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Chapter 7

Molecular Dynamics of Gd(III) Complexes in Aqueous Solution by HF EPR

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The study of electron spin relaxation in aqueous Gd(III) complexes is the source of new insights into the physics and chemistry of magnetic resonance imaging (MRI) contrast agents. The coupling of the seven unpaired electrons of the Gd(III) ion with the surrounding water protons observed in MRI is the basis of the contrast agent effectiveness. Therefore, understanding the behavior of the electron spin system can provide valuable information for the development of new compounds.

The availability of high frequency electron paramagnetic resonance (HF EPR) spectrometers is vital for complete relaxation studies, and played an important role in improving our knowledge of Gd(III) electron spin relaxation in the last few years. HF EPR has been an invaluable tool to improve our understanding of the underlying relaxation mechanisms.

1. INTRODUCTION AND HISTORICAL BACKGROUND

Paramagnetic Gd(III) complexes are widely used as contrast agents in medical magnetic resonance imaging (MRI) due to the enhancement of the

relaxation rate of the neighboring protons that they induce (Caravan *et al.*, 1999a; Merbach and Tóth, 2001). This enhancement, called *relaxivity*, is a consequence of the dipolar coupling between the proton nuclear spin and the electronic spin of the metal ion. Among other factors, relaxivity is determined by (1) the rotational correlation time of the complex τ_R , (2) the water residence time τ_m in the first coordination shell of the metal ion, and (3) the electronic spin relaxation times T_{1e} and T_{2e} . While the molecular factors influencing (1) and (2) are rather well understood, the electronic spin relaxation of Gd(III) complexes relevant for MRI remains the subject of much discussion (Borel *et al.*, 2000; Clarkson *et al.*, 1998; Powell *et al.*, 1993; Powell *et al.*, 1996). The influence of the electronic spin relaxation on the relaxivity, which may be quite important in some cases (Borel *et al.*, 2001), is essentially governed by the decay of the electronic spin magnetization in the direction parallel to the external field. This decay is described by the longitudinal electronic relaxation time T_{1e} . For Gd(III) complexes, it is too short to be directly measurable by the commonly available techniques. Nevertheless, standard electron paramagnetic resonance allows the investigation of the decay of the electronic spin magnetization perpendicular to the external field, usually characterized by a transverse electronic relaxation time T_{2e} . The analysis of the transverse relaxation data allows the subsequent estimation of T_{1e} within the framework of a given model of the electronic relaxation. For a reasonable prediction of T_{1e} , one needs a model which correctly describes the underlying physics. Extensive experimental data is also required to determine accurately the underlying parameters. Consequently, the last few years have witnessed a considerable interest for new studies, both experimental and theoretical, on this particular subject.

The $^8S_{7/2}$ ion Gd(III) is well known to undergo zero-field splitting in the solid state, as observed in a number of compounds such as gadolinium chloride (Hutchinson and Wong, 1958) or Gd(III) doped into lanthanide ethylsulfates (Abragam and Bleaney, 1970; Smith *et al.*, 1977). Proposed thirty years ago by Hudson and Lewis (Hudson and Lewis, 1970), the basic theory of the EPR line shape of Gd(III) complexes uses a transient zero-field splitting (modulated by rotation or molecular distortions) as the main relaxation mechanism. This basic assumption leads to the calculation of a 7x7 (transverse) or 8x8 (longitudinal) relaxation matrix following Redfield (Redfield, 1965). The eigenvalues of these matrices can then be evaluated to calculate the line shape (Binsch, 1968). An important feature of this theory is that the transverse electronic spin relaxation, which governs the EPR line shape, can not be described by a single T_{2e} . Four different relaxation times are necessary as the experimental spectrum results from a superposition of

four transitions with different intensities, so the line shape problem can not be solved analytically.

Both the observation frequency ω and the correlation time τ for the Hamiltonian fluctuations play an important role in magnetic relaxation processes out of the extreme narrowing regime ($\omega\tau \ll 1$). This is generally the case for EPR measurements in solution. For example, Brownian rotation ($1/\tau_R \geq 10^{11}$ s at room temperature for molecules larger than a few atoms in aqueous solution) is often an efficient mechanism for the modulation of a given interaction (g/A anisotropy, dipolar coupling...). Even at X-band ($\omega \cong 6 \times 10^{11}$ s⁻¹) such a correlation time is certainly not short enough to justify the extreme narrowing approximation. This consideration, and the uncertainty regarding the nature of the ZFS fluctuation itself, led to the first variable temperature and frequency studies of Gd(III) complexes in solution (X- and Q-band by Reuben (Reuben, 1971)). The short correlation times obtained through the analysis of the peak-to-peak widths using the relaxation matrix of Hudson and Lewis (5 to 8 ps) suggested that the modulation of the ZFS should arise from symmetry fluctuations of the complex (low frequency vibrations, collisions with solvent molecules) rather than from the reorientation of the complex.

In order to simplify this theory, Powell et al. (Powell *et al.*, 1993) later proposed empirical formulas to describe both the transverse and longitudinal relaxation times, which they later applied in a unified model to simultaneously interpret ¹⁷O-NMR, ¹H-NMR, and EPR (Gonzalez *et al.*, 1994; Powell *et al.*, 1996) of Gd(III) polyaminocarboxylate complexes relevant for MRI. The empirical equations allowed an easy calculation of average longitudinal and transverse relaxation times, to be used in the Solomon-Bloembergen-Morgan (Bloembergen, 1957; Bloembergen and Morgan, 1961) equations describing the nuclear magnetic relaxation in the presence of a paramagnetic agent. These studies took advantage of the development of high frequency EPR spectrometers such as Lebedev's (Lebedev, 1990) to considerably extend the observation frequency range. New effects were observed, such as a concentration dependence of the observed peak-to-peak width at high frequency. The simultaneous analysis of EPR and NMR relaxation data also suggested the existence of a magnetic field independent contribution to the electron spin relaxation rates (Micskei *et al.*, 1993; Powell *et al.*, 1996), attributed to a spin rotation mechanism (Curl, 1965; Nyberg, 1967). However, even with the addition of this relaxation process, the obtained results were sometimes in a very poor agreement with the experimental EPR data (Aime *et al.*, 1997a).

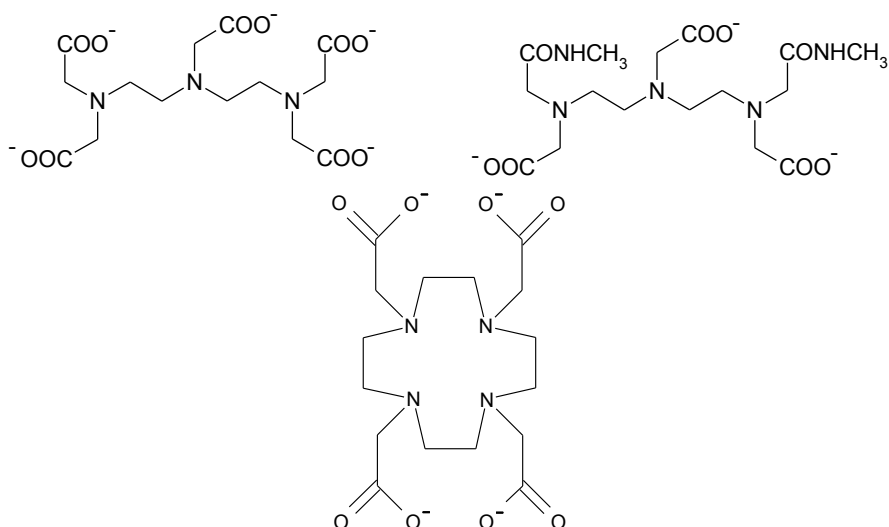


Figure 1. DTPA⁻, DTPA-BMA³⁻ and DOTA⁴⁻ ligand structures

Various authors suggested a more rigorous calculation of the line shape, also accounting for the dynamic frequency shift, which is a small displacement in the transition frequencies, often neglected. Poupko *et al.* (Poupko *et al.*, 1974) calculated the imaginary part of the complex Redfield relaxation matrix for $S = 3/2$, $5/2$ and $7/2$, the real part of the last being given by Hudson and Lewis (Hudson and Lewis, 1970). They applied their theory to the numerical analysis of X- and Q-band variable temperature spectra of $Gd(NO_3)_3$ in DMF, using not only the usual peak-to-peak width but also the resonance field and the asymmetry of the line shape. They obtained a fair agreement between the experimental data and the simulations using their best fitting parameters. With the increase of the available computer power, this approach has become quite affordable even if the line shape analysis involves repeated matrix diagonalizations. Since the empirical formulas of Powell had proved unable to account for the observed peak-to-peak widths in a number of studies performed in our lab, we applied the Poupko approach to three different complexes observed at 9.425, 75, 150 and 225 GHz (Borel *et al.*, 2000). We were able to account semi quantitatively for the observed peak-to-peak widths and resonance fields, but the analysis of the high-frequency data was only possible by including a magnetic field independent term, which was attributed to spin rotation following Powell. Alternatively, Strandberg and Westlund (Strandberg and Westlund, 1999) used the superoperator formalism to calculate a reduced relaxation matrix, yielding an analytical expression of the line shape although the peak-to-peak width and resonance field still required solving high order polynomial

equations. Unfortunately, the experimental data reported to support this interesting theoretical work was scarce. Clarkson and coworkers (Clarkson *et al.*, 1998; Smirnova *et al.*, 1998) used an approach developed by Alexander (Alexander *et al.*, 1977) for powder spectra in order to calculate high frequency (Q-band and higher) line widths and shifts, yielding elegant analytical equations. However they clearly stated that this theory could not always account for lower frequency (for example X-band) observed values. Furthermore, they also needed a frequency independent contribution R_0 to the peak-to-peak widths, without proposing an underlying mechanism.

The studies above, performed for the over such a wide temperature and frequency range, showed the shortcomings of the model transient ZFS model. Very recently, Rast *et al.* (Rast *et al.*, 2001b; Rast *et al.*, 1999; Rast *et al.*, 2000) developed a refined model of the electronic relaxation of the S states of metal ion complexes in solutions. This refined treatment now includes the contribution of the static crystal field surrounding the Gd(III) ion caused by its modulation by the rotation of the whole complex, besides a part due to the usual transient crystal zero-field splitting (ZFS) caused by vibration, intramolecular rearrangement, and collision with surrounding solvent molecules. A good agreement with the measured peak-to-peak distances was obtained for $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$, $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$, and $[\text{Gd}(\text{DTPA-BMA})(\text{H}_2\text{O})]$ complexes in a new analysis of the experimental data measured by Powell (Rast *et al.*, 1999; Rast *et al.*, 2000). The final refinement of this theory, including a rigorous calculation of the EPR line shape, including dynamic frequency shifts and instrumental factors such as spectrum phasing, was successfully applied to the analysis of multiple frequency and temperature spectra of $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ and $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ (Rast *et al.*, 2001b). In the framework of this new model, and contrarily to previous works (Borel *et al.*, 2000; Micskei *et al.*, 1993), it is not necessary to include the spin rotation mechanism in the interpretation of the measurements as this effect is expected to be very weak for molecules larger than a few atoms (Curl, 1965; Nyberg, 1967). The above model was also successful for describing the proton NMRD behavior of probe solutes like the tetramethylammonium $\text{N}(\text{CH}_3)_4^+$ ions of well known spatial dynamics with respect to the $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ complex, without additional fitting parameters (Rast *et al.*, 2001a).

However, this new model, as well as most of the previous approaches of this problem, was developed in the framework of the Redfield relaxation theory (Abragam, 1961b; Redfield, 1965) describing the time dependence of the correlation functions of the spin system components. This theory has essentially two limitations. Denoting by ω_0 the unperturbed Zeeman angular frequency and by H_1 the time dependent perturbing Hamiltonian inducing electronic transitions between the Zeeman levels, one must have $|H_1| \tau_c \ll 1$

and $|H_1|^2\tau_c \ll \omega_0$, where τ_c is the correlation time of the fluctuating term H_1 . The first condition can be violated when we consider large complexes. When the relevant time τ_c is the rotational correlation time of the complex, its inverse which is the rotational diffusion constant D_R can reach values of the same order as H_1 , especially in the low temperature region where D_R decreases. The second condition corresponds to the secular approximation (Abragam, 1961a) and may be hardly satisfied when experiments are performed at low fields, mainly for large complexes and at temperatures just above 0 °C.

To overcome these problems, a new approach using Monte-Carlo (MC) simulations of the electronic relaxation processes was presented (Rast *et al.*, 2001c). In this method independent Brownian rotational trajectories of Gd(III) complexes are generated in discrete time steps. Similar numerical approaches had already been used in the past (for example in the work of Abernathy and Sharp (Abernathy and Sharp, 1997), but in our case the simulated Hamiltonian took into account all contributions (static and transient) to the relaxation process. A MC procedure for the reorientation of the Gd(III) complexes, combined with a Ornstein-Uhlenbeck process (Bauer, 1991; Kannan, 1979) used to model the transient zero-field splitting, was applied to the electronic relaxation theory beyond the Redfield limit where there is no analytical solution. The comparison of the simulation results with the Redfield predictions allowed a rigorous estimation of the error induced by the Redfield approximation outside its limits. The slow molecular tumbling at low temperature was found to be of no consequence for the relatively small studied complexes ($[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ and $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^{2-}$) in the range of conventional EPR (0.34 T and above), but the extrapolation of the Redfield theory down to low fields (0.1 T and below) lead to significant discrepancies. For example, the simulated electronic relaxation times were over 20 % longer than the Redfield predictions for the aqua ion. This was an important finding since such low magnetic fields are routinely used in NMRD experiments on Gd(III) complexes.

Although this improved theory brought new insights into the phenomena underlying electron spin relaxation, it also dug an increasingly wide gap between the $^1\text{H}/^{17}\text{O}$ -NMR experiments commonly performed in the study of potential MRI contrast agents and the state of the art in the field of EPR. In particular, it became important to replace the simultaneous fitting approach first proposed by Powell *et al.* (Powell *et al.*, 1996) with an integrated and theoretically sound approach combining ^{17}O -NMR, NMRD and EPR experimental data with a full description of electron spin relaxation taking possible violations of Redfield's approximation into account. This was successfully accomplished with the octa aqua ion $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ as a test case (Borel *et al.*, 2002). Furthermore, newly developed experimental methods

have made the direct measurements of short T_{1e} possible (Atsarkin *et al.*, 2001). It was found that the combination of the static and transient crystal field effects was able to correctly predict the observed results (Borel *et al.*,).

2. THEORETICAL SECTION

2.1 Overview

Neglecting any hyperfine interaction, the spin Hamiltonian of an $S > 1/2$ metal ion without orbital moment such as Gd(III) ($S = 7/2$, half-filled $4f$ shell) is assumed to be divided into two contributions, namely a Zeeman term due to the external magnetic field and a zero field splitting (ZFS) term caused by the crystal field around the ion.

$$\hat{H} = \hat{H}_{Zeeman} + \hat{H}_{ZFS} \quad (1)$$

The Zeeman term is constant in a uniform magnetic field. We denote it H_0 . The crystal field attached to the molecular frame M is randomly modulated over time in the laboratory frame L . The corresponding term, written H_1 , is therefore time dependant.

$$\hat{H} = \hat{H}_0 + \hat{H}_1^L(t) \quad (2)$$

The time-dependant ZFS term is the origin of the longitudinal and transverse electron spin relaxation. It is further divided into two contributions depending on the nature of the modulating motion. On one hand, a so called *static* part H_{1S} is due to the average coordination polyhedron. It is constant in the M frame, but modulated in the L frame by molecular tumbling in solution. On the other hand, the *transient* part H_{1T} is modulated by the deformations of the coordination polyhedron, for example due to solvent collisions or exchanges in the first coordination shell of the ion. This second term is averaged out over time even in the M frame but can be non-zero at a given time t .

$$\hat{H}_1^L(t) = \hat{H}_{1S}^L(t) + \hat{H}_{1T}^L(t) \quad (3)$$

The treatment of this time-dependant Hamiltonian using the Redfield relaxation theory is the basis of the theory presented in the following section.

The electron spin relaxation is governed by the amplitude of the static and transient ZFS Hamiltonians and by the respective correlation times for their modulation in the laboratory frame. Since molecular tumbling and vibrations happen on different time scales, the relative importance of the static and transient ZFS contributions to relaxation depends on the observation frequency. While conventional X-band EPR is mainly influenced by the rotational modulation of the static ZFS, HF EPR is an irreplaceable tool for the study of the transient ZFS.

The calculation of the relaxation matrix based on this Hamiltonian leads to the prediction of a multi-exponential decay of the transverse magnetization described by several relaxation times T_{2ej} . Although the same prediction is made for the longitudinal relaxation, an essentially mono-exponential decay is calculated in this case.

A rigorous calculation of the continuous wave EPR lineshape shows the existence of a *dynamic frequency shift* (Fraenkel, 1965; Fraenkel, 1967) that is a variable displacement of the central resonance field. This shift can be used together with the peak-to-peak width for the analysis of EPR spectra of Gd(III) complexes in solution. When possible, the calculation of the complete spectrum is the best way to analyze the data.

2.2 Theory and practical implementation

2.2.1 Crystal field Hamiltonian

First, we define the static crystal field ZFS Hamiltonian on the basis of the electron spin components. In the M frame it can be expressed as linear combinations of irreducible tensor operators of rank k , T_q^k ($|q| < k$) (Buckmaster *et al.*, 1972).

$$\hat{H}_{1S}^M = \sum_{k,\eta} B^{k\eta} \sum_{q=-k}^{+k} b_q^{k\eta} \hat{T}_q^k \quad (4)$$

k is even and limited to $K = 2S$, i.e. $K = 4$ for d electrons and 6 for f electrons. The real coefficients $B^{k\eta}$ determine the magnitude of each contribution. The linear combinations $\sum b_q^{k\eta} T_q^k$ have complex coefficients $b^{k\eta}$ and must be invariant under the symmetry operations of the point group of the molecule. These coefficients can be always be chosen orthonormal:

$$\sum_{q=-k}^k b_q^{k\eta} * b_q^{k\eta'} = \delta_{\eta\eta'} \quad (5)$$

Depending on the symmetry, there may be several such combinations of same rank k , making the supplementary index η necessary. The number of possible linear combinations is given by the coefficient of the fully symmetric irreducible representation after reduction of the representation D_k^+ of the full rotation group (spherical harmonics of order k) in the point symmetry group of the system. For example, in the D_{4d} symmetry, one finds that there is only one linear combination of tensors in any of the orders $k = 2, 4, 6$:

$$\begin{aligned} D_2^+ &= A_1 + E_2 + E_3 \\ D_4^+ &= A_1 + B_1 + B_2 + E_1 + E_2 + E_3 \\ D_6^+ &= A_1 + B_1 + B_2 + 2E_1 + 2E_2 + E_3 \end{aligned}$$

In the molecular frame, the best known form of the Hamiltonian (4) is the usual second order ZFS term:

$$D \left(\hat{S}_z^2 - \frac{1}{3} \hat{S}^2 \right) + \frac{E}{2} (\hat{S}_+^2 + \hat{S}_-^2) = D \sqrt{\frac{2}{3}} \hat{T}_0^2 + E (\hat{T}_2^2 + \hat{T}_{-2}^2) \quad (6)$$

Thus our static crystal field Hamiltonian is in principle a generalized form of the ZFS found in earlier papers by various researchers (Borel *et al.*, 2000; Clarkson *et al.*, 1998; Hudson and Lewis, 1970; Nilsson and Kowalewski, 2000; Poupko *et al.*, 1974; Powell *et al.*, 1993; Strandberg and Westlund, 1996). A comparison of equations (4) and (6) in axial symmetry ($E = 0$ in equation (6)) shows that the identity of B^2 (there is only one single η in this case) with the ZFS spin Hamiltonian coefficient $(2/3)^{1/2}D$. Adding an orthorhombic deformation leads to a second tensor combination with $B^{2\eta} = 2^{1/2}E$. This corresponds to a D_{2h} , D_2 or C_{2v} symmetry. In the lower C_1 , C_i , C_{2h} , C_2 or C_s point groups there are more than two linear combinations of 2nd order irreducible tensors. The 4th order contribution is less frequently present in the literature, but its importance was discussed for example for $S = 2$ complexes of d elements, such as Mn^{3+} compounds (Abernathy *et al.*, 1998)

Let us now consider the transformation of the Hamiltonian from the M frame to the L frame. It is performed by a rotation $R(\alpha, \beta, \gamma)$ depending on the

instantaneous orientation of the M frame with respect to the L frame, using the associated Wigner matrix of rank k .

$$\hat{H}_{1S}^L(t) = \sum_{k,\eta} B^{k\eta} \sum_{p,q=-k}^{+k} b_q^{k\eta} \hat{T}_q^k D_{pq}^k(R(t)) \quad (7)$$

For the static ZFS, the $B^{k\eta}$ coefficients are constant, and the time dependence only appears in the Wigner rotation matrices. For the transient ZFS term, these coefficients are also functions of time. If we restrict our development to 2nd order we obtain:

$$\hat{H}_{1T}^L(t) = \sum_{\eta} B^{2\eta T}(t) \sum_{p,q=-2}^{+2} b_q^{2\eta T} \hat{T}_q^2 D_{pq}^2(R(t)) \quad (8)$$

The total crystal field Hamiltonian in the laboratory frame is then as follows:

$$\hat{H}_1^L(t) = \sum_{k,\eta} B^{k\eta} \sum_{p,q=-k}^{+k} b_q^{k\eta} \hat{T}_q^k D_{pq}^k(R(t)) + \sum_{\eta} B^{2\eta T}(t) \sum_{p,q=-2}^{+2} b_q^{2\eta T} \hat{T}_q^2 D_{pq}^2(R(t)) \quad (9)$$

2.2.2 EPR line shape

We have now built the Hamiltonian which governs the time evolution of our quantum mechanical system and we turn our attention to the line shape. The density operator in the interaction picture σ^I expressed in a basis of spin states $-S \leq \alpha, \beta, \gamma, \text{ etc.} \leq +S$ follows a system of first order differential equations

$$\frac{d\sigma_{\alpha,\alpha'}^I}{dt} = \sum_{\beta,\beta'} R_{\alpha\alpha',\beta\beta'}(\omega_0) \sigma_{\beta,\beta'}^I \quad (10)$$

with the restriction that $\alpha - \alpha' = \beta - \beta'$, expressing the secular approximation which eliminates the rapidly oscillating elements of the relaxation matrix R .

$$\begin{aligned}
R_{\alpha\alpha'\beta\beta'}(\omega_0) &= \int_0^\infty d\tau \left[e^{i(\beta-\alpha)\omega_0\tau} \overline{\langle \beta' | \hat{H}_1^L(t) | \alpha' \rangle} \langle \beta | \hat{H}_1^L(t-\tau) | \alpha \rangle \right]^* \\
&+ e^{i(\alpha'-\beta')\omega_0\tau} \overline{\langle \alpha | \hat{H}_1^L(t) | \beta \rangle} \langle \alpha' | \hat{H}_1^L(t-\tau) | \beta' \rangle^* \\
&- \delta_{\alpha'\beta'} \sum_\gamma e^{i(\beta-\gamma)\omega_0\tau} \overline{\langle \alpha | \hat{H}_1^L(t) | \gamma \rangle} \langle \beta | \hat{H}_1^L(t-\tau) | \gamma \rangle^* \\
&- \delta_{\alpha\beta} \sum_\mu e^{i(\gamma-\beta')\omega_0\tau} \overline{\langle \gamma | \hat{H}_1^L(t) | \alpha' \rangle} \langle \gamma | \hat{H}_1^L(t-\tau) | \beta' \rangle^*
\end{aligned} \tag{11}$$

where the bar represents the ensemble average over the various orientations of the complex. Replacing the integrals with spectral density functions $J(\omega)$, we get

$$\begin{aligned}
J_{\alpha\beta\alpha'\beta'}(\omega) &= \int_0^{+\infty} \overline{\langle \alpha | H_1(t) | \beta \rangle} \langle \beta' | H_1(t-\tau) | \alpha' \rangle e^{-i\omega\tau} d\tau \\
R_{\alpha\alpha'\beta\beta'} &= J_{\alpha\beta\alpha'\beta'}(\omega_{\alpha'\beta'}) + J_{\alpha\beta\alpha'\beta'}(\omega_{\alpha\beta}) - \delta_{\alpha'\beta'} \sum_\gamma J_{\gamma\beta\gamma\alpha}(\omega_{\gamma\beta}) - \delta_{\alpha\beta} \sum_\gamma J_{\gamma\alpha'\gamma\beta'}(\omega_{\gamma\beta'})
\end{aligned}$$

Let us consider a spin operator component S_i with $i = x, y, z$, and its time correlation function $G_i(t)$:

$$G_i(t) = \frac{1}{2S+1} \text{tr} \overline{S_i(t) S_i(0)} \tag{13}$$

The bar indicates the mean value of the matrix elements of these operators and tr is the trace operation. Within the high temperature semiclassical formalism, the absorption line shape under an oscillating field polarized in the x direction is (Abragam, 1961b)

$$F(\omega) = \text{Re} \int_{-\infty}^{\infty} G_x(t) e^{i\omega t} dt \tag{14}$$

In what follows it is useful to define a slowly time dependent operator

$$\hat{S}_i(t) = e^{-i\hat{H}_0 t} \hat{S}_i(t) e^{i\hat{H}_0 t} \tag{15}$$

whose matrix elements have the same time evolution as σ^{\dagger} except a minus sign before ω_0 , i.e.

$$\frac{d\widehat{\tilde{S}}_{\alpha,\alpha'}}{dt} = \sum_{\beta,\beta'} R_{\alpha\alpha',\beta\beta'} (-\omega_0) \widehat{\tilde{S}}_{\beta,\beta'} \quad (16)$$

We can express the time correlation function $G_x(t)$ in the basis of the spin states diagonalizing S_z

$$G_x(t) = \frac{1}{2S+1} \sum_{\alpha,\alpha'} \overline{\langle \alpha | \hat{S}_x(t) | \alpha' \rangle} \langle \alpha' | \hat{S}_x | \alpha \rangle \quad (17)$$

The summation can be restricted to the (α, α') pairs where $\alpha - \alpha' = \pm 1$. The sum over the pairs $\alpha - \alpha' = -1$ is the complex conjugate of the sum over the pairs $\alpha - \alpha' = +1$, so we can write

$$\begin{aligned} G_x(t) &= \frac{2}{2S+1} \operatorname{Re} \sum_{\alpha=-S+1}^S \overline{\langle \alpha | \hat{S}_x(t) | \alpha - 1 \rangle} \langle \alpha - 1 | \hat{S}_x | \alpha \rangle \\ &= \frac{2}{2S+1} \operatorname{Re} \sum_{\alpha=-S+1}^S e^{i\omega_0 t} \overline{\langle \alpha | \hat{S}_x(t) | \alpha - 1 \rangle} \langle \alpha - 1 | \hat{S}_x | \alpha \rangle \end{aligned} \quad (18)$$

Defining a vector $\mathbf{X}(t)$ with components $X_\alpha = \overline{\langle \alpha | \hat{S}_x | \alpha - 1 \rangle}$ we can rewrite the time evolution equation as

$$\frac{dX_\alpha}{dt} = \sum_{\beta} R_{\alpha,\alpha-1,\beta,\beta-1} (-\omega_0) X_\beta \quad (19)$$

with initial conditions $X_\alpha(0) = \langle \alpha | S_x | \alpha - 1 \rangle = \{S(S+1) - \alpha(\alpha - 1)\}^{1/2}/2$, and the time correlation function $G_x(t)$ as

$$G_x(t) = \frac{2}{2S+1} \operatorname{Re} \sum_{\alpha=-S+1}^S e^{i\omega_0 t} X_\alpha(t) X_\alpha(0) \quad (20)$$

Similarly the longitudinal relaxation behavior is described by

$$G_z(t) = \frac{2}{2S+1} \operatorname{Re} \sum_{\alpha=-S}^S e^{i\omega_0 t} Z_\alpha(t) Z_\alpha(0) \quad (21)$$

where the matrix elements $Z_\alpha(t)$ satisfy:

$$\frac{dZ_\alpha}{dt} = \sum_{\beta} R_{\alpha,\alpha,\beta,\beta}(-\omega_0)Z_\beta \quad (22)$$

Generally, the spectral densities are complex functions, so the matrix $R_{\alpha\alpha'\beta\beta'}$ is also complex. Indeed, If we calculate the transform of the time correlation functions for the matrix elements of the Hamiltonian assuming an exponential decay:

$$\begin{aligned} g_{\alpha\beta\alpha'\beta'}(\tau) &= \overline{\langle \alpha | H_1(t) | \beta \rangle} \langle \beta' | H_1(t + \tau) | \alpha' \rangle \\ J_{\alpha\beta\alpha'\beta'}(\omega) &= \int_{-\infty}^{+\infty} g_{\alpha\beta\alpha'\beta'}(\tau) e^{-i\omega\tau} d\tau \\ \int_{-\infty}^{+\infty} g_{\alpha\beta\alpha'\beta'}(\tau) e^{-i\omega\tau} d\tau &= g_0 \int_{-\infty}^{+\infty} \exp\left(\tau\left(-\frac{1}{\tau_c} - i\omega\right)\right) d\tau \\ &= g_0 \left\{ \frac{\tau_c}{1 + (\omega\tau_c)^2} - i \frac{\omega\tau_c^2}{1 + (\omega\tau_c)^2} \right\} \end{aligned} \quad (23)$$

It has been shown that the relevant Redfield matrix for the transverse relaxation $R_{2\alpha\beta} = R_{\alpha,\alpha-1,\beta,\beta-1}$ is complex and symmetric, but is not a normal matrix, (Binsch, 1968; Rast *et al.*, 2000) leading to complex eigenvalues. The imaginary part of the relaxation matrix has rarely been used. Poupko (Poupko *et al.*, 1974), followed by later work in our laboratory (Borel *et al.*, 2000), took it into account in the analysis of EPR spectra of Gd(III) complexes in solution. Strandberg (Strandberg and Westlund, 1996) also included it in a simulation of EPR line shapes and NMRD profiles. Finally, the slow motion (or high frequency) limit theory used by Clarkson and coworkers produced an elegant but unfortunately limited result for the frequency dependence of the dynamic frequency shift (Clarkson *et al.*, 1998; Smirnova *et al.*, 1998). Unlike its transverse counterpart, the relevant matrix $R_{1\alpha\beta} = R_{\alpha\alpha\beta\beta}$ for the longitudinal relaxation is a real symmetric matrix. The technical details concerning the diagonalization of these matrices are discussed in the computational details section. In our case we have checked that the eigenspace of $R_{2\alpha\beta}(\omega_0) = R_{\alpha,\alpha-1,\beta,\beta-1}(\omega_0)$ ($\alpha, \beta = -S+1, \dots, S$) is $2S$ -dimensional and its eigenvalues are denoted by $\Lambda_\lambda = \Lambda_\lambda^r + i\Lambda_\lambda^i$, $\lambda = -S+1, \dots, S$ with the corresponding eigenvectors η_λ , which have to be chosen to fulfill the following relation:

$$\eta_\lambda \cdot \eta_\lambda = 1 \text{ instead of } \eta_\lambda^* \cdot \eta_\lambda = 1 \quad (24)$$

else the eigenvectors are only defined to an arbitrary complex phase factor and calculation of the intensities is no longer possible. As it stands, only 4 of the 7 transitions have non-zero intensity. At a given external magnetic field B_0 with an associated frequency ω_0 , we obtain an explicit formula for the Fourier transform of $G_x(t)$ which is denoted by $I(\omega_0, \omega_0)$ (Poupko *et al.*, 1974). With \hat{U} the matrix that diagonalizes $R_{2\alpha\beta}(\omega_0)$ this Fourier transform can be safely approximated for $\omega_0 \approx \omega_0$ as:

$$\begin{aligned}
I(\omega, \omega_0) &= \text{Re} \left\{ \bar{X} \hat{U} [i(\omega_0 - \omega) \hat{1} + \hat{\Lambda}]^{-1} \bar{U} \bar{X} \right\} \\
&= \sum_{\lambda} \text{Re} \left\{ \frac{(\bar{X} \hat{\eta}_{\lambda}^r)^2 (\Lambda_{\lambda}^r)}{\left[\omega - \left(\omega_0 + \Lambda_{\lambda}^i \right) \right]^2 + \left(\Lambda_{\lambda}^r \right)^2} \right\} \\
&\quad - \text{Im} \left\{ \frac{(\bar{X} \hat{\eta}_{\lambda}^r)^2 \left[\omega - \left(\omega_0 + \Lambda_{\lambda}^i \right) \right]}{\left[\omega - \left(\omega_0 + \Lambda_{\lambda}^i \right) \right]^2 + \left(\Lambda_{\lambda}^r \right)^2} \right\}
\end{aligned} \tag{25}$$

where the contribution to the absorption centered at $-\omega_0$ has been dropped. The absorption part of the EPR spectrum at fixed frequency and variable field B_0 is proportional to the derivative $dI(\omega_0, g\mu_B B_0/\hbar)/dB_0$.

We now turn to the calculation of the spectral densities in our model of the Hamiltonian fluctuations. In the calculation of the spectral densities defined by equation (12):

$$J_{\alpha\beta\alpha'\beta'}(\omega) = \int_0^{+\infty} \overline{\langle \alpha | H_{1S}^L(t) + H_{1T}^L(t) | \beta \rangle \langle \beta' | H_{1S}^L(t-\tau) + H_{1T}^L(t-\tau) | \alpha' \rangle} e^{-i\omega\tau} d\tau
\tag{26}$$

we find a term involving only the rotation dependent modulation of the static part of the crystal field described by H_{1S}^L , a pure transient term involving only H_{1T}^L , and cross terms. By assuming that the stochastic

fluctuations described by H_{1T}^M are independent from the rotations, the cross terms vanish. Assuming that the complex undergoes a Brownian rotation with a characteristic $\tau_D = 1/D_R$ (D_R being the rotational diffusion constant) we write

$$\tau_k = \tau_D / \{k(k+1)\} \quad (27)$$

Since 2nd order effects are most commonly used in the description of magnetic relaxation processes in solution, we follow the convention that $\tau_R = \tau_2 = \tau_D/6$. When comparing results from different studies, care must be taken to understand the respective definitions, either $\tau_R = \tau_2$ (frequently used by various authors) or $\tau_R = \tau_D$ (Rast *et al.*, 2001b; Rast *et al.*, 1999; Rast *et al.*, 2000). By inserting the Hamiltonian expression (7) into equation (12) and using the orthogonality property (28)

$$\overline{D_{pq}^{k*}(R(t))D_{p'q'}^{k'}(R(t-\tau))} = \frac{1}{2k+1} e^{-|\tau|/\tau_k} \delta_{kk'} \delta_{pp'} \delta_{qq'} \quad (28)$$

we obtain the following expression for the spectral densities:

$$J_{\alpha\alpha' \beta\beta'}(\omega) = \sum_{q,q'} \sum_k \sum_{\eta,\eta'} \frac{1}{2k+1} b_q^{k\eta*} b_q^{k\eta'} B^{k\eta} B^{k\eta'} \int_0^\infty e^{i\omega\tau} e^{-\tau/\tau_k} \langle \alpha | \tilde{T}_{q'}^k | \alpha' \rangle \langle \beta | \tilde{T}_{q'}^k | \beta' \rangle^* dt \quad (29)$$

In equation (29), the integral can be rewritten in terms of $3j$ symbols using the Wigner-Eckart theorem and evaluated, taking into account the imaginary part of the transform according to equation (23) and the selection rules $\alpha = \alpha' + q'$ and $\beta = \beta' + q'$:

$$J_{\alpha\alpha' \beta\beta'}(\omega) = \sum_k \frac{1}{2k+1} \left| \langle S || T^k || S \rangle \right|^2 \left(\frac{\tau_k}{1 + \omega^2 \tau_k^2} + i \frac{\omega \tau_k^2}{1 + \omega^2 \tau_k^2} \right) \times \sum_{\eta} (B^{k\eta})^2 (-1)^{S-\alpha} \begin{pmatrix} S & k & S \\ -\alpha & \alpha - \alpha' & \alpha' \end{pmatrix} (-1)^{S-\beta} \begin{pmatrix} S & k & S \\ -\beta & \beta - \beta' & \beta' \end{pmatrix} \quad (30)$$

with the reduced matrix element $\langle S \| T^k \| S \rangle = \sqrt{\frac{(k!)^2 (2S + k + 1)!}{2^k (2k)! (2S - k)!}}$.

Let us now consider the contribution of the transient ZFS interaction to the relaxation matrix. It is very difficult to treat all the relevant effects (solvent collisions, coordination shell rearrangements) in a rigorous way. For this reason we use a simplified (2nd order) transient ZFS Hamiltonian similar to the one of most authors (Powell *et al.*, 1993; Rubinstein *et al.*, 1971):

$$\hat{H}_{1T}^L(t) = \sum_{\eta} B^{2\eta T}(t) \sum_{p,q=-2}^{+2} b_q^{2\eta T} \hat{H}_q^2 D_{pq}^2(R(t)) \quad (31)$$

In equation (31), $B^{2\eta T}$ is a time dependant real random function. We assume its time correlation function to be given by the simple form:

$$\overline{B^{2\eta T}(t) B^{2\eta T}(t - \tau)} = (B^{2\eta T}(0))^2 e^{-|\tau|/\tau_v} \quad (32)$$

τ_v being a unique characteristic correlation time. As mentioned earlier, the cross correlation terms vanish due to the independence of the rotations and the effects leading to the transient ZFS. Choosing orthonormal coefficients $b_q^{2\eta T}$ according to equation (5) and using the orthogonality property (28), we obtain the following expression for the transient ZFS spectral densities:

$$J_{\alpha\alpha', \beta\beta'}^T(\omega) = \frac{1}{5} \left| \langle S \| T^2 \| S \rangle \right|^2 \left(\frac{\tau'}{1 + \omega^2 \tau'^2} + i \frac{\omega \tau'^2}{1 + \omega^2 \tau'^2} \right) \times \sum_{\eta} (B_{2\eta T}(0))^2 (-1)^{S-\alpha} \begin{pmatrix} S & 2 & S \\ -\alpha & \alpha - \alpha' & \alpha' \end{pmatrix} (-1)^{S-\beta} \begin{pmatrix} S & 2 & S \\ -\beta & \beta - \beta' & \beta' \end{pmatrix} \quad (33)$$

with a combined correlation time τ' defined by $1/\tau' = 1/\tau_v + 1/\tau_2$. Adding expressions (30) and (33) yields the complete spectral densities necessary for the calculation of the Redfield matrix elements in equation (12). Consequently, the matrix elements can be expressed in terms of a reduced number of independent adjustable parameters, namely:

- for each value of $k = 2, 4, 6$, a static ZFS magnitude parameter $a_k = \sqrt{\sum_{\eta} (B^{k\eta})^2}$
- the correlation time τ_D (or equivalently the rotational diffusion constant D_R) which provides the τ_k through equation (27);
- the transient ZFS magnitude parameter $a_{2T} = \sqrt{\sum_{\eta} (B^{2T}(\eta))^2}$;
- the transient ZFS fluctuation correlation time τ_v .

For completeness on further parameter must be added for the line shape calculation according to equation (25), i.e. the natural g -factor of the molecule. Furthermore, it is assumed that the correlation times have a temperature dependence described by an Arrhenius law with respective activation energies E_R for the rotations and E_v for the vibrations:

$$\tau_D = \tau_D^{298} \exp\left\{\frac{E_R}{R} \left(\frac{1}{T} - \frac{1}{298.15}\right)\right\} \quad (34)$$

$$\tau_v = \tau_v^{298} \exp\left\{\frac{E_v}{R} \left(\frac{1}{T} - \frac{1}{298.15}\right)\right\} \quad (35)$$

We see that the two contributions are additive at the Redfield matrix elements level. However it is not generally possible to separate them in the final effect (the magnetization decay) since the eigenvectors and transition intensities depend on the input parameters, as already recognized for the simple 2nd order ZFS mechanism (Hudson and Lewis, 1970).

2.2.3 Consequences for ¹H and ¹⁷O NMR

We give in this section a brief outline of the consequences of the presented electron spin relaxation model in the analysis of the ¹H and ¹⁷O NMR relaxation data of Gd(III) complexes in solution. For such studies, a good understanding of the electron spin relaxation is an important step towards a more rational design of MRI contrast agents. In this respect, HF EPR is a very important tool in sight of the high magnetic fields used in these experiments (4.7 T and more for ¹⁷O NMR).

Since most of the equations relevant for NMR have been frequently presented in the literature (Caravan *et al.*, 1999a; Merbach and Tóth, 2001), we will only describe the modifications brought by our electron spin relaxation model.

2.2.3.1 Time correlation functions

NMR time correlation functions in the absence of cross-relaxation can be written as a product of the time correlation functions for the various active relaxation mechanisms (Vigouroux *et al.*, 1999):

$$g(t) = g_a(t)g_b(t)\dots g_x(t) \quad (36)$$

The 1D NMR line shape is simply the Fourier transform of the overall time correlation function:

$$I(\omega) = \int_0^{\infty} e^{-i\omega t} g(t) dt \quad (37)$$

In the case of solutions of paramagnetic agents, this leads eventually to the well-known equations of Solomon-Bloembergen (Bloembergen, 1957; Bloembergen and Morgan, 1961) and Freed (Freed, 1978; Hwang and Freed, 1975) for ^1H relaxation, and to the Swift-Connick (Swift and Connick, 1962) equations for ^{17}O .

Whereas it is observed that the longitudinal relaxation can be adequately described by a single correlation time T_{1e} (i.e. $g_{ze}(t) = \exp(-t/T_{1e})$), the transverse relaxation function of $S = 7/2$ ions is generally a combination of four time correlation functions with different intensities I_k , and characteristic times T_{2ek} , $k = 1..4$.

$$g_{xe}(t) = \sum_{k=1}^N I_k \exp(-t/T_{2ek}) \quad (38)$$

Consequently, this multi-exponential behavior should be reflected in all equations where transverse electronic relaxation plays a role.

2.2.3.2 Outer-sphere relaxivity

Outer sphere relaxivity describes the contribution to relaxivity due to solvent molecules in the neighborhood of the paramagnetic center. As found

by Freed (Freed, 1978), the spectral density for dipolar relaxation modulated by free diffusion and finite electronic relaxation is given by equation (39).

$$J_n(\omega) = 2 \operatorname{Re} \int_0^{\infty} G(t) \exp\left([-i\omega + 1/T_{ne}]t\right) dt, \quad n = 1, 2 \quad (39)$$

where $G(t)$ is the time correlation function obtained from the solution of Smoluchowski's diffusion equation. If we now substitute the electronic decaying exponential with our expression of $g_{xe}(t)$ (equation (38)) we obtain the correct form of $J_2(\omega)$:

$$\begin{aligned} J_2(\omega) &= 2 \operatorname{Re} \int_0^{\infty} G(t) g_{xe}(t) \exp(-i\omega t) dt = 2 \sum_{k=1}^4 \operatorname{Re} I_k \int_0^{\infty} G(t) \exp\left([-i\omega + 1/T_{2ek}]t\right) dt \\ &= \sum_{k=1}^4 I_k J_{2 \text{ Freed}}(\omega, T_{2ek}) \end{aligned} \quad (40)$$

Thus we see that the effect of a multi-exponential electronic relaxation is only to replace the single T_{2e} -dependant spectral density with a linear combination of individual spectral densities with respective coefficients I_k , $k = 1..4$. Incidentally, the effect of the dynamic frequency shift (imaginary part of T_{2ek}) is negligible as it is always small compared to the electronic frequency ω used for J_2 .

2.2.3.3 Inner-sphere relaxivity and ^{17}O longitudinal relaxation

Inner sphere relaxivity is the contribution caused by water molecules directly bound to the paramagnetic center and transferred. Both ^1H and ^{17}O inner-sphere longitudinal dipolar relaxation rates depend on the transverse electronic relaxation through the second dipolar correlation time τ_{d2} defined by equation (41).

$$\frac{1}{\tau_{d2}} = \frac{1}{\tau_m} + \frac{1}{\tau_R} + \frac{1}{T_{2e}} \quad (41)$$

This definition expresses the relative independence of the chemical exchange, molecular rotation and electronic relaxation processes that modulate the dipolar interaction. Similarly to the previous example, the corresponding spectral density must then be rewritten as equation (42).

$$\begin{aligned}
J_2(\omega) &= \int_0^{\infty} g_M(t)g_R(t)g_{xe}(t) \exp(-i\omega t) dt = \sum_{k=1}^4 I_k \int_0^{\infty} g_M(t)g_R(t) \exp\left([-i\omega + 1/T_{2ek}]t\right) dt \\
&= \sum_{k=1}^4 I_k J_{2, std}(\omega, T_{2ek})
\end{aligned} \tag{42}$$

However, one may question the independence of the relaxation mechanisms. Indeed, electronic relaxation is itself a function of rotational diffusion, which modulates the static crystal field in the laboratory frame. The consequences of this correlation are twofold (Kowalewski *et al.*, 1985): (i) cross relaxation effects appear between the nuclear dipolar relaxation and the electron relaxation, and (ii) cross terms also appear between the dipolar and scalar relaxation processes. We can overlook (i) since it only affects the transverse nuclear relaxation (Benetis *et al.*, 1983a), and thus plays no role in our study of ^1H relaxation where only T_1 is considered. The second effect, arising from the artificial separation of the electron-nucleus coupling into two contribution, can also be neglected for the inner-sphere protons where scalar relaxation is negligible. For ^{17}O , one should in principle take this effect into account. However, in our case it can be conveniently neglected, as it is only important when the time-dependant interaction (static crystal field) is stronger than the electron Zeeman interaction (Benetis *et al.*, 1983b; Benetis *et al.*, 1984). In the conditions of ^{17}O -NMR (minimum external field 1.4 T in our data), this is not the case for the Gd(III) aqua ion, nor for any of the polyaminocarboxylate complexes studied so far.

The same argument might be raised regarding chemical exchange (which modulates the crystal field tensor by changing the coordination sphere). This does not hold for Gd(III) complexes where chemical exchange is at least two orders of magnitude slower than electronic relaxation: we can safely assume a fixed coordination sphere (except for small vibrations) on the EPR time scale.

2.2.3.4 ^{17}O transverse (scalar) relaxation

In a very similar manner, the scalar relaxation mechanism dominating the transverse relaxation of inner sphere ^{17}O is influenced by T_{2e} through the second scalar correlation time τ_{2S} :

$$\frac{1}{\tau_{2S}} = \frac{1}{\tau_m} + \frac{1}{T_{2e}} \tag{43}$$

The spectral densities should therefore be substituted accordingly, yielding equation (44).

$$\frac{1}{T_{2sc}} = \frac{(A/h)^2}{3} S(S+1) \left[\tau_{1S} + \sum_{k=1}^4 I_k \frac{\tau_{2Sk}}{1 + \omega^2 \tau_{2Sk}^2} \right] \quad (44)$$

There is no need to consider cross-relaxation effects in this case, since the dipolar contribution is negligible compared to the scalar term.

2.2.4 Computational details

As briefly mentioned earlier, only 4 out of the 7 eigenvectors of the $R_{2\alpha\beta}$ transverse relaxation matrix lead to non zero intensities. Indeed the Redfield matrix is symmetric (Rast *et al.*, 2000) with respect to the principal diagonal ($R_{\alpha\alpha'\beta\beta'} = R_{\beta\beta'\alpha\alpha'}$) and the antidiagonal ($R_{\alpha\alpha'\beta\beta'} = R_{\beta'\beta\alpha'\alpha}$). Thus we are able to transform the matrix in block-diagonal form by a similarity transformation with the symmetric matrix T :

$$T = T^{-1} = \begin{cases} \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & & & & 1 \\ & \dots & & & \\ & & 1 & 1 & \\ & & 1 & -1 & \\ & \dots & & & \dots \\ 1 & & & & -1 \end{pmatrix} & \text{(even-sized } R) \\ \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & & & & 1 \\ & \dots & & & \\ & & 1 & 1 & \\ & & & \sqrt{2} & \\ & & 1 & -1 & \\ & \dots & & & \dots \\ 1 & & & & -1 \end{pmatrix} & \text{(odd-sized } R) \end{cases} \quad (45)$$

The transformed matrix $TR_{2\alpha\beta}T$ is reduced to block diagonal form with two blocks. We need then only diagonalize the block for which $\Sigma_{\beta} T_{\alpha\beta} X_{\beta}(0) \neq 0$ so that $(X\eta_{\lambda})^2 \neq 0$ in equation (25). The same procedure

can be used for the longitudinal matrix $R_{1\alpha\beta}$. We obtain two reduced relaxation matrices $R_1 = TR_{1\alpha\beta}T$ and $R_2 = TR_{2\alpha\beta}T$ with the general form:

$$R_{i=1,2} = \sum_k \left\langle S \| T^k \| S \right\rangle^2 a_k^2 \begin{pmatrix} A & E & H & J \\ E & B & F & I \\ H & F & C & G \\ J & I & G & D \end{pmatrix} \quad (46)$$

where $k = 2, 4, 6, 2T$ and the matrix elements $A...J$ are combinations of spectral densities with linear coefficients following equations (11), (30), (33) and (45). This 4×4 block form is similar to the one obtained by Strandberg (Strandberg and Westlund, 1996) using the simple 2nd order ZFS relaxation mechanism. It not only reduces the computational cost of the fitting procedure, but also avoids some numerical problems due to the presence of almost degenerate eigenvalues of the $R_{2\alpha\beta}$ matrix.

Let us now consider the fitting procedure in more detail. The measured EPR spectra are a superposition of absorption and dispersion contributions and of a base line which is a linear function of the magnetic field B_0 . For a given set of the nine fitting parameters ($a_2, a_4, a_6, a_{2T}, \tau_R, E_R, \tau_v, E_v$ and g), the theoretical spectrum is then

$$\frac{d\varphi^{th}(B_0)}{dB_0} = \xi_1 \frac{d\varphi_a^{th}(B_0)}{dB_0} + \xi_2 \frac{d\varphi_d^{th}(B_0)}{dB_0} + \xi_3 B_0 + \xi_4 \quad (47)$$

where $d\varphi_a/dB_0$ is the derivative of the absorption line shape (25), and $d\varphi_d/dB_0$ is the derivative of the dispersion contribution (Rast *et al.*, 2001b). Thus, for each experimental spectrum $d\phi_n^{exp}/dB_0$, where the index n corresponds to a particular temperature and frequency, the associated theoretical spectrum is that given by the parameters $\xi_{1n}, \xi_{2n}, \xi_{3n}, \xi_{4n}$. which minimize the difference between the experimental spectrum and the spectrum calculated from the nine adjustable parameters using equations (25) and (47). It was especially important to acknowledge the dispersion contribution in order to analyze our HF EPR spectra, where the experimental phasing procedure at measurement time was not always able to yield pure absorption spectra.

The central field B_c^{th} and the peak-to-peak distance ΔH_{pp}^{th} can be extracted from the expression of the absorption line shape by searching the zeros of the first and second derivatives.

2.3 Beyond the Redfield limit

The presented approach has been developed within the framework of the Redfield theory of magnetic relaxation. It is then only valid if the two following conditions are verified:

$$|H_1|\tau_c \ll 1 \quad (48)$$

$$|H_1|^2\tau_c \ll \omega_0 \quad (49)$$

where ω_0 is the unperturbed Zeeman angular frequency, H_1 the time dependent perturbing Hamiltonian inducing electronic transitions between the Zeeman levels, and τ_c is the correlation time of the fluctuating term H_1 . The first condition can be violated when we consider large, slowly tumbling complexes. When the relevant time τ_c is the rotational correlation time of the complex, its inverse which is the rotational diffusion constant D_R can reach values of the same order as H_1 , especially in the low temperature region where D_R decreases. The second condition corresponds to the secular approximation (Abragam, 1961a) and may be hardly satisfied when experiments are performed at low fields, mainly for large complexes and at temperatures just above 0 °C.

Since the problem is rather insignificant from the point of view of HF EPR, we will only briefly consider the numerical calculation of the line shape using Monte Carlo simulations (Rast *et al.*, 2001c). As mentioned earlier, we are interested in the decay of the magnetization, described by equation (50), where $i = x, y, \text{ or } z$.

$$G_i(t) = \frac{1}{2S+1} \text{tr} \overline{S_i(t)S_i(0)} \quad (50)$$

Under a time dependent Hamiltonian $H(t)$, the spin operators $S_i(t)$ are given by:

$$\hat{S}_i(t) = \hat{U}(t)^\dagger \hat{S}_i \hat{U}(t) \quad (51)$$

where $U(t)$ is the unitary time evolution operator satisfying the Schrödinger equation (52)

$$\frac{d\hat{U}(t)}{dt} = -i\hat{H}(t)\hat{U}(t) \quad (52)$$

with the initial condition $U(0) = 0$. The numerical resolution of this equation can be performed by generating a large number (500-3000) of independent realizations of the L frame Hamiltonian $H_1^L(t)$ (equation (9)). For each realization, equation (52) is integrated over a time interval $[0, t_{max}]$ using a short enough time step Δt so that we can approximate $H(t)$ by $H(n\Delta t)$ for $n\Delta t \leq t \leq (n+1)\Delta t$. The time evolution operator is then given by:

$$\hat{U}((n+1)\Delta t) = e^{-i\hat{H}(n\Delta t)\Delta t}\hat{U}(n\Delta t)$$

Practically, the realizations of $H_1^L(t)$ require two different steps, namely the simulation of the transient ZFS crystal field parameters $B^{2\eta^1}(t)$ and that of the Wigner matrices expressing the transformation from the molecular frame into the laboratory frame.

This briefly outlined technique, implemented in a computer program, allows a systematic study of the validity of the Redfield approximation for a given set of crystal field parameters and correlation times. The calculations performed using the available data on $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ and $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ (see below) showed that for such small complexes the Redfield limit is not a problem at the usually available EPR frequencies (X-band and above) at any temperature between 0 and 100 °C (Rast *et al.*, 2001c). However, at lower magnetic field (0.1 T and below) the Redfield theory overestimates the electron spin relaxation rate by 15 % or more. This point is an important one for the analysis of NMR relaxation data in the presence of Gd(III) complexes, as shown in the following section.

3. RECENT RESULTS AND DEVELOPMENTS

The successful application of the theory to recent experimental data is presented and discussed.

3.1 Analysis of multiple frequency and temperature spectra of Gd(III) complexes

Extensive data has been obtained (Borel *et al.*, 2001; Borel *et al.*, 2000) for full EPR spectra of $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ and $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ in water at various concentrations at the spectrometer frequencies of 9.425 GHz, 75 GHz, 150 GHz, and 225 GHz, and temperatures between 0 °C and 100 °C.

A significant source of uncertainty in the determination of the model parameters arises from the extraction of the peak-to-peak distances ΔH_{pp}^{exp} and central fields B_c^{exp} which are biased, whatever the extraction method.

Indeed, for each experimental spectrum, the associated peak-to-peak distance and apparent g -factor are those of a theoretical spectrum of the form (47) which best fits the experiments and obviously corresponds to a particular molecular and line shape model. Such an indirect procedure is necessary because each experimental EPR spectrum is a superposition of absorption and dispersion contributions related to an unknown phasing problem with an additional effect of shifted and tilted baseline.

In earlier studies approximate values of ΔH_{pp}^{exp} and B_c^{exp} were obtained through two different methods. First, a direct reading procedure from the spectra was used (Borel *et al.*, 2000; Powell *et al.*, 1993) but it is particularly affected by the uncontrollable error due to the lack of knowledge of the phasing of the spectra and of the baseline positions. Second, as already done for the HF EPR (75-225 GHz) measurements in earlier papers (Borel *et al.*, 2000; Caravan *et al.*, 1999b), ΔH_{pp}^{exp} and ΔH_{pp}^{exp} can be determined by fitting a single Lorentzian curve and its corresponding dispersion part to each experimental spectrum in order to address the phase problem. This implies a monoexponential decay T_{2e} of the transverse magnetization, which is clearly inadequate in sight of our physical relaxation model involving four different exponentials. However, we found that a single Lorentzian line almost perfectly fits the different $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ spectra whereas the spectra of $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ are less well reproduced, but the values of T_{2e} do not correspond to a true physical description of the system and are only independent fitted parameters. Nevertheless, the comparison of peak-to-peak distances and central fields from theory and experiment remains a comprehensive way to present the results.

For all these reasons, in this work, the crystal field parameters, correlation times, activation energies, and g -factors were adjusted simultaneously, within our physical model, to the whole set of full, not phase corrected, spectra as described in the computational details section.

In figure 1, we show some examples of experimental spectra and their counterparts calculated from our best fitting model for the $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ complex. To summarize the results, we calculated the peak-to-peak distances and central fields of the theoretical absorption spectra and compared them with the data extracted from the experimental spectra used in the fit. In figure 2, for the convenience of the graphical representation, we do not show the central fields, but we depict the apparent g -factor g^{app} which is defined by

$$g^{app} = \frac{h\omega}{\mu_B B_c} \quad (53)$$

where ω is the operating frequency of the spectrometer and B_c the central field. The continuous lines are the results for ΔH_{pp}^{th} and B_c^{th} from our model using the parameters shown in table 1.

3.1.1 $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$

The $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ complex is discussed in more detail because the known square antiprism symmetry of the static crystal field allows a deeper insight in the physics of this complex.

The numerical adjustment of the theoretical spectra to the experimental data with respect to the nine adjustable parameters is rather difficult because of possible mutual compensation effects. We found that the g -factor is very well determined at the end of a least-square fit whereas it is more difficult to adjust the other parameters. We decided to start from the parameters of the previous work by Rast (Rast *et al.*, 2000) including the 4th and 6th order crystal field contributions, but limited to the peak-to-peak distance analysis. The rotational correlation time τ_D was fixed at 140 ps and the corresponding activation energy E_R at 18.9 kJ/mol in the fitting procedure in order to maintain them at the values predicted by the Stokes-Einstein model as discussed by Rast (Rast *et al.*, 2000). The guessed starting value of the g -factor was 1.9927. **The constraint minimization led to a value of $F_{min} = 0.014$ of F_S which is somewhat lower than the value 0.019 found for F_S using the initial parameters and the above g value.**

The agreement with experimental line shapes, peak-to-peak distances, and dynamic shifts for all the studied frequencies and temperatures is excellent for the new parameter set as it is demonstrated in figure 1 for typical examples of whole spectra and in figure 2a for the peak-to-peak distances and apparent g -factors. The line shape is very well reproduced even in the wings of the spectra, underlining the quality of our fit.

It should be stressed that it was not necessary to include any contribution from the spin rotation mechanism in our model in order to interpret the various experiments. This contribution to the transverse relaxation, which is independent of the spectrometer frequency, was introduced in other works to account for an excess electron spin relaxation rate in ^{17}O NMR measurements (Powell *et al.*, 1996) or HF EPR spectra (Borel *et al.*, 2000). It generally led to an approximate agreement with the experimental data. It does not seem to be effective, a result quite understandable according to the large size and therefore to the large inertial moment of the magnetic complex (Nyberg, 1967). A good agreement with the experiments is possible only with two different, but frequency dependent crystal field contributions. The

short correlation time for the transient ZFS ($\tau_v \sim 1$ ps) is such that the corresponding spectral densities will not vanish even at very high frequencies. We observed that the contribution of the static crystal field Hamiltonian is dominant at X-band, but is far less important at higher frequencies.

For the g -factor, we found reasonable values comparable to those in other Gd(III) salts in solids (Abragam and Bleaney, 1970). The perfect agreement of the experimental spectra with their theoretical counterparts in the framework of our model justifies the choice of τ_D and $E_R = 18.9$ kJ/mol from the Stokes-Einstein model of rotational diffusion (Rast *et al.*, 2001b; Rast *et al.*, 2000). These values are in reasonable agreement with $\tau_D = 6\tau_R = 246$ ps and $E_R = 15$ kJ/mol deduced from independent NMR experiments (Powell *et al.*, 1996).

The total crystal field splitting of the 8S multiplet can be calculated thanks to the D_{4d} symmetry of the $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ complex (Rast *et al.*, 2000). The crystal field Hamiltonian reduces to:

$$\hat{H} = \sum_{k=2,4,6} B^k \hat{T}_0^k \quad (54)$$

where T_0^k is an irreducible tensor of order k (Buckmaster *et al.*, 1972), and the coefficients B^k are such that $a_k = |B^k|$. From the diagonalization of the crystal field Hamiltonian we obtained a total crystal field splitting of the order of 0.4 cm^{-1} whatever the choice of the signs of the coefficients B^2 , B^4 , B^6 . This value is in reasonable agreement with that observed for Gd(III) in lanthanum ethylsulfate (0.25 cm^{-1}) in the solid state (Abragam and Bleaney, 1970).

It is not very useful to compare our crystal field parameters a_2 and a_{2T} to the zero-field splitting parameter Δ^2 of previous works (Borel *et al.*, 2000; Powell *et al.*, 1993; Powell *et al.*, 1996), because Δ^2 reflects an averaged effect of the transient and static zero-field splitting. This is a consequence of the rather simple model including only one second order term in the Hamiltonian and a unique correlation time in order to describe all the crystal field fluctuations.

An important interest in understanding the EPR spectra of Gd(III) complexes lies in the evaluation of the longitudinal electronic relaxation for the study of the NMR relaxation of protons in presence of these complexes. It was observed that $G_z(t)$ is practically a mono-exponential function with a characteristic time T_{1e} having a relative weight of at least 97 % (Rast *et al.*, 2001b; Rast *et al.*, 2000).

3.1.2 [Gd(DOTA)(H₂O)]⁻

In the fitting procedure of the whole set of experimental spectra for the [Gd(DOTA)(H₂O)]⁻ complex we have to be more cautious than in the previous case. The rotation correlation time is longer than for the [Gd(H₂O)₈]³⁺ complex so that the Redfield limit may be violated at low temperatures, mainly for the X-band (Rast *et al.*, 2000). Therefore, the spectra recorded at temperatures lower than 17 °C were not included in the fit. In a first adjustment, we fixed $a_4 = a_6 = 0$ in order to reduce compensation effects between the parameters. In subsequent adjustments we let freely vary also a_4 and a_6 , but their values remained negligible. The lower limit of the activation energy E_v was set to 6 kJ/mol. The quality of the adjustment of the spectra is almost as good as for [Gd(H₂O)₈]³⁺ **as shown by the similar value of F_{min} of F_S** . We neglected the fact that the m-[Gd(DOTA)(H₂O)]⁻ isomer exists in an approximately 4-fold lower quantity besides the M-[Gd(DOTA)(H₂O)]⁻ isomer (Aime *et al.*, 1997b) in order to avoid the introduction of too many parameters. Nevertheless, the agreement with the experiments is good, without any spin rotation mechanism.

The theoretical and experimental values for the peak-to-peak distances and the apparent g -factor g^{app} for the [Gd(DOTA)(H₂O)]⁻ complex are presented in figure 2b. It must be stressed that the so-called "experimental" peak-to-peak distances and apparent g -factors are less well defined as in the case of the aqua complex since the experimental line shapes are no more Lorentzian. The rotational correlation time $\tau_D^{298} = 487$ ps is very close to that $6\tau_R^{298} = 462$ ps of NMR studies (Powell *et al.*, 1996). The activation energy for the rotation of the complex is about the same as for the hydrated Gd(III) complex. This is expected in the framework of the Stokes-Einstein model for a Brownian rotation in a viscous medium. The rotational correlation time τ_D^{298} is roughly proportional to the volumes of the complexes (Rast *et al.*, 2000). The ratio of the volumes of the [Gd(DOTA)(H₂O)]⁻ and [Gd(H₂O)₈]³⁺ complexes is estimated from the corresponding Connolly surfaces (Connolly, 1983) to be 2.3, while our fits lead to a ratio of 3.5, showing the correct tendency.

In general a full knowledge of the Hamiltonian is not possible without further information because the EPR study does not give access to the coefficients $B^{k\eta}$ in the static crystal field Hamiltonian (4), but only to the parameters a_k which are the roots of the sums of $(B^{k\eta})^2$ according to equation (30). In the present case, $B^{4\eta}$ and $B^{6\eta}$ can be approximated to zero according to the very weak values of a_4 and a_6 obtained with our fitting procedure (see Table 2). The total static crystal field splitting of the $S = 7/2$ multiplet was found to be 0.26 cm⁻¹. For both [Gd(DOTA)(H₂O)]⁻ isomers,

the symmetry group is C_4 , leading to 3 invariant linear combinations, both for $k=4$ and for $k=6$. So, we need three coefficients $B^{4\eta}$, $\eta = 1, 2, 3$ and three coefficients $B^{6\eta}$, $\eta = 1, 2, 3$ in order to define the static crystal field Hamiltonian.

As for the hydrated Gd(III) ion, the adjusted g -factor is in reasonable agreement with known g values for Gd(III) hydrated salts (Abragam and Bleaney, 1970).

Table 1. Electron spin relaxation parameters obtained by least square fitting

	$[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$	$[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$
$a_2 [10^{-10} \text{ s}^{-1}]$	0.38	0.35
$a_4 [10^{-10} \text{ s}^{-1}]$	0.024	0
$a_6 [10^{-10} \text{ s}^{-1}]$	0.021	0
$\tau_R [\text{ps}]$	23.3	81.8
$E_R [\text{kJ/mol}]$	18.9	16.4
$a_{2T} [10^{-10} \text{ s}^{-1}]$	0.65	0.43
$\tau_v [\text{ps}]$	0.63	0.54
$E_v [\text{kJ/mol}]$	9.2	6.0
g	1.99273	1.99252

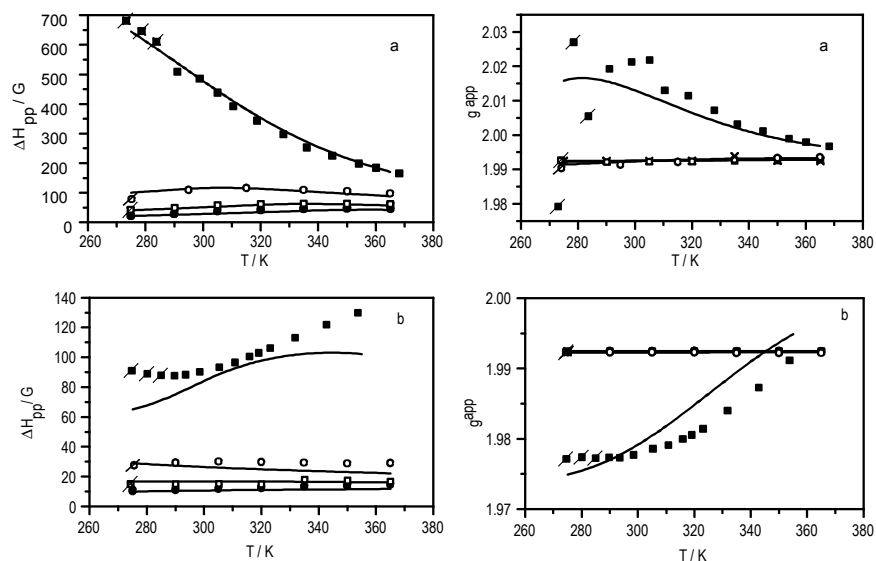


Figure 2. fits

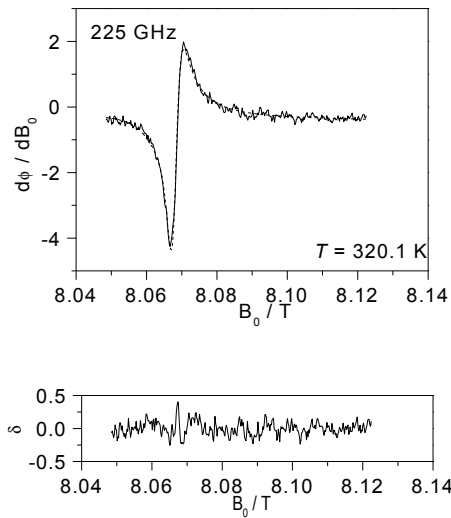


Figure 3. aqua ion 320.1 225

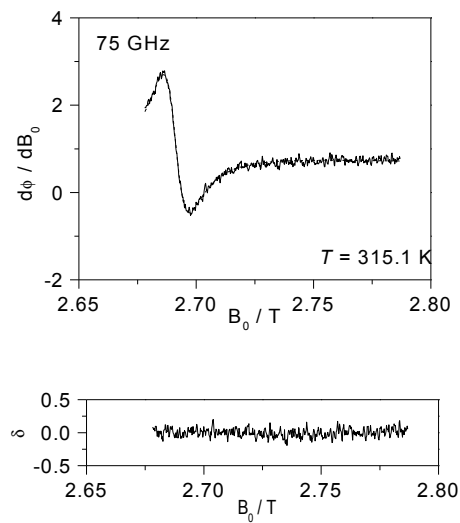


Figure 4. aqua ion 315 75

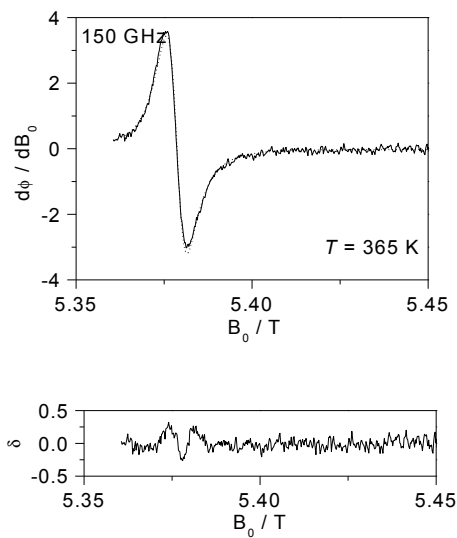


Figure 5. aqua ion 365 150

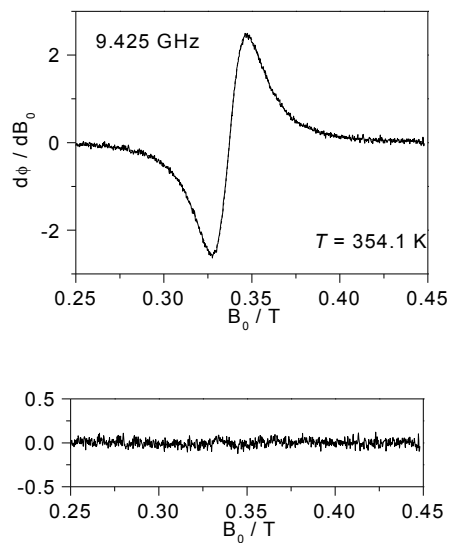


Figure 6. aqua ion 354.1 X

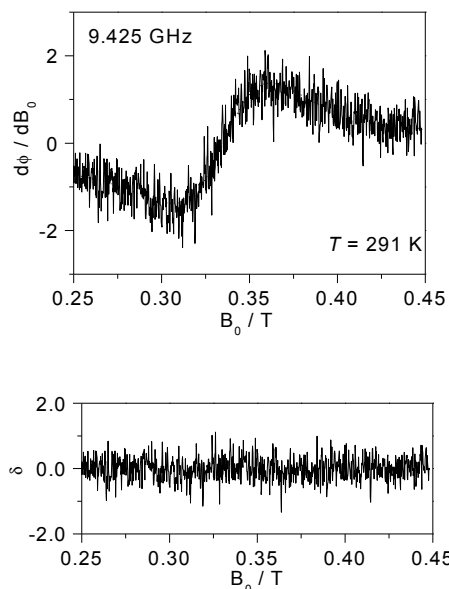


Figure 7. aqua ion 291 K

3.2 Combined analysis of NMR and EPR relaxation data

We performed a non-linear least square fitting of the combined model of $^{17}\text{O}/^1\text{H}$ NMR and EPR presented in the theoretical section against the extensive variable temperature data (Borel *et al.*, 2000; Powell *et al.*, 1996) available about the Gd(III) octa aqua ion and newly recorded NMRD profiles. The low field part of a given NMRD profile was calculated using one single average point at 0.14 MHz proton frequency with the electron spin relaxation rates obtained through a Monte Carlo simulation. The initial parameters in the fitting procedure were those of Powell (Powell *et al.*, 1996) (see Table 1) except for the following: the Gd-H relative diffusion constant was fixed to the sum of the water ($22.36 \times 10^{10} \text{ m}^2/\text{s}$ (1986)) and aqua ion ($3.9 \times 10^{10} \text{ m}^2/\text{s}$ (Vigouroux *et al.*, 1998)) self-diffusion coefficients, and the electronic parameters a_2 , a_4 , a_6 , a_{2T} , τ_v and g of Rast *et al.* (Rast *et al.*, 2001b) were used for the electronic part. The rotational correlation time τ_R was the one of Powell (41 ps), while its activation energy was restrained to reasonable values (16-19 kJ/mol) as discussed by Rast based on the temperature dependence of water viscosity. We emphasize again that τ_R reported here is the second order correlation time $\tau_2 = 1/(6 \times D_R)$ relevant for NMR. This convention is rather arbitrary from the EPR point of

view, since the fourth ($\tau_4 = 1/(20 \times D_R)$) and sixth order ($\tau_6 = 1/(42 \times D_R)$) correlation times are also used. However it allows an easier comparison with earlier simultaneous fitting studies such as Powell's. In general, care should be taken not to confuse the NMR definition ($\tau_R = \tau_2$) and the more general, six times longer rotational diffusion correlation time ($\tau_D = 1/D_R$).

The 14 free parameters in the model (room temperature water exchange rate k_{ex}^{298} , activation enthalpy ΔH^\ddagger , rotational correlation time τ_R and associated activation energy E_R , transient zero field splitting correlation time τ_v and associated activation energy E_v , ^{17}O scalar coupling constant A/h , ^{17}O quadrupolar coupling constant $\chi(1+\eta^2/3)^{1/2}$, activation energy for the relative ^1H -Gd(III) diffusion E_{GdH} , Gd(III) electronic g -factor, static (a_2, a_4, a_6) and transient (a_{2T}) crystal field parameters) were simultaneously adjusted to the multiple temperature and magnetic field/frequency data (^{17}O -NMR $1/T_1, 1/T_2$ and chemical shifts, EPR peak-to-peak width and resonance field, ^1H -NMRD above 10 MHz and an averaged low frequency point at 0.141 MHz). For the analysis of ^1H NMRD, we fixed the inner-sphere Gd-H distance to 3.05 Å instead of 3.1 Å. This shorter value was evaluated as the average between the experimental Sm-D (3.11 Å) and Dy-D (3.03 Å) obtained from neutron diffraction measurements, slightly biased towards the clearly 8-coordinated $[\text{Dy}(\text{H}_2\text{O})_8]^{3+}$ value (Cossy *et al.*, 1995). We reverted to the use of reduced values (peak-to-peak width ΔH_{pp} and central field) instead of the full EPR spectra to simplify the parallel treatment of ^{17}O -NMR and NMRD, although the analysis of the full line shape is in principle better (Rast *et al.*, 2001b). Since the deviation from the pure Lorentzian line shape was observed to be very small for $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$, the choice of method is mostly a matter of taste in this case.

The fit function was included in the more general program VISUALISEUR (Yerly, 2001), running on the MATLAB (2000) environment. We used FORTRAN subroutines derived from the EPR program used for the analysis of the full EPR in order to calculate peak to peak widths, center fields, and the electronic relaxation rates within the Redfield approximation. For low-frequency NMRD, the Monte Carlo program described in the theoretical section was used to simulate the longitudinal and transverse electron spin correlation functions, from which the effective relaxation time was extracted by a linear regression. To reduce the computation time, only 1000 time steps were used to generate the spin dynamics instead of 16000 (Rast *et al.*, 2001c). As shown in Fig. 1, this was sufficient to reproduce the relaxation times reported in the original paper, and allowed the calculation of one low-field relaxivity value in 5 minutes on a workstation (Linux on a 700 MHz AMD Duron CPU).

3.3 Results and discussion

The calculated parameters are reported in Table 1, together with the parameters obtained by Powell (Powell *et al.*, 1996). The experimental results and theoretical curves are shown in Figure 2. The agreement between the experimental data and the simulated curves is very good, even for NMRD points between 1 and 10 MHz, which were not included in the fitting procedure.

Table 2. parameters obtained through simultaneous fitting of EPR, ^{17}O -NMR and NMRD data. Underlined values were either fixed or have reached their imposed limit.

	This work (Borel <i>et al.</i> , 2002)	NMR/EPR (Powell <i>et al.</i> , 1996)	EPR only (Rast <i>et al.</i> , 2001b)
ΔH^\ddagger [kJ/mol]	18.2 ± 5	15.3	-
k_{ex}^{298} [10^6 s^{-1}]	682 ± 140	804	-
E_{R} [kJ/mol]	<u>19</u>	15.0	<u>18.9</u>
τ_{R}^{298} [ps]	35.3 ± 1	41	<u>23.3</u>
E_{v} [kJ/mol]	14.9 ± 2	-	9.2
τ_{v}^{298} [ps]	1.05 ± 0.3	-	0.63
A/\hbar [10^6 rad/s]	-5.21 ± 0.04	<u>-5.3</u>	-
D_{GdH}^{298} [$10^{-10} \text{ m}^2 \text{ s}^{-1}$]	<u>26</u>	<u>23</u>	-
E_{DGdH} [kJ/mol]	<u>22</u>	22	-
Gd-O [\AA]	<u>2.5</u>	<u>2.5</u>	-
Gd-H [\AA]	<u>3.05</u>	<u>3.1</u>	-
$\chi(1+\eta^2/3)^{1/2}$ [MHz]	6.12 ± 1.4	<u>7.58</u>	-
g	<u>1.993</u>	<u>2</u>	1.99273
a_2 [10^{10} s^{-1}]	0.0946 ± 0.14	-	0.38
a_4 [10^{10} s^{-1}]	<u>0</u>	-	0.024
a_6 [10^{10} s^{-1}]	0.0232 ± 0.003	-	0.021
$a_{2\text{T}}$ [10^{10} s^{-1}]	0.687 ± 0.04	-	0.65

In general, we observe that the parameters specific to NMR are left rather unchanged by the new model of EPR relaxation. The water exchange rate is somewhat decreased compared to the work of Powell, but within the calculated standard error. The exchange activation enthalpy is also similar to the earlier value. The scalar coupling constant is mostly unaffected by the simultaneous adjustment, since it is essentially determined by the ^{17}O chemical shifts. As discussed by Powell *et al.*, the calculated quadrupolar

coupling constant is very sensitive to the choice of the Gd-O distance so only one of these parameters should be considered adjustable. By fixing the Gd-O distance to 2.5 Å, they obtained a coupling constant of 2.0 ± 2.3 MHz (compared to 7.58 MHz for acidified water), whereas fixing the coupling constant to 7.58 yielded a Gd-O distance of 2.76 Å. Since the distance has been determined both by experimental (Kurisaki *et al.*, 1993) and theoretical methods (Hengrasmee and Probst, 1991; Schafer and Daul, 1997) to be in the 2.4-2.6 Å region, we preferred to use the fixed 2.5 Å value. Our result for $\chi(1+\eta^2/3)^{1/2}$ is 6.12 ± 1.38 MHz, and thus closer to the value for free water. It is useful to compare this value to the one determined by Leyte and coworkers (Struis *et al.*, 1987) for ^{17}O in the first coordination shell of Mg^{2+} ($\chi = 5.7 \pm 0.3$ MHz, $\eta = 0.93$). A rough estimation based on the ratio of the radial electric field gradients ($\text{Mg}^{2+}\text{-O} \approx 2.1$ Å, $\text{Gd(III)-O} \approx 2.5$ Å) yields $\chi(\text{Gd-O})/\chi(\text{Mg-O}) = 0.889$, or $\chi(\text{Gd-O}) = 5.1$ MHz. Using the same asymmetry parameter, we obtain for $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ the estimation that $\chi(1+\eta^2/3)^{1/2} = 5.8$ MHz, in very good agreement with our result.

Since the influence of the rotational correlation time on the electron spin relaxation is part of the new theory, it is not surprising that the adjusted value should change compared with the earlier studies. Indeed the rotation and the electron spin relaxation are highly correlated in our simultaneous fitting approach, since the dipolar correlation time dominating the low field relaxivity is simply the reciprocal sum of the electron spin relaxation time and the rotational correlation time (see equation (41)). Therefore, the fitting procedure imposes rather strict constraints on this parameter, even more so since we have set boundaries compatible with the temperature dependence of the viscosity of water for the activation energy. The value we obtain (35.3 ± 1.0 ps) is certainly compatible with the estimations based on the Stokes Einstein relation (22 ps if a microviscosity correction factor is included, 53 ps if it is not (Rast *et al.*, 2000)).

The change in the rotation correlation time is reflected by a change in the crystal field parameters compared with the EPR-only analysis. In turn, this affects the Gd(III) g -factor since this parameter is essentially determined by the EPR resonance field, where the electron spin relaxation induces dynamic frequency shifts (Fraenkel, 1965; Poupko *et al.*, 1974). These shifts become smaller at high frequencies, so HF EPR gives us a good estimation of the natural g -factor. Based on earlier studies in the solid (Abragam and Bleaney, 1970) and in solution (Rast *et al.*, 2001b), we set an upper boundary of 1.9930 for g . Even if the calculated value has hit this limit, the final adjustment is very good as can be seen from temperature and spectrometer frequency dependence of the apparent g -factor, g^{app} (Fig. 2).

The transient zero field splitting parameters a_{2T} , τ_v and E_v are very close to those obtained through EPR only. Thus their effect on the EPR line shape

(negligible at X-band, increasing contribution at higher frequencies) is essentially the same. This means that the crystal field parameters obtained by solution EPR only are not very precisely determined. In particular, error compensation between the 5 parameters in question ($a_2, a_4, a_6, \tau_R, E_R$) during the fit seems to be a serious problem, that could be solved through the use of independent constraints (based either on NMR, or solid state EPR, or maybe taking advantage of the recently developed methods for the direct determination of T_{1e} (Atsarkin *et al.*, 1995).

With our parameters, the 4th order contribution vanishes, so there are only two possible combinations for the crystal field Hamiltonian (54). Either B^2 and B^6 have the same sign, with a total splitting of 0.37 cm^{-1} , or their sign is different and the splitting is 0.38 cm^{-1} . One of the terms is obviously dominant, and indeed we find that the 6th order contribution alone leads to a splitting of 0.36 cm^{-1} . It is somewhat strange that the highest order term should contribute so much to the effect. There may be some compensation between the various orders, as it has been noted in the pure EPR studies (Rast *et al.*, 2001b). Nevertheless the overall value is in reasonable agreement with the available direct experimental measurements (0.25 cm^{-1} for Gd(III) in a solid lanthanum ethyl sulfate matrix (Abragam and Bleaney, 1970)).

Using our parameters, the low field limit of the electron relaxation time in the Redfield approximation is 89 ps at 298 K for both T_{1e} and T_{2e} , and 60 ps at 283 K. The MC simulation yields longer values, with $T_{1e} = 122 \text{ ps}$, $T_{2e} = 117 \text{ ps}$ at room temperature, and $T_{1e} = 95 \text{ ps}$ and $T_{2e} = 90 \text{ ps}$ at 283 K. These small apparent differences between T_{1e} and T_{2e} can be explained by numerical errors. The Redfield error can thus be estimated to 25 % at room temperature (similar to the result calculated from the parameter set obtained by EPR only (Rast *et al.*,)) and 36 % at 283 K. In the NMRD profile, at low field ($< 1 \text{ MHz}$), τ_R and $T_{1,2e}$ are strongly correlated. Since τ_R is usually well known from ^{17}O and ^1H -NMR experiments at higher fields, it is tempting to obtain microscopic electron spin parameters (τ_{S0} , Δ^2 or a_k and the respective correlation times depending on the model) based on these measurements. However, to extract either of these quantities using a simple Solomon-Bloembergen-Morgan-like approach of the electron spin relaxation will probably yield results irrelevant at higher magnetic fields where the Redfield theory becomes applicable. Since the influence of $T_{1,2e}$ on NMR decreases at higher fields (rotation becoming the dominant term for dipolar relaxation), it is quite conceivable to obtain in this fashion electron spin parameters compatible with ^{17}O -NMR and NMRD, but failing to describe EPR experiments.

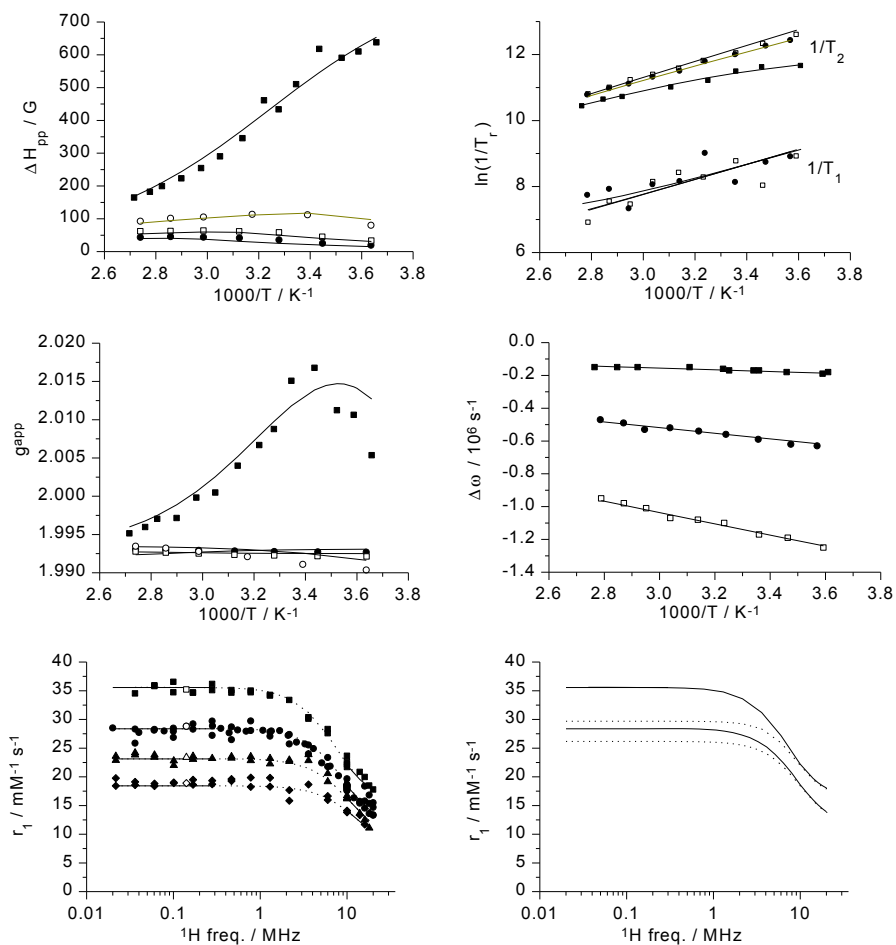


Figure 8. EPR peak-to-peak width and apparent g -factor at X-band (■), 75 GHz (○), 150 GHz (□) and 225 GHz (●); reduced ^{17}O relaxation rates and chemical shifts at 1.41 T (□), 4.7 T (●) and 9.4 T (■). NMRD profiles at 283.2 K (■), 298.2 K (●), 310.4 K (#), 323.0 K (◆) with the empty symbols corresponding to averaged values over the low-field part of the profile; comparison with the predictions of Redfield's theory using the same electronic parameters at 10 °C and room temperature (dotted lines).

4. CONCLUSION AND PROSPECTIVE OUTLOOK

The availability of HF EPR has tremendously increased the range of accessible frequencies for relaxation studies. In the field of Gd(III)-based

MRI contrast agents, it allowed a systematic study of the electron spin relaxation in solution up to the high magnetic fields commonly used for modern NMR (Powell *et al.*, 1993; Powell *et al.*, 1996). As the experimental data accumulated, the shortcomings of the accepted transient 2nd order ZFS (Hudson and Lewis, 1970; Poupko *et al.*, 1974) relaxation mechanism became more visible (Aime *et al.*, 1997a). Using increasingly high frequencies, various research groups (Borel *et al.*, 2000; Smirnova *et al.*, 1998) probed the EPR line shape and found that another relaxation mechanism was required to account for the observed peak-to-peak width.

A rigorous derivation of the relaxation rates for a $S = 7/2$ ion (Rast *et al.*, 2000) and its application to the analysis of the full EPR line shape at frequencies between X-band and 225 GHz (Rast *et al.*, 2001b) showed that two qualitatively different contributions had to be taken into account. The static ZFS, modulated by the molecular tumbling in solution, has a greater contribution to the relaxation at low frequency (X-band). The transient ZFS, modulated by anharmonic vibrations and solvent collisions with a very short correlation time, becomes very significant at high frequency and/or magnetic field. With this improved physical model, it was finally possible to perform a rigorous simultaneous analysis of EPR and NMR data, where the physical meaning of all adjustable parameters was discussed (Borel *et al.*, 2002).

In the future, we hope that HF EPR will be a useful tool for a more precise determination of the molecular motions responsible for the transient ZFS modulation. Furthermore, the high frequency limit of the older theory has led to some very elegant analytical equations in the past (Clarkson *et al.*, 1998; Smirnova *et al.*, 1998) and one may imagine that a similar development could be written for the modern theory.

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