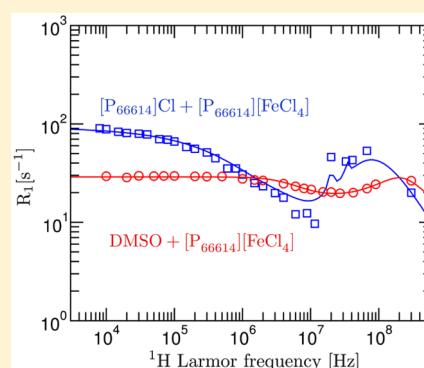


# $^1\text{H}$ NMR Relaxation Study of a Magnetic Ionic Liquid as a Potential Contrast Agent

Carla I. Daniel,<sup>\*,†</sup> Fabián Vaca Chávez,<sup>‡</sup> Carla A. M. Portugal,<sup>†</sup> João G. Crespo,<sup>†</sup> and Pedro J. Sebastião<sup>§</sup><sup>†</sup>REQUIMTE/LAQV, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Lisbon, Portugal<sup>‡</sup>FaMAF, Universidad Nacional de Córdoba, IFEG CONICET, X5016LAE Córdoba, Argentina<sup>§</sup>Center of Physics and Engineering of Advanced Materials, Departamento de Física Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal

## S Supporting Information

**ABSTRACT:** A proton nuclear magnetic relaxation dispersion  $^1\text{H}$  NMRD study of the molecular dynamics in mixtures of magnetic ionic liquid  $[\text{P}_{66614}][\text{FeCl}_4]$  with  $[\text{P}_{66614}][\text{Cl}^-]$  ionic liquid and mixtures of  $[\text{P}_{66614}][\text{FeCl}_4]$  with dimethyl sulfoxide (DMSO) is presented. The proton spin–lattice relaxation rate,  $R_1$ , was measured in the frequency range of 8 kHz–300 MHz. The viscosity of the binary mixtures was measured as a function of an applied magnetic field,  $B$ , in the range of 0–2 T. In the case of DMSO/ $[\text{P}_{66614}][\text{FeCl}_4]$  the viscosity was found to be independent from the magnetic field, while in the case of the  $[\text{P}_{66614}][\text{Cl}^-]/[\text{P}_{66614}][\text{FeCl}_4]$  system viscosity decreased with the increase of the magnetic field strength. The spin–lattice relaxation results were analyzed for all systems taking into account the relaxation mechanisms associated with the molecular motions with correlation times in a range between  $10^{-11}$  and  $10^{-7}$  s, usually observed by NMRD, and the paramagnetic relaxation contributions associated with the presence of the magnetic ions in the systems. In the case of the DMSO/ $[\text{P}_{66614}][\text{FeCl}_4]$  system the  $R_1$  dispersion shows the relaxation enhancement due to the presence of the magnetic ions, similar to that reported for contrast agents. For the  $[\text{P}_{66614}][\text{Cl}^-]/[\text{P}_{66614}][\text{FeCl}_4]$  system, the  $R_1$  dispersion presents a much larger paramagnetic relaxation contribution, in comparison with that observed for the DMSO/ $[\text{P}_{66614}][\text{FeCl}_4]$  mixtures but different from that reported for other magnetic ionic liquid system. In the  $[\text{P}_{66614}][\text{Cl}^-]/[\text{P}_{66614}][\text{FeCl}_4]$  system the relaxation enhancement associated with the paramagnetic ions is clearly not proportional to the concentration of magnetic ions, in contrast with what is observed for the DMSO/ $[\text{P}_{66614}][\text{FeCl}_4]$  system.



## INTRODUCTION

Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) is a widely known noninvasive experimental technique used to characterize molecular order/structure and dynamics in a large variety of systems.<sup>1,2</sup> In particular,  $^1\text{H}$  NMR imaging is a powerful tool to obtain information on the morphology, function, and metabolism of complex systems like porous materials, composites, and biological systems, among many others.

Magnetic nanoparticles as contrast agents for NMR imaging have been the target of numerous research works due to their unique magnetic properties and the ability to contribute to probe molecular interactions at the cellular and molecular level.<sup>3–5</sup> The paramagnetic metal ions present in magnetic contrast agents possess permanent magnetic moments that contribute to strongly increase the local magnetic field in the vicinity of each ion. Through paramagnetic relaxation they produce a decrease of spin–lattice ( $T_1$ ) and spin–spin ( $T_2$ ) relaxation times of neighboring hydrogen nuclei, a phenomenon called “proton relaxation enhancement (PRE).”<sup>6</sup> Therefore, in medical NMR imaging tissues with different concentrations of paramagnetic ions will have distinct spin–lattice relaxation

times which can be used to produce images with higher contrast.<sup>7</sup> The PRE effect can be useful not only for clinical diagnosis but also to increase contrast in NMR imaging in general as in the case of the study of chemical reactions and processes.<sup>8</sup> Magnetic colloids, magnetic nanoparticles, paramagnetic and super paramagnetic compounds, and magnetic ionic liquids are systems of high interest for the enhancement of NMR imaging quality. The development and characterization of new magnetic compounds has been an important research subject.<sup>3–5,9,10</sup> The magnetic behavior of the metal ions makes these compounds effective proton relaxation agents because the contrast effect is produced indirectly by the changes in the local magnetic environment.<sup>6,11</sup> Different paramagnetic metal ions can be used, Fe(III), Gd(III), Mn(II), and Dy(III), according to their magnetic susceptibilities and levels of toxicity for specific applications.<sup>12</sup>

Received: May 19, 2015

Revised: August 6, 2015

Published: August 7, 2015

The effect of paramagnetic relaxation can be described by the so-called Curie relaxation that considers fluctuations of the dipolar interactions between the paramagnetic particles' global magnetic moments and the proton nuclear magnetic moments of neighbor hydrogen nuclei either temporarily bounded to the magnetic particle or within the first neighbor layer spheres (inner spheres) or in outer layer spheres.<sup>6,13–16</sup>

Nowadays, the commercial contrast agents are based on the Gd(III) paramagnetic ion, due to high magnetic response in comparison with the other metal ions described before.<sup>12</sup> However, the toxicity of these compounds as contrast agents is high. In particular the Gd(III) toxicity is higher than Fe(III).<sup>12</sup> To reduce the levels of cell toxicity, the paramagnetic ions may be used as contrast agents, in the form of complexes (or chelates) with organic ligands.<sup>17,18</sup> The toxicity of Gd(III) and Fe(III) is identical when these elements are used as members of complexes or chelate systems. In this case, Gd(III)-based contrast agents are preferred due to their high magnetic relaxivity values observed in the magnetic resonance applications.<sup>17–19</sup>

Besides the magnetic behavior of magnetic nanoparticles and magnetic colloids, new magnetic ionic liquids (MILs) have been explored due to their particular magnetic features. In MILs, usually the anionic counterparts are replaced by others containing a paramagnetic metal complex. Recent studies of different magnetic ionic liquids have shown that the MIL physicochemical properties might change when submitted to different magnetic field conditions.<sup>20–23</sup> The influence of the magnetic field on the physicochemical properties of MILs might be explained by the dependence between the magnetic field intensity and the structural arrangement of the ionic paramagnetic network and a peculiar coupling between magnetic moments of the paramagnetic ions.<sup>24</sup> The previous <sup>1</sup>H NMR study, by Daniel et al.,<sup>24</sup> of the molecular dynamics of a magnetic ionic liquid system comprising a mixture of [Aliquat][Cl]/[Aliquat][FeCl<sub>4</sub>] showed the relation between the viscosity and the self-diffusion of the studied ionic liquid systems in the presence of different magnetic fields. The results of the proton spin–lattice relaxation rate ( $T_1^{-1}$ ) revealed a strong enhancement of  $T_1^{-1}$  at Larmor frequencies higher than 10 MHz (magnetic fields larger than 0.2 T) as observed for contrast agent systems with superparamagnetic particles.<sup>13</sup> Also, it was observed that the MIL viscosity decreased with increasing magnetic field intensity consistent with an increase of the MIL self-diffusion coefficient. The specific MIL behavior was analyzed and related to the paramagnetic moments of the anion [FeCl<sub>4</sub>], to the particular molecular arrangement, and to the electrostatic equilibrium between the ionic species.<sup>24</sup>

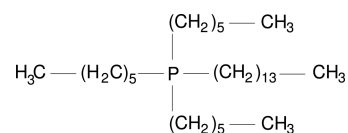
Some recent works have reported the possibility of using magnetic ionic liquids as potential contrast agents.<sup>25,26</sup> In fact, ionic liquids can be designed by changing both cations and anions<sup>27</sup> and offer the possibility to adjust their physicochemical properties for specific applications,<sup>28,29</sup> taking into account eventual limitations due to toxicity effects in the case of medical applications. Studies were published concerning the understanding about factors that influence toxicity. In terms of the magnetic anion toxicity, a study in human cells<sup>30</sup> demonstrated that iron complexes are preferable to gadolinium ones. Along with this finding, some works have shown that long aliphatic chains in the cations can also contribute to an increase of toxicity of the paramagnetic ionic liquids, depending on the medium of application (bacteria, human cells).<sup>30,31</sup> Since the magnetic ionic liquid properties are magnetic field dependent, a

new ionic liquid/magnetic ionic liquid pair, [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>], was selected to be studied, aiming at understanding how the magnetic field influences the molecular structure and molecular packing of the cations and its subsequent impact on the properties of the ionic system. Considering the cations of [P<sub>66614</sub>][FeCl<sub>4</sub>] and [Aliquat][FeCl<sub>4</sub>], it is reasonable to expect that the molecular packing of phosphonium salt [P<sub>66614</sub>]<sup>+</sup> molecules (which have four long chains) might be different from that of the quaternary ammonium [Aliquat]<sup>+</sup> molecules (which have three long chains and one methyl group), the latter favoring a closer approach between the ions pairs in the ionic liquid. These differences may possibly translate into different magnetic induced molecular dynamics and structural rearrangements.

Here is presented a study of the molecular dynamics by <sup>1</sup>H NMR relaxation and a study of the physicochemical properties as a function of the magnetic field of the ionic liquid systems: [P<sub>66614</sub>][Cl], a mixture [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>], and also a mixture of [P<sub>66614</sub>][FeCl<sub>4</sub>] with dimethyl sulfoxide (DMSO). The proton spin–lattice relaxation measurements were done between 8 kHz and 300 MHz, and the self-diffusion, *D*, was determined directly using the pulse field gradient (PFG) NMR technique at a magnetic field intensity of 7 T. Due to the relation between the diffusion and viscosity, studies were performed to find a correlation between the viscosity and magnetic relaxation behavior. A comparison between the relaxation profiles obtained in this work for the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] system and DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>] solutions and the profiles reported for other contrast agents systems is presented.

## EXPERIMENTAL SECTION

**Materials.** The ionic systems selected for this study are based on phosphonium salts where the cation has the structure presented in Figure 1 and is hereafter referred to as [P<sub>66614</sub>]<sup>+</sup>.



**Figure 1.** Molecular structure of the [P<sub>66614</sub>]<sup>+</sup> cation. The charge is localized at the phosphorus atom.

Two ionic liquids were considered, [P<sub>66614</sub>][Cl] and the mixture of [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] 1% (v/v), where chloride anions were partially replaced by magnetic [FeCl<sub>4</sub>]<sup>−</sup> anions. The IL systems were synthesized by Afonso et al., from Faculdade de Farmácia, Universidade de Lisboa, according to the experimental procedure described in refs 32 and 33. The density of the IL systems was measured gravimetrically using a pycnometer, and the percentage of the magnetic element, Fe<sup>3+</sup>, in each sample was determined by inductively coupled plasma (ICP). The molecular weight and density of the two ionic liquid systems are presented in Table 1.

**Methods.** <sup>1</sup>H NMR Assays. The assays of <sup>1</sup>H NMR were performed following a procedure previously described for similar systems.<sup>24,34</sup> The proton spin–lattice relaxation rates *R*<sub>1</sub> ( $\equiv 1/T_1$ ) were measured at 22 °C for a broad Larmor frequency range between 8 kHz and 300 MHz. Three complementary NMR setups were used for the measurements: a conventional Bruker Avance II NMR console operating either a 7 T superconductor electromagnet or a variable field (0.2–2

**Table 1.** Physical Parameters of the Ionic Liquid Systems Used<sup>a</sup>

IL	molecular weight (g/mol)	density (g/cm <sup>3</sup> )
[P <sub>66614</sub> ][Cl]	518.3	0.891
[P <sub>66614</sub> ][Cl]/[P <sub>66614</sub> ][FeCl <sub>4</sub> ]	519.9	1.11

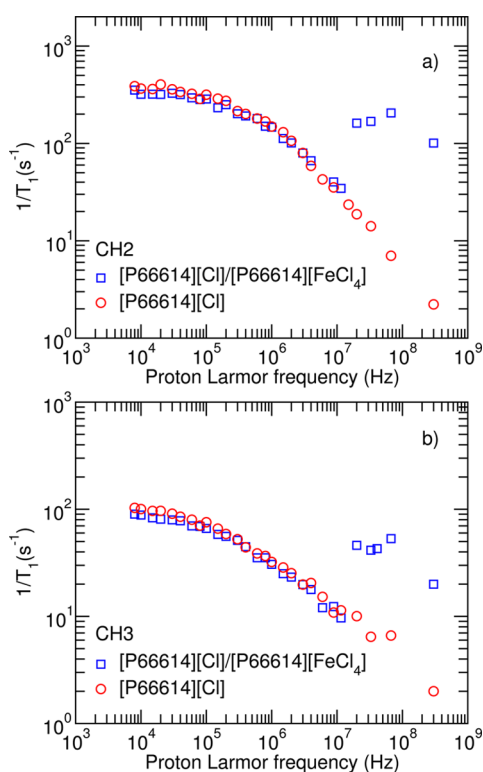
<sup>a</sup>The molar concentration of [P<sub>66614</sub>][FeCl<sub>4</sub>] in the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] mixture is 0.014 mol/L.

T) electromagnet and a fast field-cycling NMR relaxometer.<sup>35</sup> The details of the experimental techniques used with each equipment can be found in the literature.<sup>24,34,36–38</sup>

**Viscosity Measurements.** The measurements of viscosity were carried out in a capillary viscometry setup using the conventional protocol described in the literature.<sup>24,29</sup> The experiments were conducted with and without applied magnetic field to analyze the influence of the magnetic field on the ionic liquids' viscosity.

## RESULTS

For both ionic liquid systems it was found that the spin–lattice relaxation was described by a two-component exponential decay. Two spin–lattice relaxation rates  $R_{11}$  and  $R_{12}$  were determined considering a relative weight of the two relaxation components that was attributed to the number of hydrogen protons of the CH<sub>3</sub> (terminal methyl groups) and CH<sub>2</sub> (ethyl groups) groups of the carbonated chains. In Figure 2 are presented the proton spin–lattice relaxation rates for the two ionic liquid systems. In Figure 2(a) are presented the values of  $R_{11}$ , and in Figure 2(b) are presented the values of  $R_{12}$ , in the Larmor frequency range between 8 kHz and 300 MHz.



**Figure 2.** Larmor frequency dependence of proton spin–lattice relaxation rates for the systems [P<sub>66614</sub>][Cl] and MIL [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] 1% (v/v) mixture:  $R_{11}$  (a) and  $R_{12}$  (b).

As can be observed in both Figures 2(a) and 2(b) the values of  $R_{11}$  and  $R_{12}$  for the two ionic liquid systems are quite similar for frequencies below 10 MHz but differ significantly for higher frequencies. The difference between IL and MIL  $R_{11}$  and  $R_{12}$  behaviors at high frequencies is similar to that reported previously for the IL/MIL [Aliquat][Cl] based system.<sup>24</sup> In that work this difference was possibly associated with the paramagnetic relaxation contribution due to the presence of the magnetic ions in the MIL system. Such strong spin–lattice relaxation increase at high frequencies due to paramagnetic relaxation was also reported for liquid mixtures with contrast agents of superparamagnetic particles.<sup>13</sup>

However, the similarity between the IL and MIL  $R_{11}$  and  $R_{12}$  behaviors at frequencies below 10 MHz is quite unexpected in view of the results reported for the [Aliquat][Cl] IL systems<sup>24</sup> and taking into account the usually observed linear dependence of the relaxation rate on the concentration of paramagnetic particles.<sup>7</sup> Additionally for the MIL is observed an enhancement of the  $R_1$  at 20 and 33 MHz which can be associated with the cross relaxation among <sup>1</sup>H and <sup>35</sup>Cl spins.<sup>39</sup>

The values of viscosity of both ionic liquid systems are presented in Table 2. As expected the viscosity of the

**Table 2.** Viscosity Determined Experimentally as a Function of Applied Magnetic Field for the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] 1% (v/v) Solution (in Parentheses the Values for the [P<sub>66614</sub>][Cl] IL)<sup>a</sup>

B (T)	$\eta$ (Pa·s)
$\sim 45 \times 10^{-6}$	1.97 (2.06)
0.47	1.93 (2.06)
1	1.81 (2.06)
1.3	1.73 (2.06)
1.8	1.71 (2.06)

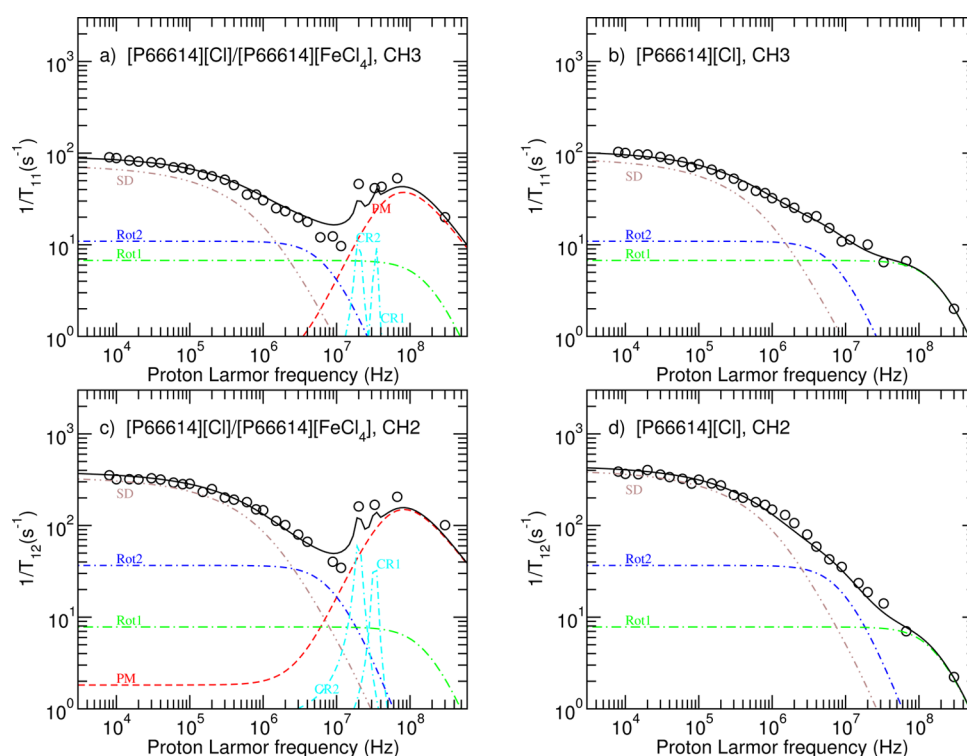
<sup>a</sup>The viscosity of DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>] 1% (v/v) was  $\eta_{\text{DMSO}} = 2.15$  Pa·s, independent of the applied magnetic field.

nonmagnetic ionic liquid is independent of the magnetic field. As can be observed the viscosity of the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] decreases with increasing magnetic field as reported in the literature for different magnetic ionic liquids.<sup>24,29</sup>

## ANALYSIS AND DISCUSSION

The <sup>1</sup>H NMR  $R_1$  dispersions presented in Figure 2 were analyzed taking into account the relaxation processes associated with the molecular motions usually found in low molecular mass organic materials like liquid crystals and ionic liquids.<sup>24,36,38,40</sup> The presence of paramagnetic ions adds an additional degree of complexity to the analysis of  $R_1$  dispersion data as the coupling between the magnetic moment of the paramagnetic ions with proton's magnetic moment leads to the inclusion of an additional relaxation process parameter in the analysis.<sup>24</sup> In the case of the phosphonium salt based systems only the cations possess hydrogen protons; therefore, the relaxation information regarding molecular motions that is obtained reflects mainly the global motions of the cations and the alkyl chain dynamics.

The relaxation model considered here follows that presented previously for a similar system where the cations possessed a nitrogen central atom bounded with just three long aliphatic chains and a methyl group. The total relaxation rate is the sum of the relaxation contributions: translational and rotational self-



**Figure 3.** Experimental results and model fitting curves for the two spin–lattice relaxation rates as a function of frequency for the IL systems, as explained in the text.

**Table 3. Relaxation Model Parameters Obtained for the Best Fit of Equation 1 to the  $R_1$  Experimental Results for the  $[P_{66614}][Cl]$  and  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  Systems<sup>a</sup>**

	$[P_{66614}][Cl]$		$[P_{66614}][Cl]/[P_{66614}][FeCl_4]$	
	CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>2</sub>	CH <sub>3</sub>
$\sqrt{\langle r^2 \rangle}$ ( $10^{-10}$ m)	$1.6 \pm 0.027$	$2.5 \pm 0.014$	$1.6 \pm 0.027$	$2.5 \pm 0.014$
$\tau_{d1}$ ( $10^{-9}$ s <sup>-1</sup> )	–	–	$6.02 \pm 0.73$	$6.35 \pm 0.59$
$\tau_s$ ( $10^{-11}$ s <sup>-1</sup> )	–	–	$1.0 \pm 0.064$	–
$\tau_{d0}$ ( $10^{-8}$ s <sup>-1</sup> )	–	–	$7.34 \pm 0.35$	–
$A_{Rot1}$ ( $10^8$ s <sup>-2</sup> )	$7.33 \pm 0.3$	$1.85 \pm 0.2$	$7.33 \pm 0.3$	$1.85 \pm 0.2$
$\tau_1$ ( $10^{-8}$ s <sup>-1</sup> )	$1.0 \pm 0.1$	$1.18 \pm 0.1$	$1.0 \pm 0.1$	$1.18 \pm 0.1$
$A_{Rot2}$ ( $10^9$ s <sup>-2</sup> )	$3.03 \pm 0.1$	$2.81 \pm 0.1$	$3.03 \pm 0.1$	$2.81 \pm 0.1$
$\tau_2$ ( $10^{-10}$ s <sup>-1</sup> )	$5.16 \pm 0.2$	$4.8 \pm 0.1$	$5.16 \pm 0.2$	$4.8 \pm 0.1$
$A_{CR1}$ ( $10^7$ s <sup>-2</sup> )	–	–	$1.3 \pm 0.4$	$2.5 \pm 0.11$
$\tau_{CR1}$ ( $10^{-7}$ s <sup>-1</sup> )	–	–	$5.0 \pm 3.2$	$5.0 \pm 3.2$
$A_{CR2}$ ( $10^8$ s <sup>-2</sup> )	–	–	$1.5 \pm 0.3$	$2.5 \pm 0.9$
$\tau_{CR2}$ ( $10^{-7}$ s <sup>-1</sup> )	–	–	–	$5.0 \pm 0.2$

<sup>a</sup>The follow fitting parameters are common for both systems:  $\tau_{D_0} = (1.46 \pm 0.06) \times 10^{-8}$  s<sup>-1</sup>,  $d \approx 7.3 \times 10^{-10}$  m,  $M \approx 0.014$  mol/L,  $S \approx 400$ ,  $n = 7 \times 10^{22}$  spins/m<sup>3</sup>,  $p \approx 1.13$ , and  $\tau_v \approx 3.85 \times 10^{-10}$  s,  $\omega_1/(2\pi) \approx 33$  MHz, and  $\omega_2/(2\pi) \approx 20$  MHz.

diffusion, chain dynamics, paramagnetic relaxation, and cross relaxation between the hydrogen proton <sup>1</sup>H system and the chloride <sup>35</sup>Cl spin system.<sup>24</sup> Given the complexity of the molecular system and the presence of a molecular packing with the strong interdigitation of the molecular chains of different cations, the use of the relaxation models considered for liquid crystals and simpler ionic liquids<sup>24,34,40</sup> must be considered as a first approximation.

The model considered for the analysis of the  $R_1$  experimental results can be expressed by the sum of the contributions mentioned before. In the case of the MIL system the contribution corresponding to the paramagnetic relaxation was also included.

$$R_1(\nu_L) = R_1^{SD}(\nu_L) + [R_1^{Rot1}(\nu_L) + R_1^{Rot2}(\nu_L)] \\ R_1^{CR}(\nu_L) + [R_1^{PM}(\nu_L)]_{MIL} \quad (1)$$

The cross-term contributions in eq 1 were neglected assuming that the relaxation mechanisms are statistically independent. The theoretical details of each relaxation model are presented in the Supporting Information. The model fitting parameters were:  $d$ ,  $\tau_D$ ,  $\langle r^2 \rangle$ ,  $\tau_d$ ,  $\tau_{d1}$ ,  $\tau_s$ ,  $\tau_1$ ,  $A_{Rot1}$ ,  $\tau_2$ , and  $A_{Rot2}$  and a pair of  $\tau_{CRi}$ ,  $A_{CRi}$  for each cross-relaxation peak, where  $d$  is an average width associated with the volume defined by the aliphatic chains;  $\langle r^2 \rangle$  is the mean-square jump distance;  $\tau_s$  is the longitudinal electronic relaxation time;  $\tau_1$  and  $\tau_2$  are correlation

times associated with the rotations of the aliphatic chains; and  $A_{\text{Rot1}}$  and  $A_{\text{Rot2}}$  depend on the proton spin dipolar coupling constant and effective interspin distance.  $\tau_{\text{CRi}}$  and  $A_{\text{CRi}}$  are parameters associated with the width and amplitude of the cross-relaxation process. Due to the differences in the relaxation of the IL systems, two correlation times for the translation diffusion processes had to be considered:  $\tau_{\text{D}}$  for the nonmagnetic IL system and  $\tau_{\text{d}}$  and  $\tau_{\text{d1}}$  for the MIL system. In the case of the MIL system the viscosity dependence on the magnetic field was considered in the fits assuming an empirical model previously introduced for the [Aliquat][FeCl<sub>4</sub>] system.<sup>24</sup> In addition the iron molar concentration measured by ICP was  $M = 1.4 \times 10^{-2} \text{ mol L}^{-1}$ , and the <sup>1</sup>H spin density  $n = 7 \times 10^{22} \text{ spins/m}^3$  was estimated taking into account the IL and MIL molecular structures and the values of Table 1.

The model was fitted to the experimental results using a nonlinear least-squares minimization procedure with a global minimum target.<sup>41</sup> The [P<sub>66614</sub>][Cl] and [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] relaxation results were fitted simultaneously in two subprocesses: the  $R_{11}$  and  $R_{12}$  fits. In Figure 3 are presented the plots corresponding to the best global fit, whereas the fitting parameters are listed in Table 3.

In general terms the fit results obtained for the [P<sub>66614</sub>][Cl]-based systems are similar to the ones found for the [Aliquat][Cl]. However, a closed analysis reveals some interesting differences. In fact, the model fit quality for the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] system is worse than that obtained for the [Aliquat][FeCl<sub>4</sub>], in particular, in what concerns the description of the slower rotations and the paramagnetic relaxation contributions. Also, the small difference observed in the values of  $R_{11}$  and  $R_{12}$  of [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] for frequencies below 1 MHz could not be explained by the same values of  $d$  and  $\tau_{\text{d}}$ . As a consequence it was not possible to fit the paramagnetic relaxation contribution with the same quality as for the [Aliquat][FeCl<sub>4</sub>] system. The presence of [FeCl<sub>4</sub>]<sup>-</sup> in the mixture of [P<sub>66614</sub>][Cl] is not only associated with the additional paramagnetic relaxation contribution to the proton spin–lattice relaxation but also seems to affect the molecular dynamics of the cations in a way that was not observed for the [Aliquat][FeCl<sub>4</sub>] system previously studied.

The values obtained for the fitting parameters present in Table 3 are consistent with those found for the quaternary ammonium magnetic ionic liquid system [Aliquat][FeCl<sub>4</sub>] mixtures,<sup>24</sup> taking into account the differences observed in the relaxation dispersion. In particular, the cross-relaxation contributions are less important than for the [Aliquat][Cl] mixtures.

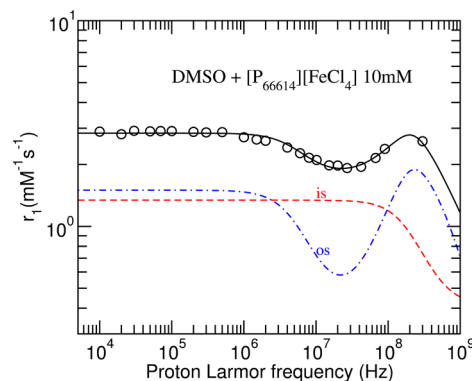
It is interesting to note that the expression usually considered to estimate the concentration effect of a contrast agent in a solution

$$\frac{1}{T_1} = \left[ \frac{1}{T_1} \right]_{\text{Solvent}} + r_1[C] \quad (2)$$

where  $[C]$  is the concentration of the paramagnetic particles;  $[1/T_1]_{\text{Solvent}}$  is the relaxation rate without the presence of the contrast agent; and  $r_1$  is the relaxivity of the contrast agent, seems not to be valid in the case of the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] system, as it can be understood from the data in Figure 2, assuming that [P<sub>66614</sub>][Cl] acts as a solvent of [P<sub>66614</sub>][FeCl<sub>4</sub>].

In order to test the properties of the [P<sub>66614</sub>][FeCl<sub>4</sub>] as a contrast agent and to check if the superparamagnetic-like

relaxation effect observed for the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] system can be observed using a nonionic liquid solvent, additional measurements were made using solutions of [P<sub>66614</sub>][FeCl<sub>4</sub>] in DMSO. The viscosity measurements showed that viscosity was independent of the magnetic field for DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>] 1% (v/v) (see Table 2). In Figure 4 are



**Figure 4.** Experimental results and model fitting curves for the relaxivity as a function of frequency for the 10 mM DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>] system, as explained in the text.

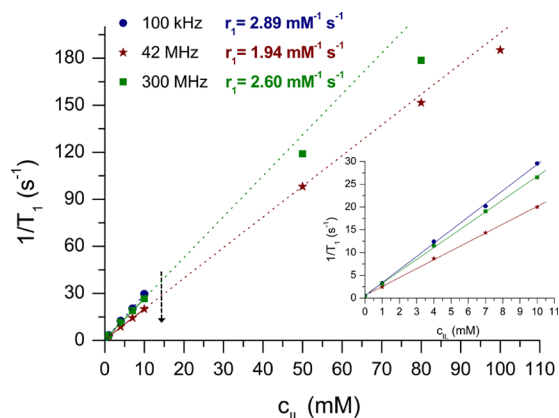
presented the relaxivity results according to eq 2, as a function of the proton Larmor frequency for a 10 mM sample DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>]. The measured  $R_1$  corresponds to the DMSO protons in the view of a small concentration of the ionic liquid. The  $R_1$  0.52 s<sup>-1</sup> of the pure DMSO was frequency independent in the range of 8 kHz to 300 MHz. As it can be noticed, the relaxivity dispersion presents a much less pronounced paramagnetic contribution in comparison with the relaxation enhancement effect observed for the [P<sub>66614</sub>][Cl]/[P<sub>66614</sub>][FeCl<sub>4</sub>] system with a close molar concentration (14 mM). The relaxivity dispersion is described by the sum of inner-sphere,  $(T_1^{-1})_{\text{is}}$ , and outer-sphere,  $(T_1^{-1})_{\text{os}}$ , relaxation contributions.

$$r_1 = (T_1^{-1})_{\text{is}} + (T_1^{-1})_{\text{os}} \quad (3)$$

The details of the models used for these two relaxation mechanisms can be found in the Supporting Information. The only free fitting parameters were the distance between the FeCl<sub>4</sub><sup>-</sup> ions and the DMSO molecules,  $r_{\text{FeH}}$  and  $R_{\text{FeH}}$ , for the is and os relaxation contributions, respectively, the correlation time  $\tau_{\text{mH}}$  for the is inner relaxation, and the correlation time  $\tau_{\text{v}}$  and the mean square fluctuations  $\Delta^2$  of the electronic zero-field-splitting (ZFS) relaxation contribution. The values obtained from the fit were:  $r_{\text{FeH}} = (3.5 \pm 0.2) \text{ \AA}$ ,  $R_{\text{FeH}} = (8.0 \pm 0.3) \text{ \AA}$ ,  $\tau_{\text{mH}} = (1.12 \pm 0.07) \times 10^{-12} \text{ s}$ ,  $\tau_{\text{v}} = (2.6 \pm 0.25) \times 10^{-12} \text{ s}$ , and  $\Delta^2 = (2.9 \pm 0.3) \times 10^{10} \text{ s}^{-2}$ . During the mixing process of [P<sub>66614</sub>][FeCl<sub>4</sub>] MIL with DMSO no chemical reaction was observed involving the FeCl<sub>4</sub><sup>-</sup>. This observation was further confirmed by preparing a 10 mM solution of FeCl<sub>3</sub> hexahydrated and DMSO. The relaxivity results obtained for this system can be found in the Supporting Information for comparison. It is worthwhile to mention that the physically consistent fits could only be obtained considering that the FeCl<sub>4</sub><sup>-</sup> ions were surrounded by around eight DMSO molecules with very short resident times. In view of the fact that the chlorine atoms remain covalently bounded to Fe there is no actual binding between DMSO molecules to Fe. Therefore, it is reasonable to obtain  $\tau_{\text{mH}}$  values close to the characteristic times of methyl group rotation,<sup>42</sup> in contrast to

the long resident times of water molecules in the case of conventional contrast agent paramagnetic complexes.

In Figure 5 are presented results of the proton spin–lattice relaxation rate as a function of the ionic liquid concentration in



**Figure 5.** Experimental results of the DMSO spin–lattice relaxation as a function of  $[P_{66614}][FeCl_4]$  concentration. Relaxivities were estimated for three selected Larmor frequencies, as explained in the text. The arrow in the inset figure represents the concentration corresponding to the mixture  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  studied here.

DMSO for three selected Larmor frequencies. As it can be observed, the spin–lattice relaxation of the DMSO/ $[P_{66614}][FeCl_4]$  solutions is certainly well described by eq 2 for concentration below  $\sim 10$  mM. The values of relaxivity depend on the frequency and vary in the range  $2\text{--}3\text{ mM}^{-1}\text{ s}^{-1}$ . These values are higher than the iron(III) complexes recently reported which are good candidates for further development in order to be used as MRI contrast agents.<sup>43</sup>

From the results obtained it is possible to conclude that  $[P_{66614}][FeCl_4]$  acts as a typical contrast agent enhancing the spin–lattice relaxation rate with a relaxivity well described by the usually accepted paramagnetic relaxation mechanisms for inner sphere and outer sphere interactions. In contrast, in the mixture of  $[P_{66614}][FeCl_4]$  with  $[P_{66614}][Cl]$  ionic liquid the effect of the paramagnetic ions on the spin–lattice relaxation of the solvent molecules protons' spins system cannot be described by the linear combination of the nonparamagnetic and paramagnetic relaxation contributions (eq 2) where the paramagnetic contribution is proportional to the concentration. In fact, the relaxation enhancement effect due to the presence of  $[FeCl_4]^-$  ions must be negligible for frequencies below 10 MHz. Actually, a detailed observation of the experimental results (see Figures 2 and 3) reveals that at low frequencies the relaxation rate for the  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  system is smaller than that of  $[P_{66614}][Cl]$ . Therefore, it seems that the presence of the  $[FeCl_4]^-$  ions affects more the motions of the cations' aliphatic chains, more than Cl. Together with the paramagnetic relaxation it produces just a small change in the spin–lattice relaxation at low frequencies.

The superparamagnetic relaxation observed for the  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$   $R_1$  dispersion as well as the viscosity's dependence on the magnetic field seems to be associated with the ionic nature of the  $[P_{66614}][Cl]$  solvent in comparison with the nonionic DMSO.

## CONCLUSIONS

In this work is presented an  $^1H$  nuclear magnetic relaxation dispersion study of the molecular dynamics of the neat ionic liquid  $[P_{66614}][Cl]$  and the binary mixtures of magnetic ionic liquid  $[P_{66614}][FeCl_4]$  with  $[P_{66614}][Cl]$  and with DMSO. The proton spin–lattice relaxation was measured over the broad frequency range between 8 kHz and 300 MHz at 22 °C. In addition, viscosity measurements were made as a function of an applied magnetic field in the range 0–2 T. The longitudinal magnetization decay with time was found to be biexponential and characterized by relaxation rates  $R_{11}$  and  $R_{12}$  in consistency with the number of  $CH_2$  and  $CH_3$  groups in the cation molecules, respectively.

For both  $[P_{66614}][Cl]$  and the mixtures DMSO/ $[P_{66614}][FeCl_4]$  it was observed that the viscosity was independent from the magnetic field. In the case of the mixtures of  $[P_{66614}][FeCl_4]$  with  $[P_{66614}][Cl]$  it was observed that the viscosity decreased with the magnetic field strength, and at 2 T the viscosity was 13% less than at 0 T.

The spin–lattice relaxation results were analyzed for all MIL mixtures taking into account the relaxation mechanisms associated with the molecular motions typically observed for these systems. In the case of DMSO/ $[P_{66614}][FeCl_4]$  and  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  spin–lattice relaxation results additional paramagnetic relaxation contributions were considered due to the presence of the magnetic ions.

The spin–lattice relaxation dispersion observed for the DMSO/ $[P_{66614}][FeCl_4]$  was quite different from that detected for the pure DMSO as expected due to the presence of iron ions in the mixtures. In fact, the  $[FeCl_4]^-$  anions constitute a paramagnetic relaxation agent increasing the proton spin–lattice relaxation rate with a paramagnetic contribution that depends linearly on the concentration of the  $[FeCl_4]^-$  ions for small concentrations, as usually found for known iron-based contrast agents.

The  $R_1$  dispersions observed for the  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  system are significantly different from those where DMSO was the solvent. The  $R_1$  dispersion obtained for systems using  $[P_{66614}][Cl]$  as solvent evidences a combination of relaxation mechanisms associated with molecular motions obviously not found when it is replaced by DMSO, due to the considerable differences in the molecular structure and consequently in the local molecular organization considering the ionic character of the phosphonium salt. In the case of the  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  system the paramagnetic relaxation contribution is dominant in the high frequency range, as was previously observed for a quaternarium ammonium magnetic ionic liquid system, but is negligible at lower frequencies. In this system the proton spin–lattice relaxation clearly does not depend linearly on the concentration of  $[FeCl_4]^-$  ions. The presence of the  $[FeCl_4]^-$  ions in the  $[P_{66614}][Cl]$  ionic medium seems to affect the local molecular organization and the relative contribution of molecular motions to the spin–lattice relaxation. The differences observed in the  $R_1$  dispersion of  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  with respect to that of  $[P_{66614}][Cl]$  reflect the contribution of a paramagnetic relaxation and the changes in the molecular order, dynamics, and packing.

When comparing the paramagnetic relaxation contributions detected for the  $[P_{66614}][Cl]/[P_{66614}][FeCl_4]$  and DMSO/ $[P_{66614}][FeCl_4]$  the stronger enhancement of the  $R_1$  dispersion due to the amplitude of this mechanism in the  $[P_{66614}][Cl]/$

[P<sub>66614</sub>][FeCl<sub>4</sub>] system is perhaps due to the coupling between the magnetic moments of the [FeCl<sub>4</sub>]<sup>-</sup> ions as a result of the ionic nature of the [P<sub>66614</sub>][Cl] acting as a solvent in comparison with an organic solvent such as DMSO.

The results obtained in this work suggest the possibility of using MILs as contrast agents, provided that their toxicity is reduced. One possibility that requires future studies is the replacement of the IL cations (e.g., phosphonium or quaternary ammonium) by biocompatible water-soluble cations, like those present in several vitamin complexes, coordinated with a magnetic anion, such as [FeCl<sub>4</sub>].

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcc.5b04772.

Paramagnetic relaxation model equations and the fitting reports obtained as the result of the least-squares minimization procedure with a global minimum target with a consistent set of fitting parameters. In addition, it is presented the relaxivity results and fitting curves obtained for DMSO/hexahydrated FeCl<sub>3</sub> for comparison with the DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>] solution (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: cid17734@campus.fct.unl.pt.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

FCV and PJS wish to thank Fundação para a Ciência e a Tecnologia, Portugal, through project PTDC/CTM/103664/2008 "Development of Novel Organic Energetic Materials based on Ionic Liquids". CD thanks Fundação para a Ciência e a Tecnologia, Portugal, for the financial support through the Doctoral fellowship SFRH/BD/81552/2011.

## ■ REFERENCES

- (1) Roland, C. M. Characteristic Relaxation Times and Their Invariance to Thermodynamic Conditions. *Soft Matter* **2008**, *4*, 2316–2322.
- (2) Callaghan, P. *Principles of Nuclear Magnetic Resonance Microscopy*; Oxford University Press: New York, 2003.
- (3) Dorazio, S. J.; Morrow, J. R. The Development of Iron(II) Complexes as ParaCEST MRI Contrast Agents. *Eur. J. Inorg. Chem.* **2012**, *2012*, 2006–2014.
- (4) Zhao, X. L.; Zhao, H. L.; Chen, Z. Y.; Lan, M. B. Ultrasmall Superparamagnetic Iron Oxide Nanoparticles for Magnetic Resonance Imaging Contrast Agent. *J. Nanosci. Nanotechnol.* **2014**, *14*, 210–220.
- (5) Kenouche, S.; Larionova, J.; Bezzi, N.; Guari, Y.; Bertin, N.; Zanca, M.; Lartigue, L.; Cieslak, M.; Godin, C.; Morrot, G.; et al. NMR investigation of functionalized magnetic nanoparticles Fe<sub>3</sub>O<sub>4</sub> as T<sub>1</sub>-T<sub>2</sub> contrast agents. *Powder Technol.* **2014**, *255*, 60–65.
- (6) Runge, V. M.; Clanton, J. A.; Lukehart, C. M.; Partain, C. L.; James, A. E. Paramagnetic Agents For Contrast-enhanced Nmr Imaging - A Review. *AJR, Am. J. Roentgenol.* **1983**, *141*, 1209–1215.
- (7) Merbach, A.; Helm, L.; Toth, E., Eds. *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, 2nd ed.; Wiley: New York, 2013.
- (8) Britton, M. M. Magnetic Resonance Imaging of Chemistry. *Chem. Soc. Rev.* **2010**, *39*, 4036–4043.
- (9) Pierre, V. C.; Botta, M.; Aime, S.; Raymond, K. N. Fe(III)-Templated Gd(III) Self-Assemblies - A New Route Toward

Macromolecular MRI Contrast Agents. *J. Am. Chem. Soc.* **2006**, *128*, 9272–9273.

(10) Tsitovich, P. B.; Burns, P. J.; McKay, A. M.; Morrow, J. R. Redox-Activated MRI Contrast Agents Based on Lanthanide and Transition Metal Ions. *J. Inorg. Biochem.* **2014**, *133*, 143–154.

(11) Werner, E. J.; Datta, A.; Jocher, C. J.; Raymond, K. N. High-Relaxivity MRI Contrast Agents: Where Coordination Chemistry Meets Medical Imaging. *Angew. Chem., Int. Ed.* **2008**, *47*, 8568–8580.

(12) White, D. L. Paramagnetic Iron (iii) Mri Contrast Agents. *Magn. Reson. Med.* **1991**, *22*, 309–3012.

(13) Roch, A.; Muller, R. N.; Gillis, P. Theory of Proton Relaxation Induced by Superparamagnetic Particles. *J. Chem. Phys.* **1999**, *110*, 5403–5411.

(14) Sebastião, P. J.; Cruz, C.; Ribeiro, A. C. In *Nuclear Magnetic Resonance Spectroscopy of Liquid Crystals*; Dong, R. Y., Ed.; World Scientific Co.: River Edge, NJ, 2009; Chapter 5. Advances in Proton NMR Relaxometry in Thermotropic Liquid Crystals, pp 129–167.

(15) Caravan, P. Strategies for Increasing the Sensitivity of Gadolinium Based MRI Contrast Agents. *Chem. Soc. Rev.* **2006**, *35*, 512–523.

(16) Caravan, P. Protein-Targeted Gadolinium-Based Magnetic Resonance Imaging (MRI) Contrast Agents: Design and Mechanism of Action. *Acc. Chem. Res.* **2009**, *42*, 851–862.

(17) Zhou, Z. X.; Lu, Z. R. Gadolinium-Based Contrast Agents for Magnetic Resonance Cancer Imaging (vol 5, pg 1, 2013). *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2013**, *5*, 190–190.

(18) Lin, S.-P.; Brown, J. J. MR contrast agents: Physical and pharmacologic basics. *J. Magn. Reson. Imag.* **2007**, *25*, 884–899.

(19) Liang, X. Y.; Sadler, P. J. Cyclam complexes and their applications in medicine. *Chem. Soc. Rev.* **2004**, *33*, 246–266.

(20) Lee, S. H.; Ha, S. H.; Ha, S.-S.; Jin, H.-B.; You, C.-Y.; Koo, Y.-M. Magnetic Behavior of Mixture of Magnetic Ionic Liquid [Bmim]-[FeCl<sub>4</sub>] and Water. *J. Appl. Phys.* **2007**, *101*, 09J102.

(21) de Pedro, I.; Rojas, D. P.; Albo, J.; Luis, P.; Irabien, A.; Blanco, J. A.; Rodriguez Fernandez, J. Long-range Magnetic Ordering in Magnetic Ionic Liquid: [Emim][FeCl<sub>4</sub>]. *J. Phys.: Condens. Matter* **2010**, *22*, 296006.

(22) de Pedro, I.; Rojas, D. P.; Blanco, J. A.; Rodriguez Fernandez, J. Antiferromagnetic Ordering in Magnetic Ionic Liquid [Emim][FeCl<sub>4</sub>]. *J. Magn. Magn. Mater.* **2011**, *323*, 1254.

(23) Hayashi, S.; Saha, S.; Hamaguchi, H. O. A New Class of Magnetic Fluids: [Bmim][FeCl<sub>4</sub>] and [NBmim][FeCl<sub>4</sub>] Ionic Liquids. *IEEE Trans. Magn.* **2006**, *42*, 12.

(24) Daniel, C. I.; Vaca Chávez, F.; Feio, G.; Portugal, C. A. M.; Crespo, J. G.; Sebastião, P. J. <sup>1</sup>H NMR Relaxometry, Viscometry, and PFG NMR Studies of Magnetic and Nonmagnetic Ionic Liquids. *J. Phys. Chem. B* **2013**, *117*, 11877–11884.

(25) Branco, A.; Branco, L. C.; Pina, F. Electrochromic and Magnetic Ionic Liquids. *Chem. Commun.* **2011**, *47*, 2300–2302.

(26) Santos, E.; Albo, J.; Irabien, A. Magnetic Ionic Liquids: Synthesis, Properties and Applications. *RSC Adv.* **2014**, *4*, 40008–40018.

(27) Hu, Y.; Xu, C. Effect of the Structures of Ionic Liquids on Their Physical-Chemical Properties and the Phase Behaviour of the Mixtures Involving Ionic Liquids. *Chem. Rev.* **2006**, *0*, 0.

(28) Jiang, Y.; Guo, C.; Liu, H. Magnetically Rotational Reactor For Absorbing Benzene Emissions by Ionic Liquids. *China Particulol.* **2007**, *5*, 130–133.

(29) Santos, E.; Albo, J.; Daniel, C.; Portugal, C.; Crespo, J.; Irabien, A. Permeability Modulation of Supported Magnetic Ionic Liquid Membranes (SMILMs) by an External Magnetic Field. *J. Membr. Sci.* **2013**, *430*, 56–61.

(30) Frade, R. F. M.; Simeonov, S.; Rosatella, A. A.; Siopa, F.; Afonso, C. A. M. Toxicological Evaluation of Magnetic Ionic Liquids in Human Cell Lines. *Chemosphere* **2013**, *92*, 100–105.

(31) Ventura, S. P. M.; Marques, C. S.; Rosatella, A. A.; Afonso, C. A. M.; Goncalves, F.; Coutinho, J. A. P. Toxicity Assessment of Various Ionic Liquid Families Towards *Vibrio Fischeri* Marine Bacteria. *Ecotoxicol. Environ. Saf.* **2012**, *76*, 162–168.

(32) Del Sesto, R. E.; McCleskey, T. M.; Burrell, A. K.; Baker, G. A.; Thompson, J. D.; Scott, B. L.; Wilkes, J. S.; Williams, P. Structure and Magnetic Behavior of Transition Metal Based Ionic Liquids. *Chem. Commun.* **2008**, 447–449.

(33) Albo, J.; Santos, E.; Neves, L. A.; Simeonov, S. P.; Afonso, C. A. M.; Crespo, J. G.; Irabien, A. Separation Performance of CO<sub>2</sub> Through Supported Magnetic Ionic Liquid Membranes (SMILMs). *Sep. Purif. Technol.* **2012**, 97, 26.

(34) Neves, L. A.; Sebastião, P. J.; Coelho, I. M.; Crespo, J. G. Proton NMR Relaxometry Study of Nafion Membranes Modified With Ionic Liquid Cations. *J. Phys. Chem. B* **2011**, 115, 8713–8723.

(35) Sousa, D. M.; Marques, G. D.; Cascais, J. M.; Sebastião, P. J. Desktop Fast-Field Cycling Nuclear Magnetic Resonance Relaxometer. *Solid State Nucl. Magn. Reson.* **2010**, 38, 36–43.

(36) Aluculesei, A.; Vaca Chávez, F.; Cruz, C.; Sebastião, P. J.; Nagaveni, N. G.; Prasad, V.; Dong, R. Y. Proton NMR Relaxation Study on the Nematic-Nematic Phase Transition in A131 Liquid Crystal. *J. Phys. Chem. B* **2012**, 116, 9556–63.

(37) Gradišek, A.; Apih, T.; Domenici, V.; Novotna, V.; Sebastião, P. J. Molecular Dynamics in a Blue Phase Liquid Crystal: a <sup>1</sup>H Fast Field-Cycling NMR Relaxometry Study. *Soft Matter* **2013**, 9, 10746–10753.

(38) Martins, C. F.; Neves, L.; Coelho, I. M.; Vaca Chávez, F.; Crespo, J. G.; Sebastião, P. J. Temperature Effects on the Molecular Dynamics of Modified Nafion (R) Membranes Incorporating Ionic Liquids' Cations: A <sup>1</sup>H NMRD Study. *Fuel Cells* **2013**, 13, 1166–1176.

(39) Anardo, E.; Pusiol, D. J.; Aguilera, C. NMR-Study of the T<sub>1</sub> Relaxation Dispersion In the Smectic Mesophase of 4-chlorophenyl 4-undecyloxybenzoate. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1994**, 49, 8600–8607.

(40) Sebastião, P. J.; Cruz, C.; Ribeiro, A. C. In *Nuclear Magnetic Resonance Spectroscopy of Liquid Crystals*; Dong, R. Y., Ed.; World Scientific: Singapore, 2010; pp 129–167.

(41) Sebastião, P. J. The Art of Model Fitting to Experimental Results. *Eur. J. Phys.* **2014**, 35, 015017.

(42) Spiess, H. W.; Schweitzer, D.; Haeberlen, U. Molecular Motion in Liquid Toluene from a Study of <sup>13</sup>C and <sup>2</sup>D Relaxation Times. *J. Magn. Reson.* **1973**, 9, 444–460.

(43) Cardoso, B. d. P.; Vicente, A.; Ward, J. B.; Sebastião, P. J.; Vaca Chávez, F.; Barroso, S.; Carvalho, A.; Keely, S. J.; Martinho, P. N.; Calhorda, M. J. Fe(III) SalEen Derived Schiff Base Complexes as Potential Contrast Agents. *Inorg. Chim. Acta* **2015**, 432, 258–266.



# <sup>1</sup>H-NMR relaxation study of a magnetic ionic liquid as a potential contrast agent

Carla I. Daniel,<sup>\*,†</sup> Fabián Vaca Chávez,<sup>‡</sup> Carla A. M. Portugal,<sup>¶</sup> João G. Crespo,<sup>¶</sup> and Pedro J. Sebastião<sup>§</sup>

<sup>†</sup>*REQUIMTE/LAQV, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa*

<sup>‡</sup>*Condensed Matter Physics Centre, University of Lisbon, Lisbon, Portugal.*

<sup>¶</sup>*REQUIMTE/CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa*

<sup>§</sup>*Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal; Centro de Física e Engenharia de Materias Avançadas, Universidade de Lisboa, Lisbon, Portugal*

E-mail: cid17734@campus.fct.unl.pt

## Theoretical models

### Translational self-diffusion

In the case of isotropic liquids or isotropic phases of liquid crystal compounds the contribution of translational self-diffusion (SD) to the relaxation can be expressed by the Torrey's model<sup>1</sup> with a

$$\left(\frac{1}{T_1}\right)_{\text{SD}} = C_d \frac{n\tau_D}{d^3} [\mathcal{T}(\omega\tau_D) + 4\mathcal{T}(2\omega\tau_D)], \quad (1)$$

where  $\omega = 2\pi\nu_L$ ,  $C_d = (1/2)(3\mu_0\gamma^2\hbar/(8\pi))^2$  is the strength of the dipolar interaction and  $\mathcal{T}(\omega\tau_D)$  is a dimensionless analytical function that depends on the average time between

diffusion jumps  $\tau_D$ , the mean-square jump distance  $\langle r^2 \rangle$ , and the molecular width  $d$ .  $\tau_D$  is related with the self-diffusion constant  $D$  by the relation  $\langle r^2 \rangle = 6\tau_D D$ .  $n$  is the density of  $^1\text{H}$  spins.

### Rotations/reorientations

Molecular rotations/reorientations (Rot) may be characterized by one or more correlation times according to the number of independent rotational axis considered to describe this motion. Usually, rotations along the molecular long axis and rotations/reorientations along a molecular transverse axis have different correlations times and the most simple model used to describe this relaxation process is given a  $\text{Rot}_1 + \text{Rot}_2$  where  $\text{Rot}_i$  is given by the Bloemberger, Purcel and Pound (BPP) model:

$$\left(\frac{1}{T_1}\right)_{\text{Rot}_i} = A_{\text{Rot}_i} \left[ \frac{\tau_{\text{Rot}_i}}{1 + \omega^2 \tau_{\text{Rot}_i}^2} + \frac{4\tau_{\text{Rot}_i}}{1 + 4\omega^2 \tau_{\text{Rot}_i}^2} \right] \quad (2)$$

with  $A_{\text{Rot}_i} = 9\mu_0^2 \gamma^4 \hbar^2 / (128\pi^2 r_{i_{eff}}^6)$  where  $r_{i_{eff}}$  is an effective inter-spin distance.<sup>2</sup>

### Cross-relaxation

$^{35}\text{Cl}$  has nuclear spin 3/2 and cross-relaxation (CR) between the proton spins and  $^{35}\text{Cl}$  nuclear spins can occur. Cross-relaxation has indeed been observed between proton spins and nitrogen and also between proton spins and  $^{35}\text{Cl}$  spins.<sup>3-5</sup> Cross-relaxation may become significant when the proton's Larmor frequency is close to each one of the quadrupole frequencies of the other nucleus. The relaxation rate can be expressed by<sup>3</sup>

$$\left(\frac{1}{T_1}\right)_{\text{CR}_i} = A_{\text{CR}_i} \frac{\tau_{\text{CR}_i}}{1 + (\omega - \omega_i)^2 \tau_{\text{CR}_i}^2} \quad (3)$$

where  $\omega_i$ , with  $i = 1, 2, \dots$ , are the frequencies that correspond to the  $^{35}\text{Cl}$  spin energy levels and  $A_{\text{CR}_i}$  are parameters related with the strength of the interaction.

## Paramagnetic relaxation induced by superparamagnetic particles

Proton spin-lattice relaxation can be affected by the presence of magnetic ions in two ways: i) the so-called *inner-sphere* relaxation, which occurs when relaxing protons bind temporarily to ions or ion complexes, and the ii) *outer-sphere* applies to protons that do not bind but move or diffuse close to magnetic ions or particles.<sup>6</sup> In a recent study of molecular dynamics in magnetic ionic liquid systems by proton spin-lattice relaxometry,<sup>7</sup> it was shown that the paramagnetic relaxation observed was better described considering an effective superparamagnetic outer-sphere contribution given by equation:

$$\left(\frac{1}{T_1}\right)_{PM} = 6\tau_d c \left\{ S_c^2 j_1(\omega, \tau_d, \tau_s \rightarrow \infty) + \left[ S(S+1) - S_c \cotg \frac{x}{2S} - S_c^2 \right] j_1(\omega, \tau_d, \tau_s) \right\} \quad (4)$$

where  $S$  is the electronic spin along the applied magnetic field,  $c$  is a quantity proportional to the molar concentration of magnetized particles,  $[M]$ .  $r$  is the distance of closest approach between the anion and the protonated cation,  $\tau_d = \langle r^2 \rangle / D$ ,  $D$  is the diffusion time constant,  $\tau_s$  is the longitudinal electronic relaxation time and  $\omega$  is the proton Larmor frequency.  $S_c$  is given by

$$S_c = \frac{2S+1}{2} \tanh^{-1} \left( (2S+1) \frac{\omega}{\omega_r} \right) - \frac{1}{2} \tanh^{-1} \left( \frac{\omega}{\omega_r} \right) \quad (5)$$

where  $\omega_r = 2\gamma kT / (\hbar\gamma_S)$  and  $\gamma_S$  is the electron's gyromagnetic ratio. The corresponding spectral density for outer-sphere relaxation is<sup>6</sup>

$$j_1(\omega, \tau_d, \tau_s) = \text{Re} \left\{ \frac{1 + \Omega^{1/2}/4}{1 + \Omega^{1/2} + 4\Omega/9 + \Omega^{3/2}/9} \right\} \quad (6)$$

where  $\Omega = (i\omega + 1/\tau_s)\tau_d$ .

## Relaxivity Dispersion

In the case of the magnetic ionic liquid/DMSO solutions presented in this work we considered the inner-sphere relaxivity contribution expressed by:<sup>8</sup>

$$r_1^{is} \approx \frac{1}{1000} \frac{q^{st}}{14.04} \frac{1}{T_{1m}^H} \quad (7)$$

being  $q^{st}$  the number of DMSO molecules temporarily bind to the iron particles and  $T_{1m}^H \gg \tau_m$  where  $\tau_m$  is the DMSO residence binding time to the  $\text{FeCl}_4^-$  (or  $\text{FeCl}_3$ ).

$$\frac{1}{T_{1m}^H} = \frac{2}{15} \left( \frac{\mu}{4\pi} \right)^2 \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{r_{Fe}^6} S_p (S_p + 1) [3J(\omega_I, \tau_{d1}) + 7J(\omega_S, \tau_{d2})] \quad (8)$$

$$J(\omega, \tau_{di}) = \frac{S^2 \tau_{dig}}{1 + \omega^2 \tau_{dig}^2} + \frac{(1 - S^2) \tau_{di}}{1 + \omega^2 \tau_{di}^2} \quad (9)$$

$$\tau_{di} = \frac{1}{\tau_{mH}} + \frac{1}{T_{iS}} \quad (10)$$

$$\tau_{dig} = \frac{1}{\tau_{mg}} + \frac{1}{T_{iS}} \quad (11)$$

$$\frac{1}{T_{1s}} = 2C \left[ \frac{1}{1 + \omega_s^2 \tau_v^2} + \frac{4}{1 + 4\omega_s^2 \tau_v^2} \right] \quad (12)$$

$$\frac{1}{T_{2s}} = C \left[ \frac{5}{1 + \omega_s^2 \tau_v^2} + \frac{2}{1 + 4\omega_s^2 \tau_v^2} + 3 \right] \quad (13)$$

with

$$C = \frac{1}{50} \Delta^2 \tau_v [4S_p (S_p + 1) - 3] \quad (14)$$

The outer-sphere relaxivity contribution is given by:

$$r_1^{os} = \frac{32N_A\pi}{405} \left(\frac{\mu}{4\pi}\right)^2 \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{RD} S_p(S_p + 1) [3J^{os}(\omega_I, \tau_d), T_{1S} + 7J^{os}(\omega_S, \tau_d), T_{2S}] \quad (15)$$

with  $\tau_d = R^2/D$

$$J^{os} = \text{Re} \left\{ \frac{1 + \frac{z}{4}}{1 + z + \frac{4}{9}z^2 + \frac{1}{9}z^3} \right\} \quad (16)$$

being,  $z = i\omega\tau_d + \frac{\tau_d}{T_j^S}$  is a complex and  $j = 1, 2$

### DMSO/FeCl<sub>3</sub> and DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>]

It is presented the relaxivity results and fitting curves obtained for DMSO/hexahydrated FeCl<sub>3</sub> for comparison with the DMSO/[P<sub>66614</sub>][FeCl<sub>4</sub>] solution.

## References

- (1) Torrey, H. C. Nuclear Spin Relaxation by Translational Diffusion. *Phys. Rev.* **1953**, *92*, 962–969.
- (2) Bloembergen, N.; Purcell, E. M.; Pound, R. V. Relaxation Effects in Nuclear Magnetic Resonance Absorption. *Phys. Rev.* **1948**, *73*, 679–712.
- (3) Kimmich, R.; Winter, F.; Nusser, W.; Spohn, K. H. Interactions and Fluctuations Deduced From Proton Field-cycling Relaxation Spectroscopy of Polypeptides, Dna, Muscles, and Algae. *J. Magn. Reson.* **1986**, *68*, 263–282.
- (4) Pusiol, D. J.; Humpfer, R.; Noack, F. Nitrogen Nuclear-quadrupole Resonance Dips in The Proton Spin Relaxation Dispersion of Nematic and Smectic Thermotropic Liquid-crystals. *Z. Naturforsch., A: Phys. Sci.* **1992**, *47*, 1105–1114.
- (5) Anorado, E.; Pusiol, D. J., D. J.; Aguilera, C. NMR-Study of the T<sub>1</sub> Relaxation Disper-

- sion In the Smectic Mesophase of 4-chlorophenyl 4-undecyloxybenzoate. *Phys. Rev. B: Condens. Matter* **1994**, *49*, 8600–8607.
- (6) Gillis, P.; Roch, A.; Brooks, R. A. Corrected Equations for Susceptibility-induced  $T_2$ -shortening. *J. Magn. Reson.* **1999**, *137*, 402–407.
- (7) Daniel, C. I.; Vaca Chávez, F.; Feio, G.; Portugal, C. A. M.; Crespo, J. G.; Sebastião, P. J.  $^1\text{H}$  NMR Relaxometry, Viscometry, and PFG NMR Studies of Magnetic and Nonmagnetic Ionic Liquids. *J. Phys. Chem. B* **2013**, *117*, 11877–11884.
- (8) Merbach, A., Helm, L., Toth, E., Eds. *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, 2nd ed.; Wiley, 2013.

## *fitteia* Report

(internet based fitter service)

*The Art of Model Fitting to Experimental Results*<sup>1</sup>

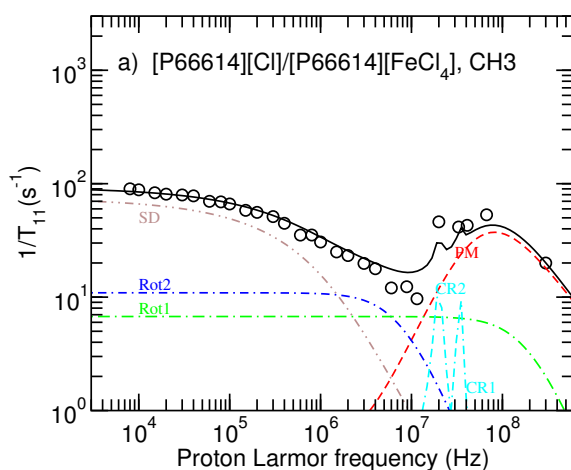
Subject	Plots-Paper-P66614, CH3_final
Date	Wednesday 5 <sup>th</sup> November, 2014, 18:11
Affiliation	carla.daniel@dq.fct.unl.pt 194.210.232.202
Abstract	Fit report produced with the fit results of function: $y = ((T < 2) ? iT1ISpara(f, 300.0, \tau_{d1}/(1 + \text{pow}(2*\pi*f*\tau_{d1}, p)), \tau_{d1}, M, r, S) : 1e-9) +$ $BPP(f, Arot, \tau) + BPP(f, Arot1, \tau1) + (T < 2) ? CROSSRELAX(f, adip, tdip, fdip)$ $: 1e-10 + (T < 2) ? CROSSRELAX(f, adip1, tdip1, fdip1) : 1e-10 + (T < 2) ? Torrey1(f,$ $d, r*1e10, n, \tau_{d1}/(6.0*(1 + \text{pow}(2*\pi*f*\tau_{d1}, p)))) : Torrey1(f, d, r*1e10, n, \tau_{d1})$ to the 55 experimental points, considering 10 free parameters.

$$\begin{aligned} \tau_{d1} &= 6.3465 \times 10^{-09} \pm 5.9527 \times 10^{-10} \\ \tau_{d1} &= 1 \times 10^{-11} \pm 6.431 \times 10^{-13} \\ \tau_{d1} &= 7.3387 \times 10^{-08} \pm 3.4833 \times 10^{-09} \\ Arot &= 1.85 \times 10^{+08} \text{ (fixed)} \\ \tau &= 1.18 \times 10^{-08} \text{ (fixed)} \\ Arot1 &= 2.81 \times 10^{+09} \text{ (fixed)} \\ \tau1 &= 4.8 \times 10^{-10} \text{ (fixed)} \\ M &= 0.014 \text{ (fixed)} \\ r &= 2.5314 \times 10^{-10} \pm 1.3679 \times 10^{-12} \\ S &= 400 \text{ (fixed)} \\ d &= 8 \pm 0.017602 \end{aligned}$$

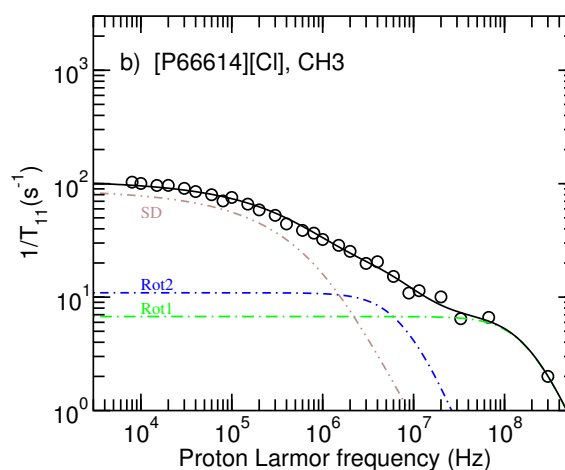
$$\begin{aligned} n &= 7 \times 10^{+22} \text{ (fixed)} \\ \tau_{d1} &= 1.4574 \times 10^{-08} \pm 6.9147 \times 10^{-10} \\ adip &= 2.5352 \times 10^{+07} \pm 1.108 \times 10^{+07} \\ tdip &= 5 \times 10^{-07} \pm 3.2912 \times 10^{-07} \\ fdip &= 3.4 \times 10^{+07} \text{ (fixed)} \\ \tau_{d1} &= 3.85 \times 10^{-10} \text{ (fixed)} \\ p &= 1.1303 \text{ (fixed)} \\ adip1 &= 2.518 \times 10^{+07} \pm 9.2404 \times 10^{+06} \\ tdip1 &= 5 \times 10^{-07} \text{ (fixed)} \\ fdip1 &= 2 \times 10^{+07} \pm 3.1437 \times 10^{+05} \end{aligned}$$

$$\begin{aligned} \chi^2[2] &= 13.727 \\ \chi^2_t &= 146.008 \end{aligned}$$

$$\chi^2[1] = 132.281$$



recta-1.pdf



recta-2.pdf

<sup>1</sup>"The Art of Model Fitting to Experimental Results", P.J. Sebastião, *Eur. J. Phys.* **35** (2014) 015017

## *fitteia* Report

(internet based fitter service)

*The Art of Model Fitting to Experimental Results*<sup>1</sup>

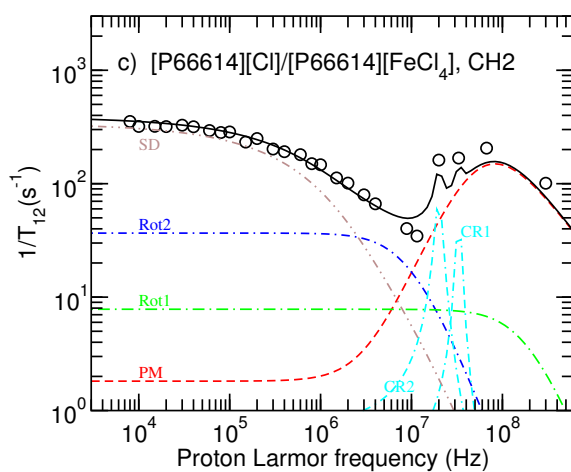
Subject	Plots-Paper-P66614, CH2_final
Date	Wednesday 5 <sup>th</sup> November, 2014, 18:12
Affiliation	carla.daniel@dq.fct.unl.pt 194.210.232.202
Abstract	Fit report produced with the fit results of function: $y = ((T < 2) ? iT1ISpara(f, 300.0, \tau_{d1}/(1 + \text{pow}(2*\pi*f*\tau_{d1}, p)), \tau_{d1}, M, r, S) : 1e-9) +$ $BPP(f, Arot, \tau) + BPP(f, Arot1, \tau1) + (T < 2) ? CROSSRELAX(f, adip, tdip, fdip)$ $: 1e-10 + (T < 2) ? CROSSRELAX(f, adip1, tdip1, fdip1) : 1e-10 + (T < 2) ? Torrey1(f,$ $d, r*1e10, n, \tau_{d1}/(6.0*(1 + \text{pow}(2*\pi*f*\tau_{d1}, p)))) : Torrey1(f, d, r*1e10, n, \tau_{d1})$ to the 53 experimental points, considering 10 free parameters.

$$\begin{aligned} \tau_{d1} &= 6.0183 \times 10^{-09} \pm 7.3524 \times 10^{-10} \\ \tau_{d1} &= 1 \times 10^{-11} \pm 1.7137 \times 10^{-12} \\ \tau_{d1} &= 7.34 \times 10^{-08} \text{ (fixed)} \\ Arot &= 7.33 \times 10^{+08} \text{ (fixed)} \\ \tau &= 1.0009 \times 10^{-08} \text{ (fixed)} \\ Arot1 &= 3.03 \times 10^{+09} \text{ (fixed)} \\ \tau1 &= 5.16 \times 10^{-10} \text{ (fixed)} \\ M &= 0.014 \text{ (fixed)} \\ r &= 1.5859 \times 10^{-10} \pm 2.6898 \times 10^{-12} \\ S &= 400 \text{ (fixed)} \\ d &= 4.5148 \pm 0.068607 \end{aligned}$$

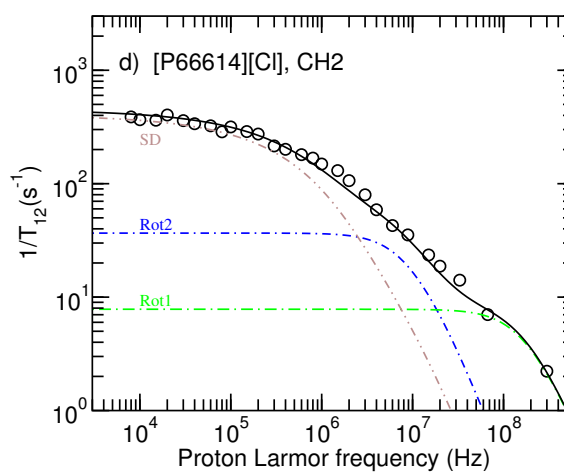
$$\begin{aligned} n &= 7 \times 10^{+22} \text{ (fixed)} \\ \tau_{d1} &= 1.46 \times 10^{-08} \text{ (fixed)} \\ adip &= 1.2856 \times 10^{+08} \pm 4.3852 \times 10^{+07} \\ tdip &= 5 \times 10^{-07} \pm 3.2303 \times 10^{-07} \\ fdip &= 3.3206 \times 10^{+07} \pm 1.6025 \times 10^{+06} \\ \tau_{d1} &= 3.85 \times 10^{-10} \text{ (fixed)} \\ p &= 1.1303 \text{ (fixed)} \\ adip1 &= 1.479 \times 10^{+08} \pm 3.2848 \times 10^{+07} \\ tdip1 &= 5 \times 10^{-07} \pm 1.9932 \times 10^{-08} \\ fdip1 &= 2 \times 10^{+07} \pm 3.356 \times 10^{+05} \end{aligned}$$

$$\begin{aligned} \chi^2[2] &= 28.6349 \\ \chi^2_t &= 98.3727 \end{aligned}$$

$$\chi^2[1] = 69.7377$$



recta-1.pdf



recta-2.pdf

<sup>1</sup>"The Art of Model Fitting to Experimental Results", P.J. Sebastião, *Eur. J. Phys.* **35** (2014) 015017



## *fitteia* Report

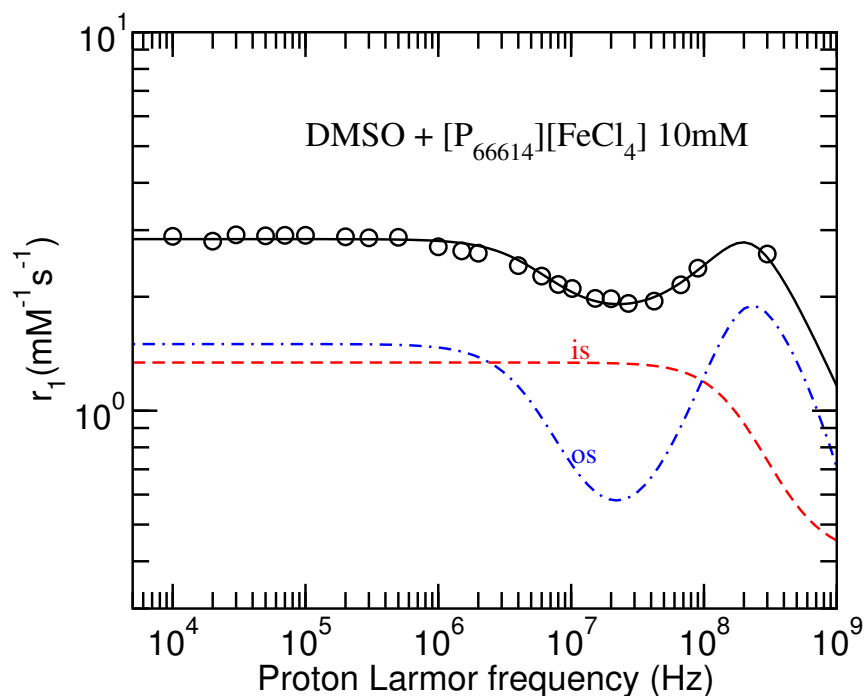
(internet based fitter service)

*The Art of Model Fitting to Experimental Results*<sup>1</sup>

Subject	P66614-FeCl4-DMSO, Fit-10mM-r1-final
Date	Friday 24 <sup>th</sup> July, 2015, 15:02
Affiliation	carla.daniel@dq.fct.unl.pt 84.90.100.162
Abstract	Fit report produced with the fit results of function: $y = x/14040 * iT1innerSmallS(f, 295.0, tmG, tmH, tv, ZFS, r, S0*n, S) + iT1outerSmallS(f, 295.0, D, tv, ZFS, R, S0*n)$ to the 23 experimental points, considering 5 free parameters.

$tmG = 1$ (fixed)	$D = 7 \times 10^{-10}$ (fixed)
$tmH = 1.1197 \times 10^{-12} \pm 6.5915 \times 10^{-14}$	$tv = 2.5882 \times 10^{-12} \pm 2.5312 \times 10^{-13}$
$r = 3.5 \times 10^{-10} \pm 2.2172 \times 10^{-11}$	$ZFS = 2.8787 \times 10^{+10} \pm 2.1614 \times 10^{+09}$
$S0 = 3$ (fixed)	$R = 7.9588 \times 10^{-10} \pm 2.9725 \times 10^{-11}$
$n = 1.0001$ (fixed)	$x = 8$ (fixed)
$S = 0$ (fixed)	

$$\chi^2[1] = 5.28254 \quad \chi^2_t = 5.28254$$



recta-1.pdf

<sup>1</sup>"The Art of Model Fitting to Experimental Results", P.J. Sebastião, *Eur. J. Phys.* **35** (2014) 015017

## *fitteia* Report

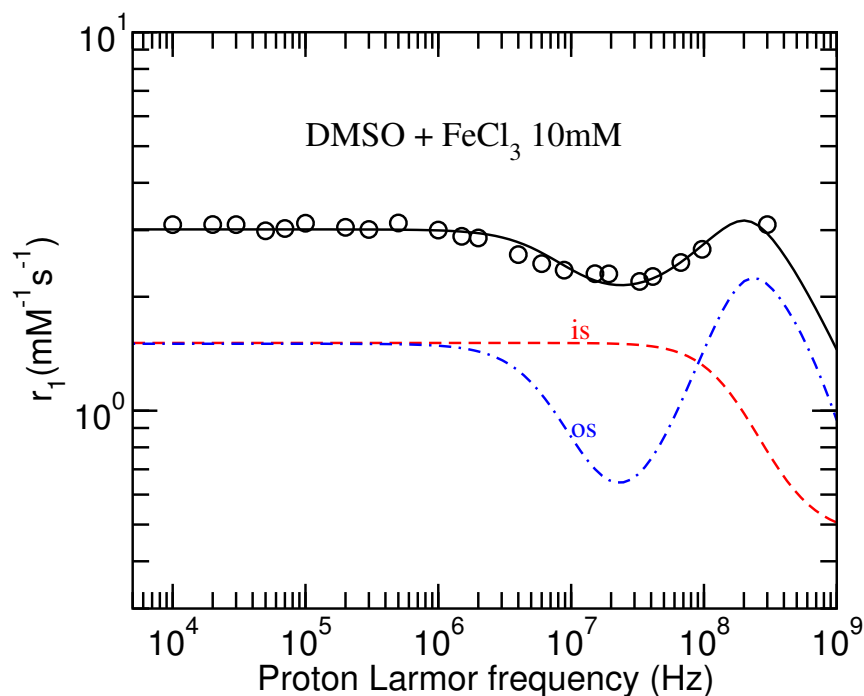
(internet based fitter service)

*The Art of Model Fitting to Experimental Results*<sup>1</sup>

Subject	FeCl3-DMSO, Fit-10mM-r1-final
Date	Friday 24 <sup>th</sup> July, 2015, 15:03
Affiliation	carla.daniel@dq.fct.unl.pt 84.90.100.162
Abstract	Fit report produced with the fit results of function: $y = x/14040 * iT1innerSmallS(f, 295.0, tmG, tmH, tv, ZFS, r, S0*n, S) + iT1outerSmallS(f, 295.0, D, tv, ZFS, R, S0*n)$ to the 23 experimental points, considering 6 free parameters.

$tmG = 1$ (fixed) $tmH = 1.2759 \times 10^{-12} \pm 8.5858 \times 10^{-14}$ $r = 3.5 \times 10^{-10} \pm 1.3408 \times 10^{-11}$ $S0 = 3$ (fixed) $n = 1.0001$ (fixed) $S = 0$ (fixed)	$D = 7 \times 10^{-10}$ (fixed) $tv = 3.0213 \times 10^{-12} \pm 2.6997 \times 10^{-13}$ $ZFS = 3.0863 \times 10^{+10} \pm 2.5376 \times 10^{+09}$ $R = 7.2522 \times 10^{-10} \pm 3.0103 \times 10^{-11}$ $x = 8 \pm 4.347$
---	--

$$\chi^2[1] = 11.9318 \quad \chi^2_t = 11.9318$$



recta-1.pdf

<sup>1</sup>"The Art of Model Fitting to Experimental Results", P.J. Sebastião, *Eur. J. Phys.* **35** (2014) 015017