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# Electronic fine structure calculation of $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$ using LF-DFT: The zero field splitting

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## ABSTRACT

Zero field splitting plays an important role in determining the electron spin relaxation of Gd(III) in solution. We understand the ZFS as an effect depending on the f electron structure and treat it in the framework of ligand field-density functional theory (LF-DFT). We apply this theory to calculate the ZFS of  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  from first principles, having an insight concerning the contributions determining the ZFS.

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## 1. Introduction

Paramagnetic Gd(III) induces a strong NMR-relaxation enhancement of neighboring water protons and therefore a wide application of Gd(III) exists as contrast agent in medical magnetic resonance imaging (MRI) [1]. The free Gd(III) ions are very toxic, so binding them to stable complexes is a prerequisite for their in vivo use [2]. The macrocyclic ligand DOTA (1,4,7,10-tetraaza-1,4,7,10-tetrakis (carboxymethyl) cyclododecane) [3] has been developed for such a complexation and nowadays  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  is one of the most successful MRI contrast agents [3].

The efficiency of the induced NMR relaxation is, among others, influenced by the spin relaxation of the Gd(III) unpaired electrons. Since zero field splitting plays a dominant role in the electron spin relaxation of Gd(III), one “[...] can say, that for Gd(III) ions, the structure and dynamics of the electronic density of the chelate frame-

work surrounding the metal determine the ZFS and therefore the electron spin relaxation rates in solution.” [4]. Electron spin relaxation in gadolinium complexes is described by a static ZFS modulated by rotational motion of the compound and by a transient ZFS modulated by inharmonic distortions of the coordination environment of Gd(III) [5]. Broadly speaking, the efficiency of the induced NMR relaxation is influenced by the exchange rate of water molecules bound to the metal with the bulk solution (linked to electrostatic and steric effects), the rotational correlation time (linked to the size of the molecule) and the spin relaxation of the Gd(III) electrons [1].

It is generally accepted that the main cause of the electron spin relaxation of the Gd(III) electrons is ZFS, namely splitting of the  $^8S_{7/2}$  ground state multiplet in the absence of an external magnetic field, due to small admixtures of states with other  $L$  and  $S$  values into the  $L = 0$  ground state through the ligand field and spin-orbit coupling. To minimize the static ZFS and therefore electron spin relaxation it is important to know how non-spherical coordination influences ZFS. A quantitative understanding of the structural causes of the ZFS can therefore provide useful clues for the design of contrast agents with improved electronic properties.

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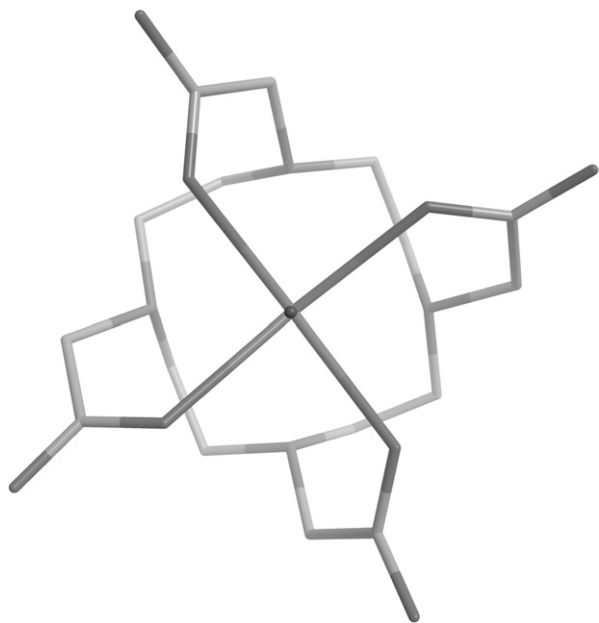


Fig. 1. Schematic representation of  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  in the SA geometry used for the calculations; the coordinated water molecule (with the Gd-O( $\text{H}_2$ ) axis pointing out of plane) has been omitted for clarity.

“The magnetic and spectroscopic properties of the lanthanide ions depend on the f electron structure, which is generally understood in the framework of a model where the f orbitals are considered shielded from the chemical environment.” [6]. The ZFS is therefore very small in Gd(III) complexes and difficult to assess with quantum chemical calculations [7]. We can obtain a description of the multiplet structure and energies of states in this given basis of f spinors using the ligand field density functional theory (LF-DFT) [8]. LF-DFT is a DFT-based LF model, mapping the energies of the microstates of the whole LF-manifold from DFT single-determinant calculations to the corresponding LF microstates, thus allowing us to estimate all Racah and LF-parameters in a least square sense. With these parameters, and including spin-orbit coupling, a LF calculation is then performed. This theory has already been adapted to a smaller Gd(III) system,  $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$  [6].

We calculate in this work the static ZFS of  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  from first principles and give an insight concerning contributions that determine its amplitude. The  $\text{Gd}^{3+}$  ion in the DOTA complex is nine coordinated with four nitrogen atoms and four carboxylate oxygens forming an anti-prismatic cage (Fig. 1). On top of the square formed by the four oxygens is a water molecule coordinated. In aqueous solution the complex exists in two diastereoisomeric forms called square-antiprismatic (SA) and twisted square antiprismatic (TSA) [9]. In the SA form, which is the major isomer found for  $[\text{Gd}(\text{DOTA})(\text{H}_2\text{O})]^-$  in aqueous solution, the complex is in the  $\Delta(\lambda\lambda\lambda\lambda)$  (Fig. 1) or  $\Lambda(\delta\delta\delta\delta)$  enantiomeric form.

## 2. Theoretical part

As in reference [6], we use a model where the f orbitals are considered shielded from the chemical environment

and so we work in a ligand field approach considering the complex as an ‘ionic molecule’. Thus, we interpret the magnetic and spectroscopic properties of the lanthanide ions as depending on the f electron fine structure. We perform all calculations starting in the basis of the 14 gadolinium 4f spinors. Our Ansatz is for the Ligand Field part the same as in reference [6] and so we give here just a short survey of the most important parts and underline the essential differences. We write the general Hamiltonian acting upon the atomic metal f orbitals, which besides the central potential of the nucleus looks like in reference [6] as

$$H = H_{\text{ER}} + H_{\text{SO}} + H_{\text{LF}} \quad (1)$$

where the three terms correspond to the inter-electron repulsion ( $H_{\text{ER}}$ ), the spin-orbit coupling ( $H_{\text{SO}}$ ) and the ligand field ( $H_{\text{LF}}$ ), respectively.

The matrix elements for each of these operators can be expressed in a basis of single Slater determinants,  $\Psi_\mu = \phi_1 \times \dots \times \phi_n$ , where  $\phi_i$  is a single-occupied spinors and n ist the number of f electrons. So our 14 gadolinium 4f spinors span a set of  $\binom{14}{7}$  single Slater determinants, which we use as our new working basis, that is  $\mu = 1, 2, \dots, 34332$ . We can write the matrix elements of  $H_{\text{ER}}$  as linear combinations of a limited number of reduced two-electron electrostatic matrix elements. Working with f electrons, we use the four Slater-Condon parameters  $F_k$  ( $k = 0, 2, 4, 6$ ). With this convention, the matrix elements of the inter-electron repulsion are given by

$$\begin{aligned} \langle \Psi_\mu | H_{\text{ER}} | \Psi_\nu \rangle &= \sum_{g,h,i,j=1}^n A_{\text{ER}}^{ghij} \langle \phi_g \phi_h | H_{\text{ER}} | \phi_i \phi_j \rangle \quad (a) \\ &= \sum_{g,h,i,j=1}^n \sum_{k=0,2,4,6} A_{\text{ER}}^{ghij} C(k, g, h, i, j) F_k \quad (b) \end{aligned} \quad (2)$$

“The real coefficients  $A_{\text{ER}}$  combine the Coulomb and exchange matrix elements in an orbital basis set according to Slater’s rules. The  $C(k, g, h, i, j)$  are products of the vector coupling coefficients for real spherical harmonics.” [6]. Using Slater’s rules, the spin-orbit coupling elements are simply given by

$$\langle \Psi_\mu | H_{\text{SO}} | \Psi_\nu \rangle = \zeta \sum_{i \in \mu, j \in \nu} A_{\text{SO}}^{ij} \langle \phi_i | l \cdot s | \phi_j \rangle \quad (3)$$

where  $\zeta = \langle \frac{1}{r} \frac{dV}{dr} \rangle$  is the spin-orbit coupling constant. The ligand field terms are described by linear combinations of the matrix elements of the effective ligand field potential  $V_{\text{LF}}$  acting upon the f orbitals. The  $7 \times 7$  matrix is reduced to a set of 28 independent matrix elements by the Hermiticity of the ligand field Hamiltonian

$$\langle \Psi_\mu | H_{\text{LF}} | \Psi_\nu \rangle = \sum_{i \in \mu} \sum_{j \in \nu} A_{\text{LF}}^{ij} \langle f_i | V_{\text{LF}} | f_j \rangle. \quad (4)$$

In order to get all the required parameters for equation (1), we use LF-DFT [8]. LF-DFT is a DFT-based LF model, mapping the energies of the microstates in the LF-manifold from DFT single-determinant calculations to the corresponding LF microstates, thus allowing us to estimate all

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