

Supplementary Information

Thermal and concentration effects on ^1H NMR relaxation of Gd^{3+} -aqua using MD simulations and measurements

Thiago J. Pinheiro dos Santos, Arjun Valiya Parambathu , Carla C. Fraenza, Casey Walsh, Steve G. Greenbaum, Walter G. Chapman, Dilip Asthagiri, and Philip M. Singer

AMOEBA Forcefield parameters

Below we summarize the AMOEBA polarizable forcefield parameters for both the water²³ and the ions²⁴.

- Atom name:

Type	Class	Symbol	Description	Atomic	Mass	Valence
1	1	O	Water Oxygen	8	15.999	2
2	2	H	Water Hydrogen	1	1.008	1
3	3	Gd	Gadolinium(III)	64	157.250	0
4	4	Cl	Chloride	17	35.453	0

- VdW parameters:

Class	Sigma (nm)	Epsilon (kJ/mol)	Reduction
1	0.3405	0.46024	1.00
2	0.2655	0.056484	0.91
3	0.3650	41.8400	1.00
4	0.4130	1.42256	1.00

- Bond stretching parameters:

Class 1	Class 2	K (kJ/mol)	d (nm)
1	2	232986.04	0.09572

- Angle bending parameters:

Class 1	Class 2	Class 3	K (kJ/mol)	Angle (deg)
2	1	2	0.06206909	108.5

- Urey-Bradley force parameters:

Class 1	Class 2	Class 3	K (kJ/mol)	d (nm)
2	1	2	-3179.84	0.15326

- Atomic dipole polarizability parameters:

Type	Alpha	Damp	Group	Atom	Type
1	0.837	0.390			2
2	0.496	0.390			1
3	0.790	0.390			
4	4.000	0.390			

- Atomic multipole parameters:

Type						
1	-2	-2	-0.51966			
			0.00000	0.00000	0.14279	
			0.37928			
			0.00000	-0.41809		
			0.00000	0.00000	0.03881	
2	1	2	0.25983			
			-0.03859	0.00000	-0.05818	
			-0.03673	-0.10739		
			-0.00203	0.00000	0.14412	
3	0	0	3.00000			
			0.00000	0.00000	0.00000	
			0.00000			
			0.00000	0.00000		
			0.00000	0.00000	0.00000	
4	0	0	-1.00000			
			0.00000	0.00000	0.00000	
			0.00000			
			0.00000	0.00000		
			0.00000	0.00000	0.00000	

Complementary simulation results

Table S1 Simulation box details obtained from NpT simulations and experimental data from NIST database⁴³ at different temperatures.

T (°C)	MD simulations						NIST ⁴³	
	N_W	$N_{Gd^{3+}}$	V (nm ³)	L (Å)	[W] (mM)	[Gd] (mM)	[W] (mM)	η (mPa.s)
5	2006	1	60.228 ± 0.419	39.198	55307.49	27.57	55507	1.5182
10	2006	1	60.096 ± 0.411	39.170	55428.71	27.63	55492	1.3059
15	2006	1	59.992 ± 0.383	39.147	55524.98	27.68	55459	1.1376
25	2006	1	60.031 ± 0.410	39.155	55488.43	27.66	55345	0.8900
37	2006	1	60.189 ± 0.402	39.190	55343.34	27.59	55138	0.6913

Table S2 Simulation box details obtained from NpT simulations and experimental data from NIST database⁴³ at different concentrations of ions.

T (°C)	MD simulations							NIST ⁴³
	N_W	$N_{Gd^{3+}}$	N_{Cl^-}	V (nm ³)	L (Å)	[W] (mM)	[Gd] (mM)	[W] (mM)
25	1003	1	3	30.046 ± 0.283	31.088	55432.01	55.27	55345
25	2006	1	0	60.031 ± 0.410	39.155	55488.43	27.66	55345
25	2006	1	3	60.047 ± 0.424	39.159	55473.54	27.65	55345
25	2006	2	6	60.063 ± 0.398	39.162	55459.04	55.29	55345

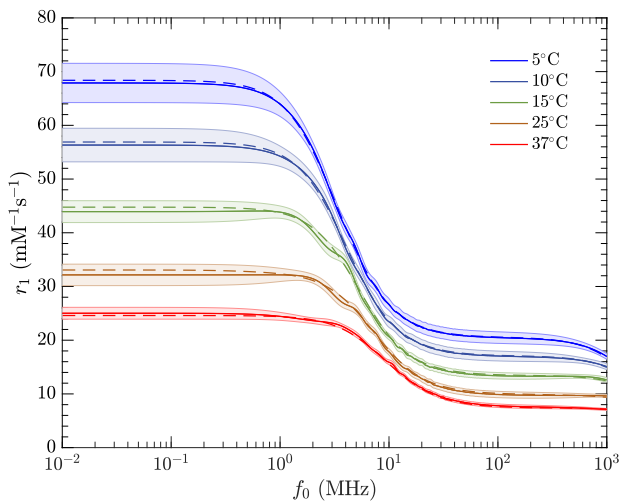


Fig. S1 Comparison of the longitudinal NMR relaxivity r_1 of Gd^{3+} -aqua at different temperatures. The straight line (—) corresponds to the results obtained through the FFT approach (Equation (7)) and the shaded area represents its error bars, while the dashed line (---) results obtained through the Tikhonov regularization using the underlying distribution $P(\tau)$ (Equation (16)).

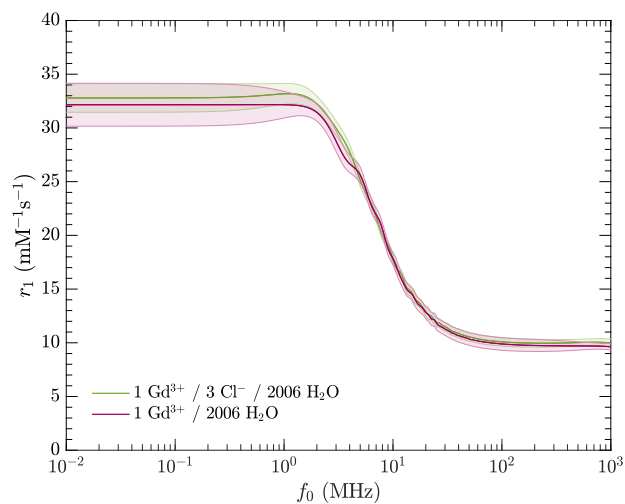


Fig. S2 Longitudinal NMR relaxivity r_1 of Gd^{3+} -aqua obtained through the FFT approach (Equation (7)) with and without the Cl^- anions in the simulation box. As shown, the presence of the counter-ion at infinite dilution implies that Gd^{3+} - Cl^- interactions are negligible and relaxivity is not affected.

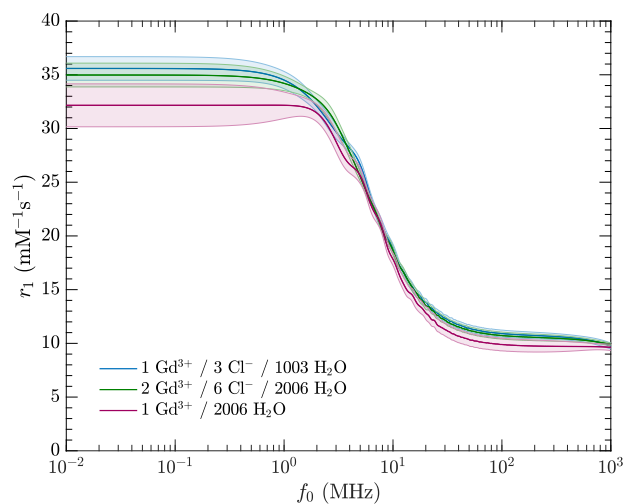


Fig. S3 Longitudinal NMR relaxivity r_1 of Gd^{3+} -aqua obtained through the FFT approach (Equation (7)) at different nominal concentrations of Gd^{3+} in the simulation box. Provided that Gd^{3+} - Gd^{3+} and Gd^{3+} - Cl^- interactions are negligible, the infinite dilution limit is probed and NMR relaxivity associated with the paramagnetic ion is not affected.

Measurements of self-diffusion

The measured self-diffusion coefficient of water at 25°C was found to be $D_W \simeq 2.2 \cdot 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$ for both $[\text{Gd}] = 0$ and 2 mM solutions, i.e., independent of Gd^{3+} concentration up to $[\text{Gd}] = 2 \text{ mM}$. These measurements are within 10 % of the MD simulations $D_W \simeq 2.0 \cdot 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$ at 25°C (Figures 3(a) and 3(b)) where $[\text{Gd}] = 28 \text{ mM}$ (Table S1), indicating that the concentration of gadolinium does not strongly affect D_W . Additional D_W measurements at $[\text{Gd}] = 28 \text{ mM}$ were not possible due to the prohibitively short T_1 .

NMR diffusion experiments were performed with a 400 MHz Bruker spectrometer operating at a magnetic field of 9.4 T, using a stimulated echo sequence. The gradient strength G took 16 different values following a linear increase and their values were in the range of 2-98% of a maximum strength $50 \text{ G} \cdot \text{cm}^{-1}$. The gradient pulse duration δ and the diffusion time Δ were 2 ms and 100 ms, respectively. The self-diffusion coefficients D_W were then extracted by fitting the echo signal decay with the Stejskal-Tanner equation⁴²:

$$I = I_0 \exp \left[-(\delta G \gamma)^2 \left(\Delta - \frac{\delta}{3} \right) D_W \right], \quad (27)$$

where I is the amplitude of the attenuated echo signal, I_0 is the initial intensity, and γ is the gyro-magnetic ratio for ^1H .

Activation energy at constant frequency f_0

Table S3 Thermal activation energy E_f for the longitudinal NMR relaxivity r_1 at different frequencies f_0 .

f_0 (MHz)	E_f (kJ.mol ⁻¹)		
	MD simulations	Reference ⁵¹	Reference ⁵²
10	11.4		10.4
20	15.8	10.05	16.9
50	20.6		21.0
100	21.9		
200	22.3		
400	22.1		

In this section, we discuss the NMR relaxivity r_1 of the Gd^{3+} –aqua complex in terms of the thermal activation energy E_f at different frequencies. This is relevant to elucidate that the molecular modes of relaxation discussed in Section 3.3 contribute to the total relaxation with different activation energies. Assuming an exponential law on the temperature dependency of the NMR relaxivity r_1 , we have that

$$r_1(f_0) = r_1^\infty(f_0) \exp \left[\frac{E_f(f_0)}{RT} \right]. \quad (28)$$

Table S3 presents the activation energies E_f of the NMR relaxivity r_1 at different frequencies f_0 across five simulated temperatures, as well as a comparison with experimental values^{51,52}. As previously discussed, we did not calculate the activation energy at frequencies lower than 5 MHz since our simulations do not capture important electron-spin relaxation mechanisms.

The simulations results in Table S3 show that E_f increases with f_0 , which is only possible if the different molecular modes have different activation energies.