Inorg. Chem. **1992**, *31*, 234-239

Contribution from the Department of Chemistry, Wake Forest University, Winston-Salem, North Carolina 27109, and Department of Radiology, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103

Aqueous Proton NMR Relaxation Enhancement by Manganese(II) Macrocyclic Complexes: Structure–Relaxivity Relationships

Susan C. Jackels,* Melinda M. Durham, James E. Newton, and Todd C. Henninger

Received July 3, 1990

The magnetic field dependence of the aqueous proton NMR longitudinal relaxation rate (NMRD profile) has been studied for eight Mn^{2+} macrocyclic complexes. In one series of four complexes, the macrocyclic ring includes pyridine, two imines, and two or three amines, and its size is increased from 15 to 18 members. In a second series of complexes having 15-membered rings and five nitrogen donor atoms, the degree of saturation in the macrocyclic ring is varied. An additional complex is made coordinatively saturated by addition of two ethylamino pendant arms that fill the axial sites. The complexes were all isolated as halide salts and were characterized by elemental analyses, IR spectra, magnetic moments, and conductivities. EPR spectra of frozen aqueous/glycerol solutions are consistent with the number of coordinated water molecules varying between zero and two. The NMRD profiles show that, in the series in which the ring size is varied, the relaxivity is correlated to first order with the number of coordinated water molecules and the effect of geometry (through the zero-field splitting) is smaller. For this series the magnitude of the relaxivity per coordinated water molecule is approximately a factor of two higher than that per coordinated water molecule in the hexaaquamanganese(II) and $MnEDTA(H_2O)^{2-}$ complexes. In contrast, in the series of 15-membered ring complexes in which the degree of saturation is varied, relaxivity per coordinated water molecule decreases with increasing saturation in the ligand. In the limit of complete saturation, the same value of relaxivity per coordinated water molecule is observed as for the hexaaquamanganese(II) and $MnEDTA(H_2O)^{2-}$ complexes. From parameters obtained by fitting the NMRD profiles with the dipolar Solomon–Bloembergen–Morgan equations, it is seen that the effective distance between the metal center and proton nucleus is significantly shortened in cases with ligand unsaturation. Since there is no evidence for abnormally short Mn–O bonds in these complexes, it can be concluded that the unusually high relaxivity results from a departure from the point dipole model in the unsaturated complexes.

Introduction

At present there is renewed interest in aqueous proton NMR relaxation rates in solutions of paramagnetic metal complexes due to the recent applications of complexes as diagnostic agents in medical magnetic resonance imaging.[1,2] In tissue, the complexes cause increases in the aqueous proton NMR relaxation rate of water and thereby enhance contrast in magnetic resonance images.[3] Complexes of gadolinium(III) with ligands such as DTPA (diethylenetriaminepentaacetate)[4] or DOTA (1,4,7,10-tetraazacyclododecanetetraacetate)[5] have been most useful because of their high stability, high magnetic moment, and long electron spin relaxation time. Complexes of Mn(II and III)[6,7] and Fe(III)[8] also are potential contrast agents. The quantitative understanding of aqueous proton NMR relaxation rates in solutions of paramagnetic chelates is important toward understanding the relationship between relaxation rate and structure of the complex and maximizing the relaxation enhancement effect.

Relaxation rates in solutions of paramagnetic aquated ions were studied in the 1950s and are quantitatively predicted through a model featuring the dipole–dipole interaction of the electron spin moment of the metal ion and the nuclear spin of the proton as expressed in the Solomon–Bloembergen–Morgan equation (dipolar contribution only) for T_1 relaxation of protons in a coordinated water molecule

$$\left(\frac{1}{T_1}\right)_M = \left(\frac{2}{15}\right)\left(\frac{\gamma_I^2 g^2 S(S+1)\beta^2}{r^6}\right)\left\{\frac{7\tau_c}{1+\omega_s^2\tau_c^2}+\frac{3\tau_c}{1+\omega_I^2\tau_c^2}\right\} \quad (1)$$

where γ_I is the proton gyromagnetic ratio, g is the electronic g factor, S is the total electron spin of the metal ion, β is the Bohr magneton, r is the proton–metal ion distance, and ω_s and ω_I are the electronic and proton Larmor frequencies. The correlation time τ_c is given by

$$\frac{1}{\tau_c} = \frac{1}{\tau_r} + \frac{1}{\tau_M} + \frac{1}{\tau_s} \quad (2)$$

where τ_r is the rotational correlation time (on the order of 10^{-11} s for a moderate molecular weight complex), τ_M is the average residence time of a water molecule in the coordinated state (on the order of 10^{-6}–10^{-9} s for a labile metal ion), and τ_s is the electron spin relaxation time of the metal ion (on the order of 10^{-9} s for Mn(II)). Bloembergen and Morgan developed the following equation to express the frequency dependence of τ_s:

$$\frac{1}{\tau_s} = C\left(\frac{\tau_v}{1+\omega_s^2\tau_v^2}+\frac{4\tau_v}{1+4\omega_s^2\tau_v^2}\right) \quad (3)$$

Here C is proportional to the square of the fluctuations in the zero-field splitting, τ_v is the correlation time for the fluctuations, and the other parameters are as defined above. When eq 3 is incorporated into the definition of τ_c given in eq 2, the resulting equation, eq 1, is known as the dipolar Solomon–Bloembergen–Morgan (SBM) equation. Under conditions of rapid aqueous exchange, the observed ^1H relaxation rate is related to $(1/T_1)_M$ by eq 4, where $(1/T_1)_{solv}$ is the relaxation rate of pure water, q

$$(1/T_1)_{obs} = (1/T_1)_{solv} + (q[M]/55.5)(1/T_1)_M \quad (4)$$

is the number of coordinated water molecules in the complex and [M] is the concentration of the complex. This equation is often expressed in terms of relaxivity, R_1

$$(1/T_1)_{obs} = (1/T_1)_{solv} + R_1[M] \quad (5)$$

where R_1 is equal to $(q/55.5)(1/T_1)_M$. A full discussion of the theory and references can be found in ref 9.

It would be useful to extend this understanding to include prediction of the magnitude and field dependence of the relaxation enhancement by metal chelate complexes. However, in some cases the effect of metal chelates relative to their aquated ions has not been accurately predicted by simple variation of the number of

---

* Address correspondence to Wake Forest University.

(1) Koenig, S. H.; Brown, R. D., III. *Magn. Reson. Med.* **1984**, *1*, 478.

(2) For recent reviews see: (a) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901. (b) Jackels, S. C. In *Pharmaceuticals in Medical Imaging*; Swanson, D. P., Chilton, H. M., Thrall, J. H., Eds.; Macmillan: New York, 1990; Chapter 20.

(3) Carr, D. H.; Brown, J.; Byddder, G. M., et al. *Lancet* **1984**, 484.

(4) Weinmann, H.-J.; Brasch, R. C.; Press, W.-R.; Wesbey, G. E. *Am. J. Roent.* **1984**, *142*, 619.

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

(6) Rocklage, S. M.; Cacheris, W. P.; Quay, S. C.; Hahn, F. E.; Raymond, K. N. *Inorg. Chem.* **1989**, *28*, 477.

(7) Chen, C.; Cohen, J. S.; Myers, C. E.; Shon, M. *FEBS Lett.* **1984**, *168*, 70.

(8) Lauffer, R. B.; Vincent, A. C.; Padmanabhan, S.; Meade, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 2216.

(9) Bertini, I.; Luchinat, C. *NMR of Paramagnetic Molecules in Biological Systems*; Benjamin/Cummings: Menlo Park, CA, 1986.

0020-1669/92/1331-0234$03.00/0

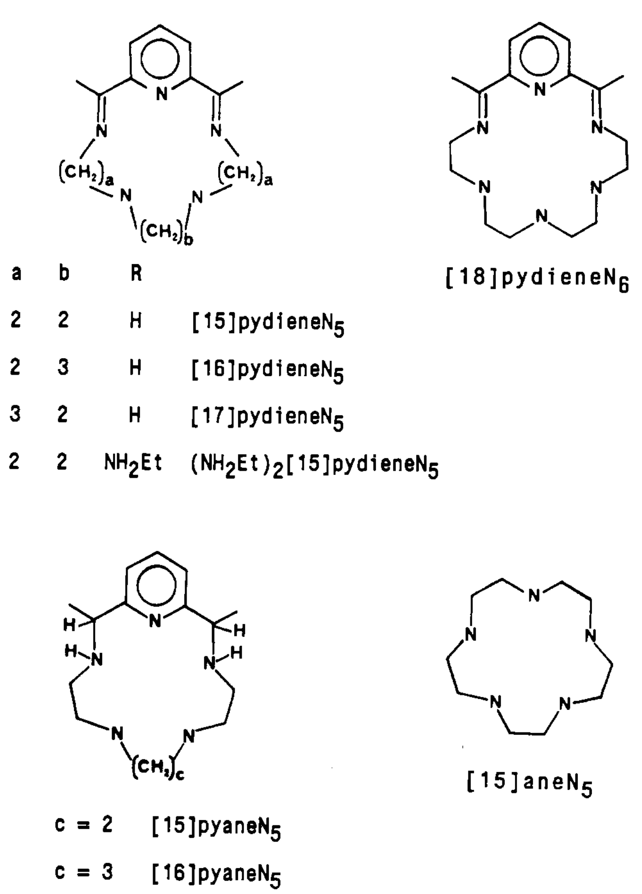


Figure 1. Macrocyclic ligands.

coordinated water molecules and the SBM equations.[10] The chelating ligand can affect the relaxation rate in four major ways: (1) restricting the number of aqueous coordination sites; (2) altering the intrinsic Mn–OH_2 proton relaxation rate through effects of bonding and/or coordination geometry; (3) providing additional relaxation mechanisms through specific solvent interactions such as hydrogen bonding; (4) changing the effective correlation times through the electron spin relaxation rate, the aqueous exchange rate, or the rotational tumbling rate.

The purpose of the project reported herein is to study a family of solution-characterized metal complexes in which there are structural variations designed to experimentally demonstrate the relationships between aqueous proton relaxation rate and structure of the chelating ligand and its complex. A better understanding of the effects of the chelating ligand on relaxation by paramagnetic ions can be achieved by investigating the magnetic field dependences of the relaxation rate[11] and comparing the results to the prediction of the SBM theory. Macrocyclic ligands were chosen because they form highly stable complexes that are kinetically inert to exchange in solution and provide one or more coordination sites for rapidly exchanging water molecules. Additionally, macrocyclic ligands are synthetically versatile and can be used to vary the coordination geometry, the number of coordinated water molecules, and the degree of saturation in the ligand. Mn(II) was selected because it is an effective relaxation enhancer due to its high magnetic moment and long electron spin relaxation time.

Table I. Conductance Measurements and Magnetic Moments

compd	Λ_M[a]	Λ_0[a]	slope[a]	μ_{eff}[b]
Mn([15]pydieneN_5)Cl_2·6H_2O	221	126	209	5.85
Mn([15]pyaneN_5)Cl_2	187	100	124	5.92
Mn([15]aneN_5)ClPF_6·$^3/_2H_2O$	207	117	296	5.83
Mn[(NH_2Et)$_2$[15]pydieneN_5]Cl_2·3H_2O	239	140	250	5.84
Mn([16]pydieneN_5)Cl_2·2H_2O	182	97	126	5.72
Mn([16]pyaneN_5)Cl_2	220	118	162	5.76
Mn([17]pydieneN_5)Cl_2	186	105	179	5.87
Mn([18]pydieneN_6)I_2·$^3/_2H_2O$[c]				5.99
2:1 electrolyte in H_2O	225–270	75–150	200	

[a] Λ_M is the molar conductance for a 10^{-3} M solution, Λ_0 is the conductance at infinite dilution (units: Ω^{-1} cm^2 equiv^{-1}), and the Onsager slope is in units of Ω^{-1} cm^{-1}. All measurements are in aqueous solution. [b] In units of μ_B. [c] Not stable enough for accurate measurement.

The well-established methods for preparing highly stable macrocyclic complexes of Mn(II) were used[12-18] to synthesize complexes of the ligands shown in Figure 1. In one series of ligands the macrocyclic ring contains pyridine, two imines, and two or three amines while the ring size is varied from 15 through 18. In a second series of complexes, all having 15 members and five nitrogen donor atoms, the degree of saturation is varied. A coordinatively saturated complex was prepared by attaching two ethylamino pendant arms to fill the axial sites. The complexes were isolated as halide salts and characterized by elemental analyses, IR and EPR spectra, magnetic moments, and conductivities. The complexes of [15]aneN_5 and (NH_2Et)$_2$[15]pydieneN_5 were new and their synthesis and characterization have been reported separately.[17,18] For each complex the NMRD profile was measured at three temperatures. These results are examined in relation to the solution structures derived from characterization data and in comparison to other Mn(II) complexes and the prediction of the SBM theory.

Experimental Section

Materials. The starting materials for the preparation of the compounds were purchased from Aldrich Chemical Co. and Fisher Scientific Co. and used without further purification. $MnCl_2$ was purchased as the tetrahydrate and was dried under vacuum at room temperature to remove most of the hydration.

Methods. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Infrared spectra were obtained on mineral oil mulls on KBr plates using a Perkin-Elmer 1330 infrared spectrometer. A Cahn 7600 Faraday balance was used to determine magnetic moments using Hg(Co(SCN)$_4$)) as the standard. Diamagnetic corrections were estimated using Pascal's constants. Conductance measurements were obtained using a YSI 35 conductance meter and an immersion cell. EPR spectra on polycrystalline samples at room temperature were obtained using a Varian E-109 spectrometer with a Varian E-102 microwave bridge at 9.1 GHz. EPR spectra of complexes in aqueous/glycerol glass (50/50) at approximately 10 K were obtained in the laboratory of W. Orme-Johnson at the Massachusetts Institute of Technology using a Varian E-line spectrometer and cryogenic equipment designed in house. Nuclear magnetic relaxation dispersion (NMRD) profiles were obtained using a field cycling relaxometer in the laboratory of Seymour H. Koenig at the IBM T. J. Watson Research Center. The instrument[11] is capable of making rapid measurements of $1/T_1$ over the range of 0.01–50 MHz with an uncertainty in $1/T_1$ of ± 0.5%. In this method, the sample is allowed to reach its equilibrium magnetization in a high field corresponding to 50 MHz resonance frequency. Then the field is reduced very rapidly, using a highly regulated current in a liquid-nitrogen-cooled solenoid, to the "measure field" at which T_1 is to be determined. After a variable time interval, the field is switched to that corresponding to 7.5 MHz where the magnetization is determined using a spin-echo pulse sequence. This specially designed instrument has been described in ref 11. The concentrations of solutions of manganese complexes were determined by ICP atomic absorption spectrophotometry.

---

(10) Rusnak, L. L.; Jordan, R. B. *Inorg. Chem.* **1976**, *15*, 709.

(11) (a) Koenig, S. H.; Brown, R. D., III. In *NMR Spectroscopy of Cells and Organisms*; Gupta, R. K., Ed.; CRC Press: Boca Raton, FL, 1989; Vol. II, p 75. (b) Koenig, S. H.; Brown, R. D., III. In *Metal Ions In Biological Systems*, Siegel, H., Ed.; Marcel Dekker: New York, 1987; Vol. 21, Chapter 6.

(12) Alexander, M. D.; Van Heuvelen, A.; Hamilton, H. G., Jr. *Inorg. Nucl. Chem. Lett.* **1970**, *6*, 445.

(13) Rakowski, M. C.; Rycheck, M.; Busch, D. H. *Inorg. Chem.* **1975**, *14*, 1194.

(14) Dabrowiak, J. C.; Nafie, L. A.; Bryan, P. S.; Torkelson, A. T. *Inorg. Chem.* **1977**, *16*, 540.

(15) Drew, M. G. B.; Bin Othman, A. H.; McFall, S. G.; McIlroy, P. D. A.; Nelson, S. M. *J. Chem. Soc., Dalton Trans.* **1977**, 438.

(16) Nelson, S. M. *Pure Appl. Chem.* **1980**, *52*, 2461.

(17) Newton, J. E.; Jackels, S. C. *J. Coord. Chem.* **1988**, *19*, 265.

(18) Wagnon, B. K.; Jackels, S. C. *Inorg. Chem.* **1989**, *28*, 1923.

Preparations. Mn([15]pydieneN$_5$)Cl$_2$·6H$_2$O, Mn([16]pydieneN$_5$)Cl$_2$·2H$_2$O, and Mn([17]pydieneN$_5$)Cl$_2$. These three complexes were prepared by modifications of the method of Alexander et al.[12] Solutions of stoichiometric amounts of MnCl$_2$ and 2,6-diacetylpyridine in absolute EtOH and of the appropriate polyamine in absolute EtOH were combined and heated under reflux for 1–3 h. The complex precipitated upon cooling. The first and third were orange powders while the second was yellow. Recrystallization from aqueous ethanol afforded crystalline compounds with elemental analyses consistent with the formulations listed in Table I.

Mn([18]pydieneN$_6$)I$_2$·$^3/_2$H$_2$O. This complex is previously unreported in the literature, so its preparation will be described in detail. MnCl$_2$ (3.5 g, approximately 0.03 mol) and diacetylpyridine (3.26 g, 0.02 mol) were dissolved in 40 mL of EtOH. Tetraethylenepentamine (3.79 mL, 0.02 mol) was dissolved in 10 mL of EtOH and was added dropwise to the first solution. The mixture was heated at reflux for 2 h during which the volume was reduced by about one-third. The red solution was filtered while hot, and a solution of KI (6.6 g, 0.04 mol) in 10 mL of H$_2$O was added dropwise. A golden microcrystalline precipitate formed upon cooling. This product (4.1 g) was collected and recrystallized from 50 mL of EtOH and 25 mL of H$_2$O, and then collected and dried at room temperature under vacuum to give the analytically pure product with the formulation as shown in Table I (1.4 g).

Mn([15]pyaneN$_5$)Cl$_2$. This complex was prepared[13] by catalytic reduction of Mn[15]pydieneN$_5$ using Ni–Al alloy in aqueous NaOH under N$_2$. A 17.0-g sample of [Mn([15]pydieneN$_5$)]Cl$_2$·6H$_2$O was dissolved in 75 mL of H$_2$O and purged with N$_2$. Ni–Al catalyst (3 g, Aldrich Chemical Co) and solid NaOH (3 g) were added alternately at a rate suitable to avoid frothing. The mixture was stirred for 3 h and then another 1 g of NaOH was added. The mixture was filtered, resulting in a pale yellow orange solution. The solution was neutralized to pH 7–8 with HCl, and the resulting precipitate of aluminum hydroxide was filtered off. Absolute EtOH was added to the filtrate followed by NH$_4$PF$_6$ (5.6 g in 15 mL of H$_2$O). Upon evaporation under reduced pressure and cooling, a pale yellow precipitate appeared. This solid was collected, washed with H$_2$O and dried under vacuum at room temperature (about 6.3 g). This mixed salt (ClPF$_6$) of the desired complex was converted to the dichloride by dissolving it in CH$_3$CN, filtering the solution, and adding Et$_4$NCl (2.5 g in 10 mL of CH$_3$CN). A microcrystalline orange solid formed immediately. This product was washed with CH$_3$CN, collected, and dried under vacuum at room temperature, yielding 3.9 g of Mn([15]pyaneN$_5$)Cl$_2$.

Mn([16]pyaneN$_5$)Cl$_2$. First, the protonated ligand salt [16]pyaneN$_5$·4HNO$_3$·H$_2$O was prepared by the method of Rakowski et al.[13] Then this ligand salt was suspended in MeOH while 4 equiv of NaOMe were added. All solids dissolved, and excess NaOMe was added until the solution tested strongly basic by pH paper. The resulting solution was filtered and evaporated to dryness under reduced pressure, and the residue was extracted three times with CHCl$_3$. The combined clear colorless extracts were evaporated to dryness, resulting in a white solid that was dried in a vacuum at room temperature. The yield of [16]pyaneN$_5$ was quantitative. The manganese complex was prepared by combining stoichiometric amounts of MnCl$_2$ and [16]pyaneN$_5$ in EtOH. After heating for 2 h, the volume was reduced by boiling and the solution was stored in a refrigerator for several days. The pale peach-colored solid was collected by suction filtration and dried under vacuum at room temperature.

Mn([15]aneN$_5$)ClPF$_6$·$^3/_2$H$_2$O and Mn[(NH$_2$Et)$_2$[15]pydieneN$_5$]Cl$_2$·3H$_2$O. These compounds were prepared as described in refs 17 and 18.

Results and Discussion

Characterization of Complexes. All of the compounds had satisfactory elemental analyses, confirming that the compounds are Mn(II) salts with composition as shown in Table I. The magnetic moments given in Table I indicate that all contain high-spin Mn(II). The magnetic moments of the 16-membered ring complexes are similar to those reported previously for other halide salts of the same Mn(II) complex and have been attributed to antiferromagnetic interaction caused by bridging of metal centers through axial ligands in the solid state.[15] Since the proton relaxation rate depends on the detailed structure of the complex in aqueous solution, special attention was given to solution characterization methods.

Conductance measurements on aqueous solutions over the concentration range 10^{-2}–10^{-4} M give the results shown in Table I. The molar conductivities at 10^{-3} M all fall in the range expected for 2:1 electrolytes having a relatively high molecular weight cation.[19,20] These results are supported by plots of the Onsager limiting law that give slopes and intercepts as shown in Table I. The high slope for the Mn[15]aneN$_5$$^{2+}$ complex is consistent with other results[17] indicative of a significant amount of dissociation of the macrocyclic ligand especially at low concentration. For this reason all solution measurements on this complex were performed on solutions containing a 100% excess of macrocyclic ligand in order to ensure complete complexation of Mn(II). No evidence for macrocyclic ligand dissociation was seen in any of the other cases, although the complexes of the 17 and 18-membered ring systems did show instability in aqueous solution over a period of hours. This was evidenced by formation of a brown precipitate.

Table II. EPR Absorptions for Manganese Compounds in the Polycrystalline Solid State[a]

compd	EPR absorptions, G
Mn([15]pydieneN$_5$)Cl$_2$·6H$_2$O	600 w, sh; 1100 sh; 1900 sh; 2800 sh; 3200 main; 4750 sh; 6200; 8200 sh
Mn([15]pyaneN$_5$)Cl$_2$	3200 br, main
Mn([15]aneN$_5$)ClPF$_6$·$^3/_2$H$_2$O	1250 sh; 2300 main; 3600 sh; 6150 sh; 8600 sh; 9700 sh
Mn[(NH$_2$Et)$_2$[15]pydieneN$_5$]Cl$_2$·3H$_2$O	450 sh; 1400 main; 2200 sh; 3100; 4100 sh; 5600; 8150 sh
Mn([16]pydieneN$_5$)Cl$_2$·2H$_2$O	2400 main; 3350 sh; 4800 sh; 6350 sh; 8600 sh
Mn([16]pyaneN$_5$)Cl$_2$	3250 br, main
Mn([17]pydieneN$_5$)Cl$_2$	1660 main; 3400; 5200 sh; 7700 sh; 8400 sh
Mn([18]pydieneN$_6$)I$_2$·$^3/_2$H$_2$O	near zero; 1000 sh; 2250 main; 3000 sh; 5100 sh; 6900 sh

[a] Conditions: 298 K; 9.1 GHz; 20 mW microwave power; 100 kHz modulation frequency.

Table III. EPR Absorptions for Manganese Complexes in Glycerol/D$_2$O Glass[a]

compd	EPR absorptions, G
Mn([15]pydieneN$_5$)Cl$_2$·6H$_2$O	500 w, sh; 1150 sh; 2200 sh; 2950 main; 5000 sh
Mn([15]pyaneN$_5$)Cl$_2$	500 w, sh; 1200 sh; 1900 sh; 2900 main; 5000 sh
Mn([15]aneN$_5$)ClPF$_6$·$^3/_2$H$_2$O	400 sh; 900 sh; 2100 sh; 3000 main; 4500 sh
Mn[(NH$_2$Et)$_2$[15]pydieneN$_5$]Cl$_2$·3H$_2$O	1350 main; 2300 sh; 3200; 4650 sh; 7000 sh
Mn([16]pydieneN$_5$)Cl$_2$·2H$_2$O	600 sh; 1000 sh; 1800 sh; 2900 main; 5000 sh
Mn([16]pyaneN$_5$)Cl$_2$	3250 br, main
Mn([17]pydieneN$_5$)Cl$_2$	500 sh; 1100 sh; 2100 sh; 3150 main; 4400 sh
Mn([18]pydieneN$_6$)I$_2$·$^3/_2$H$_2$O	600 sh; 1200 sh; 2300 main; 3700 sh; 6000 sh

[a] Conditions: 14 K; 1:1 glycerol:D$_2$O; 9.1 GHz; 1 mW microwave power; 100 kHz modulation frequency.

EPR spectra of the complexes are especially helpful for characterizing the coordination sphere in solution. The EPR absorptions for the complexes in the solid state and in frozen glycerol/D$_2$O glass (14 K) are listed in Tables II and III. The EPR spectra of some of the complexes in the solid state have been described previously.[17,18,21] Dowsing and Gibson[22,23] have shown that in general the zero-field parameters for high-spin Mn(II) complexes can be estimated from a comparison of the observed

---

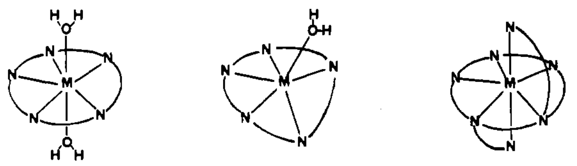
(19) Davies, J. A.; Hartley, F. R.; Murray, S. G. *Inorg. Chim. Acta* **1980**, *43*, 69.

(20) Feltham, R. D.; Hayter, R. G. *J. Chem. Soc.* **1964**, 4582.

(21) Van Heuvelen, A.; Lundeen, M. D.; Hamilton, H. G., Jr.; Alexander, M. D. *J. Chem. Phys.* **1969**, *50*, 489.

(22) Dowsing, R. D.; Gibson, J. F. *J. Chem. Phys.* **1964**, *50*, 294.

(23) Dowsing, R. D.; Gibson, J. F.; Goodgame, M.; Hayward, P. J. *J. Chem. Soc. A* **1969**, 187.



[15]pydieneN$_5$
[16]pydieneN$_5$
[15]pyaneN$_5$
[16]pyaneN$_5$

[17]pydieneN$_5$
[15]aneN$_5$
[18]pydieneN$_6$

(NH$_2$Et)$_2$[15]pydieneN$_5$

Figure 2. Structural classification of manganese(II) complexes of the ligands shown.

EPR lines with diagrams of calculated lines for various D and λ values. Here D is the axial zero-field-splitting parameter and E is a measure of the asymmetry of the field along the x and y directions. λ is the ratio of E and D and varies between 0 for axial or octahedral symmetry and 1/3 for rhombic symmetry.[24] Typically, complexes with axially symmetric ligand fields have $\lambda = 0$ and D in the range of zero to several reciprocal centimeters depending on the nature of the axial ligands. For axial systems this gives a spectrum with the major EPR line centered near $g = 2$ (3400 G) for small values of λ and near $g = 6$ (1100 G) for large values of D. As the symmetry is lowered, the major absorption splits and shifts toward $g = 4.3$ corresponding to the increase in λ.

The spectrum of Mn([15]pydieneN$_5$)Cl$_2$·6H$_2$O has been interpreted by Van Heuvelen et al.[21] as indicating approximate axial symmetry (λ near zero) with D about 0.1 cm^{-1}. Crystallographic results[25-27] on similar Mn(II) complexes having [15]pydieneN$_5$ or [15]pydieneN$_3$O$_2$ ligands show that in both cases the N$_5$ or N$_3$O$_2$ donor atoms closely approximate a planar pentagon. For Mn([15]pydieneN$_5$)Cl$_2$·6H$_2$O, it is not known whether water or chloride is coordinated in the solid state, but due to the similar ligand field strength of these two ligands similar D values are expected in either case. Accordingly, the spectrum of Mn([15]pydieneN$_5$)$^{2+}$ observed in frozen aqueous glycerol is also indicative of approximate axial symmetry (main absorption near $g = 2$). The high- and low-field shoulders on the main absorption are consistent with a small value of D, about 0.1 cm^{-1}. A comparison of the solid state absorptions for Mn([16]pydieneN$_5$)$^{2+}$ and Mn([15]pydieneN$_5$)$^{2+}$ reveals that the main absorption is shifted by 900 G toward lower field in the former case. This shift is consistent with lowering of symmetry from axial toward rhombic. Thus the replacement of a five-membered chelate ring by a six-membered ring and the increase in total ring size may lead to a significant distortion of the N$_5$ macrocyclic ring in this case. The only crystallographic results available[27] are for a compound that has *o*-phenanthroline cocrystallized with Mn([16]pydieneN$_5$)$^{2+}$, and in this case the pyridine and phen groups are stacked in a lamellar fashion and the N$_5$ atoms are nearly planar (maximum deviation from the N$_5$ plane 0.03 Å). For the chloride salts of the two macrocyclic complexes, the frozen-solution spectra are almost identical. Thus, in solution the same approximately axially symmetric structure is assigned for the 15- and 16-membered ring complexes. The partially saturated complex, Mn([15]pyaneN$_5$)$^{2+}$, gives results similar to those for the parent diene ligand and is assigned the same structure in solid state and in solution. Although the EPR results for Mn([16]pyaneN$_5$)$^{2+}$ indicate magnetic interactions in both the solid state and in solution, thus rendering the EPR spectra uninformative, a reasonable assumption is that the structure of this complex is similar to that of Mn([16]pydieneN$_5$)$^{2+}$ and the analogous 15-membered ring cases. Therefore, in Figure 2 these four complexes are grouped together under the structure having approximate axial symmetry with two axial water molecules in aqueous solution.

In contrast to the 15- and 16-membered ring cases, Mn([17]pydieneN$_5$)$^{2+}$ presents evidence of a folded macrocyclic ligand that causes steric crowding on one side of the complex so that only one axial ligand is coordinated. This is seen in the formation of mixed salts such as ClPF$_6$ that have 1:1 electrolyte behavior in nonaqueous solution. Dabrowiak et al.[14] concluded that the ligand was folded in the solid state from infrared stretches in the NH region. The crystal structure[15] of Mn([17]pydiene)N$_5$(NCS)$_2$ does have both NCS ligands coordinated, but these are at significantly different Mn–N distances (2.17 and 2.29 Å) and the N$_5$ plane deviates from planarity much more than in the 15- and 16-membered ring cases (maximum deviation 0.46 Å). The EPR spectrum of Mn([17]pydieneN$_5$)Cl$_2$ in the polycrystalline solid state (Table II) has the main absorption near $g = 4$ consistent with rhombic symmetry and a folded ligand. In frozen solution the main absorption is observed at 3150 G near $g = 2$; however, there is also a very prominent absorption near $g = 4$. This spectrum is consistent with a folded ligand having less distortion than in the solid state and one axial ligand. Mn([15]aneN$_5$)$^{2+}$ is similar to Mn([17]pydieneN$_5$)$^{2+}$ in that it forms mixed salts, has a rhombic EPR spectrum in the polycrystalline solid state, and in frozen solution has the main absorption near $g = 2$ with an additional prominent feature near $g = 4$. The characterization of this complex has been previously reported,[17] and it is placed in the same structural category with Mn([17]pydieneN$_5$)$^{2+}$.

Mn([18]pydieneN$_6$)I$_2$·$^3/_2$H$_2$O has a polycrystalline solid-state EPR spectrum with rhombic character intermediate between Mn([16]pydieneN$_5$)Cl$_2$ and Mn([17]pydieneN$_5$)Cl$_2$. Due to the six nitrogen donors supplied by the macrocyclic ligand, it was anticipated that this complex might be coordinatively saturated by the macrocycle. In frozen aqueous solution this complex has the main absorption significantly shifted toward $g = 4$, consistent with rhombic distortion. These results cannot discriminate between a coordinatively saturated complex and a seven-coordinate species containing one bound water molecule. It will be seen below that the magnetic resonance data clearly indicate the presence of one coordinated water molecule.

Mn[(NH$_2$Et)$_2$[15]pydieneN$_5$]Cl$_2$·3H$_2$O is a very interesting case because the EPR spectra under both solid-state and solution conditions are nearly identical, with the main absorption occurring near $g = 4.8$. Thus, this case is axially symmetric like [15]pydieneN$_5$ but the axial splitting is greater than 0.2 cm^{-1}, consistent with the ethylamino groups coordinated in both solid state and in solution. For all of the complexes the lack of nuclear hyperfine structure in the low-temperature spectra and in the solid state is consistent with a significant amount of ZFS due to the asymmetry of the crystal field.[28] In room-temperature aqueous solution, all of the complexes exhibit relatively intense sextet EPR spectra with variable broadening and splitting due to nitrogen hyperfine interactions.

In summary, the complexes can be grouped into three structural categories as listed in Figure 2. The number of aqua ligands postulated for each complex is consistent with the symmetry at the metal center as determined from the EPR spectra in frozen solution. Thus, axial symmetry implies a planar macrocycle and two axial ligands; rhombic symmetry implies a distorted or folded macrocycle and one axial ligand. The presence of multiple species in solution due to NH or CH isomers cannot be ruled out; however, the EPR spectra are reasonably sharp and indicative of a single major species in each case.

NMRD Profiles. Figure 3 shows the NMRD profiles of all the complexes having [X]pydieneN$_y$ ligands. Data for 5 °C are included because all of the complexes are sufficiently stable in solution for data collection at this temperature. The four complexes having [15–18]pydieneN$_y$ ligands have sigmoidal-shaped

---

(24) Blumberg, W. E. In *Magnetic Resonance in Biological Systems*; Ehrenberg, A., Malmstrom, B. E., Vanngard, T., Eds.; Pergamon Press: London, 1967; p 119.

(25) Drew, M. G. B.; Bin Othman, A. H.; McFall, S. G.; McIlroy, P. D. A.; Nelson, S. M. *J. Chem. Soc., Dalton Trans.* **1977**, 1173.

(26) Alcock, N. W.; Liles, D. C.; McPartlin, M.; Tasker, P. A. *J. Chem. Soc., Chem. Commun.* **1974**, 727.

(27) Drew, M. G. B.; Bin Othman, A. H.; McFall, S. G.; Nelson, S. M. *J. Chem. Soc., Chem. Commun.* **1977**, 558.

(28) Birdy, R. B.; Goodgame, M. *Inorg. Chem.* **1979**, *18*, 472.

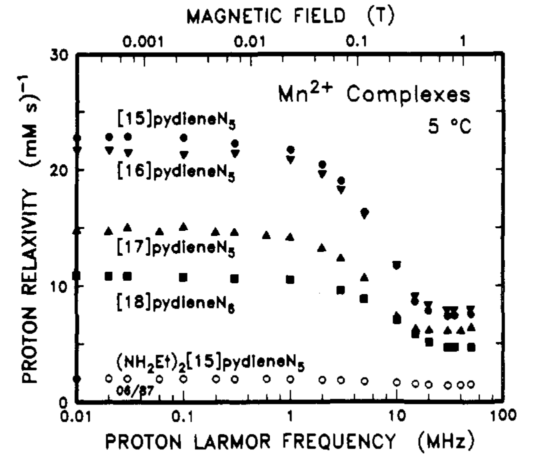


Figure 3. Aqueous proton relaxivity versus proton Larmor frequency (NMRD profiles) for aqueous solutions of Mn(II) complexes at 5 °C.

Table IV. Frequencies (MHz) of the Inflection Points in the NMRD Profiles of Manganese Complexes at Different Temperatures

complex	5 °C	25 °C	35 °C
$Mn([15]pydieneN_5)(H_2O)_2^{2+}$	5.5	5.8	5.8
$Mn([15]pyaneN_5)(H_2O)_2^{2+}$	5.9	6.2	6.5
$Mn([15]aneN_5)(H_2O)^{2+}$	7.1	11.5	13.4
$Mn([16]pydieneN_5)(H_2O)_2^{2+}$	6.2	5.5	5.6
$Mn([16]pyaneN_5)(H_2O)_2^{2+}$	4.8	5.1	5.4
$Mn([17]pydieneN_5)(H_2O)^{2+}$	5.3	8.1	
$Mn([18]pydieneN_6)(H_2O)^{2+}$	9.0		

curves qualitatively consistent with proton relaxation by dipolar interaction between the coordinated water protons and paramagnetic center as described by eq 1. No indication of a dispersion at low field arising from scalar interaction is seen. Also, the absence of low-field dispersion verifies that there is no detectable hexaaquamanganese(II) ion in the solutions. The low-field relaxivities ($\omega_S\tau_c \ll 1$) span a range from 7 to 23 (mM s)$^{-1}$, and at high field these are seen to disperse to about 30% of the low-field limit as predicted by eq 1. The correlation time for each curve can be estimated from the frequency at the inflection point of the dispersion where $\omega_S\tau_c = 1$. The inflection frequencies are listed in Table IV. With the exception of $Mn([18]pydieneN_6)^{2+}$, each curve has its inflection at about 6 MHz corresponding to τ_c of about 4.0×10^{-11} s. This correlation time is shorter than that expected for rotational motion of small chelates in solution at 5 °C (on the order of $(10\text{–}20) \times 10^{-11}$ s for a 4.5-Å-diameter complex as predicted by the Stokes–Einstein equation).[9] Thus, it is likely that electron spin relaxation makes a significant contribution to shorten the observed correlation time (eq 2). Another indication of the contribution of electron spin relaxation is seen in the slight upward turn of the curves in the high-field region due to the field dependence of τ_s predicted by eq 3.

The lowest curve in Figure 3 is that of $Mn[(NH_2Et)_2[15]pydieneN_5]^{2+}$ which has no coordinated water molecules and therefore relaxes by an outer-sphere mechanism.[18] The relaxivity at the low-field limit is approximately half that observed for coordinatively saturated anionic Mn(II) chelates, such as $Mn(DTPA)^{3-}$, because this cationic complex is solvated with the oxygen ends of the water dipoles.[18] Thus, the distance of closest approach of water protons is about 1 Å longer for cations than for the anions. The best-fit theoretical parameters using the outer-sphere formalism of Freed[29] at 25 °C are as follows: distance of closest approach, 4.6 Å; τ_{s0} = 54 ps; τ_v = 16 ps; τ_D = 32 ps; error in fit; 3.2%. For comparison,[11] in $Mn(DTPA)^{3-}$ the parameters are as follows: distance of closest approach, 3.5 Å; τ_{s0} = 231 ps; τ_v = 39 ps; τ_D = 14.5 ps. The relaxivity of the coordinatively saturated $(NH_2Et)_2[15]pydieneN_5$ complex provides a reasonable estimate of the outer-sphere contribution to relaxivity for all of the $[X]pydieneN_y$ complexes in Figure 3.

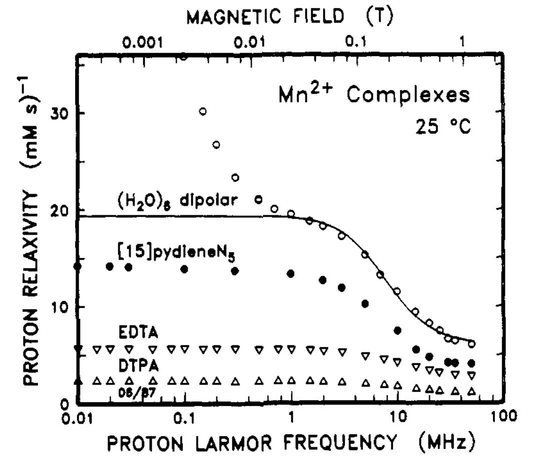


Figure 4. Comparison of the NMRD profiles for $Mn(H_2O)_6^{2+}$ (the dipolar term is represented as a solid line), $Mn([15]pydieneN_5)(H_2O)_2^{2+}$, $Mn(EDTA)(H_2O)^{2-}$ and $Mn(DTPA)^{3-}$ in aqueous solution at 25 °C.

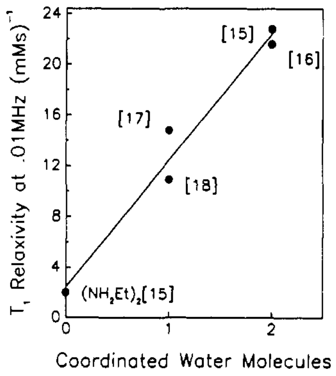


Figure 5. Plot of the longitudinal relaxivity (R_1) at 0.01 MHz versus the number of coordinated water molecules in the complex for the Mn(II) complexes of the $[X]pydieneN_y$ complexes. [X] is given in the figure.

Figure 4 shows a comparison of the NMRD profiles for $Mn([15]pydieneN_5)(H_2O)_2^{2+}$, the hexaaquamanganese(II) ion dipolar contribution, $Mn(EDTA)(H_2O)^{2-}$, and $Mn(DTPA)^{3-}$ (the latter three are taken from ref 30). It is instructive to estimate the inner-sphere relaxivity per coordinated water molecule from the low-frequency relaxivity of each curve. The DTPA complex is coordinatively saturated, and its relaxivity gives a reasonable estimate of the outer-sphere contribution for anionic complexes such as $Mn(EDTA)H_2O^{2-}$. Subtracting the two values gives an estimate of 3 (mM s)$^{-1}$ per water molecule for the inner-sphere relaxivity in the EDTA complex. Subtracting 1 (mM s)$^{-1}$ for the cationic outer-sphere contribution from the dipolar relaxivity of the hexaaquamanganese(II) ion and dividing by 6 gives also a relaxivity per coordinated water molecule of 3 (mM s)$^{-1}$. However, subtracting an outer-sphere contribution of 1 (mM s)$^{-1}$ from the relaxivity of $Mn([15]pydieneN_5)(H_2O)_2^{2+}$ and dividing by 2 gives a relaxivity of 6.8 (mM s)$^{-1}$ per coordinated water molecule. Thus, the relaxivity of $Mn([15]pydieneN_5)(H_2O)_2^{2+}$ is higher by a factor of 2.3 than expected in comparison with the inner-sphere relaxivity of the hexaaquamanganese(II) ion dipolar term and the EDTA complex, assuming similar correlation times. The other $[X]pydieneN_y$ complexes have relaxivities per coordinated water molecule in agreement with the $[15]pydieneN_5$ complex.

The similarity in relaxation behavior of the $[X]pydieneN_y$ complexes is further illustrated in Figure 5 where the expected linear correlation between the number of coordinated aqua ligands and the low-field relaxivity is shown. There is clearly also a smaller dependence upon factors other than the number of coordinated water molecules seen in the points with the same q. This could be attributed to differences in correlation time, g value, or ZFS.

---

(29) Freed, J. H. *J. Chem. Phys.* **1978**, *68*, 4034.

(30) Koenig, S. H.; Brown, R. D., III; Brewer, C. F. *Magn. Reson. Med.* **1984**, *75*, 3297.

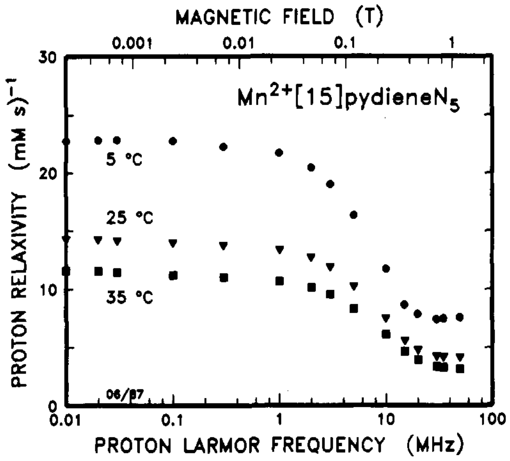


Figure 6. NMRD profiles for an aqueous solution of Mn([15]pydieneN$_5$)(H$_2$O)$_2$$^{2+}$ at three temperatures.

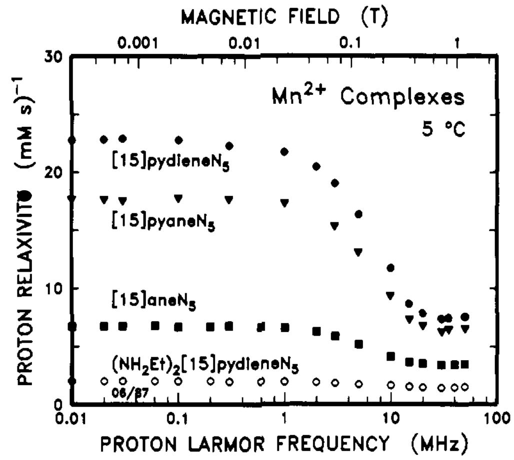


Figure 7. NMRD profiles for aqueous solutions of Mn(II) complexes at 5 °C.

Table V. SBM Parameters from Curve Fits of 5 °C NMRD Profiles[a]

complex	R_{eff}, Å	τ_{s0}, ps	τ_v, ps	q
Mn([15]pydieneN$_5$)	2.56	62	0.0	2
Mn([15]pyaneN$_5$)	2.65	55	0.0	2
Mn([15]aneN$_5$)	2.82	47	2.2	1
Mn([16]pydieneN$_5$)	2.53	52	0.7	2
Mn([16]pyaneN$_5$)	2.60	73	0.0	2
Mn([17]pydieneN$_5$)	2.48	64	1.7	1
Mn([18]pydieneN$_6$)	2.42	33	1.0	1

[a] Note: τ_r fixed at Stokes value (156 ps) and τ_M fixed at aqua ion value (330 ps).

It is pertinent that all of the complexes in room-temperature aqueous solution exhibit relatively intense sextet EPR spectra with variable broadening and splitting due to nitrogen hyperfine interaction. The spectra are consistent with the transitions between the $m_s \pm {}^1/_2$ levels with g close to the free electron value and ZFS $< h/\omega_s$.[31]

In Figure 6 are plotted the NMRD profiles for Mn([15]pydieneN$_5$)(H$_2$O)$_2$$^{2+}$ at three temperatures. The temperature dependence of the low-field relaxivity, which increases with decreasing temperature, indicates that the relaxation rate is in the rapid exchange limit and the temperature dependence is thus due to the variation of the correlation time with temperature. In fact, the low-field relaxation rate does vary approximately linearly with η/T as expected for the correlation time dominated by rotational motions.[9] However, this is not observed in the higher frequency region since the frequencies of the inflection points are the same at all three temperatures (see Table IV). The invariance of the inflection point could possibly be due to compensating contributions of rotational and electron spin correlation times and their individual temperature and field dependences in the region of the dispersion. For the other pyridine-containing macrocycles, the inflection frequency does show a slight temperature dependence (see Table IV), but much smaller than that expected for rotational motion. The behavior is distinctly different for the Mn([15]aneN$_5$) complex where the behavior of the inflection frequency is consistent with the temperature dependence of rotational motion.

Figure 7 shows the NMRD profiles of a series of complexes all containing a 15-membered ring macrocycle but differing in degrees of unsaturation. As in the series where the macrocyclic ring size was varied and unsaturation kept constant, a large range in low-field limiting relaxivities is observed and the profiles qualitatively behave according to eq 1 with a sigmoidal dispersion inflection at 6–10 MHz. Comparing the [15]pydieneN$_5$ and [15]pyaneN$_5$ complexes, both of which have two coordinated water molecules, a 20% decrease in low-field relaxivity is seen for the latter. However, the largest difference is seen for the [15]aneN$_5$ complex, which decreases to approximately 45% of the relaxivity per coordinated water molecule observed for Mn([15]pydieneN$_5$)$^{2+}$. In fact, after the outer-sphere contribution is subtracted, the relaxivity per coordinated water molecule in Mn[15]aneN$_5$(H$_2$O)$^{2+}$ is the *same* as in the hexaaquamanganese(II) ion and Mn(EDTA)H$_2$O^{2-}! The reason for the variation in relaxivity among these complexes is seen from the parameters obtained from fitting the curves according to eqs 1–3 as shown in Table V. Here it was assumed that the rotational correlation time is constant at the Stokes-Einstein value of 156 ps, and the exchange time is equal to the hexaaquamanganese(II) value of 330 ps for all of the complexes in the series. The parameters τ_{s0} and τ_v do not vary significantly among the complexes, but R_{eff} does. Since R_{eff} enters into eq 1 as the sixth power, its variation is responsible for the trend in relaxivities. The R_{eff} for Mn([15]aneN$_5$) is very close to the best-fit values obtained for the hexaaquamanganese(II) ion and Mn(EDTA)H$_2$O^{2-}, 2.80 and 2.91 Å, respectively. These distances are close to the physical distances predicted from the Mn–O distance determined by X-ray diffraction[32] and by EXAFS in aqueous solution.[33] In addition, these distances are consistent with that predicted from quantum mechanical calculations of relaxivity using the dipolar model.[34] A departure from the physical value for R_{eff} is indicative of departure from the approximation of the metal electron spin distribution as a point dipole situated at the metal nucleus.[35] The shorter R_{eff} values for the [X]pydieneN$_y$ and [X]pyaneN$_5$ complexes having unsaturated ligands could thus arise from departure from the point dipole model due to spin delocalization facilitated by the unsaturated ligand. An electronic mechanism for the shortening of R_{eff} is further implicated from the fact that the physical Mn–O distances determined crystallographically for Mn([16]pydieneN$_5$)(H$_2$O)$_2$$^{2+}$ are very close to those observed in the hexaaquamanganese(II) ion.[27] The effect of ligand unsaturation on metal ion relaxation enhancement in metal chelates thus could provide a mechanism for achieving modest improvements in NMR contrast agents.

Acknowledgment. S.C.J. wishes to thank Seymour H. Koenig for many helpful discussions, Ms. Marga Spiller for obtaining the NMRD profiles, Miro Plechaty for ICP analyses, and W. H. Orme-Johnson for the use of his EPR spectrometer. Also, the support of the National Institutes of Health (Grant GM-41919) is gratefully acknowledged.

---

(31) Neri, N.; Tiezzi, E.; Valensin, G. *Chem. Rev.* **1982**, *82*, 359.

(32) Montgomery, M.; Chastain, R. V.; Lingafelter, E. C. *Acta Crystallogr.* **1966**, *20*, 731.

(33) Sham, T. K.; Hastings, J. B.; Perlman, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 5904.

(34) Sahoo, N.; Das, T. P. *J. Chem. Phys.* **1989**, *91*, 7740.

(35) Nordenskiold, I.; Laaksonen, A.; Kowalewski, J. *J. Am. Chem. Soc.* **1982**, *104*, 379.