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Molecular Dynamics Simulations of the Internal Mobility of Gd^{3+}-Based MRI Contrast Agents: Consequences for Water Proton Relaxivity

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Abstract: The increasing use of contrast agents in magnetic resonance imaging (MRI) for medical diagnosis is due to the ability, called *relaxivity*, of these paramagnetic compounds to accelerate the relaxation of the surrounding water proton spins. A new classical force field for molecular dynamics simulations of Gd^{3+} polyaminocarboxylates has recently been published, which allows the study of the chelate internal mobility. We present two selected examples where such motions can affect relaxivity. Knowing the relationship between the bound water proton and oxygen mobility is important for the combined analysis of multinuclear NMR studies, and we show that they differ significantly. Next, we observe symmetry changes over time in the Gd^{3+} coordination polyhedron of the acyclic complexes. We propose that such rearrangements can play a role in the electron spin relaxation of Gd^{3+} chelates, an important result considering the uncertainty still attached to this particular factor.

Keywords: Computational chemistry · Gadolinium · Magnetic resonance imaging · Relaxation

Introduction

Paul C. Lauterbur (USA) and Sir Peter Mansfield (UK) invented Magnetic Resonance Imaging (MRI) in the 1970s [1][2]. Since its introduction into the medical world in the beginning of the 1980s, it has become an increasingly popular diagnosis method owing to its non-invasive nature and the absence of serious health hazards – only patients with metal or pacemakers inside their bodies may not be examined due to the intense magnetic field. In 2002, 22 000 MRI cameras worldwide performed more than 60 million examinations. For this resounding success, Lauterbur and Mansfield jointly received the Nobel Prize in Medicine for 2003.

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The basic principle of MRI is to record the NMR signal of water protons (an abundant target, since 70% of the body mass is water) with the help of magnetic field gradients, leading to a three-dimensional map of the tissues. In order to shorten the examination time or increase the image quality, physicians sometimes use drugs known as *contrast agents*. MRI contrast agents are paramagnetic compounds that shorten the proton magnetic relaxation times T_1 and T_2 thanks to the fluctuating dipolar interaction between the electronic and nuclear spins. This relaxation enhancement, called *relaxivity*, is governed by various factors such as the distance between the spins and its fluctuation of time (chemical exchange or diffusion), the rotational motion of the molecule with respect to the external magnetic field and the behaviour of the electron spin itself. The rational design of better contrast agents requires understanding the relationship between the molecular structure and the various parameters that determine the relaxivity [3][4].

First and foremost, relaxivity is proportional to $S(S+1)$, where S is the electronic spin. The Gd^{3+} cation has the highest spin ($S = 7/2$) in the stable elements and no orbital momentum due to its half-filled 4*f* shell, and exhibits thus a fairly slow electron spin relaxation. This makes it the building block of choice for MRI contrast agents. However, it is necessary to decrease the Gd^{3+} toxicity by encapsulating it within a chelate, with a seriously negative impact on relaxivity [5]. This reduces the number of water molecules in close contact with the metal (down to one single *inner sphere* water molecule) and slows down the exchange with the bulk. The latter is especially problematic when combined with the favoured route towards high-relaxivity contrast agents, namely macromolecules with slow rotational diffusion [6–12]. For these compounds, the slow water exchange limits the relaxivity gain obtained through the longer rotational time. Finally, there is still much discussion about the electron spin relaxation, with several competing models proposed over the years [13–16].

Beside experimental studies (potentiometric titrations [17], UV-visible [18], luminescence [19], NMR [20][21], and EPR [15][16] spectroscopies), computational chemistry has proven to be a uniquely useful tool to gain detailed information about such complexes, for example their structure [22][23] and solvation [24]. The recent development of a force field able to reproduce the intramolecular behaviour of a Gd^{3+} complex in aqueous solution by molecular dynamics (MD) simulation [25][26] has opened a new way to investigate the domain

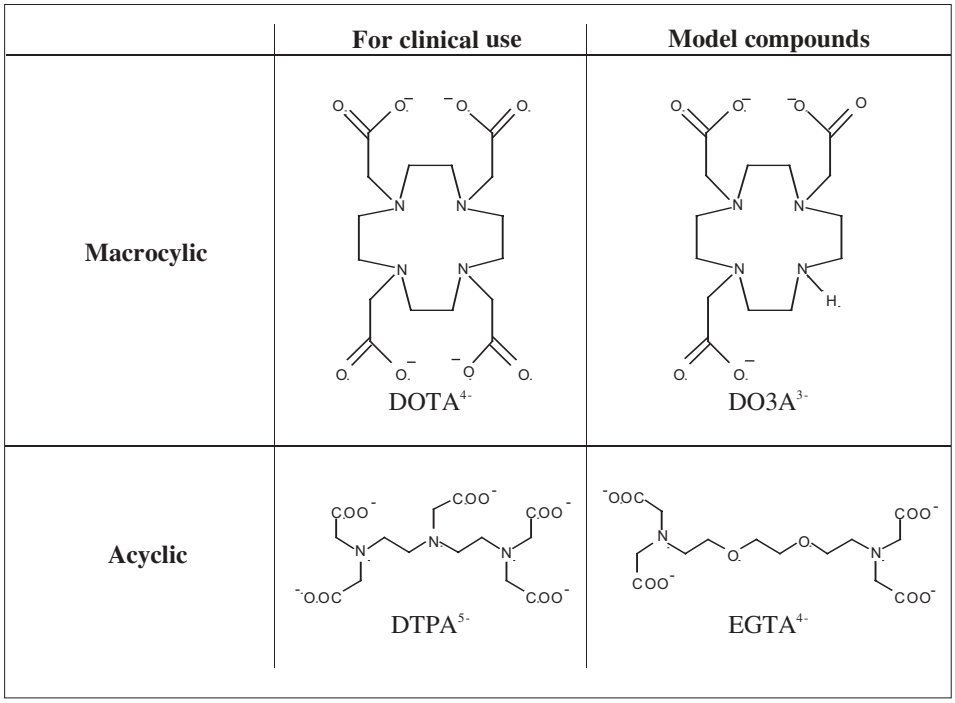

Fig. 1. Structures of the ligands used in the studied complexes: $[Gd(DOTA)(H_2O)]^-$, $[Gd(DO3A)(H_2O)_2]$, $[Gd(DTPA)(H_2O)]^{2-}$ and $[Gd(EGTA)(H_2O)]^-$.

of MRI contrast agents. Since this force field does not use any covalent bonds between the metal and the ligand donor atoms, it allows the study at the molecular level and picosecond time scale of the internal motions that are involved in the relaxivity process.

In this paper we summarize some recent results [26] obtained within the ongoing computational study of Gd^{3+} complexes in our lab [24][25][27–29]. The method has been described in detail elsewhere [25][26] and will not be repeated here. We characterise the molecular mobility of various chelates using MD simulations and relate the observed motions with relaxivity. A popular class of chelating ligands are polyaminocarboxylates (see Fig. 1 for the ligands used in the present study). The picosecond resolution, combined with the versatility of the new force field, makes classical MD simulation an attractive tool for the understanding of the more obscure contrast agents properties, such as the Gd^{3+} electron spin relaxation, and the internal motion of the water molecules bound to the metal ion.

Selected Results and Discussion

Let us first summarize the structural results. The force field generally conserves the coordination number CN = 9 of the Gd^{3+} ion throughout the simulation. Gd-N distances were within 2–4% from the crystalline value, and Gd-carboxylate within 5–7%. During the DOTA, DTPA and EGTA simulations, we observed the departure of the bound water molecule. Such an event should not occur on our time scale since the total simulation time (1 ns) is far less than the shortest experimental water residence time in our complexes ($[Gd(EGTA)(H_2O)]^-$, 3.3×10^{-8} s). Of course, since the experimental value is an average over a large number of molecules, such events cannot be ruled out during a simulation. However, their rarity makes them statistically insignificant.

Table. Calculated 2nd order rotational correlation times of studied complexes

Ligand	$DOTA^{4-}$	$DO3A^{3-}$	$DTPA^{5-}$	$EGTA^{4-}$
τ_R(polyhedron) / ps	52	37	50	43
τ_R(Gd-OW) / ps	51	36, 33	46	41
τ_R(‹Gd-HW›) / ps	41	27	32	31
τ_R(expl) / ps	77	66	58	58
τ_R(HW) / τ_R(OW)	0.82	0.82	0.64	0.72

Rotational Correlation Times

As pointed out earlier, the rotational correlation time of the molecule is an important parameter to consider for the design of high-relaxivity contrast agents. It also plays a major role in the mechanisms that determine ^{17}O-NMR [30] and EPR [31] relaxation in solution. For a simultaneous analysis of multiple magnetic resonance experiments, one must therefore address the question of the equivalence of the correlation times relevant to each method. For NMR, the correlation time describes the tumbling of the vector that joins the electron spin (assumed to be a point dipole on the metal ion) and the nucleus of interest, *i.e.* the Gd-O_{water} and Gd-H_{water} vectors respectively. For EPR, it describes the reorientation of the ZFS tensor, and therefore of the whole coordination polyhedron. Generally, it has been assumed that the three values were the same within the experimental error.

It is straightforward to calculate the rotational correlation time for an arbitrary vector from MD simulations [32]. In the Table, we report the calculated correlation times for the coordination polyhedron (approximated by a signed sum of the individual Gd-O and Gd-N vectors), the inner-sphere water hydrogen and oxygen atoms, as well as the experimental values from the literature (simultaneous fit of experimental ^{1}H-NMR, ^{17}O-NMR and EPR data [21][30][33]). The MD correlation times are shorter by 15–57% than their experimental counterparts. It is actually a systematic trend in our simulations, as the H_2O rotation correlation time in the bulk is underestimated by a similar amount. With this in mind, we can still observe that the oxygen and polyhedron correlation times (τ_R(O) and τ_R(poly)) are almost identical, whereas the hydrogen correlation time τ_R(H) is about 20 (macrocyclic complexes) to 35% (acyclic complexes) shorter. It appears that the bound water molecule retains some motional freedom regarding the orientation of the OH bond with respect to the metal ion (rotation around the Gd-O vector, variable tilting of the H-O-H plane). This finding was first published for the $[Gd(EGTA)(H_2O)]^-$ MD simulations [25] and soon found experimental support [34], with a ratio $\tau_R(H)/\tau_R(O) = 0.65\pm0.3$ for DOTA-like complexes.

Coordination Polyhedron Dynamics

The coordination polyhedron of trivalent lanthanides can assume different conformations, namely a square antiprism (SAP; CN=8; D_{4d} symmetry), a monocapped square antiprism (MSA; CN=9; C_{4v}) or a tricapped trigonal prism (TTP; CN=9; D_{3h}). In the case of aqua ions,

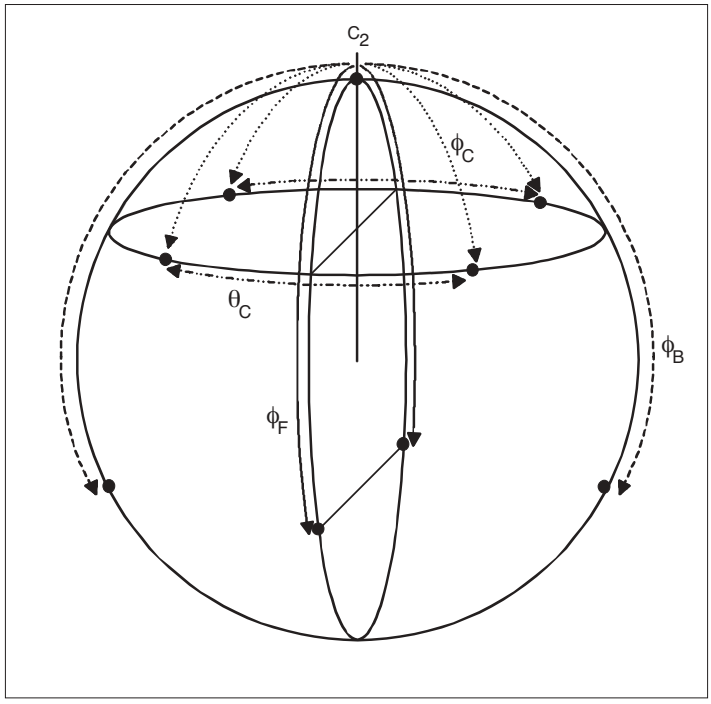

Fig. 2. Definition of the Kepert angles that characterize the MSA and TTP geometries.

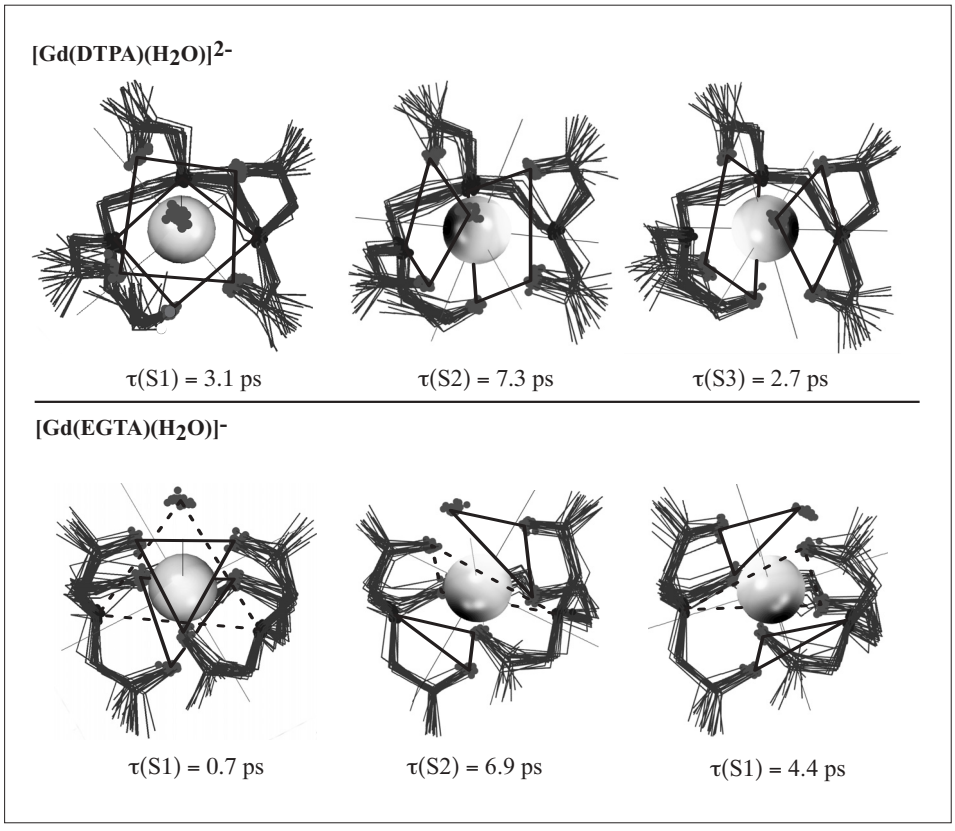

Fig. 3. Summary of the identified coordination polyhedra of acyclic complexes ($[Gd(DTPA)(H_2O)]^{2-}$, MSA polyhedra, and $[Gd(EGTA)(H_2O)]^{-}$, TTP polyhedra) and their respective lifetimes.

Kowall *et al*. [29] showed the orientation of the main symmetry axis of the molecule could change by 90° during the water exchange process through an interconversion between the MSA and TTP structures of the nine-coordinated transition state. The actual symmetry is lower in our polyaminocarboxylate chelates due to the mix of oxygen and nitrogen atoms in the coordination sphere, but it is still possible to find the closest ideal polyhedron using suitable numerical descriptors. We used a two-step algorithm. First we look for the best-fitting MSA or TTP for a given structure (MD snapshot) by applying the symmetry operations of the point group to all donor atoms and estimating a quality factor related to the root mean square displacements [25]. In order to confirm our symmetry assignment, we calculate the angles defined by Kepert [35] (Fig. 2). For a MSA structure, the reference angles are $\phi_B = 127°$, $\phi_F = 127°$, $\phi_C = 68.9°$, $\theta_C = 45°$. For a TTP, $\phi_B = 134.7°$, $\phi_F = 120°$, $\phi_C = 69.4°$, $\theta_C = 40.6°$. The C_2 axis is either the main C_4 axis of a putative MSA polyhedron or the secondary C_2 axis yielding the best MSA quality factor for a putative TTP. After identifying the symmetry, it becomes possible to classify the generated structures into a small number of sets sharing identical donor atom positions of the coordination polyhedron. For both macrocyclic complexes $[Gd(DOTA)(H_2O)]^{-}$ and $[Gd(DO3A)(H_2O)_2]$ only one MSA polyhedron was observed during the simulation, in good agreement with the solid-state structure. All Kepert angles were within 2° of the reference value. For $[Gd(EGTA)(H_2O)]^{-}$, three different TTP structures (labelled S1, S2 and S3) were identified, with frequent interconversions. Again, the Kepert angles were nearly ideal. Finally, $[Gd(DTPA)(H_2O)]^{2-}$ displayed one single TTP structure (S4) in 87% of the stored MD configurations. This series of highly distorted TTP polyhedra (Kepert angles half-way between MSA and TTP) can be further divided into three frequently exchanging sets (S1, S2, S3), depending on the particular C_2 axis leading to the best MSA. The other significant TTP in the simulation (S5) occurred 11.7% of the time, and was actually so close to the S1 structure that S1(S4) and S1(S5) can be seen as one single set.

We calculated the lifetimes of the fast exchanging structures from Impey's persistent coordination function [36], widely used to properly define the residence time of exchanging solvent molecules. An average lifetime can be calculated from the weighted mean correlation function. It is interesting to relate these lifetimes with the so-called ZFS modulation correlation time τ_v, as the rearrangements we observed have a direct influence on the ligand field experienced by the seven unpaired 4*f* electron of the gadolinium centre. Indeed, modulation of the ZFS through molecular deformations is assumed to be one of the electron spin relaxation pathways of the $S = 7/2$ Gd^{3+} ion. We calculated mean lifetimes of 7.2 and 6.8 ps for $[Gd(DTPA)(H_2O)]^{2-}$ and $[Gd(EGTA)(H_2O)]^{-}$ respectively. This is somewhat longer than the typical τ_v in Rast's model (1.33 ps for $[Gd(DTPA)(H_2O)]^{2-}$), but the magnitude agreement is compelling (Fig. 3). Admittedly, we do not observe such rearrangements in the $[Gd(DOTA)(H_2O)]^{-}$ and $[Gd(DO3A)(H_2O)_2]$ complexes, but this might be due to the inadequacy of our descriptors. Therefore, we think that such non-harmonic fluctuations of the coordination polyhedron may well play a role in the

electron spin relaxation process of all Gd^{3+} polyaminocarboxylates in solution, and possibly for Gd^{3+} and Eu^{2+} complexes in general. Following the example of Odelius *et al*. for the Ni^{2+} aqua ion [37], MD simulations combined with *ab initio* fine structure calculations [38] offer an attractive way to study the time evolution of the ZFS and thus the electron spin relaxation of such compounds.

Conclusion

Classical molecular dynamics simulation, when used with the appropriate force field, is an incredibly versatile tool for the study of various chemical systems. We applied it to Gd^{3+} polyaminocarboxylate complexes relevant for MRI. Thanks to these simulations, we obtained new insights into the molecular factors that determine the efficiency of the chelates as MRI contrast agents (relaxivity). The internal motion of a bound water molecule decreases the proton rotational correlation time by 20–30% compared to the overall molecular tumbling rate, which reduces the relaxivity. Fluctuations of the coordination polyhedron symmetry provide a possible mechanism for the electron spin relaxation, again with a negative impact. Hopefully a better understanding of these phenomena will provide useful clues for the design of improved contrast agents.

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