

# EPR on aqueous Gd<sup>3+</sup> complexes and a new analysis method considering both line widths and shifts

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We performed variable temperature (0–100 °C), concentration and frequency (9.425, 75, 150 and 225 GHz) continuous wave electron paramagnetic resonance (EPR) measurements on three different Gd(III) compounds: [Gd(H<sub>2</sub>O)<sub>8</sub>]<sup>3+</sup>, [Gd(DOTA)(H<sub>2</sub>O)]<sup>-</sup> (DOTA: 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecane) and [Gd(DTPA-BMA)(H<sub>2</sub>O)] (DTPA-BMA: 1,5-[bis(*N*-methylcarbamoyl)methyl]-1,3,5-tris(carboxymethyl)-1,5-diamino-3-azapentane) in aqueous solution. A simultaneous analysis of peak-to-peak widths and dynamic frequency shifts provides access to the transverse electronic relaxation, which is described using a transient zero field splitting (ZFS) mechanism with a spin rotation contribution. Our simultaneous analysis procedure involves numerical calculations using the full relaxation matrix and yields results in acceptable agreement with experimental data for reasonable values of the ZFS parameters (trace of the square of the ZFS Hamiltonian  $\Delta^2 = 10^{19}$ – $10^{20}$  s<sup>-2</sup> depending on the complex, correlation time of the fluctuations  $\tau_v^{298} = 10^{-11}$ – $10^{-10}$  s). We also discuss the relationship between our approach and recent developments found in the literature.

## 1 Introduction

Gadolinium(III) complexes with polyaminocarboxylate ligands are routinely used as magnetic resonance imaging (MRI) contrast agents.<sup>1</sup> Their activity lies in the magnetic relaxation enhancement (*relaxivity*) induced by their unpaired electrons on the water protons in tissues. This effect is governed by several correlation times, such as the rotational correlation time  $\tau_R$ , the number  $q$  and residence time  $\tau_m$  of water molecules in the first coordination sphere of the metal and the electron longitudinal  $T_{1e}$  and transverse  $T_{2e}$  relaxation times. A number of methods have been used along the years to measure these various parameters, including <sup>1</sup>H and <sup>17</sup>O-NMR, UV–visible spectroscopy. A complete understanding of the magnetic properties of these Gd(III) compounds requires the simultaneous use of all available techniques, which explains the renewed interest in the EPR spectroscopy of Gd(III) chelates in aqueous solution.<sup>2,3</sup> Although the essential theory has been established for a long time,<sup>4</sup> its application to real problems led to unsatisfactory results when it came to the integration of various experimental methods in a simultaneous fitting approach:<sup>5,6</sup> the electronic parameters derived from the various NMR experiments were generally not in satisfactory agreement with the observed EPR linewidths. In order to make better use of multiple frequency and temperature measurements, an improvement of the relaxation theory used so far<sup>2</sup> is needed. Such an improvement was proposed by Poupko and coworkers,<sup>7</sup> which includes the so-called *dynamic frequency shifts*. Their approach predicts changes in the lineshape due to different shifts of the various transitions in the system. It effectively doubles the amount of information that one can extract from an EPR spectrum: besides the usually used peak-to-peak width, the observed resonance field becomes a new observable whose frequency and temperature behavior is governed by the same basic equations. Thus in a numerical fitting procedure stronger con-

straints will be imposed on the calculated microscopic quantities. Consequently one may hope to gain a better definition of these parameters by avoiding the multiple-minima problem that can be encountered in such a complicated equation system as the one currently used to describe the magnetic relaxation of MRI contrast agents.

## 2 Theory

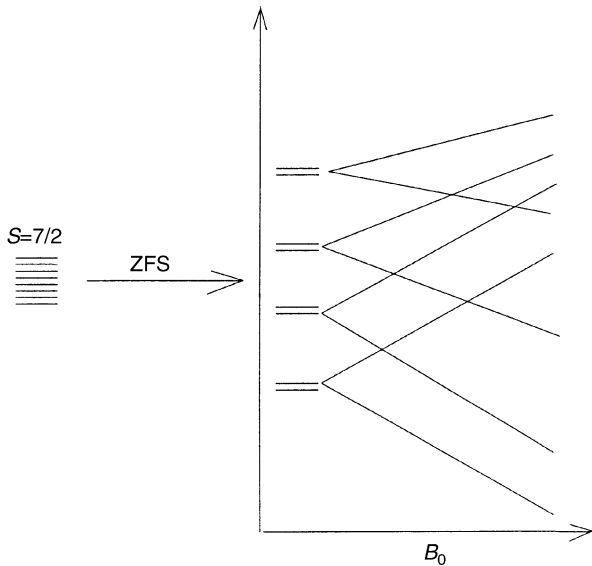
### 2.1 Zero field splitting (ZFS)

ZFS is a phenomenological description of the interelectronic interaction in paramagnetic compounds possessing two or more unpaired electrons. In the spin Hamiltonian formalism it is written with a quadratic spin dependence<sup>8</sup> (eqn. (1)). In this equation the parameters  $D$  and  $E$  describe the magnitude of the operator  $\hat{D}$  parallel and perpendicular to the  $z$  axis.

$$\hat{H}_{\text{ZFS}} = \hat{S} \cdot \hat{D} \cdot \hat{S} = D(\hat{S}_z^2 - \frac{1}{3}\hat{S}^2) + E(\hat{S}_+^2 + \hat{S}_-^2) \quad (1)$$

The effect of such a perturbation is to lift the  $2S + 1$  degeneracy at zero field (hence the name). One gets  $S + 1/2$  (for half-integer  $S$ ) or  $S + 1$  (for integer  $S$ ) zero-field spin states, which can be written as linear combinations of the Zeeman  $m_S$  states. For half-integer  $S$  all resulting spin states are doubly degenerate (Fig. 1) whereas for integer  $S$  one of them ( $m_S = 0$ ) is non degenerate. Upon application of an external magnetic field  $B_0$ , the double degeneracy of the resulting levels will be lifted.

For high spin ions in a symmetrical environment (for example aquaions of Cr(III), Fe(III), Mn(II), Gd(III), Eu(II)) the ZFS is averaged out. We assume that this should also be the case for lanthanide polyaminocarboxylates, where  $f$  electrons are rather shielded from the ligand field. However, distortions caused by solvent collisions can induce a transient ZFS, which acts as an efficient relaxation mechanism causing line broadening in EPR spectra.<sup>9</sup>



**Fig. 1** Qualitative description of the energy levels of a 7/2 spin with ZFS and external field  $B_0$ .

## 2.2 ZFS and relaxation

The problem of an electronic spin  $S$  relaxing under a transient ZFS is similar to the one of a nuclear spin enduring quadrupolar relaxation.<sup>10</sup> If the characteristic time describing the fluctuations of the Hamiltonian is short compared to the resulting relaxation time, the Redfield theory can be used to derive a relaxation matrix  $\mathbf{R}_{\alpha\alpha'\beta\beta'}$  between the spin states  $\alpha, \alpha', \beta$  and  $\beta'$  of the system (eqn. (2)). Its elements are sums of the spectral density functions  $J$  obtained as Fourier transforms of the time correlation functions for the time-dependent Hamiltonian (eqn. (3)).

$$\mathbf{R}_{\alpha\alpha'\beta\beta'} = \frac{1}{2} \begin{bmatrix} J_{\alpha\beta\alpha'\beta'}(\omega_{\alpha'\beta'}) + J_{\alpha\beta\alpha'\beta'}(\omega_{\alpha\beta}) \\ -\delta_{\alpha'\beta'} \sum_{\gamma} J_{\gamma\beta\gamma\alpha}(\omega_{\gamma\beta}) \\ -\delta_{\alpha\beta} \sum_{\gamma} J_{\gamma\alpha'\gamma\beta'}(\omega_{\gamma\beta'}) \end{bmatrix} \quad (2)$$

$$G_{\alpha\beta\alpha'\beta'}(\tau) = \overline{\langle \alpha | H_1(t) | \beta \rangle \langle \beta' | H_1(t + \tau) | \alpha' \rangle}$$

$$J_{\alpha\beta\alpha'\beta'}(\omega) = \int_{-\infty}^{+\infty} G_{\alpha\beta\alpha'\beta'}(\tau) e^{-i\omega\tau} d\tau \quad (3)$$

Normally an exponential decay for  $G$  (eqn. (4)) is assumed, with a correlation time  $\tau_c$  and a pre-exponential term  $G_0$ . This yields a Lorentzian expression for  $J$  (eqn. (5)).

$$G(\tau) = G_0 \exp(-|\tau|/\tau_c) \quad (4)$$

$$J(\omega) = G_0 \frac{\tau_c}{1 + (\omega\tau_c)^2} \quad (5)$$

However, this is only an approximation (as has already been pointed out by Abragam),<sup>11</sup> since this Lorentzian is only the

real part of the transform of the decaying exponential:

$$\int_0^{+\infty} G_{\alpha\beta\alpha'\beta'}(\tau) e^{-i\omega\tau} d\tau = G_0 \int_0^{+\infty} \exp\left(\tau\left(-\frac{1}{\tau_c} - i\omega\right)\right) d\tau$$

$$= G_0 \left\{ \frac{\tau_c}{1 + (\omega\tau_c)^2} - i \frac{\omega\tau_c^2}{1 + (\omega\tau_c)^2} \right\} \quad (6)$$

The imaginary part is the so called *dynamic frequency shift* (DFS),<sup>12,13</sup> which will cause a small change in the observed transition frequency. Since this shift is in general much smaller than the linewidth, it is often neglected.<sup>11</sup> However, it has been shown that DFS can play an important role in the EPR spectra of  $S > 1$  ions:<sup>7</sup> each transition in the system has a distinct relaxation rate and shift.

Expressions for  $G_0$  are derived from a decomposition of the time-dependent Hamiltonian into a sum of operators:<sup>4</sup>

$$\hat{H}(t) = \sum_{p=-2}^{+2} (-1)^p \hat{T}_{-p}^2 \sum_{q=-2}^{+2} F_q^2 D_{pq}^2(\Omega(t)) \quad (7)$$

$F^{2q}$  is a space coefficient of the Hamiltonian,  $\hat{T}^{2p}$  a combination of spin operators and  $D^{pq}$  a Wigner matrix of second order corresponding to the transformation from the molecular frame to the laboratory frame. This transformation is time-dependant, and when calculating the time correlation function of  $H$  one will obtain terms such as:

$$\overline{D_{pq}^2 *(\Omega(t)) D_{p'q'}^2 *(\Omega(0))} \quad (8)$$

Orthogonality of Wigner matrices will cancel such terms unless  $q = q'$  and  $p = p'$ , where a normalization coefficient 1/5 will appear. Finally one obtains:

$$\begin{aligned} R_{\alpha\alpha'\beta\beta'}^r &= R_{\alpha\alpha'\beta\beta'}^r + iR_{\alpha\alpha'\beta\beta'}^i \\ R_{\alpha\alpha'\beta\beta'}^r &= J_{\alpha\beta\alpha'\beta'}(\omega_{\alpha'\beta'}) + J_{\alpha\beta\alpha'\beta'}(\omega_{\alpha\beta}) \\ &\quad - \delta_{\alpha'\beta'} \sum_{\gamma} J_{\gamma\beta\gamma\alpha}(\omega_{\gamma\beta}) - \delta_{\alpha\beta} \sum_{\gamma} J_{\gamma\alpha'\gamma\beta'}(\omega_{\gamma\beta'}) \\ R_{\alpha\alpha'\beta\beta'}^i &= -\delta_{\alpha'\beta'} \sum_{\gamma} K_{\gamma\beta\gamma\alpha}(\omega_{\gamma\beta}) - \delta_{\alpha\beta} \sum_{\gamma} K_{\gamma\alpha'\gamma\beta'}(\omega_{\gamma\beta'}) \\ J_{\alpha\beta\alpha'\beta'}(\omega_{\alpha'\beta'}) &= \frac{1}{5} j[(\alpha' - \beta')\omega_0] \\ &\quad \times \sum_{pq} \langle \alpha | \hat{T}_{-p}^2 | \beta \rangle \langle \alpha' | \hat{T}_{-p}^2 | \beta' \rangle * (F_q^2)^2 \\ K_{\alpha\beta\alpha'\beta'}(\omega_{\alpha'\beta'}) &= \frac{1}{5} (\alpha' - \beta') \omega_0 \tau j[(\alpha' - \beta')\omega_0] \\ &\quad \times \sum_{pq} \langle \alpha | \hat{T}_{-p}^2 | \beta \rangle \langle \alpha' | \hat{T}_{-p}^2 | \beta' \rangle * (F_q^2)^2 \\ j(n\omega_0 \tau) &= \frac{\tau}{1 + (n\omega_0 \tau)^2} \end{aligned} \quad (9)$$

For a time-dependent ZFS Hamiltonian the  $\hat{T}$  operators and  $F$  coefficients are given in Table 1.

When considering transverse relaxation (which is the case for continuous wave EPR), spin states  $\alpha$  and  $\alpha'$  (respectively  $\beta$  and  $\beta'$ ) are related by a  $\Delta m_s = \pm 1$  transition. The corresponding matrix elements form the transverse relaxation matrix  $\mathbf{R}_2$ , which for  $S = 7/2$  enduring a transient ZFS is written as eqn. (10), with the correlation time  $\tau_v$  and  $\Delta^2 = 2/3$

**Table 1** Second order tensors  $\hat{T}_p^2$  and coefficients  $F_q^2$  for transient ZFS relaxation

	$\hat{T}_p^2$	$F_q^2$
$p, q = 0$	$\sqrt{\frac{3}{2}}(\hat{S}_z^2 - \frac{1}{2}\hat{S}^2)$	$\sqrt{\frac{2}{3}}D$
$p, q = \pm 1$	$\mp \frac{1}{2}(\hat{S}_{\pm}\hat{S}_z + \hat{S}_z\hat{S}_{\pm})$	0
$p, q = \pm 2$	$\frac{1}{2}(\hat{S}_{\pm})^2$	$E$

$D^2 + E^2$ . This matrix is identical to that given by Hudson and Lewis<sup>4</sup> except the underlined imaginary part induced in the diagonal elements by the dynamic frequency shifts.

$$\mathbf{R}_2 = \frac{1}{2} \Delta^2 \tau_v \begin{pmatrix} A & E & F & 0 & 0 & 0 & 0 \\ E & B & G & H & 0 & 0 & 0 \\ F & G & C & 0 & I & 0 & 0 \\ 0 & H & 0 & D & 0 & H & 0 \\ 0 & 0 & I & 0 & C & G & F \\ 0 & 0 & 0 & H & G & B & E \\ 0 & 0 & 0 & 0 & F & E & A \end{pmatrix}$$

$$\begin{aligned} A &= -(54J_0 + 174J_1 + 66J_2) + \underline{i\omega_0 \tau_v(78J_1 - 48J_2)} \\ B &= -(24J_0 + 174J_1 + 126J_2) + \underline{i\omega_0 \tau_v(18J_1 + 12J_2)} \\ C &= -(6J_0 + 784J_1 + 186J_2) + \underline{i\omega_0 \tau_v(-18J_1 + 48J_2)} \\ D &= -(30J_0 + 210J_2) + \underline{i\omega_0 \tau_v(-30J_1 + 60J_2)} \\ E &= 24\sqrt{21}J_1 \\ F &= 6\sqrt{105}J_2 \\ G &= 2\sqrt{30}J_1 \\ H &= 60\sqrt{3}J_2 \end{aligned} \quad J_n = \frac{1}{1 + (n\omega_0 \tau_v)^2} \quad (10)$$

The temperature dependence of  $\mathbf{R}_2$  can be calculated assuming an Arrhenius behavior for  $\tau_v$ :

$$\tau_v = \tau_v^{298} \exp\left\{\frac{E_v}{R} \left(\frac{1}{T} - \frac{1}{298.15}\right)\right\} \quad (11)$$

Seven relaxation rates, dynamic frequency shifts and intensities (four of which are non-zero) are obtained through diagonalization of  $\mathbf{R}_2$ . The numerical results are displayed in Fig. 2. Let  $\hat{U}$  be the complex matrix that diagonalizes  $\mathbf{R}_2$  and  $\mathbf{A}u$  the diagonal matrix of complex eigenvalues  $A_\lambda^i + iA_\lambda^j$ . The lineshape equation becomes eqn. (12)<sup>14</sup>

$$\begin{aligned} I(\omega) &= \text{Re}\{\hat{X}\hat{U}[i(\omega_0 - \omega)\hat{1} + \mathbf{A}u]^{-1} \hat{U}^\dagger \hat{X}\} \\ &= \sum_\lambda \text{Re}\left\{ \frac{(X\eta_\lambda)^2 (-A_\lambda^j)}{[\omega - (\omega_0 + (-A_\lambda^i))]^2 + (-A_\lambda^j)^2} \right\} \\ &\quad - \text{Im}\left\{ \frac{(X\eta_\lambda)^2 [\omega - (\omega_0 + (-A_\lambda^i))]}{[\omega - (\omega_0 + (-A_\lambda^i))]^2 + (-A_\lambda^j)^2} \right\} \end{aligned} \quad (12)$$

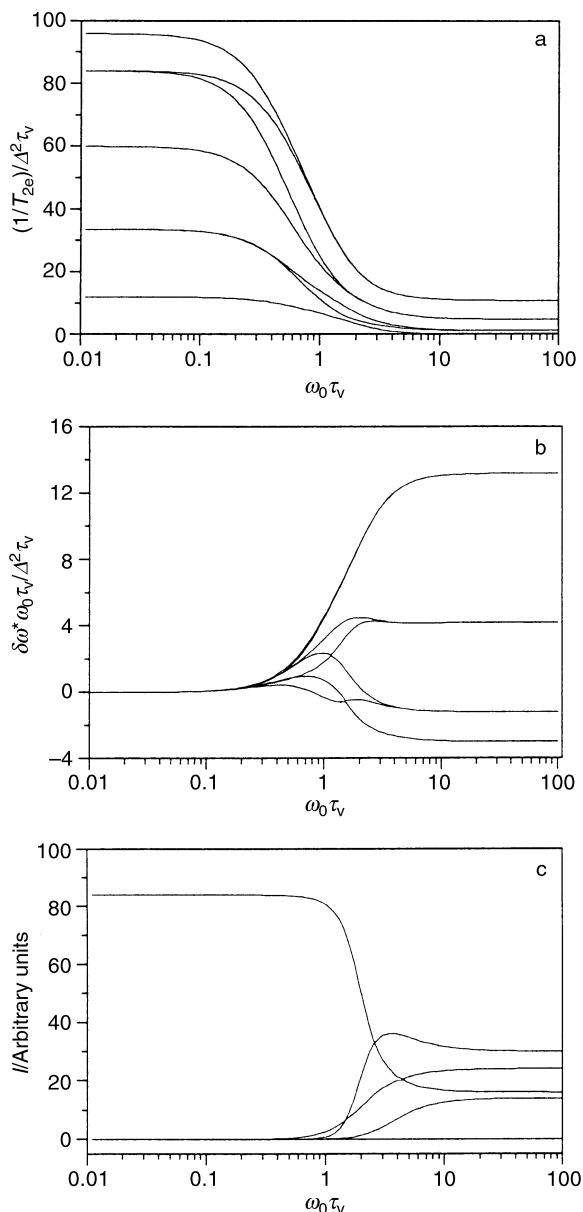
where vector elements of  $X$  are  $X_{\alpha\alpha'} = \langle \alpha | \hat{S}_+ | \alpha' \rangle = \hbar\sqrt{(7/2 - \alpha + 1)(7/2 + \alpha)}$ . This expression corresponds to a superposition of Lorentzians with width  $1/T_{2e} = A_\lambda^j$  and intensity  $I = (X\eta_\lambda)^2$ , shifted by  $\delta\omega = A_\lambda^i$  from the base frequency  $\omega_0$ .<sup>†</sup>

The relaxation matrix is complex symmetric, so one must be careful that the diagonalization matrix  $\hat{U}$  is orthogonal ( $\hat{U} \cdot \hat{U} = 1$ ) rather than unitary ( $\hat{U}^* \cdot \hat{U} = 1$ ) as would be the case for a Hermitian matrix. Thus the eigenvectors must obey the normalization equation  $\eta_\lambda \cdot \eta_\lambda = 1$  instead of  $\eta_\lambda^* \cdot \eta_\lambda = 1$  (where the star means the complex conjugate) otherwise the eigenvectors are only defined to an arbitrary complex phase factor and calculation of the intensities is no longer possible. When using vectors normalized by  $\eta_\lambda \cdot \eta_\lambda = 1$  one obtains essentially the same transition intensities as with the real-only relaxation matrix of Hudson and Lewis.<sup>4</sup>

### 2.3 Other possible relaxation mechanisms

It has been observed by several authors<sup>5,15</sup> that the proposed transient ZFS mechanism was not sufficient to explain the observed relaxation rates: Powell *et al.*<sup>5</sup> have suggested an

<sup>†</sup> Eqn. (12) as given by Poupko and Luz<sup>7</sup> contains a sign error for the  $\text{im}\{\dots\}$  part. However, this error is not very significant as this contribution vanishes around the resonance region and can thus be neglected.



**Fig. 2** Transverse electron spin relaxation rates (a), dynamic frequency shifts (b) and EPR transition intensities (c) obtained from matrix diagonalization of  $\mathbf{R}_2$  (eqn. (10)).

additional spin rotation mechanism<sup>16</sup> to account for <sup>17</sup>O relaxation rates in NMR experiments, but found that its impact on transverse electron spin relaxation was negligible. On the other hand, Clarkson and coworkers<sup>15</sup> needed a frequency independent relaxation rate of  $7.6 \times 10^7 \text{ s}^{-1}$  (e.g. 4.7 G in peak-to-peak width) in their analysis of EPR linewidths. We use a similar approach to Powell *et al.* in this respect and add a spin rotation term to each of the four non-zero transitions:

$$\frac{1}{T_{ieSR}} = \frac{\delta g_L^2}{9\tau_{re}} \quad i = 1, 2 \quad (13)$$

where the spin rotation correlation time  $\tau_{re}$  has the usual Arrhenius behavior. The numerator is the sum of the squared  $g$  deviations from the free electron value ( $g_L = 2.0023$ ) in all three directions of space. Unfortunately these deviations are not immediately accessible in our experimental approach, so we fitted the parameter to  $\delta g_L^2/\tau_{re}^{298}$  and the Arrhenius activation energy  $E_{re}$  for the correlation time  $\tau_{re}$ . Although the proposed spin rotation mechanism cannot be unambiguously proven, it has the advantage of a simple frequency independent expression.

The fluctuating intermolecular dipole-dipole interaction between like electron spins in solution is an additional cause of line broadening. This effect is further discussed in the experimental part.

## 2.4 Comparison with recent literature

Clarkson *et al.*<sup>3,15</sup> recently used an approach developed by Alexander *et al.*<sup>17</sup> for powder spectra in order to calculate high frequency (Q-band and higher) EPR line widths and shifts. However, they clearly state that this theory cannot always account for lower frequency (for example X-band) observed values.

It is possible to show that in its validity region ( $\omega\tau \gg 1$ ) their theory is completely equivalent to the one proposed here. The main assumption made is that the spectrum is dominated by the central  $m_S = -1/2 \rightarrow 1/2$  transition, whose width is calculated using the relaxation matrix of Hudson and Lewis<sup>4</sup> and the shift using Alexander's equations. Their final result is that for  $S = 7/2$  the observed  $g$ -factor depends on the frequency as described by eqn. (14).

$$g_{\text{obs}} = g_0 \left( 1 - \frac{3\Delta^2}{\omega^2} \right) \quad (14)$$

If we consider the predictions of the DFS theory we observe (numerically) that for  $\omega\tau \gg 1$  the  $m_S = -1/2 \rightarrow 1/2$  transition is indeed dominant in intensity (it is the sharpest line as well). It corresponds to the following eigenvector and value (eqn. (15)):

$$R_2 \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} = \frac{1}{5} \Delta^2 \tau_v (2H + D) \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (15)$$

Only matrix element  $D$  has non zero imaginary part, therefore it determines the dynamic frequency shift which takes a very simple form (eqn. (16)) for  $\omega\tau_v \gg 1$ .

$$\delta\omega = -\frac{1}{5} \Delta^2 \tau_v \omega \tau_v \left( \frac{-30}{1 + (\omega\tau_v)^2} + \frac{60}{1 + (2\omega\tau_v)^2} \right) \simeq \frac{3\Delta^2}{\omega} \quad (16)$$

The corresponding shift  $\delta g$  (eqn. (17)) can be calculated from the resonance equation expressed with respect to the non-modified frequency and  $g$ -factor, respectively. The final result is thus identical to the Clarkson formula (eqn. (14)):

$$\frac{\delta g}{g} \simeq \frac{\delta\omega}{\omega} = \frac{-3\Delta^2}{\omega^2} \quad (17)$$

One may also notice that in the validity region of this approximation the transverse relaxation rate takes a simple analytical form as given by the real part of eqn. (15).

Strandberg and Westlund<sup>18</sup> published a different though mathematically equivalent approach to ours. By reducing the relaxation matrix to the  $4 \times 4$  matrix of nonzero transitions, they obtain an analytical expression for the EPR absorption lineshape. However, solving this expression to obtain the resonance field and linewidth is not feasible analytically as it includes terms of third and fourth degree with respect to the frequency. Furthermore this expression rather obscures the underlying structure of the observed absorption band (superposition of four transitions) and its first and second derivatives are less easily calculated than for the well-known Lorentzian function. On the other hand, their approach efficiently addresses the problem of multiple matrix diagonal-

izations, which could make it attractive for implementation when such operations are not readily available.

## 3 Experimental section

Measurements were performed on a Bruker ESP-300E spectrometer for X-band (9.425 GHz) experiments (Lausanne), and on a home-built spectrometer for higher frequencies (Budapest).<sup>19</sup> The microwave source for the Budapest spectrometer is a 75 GHz quartz stabilized Gunn resonator (Radiometer Physics) with frequency multipliers allowing for 150 and 225 GHz frequencies respectively. At X-band the temperature was measured using a thermometer substituted for the sample; at higher frequencies a Pt resistor built into the probe head was used.

[Gd(H<sub>2</sub>O)<sub>8</sub>]<sup>3+</sup> solutions were prepared by dissolving Gd<sub>2</sub>O<sub>3</sub> in excess HCl. [Gd(DTPA-BMA)(H<sub>2</sub>O)] and Na[Gd(DOTA)(H<sub>2</sub>O)] were dissolved in bidistilled water. The concentration range was between 0.005 M and 0.35 M. ‡ Gadolinium oxide was purchased from Fluka (99.9% purity), while the DOTA and DTPA-BMA complexes were provided by Guerbet CA, Paris, and Nycomed-Amersham Imaging, Oslo, respectively.

Peak-to-peak widths were measured using spectrometer software (Lausanne) or fitting to a Lorentzian line shape (Budapest). Resonance field was measured with respect to an external reference (diphenyl-picryl-hydrazine DPPH,  $g = 2.0023$ , in Lausanne, bisdiphenylene-phenyl-allyl BDPA,  $g = 2.00359$ , in Budapest). A custom program§ implementing eqn. (12) was used to calculate the best fitting parameters ( $\tau_v^{298}$ ,  $E_v$ ,  $\Delta^2$ ,  $g$ ,  $\delta g_L^2/\tau_{Re}^{298}$  and  $E_{Re}$ ) for the peak-to-peak widths  $\Delta H_{p/p}$  and center fields  $B_0$ .

### 3.1 Concentration effects on relaxation

It was observed in previous studies<sup>2</sup> that the linewidth of Gd(III) complexes in solution is concentration dependent, especially at high frequencies, due to intermolecular dipole-dipole relaxation between like 7/2-spins. Several descriptions of this effect have been used so far<sup>2,5</sup> but their combination with the present theory of ZFS relaxation remains unclear. In order to avoid this effect, it would be best to work with very dilute solutions. Unfortunately the relatively low sensitivity of the high frequency EPR spectrometer used in this study precluded this option and we could only use concentrations as low as 0.01 M. We have assumed a linear concentration dependence for the linewidth, without any assumption on the frequency and temperature dependence. We used cubic splines<sup>20</sup> interpolation to calculate the linewidth when a temperature was missing at one given concentration.¶

## 4 Results and discussion

$\Delta H_{p/p}$  extrapolated to infinite dilution and  $g$ -factors of [Gd(H<sub>2</sub>O)<sub>8</sub>]<sup>3+</sup> and of two commercially available MRI contrast agents [Gd(DOTA)(H<sub>2</sub>O)]<sup>-</sup> and [Gd(DTPA-BMA)(H<sub>2</sub>O)] are shown in Fig. 3, together with fitted curves. || Best fitting parameters can be found in Table 2.

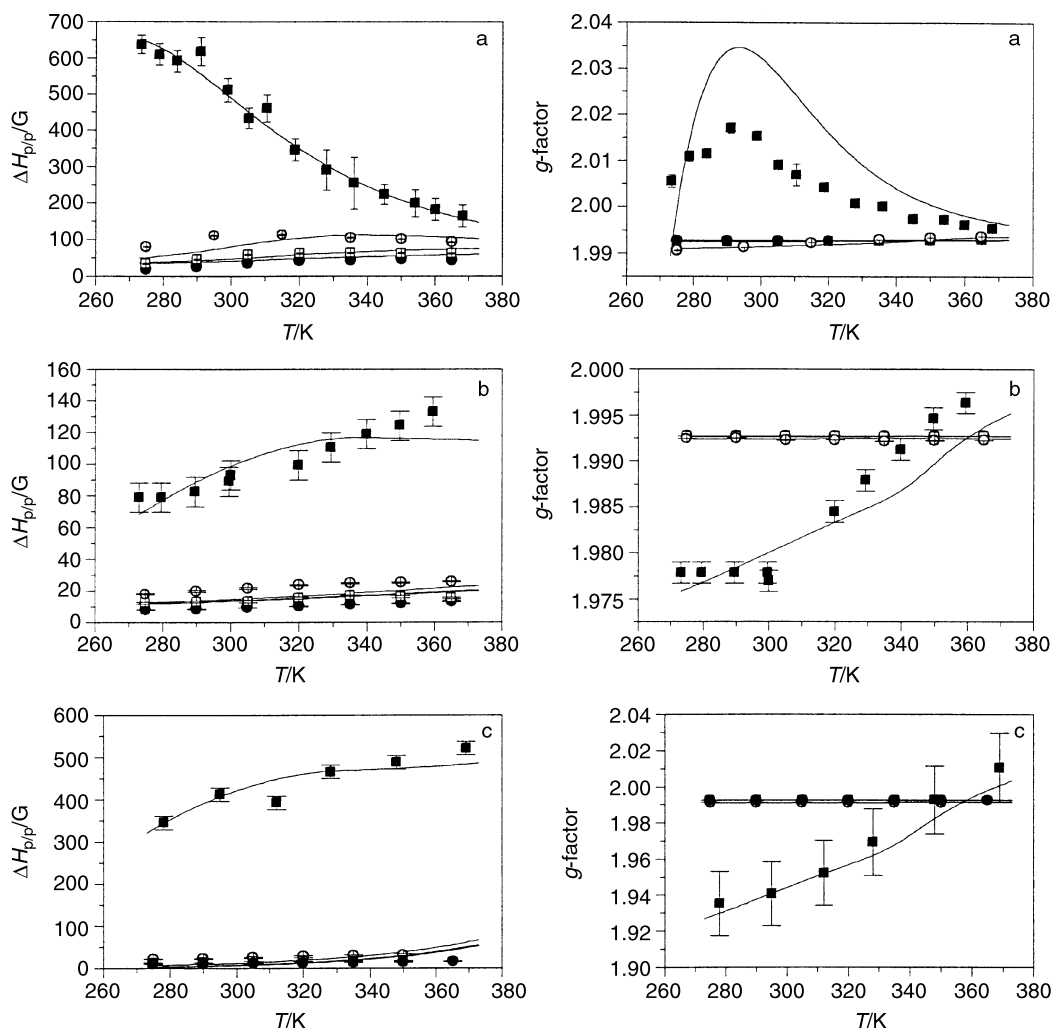
Clearly it can be seen that the theory in its present state is able to account for the observed features of the spectra, *i.e.* a variation of both the linewidth and the resonance field with

‡ Sample concentrations are given in detail as electronic supplementary material. See <http://www.rsc.org/suppdata/cp/a9/a909553e>.

§ Source code is available as electronic supplementary material. See <http://www.rsc.org/suppdata/cp/a9/a909553e>.

¶ The source code for this procedure is available as electronic supplementary material. See <http://www.rsc.org/suppdata/cp/a9/a909553e>.

|| Exhaustive tables containing all peak-to-peak width and center field measurements are available as electronic supplementary material, with a few examples of experimental and simulated spectra. See <http://www.rsc.org/suppdata/cp/a9/a909553e>.



**Fig. 3** Peak-to-peak width and apparent  $g$ -factor at X-band ( $\blacksquare$ ), 75 MHz ( $\circ$ ), 150 MHz ( $\square$ ) and 225 MHz ( $\bullet$ ) for  $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$  (a),  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  (b) and  $[\text{Gd}(\text{DTPA-BMA})(\text{H}_2\text{O})]^-$  (c).

frequency and temperature. We predict and indeed observe a large variation of  $g$  at low frequency (X-band). The ZFS parameters obtained,  $\Delta^2$  and  $\tau_v^{298}$ , are of the same order of magnitude as those found in previous EPR<sup>2,15,18</sup> or EPR/NMR<sup>5</sup> combined studies (Table 3). The correlation time  $\tau_v^{298}$  is significantly longer for the polyaminocarboxylate complexes. This is coherent with the finding of Powell *et al.*<sup>2</sup> that it approaches the expected correlation time for the rotation of the complexes. The smaller value of  $\Delta^2$  for  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  could be explained by the greater rigidity of the complex, which will reduce the amplitude of the time-dependent distortions. Fitted values of  $\Delta H_{\text{pp}}$  and  $g$  are generally in acceptable agreement with the experimental results with some exceptions (notably the X-band  $g$ -factor of the aquaion). The errors calculated by the program on the fitting parameters are fairly low and in some cases too small to be meaningful (Table 2). We also used Clarkson's approach

to evaluate  $\Delta^2$  for our variable temperature experimental data. We performed at each temperature a linear fitting of  $g_{\text{obs}}$  vs.  $1/\omega^2$  (see eqn. (14)) and calculated the corresponding  $g_0$  and  $\Delta^2$ . As in the case of the linewidth, we use cubic splines to interpolate  $g_{\text{obs}}$  values at temperatures where not all frequencies were measured. We only used the measurements at 75 GHz and higher as it was recognized already that X-band ( $\sim 9.5$  GHz) was out of the validity region for the  $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$  complex.<sup>15</sup>

The values we obtain for  $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$  using this simpler approach show a temperature dependence of  $\Delta^2$  well beyond the error margin (Fig. 4). For the aquaion and DOTA complex, the 75 GHz  $g_{\text{obs}}$  value is actually larger than at 150 and 225 GHz in the high temperature region, contrary to the prediction of eqn. (14) where  $g_{\text{obs}}$  should decrease linearly with  $1/\omega^2$ . Inclusion of these data points in the linear fitting would produce negative  $\Delta^2$  values, which is physically meaningless.

**Table 2** Best-fitting parameters obtained from the least-square procedure

	$[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$	$[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$	$[\text{Gd}(\text{DTPA-BMA})(\text{H}_2\text{O})]^-$
$\tau_v^{298}/10^{-12}$ s	$10.9 \pm 0.0^a$	$49.7 \pm 0.1$	$41.9 \pm 0.0^a$
$E_v/\text{kJ mol}^{-1}$	$21.48 \pm 0.03$	$10.56 \pm 0.74$	$8.38 \pm 0.35$
$\Delta^2/10^{19}$ s <sup>-2</sup>	$7.58 \pm 0.02$	$1.22 \pm 0.00^a$	$5.49 \pm 0.01$
$g$	$1.9928 \pm 0.00^a$	$1.9926 \pm 0.00^a$	$1.9926 \pm 0.00^a$
$(\delta g^2/9\tau_{\text{Re}}^{298})/10^8$ s <sup>-1</sup>	$5.05 \pm 0.00^a$	$1.98 \pm 0.00^a$	$0.78 \pm 0.01$
$E_{\text{Re}}/\text{kJ mol}^{-1}$	$0.00 \pm 6.33$	$3.43 \pm 4.08$	$27.56 \pm 9.66$

<sup>a</sup> The calculated error is much smaller than the displayed numerical accuracy.

**Table 3** Comparison of transient ZFS parameters with previous studies

		[Gd(H <sub>2</sub> O) <sub>8</sub> ] <sup>3+</sup>	[Gd(DOTA)(H <sub>2</sub> O)] <sup>-</sup>	[Gd(DTPA-BMA)(H <sub>2</sub> O)]
$\tau_v^{298}/10^{-12}$ s	Ref. 2 <sup>a</sup>	7.2	—	140
	Ref. 5 <sup>b</sup>	7.3	11	25
	Ref. 15 <sup>a</sup>	—	24	—
	Ref. 18 <sup>a</sup>	6	20	—
	This work	10.9	49.7	41.9
$E_v/\text{kJ mol}^{-1}$	Ref. 2 <sup>a</sup>	15.4	—	17.6
	Ref. 5 <sup>b</sup>	18.3	1.0	3.9
	This work	21.48	10.56	8.38
	ref. 2 <sup>a</sup>	9.3	—	3.8
$\Delta^2/10^{19}$ s <sup>-2</sup>	Ref. 5 <sup>b</sup>	11.9	1.6	4.1
	Ref. 15 <sup>a</sup>	—	1.1	—
	Ref. 18 <sup>a</sup>	8.87	1.15	—
	This work	7.58	1.22	5.49

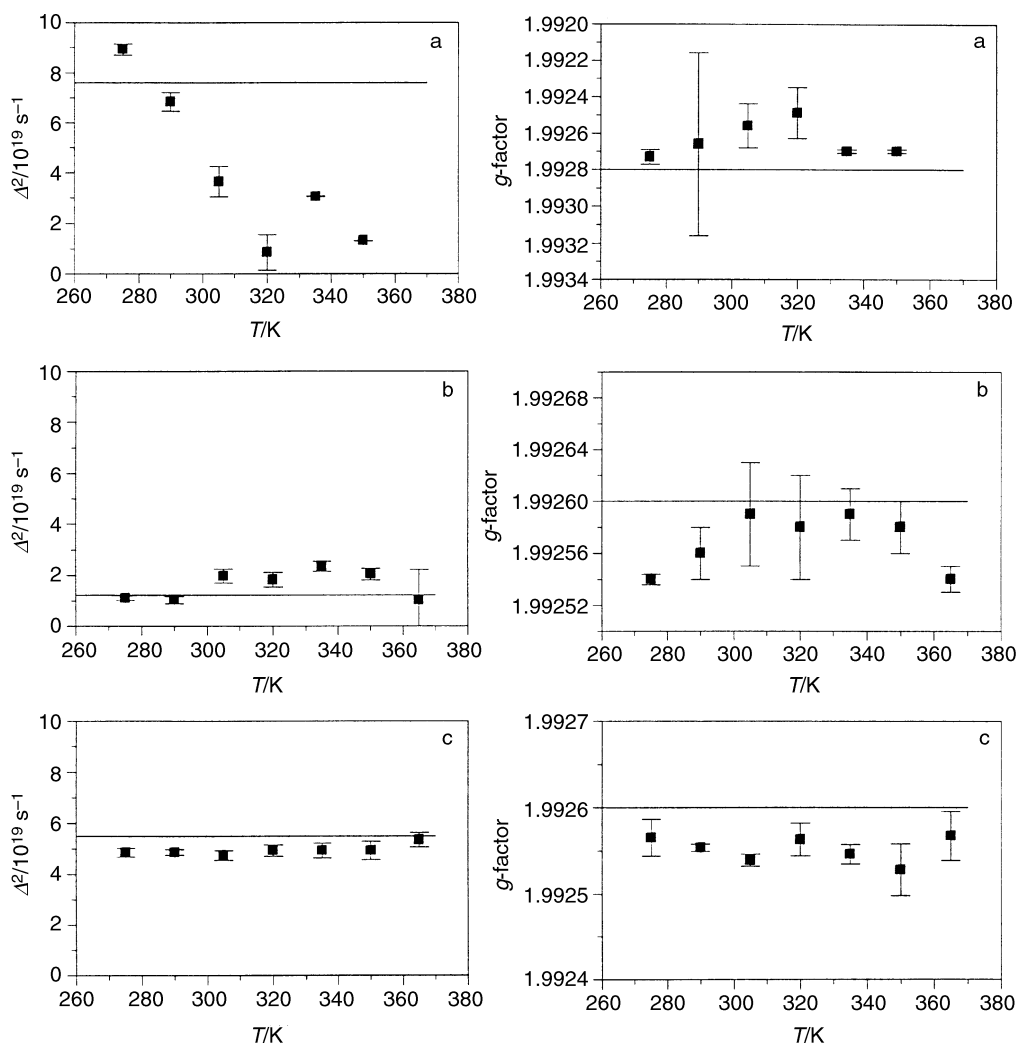
<sup>a</sup> EPR only. <sup>b</sup> EPR and NMR.

We considered the possibility that this finding could be due to equilibria involving changes in the first coordination sphere.

For example the Gd(III) aquaion could show the following coordination equilibrium:  $[\text{Gd}(\text{H}_2\text{O})_8]^{3+} + \text{H}_2\text{O} \rightleftharpoons [\text{Gd}(\text{H}_2\text{O})_9]^{3+}$ . However, the coordination number of the Gd(III) aquaion at room temperature has been established to be eight using a number of techniques.<sup>21–24</sup> Furthermore it has been shown by Cossy *et al.*<sup>25,26</sup> using <sup>17</sup>O-NMR chemical shifts that the coordination number of the neighboring lanthanide ions did not change with temperature within the inherent method accuracy, thus the apparent temperature dependence

is clearly a problem of the theory itself. Indeed, with the parameters obtained from the full complex relaxation matrix (Table 2) we have  $\omega\tau_v = 5.2$  at 298.15 K and 0.96 at 370 K for the 75 GHz frequency, which is out of the validity region for Clarkson's theory ( $\omega\tau_v \gg 1$ ).

In the case of  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  we still observe a change but the simple numerical argument  $\omega\tau_v \gg 1$  does not hold: even at 370 K our parameters lead to  $\omega\tau_v > 10$  for the  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  chelate. There is a known equilibrium between a minor m and a major M isomer of the lanthanide complexes with DOTA.<sup>27</sup> The temperature depen-



**Fig. 4**  $\Delta^2$  and  $g$  from Clarkson's analysis for  $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$  (a)  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  (b) and  $[\text{Gd}(\text{DTPA-BMA})(\text{H}_2\text{O})]$  (c). Straight horizontal lines are the results obtained from the full relaxation matrix treatment.

dence of this equilibrium has been studied using  $^1\text{H-NMR}$  for several lanthanide DOTA complexes, including europium which is both structurally and dynamically similar to the gadolinium analogue. The expected decrease in the isomerization equilibrium constant for  $[\text{Eu}(\text{DOTA})(\text{H}_2\text{O})]^-$  goes from 4–5 at 273 K to 2.4–3 at 380 K depending on the thermodynamic parameters used. One should probably take this equilibrium into account for a rigorous analysis but this would double the number of free parameters in our analysis and would make the reliability of the results most questionable.

Regarding the  $[\text{Gd}(\text{DTPA-BMA})(\text{H}_2\text{O})]$  complex, the possible isomers and their dynamic equilibrium are less well known. Geraldes *et al.*<sup>28</sup> studied the bis-propylamide derivatives  $[\text{Ln}(\text{DTPAPA}_2)(\text{H}_2\text{O})]$  in solution by variable temperature  $^{13}\text{C-NMR}$ . They showed that four diastereomeric pairs occur in aqueous solution. Three dynamic processes have been identified: (i) rapid rotation of the carboxylate groups, (ii) racemization at the middle N atom *via* interconversions between the two possible conformations of the ethylene bridges, and (iii) racemization at the terminal N atoms of the diethylenetriamine backbone *via* decoordination–inversion–recoordination. However, to the best of our knowledge no data is available regarding their relative stability. Nevertheless one obtains temperature-independent parameters  $\Delta^2$  and  $g$  when using Clarkson's theory so these equilibria seem to be negligible for our purpose. These parameters differ slightly from those obtained with our complete treatment but this could be a result of the simultaneous fitting of the linewidth and center field in our approach: errors on one of the experimental values will propagate on the other one.

## 5 Conclusion

We have presented EPR measurements of three Gd(III) complexes (aquaion  $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ , polyaminocarboxylate complexes  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  and  $[\text{Gd}(\text{DTPA-BMA})(\text{H}_2\text{O})]$ ) in aqueous solution over a wide frequency and temperature range and analyzed the observed spectra using a more complete theoretical development than in previous studies. This newer approach, used here for the first time with such extensive experimental data, is in principle more complicated but quite usable on today's computers. The main improvement over the previous theory is that we can now extract twice as much information from one given spectrum: the line width and position are important to study the transverse electronic relaxation of such compounds, and simultaneous fitting of both values applies stronger constraints on the fitting parameters. We also compared our technique with some recent work, especially that published by Clarkson and coworkers. Clarkson's approach appears to be a subset of ours in the  $\omega\tau_v \gg 1$  limit so when using this approximation one should be careful to check that the obtained parameters are in its validity domain.

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