

Gd(III) Polyaminocarboxylate Chelate: Realistic Many-Body Molecular Dynamics Simulations for Molecular Imaging Applications

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Realistic molecular dynamics simulations of polyaminocarboxylate complexes of gadolinium (III) ion in water are performed, providing coordination numbers and average residence times in quantitative agreement with available experimental data. A theoretical analysis, based on fitting a fluctuating charges model on ab initio data, also indicates that charge transfer between the ion and the ligand is significant.

Owing to its high spin S of $7/2$, the f^7 gadolinium (III) ion is widely used in magnetic resonance imaging (MRI) to enhance image contrast. The imaging is based on ^1H NMR of the aqueous protons in the organism. The existence of the Gd(III) ion in the abnormal tissue enhances the contrast, modifying the nuclear magnetic relaxation times of the water proton in its vicinity. Because aqueous Gd(III) ions are toxic, it is desirable to use organic Gd(III) complexes instead, in order to avoid a possible release of the free ion in the human body. With the aim at developing more efficient contrast agents, a balance between the stability of the complex and its efficiency must be maintained. As already pointed out by Botta,¹ the exchange rate of the water molecules that belong to the first coordination sphere with their environment plays a strong role in the efficiency. The local coordination properties of the complexes and the resulting chemical mechanisms have been widely studied experimentally,^{2–4} and recent measurements^{3,4} provide crucial information on the dynamics of the water exchange mechanism. Alternatively, the failure of conventional additive potentials used in classical molecular dynamics (MD) simulations carried out over the recent years highlights the importance of many-body effects for highly charged ions in polar solvents such as water.^{5,6} Among these effects, polarization is very important and can represent up to about 60% of the interaction energy.⁷ In recent work,^{7,8} we have shown that a refined force field including these effects can give quantitative structural and dynamical data on the hydration processes of lanthanide (III) ions that agree with experimental measurements.^{9,10}

In the present communication, we extend the methodology used previously for the hydrated gadolinium (III)⁸ to the study of a gadolinium (III) polyaminocarboxylate chelate, namely the propylene diamine tetraacetic acid (PDTA), in aqueous solvent.

In the PDTA complex, the first coordination shell of the ion was experimentally reported to contain two water molecules,⁴ with a high water exchange rate ($k = 102 \times 10^6 \text{ s}^{-1}$ at 298 K), faster than complexes with one water molecule such as DTPA (diethylene triamine pentaacetate), the latter being experimentally well known and used for MRI applications.

As a first step, we have chosen a “model” $\text{Gd}^{3+}\text{--L}$ system, for which ab initio calculations are tractable. Here L consists of the glycine N-(methylcarboxylate) derivative ligand, which includes the most important functional groups existing in PDTA and in many MRI contrast agents, i.e., carboxylate. Ab initio calculations were used to parameterize a potential energy surface (PES) in the framework of the AMOEBA force field.^{11–13} AMOEBA was chosen for its good performances in reproducing gas-phase and condensed-phase properties of water,¹² and proved to be a reliable frame for the Gd(III) aquaion.⁸ Even though it includes explicit many-body polarization interactions, this force field allows large systems to be simulated over relatively long time scales. In the context of the present study, AMOEBA also has the appealing feature that it is entirely based on ab initio data and does not incorporate any experimental information. The parameters for the aquaion were taken as in our previous paper.⁸ The geometry of the $\text{Gd}^{3+}\text{--L}$ complex was optimized at the MP2/LC-ECP (large core effective core potential^{14,15}) level. The parameters for the ligand were adjusted from ab initio calculations on the $\text{Gd}^{3+}\text{--L}$ complex performed at the CCSD-(T)/LC-ECP level (associated to a core polarization potential¹⁶), energetically corrected from the basis set superposition error. The resulting force field has then been used to study the properties of PDTA.

The hydration of the $\text{Gd}^{3+}\text{--L}$ complex with an increasing number of water molecules (from 1 to 6) was studied by a Monte Carlo (MC) PES exploration in order to locate low-energy conformations. Some optimized structures were further refined by ab initio MP2/LC-ECP calculations to validate geometries and interaction energies. Full geometry optimizations were

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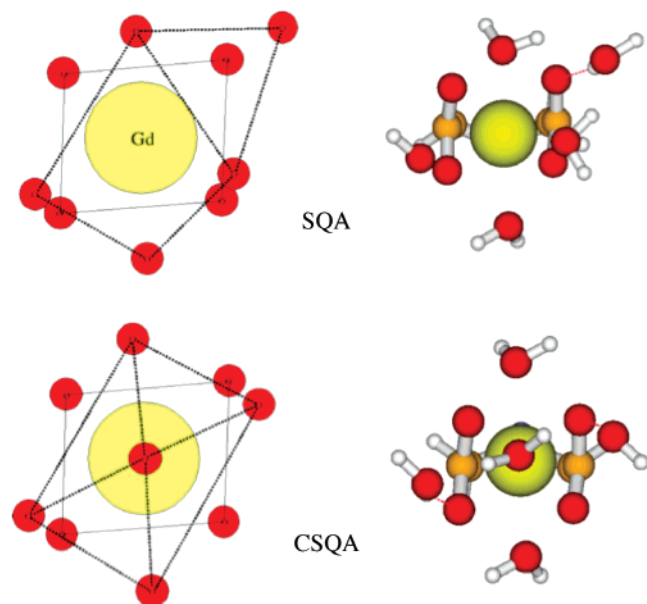


Figure 1. General views of the Gd^{3+} -L complex hydrated with five water molecules (right side) and arrangements of the oxygen atoms (left side, red colors), in the SQA (8 + 1 water molecule in the second shell) and CSQA (8 + 1 face-capped with a water molecule) arrangements.

carried out for the smaller clusters, containing 1 or 2 water molecules, and single-point calculations were performed for the larger clusters. Among all the structures obtained, our results indicate clearly that the square antiprismatic (SQA) arrangement is preferred energetically with the highest occurrence in the MC PES explorations performed at 300 and 600 K. This is in agreement with experimental data on the aquaion $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$ (ref 17). A capped square antiprismatic (CSQA) structure is also obtained, corresponding to a distortion and an addition of a water molecule to the SQA structure. Such a CSQA structure has previously been reported in the MD simulations of Floris and Tani.⁶ In the SQA-type arrangement, the facets are rectangular or rhombohedral rather than squares, due to the presence of carboxylate functions (see Figure 1). The average static coordination number (CN) ranges from 8 (SQA) to 9 (CSQA) in the sample of conformations studied. In addition, for the complex with five water molecules, 8- and 9-coordinated complexes are nearly iso-energetic (within 0.1 kcal/mol), the 8-coordinated SQA-type conformation being the most frequently observed.

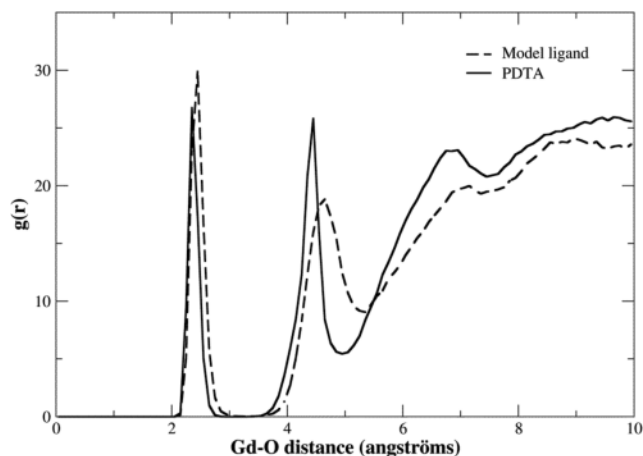


Figure 2. Radial distribution functions $g(r)$ for all Gd-O pairs (water molecules and carboxylate functions) for the Gd^{3+} -L and $[\text{Gd}(\text{PDTA})(\text{H}_2\text{O})_2]^-$ complexes.

As in our previous effort, MD simulations have been carried out with rigid spherical boundary conditions. The complex was incorporated inside a cluster of 213 water molecules. MD simulations were performed at 300 K with a 1 fs time step for a total simulated time of 1 ns. The radial distribution functions $g(r)$ of oxygen atoms around the Gd ion have been calculated, in addition to the coordination number. Short-time averages performed over 40 fs were used to filter out some of the noise on the instantaneous CN. The main results are summarized in Table 1 for the aquaion, the Gd^{3+} -L complex, the $[\text{Gd}(\text{PDTA})(\text{H}_2\text{O})_2]^-$ complex, and the $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})_2]^{2-}$ complex. The PDTA ligand mainly differs from DTPA by one N-carboxylate function.

Concerning the model ligand L, the first peak of the radial distribution function is well resolved and centered at 2.43 Å (see Figure 2), thus defining clearly a first coordination shell with an average CN of 8.3, in agreement with the above MC PES exploration on small clusters. This value, lower than that of the aquaion, reflects the changes in the water-gadolinium interaction induced by the ligand. The second coordination shell is more disordered than the first, with a broader peak centered at 4.60 Å. However, from the shape of the radial distribution function, it is difficult to determine accurately the number of water molecules in this sphere by the direct integration of the peak. Nevertheless, the nature of the ligand around the ion seems to have a limited influence on Gd-O distances. By looking at the variations of the Gd-C distances for the carboxylate groups,

TABLE 1: Molecular Dynamics Results for the Gd^{3+} Complexes (Gd-O, Gd-C and Gd-N refer to the locations of the peaks in the corresponding radial distribution functions)

data	aquaion ^a	model ligand	PDTA	DTPA ^b
average CN	8.6	8.3	8.0 including 2 H ₂ O	(not available)
Gd-O (Å)			2.43 for water O 2.35 for carboxylate O	1 H ₂ O
(1st sphere)	2.44	2.43	4.43	2.39
(2nd sphere)	4.65	4.60		4.41
Gd-C (Å)		2.75 and 6.11	3.25	-
Gd-N (Å)			2.67	2.68
(carboxylates)				
no. H ₂ O	16.1		12.2	
in 2nd sphere				
resid. time (ns)	0.37	0.78	> 2 (exp.: 10)	244
average Gd charge	+1.91	+1.63	+1.27	

^a Ref 8. ^b Ref 21 for experimental data.

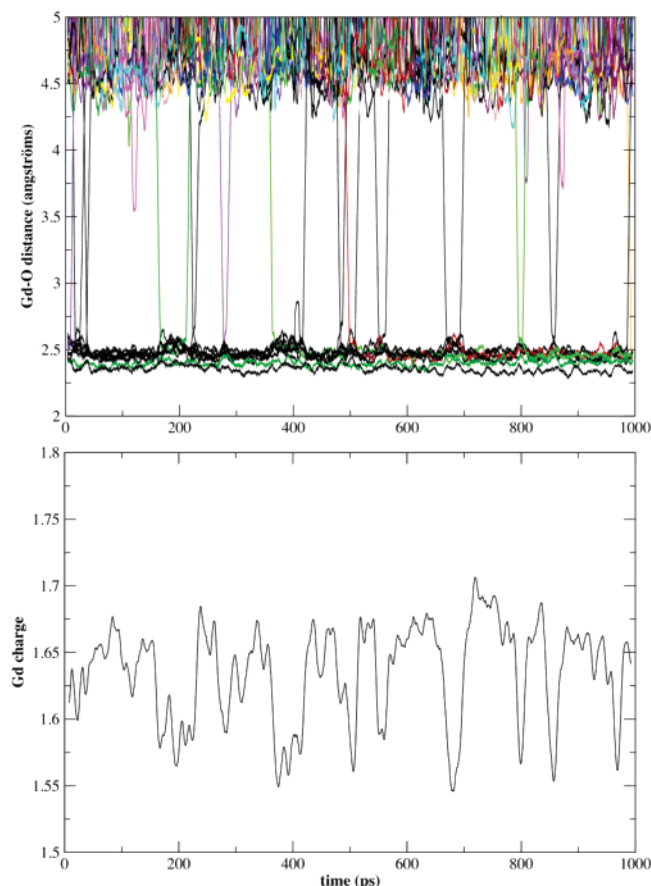


Figure 3. Time evolution of the short-time averaged (over 40 fs) Gd–O distance and charge on gadolinium for the Gd^{3+} –L complex.

an opening of the model ligand was observed at the beginning of the simulation. The ligand still remains open throughout all the MD simulation, leading to a conformation in which the complex is bound only by a single carboxylate group, leaving some room in the first coordination shell for more water molecules. As a result, this complex with two carboxylate groups is not strongly stable from the chemical point of view, thereby suggesting a possible undesirable way to deliver the free ion.

The variations of the short-time averaged coordination number during the course of the simulation are represented in Figure 3. The water exchange events are clearly visible on this figure. The number of water exchanges between the first and second coordination shells occurring along the MD simulation allows the residence time of a water molecule in the first sphere to be evaluated. Using the notion of persistence of a water molecule,¹⁸ the average residence time is found to be 0.78 ns. The changes in water–gadolinium interactions due to the ligand increase the residence time with respect to the aquaion.⁸

Since the AMOEBA force field does not explicitly take charge transfer effects into account, we used a distinct fluctuating charges (fluc-q) model for post-processing the MD trajectories in order to qualitatively evaluate the extent of charges transfer in the complexes.^{19,20} The details of the fluc-q model can be found in our previous publication.⁸ As was the case for the AMOEBA force field parameters, the fluc-q parameters were obtained by fitting *ab initio* data on small systems. For the Gd^{3+} –L system, the average value of the charge on the lanthanide ion is found to be +1.63. As shown in Figure 3, a strong correlation is found between the coordination number and the instantaneous value of the charge carried by the gadolinium ion, both quantities showing large changes at the occurrences of water exchanges. The charge distribution is

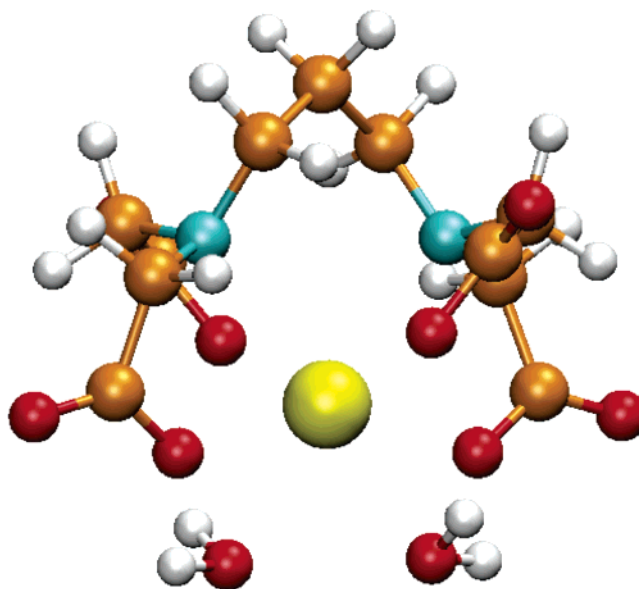


Figure 4. General view of the $[\text{Gd}(\text{PDTPA})(\text{H}_2\text{O})_2]^-$ complex hydrated with two water molecules (H in white, C in orange, N in cyan, O in red, and Gd in yellow).

bimodal, the peaks being centered on the averaged values +1.65 (most often) or +1.57. From the analysis of the MD trajectories, the charges of +1.57 and +1.65 can be unambiguously related to conformations with instantaneous coordinations of 9 and 8, respectively. As shown previously,⁸ charge-transfer effects are important in the hydration of the bare Gd^{3+} ion. By performing the fluc-q analysis on the Gd^{3+} –L system without any water molecule, we find that the ligand alone accounts for 90% of the charge transferred, the remaining 10% being attributed to the water molecules. Therefore charge transfer effects are magnified by the presence of the ligand.

The AMOEBA force field, extended to describe the model ligand, has then been used on the chemically similar PDTPA ligand (see Figure 4), which is a hexadentate acyclic molecule coordinated to the gadolinium ion by two nitrogen atoms and four oxygen atoms from the carboxylate functions. Experimental data available for the $[\text{Gd}(\text{PDTPA})(\text{H}_2\text{O})_2]^-$ complex indicate that the first coordination sphere of the ion contains two water molecules, with a residence time of about 10 ns.²¹ In Figure 2, the Gd–O radial distribution function shows well-defined peaks characteristic of the first and second coordination shells. The first shell is centered at about 2.36 Å, with a total CN of 8.0, including two water oxygen atoms, four carboxylate oxygen atoms, and two nitrogen atoms from PDTPA. The decrease of both the CN and the distance of the first peak, with respect to the model ligand system, is due to the presence of a larger ligand that does not open itself in the simulation and remains strongly bound to the ion. As in experiments,⁴ two water molecules are statistically present in the first coordination sphere. Contrary to the model ligand system, our calculations indicate two different groups of Gd–O distances for the two water molecules and the carboxylate functions, with the values of 2.43 and 2.35 Å, respectively. A second shell, centered at 4.43 Å with 12 water molecules, is completed with the carbon atoms of the ligand. The average second shell Gd–C distance is 3.25 Å, which again emphasizes the strong complexation of the ligand to the ion. All average distances obtained from the trajectory analysis compare well with available experimental data²¹ on DTPA (see Table 1). No water exchange is observed during a MD simulation of 2 ns. Even though we were unable to reach much longer time scales due to the large computational effort involved,

this result is consistent with the experimental value of 10 ns.²¹ Using the fluc-q model, the average gadolinium charge is evaluated to be +1.27. Here, the charge is constant (with a small fluctuation of ± 0.025), consistently with the absence of water exchange during the trajectory. Charge transfer effects are more important with the PDTA ligand in comparison to the model ligand. Removing the water molecules in the fluc-q analysis, only about 2% of the charge transfer can be attributed to a transfer from the water molecules to the gadolinium ion.

In conclusion, using explicit many-body MD simulations, we have obtained a realistic description of the structural and dynamical properties of a lanthanide ion complex with a carboxylate ligand and explicit water solvent at the same time. New information has been provided on the geometric arrangement of the second coordination shell, as well as evidence for a strong charge transfer between the gadolinium ion and its environment, especially the carboxylate ligand. These quantitative results could not have been obtained without taking many-body effects into account. The present simulations constitute an important step toward the realistic modeling of MRI contrast agents, and provide a new quantitative tool for future design of novel ligands for practical applications.

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