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Journal of Magnetic Resonance 158 (2002) 36–42

JMR
Journal of
Magnetic Resonance

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An evaluation of the contributions of diffusion and exchange in relaxation enhancement by MRI contrast agents

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Received 12 December 2001; revised 22 July 2002

Abstract

Magnetic compounds are known to enhance water proton relaxation, either by diffusion or by proton exchange. An experimental procedure to distinguish both mechanisms is proposed and validated by relaxation measurements made in water–methanol solutions of Dy^{3+} , Ni^{2+} , Gd^{3+} , Tempo, and AMI-25. The test discriminates according to the character of the transverse relaxation in water–methanol solutions: a mono-exponential decay corresponds to diffusion, while a bi-exponential decay indicates the contribution of a proton exchange. The study of ferritin and akaganeite particle solutions confirms the occurrence of a proton exchange between protons belonging to hydroxyl groups of the particle surface and free water protons.

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Keywords: Relaxation; Diffusion; Exchange; Water–methanol solutions; Ferritin; Ferrihydrite; Akaganeite

1. Introduction

The coupling of proton spins with larger magnetic moments, namely electronic magnetic moments, considerably speeds up the relaxation of water, hence, their use as contrast agents for magnetic resonance imaging (MRI). Most common among the MRI contrast agents are paramagnetic gadolinium ion complexes and superparamagnetic magnetite particles. Relaxation is always caused by a time-modulated interaction between the protons and the magnetic center [1–3]. Coupling can be of dipolar and scalar nature, while time modulation arises from translational diffusion of the protons, rotational diffusion of the magnetic compound, and exchange of protons between binding sites and free water; and for paramagnetic ions and superparamagnetic particles, electronic and Néel relaxation, respectively [4,5].

Inner sphere (IS) and outer sphere (OS) models describe these relaxation mechanisms for paramagnetic ions. Inner sphere theory accounts for the exchange

between coordinated water molecules and bulk water. Outer sphere theory describes the relaxation induced by the diffusion of water molecules within the magnetic field gradients around the paramagnetic hydrated ion. The IS contribution is generally larger than that of OS. First, because the distance between the paramagnetic ion and a coordinated water molecule is on an average smaller than that between the hydrated ion and a diffusing water molecule. Second, because the residence time on the binding site is often longer than the diffusion time. However, for chelated ions and in the absence of water exchange, the OS mechanism dominates relaxation. The relaxation properties of the most used paramagnetic ions are well known [4–13].

Relaxation induced by magnetite particles is assigned to the diffusion of water molecules around the superparamagnetic iron core. It is well described by an OS theory adapted to account for the anisotropy of magnetite crystals [14,15] and for particle clustering [16].

However, the relaxation process of water in the presence of some magnetic compounds, namely ferritin and hydrated iron oxide particles, remains obscure. Ferritin is the natural iron storing protein of many living systems. In humans, it is mainly located in the liver, spleen, and brain [17]. The apoprotein, constituted by 24 subunits forming a

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¹ Y. Gossuin is supported by a scientific grant from F.N.R.S (Fonds National de la Recherche Scientifique).

spherical shell of 13 nm in diameter, is called apoferritin. Iron is stored in an 8 nm diameter inner cavity, as a ferrihydrite ($5\text{Fe}_2\text{O}_3 \cdot 9\text{H}_2\text{O}$) mineral core [18]. Ferrihydrite is an antiferromagnetic hydrated iron oxide while nanometric particles of this material are superparamagnetic. At room temperature, the magnetization of a ferritin solution does not saturate up to 5 T and remains simply proportional to the applied field [19,20]. Water relaxation in ferritin solutions was long attributed to the OS mechanism [21,22], but this interpretation is contradicted by the observed linear dependence [22,23] of the transverse relaxation rate constant R_2 on the static field B_0 (at high fields, the prediction of OS theory is quadratic), and with the order of magnitude of R_2 . A similar uncommon linear field dependence of R_2 has also been reported for aqueous solutions of commercial hydrated iron oxide particles [24,25]: Niferex (ferrihydrite + dextran, 6 nm) and Fercayl (akaganeite + dextran, 24 nm). Based on the observation that the relaxation of some hydrated iron oxide particles, especially akaganeite particles, depends on pH, a proton exchange model was proposed to describe the NMR properties of these compounds [25,26]. Diffusion or proton exchange, the origin of water relaxation induced by hydrated iron oxide nanoparticles, remains an open question.

This study presents a simple method, aimed at answering this question, based on the use of water–methanol solution of the considered magnetic compound. This method is first validated for Dy^{3+} , Ni^{2+} , Gd^{3+} , Tempo, and AMI-25 solutions, whose relaxation mechanisms are well known. It is then applied to ferritin and Fercayl solutions and confirms our former conclusion in favor of proton exchange.

2. Results

2.1. Principle of the water–methanol solution test

When diffusion dominates the relaxation process, the relaxation rate constant is proportional to C_V , the concentration of the magnetic entity, i.e., the number of moles of magnetized entities per liter of solution (for example, Eq. (1) is valid for magnetic particles at high fields, giving the secular term of Curie OS relaxation [27]). When proton exchange dominates, the relaxation rate constant is proportional to the ratio between the total number of adsorption sites for protons per liter of solution, and C_T , the concentration of solvent protons participating in the exchange

$$R_2^{\text{DIF}} = \frac{64\pi}{105} \cdot C_V \cdot R^3 \cdot (\delta\omega_{\text{eq}})^2 \cdot \tau_D \propto C_V, \quad (1)$$

$$R_{1,2}^{\text{EX}} = \frac{C_V \cdot q}{C_T} \cdot \frac{1}{T_{1,2}^{\text{M}} + \tau_M} \propto \frac{C_V \cdot q}{C_T}, \quad (2)$$

where $\delta\omega_{\text{eq}}$ is the equatorial field of the magnetic entity expressed in angular frequency units and R is the radius of the entity. $\tau_D = R^2/D$, D is the diffusion coefficient of the protons. q is the number of protons adsorbed on one magnetic entity, $T_{1,2}^{\text{M}}$ is the relaxation time of an adsorbed proton, and τ_M is the residence time of an adsorbed proton on the magnetic entity.

In aqueous solutions, $C_T = 111 \text{ M}$ is invariant, because all water protons are potentially involved in the exchange and water is an incompressible liquid with two protons per molecule, so that Eqs. (1) and (2) depend only on C_V and are equivalent.

This equivalence disappears if one compares solutions with different values of C_T for the same value of C_V . Eqs. (1) and (2) allow us to predict that if relaxation is due to diffusion, then the relaxation rate constants of the two solutions will be the same, while different relaxation rate constants will be an indication of proton exchange.

Our method is based on the use of two miscible solvents, water and methanol. Several proton populations can be identified in these solutions: water protons, methanol protons, OH protons (water + methanol), and CH protons. Two solutions with the same concentration of magnetic entities, but with different proportions of water and methanol, will contain different proportions of these protons fractions. If one fraction is involved in an exchange process, its relaxation times in both solutions will be different, while a fraction relaxing through diffusion will have the same relaxation time in both solutions. By mixing two solvents, water and methanol, it is thus possible to estimate the amounts of protons relaxing by diffusion and relaxing by proton exchange.

The method is conditioned by two assumptions: if diffusion dominates water relaxation, it also dominates methanol relaxation. In other words, if water molecules do not bind to the magnetic entity, neither do methanol molecules. This last assumption is reasonable in water–methanol solutions. While NMR studies on pure methanol solutions of paramagnetic ions [28,29] have shown that methanol molecules bind to the ion, producing an inner sphere relaxation, it is reasonable to assume that, in water–methanol solutions with similar proportions of water and methanol, if water binds to the magnetic compound, methanol does not, because water has more affinity for binding than methanol.

2.2. Water–methanol solutions of dysprosium, nickel, and gadolinium

The relaxation of Dy^{3+} , Ni^{2+} , and Gd^{3+} in aqueous solution is mono-exponential and is mainly due to an IS mechanism [4]. In water–methanol solutions, on the contrary, the relaxation of protons is clearly bi-exponential, as shown in Fig. 1 for a Dy^{3+} solution.

To identify the two proton fractions, solutions with different proportions of water and methanol were

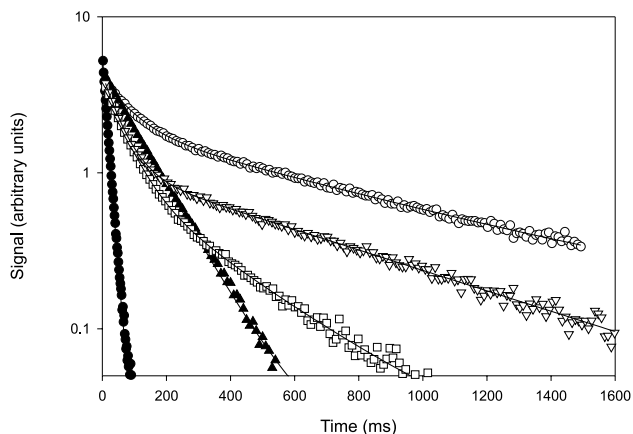


Fig. 1. Evolution of transverse magnetization during a CPMG sequence for water–methanol solutions of 12.1 mM Dy^{3+} (○), 42 mM Tempo (▲), and AMI-25 0.41 mM Fe (●) containing 50.6% of CH protons and 49.4% of OH protons; and for water–methanol solutions of ferritin 60 mM Fe (□) and Fercayl 148 mM Fe (▽) containing 27.9% of CH protons and 72.1% of OH protons. Lines are mono-exponential (Tempo and AMI-25) or bi-exponential fittings (Dy^{3+} , ferritin, and Fercayl) of the data.

prepared. The experimental fast relaxing fraction of the bi-exponential fitting and the theoretical fraction of water protons and OH protons were compared (Fig. 2, for Dy^{3+}). The fast relaxing protons are OH protons (water + methanol), while the slow relaxing protons are methanol CH protons.

Dysprosium. Fig. 3 shows the transverse relaxation rate constant of the fast fraction R_2^{OH} and of the slow fraction R_2^{CH} in four Dy^{3+} water–methanol solutions of the same volumic concentration but with different concentrations of OH protons (C_{OH}) and CH protons

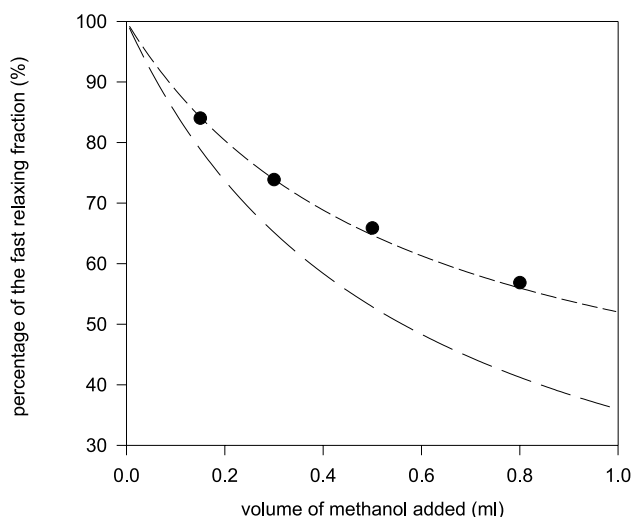


Fig. 2. Percentage of fast relaxing protons obtained from the bi-exponential fittings of the CPMG curves, for four water–methanol solutions of dysprosium containing different proportions of methanol and water. The medium dashed line is the theoretical percentage of water protons of the solutions. The short dashed line is the theoretical percentage of OH protons (water + methanol) of the solutions.

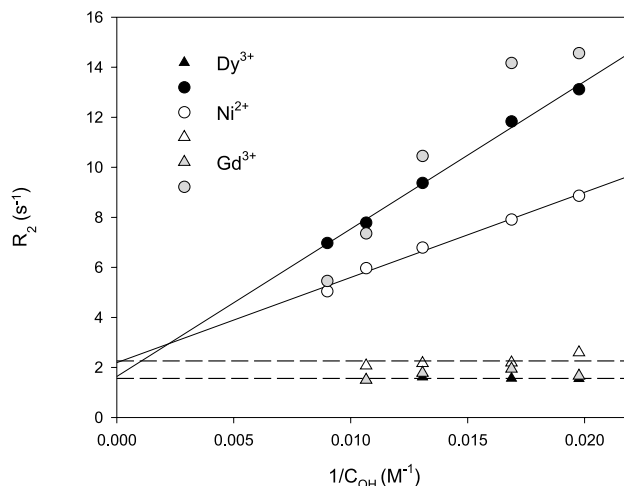


Fig. 3. Evolution of R_2^{OH} (●) and R_2^{CH} (▲) with $1/C_{\text{OH}}$ for different water–methanol solutions of 12.1 mM Dy^{3+} , 6.51 mM Ni^{2+} , and 0.51 mM Gd^{3+} . The solid line shows the linear regression of R_2^{OH} and the dashed line shows the average value of R_2^{CH} for Dy^{3+} and Ni^{2+} .

(C_{CH}). R_2^{OH} varies linearly with $1/C_{\text{OH}}$, while R_2^{CH} is independent of it.

Nickel. The fast and slow transverse relaxation rate constants of four different water–methanol solutions of nickel of the same volumic concentration, but with different C_{OH} and C_{CH} , are shown in Fig. 3. As with dysprosium, R_2^{OH} is proportional to $1/C_{\text{OH}}$ and R_2^{CH} is independent of it.

Gadolinium. The results obtained for different Gd^{3+} water–methanol solutions of the same volumic concentration are different: the relationship between R_2^{OH} and $1/C_{\text{OH}}$ appears to be sublinear and R_2^{CH} is no longer constant (Fig. 3).

2.3. Water–methanol solutions of Tempo and AMI-25

The relaxation of aqueous solutions of Tempo and AMI-25 arises from an OS mechanism and is mono-exponential [14,30]. Fig. 1 shows that the relaxation of protons in water–methanol solutions of, respectively, Tempo and AMI-25 remains mono-exponential.

2.4. Water–methanol solutions of ferritin and Fercayl

Aqueous solutions of ferritin and Fercayl show mono-exponential relaxation [22–26]. However, water–methanol solutions of these compounds exhibit bi-exponential relaxation (Fig. 1). The fast and slow relaxing proton populations correspond, respectively, to OH and CH protons (Fig. 4, for ferritin). Fig. 5 shows the evolution of R_2^{OH} and R_2^{CH} for different water–methanol solutions of ferritin and Fercayl of the same volumic concentration.

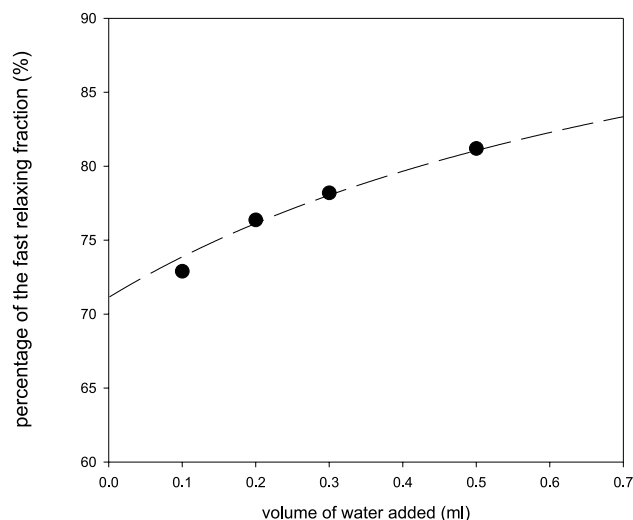


Fig. 4. Percentage of fast relaxing protons obtained from the bi-exponential fittings of the CPMG curves for four water–methanol solutions of ferritin containing different proportions of methanol and water. The short dashed line is the theoretical percentage of OH protons (water + methanol) of the solutions.

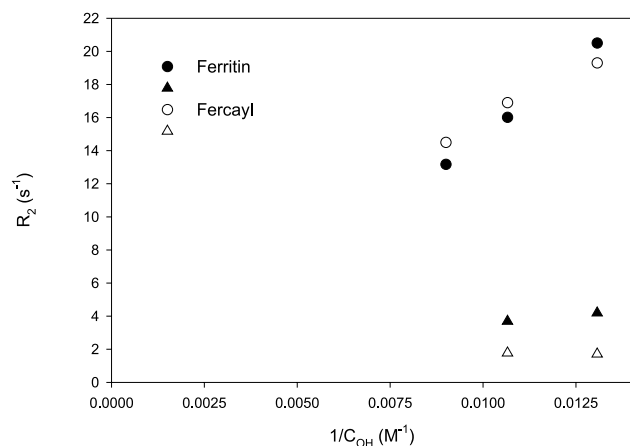


Fig. 5. Evolution of R_2^{OH} (●) and R_2^{CH} (▲) with $1/C_{\text{OH}}$ for different water–methanol solutions of ferritin 60 mM [Fe] and Fercayl 148 mM [Fe].

Water–methanol solutions of ferritin and Fercayl with high proportions of methanol are not stable. Therefore, solutions with less than 30% CH protons were used.

3. Discussion

3.1. Test samples

The bi-exponential relaxation of water–methanol solutions of Dy^{3+} , Ni^{2+} , and Gd^{3+} proves the existence of two nonexchanging populations of protons with different relaxation rate constants. These fractions have been quantitatively identified as the OH protons (water + methanol), relaxing quickly, and the CH protons, relaxing slowly. It is not surprising that the fast fraction includes methanol OH protons, because they are in fast exchange with water protons.

R_2^{CH} of Dy^{3+} and Ni^{2+} water–methanol solutions is independent of $1/C_{\text{OH}}$, for the same ion concentration. CH protons relax by diffusion and their relaxation rate constant is dependent only on the concentration of paramagnetic ions, according to Eq. (1).

Contrarily, R_2^{OH} varies linearly with $1/C_{\text{OH}}$, even for the same ion concentration. Hence, OH protons mainly relax through an exchange between bound and free protons. The comparison between the intercept of the linear regression of Fig. 3 and the corresponding mean value of R_2^{CH} confirms this interpretation (see Table 1). The intercept of R_2^{OH} plotted as a function of $1/C_{\text{OH}}$ represents the OS contribution to the relaxation of OH protons. It corresponds to a virtually infinite concentration of OH protons, so that from Eq. (2) the contribution to the relaxation rate constant from proton exchange is zero. In these conditions, OH protons relax only by diffusion and their relaxation rate constant is equal to R_2^{CH} , as shown in Table 1. Moreover, the relaxation rate constants obtained from OS theory given in Table 1 are close to R_2^{CH} for Dy^{3+} and Ni^{2+} , which is another indication favoring diffusion as the main relaxation mechanism for the CH protons. The parameters introduced in the theoretical calculations to get the results in Table 1 were $\tau_{\text{D}} = R^2/D = 36$ ps for both ions, where R is the hydrated ion radius and D is the water diffusion coefficient, and electronic relaxation times $\tau_{\text{SI}} = 0.12$ ps for Dy^{3+} [31] and $\tau_{\text{SI}} = 3$ ps for Ni^{2+} [4].

The interpretation of the results obtained for Gd^{3+} is less straightforward: R_2^{CH} seems to vary, even for the same ion concentration, and R_2^{OH} is not proportional to $1/C_{\text{OH}}$. These discrepancies are likely to be due to the long electronic relaxation time characterizing Gd^{3+} . For

Table 1
Comparison of experimental CH relaxation rate constants and theoretical OS relaxation rate constants

	Dysprosium	Nickel	Gadolinium	Ferritin	Fercayl
Intercept of R_2^{OH} versus $1/C_{\text{OH}}$	$(1.64 \pm 0.31) \text{ s}^{-1}$	$(2.19 \pm 0.19) \text{ s}^{-1}$	–	–	–
Mean R_2^{CH}	$(1.56 \pm 0.04) \text{ s}^{-1}$	$(2.26 \pm 0.23) \text{ s}^{-1}$	–	–	–
R_2^{CH} (13.6% CH protons)	–	–	$(1.5 \pm 0.05) \text{ s}^{-1}$	$(3.69 \pm 0.1) \text{ s}^{-1}$	$(1.78 \pm 0.04) \text{ s}^{-1}$
Calculated OS contribution	1.23 s^{-1}	1.72 s^{-1}	2.19 s^{-1}	27.3 s^{-1}	20.9 s^{-1}

Dy³⁺ and Ni²⁺, electronic relaxation is the fastest mechanism and dominates the relaxation. Diffusion properties of protons are not important for these ions. For Gd³⁺, on the contrary, the diffusion time ($\tau_D = 36$ ps) is shorter than the electronic relaxation time ($\tau_{SI} = 5000$ ps [4,32]) and diffusion influences the relaxation rate constants. Taking into account the fact that water molecules diffuse faster than methanol molecules and that diffusion properties of water and methanol in a water–methanol solution depend on the proportions of water and methanol of the solution, the relaxation rate constants are no longer directly comparable. However, we can calculate the theoretical OS relaxation rate constant for the solution containing 13.6% of CH protons (first point of Gd³⁺ data on Fig. 3), using the measured diffusion coefficient of methanol obtained from PGSTE sequence on a pure water–methanol solution, without ions ($D_{\text{meth}} = 1.74 \times 10^{-9}$ m²/s at 40 °C).

The theoretical OS contribution for this water–methanol Gd³⁺ solution is close to the experimental result (Table 1). The conclusion is that OH protons mainly relax through an exchange process, while CH protons relax by a diffusion mechanism.

For Tempo and AMI-25, whose relaxation in aqueous solutions is explained by diffusion, it is impossible to distinguish OH protons from CH protons, because transverse relaxation is mono-exponential: both fractions relax by diffusion.

3.2. Ferritin and Fercayl

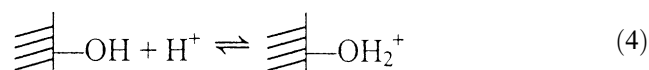
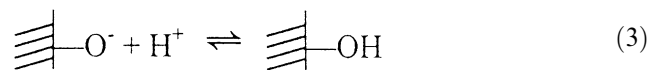
Relaxation of ferritin and Fercayl in water–methanol solutions is bi-exponential. The interpretation of this result is the same as that for paramagnetic ions: the protons are divided into two nonexchanging fractions, a fast relaxing one (OH protons) and a slow relaxing one (CH protons). According to our previous analysis, OH protons in water–methanol solutions of ferritin and Fercayl mainly relax by exchange and CH protons relax by diffusion.

As with gadolinium, the diffusion coefficient seems to be important in OS relaxation of ferritin and Fercayl. Therefore, only the CH relaxation rate constant of the solution containing 13.6% of CH protons can be compared with the theoretical OS contribution, where the differences in diffusion coefficient between water and methanol have to be accounted for. The theoretical rate constant is given by the secular term of OS theory, corresponding to the so-called Curie relaxation (Eq. (1)). The theoretical rates are larger than the experimental rates (Table 1). This discrepancy seems to indicate that Eq. (1) is not suited for the description of OS relaxation induced by hydrated iron oxide particles.

In aqueous solutions, the relaxation induced by the same compounds is thus due to proton exchange be-

tween bound and bulk protons. This result is in agreement with the previously reported influence of pH on the relaxation rate constants of Fercayl solutions.

Hydrous iron oxides, such as akaganeite (β -FeOOH) and ferrihydrite ($5\text{Fe}_2\text{O}_3 \cdot 9\text{H}_2\text{O}$), contain hydroxyl groups. OH groups located at the surface of the hydrous iron oxide particles exhibit an amphoteric behavior [33–38]



The effect of pH on relaxation rate constants can be explained if one considers that relaxation is due to an exchange of protons (not of water molecules) between protons of these OH groups and free water protons. According to reactions (3) and (4), the surface is more protonated at low pH than at high pH. Thus, exchange induced relaxation will be faster at low pH than at high pH, as previously observed [25,26].

4. Conclusion

Water–methanol solutions of a magnetic compound can help to identify the origin of proton relaxation. If relaxation is bi-exponential, OH protons likely relax through an exchange process and CH protons through a diffusion mechanism. Therefore, relaxation of aqueous solutions of the magnetic compound is also due to proton exchange. This interpretation can be confirmed by measuring R_2^{OH} and R_2^{CH} of water–methanol solutions of the same volumic concentrations but with different proportions of OH and CH protons.

A mono-exponential relaxation indicates diffusion around the magnetic entity as the main relaxation mechanism for OH and CH protons.

Using this method, we have shown that ferritin and Fercayl relaxation is mainly due to proton exchange. This result agrees with previous pH-effect studies and is consistent with the well-known acid–base properties of hydrous iron oxides.

5. Experimental

5.1. Samples

Gadolinium chloride (ref G7532), nickel chloride (ref N5756), and dysprosium chloride (ref D1034) were obtained from Sigma Chemical (Bornem, Belgium). Tempo (2,2,6,6-tetramethyl-piperidine-1-oxyl; ref 21, 400-0) was obtained from Aldrich Chemical (Bornem, Bel-

gium). Solutions of these different compounds were prepared with distilled water and methanol.

AMI-25 is a contrast agent from Guerbet (France). The average size of the magnetite core is 5 nm and the coating is composed of dextran.

Horse spleen apoferritin (ref A3641) and ferritin (ref F4503) were obtained from Sigma Chemical (Bornem, Belgium). The average loading factor (number of iron ions per molecule) of the ferritin sample, as determined from the iron mass fraction, was about 1720. The hydrodynamic size of the protein, as measured by Photon Correlation Spectroscopy (Brookhaven Instruments BI 160, USA), was 13 nm. The average diameter of the spherical ferrihydrite core, measured by Transmission Electron Microscopy (Philips CM 20 Microscope, USA), was 5.4 ± 0.8 nm. The pH of the original aqueous solutions was about 6.5 for ferritin and 7 for apoferritin.

Fercayl is clinically used for intra-muscular iron injections and is distributed by Sterop laboratories (Brussels, Belgium). It consists of a colloidal solution of akaganeite (β -FeOOH) particles coated with dextran (information provided by the supplier) with an overall size of 24 nm. The iron oxide particles are rod-like, with a long axis measuring 15 nm log-normally distributed ($\sigma = 0.072$) and with a short axis whose length is between 1.5 and 3.5 nm (measured by TEM). Akaganeite, like ferrihydrite, is a hydrated iron oxide ([18]). The pH of the original Fercayl aqueous solutions was about 6.

All measurements were performed at a pH of 6.5.

5.2. T_2 measurements

T_2 measurements were preferred to T_1 measurements, because the transverse relaxivity of ferritin and Fercayl is much larger than their longitudinal relaxivity.

Relaxation time measurements were performed on a BRUKER PC140 instrument working at a proton Larmor frequency (ν_0) of 40 MHz. T_2 was obtained at 40 °C from a Carr–Purcell–Meiboom–Gill (CPMG) sequence, with an interecho time (TE) of 1 ms. Repetition time was always longer than $5T_1$. Mono- and bi-exponential fittings were performed with the DECONVOL software, using MINUIT algorithm. Molar proportions of the different fractions of protons in water–methanol solutions were computed using the molecular weight and the densities of water and methanol.

5.3. Measurement of diffusion coefficient

The diffusion coefficient of methanol in water–methanol solution containing 13.6% of CH protons was measured at 40 °C, thanks to pulse gradient stimulated echo (PGSTE) pulse sequence, to accurately calculate the theoretical OS relaxation rate constant of the studied solutions.

Acknowledgment

The authors are indebted to Mr. P. Cooper for his help in preparing the manuscript.

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