Inorg. Chem. **1995**, *34*, 924−927

First Characterization of the Influence of Paramagnetic Heteropoly Complexes of Tungsten on Relaxation Times of Water. Separation of Various Contributions to Relaxivities

Jennifer Gilbert,[†] Darren Kassab,[†] James H. Pawlow,[†] Brian P. Santora,[†] Robert J. Fiel,[‡] Vishwas N. Joshi,[§] and Mariusz Kozik*,[†]

Department of Chemistry, Canisius College, Buffalo, New York 14208, Department of Biophysics, Roswell Park Memorial Institute, Buffalo, New York 14263, and Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

Received August 3, 1994[®]

T_1 relaxation times of water in aqueous solutions of three types of paramagnetic transition metal-substituted heteropoly complexes were measured at the magnetic field of 10.7 MHz. The three types of complexes had the following chemical formulas: **I**, α-$[XW_{11}O_{39}Z(H_2O)]^{n-}$, where X = P or Si and Z = Fe^{3+} or Mn^{2+}; **II**, α_2-$[P_2W_{17}O_{61}Z(H_2O)]^{m-}$, where Z = Mn^{2+} or Fe^{3+}; **III**, $[GdH_2W_{10}O_{36}]^{7-}$. In the first two groups of compounds, paramagnetic transition metals exist in identical ligand environments, where each is surrounded by five oxide ions and one water molecule. The individual heteropoly complexes, however, differ in net charge, size, and metal, allowing the total relaxivity to be separated into individual components. Therefore, effects of *the size, the net complex charge, the metal type, and the rotational correlation time* on the relaxivity were determined independently. The results are compared to the existing theories of relaxivity in solution.

Introduction

Magnetic resonance imaging is at present well established as a safe and nonivasive imaging technique that is particularly useful for soft tissue discrimination. The distinction among various tissues in an image is caused by the differences in ^1H nuclear magnetic relaxation times of water molecules in those tissues.[1] Unfortunately, the difference in relaxation rates for diseased vs normal tissue, and consequently the image contrast, is often insufficient for diagnostic purposes. An improvement in the contrast may be achieved by the administration of so-called contrast agents, which significantly alter the relaxation times of water molecules.[2] These agents improve contrast in MRI by differentially localizing in tissues where they increase the relaxation rates of nearby water protons. Complexes of Gd(III), Fe(III), and Mn(II, III) are at present under intensive study because their high number of unpaired electrons and long electron-spin relaxation times allow the most efficient relaxation of water protons.[1a,2] At present, three gadolinium(III) complexes, gadolinium(III) diethylenetriaminepentaacetate (Gd-DTPA), the bis(*N*-methylamide) of Gd-DTPA, and the Gd(III) chelate of the 10-(2-hydroxypropyl) derivative of 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, are in clinical use as contrast agents for MRI. None of these compounds, however, appear to have tumor-specificity. Therefore, novel target-specific MRI contrast agents need to be developed. Recent reports in the literature indicate that metalloporphyrins are very promising candidates in this respect.[3]

In this paper, we report the first solution relaxivity measurements *in vitro* for a new class of potential contrast agents: paramagnetic polyoxotungstates, the representatives of a large group of compounds commonly known as heteropoly complexes.[4] Our decision to investigate this group of compounds was primarily based on the fact that transition metal-substituted heteropoly complexes were recently recognized as purely inorganic analogs of porphyrins.[5−9] At the same time, several

---

[†] Canisius College.

[‡] Roswell Park Memorial Institute.

[§] State University of New York at Buffalo. Current address: Medical Department, Brookhaven National Laboratory, Upton, NY 11973.

[®] Abstract published in *Advance ACS Abstracts*, January 1, 1995.

(1) For reviews of MRI, see: (a) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901. (b) Tweedle, M. F.; Brittain, H. G.; Eckelman, W. C.; Gaughan, G. T.; Hagan, J. J.; Wedeking, P. W.; Runge, V. M. In *Magnetic Resonance Imaging*, 2nd ed.; Partain, C. L., Ed.; W. B. Saunders: Philadelphia, PA, 1988; Vol. 1, p 793. (c) Young, S. W. *Magnetic Resonance Imaging: Basic Principles*; Raven Press: New York, 1988; p 1. (d) Moonen, C. T.; van-Zijil, P. C.; Frank, J. A.; Le-Bihan, D.; Becker, E. D. *Science* **1990**, *250*, 53. (e) Edelman, R.; Warach, S. *New England J. Med.* **1993**, *328*, 708.

(2) Koenig, S. H. *Isr. J. Chem.* **1988**, *28*, 345.

(3) See for example: (a) Lyon, R. C.; Faustino, P. J.; Cohen, J. S.; Katz, A.; Mornex, F.; Colcher, D.; Baglin, C.; Koenig, S. H.; Hambright, P. *Magn. Reson. Med.* **1987**, *4*, 24. (b) Bohdiewicz, P. J.; Lavallee, D. K.; Fawwaz, R. A.; Newhouse, J. H.; Oluwole, S. F.; Alderson, P. O. *Invest. Radiol.* **1990**, *25*, 765. (c) Fiel, R. J.; Musser, D. A.; Mark, E. H.; Mazurchuk, R.; Alletto, J. J. *Magn. Reson. Imaging* **1990**, *8*, 255.

(4) For reviews of chemistry of heteropoly complexes see: (a) Baker, L. C. W. In *Advances in the Chemistry of Coordination Compounds*; Kirschner, S., Ed.; Macmillan: New York, 1961, p 608. (b) Souchay, P. *Ions Mineraux Condenses*; Masson: Paris, 1969. (c) Evans, H. T., Jr. *Perspect. Struct. Chem.* **1971**, *4*, 1. (d) Weakley, T. J. R. *Struct. Bonding (Berlin)* **1974**, *18*, 131. (e) Pope, M. T. *Heteropoly and Isopoly Oxometalates*; Springer: New York, 1983. (f) Day, V. W.; Klemperer, W. G. *Science (Washington, D.C.)* **1985**, *228*, 533. (g) Pope, M. T.; Muller, A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 34.

(5) (a) Katsoulis, D. E.; Pope, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 2737. (b) Katsoulis, D. E.; Pope, M. T. *J. Chem. Soc., Chem. Commun.* **1986**, 1186. (c) Harmalker, S. P.; Pope, M. T. *J. Inorg. Biochem.* **1986**, *28*, 85. (d) Katsoulis, D. E.; Tausch, V. S.; Pope, M. T. *Inorg. Chem.* **1987**, *26*, 215. (e) Katsoulis, D. E.; Pope, M. T. *J. Chem. Soc., Dalton Trans.* **1989**, 1483. (f) Liu, J.; Ortega, F.; Sethuraman, P.; Katsoulis, D. E.; Costello, C. E.; Pope, M. T. *J. Chem. Soc., Dalton Trans.* **1992**, 1901. (g) Landis, A. L., Ph.D. Thesis, Georgetown University, 1970, pp 5−6; *Diss. Abst.* **1970**, *38B*, 4225.

(6) (a) Hill, C. L.; Brown, R. B., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 536. (b) Faraj, M.; Hill, C. L. *J. Chem. Soc., Chem. Commun.* **1987**, 1487.

(7) (a) Neumann, R.; Abu-Gnim, C. *J. Chem. Soc., Chem. Commun.* **1989**, 1324. (b) Neumann, R.; Abu-Gnim, C. *J. Am. Chem. Soc.* **1990**, *112*, 6025.

(8) (a) Lyon, D. K.; Miller, W. K.; Novet, T.; Domaille, P. D.; Evitt, E.; Johnson, D. C.; Finke, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 7209. (b) Mansuy, D.; Bartoli, J.-F.; Battioni, P.; Lyon, D. K.; Finke, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 7222.

0020-1669/95/1334-0924$09.00/0

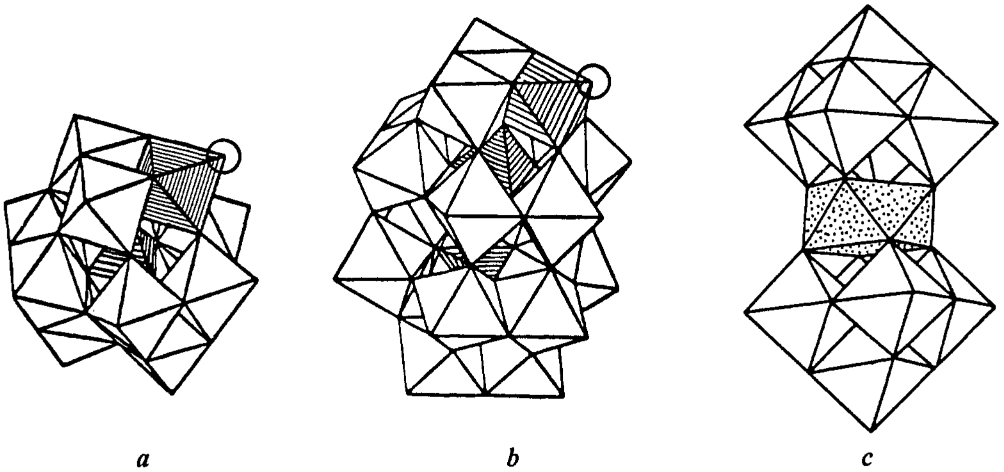

Figure 1. Structures of transition metal-substituted heteropoly complexes: (a) $[XW_{11}O_{39}Z(H_2O)]^{n-}$ (X = P, Si; Z = Fe^{3+}, Mn^{2+}); (b) $[P_2W_{17}O_{61}Z(H_2O)]^{m-}$ (Z = Mn^{2+}, Fe^{3+}); (c) $[Gd^{III}H_2W_{10}O_{36}]^{7-}$. Each vertex of a polyhedron locates an oxygen atom. A W atom is within each white octahedron. Each hatched tetrahedron contains P or Si. Each hatched octahedron contains the substituted transition metal, Fe^{3+} or Mn^{2+}. The square antiprism in (c) contains Gd^{3+}.

heteropoly complexes are known to possess antitumor[10] and antiviral[11] (including antiretroviral)[12] properties. In addition, numerous complexes having identical environments around a paramagnetic metal but having different net charges or sizes are available. Therefore, certain unique relationships concerning the roles of size, charge, and the metal type in relaxivity enhancement can be individually determined. Those relationships are the subject of this paper. The next paper in the series will address the relaxivities of heteropoly complexes in tissue.

Background

Heteropoly complexes are polyanionic, condensed oligomeric aggregates of transition-metal ions, usually in their d^0 electronic configuration, and oxide ions, held together by metal−oxygen bonds.[4] The largest number of heteropoly complexes is formed by Mo(VI) and W(VI). Mo or W in a heteropoly complex is typically surrounded by six oxide ions, forming an MO_6 octahedron. The most widely studied heteropoly anions are those with the formulas $XM_{12}O_{40}{}^{m-}$ (M = W, Mo; X = P, Si, B, Ge, etc.) and $X_2M_{18}O_{62}{}^{n-}$ (M = W, Mo; X = P, As). The former adopt the so-called "Keggin" structure. See Figure 1a. The structure has overall T_d symmetry and is based on a central XO_4 tetrahedron surrounded by twelve MO_6 octahedra arranged in four groups of three edge-shared octahedra, M_3O_{13}. These groups are linked to each other and to the central XO_4 tetrahedron by sharing corners. The $X_2M_{18}O_{62}{}^{n-}$ anions adopt the so-called "Wells−Dawson" structure. See Figure 1b. The structure can be viewed as containing two subunits (two XM_9 groups) of the Keggin structure, fused into a cluster of virtual D_{3h} symmetry. During the last 30 years a large number of "modified" Keggin- and Wells−Dawson-structure anions have been reported. They are based upon the replacement of one of the twelve or eighteen tungsten or molybdenum atoms by another octahedrally coordinated metal atom, Z. The first example of such compounds was reported by Simmons and Baker in 1962,[13] and an extensive investigation followed, which established unequivocally the large new general structural category of heteropoly anions.[14] Since then, numerous examples of "modified" Keggin and Wells−Dawson heteropoly complexes containing a variety of octahedral heteroelements have been described.[15−20] It has also been established that when the octahedral heteroatom is a first-row transition metal, its sixth outer coordination site is occupied by a water molecule,[14] which may be more or less deprotonated depending on the substituted metal, Z, and on the pH.[14,19] The anions then can be formulated: $[XM_{11}O_{39}Z(H_2O)]^{m-}$ (Keggin structure) and $[X_2M_{17}O_{61}Z(H_2O)]^{n-}$ (Wells−Dawson structure). (See Figure 1a,b). The substituted transition metal is often paramagnetic. Another type of heteropoly complex which contains paramagnetic metals is shown in Figure 1c. It has the formula $[XH_2W_{10}O_{36}]^{n-}$. Salts of the anions $[XH_2W_{10}O_{36}]^{n-}$, where X is a variety of tri- and tetravalent lanthanides and actinides, were first structurally characterized by Weakley and co-workers.[21] The paramagnetic metal in this complex achieves 8-fold

---

(9) (a) Toth, J. E.; Anson, F. C. *J. Am. Chem. Soc.* **1989**, *111*, 2444. (b) Toth, J. E.; Melton, J. D.; Cabelli, D.; Bielski, B. H. J.; Anson, F. C. *Inorg. Chem.* **1990**, *29*, 1952. (c) Rong, C.; Anson, F. C. *Inorg. Chem.* **1994**, *33*, 1064.

(10) (a) Jasmin, C.; Chermann, J.-C.; Herve, G.; Teze, A.; Souchay, P.; Boy-Loustau, C.; Raybaud, N.; Sinoussi, F.; Raynaud, M. *J. Natl. Cancer Inst.* **1974**, *53*, 469. (b) Yamase, T.; Fujita, H.; Fukushima, K. *Inorg. Chim. Acta* **1988**, *151*, 15.

(11) (a) Bussereau, F.; Picard, M.; Blancou, J.; Sureau, P. *Acta Virol. (Engl. Ed.)* **1988**, *32*, 33. (b) Kimberlin, R. H.; Walker, C. A. *Arch. Virol.* **1983**, *78*, 9.

(12) (a) Rozenbaum, W.; Dormant, D.; Spire, B.; Vilmer, E.; Gentilini, M.; Griscelli, C.; Montagnier, L.; Barre-Sinoussi, F.; Chermann, J. C. *Lancet* **1985**, 450. (b) Dormont, D.; Spire, B.; Barre-Sinoussi, F.; Montagnier, L.; Chermann, J. C. *Ann. Inst. Pasteur/Virologie* **1985**, *136E*, 75. (c) Buimovici-Klein, E.; Ong, K. R.; Lange, M.; Englard, A.; McKinley, G. F.; Reddy, M.; Grieco, M. H.; Cooper, L. Z. *Aids Res.* **1986**, *2*, 279. (d) Inoue, Y.; Take, Y.; Tokutake, Y.; Yoshida, T.; Yamamoto, A.; Yamase, T.; Nakamura, S. *Chem. Pharm. Bull.* **1990**, *38*, 285. (e) Hill, C. L.; Weeks, M. S.; Schinazi, R. F. *J. Med. Chem.* **1990**, *33*, 2767. (f) Weeks, M. S.; Hill, C. L.; Schinazi, R. F. *J. Med. Chem.* **1992**, *35*, 1216. (g) Blasecki, J. W. In *Polyoxometalates: From Platonic Solids to Anti-Retroviral Activity*; Pope, M. T., Muller, A., Eds.; Topics in Molecular Organization and Engineering, Vol. 10; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1994.

(13) Simmons, V. E.; Baker, L. C. W. *Proc. 7th Int. Conf. Coord. Chem.* **1962**, 195.

(14) Baker, L. C. W.; Baker, V. S.; Eriks, K.; Pope, M. T.; Shibata, M.; Rollins, O. W.; Fang, J. H.; Koh, L. L. *J. Am. Chem. Soc.* **1966**, *88*, 2329.

(15) Malik, S. A.; Weakley, T. J. R. *J. Chem. Soc., Chem. Commun.* **1967**, 1094.

(16) Weakley, T. J. R.; Malik, S. A. *J. Inorg. Nucl. Chem.* **1967**, *29*, 2935.

(17) Malik, S. A.; Weakley, T. J. R. *J. Chem. Soc. A* **1968**, 2647.

(18) Tourne, C.; Tourne, G.; Malik, S. A.; Weakley, T. J. R. *J. Inorg. Nucl. Chem.* **1970**, *32*, 3875.

(19) Zonnevijlle, F.; Tourne, C. M.; Tourne, G. F. *Inorg. Chem.* **1982**, *21*, 2751.

(20) Ortega, F.; Pope, M. T. *Inorg. Chem.* **1984**, *23*, 3292.

(21) (a) Peacock, R. D.; Weakley, T. J. R. *J. Chem. Soc. A* **1971**, 1836. (b) Iball, J.; Low, J. N.; Weakley, T. J. R. *J. Chem. Soc., Dalton Trans.* **1974**, 2021.

coordination by attachment to two W_5O_{18} groups. Each W_5O_{18} group consists of five edge-shared WO_6 octahedra. The overall anion symmetry is close to D_{4d}. The location of two (nonacidic) hydrogens in the compound has not been determined to date.

This paper reports relaxivity measurements for all three structural types of paramagnetic heteropoly complexes described above: Mn^{2+}- and Fe^{3+}-substituted Keggin anions (α-$[XW_{11}O_{39}Z(H_2O)]^{m-}$, where X = P or Si and Z = Mn^{2+} or Fe^{3+}), Mn^{2+}- and Fe^{3+}-substituted Wells–Dawson anions α_2-$[P_2W_{17}O_{61}Z(H_2O)]^{m-}$, where Z = Mn^{2+} or Fe^{3+}), and gadolinium(III) dodecatungstate, $[GdH_2W_{10}O_{36}]^{7-}$. All of the investigated heteropoly complexes have nondegenerate electronic ground states and a large number of unpaired electrons, which is a major criterion for a potential contrast agent.

Experimental Section

Materials. The starting materials for the preparation of the compounds were purchased from Aldrich Chemical Co. and used without further purification.

Methods. Analyses for K, Gd, and W were performed by Oneida Research Services (Whitesboro, NY) on two independent samples of $K_7[GdH_2W_{10}O_{36}]$. Water content was determined via weight loss at 550 °C. IR spectra were obtained in KBr plates using a Nicolet 5DX FT IR spectrometer in the range 4000–450 cm^{-1}. UV/vis spectra were recorded using an HP 8452A diode array spectrophotometer, and cyclic voltammetry was carried out on a PAR 273A potentiostat. Proton relaxivities in solutions of heteropoly complexes at room temperature were determined at 10.7 MHz, using a Praxis II relaxometer. T_1 relaxation times were measured for seven concentrations of each heteropoly complex in the concentration range from 0.05 to 10.0 mM (0.050, 0.25, 0.50, 1.00, 2.00, 5.00, and 10.0) in unbuffered aqueous solutions. The change in pH of the solutions in this concentration range was less than 0.1 pH unit, except for the $P_2W_{17}Fe$ complex, where it was around 1 pH unit. The plots of relaxation times vs concentration for all of the investigated complexes (including the $P_2W_{17}Fe$ complex) were straight lines with the correlation coefficient greater than 0.999.

Preparations. Transition metal-substituted Keggin and Wells–Dawson complexes were prepared according to the methods published previously.[8,17–19] The IR and UV/vis spectra and cyclic voltammograms agreed with the data published previously.[18,19,22] $K_7[GdH_2W_{10}O_{36}]$ was prepared by the procedure reported by Peacock and Weakley for 10-tungstoprazeodymate,[21a] $K_7[PrH_2W_{10}O_{36}]$, replacing $Pr(NO_3)_3$ with $Gd(NO_3)_3$. The sample was recrystallized three times from 70 °C water. Anal. Calcd for $K_7[GdH_2W_{10}O_{36}]\cdot 17H_2O$: K, 8.68; Gd, 4.99; W, 58.30; H_2O (including one molecule of constitutional water), 10.28. Found: K, 8.30; Gd, 4.84; W, 58.21; H_2O, 10.21. The IR spectrum was very similar to the spectrum of $K_7[PrH_2W_{10}O_{36}]$: 940 (vs), 890 (sh), 845 (vs), 793 (s), 715 (s), 570 (sh), 538 cm^{-1} (w).

Results and Discussion

The theory of relaxation of solvent protons by paramagnetic complexes is well-known, and it was recently reviewed in much detail.[1a] Qualitatively, the nuclear magnetic relaxation enhancement of water protons in a solution of a paramagnetic complex is primarily due to the dipolar interaction between the electron spin magnetic moment of the metal ion and the proton nuclear moment of coordinated water protons (inner-sphere contribution). The rapid exchange of aquo ligands communicates the relaxation to the bulk solvent. In addition to this inner-sphere relaxation effect, relaxation is also enhanced due to the interaction between the metal ion and water molecules that solvate the complex but are not coordinated to the metal (outer-sphere effect). As the result of these two contributions, the observed relaxation rate of the solvent nuclei, $1/T_i$, is linearly dependent on the concentration of the paramagnetic complex, M (eq 1). Relaxivity, R_i, is defined as the slope of this dependence in units of $M^{-1}\,s^{-1}$ or, more commonly, $mM^{-1}\,s^{-1}$ (eq 1).

Table 1. Relaxivities of Heteropoly Complexes at 10.5 MHz and 25 °C

complex	symbol	R_1, $mM^{-1}\,s^{-1}$
$[GdH_2W_{10}O_{36}]^{7-}$ (**1**)	GdW_{10}	5.95
$[SiW_{11}O_{39}Fe^{III}(H_2O)]^{5-}$ (**2**)	$SiW_{11}Fe$	1.90
$[PW_{11}O_{39}Fe^{III}(H_2O)]^{4-}$ (**3**)	$PW_{11}Fe$	1.36
$[SiW_{11}O_{39}Mn^{II}(H_2O)]^{6-}$ (**4**)	$SiW_{11}Mn$	5.23
$[PW_{11}O_{39}Mn^{II}(H_2O)]^{5-}$ (**5**)	$PW_{11}Mn$	3.38
$[P_2W_{17}O_{61}Fe^{III}(H_2O)]^{7-}$ (**6**)	$P_2W_{17}Fe$	2.43
$[P_2W_{17}O_{61}Mn^{II}(H_2O)]^{8-}$ (**7**)	$P_2W_{17}Mn$	5.51

$$(1/T_i)_{\text{obsd}} = (1/T_i)_{\text{d}} + R_i[\text{M}] \qquad i = 1, 2 \qquad (1)$$

On the basis of the theoretical equations used to describe the relaxation enhancement, the following approaches can be used in order to optimize the relaxivity of a metal complex: (1) increase the total electron spin, *S*, and lower electron spin relaxation time, (T_{1e}); (2) increase the number of coordinated water molecules, *q*; (3) decrease the distance between the water protons and the unpaired electron spin; (4) increase the rotational correlation time, τ_R.

Complexes of Gd(III), Mn(II), and Fe(III) have dominated the field of contrast agents because of their large total spins ($S = {}^7/_2$ for Gd(III); $S = {}^5/_2$ for Mn(II) and Fe(III)) and relatively long electron spin relaxation times (in nondegenerate electronic ground states). These were, therefore, the metals that we included in our investigations. Table 1 lists the R_1 relaxivity data obtained for all studied heteropoly complexes. The symbols from Table 1 supplemented with the charges on anions will be used throughout the discussion. For example, the α-$[SiW_{11}O_{39}Fe^{III}(H_2O)]^{5-}$ anion will be abbreviated as $SiW_{11}Fe^{5-}$. In all complexes except complex **1**, $GdW_{10}{}^{7-}$, a substituted paramagnetic metal, Me (Fe^{3+} or Mn^{2+}), in a heteropoly ion is coordinated by five oxide ions and one water molecule. The immediate surroundings of Fe and Mn are, therefore, identical. The only differences between the individual complexes are in their sizes, $XW_{11}Me$ vs $X_2W_{17}Me$, and for complexes with the identical sizes, in their net charges. The differences in the net charges are determined by the heteroatom, X, and by a paramagnetic metal, Me. The remaining discussion in this paper is concerned with the relationships in relaxivity between various transition metal-substituted Keggin and Wells–Dawson complexes. The relaxivity of gadolinium dodecatungstate in vitro and in vivo will be the subject of another paper.

Net Charge Effect. In order to quantitatively assess how the various parameters contribute to the complexes' relaxivities, we will compare first those complexes with *the same size and same substituted metal*, i.e. complexes **2** with **3** and **4** with **5**. In both pairs, there is an increase in the net negative charge on the heteropoly anion by one unit: from $PW_{11}Fe^{4-}$ to $SiW_{11}Fe^{5-}$ and from $PW_{11}Mn^{5-}$ to $SiW_{11}Mn^{6-}$. The differences in the net charges are determined by the heteroatom, P vs Si. The observed relaxivities of these complexes increase from 1.36 to 1.90 (1.40 times) in the first pair and from 3.38 to 5.23 (1.55 times) in the second pair. The two increases are very close. Therefore, we assign an average 1.48 times increase in relaxivity, as the result of an increase in negative charge on the complex by one unit. Qualitatively, the increase is easy to interpret. The larger negative charge on the complex will orient water molecules (both inner- and outer-sphere) with the hydrogen atoms closer to the complex. This effect was observed in the past in several metalloporphyrins.[23]

---

[22] Rocchioccioli-Deltcheff, C.; Thouvenot, R. *J. Chem. Res., Synop.* **1977**, 46, *J. Chem. Res., Miniprint* **1977**, 549.

Paramagnetic Metal Effect. The metal effect is calculated for two complexes with *the same net charge and the same size*, i.e. complexes **2** and **5**, $SiW_{11}Fe^{5-}$ and $PW_{11}Mn^{5-}$. Their relaxivities are 1.90 and 3.38, respectively, a 1.78 times increase from the Fe^{3+} complex to the Mn^{2+} complex. The increase can be attributed to the difference in electronic relaxation times of Fe^{3+} and Mn^{2+}. It is well-known that the electron relaxation time, T_{1e}, of Mn^{2+} is usually longer than the electron relaxation time of Fe^{3+} in the complexes of the same geometry.[24] The longer electronic relaxation time leads to an increase in relaxivity.

Independent Confirmation of the Net Charge and the Metal Effect. In order to confirm both quantitative relationships, we consider two complexes where both the net charge and the metal are changed at the same time, complexes **3** and **4**, $PW_{11}Fe^{4-}$ and $SiW_{11}Mn^{6-}$. The observed relaxivity of complex **3** is 1.36. Using the two observed relationships (net charge and metal effect) considered separately, we can calculate what the relaxivity of complex **4** should be. The increase in the negative net charge by 2 units should increase the relaxivity 1.48^2 times, and the change of the metal from Fe^{3+} to Mn^{2+} should contribute an increase of 1.78 times. Therefore, the *predicted* relaxivity of the $SiW_{11}Mn^{6-}$ complex is 5.30 ($1.36 \times 1.48^2 \times 1.78$), which is within 1.5% of the observed value of 5.23.

Size Effect. Having derived the first two relationships, we will now consider the influence of *size* on relaxivity of heteropoly complexes. In order to calculate the size effect, we will consider independently two pairs of compounds: $PW_{11}Fe^{4-}$–$P_2W_{17}Fe^{7-}$ (compounds **3** and **6**); $PW_{11}Mn^{5-}$–$P_2W_{17}Mn^{8-}$ (compounds **5** and **7**). In both pairs, there are an identical increase in the negative net charge (by 3) and the same increase in size ($PW_{11}Me$ to $P_2W_{17}Me$). In order to separate the two effects, the contribution from the net charge effect will be determined first, on the basis of the previously derived charge effect. However, the previously derived relationship concerned the complexes with identical size and different charges. In order to make the relation applicable to the new situation, we consider the *charge density* change instead of just the change in the charge. The hydrodynamic radii of transition metal-substituted Keggin ($PW_{11}Me$) and Wells–Dawson ($P_2W_{17}Me$) complexes were determined by Harmalker and Pope from ESR measurements as being equal to 5.1 and 6.4 Å, respectively.[25] Therefore, the volume ratio of the complexes is equal to 1.98. If v is a volume of a heteropoly anion, then the change in charge density from $PW_{11}Fe^{4-}$ to $P_2W_{17}Fe^{7-}$ is represented as $-4/v$ to $-7/1.98v$, or $-4/v$ to $-3.5/v$, the *increase* in the charge by 0.5 unit of charge density. The relaxivity of the $P_2W_{17}Fe^{7-}$ complex based on the charge density alone should therefore be 1.24 times *lower* ($1 + 0.50 \times 0.48$) than the relaxivity of $PW_{11}Fe^{4-}$. Application of this relationship predicts that relaxivity to be 1.10 (1.36/1.24). The observed relaxivity is 2.43. Therefore, the increase in relaxivity from 1.10 to the experimentally observed value of 2.43 (2.21 times increase) can be attributed to the size alone. Similar calculations for the $PW_{11}Mn^{5-}$–$P_2W_{17}Mn^{8-}$ pair lead to the 0.96 unit of charge density increase ($-5/v$ to $-8/1.98v$), and the predicted "charge density only" effect of lowering the relaxivity 1.46 times ($1 + 0.96 \times 0.48$) becomes 2.32 (3.38/1.46). And for the Fe complex, the increase in relaxivity from 2.32 to the experimentally determined value of 5.51 can be attributed to the size alone. Therefore, the "size alone" effect is responsible for the 2.40 times increase in relaxivity. The fact that both Fe and Mn complexes give almost identical values of the size effect indicates that the change in pH observed for the $P_2W_{17}Fe$ complex (see Experimental Section) has no significant effect on the observed relaxivity. The average of both pairs is 2.31 ± 0.10. We interpret this change as being caused by the increase in rotational correlation time, τ_R, of the $P_2W_{17}Me$ complex as compared to the PW_{11}-Me complex. The rotational correlation times of transition metal-substituted heteropoly complexes were determined by Harmalker and Pope, and they indicate that at room temperature the correlation time for the Wells–Dawson structure (3.3 ns) is 2.5 times longer than the correlation time for the Keggin structure (1.3 ns). Therefore, there is a very good quantitative agreement between the changes in rotational correlation time and the relaxivity of the complex. This effect was previously observed for several metal chelates covalently attached to protein molecules.[26-28] However, the data presented herein are, to our knowledge, the first demonstration of the size effect related to the size of the metal complex alone.

Acknowledgment. This research was supported by Research Corp. Grant C-3006 and NIH-NCI Grant 1 R15 CA54462-01.

IC9409120

---

(23) Kellar, K. E.; Foster, N. *Inorg. Chem.* **1992**, *31*, 1353.

(24) Drago, R. S. *Physical Methods in Chemistry*; W. B. Saunders: Philadelphia, PA, 1977; p 438.

(25) Harmalker, S. P.; Pope, M. T. *J. Phys. Chem.* **1978**, *82*, 2823.

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

(27) Koenig, S. H.; Baglin, C.; Brown, R. D., III; Brewer, C. F. *Magn. Reson. Med.* **1984**, *1*, 496.

(28) Lauffer, R. B.; Brady, T. J.; Brown, R. D.; Baglin, C.; Koenig, S. H. *Magn. Reson. Med.* **1986**, *3*, 541.