Test of Electron Delocalization Effects on Water-Proton Spin−Lattice Relaxation by Bromination of [Tetrakis(4-sulfonatopheny)porphine]manganese

L. Henry Bryant, Jr.,[†] **Melinda Whaley Hodges, and Robert G. Bryant***

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

The potential value of electron spin delocalization as a means for substantially increasing the ability of a paramagnetic metal complex to induce nuclear spin relaxation of water protons has been examined by covalent attachment of bromine atoms in the β-pyrrole positions of the [5,10,15,20-tetrakis(4-sulfonatophenyl)-21H,23H-porphine]manganese complexes[$Mn^{III}TPPS$]$^{3-}$ and [$Mn^{II}TPPS$].$^{4-}$ The water-proton spin−lattice relaxivities are reported as a function of magnetic field strength for the brominated and nonbrominated metalloporphyrins over the range of magnetic field strengths corresponding to proton Larmor frequencies between 0.01 and 30 MHz. The brominated metalloporphyrins increase the water-proton relaxativities compared to the nonbrominated metalloporphrins, and, at low magnetic field strengths, the brominated [$Mn^{II}TPPS$]$^{4-}$ complex rivals the efficiency of the hexaaquomanganese(II) ion. Attempts to fit the experimental data to theories for paramagnetic relaxation, which are based on the point-dipole approximation, result in distances between the paramagnetic center and the water proton that are unreasonably short based on published structural data. The excess relaxivity implies that the point-dipole approximation may be inappropriate for these porphyrin systems and electron spin delocalization may provide a significant contribution to nuclear spin relaxation that may be fruitfully exploited in construction of contrast agents for magnetic resonance imaging.

Introduction

Nuclear spin relaxation rates usually make the dominant contribution to the contrast differences seen in magnetic resonance images. Control of the water-proton spin relaxation rate provides a means for better definition of anatomical features, measurement of vascular efficiency, or modification of the image-information content.[1] Manganese-porphyrin complexes are potential MRI contrast agents[2] because they increase the nuclear spin relaxation rate[3,4] of the water protons and localize selectively in certain tissues.[5]

A variety of porphyrin structures may be synthesized by covalent attachment of different side chains to the aromatic ring system.[6] The proton relaxivities, i.e., the relaxation rate per mM of metal ion, have been compared as a function of magnetic field strengths for eight manganese(III)-porphyrin complexes.[4] The high relaxivities at proton Larmor frequencies greater than 10 MHz, originally observed for [$Mn^{III}TPPS$]^3 , appears to be a general phenomenon for manganese(III)-porphyrin complexes.[7] The relative maximum in the water-proton spin−lattice relaxation rate as a function of magnetic field strength is understood in terms of the magnetic field dependence of the electron spin relaxation rate at the metal center, which is itself field dependent and usually dominates the correlation time for the electron−nuclear coupling at low and intermediate magnetic field strengths.

The reduction of the d[4] [$Mn^{III}TPPS$]^3 complex to the more electronically symmetric d[5] [$Mn^{II}TPPS$]$^{4-}$ results in more efficient nuclear spin relaxation, particularly at low magnetic field strengths.[3] The relaxation efficiency may be further increased by the addition of cyclodextrins.[8] The high relaxation efficiencies are not easily understood quantitatively in terms of the simple models usually employed for nuclear spin relaxation induced by paramagnetic metals.[3,7,9−12] Earlier discussions have suggested that this difficulty may arise from failure of the point-dipole approximation because of electron delocalization into the large conjugated π system of the porphyrin.

In this report, we attempt to examine the effect of increasing the delocalization of the paramagnetic electron spin density into the ligand system. We examine the magnetic field dependence of the water-proton spin−lattice relaxation rates for two new manganese-porphyrin complexes that contain bromine atoms at the β-pyrrole positions, [$Mn^{III}TPPBr_6S$]$^{3-}$ and [$Mn^{II}TPPBr_6S$]$^{4-}$. The expectation is that introduction of bromine directly on the ring will increase electron spin density throughout the ligand and will increase the magnetic coupling to the solvent spins. Although these complexes decompose slowly in water, which makes purification and characterization difficult, the bromination increases the water-proton relaxation rates, which indicates that

[†] Present address: National Institutes of Health, Laboratory of Diagnostics Radiology, Research Building 10, Rm. BIN256, 10 Center Drive, DR MSC 1074, Bethesda, MD 20892-1074.

 (1) Mansfield, P.; Morris, P. G. *NMR Imaging in Biomedicine*; Academic Press: New York, 1982.
 (2) Fawwaz, R.; Bohidiewicz, P.; Lavalle, D.; Wang, T.; Oluwole, S.; Newhouse, J.; Alderson, P. *Nucl. Med. Biol.* **1990**, *17*, 65.
 (3) Hernández, G.; Bryant, R. G. *Bioconjugate Chem.* **1991**, *2*, 394−397.
 (4) Kellar, K. E.; Foster, N. *Inorg. Chem.* **1992**, *31*, 1353−1359.
 (5) Lyon, R. C.; Fuastino, P. J.; Cohen, J. S.; Katz, A.; Mornex, F.; Colcher, D.; Baglin, C.; Koenig, S. H.; Hambright, P. *Magn. Reson. Med.* **1987**, *4*, 24−33.
 (6) White, W. I. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. V.
 (7) Koenig, S. H.; Brown, R. D., III; Spiller, M. *Magn. Reson. Med.* **1987**, *4*, 252−260.

 (8) Sur, S. K.; Bryant, R. G. *J. Phys. Chem.* **1995**, *99*, 4900−4905.
 (9) Solomon, I. *Phys. Rev.* **1955**, *99*, 559−565.
 (10) Bloembergen, N. *J. Chem. Phys.* **1957**, *27*, 572−573.
 (11) Bloembergen, N.; Morgan, L. O. *J. Chem. Phys.* **1961**, *34*, 842−850.
 (12) Koenig, S. H.; Brown, R. D., III. *Magn. Reson. Med.* **1984**, *1*, 478−495.

electron delocalization may make a significant contribution to the water-proton spin relaxation rate that may be exploited to build more efficient relaxation agents.

Experimental Section

Solvents and Reagents. [$Mn^{III}TPPS$]Cl was obtained from Porphyrin Products, Inc. Reagent grade anhydrous methanol, sodium hydroxide pellets, and concentrated sulfuric acid were obtained from Mallinckrodt Chemical Company. Reagent grade *N*-bromosuccinimide, technical grade sodium hydrosulfite, and atomic absorption standard (1000 μg/mL) manganese(II) solution in 1 wt % nitric acid were obtained from Aldrich Chemical Co. HEPES buffer was obtained from Sigma. Dowex 50W-X8, hydrogen form, was obtained from J. T. Baker Chemical Co., and cellulose ester dialysis tubing (MW cutoff = 1000) was obtained from Scientific Products. All commercial materials were used without further purification.

[$Mn^{III}TPPBr_6S$]$Na_3 \cdot 14.5 H_2O$. [$Mn^{III}TPPS$]Cl (0.25 g; 0.243 mmol) was dissolved in 50 mL of anhydrous methanol and converted to sodium salt by titration with solid sodium hydroxide to pH 10. *N*-Bromosuccinimide was added in small portions, and the solution was refluxed.[13] An aliquot of the reaction mixture was periodically removed and the UV−visible spectrum recorded. After the final addition of *N*-bromosuccinimide (6.8 g; 39.0 mmol total) and 24 h reflux, no change in the absorption spectrum was observed. The reaction mixture was neutralized with sodium hydroxide and the solvent removed by evaporation under reduced pressure. The resulting residue was dissolved in 50 mL of deionized water and dialyzed against deionized water for 5 days with 10 changes of the water. Evaporation of the solvent under reduced pressure gave a dark-green solid. Yield: 0.16 g (49%). Mp > 300 °C. Spectrophophotometric data (H_2O, nm): 393, 488 (Soret), 589, 627. Anal. Calcd for $C_{44}H_{47}N_4O_{26.5}Br_6S_4Na_3Mn$: Mn, 3.07; Br, 26.82; C, 29.56; N, 3.13; H, 2.65. Found: Mn, 3.07; Br, 27.29; C, 28.07; N, 3.43; H, 2.68.

MRD Measurements. Water-proton longitudinal magnetic ^1H relaxation rates were measured over a range of magnetic field strengths corresponding to Larmor frequencies between 0.01 and 30 MHz using a field-cycling spectrometer described elsewhere.[14] [$Mn^{III}TPPS$]Na_3 and [$Mn^{III}TPPBr_6S$]Na_3 were dissolved in 50 mM HEPES buffer, pH 7.2. [$Mn^{II}TPPS$]$^{4-}$ and [$Mn^{II}TPPBr_6S$]$^{4-}$ were prepared in-situ by the reduction of [$Mn^{III}TPPS$]$^{3-}$ and [$Mn^{III}TPPBr_6S$]$^{3-}$, respectively, with a 50-fold molar excess of $Na_2S_2O_4$ over the manganese(III)-porphyrin complex under a nitrogen atmosphere.[3]

Each sample was analyzed for the presence of free manganese ion by EPR spectroscopy at ambient laboratory temperature.[15] No free manganese ion was detected in the [$Mn^{III}TPPS$]$^{3-}$ and [$Mn^{II}TPPS$]$^{4-}$ solutions over the 2 h period required to complete the magnetic relaxation dispersion measurements. Free manganese ion was detected in freshly prepared [$Mn^{III}TPPBr_6S$]$^{3-}$ and was removed by adding DOWEX 50W-X8 cation-exchange resin beads and swirling for several minutes. The solution was filtered and the pH readjusted to 7.2 with 1 M NaOH. After removal, no free manganese ion was detected over the 2 h period required to complete the relaxation rate measurements. Free manganese ion in the [$Mn^{II}TPPBr_6S$]$^{4-}$ solution was detected over the 2 h period required to complete the magnetic relaxation dispersion measurements. The concentration of free manganese ion was obtained by comparison of the EPR line intensity with that of a standardized manganese(II) solution (Aldrich) diluted with 50 mM HEPES buffer at pH 7.2.

Total metal concentration determinations by EPR were done by reducing the complex with a 50-fold molar excess of $Na_2S_2O_4$ in air. After 24 h, the concentration of manganese in each sample was obtained from the EPR intensity of the free manganese(II) spectrum. The manganese concentration for each sample was also determined spectrophotometrically by ashing an aliquot of each complex in concentrated
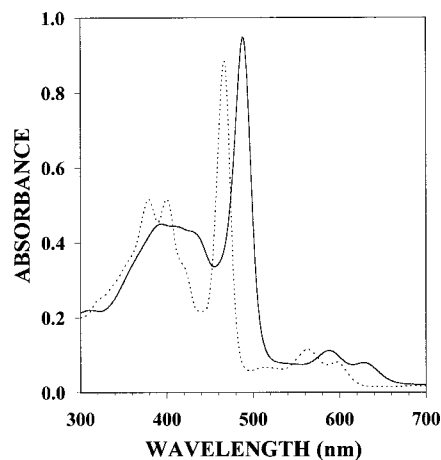
Figure 1. UV−visible spectrum of [$Mn^{III}TPPBr_6S$]$^{3-}$ (solid line) and $Mn^{III}TPPS$]$^{3-}$ (broken line) dissolved in 50 mM HEPES buffer at pH 7.2.

H_2SO_4 for 2.5 h.[16] The white solid remaining was dissolved in deionized water, 0.1 g of KIO_4 was added and the solution boiled for 5 min.[17] After cooling, the solution was diluted to 5.00 mL with deionized water. The manganese concentration was determined from the absorbance at 525 nm by reference to calibration plot ($\epsilon = 2.24 \times 10^3$ mol/L) prepared from known concentrations of manganese(II) solutions which have been oxidized with KIO_4 under conditions identical to those used for the manganese-porphyrin complexes.

Metal ion concentrations were also determined by Galbraith Laboratories (Knoxville, TN) using graphite furnace atomic absorption. The average of all these determinations had a standard deviation of less than 8% and those averages were used to compute the relaxivities. The contribution of dissociated manganese was typically 0.08 mM in a 0.52 mM [$Mn^{II}TPPBr_6S$]$^{4-}$ solution and the relaxivities from this species subtracted from the total to arrive at the relaxivity for the [$Mn^{II}TPPBr_6S$]$^{4-}$ complex.

All EPR measurements were carried out at ambient laboratory temperature using a Bruker ESP-300 spectrometer at X-band with 100 kHz magnetic field modulation, a modulation amplitude of 5 G, and 10 mW microwave power. The UV−visible data were obtained using a Cary 4E spectrophotometer. The pH was measured using a Corning 240 pH meter.

Synthesis. The procedure for bromination of water-soluble [$Mn^{III}TPPS$]$^{3-}$ was based on the reaction for other metalloporphyrin complexes using *N*-bromosuccinimide in refluxing methanol.[13] An attempt to separate [$Mn^{III}TPPBr_6S$]$^{3-}$ from lower molecular weight components by dialysis for 5 days with 10 changes of water did not eliminate EPR signals from free manganese(II) ion. More vigorous chromatographic purification attempts were unsuccessful. The persistence of uncomplexed manganese ion, despite repeated purification attempts, suggests that covalent attachment of bromine atoms to the metalloporphyrin results in a decrease in the stability of the metalloporphyrin in aqueous solution compared to nonaqueous solvents.

The UV−visible spectra of [$Mn^{III}TPPBr_6S$]$^{3-}$ and [$Mn^{III}TPPS$]$^{3-}$ in HEPES buffer at pH 7.2 are shown in Figure 1 and indicate the extent of bromination. The most intense (Soret) band is at 488 nm for [$Mn^{III}TPPBr_6S$]$^{3-}$ and at 466 nm for [$Mn^{III}TPPS$]$^{3-}$. This band shift upon bromination of the β-pyrrole positions has been observed for the β-pyrrole bromination of other metalloporphyins.[13,18−20] In nonaqueous solvents, a 5.5 nm red shift is typically observed for each bromine substituted at a β-pyrrole position for sequential addition of up to eight

(13) Hoffman, P.; Labat, G.; Robert, A.; Meunier, B. *Tett. Lett.* **1990**, *31*, 1991−1994.

(14) Hernández, G.; Brittain, H. G.; Tweedle, M. F.; Bryant, R. G. *Inorg. Chem.* **1990**, *29*, 985−988.

(15) Cohen, M. J. Townsend, *J. Nature* **1954**, *173*, 1090−1091.
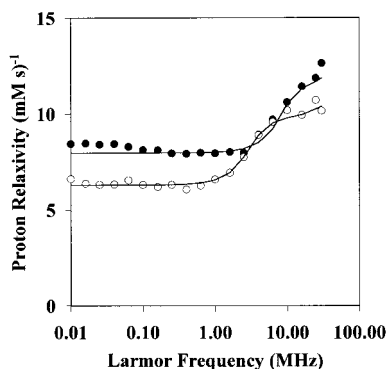
(16) Cotton, F. A. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1988; p 703.

(17) Meites, L. *Handbook of Analytical Chemistry*: McGraw-Hill: New York, 1963.

(18) Traylor, T. G.; Tsuchiya, S. *Inorg. Chem.* **1987**, *26*, 1338−1339.

(19) Bhyrappa, P.; Krishnan, V. *Inorg. Chem.* **1991**, *30*, 239−245.

(20) D'Souza, F.; Villard, A.; Caemelbecke, E. V.; Franzen, M.; Boschi, T.; Tagliatesta, P.; Kadish, K. M. *Inorg. Chem.* **1993**, *32*, 4042−4048.

Figure 2. Water-proton spin−lattice relaxivity as a function of magnetic field strength expressed as the ^{1}H Larmor frequency for $[Mn^{III}TPPBr_6S]^{3-}$ (●) and $[Mn^{III}TPPS]^{3-}$ (○) dissolved in 50 mM HEPES buffer at pH 7.2 and 298 K. The solid lines were computed using the SBM equations with the following parameters: $[Mn^{III}TPPBr_6S]^{3-}$, $r = 1.98$ Å, $\tau_{ex} = 0.5$ ns, $\tau_{rot} = 275$ ps, $\tau_{SO} = 6.8$ ps, $\tau_V = 9.5$ ps; $[Mn^{III}TPPS]^{3-}$, $r = 2.29$ Å, $\tau_{ex} = 0.1$ ns, $\tau_{rot} = 275$ ps, $\tau_{SO} = 15$ ps, $\tau_V = 30$ ps.

bromine substituents.[19] This simple correlation for metalloporphyrins with fewer attached bromine atoms is uncertain. A 23 nm shift in the Soret band for $[Co^{III}TPPBr_6]^+$, which has six bromine atoms in the β-pyrrole positions, relative to the Soret band for $[Co^{III}TPP]^+$ has been reported.[20] The shift in the Soret band for $[Mn^{III}TPPBr_6S]^{3-}$ relative to the Soret band for $[Mn^{III}TPPS]^{3-}$ is 22 nm, which suggests six bromines are substituted. The total of the six bromine atoms is also consistent with the elemental analysis. The water of crystallization in the product was measured by heating the solid sample in a drying pistol under mechanical vacuum using refluxing acetonitrile.

Magnetic Relaxation. The contribution to the water-proton spin−lattice relaxation rate from the first coordination sphere of the metal complex may be written:[7]

$$R_1 = \frac{P_m}{T_{1m} + \tau_{ex}}$$

where P_M is the probability that a water-proton is in the first coordination sphere of the manganese with a mean residence time, τ_{ex}, and T_{1M} may be modeled using several approaches differing in the treatment of the electron spin quantization. The simplest approach is the Solomon, Bloembergen, Morgan theory (SBM), which assumes that the electron spin quantization axis is that of the applied magnetic field and that the electron **g** tensor is isotropic. More recent treatments have examined the cases of **g** tensor and hyperfine tensor anisotropy, and the situation where a large zero field splitting, ZFS, redirects the electron quantization axis away from the magnetic field direction and lifts the degeneracy of the electron spin states. In the range of magnetic field strengths where neither the low nor the high field limit applies, the relaxation response is generally computed numerically. In these cases, the qualitative features of the SBM result are often preserved; however, the quantitative parametrization of the problem is more complex.[26−36] Qualitatively, the presence of a large ZFS implies that there is not a single electron Larmor frequency, and some electron contributions to the nuclear spin relaxation may disperse or drop out at very low magnetic field strengths. Thus, nuclear spin relaxation is generally less efficient, but the magnetic field dependence may display new features.

Figure 2 shows the magnetic relaxation dispersion profiles for $[Mn^{III}TPPBr_6S]^{3-}$ and $[Mn^{III}TPPS]^{3-}$ at 298K in aqueous HEPES buffer at pH 7.2. The $[Mn^{III}TPPS]^{3-}$ data are very similar to previous reports.[3,4,7] The bromination of $[Mn^{III}TPPS]^{3-}$ increases the relaxation rates. The increase in the relaxation rate with increasing field strength demonstrates that the electron spin relaxation times make a dominant contribution to the correlation time for the electron−nuclear coupling; similar results are reported for other manganese(III)porphyrins.[3,4,7] Because the electronic contribution dominates, the higher relaxation rates for the brominated complex do not result from significant increases in the rotational correlation time of the brominated compared with the
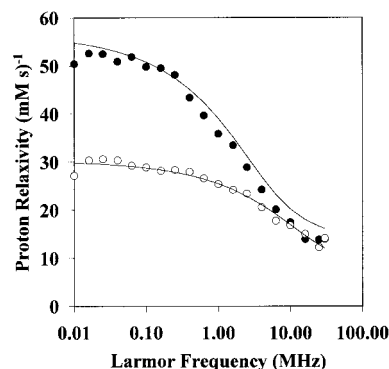
Figure 3. Water-proton spin−lattice relaxivity as a function of magnetic field strength expressed as the ^{1}H Larmor frequency for $[Mn^{II}TPPBr_6S]^{4-}$ (●) and $[Mn^{II}TPPS]^{2-}$ (○) dissolved in 50 mM HEPES buffer at pH 7.2 and 278 K. The solid lines were computed using a sum of contributions from translational and first coordination sphere contributions computed from the SBM equations with the following parameters: $[Mn^{II}TPPBr_6S]^{4-}$, $r = 3.1$ Å, Ah = 0.75 MHz, $\tau_{ex} = 10$ ns, $\tau_{rot} = 300$ ps, $\tau_{SO} = 500$ ps, $\tau_V = 1$ ps, the distance of closest approach of water protons to the manganese center, b, of 2.2 Å and a relative translational diffusion coefficient, D, of 2×10^{-6} cm^2/s; $[Mn^{II}TPPS]^{4-}$, $r = 3.1$ Å, Ah = 0.5 MHz, $\tau_{ex} = 10$ μs, $\tau_{rot} = 300$ ps, $\tau_{SO} = 1$ ns, $\tau_V = 0.5$ ps, the distance of closest approach of water protons to the manganese center, b, 2 Å and a relative translational diffusion coefficient, D, of 6×10^{-6} cm^2/s.

nonbrominated complex. Attempts to fit these data using the SBM equations do not yield satisfactory results. For example, the solid lines were computed using a rotational correlation time of 275 ps, which has been measured for the diamagnetic $[Zn^{II}TPPS]^{4-}$ complex. However, even assuming that there are two water molecules coordinated to the metal, the value of the intermoment distance required to achieve reasonable agreement with the magnitude of the relaxation rates is small, on the order of 2.0−2.3 Å. Although such values have been reported previously[4,7] and may provide a parametrization of the data, such short intermoment distances are not consistent with the reported structural chemistry. The structure of $[Mn^{III}TPPS]^{3-}$ determined by X-ray diffraction[21] shows two axial water molecules with a manganese−oxygen distance of 2.271 Å. Assuming a reasonable O−H bond distance[22] of 0.96 Å and that the water molecule HOH bond angle remains at 104.5° when coordinated, the manganese−proton distance is 3.2 Å if the water molecule dipole moment is collinear with the manganese−oxygen bond. If the plane of the water molecule were tipped to the tetrahedral angle, the manganese proton distance is reduced to 2.9 Å. Even though the averaging over vibrational motion required for evaluating $1/\langle r^3 \rangle^3$ for the manganese-proton is complex, the differences here are far too large to be attributed to this source. Similar difficulties are found for the manganese(II) cases.

The magnetic relaxation dispersion profiles for the manganese(II) complexes are shown in Figure 3. The brominated porphyrin complex is a more efficient relaxation agent than the nonbrominated complex and rivals that of the hexaaquomanganese(II) ion at low magnetic field strengths. The magnitude of the relaxation rates at low magnetic field strengths can be computed using values of r in the range of 2.9−3.1 Å and a hyperfine coupling of 0.5−2 MHz, which are reasonable. However, this parametrization fails by underestimating the relaxation rates at high magnetic field strengths. Likewise, a parameter set that fits the data at high magnetic field strengths using the SBM theory fails by overestimating the relaxation rates at low magnetic field strengths. In either case, the broad magnetic relaxation dispersion is poorly modeled.

It is possible that the two axial water ligands coordinated to the manganese(II) porphyrin have different exchange times and intermoment distances. However, even with two exchange times, which may

(21) Williamson, M. M.; Hill, C. L. *Inorg. Chem.* **1987**, *26*. 4155−4160.
(22) Eisenberg, D.; Kauzmann, W. *The Structure and Properties of Water*; Oxford University: New York, 1969; p 4.

broaden the relaxation dispersion profile in some cases, the breadth of the relaxation dispersion may not be reproduced.

The broad relaxation dispersions suggest that outer-sphere relaxation rates are more important than normal and previous reports[3,8] on [Mn^{II}TPPS]$^{4-}$ and the cyclodextrin-[MnIITPPS]$^{4-}$ complex have discussed the shape of the MRD profiles in terms of a significant outer-sphere contribution. The solid lines in Figure 3 were calculated by using the SBM equations supplemented by a significant outer-sphere contribution based on the translational diffusion model developed by Freed,[23] which works well for simple complexes.[24] The primary factors that enter the translational contribution are the distance of closest approach between the paramagnetic center and the water-proton and the translational diffusion coefficient characterizing the relative motion of the water protons and the paramagnetic center. Although these parameters may be significantly covariant, previous studies demonstrate that the mobility of water near metal complexes is nearly the same as that found in bulk water,[24,25] and the distance of closest approach between the paramagnetic solute and the water-proton are reasonably approximated by the sum of the appropriate van der Waals radii. However, to fit the manganese(II) porphyrin data, the distance of closest approach required is smaller than is reasonable based on the van der Waals radii of the manganese-porphyrin atoms. Further, this approach suggests the water translational diffusion coefficient that is smaller than usually observed by approximately a factor of 2 for the nonbrominated complex and smaller by approximately a factor of 5 for the brominated complex. In short, the relaxation is more efficient than may be reasonably accounted for by these models.

These models have assumed that the electron magnetic moment may be approximated as a point-dipole at the position of the paramagnetic metal nucleus, and that the electron spin system is quantized along the Zeeman direction with degenerate electron spin transitions at the frequency, ω_s. In symmetrical complexes of S-state ions such as manganese(II) or iron(III), the models work reasonable well; however, for complexes of lower symmetry, and for non S ground-state ions such as manganese(III), the zero-field splittings in the electron system may be substantial and the SBM model is not expected to be reliable.

The Swedish group[26−29] and the Florence group[30−32] have made significant contributions to adressing this problem, and more recently Sharp has provided an approach that treats the cases of significant zero-field splittings.[33−36] Qualitatively, these important theoretical advances shows that the magnetic relaxation dispersion becomes more complex when zero-field splittings are significant because there may be several electron spin transitions the frequency of which may be orientation dependent, and the correlation times for the electron−nuclear coupling are complicated by the several electron spin relaxation times. A significant broadening of the relaxation dispersion profile may result and new features in the dispersion profile may appear. Generally, however, these theoretical improvements do not predict an increase in the magnitude of the relaxation rate over that given by even the SBM model; in fact, the relaxation rates predicted at low fields are generally smaller. Thus, we do not discuss attempts to fit these data to more complex models. The problem of high relaxation rates remains. Thus,

we are forced to question the validity of the point-dipole approximation, i.e., the assumption that the unpaired electron spin density is completely localized at the metal atom center.

The apparent strength of the electron−nuclear spin coupling in the manganese-porphyrin complexes appears to be larger than may be explained by the point-dipole theories. It is likely that in addition to significant zero-field splittings affecting the shape of the relaxation dispersion profile, electron delocalization in the conjugated ring system may contribute to the total relaxation efficiency. For simple metal complexes, quantum mechanical computations have suggested that delocalization of the paramagnetic electron spin onto the ligand atoms may be significant for the bonded atom. Second neighbor delocalization, for example, to the protons of a coordinated water molecule was not found to be large and the point-dipole approximation apparently validated.[37−42] Although the nickel(II)-malonate complex was examined as an example of a conjugated ligand system,[41] the manganese-porphyrin complexes investigated here have not been examined as carefully from this perspective.

The electron spin resonance spectroscopy of paramagnetic metalloporphyrins demonstrates that electron spin delocalization may be significant. In metmyoglobin, for example, the electron spin density on the iron is estimated to be only 68%.[43] Although electron delocalization effects are usually ignored in the discussion of spin relaxation efficiency, a number of studies suggest that even intermolecular delocalization of electron spin density may be detected.[44−47] For example, proton and carbon chemical shifts measured in solutions of coordinately saturated paramagnetic complexes demonstrate significant effects measured in the solvent resonances that have been interpreted in terms of specific second coordination sphere interactions of such magnitude that electron delocalization is invoked.[48]

The current data set does not, by itself, provide a demonstration that the point-dipole approximation fails; however, the excess relaxivity observed and called anomalous by Koenig and collaborators,[7] raises the possibility that there may be a significant amount of electron spin density delocalized form the manganese atom which is reported by the water protons in these magnetic relaxation experiments. Further, the substitution of bromine on the β-pyrrole rings, which by most standard chemical arguments should facilitate electron withdrawal into the porphyrin ring, increases the proton relaxation rate relative to the nonbrominated complex. Qualitatively, substantial delocalization of the electron spin should decrease the apparent distance of closest approach for the translational contributions and make the apparent correlation time for the electron−nuclear coupling longer because more translational jumps are required for the diffusing nuclear spin to move away from the influence of the delocalized electron magnetic moment.

In summary, the experiments reported here demonstrate that bromination of the manganese-porphyrin ring, which should facilitate electron delocalization, increases the relaxivity of water protons. This increase suggests that electron spin delocalization effects may large enough to provide an additional avenue for improving the nuclear spin relaxation efficiency of magnetic resonance imaging contrast agents.

(23) Freed, J. H. *J. Chem. Phys.* **1990**, *94*, 2843−2847.
(24) Lester, C. C.; Bryant, R. G. *J. Phys. Chem.* **1990**, *94*, 2843−2847.
(25) Polnaszek, C. F., Bryant, R. G. *J. Chem. Phys.* **1984**, *81*, 4038−4045.
(26) Kowalewski, J.; Nordenskiold L.; Benetis, N.; Westlund, P.-O. *Prog. NMR Spectrosc.* **1985**, *17*, 141−185.
(27) Benetis, N. *J. Magn. Reson.* **1986**, *68*, 469−489.
(28) Benetis, N.; Kowalewski, J. *J. Magn. Reson.* **1985**, *65*, 13−33.
(29) Benetis, N.; Kowalewski, J.; Nordenskiold L.; Wennerstrom, H.; Westlund, P.-O. *Mol. Phys.* **1983**, *48*, 329−346.
(30) Bertini, I.; Luchinat, C.; Mancini, M.; Spina, G. *J. Magn. Reson.* **1984**, *59*, 213−222.
(31) Bertini, I.; Luchinat, C.; Kowalewski, J. *J. Magn. Reson.* **1985**, *62*, 235−241.
(32) Banci, L.; Bertini, I.; Briganti, F.; Luchinat, C. *J. Magn. Reson.* **1986**, *66*, 58−65.
(33) Sharp, R. R. *J. Chem. Phys.* **1993**, *98*, 912−921.
(34) Sharp, R. R. *J. Chem. Phys.* **1993**, *98*, 2507−2515.
(35) Bovet, J. M.; Sharp, R. R. *J. Chem. Phys.* **1993**, *99* 18−26.
(36) Sharp, R. R. *J. Chem. Phys.* **1993**, *98*, 6092−6101.

(37) Waysbort, D.; Navon, G. *J. Chem. Phys.* **1975**, *62*, 1021−1026.
(38) Waysbort, D.; Navon, G. *J. Chem. Phys.* **1978**, *68*, 3074−3077.
(39) Nordenskiold, L.; Laaksonen, A.; Kowalewski, J. *J. Am. Chem. Soc.* **1982**, *104*, 379−382.
(40) Kowalewski, J.; Laaksonen, A.; Nordenskiold, L.; Saunders: V. R. *J. Chem. Phys.* **1981**, *74*, 2927−2930.
(41) Kowalewski, J.; Laaksonen, A.; Nordenskiold, L.; Saunders: V. R. *J. Magn. Reson.* **1983**, *53*, 346−350.
(42) Sahoo, N.; Das, T. P. *J. Chem. Phys.* **1989**, *91*, 7740−7748.
(43) Scholes, C. P.; Lapidot, A.; Mascarenhas, R.; Inubushi, T.; Isaacson, R. A.; Fehr, G. *J. Am. Chem. Soc.* **1982**, *104*, 2724−2735.
(44) Rettig, M. F.; Drago, R. S. *J. Am. Chem. Soc.* **1966**, *88*, 2966−2971.
(45) Chan. S. O.; Eaton, D. R. Can. *J. Chem.* **1976**, *54*, 1332−1340.
(46) Kitaigorodskii, A. N.; Nekipelov, V. M.; Zamaraev, K. I. *Zh. Strukt. Khim.* **1978**, *19*, 796−803.
(47) Nekipelov, V. M.; Zamaraev, K. I. *Coord. Chem. Rev.* **1985**, *61*, 185−240.
(48) Bayburt, T. M.; Sharp, R. R. *J. Phys. Chem.* **1993**, *97*, 4558−4566.