization source. Samples were introduced using loop injection. IR spectra were obtained as KBr pellets on a Perkin-Elmer Spectrum BX FT-IR System. ^1H and ^{13}C NMR spectra were obtained in D_2O using a Varian Mercury spectrometer operating at 300 MHz. Cyclic voltammograms were obtained on a CH Instruments (Austin, TX) 650-A Electrochemical System with electronic iR compensation using a glassy carbon working electrode, SCE reference, and Pt wire counter electrode. The aqueous solutions used for electrochemistry contained 0.1 M NaNO_3 as supporting electrolyte.

$[\text{Mn}(\text{DOTAM})]\text{Cl}_2 \cdot 3\text{H}_2\text{O}$. DOTAM (0.502 mmol) in 30 mL of 80% methanol was heated at reflux and $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (0.550 mmol) was added. The solution quickly became pale yellow, after which it was stirred for two hours and allowed to cool. Ethanol (40 mL) was added and the combined solvents were allowed to evaporate. The product was recrystallized from water to give crystals of the dihydrate suitable for X-ray crystallographic analysis. (Yield 0.2909 g, 99.9% based on DOTAM) Anal. Calcd for $\text{C}_{16}\text{H}_{38}\text{N}_8\text{O}_7\text{MnCl}_2$: C, 33.11; H, 6.60; N, 19.31. Found: C, 32.88; H, 6.20; N, 19.11. Mass spectrum (ESI-MS: $m/z = 227.75$, $[\text{Mn}(\text{DOTAM})]^{2+}$). IR (KBr pellet) 1655 cm^{-1} , $\nu(\text{C}=\text{O})$.

$[\text{Mn}(\text{DO}_3\text{AM})][\text{MnCl}_4] \cdot \text{EtOH}$. Cyclen (5.8 mmol) and NEt_3 (6.1 mmol) were heated at reflux in 30 mL ethanol. Over a period of 3 hrs, chloroacetamide (5.8 mmol) in 15 mL ethanol was added dropwise. The mixture was allowed to stir for another hour, then an additional 5.8 mmol of chloroacetamide in ethanol was added dropwise over an additional 3 hrs. $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (1.38 mmol) in 10 mL methanol was then added. A white powder precipitated at once and, after cooling, was collected by suction filtration, and washed with 40 mL methanol. The product was recrystallized by diffusion of ethanol into an aqueous solution of the complex, producing crystals suitable for X-ray crystallographic analysis. The overall yield was 0.632 g (17% based on cyclen). Anal. Calcd for $\text{C}_{16}\text{H}_{35}\text{N}_7\text{O}_4\text{Mn}_2\text{Cl}_4$: C, 29.95; H, 5.46; N, 15.29. Found: C, 29.90;

H, 5.44; N, 15.33. Mass spectrum (ESI-MS: $m/z = 199.27$, $[\text{Mn}(\text{DO3AM})]^{2+}$). IR (KBr pellet) 1653 cm^{-1} , $\nu(\text{C}=\text{O})$.

$[\text{Mn}(\text{DO3AM})]\text{Cl}_2 \cdot 5\text{H}_2\text{O}$. $[\text{Mn}(\text{DO3AM})][\text{MnCl}_4] \cdot \text{EtOH}$ was dissolved in a minimum of water and acetone was allowed to slowly diffuse into the solution. Pale pink crystals of $\text{MnCl}_2 \cdot 6\text{H}_2\text{O}$ developed over a period of about 40 days. After crystal formation ceased, the remaining solution was collected and allowed to evaporate, giving the product as a white powder in approximately 99% yield. Mass spectrum (ESI-MS: $m/z = 199.03$, $[\text{Mn}(\text{DO3AM})]^{2+}$). Anal. Calcd for $\text{C}_{14}\text{H}_{35}\text{N}_7\text{O}_6\text{MnCl}_2$: C, 30.61; H, 5.32; N, 17.85. Found: C, 30.14; H, 5.55; N, 17.03. IR (KBr pellet) 1655 cm^{-1} , $\nu(\text{C}=\text{O})$.

1,4,7,10-tetraazacyclododecane-1-(2-hydroxycyclohexyl)-4,7,10-triacetamide (DO3AM-CyOH). Cyclen-CyOH (3.7 mmol), 2-chloroacetamide (11.3 mmol), and triethylamine (11.3 mmol) were heated at reflux in 35 mL EtOH for three hours. After the reaction mixture cooled, 30 mL of Et_2O were added and white precipitate formed. The precipitate was collected by suction filtration and washed twice with 30 mL aliquots of Et_2O . The white powder became a slightly yellow oil on standing in air, but was reprecipitated with a 9:1 mixture of acetone and methanol. The powder was collected and washed with acetone to give a 45% yield of DO3AM-CyOH. Anal. Calcd for $\text{C}_{20}\text{H}_{39}\text{N}_7\text{O}_4 \cdot 2.5\text{H}_2\text{O}$: C, 49.58.12; H, 9.00; N, 20.16. Found: C, 49.53; H, 8.98; N, 20.13. ^1H NMR: 1.1-4.2 (m) $-\text{CH}_2-$, $-\text{CH}$. ^{13}C NMR: 22.7, 23.4, 24.0, 24.6, 42.3, 46.5, 47.0 $-\text{CH}_2-$; 33.8 $-\text{CH}$; 51.6 $-\text{CH}(\text{OH})-$; 66.5, 67.4 $-\text{CH}_2\text{CONH}_2$; 126.3 $-\text{C}(\text{O})\text{NH}_2$. Mass spectrum (ESI-MS: $m/z = 442.4$, $[\text{DO3AM-CyOH} + \text{H}^+]$). IR (KBr pellet) 1672 cm^{-1} , $\nu(\text{C}=\text{O})$.

$[\text{Mn}(\text{DO3AM-CyOH})]\text{Cl}_2 \cdot 3\text{H}_2\text{O}$. DO3AM-CyOH (0.3366 mmol) in 30 mL of ethanol was heated at reflux and $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (0.3366 mmol) in 10 mL methanol was added dropwise. After 30 min, the solvent was evaporated to give a pale yellow solid, which was washed with acetone and dried. (Yield 0.2189g, 99% based on DO3AM-CyOH) Anal. Calcd for $\text{C}_{20}\text{H}_{49}\text{N}_7\text{O}_9\text{MnCl}_2$: C, 36.52; H, 7.45; N, 14.90. Found: C, 36.34; H, 7.41; N, 14.84. Mass spectrum (ESI-MS: $m/z = 248.20$, $[\text{Mn}(\text{DO3AM-CyOH})]^{2+}$). IR (KBr pellet) 1664 cm^{-1} , $\nu(\text{C}=\text{O})$.

$\text{Mn}(\text{H}_2\text{DOTA}) \cdot 2\text{H}_2\text{O}$. $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ (0.15 mmol) was dissolved in approximately 0.5 mL water, H_4DOTA (0.15 mmol) was added, and the mixture stirred for 30 min. The water was allowed to evaporate and the product precipitated as a white powder. (Yield 0.0756g, 99% based on $\text{MnSO}_4 \cdot \text{H}_2\text{O}$) Anal. Calcd for $\text{C}_{16}\text{H}_{30}\text{N}_4\text{O}_{10}\text{Mn}$: C, 38.99; H, 6.00; N, 11.35. Found: C, 38.48; H, 5.91; N, 11.22. Mass spectrum (ESI-MS: $m/z = 458.02$, $[\text{Mn}(\text{H}_2\text{DOTA}) + \text{H}^+]$). IR (KBr pellet) 1736 cm^{-1} , $\nu(\text{C}=\text{O}, \text{uncoordinated } -\text{COOH})$; 1579 cm^{-1} , $\nu(\text{C}=\text{O}, \text{coordinated } -\text{COO}^-)$. Pale yellow crystals of the anhydrous salt suitable for X-ray crystallographic analysis were grown by diffusing acetone into an aqueous solution of the complex.

$\text{Mn}(\text{DO2A}) \cdot 2\text{H}_2\text{O}$. $\text{H}_2\text{DO2A}$ (0.27 mmol) was dissolved in approximately 0.5 mL water and $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$ (0.27 mmol) was added. The mixture was stirred for several minutes and the solvent was allowed to evaporate. The product precipitated as a white powder. (Yield 0.1007 g, 99% based on $\text{H}_2\text{DO2A}$) Anal. Calcd for $\text{C}_{12}\text{H}_{26}\text{N}_4\text{O}_6\text{Mn}$: C, 38.20; H, 6.89; N, 14.85. Found: C, 38.19; H, 6.86; N, 14.95. Mass spectrum (ESI-MS: $m/z = 342.01$, $[\text{Mn}(\text{DO2A}) + \text{H}^+]$). IR (KBr pellet) 1612 cm^{-1} , $\nu(\text{C}=\text{O})$.

For several of the complexes, competitive EDTA binding studies were carried out by preparing 2:1 molar ratios of EDTA and metal complex ($\sim 1\text{mM}$) in water at pH 7.0. The T_1 values of the solutions were monitored periodically for several days. In no case was a detectable change of T_1 observed.

Relaxivity Measurements

Longitudinal relaxation rates (T_1) were obtained using a Bruker Minispec mq20 spectrometer operating at 20 MHz and 37°C using the standard saturation-recovery pulse sequence ($[90^\circ - \tau - 90^\circ]$ where τ is a variable delay time) provided by Bruker. Twenty scans were averaged for each of twenty saturation delay intervals which were used to define the magnetization curve. Fitting of the magnetization curves in aqueous solutions to a mono-exponential recovery was carried out using routines provided by Bruker. All aqueous magnetization data were successfully fit with mono-exponential curves and there was no evidence for bi-exponential behavior at any concentration. Data in mixed 1:1 mole fraction $H_2O:MeOH$ was similarly obtained, but using fifty delay intervals and fit to a bi-exponential expression using a Marquardt-Levenberg algorithm.³⁴ Fits of T_1^{-1} vs concentration were carried out using standard linear least squares fitting approaches and the slopes of the plots are reported as the relaxivities, R_1 .

X-Ray Crystallography

X-ray Crystallographic analyses were carried out by the X-ray Crystallographic Laboratory at the Department of Chemistry, University of Minnesota. Table 1 contains data collection and solution parameters for all reported structures. Full details are given in the Supporting Material. Suitable single crystals of $[Mn(DOTAM)]Cl_2 \cdot 2H_2O$, $[Mn(DO3AM)][MnCl_4] \cdot EtOH$, and $Mn(H_2DOTA)$ were each placed onto the tips of 0.1 mm diameter glass capillaries and mounted on a Bruker CCD area detector diffractometer for data collection at 173 K. The data collection was carried out using $MoK\alpha$ radiation (graphite monochromator) with a frame time of 10 sec for $[Mn(DOTAM)]Cl_2 \cdot 3H_2O$ and 60 sec for $[Mn(DO3AM)][MnCl_4] \cdot EtOH$ and $Mn(H_2DOTA)$ with a detector distance of 4.9 cm in each case. The complete sphere of reciprocal space was surveyed to a resolution of 0.77 Å for $[Mn(DOTAM)]Cl_2 \cdot 3H_2O$ and 0.84 Å for $Mn(H_2DOTA)$. For $[Mn(DO3AM)][MnCl_4] \cdot EtOH$ a randomly oriented region of reciprocal space was surveyed to the extent of 1.5 hemispheres and to a resolution of 0.84 Å. The intensity data were corrected for absorption and decay (SADABS).³⁵ Final cell constants were calculated from the xyz centroids of strong reflections (3505 for $[Mn(DOTAM)]Cl_2 \cdot 3H_2O$, 2813 for $[Mn(DO3AM)][MnCl_4] \cdot EtOH$, and 2827 for $Mn(H_2DOTA)$) from the data collection after integration (SAINT 6.01, 1999).³⁶ The structures were solved using SIR92³⁷ and refined using SHELXL-97.³⁸ The final full matrix least squares refinement parameters for each crystal are given in Table 1. The program PLATON was used for verifying the structures.³⁹

RESULTS AND DISCUSSION

Synthesis and Stability of Complexes

The complexes whose syntheses are reported in the experimental section have not been previously isolated. $Mn(H_2DOTA)$ ⁴⁰⁻⁴² and $Mn(DO2A)$ ⁴² have been previously reported as components of solutions containing the free ligands with manganese salts, but were not previously obtained as solids. The syntheses of the manganese complexes proceed by relatively straightforward direct ligand substitution reactions. Of particular note, however, is that $[Mn(DO3AM)]Cl_2$ was prepared without isolating the free ligand. Although the reaction mixture was not extensively characterized, the major expected side products of the reaction of cyclen with chloroacetamide are unreacted cyclen and the monosubstituted DO1AM (1,4,7,10-tetraazacyclododecane-1-monoacetamide). Treatment of this mixture with a substoichiometric quantity of $MnCl_2$ yields the $[Mn(DO3AM)]^{2+}$ product, presumably due to the high denticity of the ligand and consequent thermodynamic stability. Other manganese-containing side products that may form remain in solution under these conditions and $[Mn(DO3AM)]^{2+}$ is the only cationic constituent of the isolated precipitate. The DO3AM free ligand has been previously synthesized independently,^{43,44} but the *in situ* approach we report represents a novel strategy for the synthesis of a tri-substituted cyclen complex. The recrystallized product

of the reaction mixture is $[\text{Mn}(\text{DO3AM})][\text{MnCl}_4]\cdot\text{EtOH}$. This salt has been structurally characterized by X-ray crystallography as described below. Since the $[\text{MnCl}_4]^{2-}$ ion is paramagnetic and would interfere with relaxivity measurements, the ion was removed by exploiting the differential solubilities of the desired complex and MnCl_2 in a water/acetone mixture. MnCl_2 is significantly less soluble and precipitates, leaving $[\text{Mn}(\text{DO3AM})]^{2+}$ and chloride ion in solution. Attempts to grow crystals of this salt suitable for X-ray studies were unsuccessful and there remains some ambiguity regarding the solid state structure. Either the salt contains the seven-coordinate $[\text{Mn}(\text{DO3AM})]^{2+}$ cation (as found in the tetrachloromanganate salt) with two chloride counterions, or one of the chloride ions binds to form an eight coordinate $[\text{Mn}(\text{DO3AM})\text{Cl}]^+$ cation with one additional chloride as the counterion. Chloride binding to $[\text{Mn}(\text{DO3AM})]^{2+}$ should, however, be very weak. The structurally confirmed isolation of $[\text{Mn}(\text{DO3AM})][\text{MnCl}_4]\cdot\text{EtOH}$ indicates that Cl^- preferentially binds to “ $[\text{MnCl}_3]^-$ ” rather than $[\text{Mn}(\text{DO3AM})]^{2+}$. Chloride binding to Mn^{2+} is known to be very weak⁴⁵⁻⁴⁷ and the formation constant for $[\text{MnCl}_4]^{2-}$ in aqueous solution has never been determined. Thus chloride is expected to be even more weakly bound to the metal ion of $[\text{Mn}(\text{DO3AM})]^{2+}$ in solution and should be fully dissociated. Furthermore, the mass spectrum of solutions of $[\text{Mn}(\text{DO3AM})]\text{Cl}_2$ is dominated by peaks at $m/z = 199.03$ (corresponding to $[\text{Mn}(\text{DO3AM})]^{2+}$) and at $m/z = 397.00$ (corresponding to $[\text{Mn}(\text{DO3AM})]^{2+} - \text{H}^+$). Only very small peaks are apparent 433.00 and 435.00 (corresponding to $[\text{Mn}(\text{DO3AM})]^{2+} + \text{Cl}^-$).

The susceptibility of polyazamacrocyclic complexes of Mn^{2+} to air oxidation is well known and has limited the development of their coordination chemistry.¹⁶⁻²³ $\text{Mn}(\text{H}_2\text{DOTA})$, $\text{Mn}(\text{DO2A})$, $[\text{Mn}(\text{DOTAM})]^{2+}$, $[\text{Mn}(\text{DO3AM})]^{2+}$, and $[\text{Mn}(\text{HOCy-DO3AM})]^{2+}$, however, are all air stable in aqueous solution for at least several days. These results are further supported by electrochemical studies detailed in the Supporting Information. All the complexes exhibit irreversible $\text{Mn}(\text{II/III})$ oxidations at potentials greater than $+0.8\text{V}$ vs SCE. These potentials are consistent with the relatively high oxidation potentials observed in related complexes with nitrogen and oxygen donor ligands.⁴⁸ The conclusion is that cyclic polytetraamine ligands with two or more π -accepting pendant arms are capable of stabilizing Mn^{2+} to air oxidation.

Stability constants for the $\text{Mn}(\text{II})$ complexes of DOTA ($\log K = 19.89$)^{40,41} and DO2A ($\log K = 14.54$)⁴⁰ have been previously reported. For $[\text{Mn}(\text{DOTAM})]^{2+}$ and $[\text{Mn}(\text{DO3AM})]^{2+}$, thermodynamic binding studies have not been carried out. Incubation of solutions of $[\text{Mn}(\text{DOTAM})]^{2+}$ or $[\text{Mn}(\text{DO3AM})]^{2+}$ with a two-fold excess of EDTA, however, results in no changes in the relaxivities even after several days. EDTA is known⁴⁹ to bind Mn^{2+} with a dissociation constant of $\log K = 13.9$ and the reported R_1 of $[\text{Mn}(\text{EDTA})]^{2-}$ is $2.20\text{ mM}^{-1}\text{s}^{-1}$.⁵⁰ These results indicate that regardless of the thermodynamic stability of the complexes, they are kinetically inert to ligand substitution on the timescale of the relaxivity experiments.

X-ray Crystallography

$[\text{Mn}(\text{DOTAM})]\text{Cl}_2\cdot 2\text{H}_2\text{O}$ represents a relatively rare example of a structurally characterized 8-coordinate $\text{Mn}(\text{II})$ complex.⁵¹⁻⁶³ The molecular structure is illustrated in Figure 1 and some of the key structural parameters are summarized in Table 2. The four oxygen atoms define an approximate square plane, as do the four nitrogen ring atoms. The crystallographically imposed symmetry of the cation is C_2 , but the complex has essentially S_4 point group symmetry. The overall coordination geometry may be described as a slightly compressed square prism in which the basal faces are rotated about the pseudo-fourfold axis by 23° with respect to each other. The Mn-O and Mn-N bond lengths fall within the range of previously reported Mn-O and Mn-N bond lengths in 8-coordinate species.⁵¹⁻⁶³ Weak hydrogen-bonding interactions between the amide hydrogens and the oxygen of water are also apparent.

Among the 8-coordinate Mn(II) complexes that have been reported,⁵¹⁻⁶³ [Mn(DOTAM)]²⁺ most resembles other pendant-arm macrocycles such as [Mn(2-pyridylmethyl)₄cyclen]²⁺, which has 2-pyridyl groups in place of the amide groups of DOTAM,⁶² and [Mn(pyrazol-1-ylmethyl)₄cyclen]²⁺ in which imidazole nitrogens also coordinate the metal.⁵⁷ In each case the fundamental geometry is square prismatic with one of the square planes rotated about a pseudo-fourfold axis.

While DOTAM typically exhibits octadentate coordination to lanthanides,^{29,64-67} structural studies have shown that its binding to transition metal or main group cations is more diverse.³⁰ The Cd²⁺ and Zn²⁺ complexes are 6-coordinate, while the Ca²⁺ complex is a more regular 8-coordinate geometry similar to that of [Mn(DOTAM)]²⁺. The differences in coordination have been ascribed to steric interactions between the coordinated oxygens which lead to lower coordination numbers for the smaller ions.³⁰ The Mn²⁺ ion, however, has an effective ionic radius slightly smaller than that of Cd²⁺,⁶⁸ suggesting that there are other contributions that play a role in determining the observed solid state structure.

Crystals of [Mn(DO3AM)][MnCl₄].EtOH give a disordered structure. The most successful model for the structure of the [Mn(DO3AM)]²⁺ ion is shown in Figure 2 and selected structural parameters are given in Table 2. The structure shows a 7-coordinate Mn(II) coordinated by the four amine nitrogens of the ring as well as by three oxygen atoms of the pendant amide groups. There is, however, residual difference electron density on the order of 0.9 eÅ⁻³ in the area where a fourth pendant arm would be located. This is also the general vicinity of the ethanol solvate molecule. The most successful model was based on 88.5% occupation of the site by ethanol and 11.5% occupation by an amide pendant arm resulting from a 90° rotation of the complex about an axis perpendicular to the plane of the ring nitrogens.

The complex can be described as a distorted capped trigonal prism in which N10 is the capping ligand. Several other structurally characterized 7-coordinate Mn(II) complexes are based on capped trigonal prismatic geometries⁶⁹⁻⁷¹ although pentagonal bipyramidal structures have also been observed.⁷²⁻⁷⁴ A comparison with the structure of [Mn(DOTAM)]²⁺ shows that the bond lengths decrease and the bond angles increase somewhat for the lower coordination number. For example, the average Mn-N bond length for [Mn(DO3AM)]²⁺ is 2.374 Å compared to 2.428 Å for [Mn(DOTAM)]²⁺. Since the DO3AM ligand has somewhat reduced steric constraints on binding, such differences are not unexpected. A number of hydrogen-bonding interactions between amide hydrogens and chlorines of the anion are apparent in the solid state structure.

The structure of Mn(H₂DOTA) is given in Figure 3 with some of the key structural parameters summarized in Table 2. The manganese ion is located on a crystallographic C₂ axis and displays a distorted octahedral geometry at the metal with four amino nitrogen donors and two carboxylate oxygen donors occupying *cis* coordination positions. The bound carboxylates are from the 1 and 7 positions of the macrocyclic ring. The other two carboxylates are protonated and not directly coordinated to the metal ion. The closest distance between an oxygen of an uncoordinated acetate group and the metal ion is 3.01 Å. The hydrogen atoms of the -COOH groups have weak hydrogen-bonding interactions with the water molecules in the lattice.

Several metal complexes of H₂DOTA²⁻ have been previously characterized and the structure of Mn(H₂DOTA) is very similar to those of Cu(H₂DOTA) and Ni(H₂DOTA).⁷⁵ The Mn-N bond lengths are in the expected range, while the Mn-O bond lengths are somewhat shorter than those in [Mn(DOTAM)]²⁺ or [Mn(DO3AM)]²⁺. This observation may be rationalized by noting that both the increased electrostatic attraction of the negatively charged carboxylate and

the decreased steric demands in the 6-coordinate complex favor shorter Mn-O bond lengths relative to the amide complexes.

¹H Relaxivities

The ¹H relaxivities of the complexes at in water 20 MHz and 37° C are reported in Table 3. The data are also displayed graphically in Figure 4 as a plot of the relaxivity vs the crystallographically defined coordination number of the metal ion. The relaxivity of the 6-coordinate complex Mn(DO2A) is nearly as high as that of Mn²⁺(aq) in acidic media. As the coordination number of the complexes increases to seven the relaxivity decreases somewhat and for a coordination number of eight, a larger decrease is apparent. The relaxivity of [Mn(DOTAM)]²⁺ is low relative to most previously reported Mn(II) complexes.^{76,1,7,8,40,77,78} The complex Mn(H₂DOTA) is an apparent exception to these trends (however, see below), with a relaxivity significantly lower than those of the other 6-coordinate species.

Manganese(II) is a substitutionally labile species and the inner sphere contributions to the relaxivities of Mn²⁺(aq) and its small molecular complexes has most often been interpreted in terms of exchange mechanisms involving coordinated water.^{7,8,40,77} There are, however, relatively few published studies of the correlations between the relaxivities, coordination numbers, and water exchange mechanisms for Mn²⁺(aq) and its complexes.^{7,40,74,78,79} Most 7-coordinate complexes investigated so far exhibit positive volumes of activation and/or entropies of activation for water exchange and these parameters have been interpreted in terms of a dissociative interchange (I_d) mechanism for water exchange.^{7,74} While some 6-coordinate complexes also appear to exchange by I_d mechanisms,⁷⁴ for both [Mn(H₂O)₆]²⁺ and [Mn₂(ENOTA)(H₂O)],⁸⁰ a associative interchange (I_a) mechanism for exchange of bound water has been implicated.^{40,74}

The polyazamacrocyclic complexes in Table 3, however, do not have water directly bound to the metal ion in the solid state, although an inner sphere exchange of water for the 6- and 7-coordinate complexes would best account for their relatively high relaxivities. Two limiting mechanistic possibilities are suggested within this interpretive framework. The crystallographic results indicate that in this type of complex, Mn²⁺ reaches coordinative saturation at a maximum coordination number of 8. Thus for Mn(DOTAM)²⁺ an associative addition of water into the primary coordination sphere to form a transient 9-coordinate species is not possible and the observed relaxivity reflects only outer sphere contributions. For the seven-coordinate complexes, Mn(DO3AM)²⁺ and Mn(DO3AM-CyOH)²⁺, it is possible to expand the coordination sphere to form an 8-coordinate associative intermediate. This site provides a pathway for transient inner sphere coordination of water and would be expected to provide a significant contribution to the relaxivity. For complexes such as Mn(DO2A) an associative mechanism through a seven-coordinate intermediate is possible in an analogous fashion and has been experimentally demonstrated for Mn²⁺(aq).⁷⁹ Such exchanges are expected to be faster than those proceeding through eight-coordinate intermediates due to relaxed steric constraints. The relative rates for complexes with the same overall coordination number are more likely to differ due to specific steric effects than to electronic effects at the Mn²⁺ center.

The second possibility is that of a dissociative interchange mechanism involving release of one bound pendant arm to open a site for a water molecule to bind transiently. This alternative seems less chemically reasonable since it would require a very coordinatively unsaturated 5-coordinate intermediate for Mn(DO2A). Additionally, a dissociative mechanism suggests that inner sphere pathways should still contribute to the relaxivity of Mn(DOTAM)²⁺ via a 7-coordinate intermediate, but experiments in mixed protic solvents detailed below are inconsistent with this interpretation.

In 1:1 mixtures of MeOH and H₂O, there are two populations of relaxable protons.⁸¹⁻⁸³ The hydroxyl protons are highly exchangeable and thus relax primarily by inner sphere mechanisms. The methyl protons are not exchangeable and are relaxed only through an outer sphere mechanism. For a complex for which water exchange is important the magnetization *vs* time curves in the mixed solvent clearly exhibit bi-exponential behavior with the slow component corresponding to outer sphere relaxation (primarily CH₃) and the faster component to inner-sphere hydroxyl proton exchange. The best fit for Mn²⁺(aq) at 20 MHz and 37°C is shown in Figure 5 (top). The parameters of the fit are: $T_1^{\text{fast}} = 9.13 \pm 0.11$ ms (rel. contrib. = 49.5%); $T_1^{\text{slow}} = 58.82 \pm 0.69$ ms (rel. contrib. = 50.5%); $R^2 = 0.9999$, entirely consistent with an inner sphere water exchange mechanism for relaxation.

In contrast, the magnetization decay curve for [Mn(DOTAM)]²⁺ in the mixed solvent was successfully fit by a single exponential expression with $T_1 = 72.96 \pm 0.22$ ms ($R^2 = 0.9999$), also shown in Figure 5 (bottom). Attempts to fit the data to a bi-exponential expression gave only small (<5%) contributions from the second, much longer decay term with larger standard errors on the parameters (see Supporting Information). These results are consistent with solvent relaxation by [Mn(DOTAM)]²⁺ proceeding through an outer sphere mechanism only. In this case both the CH₃ and OH protons have essentially identical relaxation times due to similar through space dipole-dipole interactions with the Mn²⁺ ion. The apparent T_1 the [Mn(DOTAM)]²⁺ data is somewhat longer than that for the outer-sphere component of Mn²⁺(aq) and is consistent with the increased size of the complex relative to Mn²⁺(aq). Outer sphere relaxivities generally increase inversely with both the distance of closest approach for water molecules and the diffusion coefficient of the ion.^{1,84-88} Both of these quantities are expected to be larger for [Mn(DOTAM)]²⁺ than for Mn²⁺(aq), and thus consistent with the observed T_1 values.

It is also of note that the complexes have different charges, which might affect the relaxivities. For series of structurally related Gd³⁺ complexes, it has been generally found that the relaxivity decreases as the charge increases,^{89,90} although exceptions have also been noted.⁹¹ This effect has been rationalized in terms of a water exchange mechanism and enhanced electrostatic interactions between positive charges and the oxygen atom of the water molecule, which lead to slower water exchange rates.^{89,90} All of the amide-based complexes in Table 3 have 2+ charges while the carboxylates are neutral and Mn²⁺(aq) carries a large positive charge. If the charge of the complex were dominant, all the amide-based complexes would have relaxivities similar to that of Mn²⁺(aq) and they should be among the lowest relaxivities in the series. It is notable that Mn(DO2A) has the relaxivity most similar to Mn²⁺(aq), even though there is a large difference in charge. Thus it appears that the differences in coordination numbers are far more important overall determinants of relaxivities.

In terms of the data presented in Table 3 and Figure 4, Mn(H₂DOTA) appears to be an exception. Although the crystal structure clearly indicates a six-coordinate Mn²⁺ ion, the relaxivity of an aqueous solution of the complex is considerably lower than that of Mn(DO2A), which is also 6-coordinate. NMRD data on solutions containing Mn²⁺ and excess H₂DOTA²⁻ at pH values of 6.2-6.5 exhibit relaxivity profiles characteristic of an outer sphere mechanism.⁴⁰ It should be noted, however, that the uncoordinated -COOH groups have reported pK_a values of 2.99 and 4.26,^{41,42} and are expected to ionize to a significant extent in aqueous solution. In fact, a 1 mM solution of Mn(H₂DOTA) has a pH of 3.7, indicating significant ionization. The relaxivity *vs* pH curve for Mn(H₂DOTA) shows a prominent inflection with an effective pK_a of 2.79 and limiting R_1 values of $7.2 \text{ mM}^{-1} \text{ s}^{-1}$ at low pH (<2) and $2.7 \text{ mM}^{-1} \text{ s}^{-1}$ at high pH (>4).⁹² In contrast, for all the other complexes in Table 3, the relaxivities vary less than 10% in the pH 2-6 range. This observation is consistent with the fact that of all the complexes, only Mn(H₂DOTA) has functional groups that are protonatable or

deprotonatable over this pH range. Thus for all the complexes in Table 3, except Mn(H₂DOTA), there is only one significant species present in solution.

For Mn(H₂DOTA), however, the predominant solution structure may be considerably different from the crystal structure and the solution contains a mixture of species in a variety of protonation states. For example, deprotonation of an uncoordinated pendant acetate arm may lead to binding of the arm and a net increase in the coordination number of the metal. If such processes occur, it is predicted that the relaxivity should be relatively low at higher pH values and should increase as inner sphere relaxation pathways contribute at lower pH values. Such a pH dependence has been observed for Mn(H₂DOTA)⁹² and will be addressed in a subsequent publication.⁹³

An important additional conclusion to be drawn from the results described above is that complexes with easily expandable coordination spheres may be potential candidates for MRI contrast agents, even if there is no water directly coordinated in the solid form of the complex. In such complexes, water may be able to bind transiently to form higher coordinate intermediates that are long-lived enough to provide an efficient relaxation pathway for water protons.

Manganese complexes can exhibit relaxivities that rival that of the active ingredient of the most common clinically used gadolinium-based contrast agent, Magnevist® ([Gd(diethylenetriamine pentaacetic acid)]²⁻, $R_1 = 4.34 \text{ mM}^{-1} \text{ s}^{-1}$ at 20 MHz and 39°C).⁹⁴ In fact, both Mn(DO₂A) and [Mn(DO₃AM)]²⁺ exhibit relaxivities in water that exceed that of Magnevist under similar conditions. The implications for contrast development are that Mn²⁺, lacking crystal field stabilization effects, can assume a variety of total coordination numbers with relatively small energetic differences. For complexes of relatively low coordination number, an associative mechanism for water interaction with the metal ion is allowed thus providing an inner sphere pathway for solvent relaxation. These results suggest the possibility of many new Mn²⁺-based candidates for clinically useful contrast agents once a more complete understanding of their dynamics of interaction with water has been developed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Lauffer RB. *Chem. Rev* 1987;87:901–927.
2. Lauterbur, PC.; Mendonca-Dias, MH.; Rudin, AM. *Frontiers of Biological Energetics*. Academic Press; New York: 1978.
3. Wagnon BK, Jackels SC. *Inorg. Chem* 1989;28:1923–1927.
4. Bradshaw JE, Gillogly KA, Wilson LJ, Kumar K, Wan X, Tweedle MF, Hernandez G, Bryant RG. *Inorg. Chim. Acta* 1998;275-276:106–116.
5. Merbach, AE.; Toth, E. *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*. John Wiley & Sons, Ltd.; New York: 2001.
6. Schwert DD, Davies JA, Richardson N. *Topics in Curr. Chem* 2002;221:165–199.
7. Aime S, Anelli PL, Botta M, Brocchetta M, Canton S, Fedeli F, Gianolio E, Terreno E. *J. Biol. Inorg. Chem* 2002;7:58–67. [PubMed: 11862541]

8. Troughton JS, Greenfield MT, Greenwood JC, Dumas S, Wiethoff AJ, Wang J, Spiller M, McMurphy TJ, Caravan P. *Inorg. Chem* 2004;43:6313–6323. [PubMed: 15446878]
9. Lee JH, Koretsky AP. *Curr. Pharm. Biotech* 2004;5:529–537.
10. Bock NA, Silva AC. *Future Neurology* 2007;2:297–305.
11. Li Z, Li W, Li X, Pei F, Wang X, Lei H. *J. Inorg. Biochem* 2007;101:1036–1042. [PubMed: 17524483]
12. Zhang X, Lovejoy KS, Jasanoff A, Lippard SJ. *Proc. Natl. Acad. of Sci. U.S.A* 2007;104:10780–10785. [PubMed: 17578918]
13. Rocklage SM, Cacheris WP, Quay SC, Hahn FE, Raymond KN. *Inorg. Chem* 1989;28:477–485.
14. Lim KO, Stark DD, Leese PT, Pfefferbaum A, Rocklage SM, Quay SC. *Radiology* 1991;178:79–82. [PubMed: 1898539]
15. Small WC, DeSimone-Macchi D, Parker JR, Sukerka A, Hahn PF, Rubin DL, Zelch JV, Kuhlman JE, Outwater EK, Weinreb JC, Brown JJ, de Lange EE, Woodward PJ, Arildsen R, Foster GS, Runge VM, Aisen AM, Muroff LR, Thoeni RF, Parisky YR, Tanenbaum LN, Totterman S, Herfkens RJ, Knudsen J, Laster RE Jr, Duerinckx A, Stillman AE, Spritzer CE, Saini S, Rofsky NM, Bernardino ME. *J. of Magn. Reson. Imaging* 1999;10:15–24. [PubMed: 10398973]
16. Chiswell, B.; McKenzie, ED.; Lindoy, LF. Manganese. In: Wilkinson, G., editor. *Comprehensive Coordination Chemistry*. Vol. 4. Pergamon Press; Oxford: 1987. p. 76
17. Goodson PA, Hodgson DJ, Glerup J, Michelsen K, Weihe H. *Inorg. Chim. Acta* 1992;197:141–147.
18. Brewer KJ, Calvin M, Lumpkin RS, Otvos JW, Spreer LO. *Inorg. Chem* 1989;28:4446–4451.
19. Goodson PA, Hodgson DJ, Michelsen K. *Inorg. Chim. Acta* 1990;172:49–57.
20. Létumier F, Broeker G, Barbe J-M, Guillard R, Lucas D, Dahanoui-Gindrey V, Lecomte C, Thouin L, Amatore C. *J. Chem. Soc., Dalton Trans* 1998:2233–2239.
21. Weighardt K, Bossek U, Gebert W. *Angew. Chem., Int. Ed. Engl* 1983;22:328–329.
22. Weighardt K, Bossek U, Nuber B, Weiss J, Bonvoisin J, Corbella M, Vitolis SE, Girerd J-J. *J. Amer. Chem. Soc* 1988;110:7398–7411.
23. Hubin TJ, McCormick JA, Collinson SR, Alcock NW, Clase HJ, Busch DH. *Inorg. Chim. Acta* 2003;346:76–86.
24. Lindoy LF, Busch DH. *Prep. Inorg. Reactions* 1971;6:1–61.
25. Melson, GA., editor. *Coordination Chemistry of Macrocyclic Compounds*. Plenum; New York: 1979.
26. Connors H, McAuliffe CA, Tames J. *Rev. Inorg. Chem* 1981;3:199–257.
27. Hancock RD, Martell AE. *Chem. Rev* 1989;89:1875–1914.
28. Martell, AE.; Hancock, RD. *Metal Complexes in Aqueous Solution*. Plenum Press; New York: 1996. p. 127–133.
29. Amin S, Morrow JR, Lake CH, Churchill MR. *Angew. Chem., Int. Ed. Engl* 1994;33:773–775.
30. Maumela H, Hancock RD, Carlton L, Reibenspies JH, Wainwright KP. *J. Amer. Chem. Soc* 1995;117:6698–6707.
31. Note that by extending the reported reaction time yields of up to 90% may be obtained.
32. Van Westrenen J, Sherry AD. *Bioconjugate Chem* 1992;3:524–532.
33. de Sousa AS, Hancock RD, Reibenspies JH. *J. Chem. Soc., Dalton Trans* 1997:939–944.
34. a) Marquardt DW. *J. Soc. Ind. Appl. Math* 1963;11:431–441. Press, WH.; Flannery, BP.; Teukolsky, SA.; Vetterling, WT. *Numerical Recipes*. Cambridge University Press; Cambridge: 1986.
35. Blessing R. *Acta Cryst A* 1995;51:33–38.
36. SAINT V6.1. Bruker Analytical X-Ray Systems; Madison, WI:
37. Altomare A, Cascarano G, Giacovazzo C, Gualardi A. *J. Appl. Cryst* 1993;26:343–350.
38. SHELXTL-Plus V5.10. Bruker Analytical X-Ray Systems; Madison, WI:
39. Spek AL. *J. Appl. Cryst* 2003;36:7–13.
40. Gerald CF, Sherry AD, Brown RD III, Koenig SH. *Magn. Reson. Med* 1986;3:242–250. [PubMed: 3086656]
41. Chaves S, Delgado R, Da Silva JJRF. *Talanta* 1992;39:249–254. [PubMed: 18965370]
42. Bianchi A, Calabi L, Giorgi C, Losi P, Mariani P, Palano D, Paoli P, Rossi P, Valtancoli B. *J. Chem. Soc., Dalton Trans* 2001:917–922.

43. Woods M, Kiefer GE, Bott S, Castillo-Munquiz A, Eshelbrenner C, Michaudet L, McMillan K, Mudigunda SDK, Ogrin D, Tircsó G, Zhang S, Zhao P, Sherry AD. *J. Amer. Soc. Soc* 2004;126:9248–9256.
44. Nwe K, Richard JP, Morrow JR. *J. Chem. Soc., Dalton Trans* 2007:5171–5178.
45. Morris DFC, Short EL. *J. Chem. Soc* 1961:5148–5153.
46. Tribalat S, Caldero J-M. *Comp. Rend* 1962;255:925–927.
47. Gammons CH, Seward TM. *Geochim. Cosmochim. Acta* 1996;60:4295–4311.
48. Schultz, FA.; Duncan, CT.; Rigsby, MA. *Electrochemistry of the Group 7 Elements*. In: Scholz, F.; Pickett, CJ., editors. *Inorganic Electrochemistry*. Vol. 7a. Wiley-VCH; Weinheim: 2006. p. 401–404. and references therein
49. Byegård J, Skarnemark G, Skålberg M. *J. Radioanal. Nucl. Chem* 1999;241:281–290.
50. Tweedle MF, Gaughan GT, Hagen J, Wedeking PW, Sibley P, Wilson LJ, Lee DW. *Nucl. Med. Biol* 1988;15:31–36.
51. Neupert-Laves K, Dobler M. *Helv. Chim. Acta* 1977;60:1861–1871. [PubMed: 914629]
52. Hughes BB, Haltiwanger RC, Pierpont CG, Hampton M, Blackmer GL. *Inorg. Chem* 1980;19:1801–1803.
53. Neupert-Laves K, Dobler M. *J. Crystallogr. Spectrosc. Res* 1982;12:271–286.
54. Vardosanidze TO, Sokol VI, Sobolev AN, Shvelashvili AE, Porai-Koshits MA. *Zh. Neorg. Khim* 1985;30:1745–1751.
55. Zhorzholiani NB, Shvelashvili AE, Sobolev AN, Vardosanidze IO. *Soobshch. Akad. Nauk Gruz. SSR* 1986;123:541–544.
56. Hagen KS. *Angew. Chem., Int. Ed. Engl* 1992;31:764–766.
57. Di Vaira M, Mani F, Stoppioni P. *J. Chem. Soc., Dalton Trans* 1992:1127–1130.
58. Gultneh Y, Farooq A, Karlin KD, Liu S, Zubietta J. *Inorg. Chim. Acta* 1993;211:171–175.
59. Brychcy K, Jens KJ, Tilset M, Behrens U. *Chem. Ber* 1994;127:991–995.
60. Brooker S, McKee V, Metcalfe T. *Inorg. Chim. Acta* 1996;246:171–179.
61. Reid HON, Kahwa IA, White AJP, Williams DJ. *Inorg. Chem* 1998;37:3868–3873. [PubMed: 11670493]
62. Bu X-H, Chen W, Mu L-J, Zhang Z-H, Zhang R-H, Clifford T. *Polyhedron* 2000;19:2095–2100.
63. Junk PC, Smith MK, Steed JW. *Polyhedron* 2001;20:2979–2988.
64. Amin S, Voss DA Jr, Horrocks WD Jr, Lake CH, Churchill MR, Morrow JR. *Inorg. Chem* 1995;34:3294–3300.
65. Aime S, Barge A, Bruce JI, Botta M, Howard JAK, Moloney JM, Parker D, de Sousa AS, Woods M. *J. Am. Chem. Soc* 1999;121:5762–5771.
66. Hancock RD, Reibenspies JH, Maumela H. *Inorg. Chem* 2004;43:2981–2987. [PubMed: 15106988]
67. Bombieri G, Marchini N, Ciattini S, Mortillaro A, Aime S. *Inorg. Chim. Acta* 2006;359:3405–3411.
68. a) Shannon RD, Prewitt CT. *Acta Crystallogr* 1969;B25:925–946. b) Shannon RD, Prewitt CT. *Acta Crystallogr* 1970;B26:1046–1048.
69. Inoue MB, Navarro RE, Inoue M, Fernando Q. *Inorg. Chem* 1995;34:6074–6079.
70. Mikuriya M, Hatano Y, Asato E. *Chem. Lett* 1996:849–850.
71. Hureau CH, Blanchard S, Nierlich M, Blain G, Rivière E, Girerd J-J, Anxolabéhère-Mallart E, Blondin G. *Inorg. Chem* 2004;43:4415–4426. [PubMed: 15236555]
72. Riley DP, Weiss RH. *J. Am. Chem. Soc* 1994;116:387–388.
73. Liu Y-C, Ma S-L, Guo Q-L, Zhang J, Xu M-Q, Zhu W-X. *Inorg. Chem. Commun* 2005;8:574–577.
74. Dees A, Zahl A, Puchta R, van Eikema Hommes NJR, Heinemann FW, Ivanović-Burmazović I. *Inorg. Chem* 2007;46:2459–2470. [PubMed: 17326621]
75. Riesen A, Zehnder M, Kaden TA. *Helv. Chim. Acta* 1986;69:2067–2073.
76. Relaxivities for small molecule complexes of Mn^{2+} under similar conditions are typically in the range of $1.5\text{--}6\text{ mM}^{-1}\text{s}^{-1}$.
77. Jackels SC, Durham MM, Newton JE, Henniger TC. *Inorg. Chem* 1992;31:234–239.
78. Balogh E, He Z, Hsieh W, Liu S, Tóth E. *Inorg. Chem* 2007;46:238–250. [PubMed: 17198433]

79. Ducommun Y, Newman KE, Merbach AE. *Inorg. Chem* 1980;19:3696–3703.
80. ENOTA is 1,2-bis[1-(1,4,7-triazacyclononyl-1,4-diacetic acid)]ethane. See reference 23.
81. Luz Z, Meiboom S. *J. Chem. Phys* 1964;40:1058–1066.
82. Luz Z, Meiboom S. *J. Chem. Phys* 1964;40:1066–1068.
83. Gossuin Y, Roch A, Muller RN, Gillis P. *J. Magn. Reson* 2002;158:36–42. [PubMed: 12419669]
84. Freed JH. *J. Chem. Phys* 1978;68:4034–4037.
85. Tóth E, Helm L, Merbach AE. *Topics in Curr. Chem* 2002;221:61–101.
86. Abragam, A. *Principles of Nuclear Magnetism*. Oxford University Press; Oxford: 1961.
87. Fries PH, Belorizky E. *J. Phys. (Paris)* 1978;39:1263–1282.
88. Albrand JP, Taieb MC, Fries PH, Belorizky E. *J. Chem. Phys* 1983;78:5809–5815.
89. Gilbert J, Kassab D, Pawlow JH, Santora BP, Fiel RJ, Joshi VN, Kozik M. *Inorg. Chem* 1995;34:924–927.
90. Burai L, Tóth E, Bazin H, Benmelouka M, Jászberényi Z, Helm L, Merbach AE. *J. Chem. Soc., Dalton Trans* 2006:629–634.
91. Jocher CJ, Botta M, Avedano S, Moore EG, Xu J, Aime S, Raymond KN. *Inorg. Chem* 2007;46:4796–4798. [PubMed: 17497773]
92. Siddiqui, SA.; Chipendo, PI.; Westmoreland, TD. Abstracts of Papers; 235th National Meeting of the American Chemical Society; New Orleans, LA. Apr 6-10, 2008; Washington, D.C.: American Chemical Society; 2008. INOR 176
93. Siddiqui SA, Chipendo PI, Westmoreland TD. manuscript in preparation
94. Xie D, Kennan RP, Gore JC. *Proc. Intl. Soc. Mag. Reson. Med* 2001;9:890.

DOTAM

DO3AM

DO3Am-CyOH

H₄DOTA H₂DO2A

Scheme 1.

Figure 1. Molecular structure of $[\text{Mn}(\text{DOTAM})]^{2+}$ viewed approximately along the C_2 axis. For clarity, only the amide hydrogens are shown. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Mn-N1, 2.4351(11); Mn-N2, 2.4218(11); Mn-O1, 2.3128(10); Mn-O2, 2.3080(9); N1-Mn-N2, 73.73(4); N2-Mn-N1', 73.79(4); O1-Mn-N1, 68.96(4); O1-Mn-O2, 73.83(3); O2-Mn-N2, 68.82(4).

Figure 2.

Molecular structure of $[\text{Mn}(\text{DO3AM})]^{2+}$. For clarity, only the amide hydrogens are shown. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Mn-N1, 2.423(4); Mn-N4, 2.342(4); Mn-N7, 2.351(4); Mn-N10, 2.312(5); Mn-O21, 2.162(4); Mn-O31, 2.297(4); Mn-O41, 2.238(3); N1-Mn-N4, 74.40(14); N4-Mn-N7, 77.12(13); N7-Mn-N10, 75.71(15); N1-Mn-N10, 76.16(15); O21-Mn-N1, 74.66(13); O31-Mn-N4, 71.24(13); O41-Mn-N7, 72.22(12); O21-Mn-O31, 91.73(14); O31-Mn-O41, 76.28(13); O21-Mn-O41, 84.38(13).

Figure 3.

Molecular structure of Mn(H₂DOTA) viewed approximately along the C₂ axis. All hydrogens except –COOH have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Mn–N1, 2.3481(19); Mn–N2, 2.3803(18); Mn–O1, 2.1601(16); N1–Mn–N2, 74.72(6); N2–Mn–N1', 76.99(6); O1–Mn–N1, 73.81(6); O1–Mn–O1', 101.03(9).

Figure 4.

Graph of longitudinal relaxivities at 20 MHz and 37°C vs crystallographically defined coordination number for the complexes in Table 2.

Figure 5. Magnetization vs time curves in 1:1 MeOH:H₂O for $\text{Mn}^{2+}(\text{aq})$ fit to bi-exponential kinetics (top) and $[\text{Mn}(\text{DOTAM})]^{2+}$ fit to mono-exponential kinetics (bottom).

Table 1

Crystal Data and Refinement Parameters for [Mn(DOTAM)]Cl₂·H₂O, [Mn(DO3AM)][MnCl₄]·EtOH, and Mn(H₂DOTA).

	[Mn(DOTAM)]Cl ₂ ·2H ₂ O	[Mn(DO3AM)][MnCl ₄]·EtOH	Mn(H ₂ DOTA)
empirical formula	C ₁₆ H ₃₆ Cl ₂ MnN ₈ O ₆	C ₁₆ H ₃₅ Cl ₄ Mn ₂ N ₇ O ₄	C ₁₆ H ₂₆ MnN ₄ O ₈
fw (g mol ⁻¹)	562.37	641.19	457.35
<i>T</i> (K)	173(2)	173(2)	173(2)
Space Group	<i>C</i> 2/ <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> 2/ <i>c</i>
<i>a</i> (Å)	18.5798(15)	8.3646(8)	16.374(3)
<i>b</i> (Å)	13.6006(11)	19.483(2)	6.6559(13)
<i>c</i> (Å)	10.5800(8)	16.3627(16)	16.750(3)
<i>α</i> (°)	90	90	90
<i>β</i> (°)	110.490(1)	99.254(2)	98.381(3)
<i>γ</i> (°)	90	90	90
<i>V</i> (Å ³)	2504.4(3)	2631.9(5)	1806.0(6)
<i>Z</i>	4	4	4
Density (calc.)	1.492	1.622	1.682
<i>λ</i> (Å)	0.71073	0.71073	0.71073
<i>R</i> indices ^a [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0255 <i>wR</i> 2 = 0.0629	<i>R</i> 1 = 0.0536 <i>wR</i> 2 = 0.1177	<i>R</i> 1 = 0.0314 <i>wR</i> 2 = 0.0782
<i>R</i> indices ^a (all data)	<i>R</i> 1 = 0.0296 <i>wR</i> 2 = 0.0644	<i>R</i> 1 = 0.0673 <i>wR</i> 2 = 0.1230	<i>R</i> 1 = 0.0392 <i>wR</i> 2 = 0.0840

^a*R*1 = Σ||*F*_o| - |*F*_c||/Σ|*F*_o|; *wR*2 = [Σ(*w*(*F*_o² - *F*_c²)²)/Σ(*w*(*F*_o²)²)]^{1/2}.

Table 2Selected Bond Distances and Angles for [Mn(DOTAM)]²⁺, [Mn(DO3AM)]²⁺, and Mn(H₂DOTA).

		[Mn(DOTAM)] ²⁺	[Mn(DO3AM)] ²⁺	Mn(H ₂ DOTA)
Bond Distances(Å)				
Mn-N		2.4351(11)	2.423(4)	2.3803(18)
		2.4218(11)	2.351(4)	2.3481(19)
			2.348(4)	
			2.312(5)	
Mn-O		2.3128(10)	2.297(4)	2.1601(16)
		2.3080(9)	2.238(3)	
			2.162(4)	
Bond Angles(°)				
N-Mn-N		73.79(4)	77.12(13)	76.99(6)
		73.73(4)	76.16(15)	74.72(6)
			75.71(14)	
			74.40(14)	
O-Mn-N		73.83(3)	74.66(13)	73.81(6)
		68.96(4)	72.22(12)	
			71.24(13)	
O-Mn-O		68.82(4)	91.73(14)	101.03(9)
			84.38(13)	
			76.28(13)	

Table 3
Relaxivities of the complexes in water at 20 MHz and 37°C.

Complex	R_1 (mM ⁻¹ s ⁻¹)	Coordination No.
[Mn(H ₂ O) ₆](ClO ₄) ₂	6.76 ^a	6
Mn(DO2A)	6.20	6
Mn(H ₂ DOTA)	3.20	6
[Mn(DO3AM)]Cl ₂	4.73	7
[Mn(DO3AM-CyOH)]Cl ₂	3.32	7
[Mn(DOTAM)]Cl ₂	0.96	8

^a in 0.1M HClO₄.