A high frequency EPR study of frozen solution of Gd^{III} complexes: determination of the Zero Field Splitting parameters and simulation of the NMRD profiles

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ABSTRACT:

EPR at High Frequency (HF) can lead to a considerable simplification of spectra with a large Zero Field Splitting (ZFS). In favourable cases the value and the sign of static ZFS parameter D can be directly estimated from the spectrum at low temperature. It is the purpose of this paper to report a HF EPR study of the glasses of Gd(III) complexes at several temperatures. For the first time with that type of compounds, we are able to determine from these EPR data the average ZFS parameters and their distributions. Since the ZFS is related to the crystal field, our results constitute a first step towards establishing a relationship between molecular structure and the ZFS. The electronic properties of these gadolinium complexes are investigated at 240 GHz between 4 and 150K and the spin Hamiltonian parameters determined. Furthermore, we compare our results with those previously reported for $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ and $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ in solution. Finally, we also show the importance of determining independently the ZFS parameters in the aim to limit the adjustable parameters for the analysis of the field dependence of nuclear magnetic relaxation rates, commonly called Nuclear Magnetic Relaxation Dispersion (NMRD).

KEYWORDS: MRI, HF EPR, Gd^{III} complexes, Contrast Agents, glasses, ZFS parameters.

Introduction

Ever since Paul C. Lauterbur (USA) and Sir Peter Mansfield (UK) invented Magnetic Resonance Imaging (MRI) in the 1970's,^{1,2} that technique has become a more and more powerful tool for medical diagnosis. Indeed this method is non-invasive and devoid of serious health hazards – only patients with metal or pacemakers inside their bodies may not be examined due to the intense magnetic field. For this resounding success, Lauterbur and Mansfield shared the Nobel Prize in Medicine for 2003. However, the technological developments of the last three decades are not yet sufficient to satisfy the demands of all radiological examinations. In order to shorten the examination time or increase the image quality, physicians often use drugs known as *contrast agents*. Usually, these agents are paramagnetic Gd(III) complexes that induce an enhancement of the relaxation rate of the neighboring water protons

(*relaxivity*) due to stochastic changes of the dipolar interaction with the unpaired electrons of the metal ion.³ Several phenomena act as simultaneous modulation processes (1) the rotational diffusion of the complex, described by a correlation time τ_R , (2) chemical exchange of the water molecules directly bound to the metal with the bulk (residence time τ_m), and (3) the electronic spin relaxation, often described by the longitudinal and transverse relaxation times T_{1e} and T_{2e} . While it is well known that rotational diffusion coefficient is a function of the molecular size^[4-6] and that water exchange rate can be controlled to some extent by designing ligands with suitable steric constraints,^[7, 8] the electronic spin relaxation of Gd(III) complexes relevant for MRI remains the subject of much discussion.^[9-14]

Since the $^8S_{7/2}$ ground state of the Gd(III) ion is well known to undergo zero-field splitting in the solid state,^[15, 16] Hudson and Lewis proposed a basic theory of the EPR line shape of Gd^{III} complexes in solution assuming a transient zero-field splitting (ZFS), modulated by rotation or molecular distortions as the main relaxation mechanism.^[17] Based on this model, transverse and longitudinal relaxation matrices can be derived using the approach of Redfield.^[18] In general, the zero-field splitting (ZFS) lifts the degeneracy of the electronic spin levels of transition metal compounds when the system deviates from a spherical symmetry.^[19] More recently, Rast et al.^[11, 20] recognized that even highly symmetrical complexes such as the aqua ion $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ (point group D_{4h}) would have a permanent non-zero ZFS and developed a refined model of the electron spin relaxation of the S state metal ion complexes in solutions. This refined treatment includes a contribution of the rotational modulation of the static (i.e. average) crystal field surrounding the Gd^{III} through molecular tumbling as well as the usual transient ZFS caused by vibrations, intramolecular rearrangements, and collisions with surrounding solvent molecules. Thus, one can say that for lanthanide ions, the structure and dynamics of the electronic density of the chelate framework surrounding the metal determine the ZFS and the electron spin relaxation rates in solution. A better knowledge of the ZFS parameters of MRI contrast agents and their relationship to chelate structure and environment is necessary to establish a structure-function relationship for rational contrast agent design.

Extensive experimental data are usually required to determine accurately the underlying parameters (ZFS magnitude and correlation times). For small complexes such as the octa aqua ion^[21] or low molecular weight chelates,^[8, 22] the analysis of EPR measurements in aqueous solution at multiple frequencies and temperatures yielded parameters compatible with ^1H and ^{17}O NMR relaxation data.

Furthermore the combination of the static and transient crystal field effects was able to correctly predict the longitudinal relaxation times observed using the Longitudinally Detected EPR (LODEPR) method.^[23] However, the analysis of EPR spectra of slow-rotating molecules is not as straightforward, as the Redfield approximations are not valid for such compounds. For these systems, calculating the line shape becomes more tedious and requires computationally expensive methods, such as Monte Carlo spin dynamics^[13, 24] or solving the stochastic Liouville equation,^[25-27] as well as a deeper knowledge of the spin Hamiltonian and the associated dynamics.^[28-30] To obtain such information, it is necessary to follow a different approach in order to study independently the parameters of interest. For example, the fluctuations of the lanthanide(III) coordination polyhedron have been studied using molecular dynamics simulations.^[31, 32] In this paper, we address the other side of the problem, namely the ZFS itself. Traditionally, solid-state EPR has been the method of choice for the direct study of the electron spin Hamiltonian, with the possibility to determine all components of the g -, A - and ZFS-tensors.^[33] However, in order to be meaningful for the spin relaxation in liquids, a precise relationship between the solid state and solution parameters must be established. This was not possible using the theory of Hudson and Lewis, where the basic assumption was that of a ZFS averaged to zero. The models where a permanent non-zero ZFS is present^[11, 20, 26-28, 34] are much better in this respect. In particular, Rast's^[13, 35] model describes the transient ZFS modulation using an Ornstein-Uhlenbeck process^[36], namely random jumps around an average value with a Gaussian probability distribution. This process is actually a dynamical equivalent to the *strain* encountered in the analysis of disordered solid-state EPR spectra.^[37, 38] Gaussian strain is a phenomenological description of a distribution of the spin Hamiltonian parameters throughout the sample, for example due to differences in the hydrogen bonding pattern around the spins. This model can be applied to the g -factor^[39-41] (g -strain) and hyperfine coupling^[42, 43] (A -strain), as well as to the ZFS tensor^[44-46] (D , E -strain).

Thus we see that the determination of the ZFS parameters and their associated strains in the solid state provides us with independent access to the key factors governing the electron spin relaxation. Even the sign of the ZFS parameters can be determined through measurements at very low temperatures (< 10 K). Of course, the method is applicable to molecules of arbitrary size since rotational motion plays no role in this case. Furthermore, we can expect approximately the same disorder in a frozen glass as in a liquid. Thus we can use such samples to probe both the mean values of the ZFS tensor and their distributions,

which we can then compare with the magnitude parameters obtained from relaxation studies of aqueous solutions.

In this paper, we report and analyze the EPR spectra of several Gd^{III} chelates (Scheme 1, 2) in water-glycerol glasses.

The chelates include some well-known compounds already used for medical applications (DOTA, DTPA), as well as newer molecules, i) The macromolecule DOTA-derivative Gd-P792 exists as two different forms, (R) with six different stereoisomers determined by the configuration at each of the stereogenic centers at carbon: 4*R* (4*S*); *RSSS* (*SRRR*) and the achiral diastereoisomers *RSRS* and *RRSS*^[54] and (B) with the configuration 4*R* (4*S*). ii) The heterometallic, self-assembled Metallostarex [Fe{[Gd₂(bipy-DTTA)(H₂O)₄]₃}]⁴⁺ and its monomer [Gd₂(bipy-DTTA)(H₂O)₄]²⁻. The doped complexes, [Fe{[Y₂(bipy-DTTA)(H₂O)₄]₃}]⁴⁺ and [Y₂(bipy-DTTA)(H₂O)₄]²⁻ with Gd^{III} are also studied. iii) The dinuclear complexes [Gd₂(*p/mX*(DO3A)₂)(H₂O)₂]. The ligands contain two DO3A³⁻ metal chelating units on a xylene core as a non-coordinating linker in meta (*m*) and para (*p*) position. iv) The dinuclear [Gd₂M (tpy-DTTA)₂(H₂O)₄], (M = Fe, Ru), that self-assemble from M^{II} and two terpyridine derivatives functionalized with polyaminocarboxylate groups. In our series of Gd^{III} complexes, various aspects such as (a) the influence of the conformation, form (R) and (B), for the macrocyclic P792. (b) The influence of the metal-metal interaction for the Doped sample of [Y₂(bipy-DTTA)(H₂O)₄]²⁻ and [Fe{[Y₂(bipy-DTTA)(H₂O)₄]₃}]⁴⁺ with Gd^{III} and the Ru^{II} analogue of [Gd₂Fe(tpy-DTTA)₂(H₂O)₄]. (c) The influence of the para or meta substitution in xylene-derivative are investigated.

Experimental Section

Materials. The Gd-P792 (R, B)⁵¹ were supplied from Guerbet pharmaceuticals. Synthesis of [Gd₂M(tpy-DTTA)₂(H₂O)₄] (M^{II} = Fe^{II}, Ru^{II}),⁴⁹ [Gd₂(*mX*(DO3A)₂)(H₂O)₂], [Gd₂(*pX*(DO3A)₂)(H₂O)₂],⁴⁸ [Gd₂(bipy-DTTA)(H₂O)₄]²⁻ and [Fe{[Gd₂(bipy-DTTA)(H₂O)₄]₃}]⁴⁺,⁵⁰ have been described previously.

Samples preparation. Most samples were prepared in situ by dissolution of the ligand (10% excess) in a Gd(ClO₄)₃. The pH was adjusted to 6.5 by adding NaOH solution. Final concentrations of 5mM for all Glasses except for [Gd(DOTA)(H₂O)]⁻ and [Gd(DTPA)(H₂O)]²⁻ (0.5mM) were prepared in 1:1 (V/V) glycerol/water solution. For the [Y₂/Gd₂(bipy-DTTA)(H₂O)₄]²⁻ and [Fe{Y₂/Gd₂(bipy-DTTA)(H₂O)₄]₃]⁴⁺

the same process was followed with adding a solution mixed of 90% of $\text{Y}(\text{ClO}_4)_3$ and 10% of $\text{Gd}(\text{ClO}_4)_3$.

The Gd-P792(B) and Gd-P792(R) solutions were prepared by dissolving a weighed amount of the complex in doubly-distilled water. The pH of both samples was adjusted to 6.5.

All solutions were checked for the absence of free Gd^{III} ion using the xylenol orange test.⁵²

EPR Measurements. The EPR spectra at 240 GHz were measured at the EPR facility of the National High Magnetic Field Laboratory with a home-built quasi-optical superheterodyne spectrometer.⁵³ A configuration without cavity was used, with a teflon sample cup containing about 40 μl of the solution of the Gd^{III} complex. The glasses were formed by flash freezing the sample in liquid nitrogen before loading into the pre-cooled continuous-flow cryostat.

The energy of a 240 GHz electromagnetic radiation corresponds to a temperature of 11.5 K. Therefore, at 4 K only transitions between the lowest energy levels are observed. However, even at a very low irradiation power with B_1 field smaller than 1 μT , the spectrum was distorted due to saturation. For that reason, at the lowest temperatures, rapid-passage EPR⁶² was employed to record the spectra, using relatively high powers ($\sim 1\text{mW}$ at the sample) and small modulation amplitudes. Instead of a derivative lineshape, the absorption lineshape is directly obtained. At temperatures above 30 K, standard CW-EPR was used.

Data Analysis. The EPR spectra were fit using EPRcalc program,⁵⁴ that utilises complete diagonalization of the spin Hamiltonian, which can be written using irreducible tensor operators T_{2q} ⁶³ as follows:

$$\hat{H}(\Omega) = \hat{S}_z g_{\text{iso}} \mu_B B_0 + \sqrt{\frac{2}{3}} D \sum_{q=-2}^{+2} \hat{T}_q^2 D_{0q}^2(\Omega) + E \left(\sum_{q=-2}^{+2} \hat{T}_q^2 D_{-2q}^2(\Omega) + \sum_{q=-2}^{+2} \hat{T}_q^2 D_{2q}^2(\Omega) \right)$$

The first term represents the field dependent electron Zeeman contribution and the second and third terms, without any explicit B_0 -dependence, represent the Zero Field Splitting. The parameter g_{iso} is the isotropic g-factor, μ_B the Bohr magneton, B_0 the external magnetic field. $D_{pq}^2(\Omega)$ is a Wigner rotation matrix between the ZFS and laboratory frame. D and E are the axial and rhombic ZFS coefficients, which describe the deviation from the octahedral and the axial symmetry respectively. The distributions, in solid state, of D and E are noted D-strain (σ_D) and E-strain (σ_E) and accounted for by including a

Gaussian line-broadening that is proportional to the shift of the transitions due to a change in D and E. No correlation between σD and σE is assumed.

Results and Discussion

At high magnetic field the Zeeman interaction energy becomes larger than the zero-field splitting (ZFS), and since $h\nu$ is larger, additional transitions become observable in the spectrum,⁵⁵ which permit the determination of larger values of ZFS.⁵⁶ At high microwave frequency and low temperature $h\nu > k_B T$, spin polarization is increased, almost all of the spins are in the Zeeman ground state.

The magnitude of the Zero Field Splitting of the Gd^{III} complexes is slightly less than the X-band microwave energy (9.4 GHz). In this case, the spectrum analysis is not straightforward since the ESR spectra become very asymmetric. At higher frequencies, the Zeeman term dominates the ZFS term in the spin Hamiltonian, and the spectrum exhibits a small peak at 4K that can be easily assigned from its position to the central transition $m_s = -1/2 \rightarrow +1/2$. The use of the very high frequency EPR technique for Gd^{III} ions makes therefore the analysis simpler and more reliable. Furthermore, the change of populations of the levels at very low temperatures alters the relative intensity of transitions, thus allowing the determination of the sign of the D parameter from the relative position of the $m_s = -1/2 \rightarrow +1/2$ peak with respect to the rest of overall powder pattern. Indeed, $D > 0$ or $D < 0$ occurs depending on whether the lowest energy level at zero magnetic field is $m_s = \pm 1/2$ ($D > 0$) or $m_s = \pm 7/2$ ($D < 0$) as represented in scheme 3.

The gadolinium water-glycerol solutions formed good glasses after quenching the sample in liquid nitrogen. Figures 1 and 2 show selected experimental and calculated EPR spectra at 240GHz and variable temperature.

For all the complexes, the rapid passage spectra at 4K showed a broad lineshape superposed with a small sharp peak. The broad line is assigned to the transitions between the lower levels and the small peak to those of the central energy levels, respectively. At 40K and 150K, conventional absorption-derivative spectra were obtained. The sharp $m_s = -1/2 \rightarrow +1/2$ transition dominates the spectrum.

The ZFS parameters, D, E, σD and σE were determined from a least square fitting of 4K spectra. As is customary, we divided the Gd^{III} complexes into two groups, macrocyclic and acyclic compounds. The results for the acyclic complexes can be found in Table 1, and those for the cyclic complexes are reported in Table 2. The validity of the ZFS parameters derived from 4K spectrum was then confirmed

by their ability to simulate the higher temperatures spectra (figures 1-2). The calculated spectra are in good agreement with the experimental ones.

We first note that the sign of D is negative for all the cyclic complexes except for the Gd-P792(R) and positive for the acyclic ones. Misra et al.⁵⁶ have determined for Gd^{III} doped single crystals of CeF₃, LaF₃, PrF₃, and NdF₃ positive sign of all spin Hamiltonian parameters from intensities of lines at liquid He temperature. Before that, Buckmaster has reported negative as well as positive signs of D for several examples of Gd^{III} complexes in solid state.⁶⁵

Acyclic complexes. As it was mentioned before, we observed a positive sign of D for the acyclic group. Despite a different coordination polyhedron for (DTPA), compared to (DTTA) derivative complexes, very similar ZSF parameters were determined. In addition, the nature of the linking bridge between DTTA groups, bipyridine for the [Gd₂(bipy-DTTA)(H₂O)₄]²⁻ and terpyridine for the [Gd₂M(tpy-DTTA)₂(H₂O)₄] does not change the ZFS parameters.

Within spin dilution with Y^{III}, no spectra change has been observed, therefore, it can be concluded that the dipolar interaction between Gd^{III} centers has no influence neither on the magnitude nor the sign of D, E and their distributions. We also observed that changing the central metal ion from Fe^{II} to Ru^{II} in the [Gd₂M(tpy-DTTA)₂(H₂O)₄], does not contribute to a possible interaction between Gd^{III} ions. We also observed the same result for [Gd₂M(tpy-DTTA)₂(H₂O)₄] complexes in solution by recording EPR spectra at 240GHz and 324GHz.⁶⁷

For all the acyclic complexes, E is significantly larger than zero. Regarding to the low symmetry of those compounds, a rhombic contribution to the ZFS can be expected.

Macrocyclic complexes. With exception of the Gd-P792(R), we observed a positive sign of D for all the macrocyclic compounds. This can be by the fact that the fitting procedure does not take into account the 6 characterised stereoisomers of the P792-R^[59].

The rhombic ZFS parameter E is equal to zero in the case of the [Gd(DOTA)(H₂O)]⁻ and the Gd-P792(B), reflecting the axial symmetry of these complexes. However, the D value of Gd-P792(B) is twice as large as that of the [Gd(DOTA)(H₂O)]⁻ complex. As it is well-known, the [Gd(DOTA)(H₂O)]⁻ exists as two enantiomeric pairs of diastereoisomers. The two diastereoisomeric forms, labeled M (major) and m (minor) on the basis of the relative population in solution determined by NMR analysis, differ in

the layout of the acetate arms. In the two isomers the parallel squares, defined respectively by nitrogen and acetate oxygen atoms, are twisted by an angle of ca. 40° in M and 20° in m, providing square antiprismatic (A) and inverted antiprismatic (IA) geometry, respectively ^[58]. The increase in the molecular size for the P792(R/B) by substitution of hydrophilic arms leads may be to a change on the M/m ratio.

For $[\text{Gd}_2(\text{pX}(\text{DO3A})_2)(\text{H}_2\text{O})_2]$ and $[\text{Gd}_2(\text{mX}(\text{DO3A})_2)(\text{H}_2\text{O})_2]$, the values of ZFS parameters are nearly equal. The substituted position of xylene group in para or meta does not influence the ZFS. In contrast to the Gd-P792(B) and the $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ E values are not equal to zero. The lack of the fourth carboxylate arm in the DO3A ligand leads to a drop in the symmetry of the complex. Nevertheless, the sign of D is negative for both complexes.

Comparison with parameters from solution. It is worthwhile to compare the values of the ZFS parameters for the $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ and $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ to the previously calculated ZFS parameters in solution.⁵⁹

In the Rast et al. description, the transient ZFS modulation is described as an Ornstein-Uhlenbeck process,⁶⁰ namely random diffusion over a Gaussian distribution. This can be regarded as a dynamic equivalent of the strain we observe in the frozen solutions. It can be shown ⁶¹ that the ZFS parameter a_{2T} relevant for relaxation studies in liquids is equal to $[2/3(\sigma D/2)^2 + 2(\sigma E/2)^2]$ using the current definition of the strain parameters (full width at 0.6065 height of the Gaussian). The static ZFS parameter a_2 has been calculated in the same way and it is equal to $[2/3(D/2)^2 + 2(E/2)^2]$.

Calculated a_2 and a_{2T} parameters for $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ and $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ are reported in Table 3. The values of the static ZFS calculated from our glassy samples are similar to those obtained from relaxation studies in aqueous solution.^[61] However, the calculated transient ZFS are twice as small as that obtained in solution for both complexes. A possible explanation could be that in the program, the assumption has been made that σd and σE should be smaller than D and E, respectively. Another possible explanation, that instead of a dynamic process in solution, we consider a snapshot of this process in glasses. That may lead to decrease in the magnitude of the transient ZFS.

¹H NMRD profiles. In the aim to show the importance of determining independently electronic relaxation parameters, we used our parameters calculated from HF-EPR technique to fit NMRD profiles (figure 3) using the fewest adjusting parameters by fixing as many parameter as possible.

The general procedure for the simulation of NMRD profiles with in and out side the validity range of Redfield's approximation using Monte-Carlo simulations has been published elsewhere.⁶² The Matlab subroutine used for the calculations was modified to allow for use (D, E) non-axial static and (σD , σE) transient ZFS Hamiltonians, limited to 2nd order.

The only remaining adjustable parameters for fitting experimental NMRD profiles are the rotational correlation time τ_r , the rotational activation energy E_r , the vibrational correlation time τ_v and the vibrational activation energy E_v . The results of the fit are reported in Table 4. We reproduce with reasonable parameters, for example, the value of τ_r is in the commonly values of Rast regarding to the molecular size of $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ and $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$. The same conclusion for the values of E_r and E_v .

Based on the fitting results, further simulations were carried out to evaluate the effect of the rhombicity of the ZFS parameters on the NMRD profile at low field (figure 3). By variation of the...

Conclusions

The present investigations have been carried out to determine the Zero Field Splitting parameters for various Gd(III)-based contrast agents for MRI. The very-high frequency EPR study combined with very low temperature measurements presented here indicates a correlation between the sign of D and the chelate structure surrounding the Gd(III).

Many questions, of course remain open and many aspects of our inspections need further corroboration. For example, it is planned also to compare the EPR spectra of glasses with multifrequency EPR spectra for powders.

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SUPPORTING INFORMATION PARAGRAPH

FIGURE CAPTIONS

Figure 1 Acyclic compounds: left, the experimental (upper) and the fitted(bottom) spectra of $[\text{Gd}_2(\text{bipy-DTTA})(\text{H}_2\text{O})_4]^{2-}$ glass; right, The experimental (upper) and the fitting (bottom) spectra of $[\text{Fe}\{[\text{Gd}_2(\text{bipy-DTTA})(\text{H}_2\text{O})_4]\}_3]^{4+}$ glass.

Figure 2 Cyclic compounds: left, the experimental (upper) and the fitted (bottom) spectra of $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ glass; right, the experimental (upper) and the fitted(bottom) spectra of Gd-P792(B) glass.

Figure 3 ^1H NMRD profiles of (a) $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$, (a') $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ at 298K, (b) $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$. Experimental profiles are represented with full symbols, calculated profiles with full lines and simulated profiles with dashed lines. The temperatures for (a) and (b) are from top to bottom: (a) 277K, 283K, 291K, 298K, 305K and 312K. (b) 277K, 298K and 308K.

SCHEME TITLES

Scheme 1 Acyclic compounds,

Scheme 2 Macrocyclic compounds,

Scheme 3 Schematic representation of the observed transitions for $S=7/2$ at zero magnetic field to applied microwave are indicated by arrows.

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Scheme 1.

Scheme 2.

$[Gd(DOTA)(H_2O)]^-$

$Gd-P792(R/B)$

$R' =$

$[Gd_2(pX(DO_3A)_2)(H_2O)_2]$

$[Gd_2(mX(DO_3A)_2)(H_2O)_2]$

Scheme 3.

Figure 1

Figure 2

Figure 3

Table 2 The ZFS parameters obtained by fitting the experimental EPR spectra at 4K and 240GHz for cyclic complexes.

	D(cm ⁻¹)	E(cm ⁻¹)	σD(cm ⁻¹)	σE(cm ⁻¹)	g
[Gd(DOTA)(H ₂ O)] ⁻	-0.019	0.000	0.019	0.020	1.989
Gd-P792 (B)	-0.060	0.000	0.060	0.010	1.989
Gd -P792 (R)	0.033	0.010	0.016	0.013	1.989
[Gd ₂ (pX(DO3A) ₂)(H ₂ O) ₂]	-0.037	0.005	0.030	0.023	1.990
Gd ₂ (mX(DO3A) ₂)(H ₂ O) ₂]	-0.038	0.006	0.033	0.023	1.990

Table 1. The ZFS parameters obtained by fitting the experimental EPR spectra at 4K and 240GHz for acyclic complexes.

	D(cm ⁻¹)	E(cm ⁻¹)	$\sigma D(\text{cm}^{-1})$ ₁₎	$\sigma E(\text{cm}^{-1})$ ₁₎	g
[Gd(DTPA)(H ₂ O)] ²⁻	0.054	0.011	0.026	0.007	1.989
[Gd ₂ (bipy-DTTA)(H ₂ O) ₄] ²⁻	0.055	0.016	0.024	0.009	1.989
[Y ₂ /Gd ₂ (bipy-DTTA)(H ₂ O) ₄] ²⁻	0.054	0.016	0.027	0.007	1.989
[Fe{[Gd ₂ (Bipy-DTTA)(H ₂ O) ₄]} ₃] ⁴⁻	0.056	0.016	0.020	0.006	1.989
[Fe{Y ₂ /Gd ₂ (Bipy-DTTA)(H ₂ O) ₄ }] ₃ ⁴⁻	0.057	0.014	0.024	0.009	1.989
[Gd ₂ Fe(tpy-DTTA) ₂ (H ₂ O) ₄]	0.050	0.014	0.037	0.006	1.989
[Gd ₂ Ru(tpy-DTTA) ₂ (H ₂ O) ₄]	0.057	0.014	0.036	0.006	1.989

Table 3. The ZFS parameters determined by Rast method in solution and comparison with the parameters obtained in glasses for [Gd(DTPA)H₂O]²⁻ and [Gd(DOTA)H₂O]⁻

	[Gd(DTPA)(H ₂ O)] ²⁻		[Gd(DOTA)(H ₂ O)] ⁻	
	This work(frozen)	Rast method	This work(frozen)	Rast method
$a_2/10^{10} \text{ s}^{-1}$	0.80	0.92	0.30	0.35
$a_{2T}/10^{10} \text{ s}^{-1}$	0.22	0.43	0.23	0.43

Table 4. Parameters obtained for NMRD profiles of $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$ and for $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ by introducing the fixed ZFS parameters calculated from HF-EPR. Underlined parameters were fixed in the fit.

	$[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$	$[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$
$k_{ex}^{298}/10^6 \text{ s}^{-1}$	<u>3.8±0.4</u>	<u>4.6±0.3</u>
$\Delta H^\ddagger/\text{kJ mol}^{-1}$	<u>52.9±2.3</u>	<u>54.5±4.5</u>
$D_{\text{GdH}}^{298}/10^{-10} \text{ m}^2 \text{ s}^{-1}$	<u>23.0±5.0</u>	<u>23.0±2.9</u>
$E_{\text{DGdH}}/\text{kJ mol}^{-1}$	<u>17±1.2</u>	<u>18.1±1.7</u>
$A/\hbar/10^6 \text{ rad s}^{-1}$	<u>-3.9±0.4</u>	<u>-4.0±0.4</u>
C_{os}	<u>0.12±0.05</u>	<u>0.13±0.05</u>
$\tau_{\text{RO}}^{298}/10^{-12} \text{ s}$	80	149
$E_{\text{R}}/\text{kJ mol}^{-1}$	13.57	20.0±1.0
$\tau_{\text{RH}}/\tau_{\text{RO}}$	<u>0.65</u>	<u>0.65</u>
$\tau_v^{298}/10^{-12} \text{ s}$	0.29	0.42
$E_v/\text{kJ mol}^{-1}$	0.5	8.6
$D [\text{MHz}]$	<u>1426.2</u>	<u>-590</u>
$E [\text{MHz}]$	<u>398.5</u>	<u>0</u>
$\sigma D [\text{MHz}]$	<u>549.5</u>	<u>590</u>
$\sigma E [\text{MHz}]$	<u>386.4</u>	<u>410</u>
g	<u>1.9</u>	<u>1.9</u>
q_{WAT}	<u>1</u>	<u>1</u>
$\chi [\text{MHz}]$	<u>7.8</u>	<u>7.8</u>
$a_{\text{GdHW } 1} / \text{\AA}$	<u>3.1</u>	<u>3.1</u>
$a_{\text{GdHW } 2} / \text{\AA}$	<u>3.5</u>	<u>3.5</u>
$a_{\text{Gd-O}} / \text{\AA}$	<u>2.5</u>	<u>2.5</u>