Inorg. Chem. **2009**, *48*, 719−727

Inorganic Chemistry
Article

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

Sen Wang[†] **and T. David Westmoreland***

Department of Chemistry, Hall-Atwater Laboratories, Wesleyan University,
Middletown, Connecticut 06459

Received February 19, 2008

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 $Mn(DOTAM)Cl_2 \cdot 2H_2O$ (monoclinic $C2/c$, $a = 18.5798(15)$, $b = 13.6006(11)$, $c = 10.5800(8)$ Å, $\beta = 110.490(1)°$, $Z = 4$), $[Mn(DO3AM)][MnCl_4] \cdot EtOH$ (monoclinic $P2_1/n$, $a = 8.366(8)$, $b = 19.483(2)$, $c = 16.3627(16)$ Å, $\beta = 99.254(2)°$, $Z = 4$), and $Mn(H_2DOTA)$ (monoclinic $C2/c$, $a = 16.374(3)$, $b = 6.6559(13)$, $c = 16.750(3)$ Å, $\beta = 98.381(3)°$, $Z = 4$), 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 $Mn^{2+}(aq)$ has a lower intrinsic toxicity than many other paramagnetic metal ions, such as Gd^{3+}.[1−5] While recent advances have been made in the search for water soluble manganese-based small molecule contrast agents,[6−12] only two Mn^{2+}-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 $MnCl_2$, is employed in gastro-intestinal imaging.[15]

Since Mn^{2+} is substitutionally labile, chelating ligands are required to ensure the thermodynamic and kinetic stability of the complexes. Cyclic polyamine ligands are attractive candidates, but Mn^{2+} 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

---

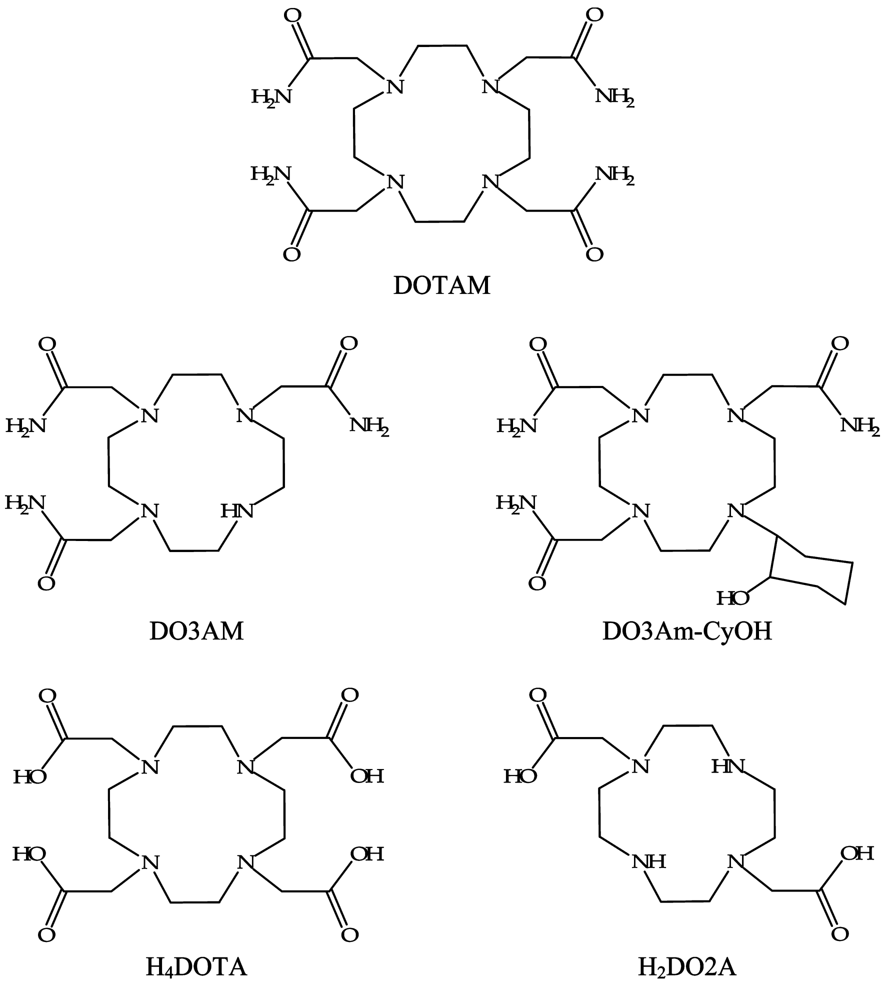
* To whom correspondence should be addressed. E-mail: westmoreland@wesleyan.edu.

[†] Current address: Molecular Imaging Program, Mail Code 5427, Stanford University, Stanford, CA 94305.

(1) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901–927.
(2) Lauterbur, P. C.; Mendonca-Dias, M. H.; Rudin A. M. *Frontiers of Biological Energetics*; Academic Press: New York, 1978.
(3) Wagnon, B. K.; Jackels, S. C. *Inorg. Chem.* **1989**, *28*, 1923–1927.
(4) Bradshaw, J. E.; Gillogly, K. A.; Wilson, L. J.; Kumar, K.; Wan, X.; Tweedle, M. F.; Hernandez, G.; Bryant, R. G. *Inorg. Chim. Acta* **1998**, *275−276*, 106–116.
(5) Merbach, A. E.; Toth, E. *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*; John Wiley & Sons, Ltd.: New York, 2001.
(6) Schwert, D. D.; Davies, J. A.; Richardson, N. *Top. Curr. Chem.* **2002**, *221*, 165–199.
(7) Aime, S.; Anelli, P. L.; Botta, M.; Brocchetta, M.; Canton, S.; Fedeli, F.; Gianolio, E.; Terreno, E. *J. Biol. Inorg. Chem.* **2002**, *7*, 58–67.
(8) Troughton, J. S.; Greenfield, M. T.; Greenwood, J. C.; Dumas, S.; Wiethoff, A. J.; Wang, J.; Spiller, M.; McMurry, T. J.; Caravan, P. *Inorg. Chem.* **2004**, *43*, 6313–6323.
(9) Lee, J. H.; Koretsky, A. P. *Curr. Pharm. Biotech.* **2004**, *5*, 529–537.
(10) Bock, N. A.; Silva, A. C. *Future Neurol.* **2007**, *2*, 297–305.
(11) Li, Z.; Li, W.; Li, X.; Pei, F.; Wang, X.; Lei, H. *J. Inorg. Biochem.* **2007**, *101*, 1036–1042.
(12) Zhang, X.; Lovejoy, K. S.; Jasanoff, A.; Lippard, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 10780–10785.
(13) Rocklage, S. M.; Cacheris, W. P.; Quay, S. C.; Hahn, F. E.; Raymond, K. N. *Inorg. Chem.* **1989**, *28*, 477–485.
(14) Lim, K. O.; Stark, D. D.; Leese, P. T.; Pfefferbaum, A.; Rocklage, S. M.; Quay, S. C. *Radiology* **1991**, *178*, 79–82.
(15) Small, W. C.; DeSimone-Macchi, D.; Parker, J. R.; Sukerkar, A.; Hahn, P. F.; Rubin, D. L.; Zelch, J. V.; Kuhlman, J. E.; Outwater, E. K.; Weinreb, J. C.; Brown, J. J.; de Lange, E. E.; Woodward, P. J.; Arildsen, R.; Foster, G. S.; Runge, V. M.; Aisen, A. M.; Muroff, L. R.; Thoeni, R. F.; Parisky, Y. R.; Tanenbaum, L. N.; Totterman, S.; Herfkens, R. J.; Knudsen, J.; Laster, R. E., Jr.; Duerinckx, A.; Stillman, A. E.; Spritzer, C. E.; Saini, S.; Rofsky, N. M.; Bernardino, M. E. *Magn. Reson. Imaging* **1999**, *10*, 15–24.
(16) Chiswell, B.; McKenzie, E. D.; Lindoy, L. F. *Manganese in Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1987; Vol. *4*, p 76.
(17) Goodson, P. A.; Hodgson, D. J.; Glerup, J.; Michelsen, K.; Weihe, H. *Inorg. Chim. Acta* **1992**, *197*, 141–147.
(18) Brewer, K. J.; Calvin, M.; Lumpkin, R. S.; Otvos, J. W.; Spreer, L. O. *Inorg. Chem.* **1989**, *28*, 4446–4451.
(19) Goodson, P. A.; Hodgson, D. J.; Michelsen, K. *Inorg. Chim. Acta* **1990**, *172*, 49–57.

10.1021/ic8003068 CCC: $40.75

Scheme 1



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]

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 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 complexes involves transient binding of water to the metal ion in an associative process. This pathway is not available to the 8-coordinate complex $[Mn(DOTAM)]^{2+}$. 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 Section

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 (DOT-

---

(20) Létumier, F.; Broeker, G.; Barbe, J.-M.; Guilard, R.; Lucas, D.; Dahaoui-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.; Bonvoison, J.; Corbella, M.; Vitolis, S. E.; Girerd, J.-J. *J. Am. Chem. Soc.* **1988**, *110*, 7398–7411.

(23) Hubin, T. J.; McCormick, J. A.; Collinson, S. R.; Alcock, N. W.; Clase, H. J.; Busch, D. H. *Inorg. Chim. Acta* **2003**, *346*, 76–86.

(24) Lindoy, L. F.; Busch, D. H. *Prep. Inorg. React.* **1971**, *6*, 1–61.

(25) *Coordination Chemistry of Macrocyclic Compounds*; Melson, G. A., Ed.; Plenum: New York, 1979.

(26) Connors, H.; McAuliffe, C. A.; Tames, J. *Rev. Inorg. Chem.* **1981**, *3*, 199–257.

(27) Hancock, R. D.; Martell, A. E. *Chem.Rev.* **1989**, *89*, 1875–1914.

(28) Martell, A. E.; Hancock, R. D. *Metal Complexes in Aqueous Solution*; Plenum Press: New York, 1996; pp 127−133.

AM),[29−31] 1,4,7,10-tetraazacyclododecane-1,7-diacetic acid (H_2DO2A),[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.

[Mn(DOTAM)]$Cl_2\cdot 3H_2O$. DOTAM (0.502 mmol) in 30 mL of 80% methanol was heated at reflux, and $MnCl_2\cdot 4H_2O$ (0.550 mmol) was added. The solution quickly became pale yellow, after which it was stirred for 2 h 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 $C_{16}H_{38}N_8O_7MnCl_2$: C, 33.11; H, 6.60; N, 19.31. Found: C, 32.88; H, 6.20; N, 19.11. Mass spectrum (ESI-MS: $m/z = 227.75$, $[Mn(DOTAM)]^{2+}$). IR (KBr pellet) 1655 cm^{-1}, ν(C=O).

[Mn(DO3AM)][$MnCl_4$]·EtOH. Cyclen (5.8 mmol) and NEt_3 (6.1 mmol) were heated at reflux in 30 mL of ethanol. Over a period of 3 h, chloroacetamide (5.8 mmol) in 15 mL of 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 h. $MnCl_2\cdot 4H_2O$ (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 of 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 $C_{16}H_{35}N_7O_4Mn_2Cl_4$: C, 29.95; H, 5.46; N, 15.29. Found: C, 29.90; H, 5.44; N, 15.33. Mass spectrum (ESI-MS: $m/z = 199.27$, $[Mn(DO3AM)]^{2+}$). IR (KBr pellet) 1653 cm^{-1}, ν(C=O).

[Mn(DO3AM)]$Cl_2\cdot 5H_2O$. [Mn(DO3AM)][$MnCl_4$]·EtOH was dissolved in a minimum of water and acetone was allowed to slowly diffuse into the solution. Pale pink crystals of $MnCl_2\cdot 6H_2O$ 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: $m/z = 199.03$, $[Mn(DO3AM)]^{2+}$). Anal. Calcd for $C_{14}H_{35}N_7O_6MnCl_2$: 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}, ν(C=O).

1,4,7,10-Tetraazacyclododecane-1-(2-hydroxylcyclohexyl)-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 of EtOH for 3 h. After the reaction mixture cooled, 30 mL of Et_2O were added, and a 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 $C_{20}H_{39}N_7O_4\cdot 2.5H_2O$: 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) -C*H*$_2$-,-C*H*. ^{13}C NMR: 22.7, 23.4, 24.0, 24.6, 42.3, 46.5, 47.0 -*C*H_2-; 33.8 -*C*H; 51.6 -*C*H(OH)-; 66.5, 67.4 -*C*H_2CONH_2; 126.3 -*C*(O)NH_2. Mass spectrum (ESI-MS: $m/z = 442.4$, [DO3AM-CyOH + H^+]). IR (KBr pellet) 1672 cm^{-1}, ν(C=O).

[Mn(DO3AM-CyOH)]$Cl_2\cdot 3H_2O$. DO3AM-CyOH (0.3366 mmol) in 30 mL of ethanol was heated at reflux, and $MnCl_2\cdot 4H_2O$ (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 0.2189 g, 99% based on DO3AM-CyOH). Anal. Calcd for $C_{20}H_{49}N_7O_9MnCl_2$: C, 36.52; H, 7.45; N, 14.90. Found: C, 36.34; H, 7.41; N, 14.84. Mass spectrum (ESI-MS: $m/z = 248.20$, $[Mn(DO3AM\text{-}CyOH)]^{2+}$). IR (KBr pellet) 1664 cm^{-1}, ν(C=O).

Mn(H_2DOTA)·2H_2O. $MnSO_4\cdot H_2O$ (0.15 mmol) was dissolved in approximately 0.5 mL of 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 0.0756 g, 99% based on $MnSO_4\cdot H_2O$) Anal. Calcd for $C_{16}H_{30}N_4O_{10}Mn$: C, 38.99; H, 6.00; N, 11.35. Found: C, 38.48; H, 5.91; N, 11.22. Mass spectrum (ESI-MS: $m/z = 458.02$, [Mn(H_2DOTA) + H^+]). IR (KBr pellet) 1736 cm^{-1}, ν(C=O, uncoordinated −COOH); 1579 cm^{-1}, ν(C=O, coordinated -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.

Mn(DO2A)·2H_2O. H_2DO2A (0.27 mmol) was dissolved in approximately 0.5 mL of water, and $MnCl_2\cdot 4H_2O$ (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 H_2DO2A) Anal. Calcd for $C_{12}H_{26}N_4O_6Mn$: C,

---

(29) Amin, S.; Morrow, J. R.; Lake, C. H.; Churchill, M. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 773–775.

(30) Maumela, H.; Hancock, R. D.; Carlton, L.; Reibenspies, J. H.; Wainwright, K. P. *J. Am. 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, A. D. *Bioconjugate Chem.* **1992**, *3*, 524–532.

(33) de Sousa, A. S.; Hancock, R. D.; Reibenspies, J. H. *J. Chem. Soc., Dalton Trans.* **1997**, 939–944.

Table 1. Crystal Data and Refinement Parameters for $[Mn(DOTAM)]Cl_2 \cdot 2H_2O$, $[Mn(DO3AM)][MnCl_4] \cdot EtOH$, and $Mn(H_2DOTA)$

	$[Mn(DOTAM)]Cl_2 \cdot 2H_2O$	$[Mn(DO3AM)][MnCl_4] \cdot EtOH$	$Mn(H_2DOTA)$
empirical formula	$C_{16}H_{36}Cl_2MnN_8O_6$	$C_{16}H_{35}Cl_4Mn_2N_7O_4$	$C_{16}H_{26}MnN_4O_8$
fw (g mol^{-1})	562.37	641.19	457.35
T (K)	173(2)	173(2)	173(2)
space group	$C2/c$	$P2_1/n$	$C2/c$
a (Å)	18.5798(15)	8.3646(8)	16.374(3)
b (Å)	13.6006(11)	19.483(2)	6.6559(13)
c (Å)	10.5800(8)	16.3627(16)	16.750(3)
α (deg)	90	90	90
β (deg)	110.490(1)	99.254(2)	98.381(3)
γ (deg)	90	90	90
V ($Å^3$)	2504.4(3)	2631.9(5)	1806.0(6)
Z	4	4	4
density (calc.)	1.492	1.622	1.682
λ (Å)	0.71073	0.71073	0.71073
R indices[a]	$R1 = 0.0255$	$R1 = 0.0536$	$R1 = 0.0314$
$[I > 2\sigma(I)]$	$wR2 = 0.0629$	$wR2 = 0.1177$	$wR2 = 0.0782$
R indices[a]	$R1 = 0.0296$	$R1 = 0.0673$	$R1 = 0.0392$
(all data)	$wR2 = 0.0644$	$wR2 = 0.1230$	$wR2 = 0.0840$

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$; $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum w(F_o^2)^2]^{1/2}$.

38.20; H, 6.89; N, 14.85. Found: C, 38.19; H, 6.86; N, 14.95. Mass spectrum (ESI-MS: $m/z = 342.01$, $[Mn(DO2A) + H^+]$). IR (KBr pellet) 1612 cm^{-1}, ν(C═O).

For several of the complexes, competitive EDTA binding studies were carried out by preparing 2:1 molar ratios of EDTA and metal complex (~ 1 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°-τ-90°] where τ is a variable delay time) provided by Bruker. Twenty scans were averaged for each of 20 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 mol 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} versus 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 Information. 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 Mo Kα radiation (graphite monochromator) with a frame time of 10 s for $[Mn(DOTAM)]Cl_2 \cdot 3H_2O$ and 60 s 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 $[Mn(DO3AM)][McCl_4] \cdot EtOH$, and 2827 for $Mn(H_2DOTA)$) from the data collection after integration (SAINT 6.01, 1999).[36] The structures were solved using SIR92[37] 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 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 because of 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

---

(34) (a) Marquardt, D. W. *J. Soc. Ind. Appl. Math.* **1963**, *11*, 431–441. (b) Press, W. H.; Flannery, B. P.; Teukolsky, S. A.; Vetterling, W. T. *Numerical Recipes*; Cambridge University Press: Cambridge, 1986.

(35) Blessing, R. *Acta Crystallogr.* **1995**, *A51*, 33–38.

(36) *SAINT*, V6.1; Bruker Analytical X-Ray Systems: Madison, WI.

(37) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Gualardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343–350.

(38) *SHELXTL-Plus*, V5.10; Bruker Analytical X-Ray Systems: Madison, WI.

(39) Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.

(40) Geraldes, C. F. G. C.; Sherry, A. D.; Brown, R. D., III.; Koenig, S. H. *Magn. Reson. Med.* **1986**, *3*, 242–250.

(41) Chaves, S.; Delgado, R.; Da Silva, J. J. R. F. *Talanta* **1992**, *39*, 249–254.

(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, G. E.; Bott, S.; Castillo-Munquiz, A.; Eshelbrenner, C.; Michaudet, L.; McMillan, K.; Mudigunda, S. D. K.; Ogrin, D.; Tircsó, G.; Zhang, S.; Zhao, P.; Sherry, A. D. *J. Amer. Chem. Soc.* **2004**, *126*, 9248–9256.

approach we report represents a novel strategy for the synthesis of a trisubstituted cyclen complex. The recrystallized product of the reaction mixture is [Mn(DO3AM)][$MnCl_4$]·EtOH. This salt has been structurally characterized by X-ray crystallography as described below. Since the $[MnCl_4]^{2-}$ ion is paramagnetic and would interfere with relaxivity measurements, the ion was removed by exploiting the differential solubilites of the desired complex and $MnCl_2$ in a water/acetone mixture. $MnCl_2$ is significantly less soluble and precipitates, leaving $[Mn(DO3AM)]^{2+}$ 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 $[Mn(DO3AM)]^{2+}$ cation (as found in the tetrachloromanganate salt) with two chloride counterions, or one of the chloride ions binds to form an eight coordinate $[Mn(DO3AM)Cl]^{+}$ cation with one additional chloride as the counterion. Chloride binding to $[Mn(DO3AM)]^{2+}$ should, however, be very weak. The structurally confirmed isolation of [Mn(DO3AM)][$MnCl_4$]·EtOH indicates that Cl^- preferentially binds to "$[MnCl_3]^-$" rather than $[Mn(DO3AM)]^{2+}$. Chloride binding to Mn^{2+} is known to be very weak,[45−47] and the formation constant for $[MnCl_4]^{2-}$ in aqueous solution has never been determined. Thus, chloride is expected to be even more weakly bound to the metal ion of $[Mn(DO3AM)]^{2+}$ in solution and should be fully dissociated. Furthermore, the mass spectrum of solutions of [Mn(DO3AM)]Cl_2 is dominated by peaks at $m/z = 199.03$ (corresponding to $[Mn(DO3AM)]^{2+}$) and at $m/z = 397.00$ (corresponding to $[Mn(DO3AM)]^{2+} - H^+$). Only very small peaks are apparent at $m/z = 433.00$ and 435.00 (corresponding to $[Mn(DO3AM)]^{2+} + Cl^-$).

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] Mn(H_2DOTA), Mn(DO2A), $[Mn(DOTAM)]^{2+}$, $[Mn(DO3AM)]^{2+}$, and $[Mn(HOCy\text{-}DO3AM)]^{2+}$, 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 Mn(II/III) oxidations at potentials greater than +0.8 V versus 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.

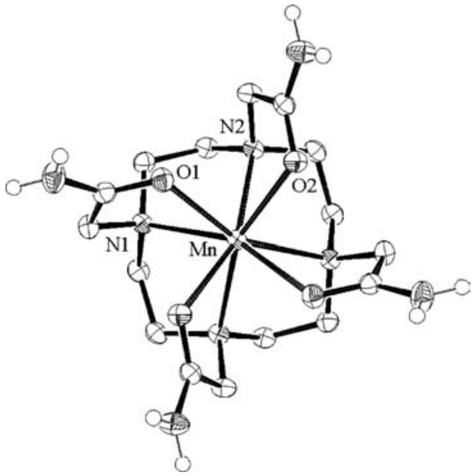


Figure 1. Molecular structure of $[Mn(DOTAM)]^{2+}$ viewed approximately along the C_2 axis. For clarity, only the amide hydrogens are shown. Selected bond lengths [Å] and angles [deg]: Mn−N1, 2.4351(11); Mn−N2, 2.4218(11); Mn−O1, 2.3128(10); Mn−O2, 2.3080(9); N1−Mn−N2, 73.73(4); N2−Mn−N1′, 73.79(4);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

Stability constants for the Mn(II) complexes of DOTA ($\log K = 19.89$)[40,41] and DO2A ($\log K = 14.54$)[40] have been previously reported. For $[Mn(DOTAM]^{2+}$ and $[Mn(DO3AM)]^{2+}$, thermodynamic binding studies have not been carried out. Incubation of solutions of $[Mn(DOTAM]^{2+}$ or $[Mn(DO3AM)]^{2+}$ with a 2-fold excess of EDTA, however, results in no changes in the relaxivities even after several days. EDTA is known[49] to bind Mn^{2+} with a dissociation constant of $\log K = 13.9$, and the reported R_1 of $[Mn(EDTA)]^{2-}$ is 2.20 mM^{-1} s^{-1}.[50] These results indicate that regardless of the thermodynamic stability of the complexes, they are kinetically inert to ligand substitution on the time scale of the relaxivity experiments.

X-ray Crystallography. [Mn(DOTAM)]Cl_2·2H_2O represents a relatively rare example of a structurally characterized 8-coordinate Mn(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-4-fold 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-

---

(44) Nwe, K.; Richard, J. P.; Morrow, J. R. *J. Chem. Soc., Dalton Trans.* **2007**, 5171–5178.

(45) Morris, D. F. C.; Short, E. L. *J. Chem. Soc.* **1961**, 5148–5153.

(46) Tribalat, S.; Caldero, J.-M. *C. R. Chim.* **1962**, *255*, 925–927.

(47) Gammons, C. H.; Seward, T. M. *Geochim. Cosmochim. Acta* **1996**, *60*, 4295–4311.

(48) Schultz, F. A.; Duncan, C. T.; Rigsby, M. A. Electrochemistry of the Group 7 Elements. In *Inorganic Electrochemistry*; Scholz, F.; Pickett, C. J., Eds.; Wiley-VCH: Weinheim, 2006, Vol. *7a*, pp 401−404; and references therein.

(49) Byegård, J.; Skarnemark, G.; Skålberg, M. *J. Radioanal. Nucl. Chem.* **1999**, *241*, 281–290.

(50) Tweedle, M. F.; Gaughan, G. T.; Hagen, J.; Wedeking, P. W.; Sibley, P.; Wilson, L. J.; Lee, D. W. *Nucl. Med. Biol.* **1988**, *15*, 31–36.

(51) Neupert-Laves, K.; Dobler, M. *Helv. Chim. Acta* **1977**, *60*, 1861–1871.

(52) Hughes, B. B.; Haltiwanger, R. C.; Pierpont, C. G.; Hampton, M.; Blackmer, G. L. *Inorg. Chem.* **1980**, *19*, 1801–1803.

(53) Neupert-Laves, K.; Dobler, M. *J. Crystallogr. Spectrosc. Res.* **1982**, *12*, 271–286.

Table 2. Selected Bond Distances and Angles for $[Mn(DOTAM)]^{2+}$, $[Mn(DO3AM)]^{2+}$, and $Mn(H_2DOTA)$

	$[Mn(DOTAM)]^{2+}$	$[Mn(DO3AM)]^{2+}$	$Mn(H_2DOTA)$
		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(deg)	
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)	

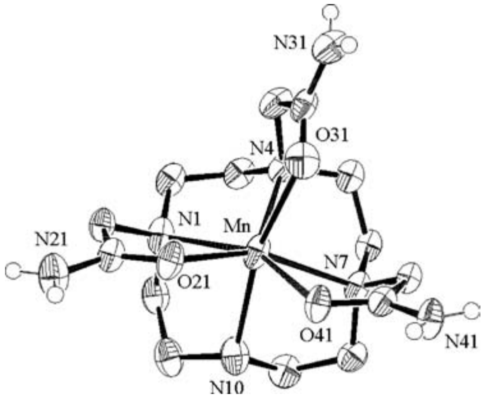


Figure 2. Molecular structure of $[Mn(DO3AM)]^{2+}$. For clarity, only the amide hydrogens are shown. Selected bond lengths [Å] and angles [deg]: Mn−N1, 2.423(4); Mn−N4, 2.342(4); Mn−N7, 2.351(4); Mn−N10, 2.312(5); Mn−O21, 2.162(4); Mn−O31, 2.297(4); Mn−O41, 2.238(3); N1−Mn−N4, 74.40(14); N4−Mn−N7, 77.12(13); 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).

arm macrocycles such as $[Mn(2\text{-pyridylmethyl})_4cyclen]^{2+}$, which has 2-pyridyl groups in place of the amide groups of DOTAM,[62] and $[Mn(pyrazol\text{-}1\text{-}ylmethyl)_4cyclen]^{2+}$ in which imadozole 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-4-fold 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 Cd^{2+} and Zn^{2+} complexes are 6-coordinate, while the Ca^{2+} 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 Mn^{2+} ion, however, has an effective ionic radius slightly smaller than that of Cd^{2+},[68] suggesting that there are other contributions that play a role in determining the observed solid state structure.

Crystals of $[Mn(DO3AM)][MnCl_4]\cdot EtOH$ 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 e Å^{-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 geometries[69−71] 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 2.374Å compared to 2.428Å

---

(54) Vardosanidze, T. O.; Sokol, V. I.; Sobolev, A. N.; Shvelashvili, A. E.; Porai-Koshits, M. A. *Zh. Neorg. Khim.* **1985**, *30*, 1745–1751.

(55) Zhorzholiani, N. B.; Shvelashvili, A. E.; Sobolev, A. N.; Vardosanidze, I. O. *Soobshch. Akad. Nauk Gruzi. SSR* **1986**, *123*, 541–544.

(56) Hagen, K. S. *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, K. D.; Liu, S.; Zubieta, J. *Inorg. Chim. Acta* **1993**, *211*, 171–175.

(59) Brychcy, K.; Jens, K. J.; 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, H. O. N.; Kahwa, I. A.; White, A. J. P.; Williams, D. J. *Inorg. Chem.* **1998**, *37*, 3868–3873.

(62) Bu, X.-H.; Chen, W.; Mu, L.-J.; Zhang, Z.-H.; Zhang, R.-H.; Clifford, T. *Polyhedron* **2000**, *19*, 2095–2100.

(63) Junk, P. C.; Smith, M. K.; Steed, J. W. *Polyhedron* **2001**, *20*, 2979–2988.

(64) Amin, S.; Voss, D. A., Jr.; Horrocks, W. D., Jr.; Lake, C. H.; Churchill, M. R.; Morrow, J. R. *Inorg. Chem.* **1995**, *34*, 3294–3300.

(65) Aime, S.; Barge, A.; Bruce, J. I.; Botta, M.; Howard, J. A. K.; Moloney, J. M.; Parker, D.; de Sousa, A. S.; Woods, M. *J. Am. Chem. Soc.* **1999**, *121*, 5762–5771.

(66) Hancock, R. D.; Reibenspies, J. H.; Maumela, H. *Inorg. Chem.* **2004**, *43*, 2981–2987.

(67) Bombieri, G.; Marchini, N.; Ciattini, S.; Mortillaro, A.; Aime, S. *Inorg. Chim. Acta* **2006**, *359*, 3405–3411.

(68) (a) Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr.* **1969**, *B25*, 925–946. (b) Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr.* **1970**, *B26*, 1046–1048.

(69) Inoue, M. B.; Navarro, R. E.; Inoue, M.; Fernando, Q. *Inorg. Chem.* **1995**, *34*, 6074–6079.

(70) Mikuriya, M.; Hatano, Y.; Asato, E. *Chem. Lett.* **1996**, 849–850.

(71) Hureau, C. H.; Blanchard, S.; Nierlich, M.; Blain, G.; Rivière, E.; Girerd, J.-J.; Anxolabéhère-Mallart, E.; Blondin, G. *Inorg. Chem.* **2004**, *43*, 4415–4426.

(72) Riley, D. P.; Weiss, R. H. *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, N. J. R.; Heinemann, F. W.; Ivanović-Burmazović, I. *Inorg. Chem.* **2007**, *46*, 2459–2470.

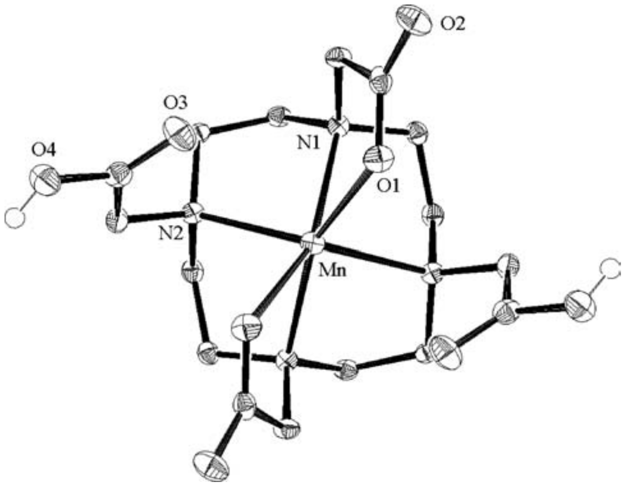


Figure 3. Molecular structure of Mn(H_2DOTA) viewed approximately along the C_2 axis. All hydrogens except −COOH have been omitted for clarity. Selected bond lengths [Å] and angles [deg]: Mn−N1, 2.3481(19); Mn−N2, 2.3803(18); Mn−O1, 2.1601(16); N1−Mn−N2, 74.72(6); N2−Mn−N1′, 76.99(6); O1−Mn−N1, 73.81(6); O1−Mn−O1′, 101.03(9).

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(H_2DOTA) is given in Figure 3 with some of the key structural parameters summarized in Table 2. The manganese ion is located on a crystallographic C_2 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 H_2DOTA^{2-} have been previously characterized, and the structure of Mn(H_2DOTA) is very similar to those of Cu(H_2DOTA) and Ni(H_2DOTA).[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.

^{1}H Relaxivities. The ^{1}H relaxivities of the complexes in water at 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 versus 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 Mn^{2+}(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(H_2DOTA) is an apparent exception to these trends (however, see below), with a relaxivity significantly lower than those of the other 6-coordinate species.

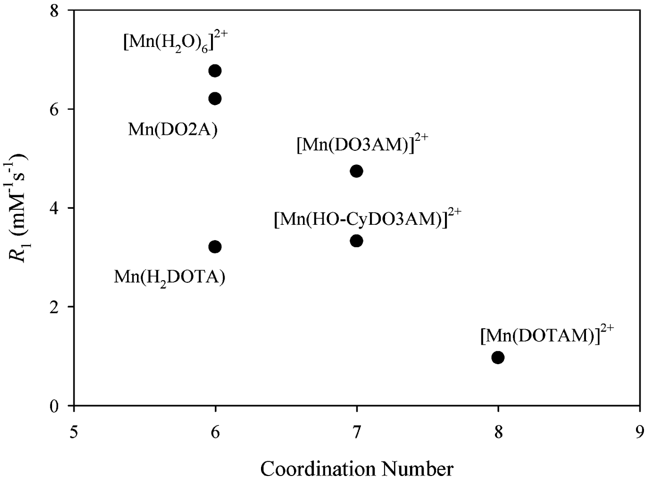


Figure 4. Graph of longitudinal relaxivities at 20 MHz and 37 °C vs crystallographically defined coordination number for the complexes in Table 3.

Table 3. Relaxivities of the Complexes in Water at 20 MHz and 37°C

complex	R_1 ($mM^{-1}s^{-1}$)	coordination no.
$[Mn(H_2O)_6](ClO_4)_2$	6.76[a]	6
Mn(DO2A)	6.20	6
Mn(H_2DOTA)	3.20	6
$[Mn(DO3AM)]Cl_2$	4.73	7
$[Mn(DO3AM\text{-}CyOH)]Cl_2$	3.32	7
$[Mn(DOTAM)]Cl_2$	0.96	8

[a] In 0.1 M $HClO_4$.

Manganese(II) is a substitutionally labile species, and the inner sphere contributions to the relaxivities of Mn^{2+}(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 Mn^{2+}(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 $[Mn(H_2O)_6]^{2+}$ and

---

(75) Riesen, A.; Zehnder, M.; Kaden, T. A. *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 1.5−6 mM^{-1} s^{-1}.

(77) Jackels, S. C.; Durham, M. M.; Newton, J. E.; Henniger, T. C. *Inorg. Chem.* **1992**, *31*, 234–239.

(78) Balogh, E.; He, Z.; Hseih, W.; Liu, S.; Tóth, E. *Inorg. Chem.* **2007**, *46*, 238–250.

(79) Ducommun, Y.; Newman, K. E.; Merbach, A. E. *Inorg. Chem.* **1980**, *19*, 3696–3703.

$[Mn_2(ENOTA)(H_2O)]$,[80] an 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, Mn^{2+} 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 $Mn(DO3AM\text{-}CyOH)^{2+}$, 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 Mn^{2+}(aq).[79] Such exchanges are expected to be faster that those proceeding through eight-coordinate intermediates because of relaxed steric constraints. The relative rates for complexes with the same overall coordination number are more likely to differ because of specific steric effects than electronic effects at the Mn^{2+} 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 H_2O, 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 versus time curves in the mixed solvent clearly exhibit bi-exponential behavior with the slow component corresponding to outer sphere relaxation (primarily CH_3) and the faster component to inner-sphere hydroxyl proton exchange. The best fit for Mn^{2+}(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.

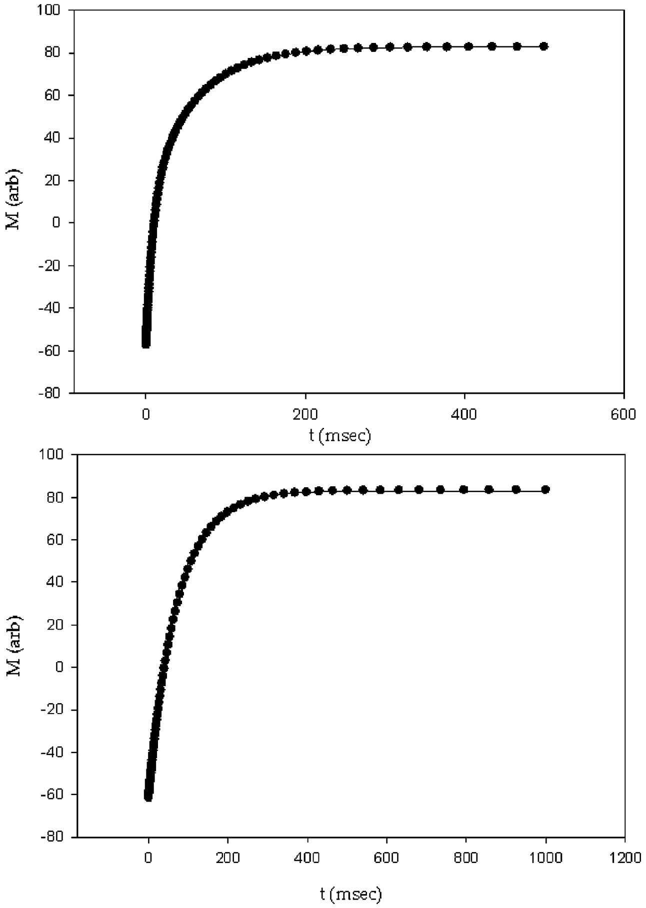


Figure 5. Magnetization vs time curves in 1:1 MeOH/H_2O for Mn^{2+}(aq) fit to bi-exponential kinetics (top) and $[Mn(DOTAM)]^{2+}$ fit to mono-exponential kinetics (bottom).

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 CH_3 and OH protons have essentially identical relaxation times because of similar through space dipole−dipole interactions with the Mn^{2+} ion. The apparent T_1 of the $[Mn(DOTAM)]^{2+}$ data is somewhat longer than that for the outer-sphere component of Mn^{2+}(aq) and is consistent with the increased size of the complex relative to Mn^{2+}(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 Mn^{2+}(aq), and thus consistent with the observed T_1 values.

It is also of note that the complexes in Table 3 have different charges, which might affect the relaxivities. For series of structurally related Gd^{3+} complexes, it has been generally found

---

(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, R. N.; Gillis, P. *J. Magn. Reson.* **2002**, *158*, 36–42.

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 Mn^{2+}(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 Mn^{2+}(aq), and they should be among the lowest relaxivities in the series. It is notable that Mn(DO2A) has the relaxivity most similar to Mn^{2+}(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(H_2DOTA) appears to be an exception. Although the crystal structure clearly indicates a six-coordinate Mn^{2+} 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 Mn^{2+} and excess H_2DOTA^{2-} 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(H_2DOTA) has a pH of 3.7, indicating significant ionization. The relaxivity versus pH curve for Mn(H_2DOTA) shows a prominent inflection with an effective pK_a of 2.79 and limiting R_1 values of 7.2 mM^{-1} s^{-1} at low pH (<2) and 2.7 mM^{-1} 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(H_2DOTA) has functional groups that are protonatable or deprotonatable over this pH range. Thus for all the complexes in Table 3, except Mn(H_2DOTA), there is only one significant species present in solution.

For Mn(H_2DOTA), 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. These predictions are consistent with the observed pH dependent relaxivity of Mn(H_2DOTA)[92] and will be the addressed in detail 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 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)]$^{2-}$, $R_1 = 4.34$ mM^{-1} 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 Mn^{2+}, 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 Mn^{2+}-based candidates for clinically useful contrast agents once a more complete understanding of their dynamics of interaction with water has been developed.

Acknowledgment. Drs. Neil R. Brooks and Victor G. Young, Jr. of the X-ray Crystallographic Laboratory at the University of Minnesota are acknowledged for the crystallographic analyses. Financial support from the National Institutes of Health (R15 GM061724) and Wesleyan University is also gratefully acknowledged.

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:H_2O solvent, and summary of electrochemical data (28 pgs). This material is available free of charge via the Internet at http://pubs.acs.org.

IC8003068

---

(84) Freed, J. H. *J. Chem. Phys.* **1978**, *68*, 4034–4037.

(85) Tóth, E.; Helm, L.; Merbach, A. E. *Top. Curr. Chem.* **2002**, *221*, 61–101.

(86) Abragam, A. *Principles of Nuclear Magnetism*; Oxford University Press: Oxford, 1961.

(87) Fries, P. H.; Belorizky, E. *J. Phys. (Paris)* **1978**, *39*, 1263–1282.

(88) Albrand, J. P.; Taieb, M. C.; Fries, P. H.; Belorizky, E. *J. Chem. Phys.* **1983**, *78*, 5809–5815.

(89) Gilbert, J.; Kassab, D.; Pawlow, J. H.; Santora, B. P.; Fiel, R. J.; Joshi, V. N.; Kozik, M. *Inorg. Chem.* **1995**, *34*, 924–927.

(90) Burai, L.; Tóth, E.; Bazin, H.; Benmelouka, M.; Jászberényi, Z.; Helm, L.; Merbach, A. E. *J. Chem. Soc., Dalton Trans.* **2006**, 629–634.

(91) Jocher, C. J.; Botta, M.; Avedano, S.; Moore, E. G.; Xu, J.; Aime, S.; Raymond, K. N. *Inorg. Chem.* **2007**, *46*, 4796–4798.

(92) Siddiqui, S. A.; Chipendo, P. I.; Westmoreland, T. D. *Abstracts of Papers*, 235th National Meeting of the American Chemical Society, New Orleans, LA, Apr 6−10, 2008; American Chemical Society: Washington, D.C., 2008; INOR 176.

(93) Siddiqui, S. A.; Chipendo, P. I.; Westmoreland. T. D., manuscript in preparation.

(94) Xie, D.; Kennan, R. P.; Gore, J. C. *Proc. Intl. Soc. Mag. Reson. Med.* **2001**, *9*, 890.