Electronic Supplementary Information for Dalton Transactions

Supporting information

Lanthanide Chelates of (*bis*)-Hydroxymethyl-substituted DTTA with Potential Application as Contrast Agents in Magnetic Resonance Imaging

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Equations used for the determination of the relaxivity parameters from the analysis of NMRD and ^{17}O NMR data; 600 MHz ^{1}H g-COSY spectrum of $[La(\mathbf{1})(H_2O)_2]^-$ in D_2O (30 mM, pH 7.0, 298 K) (**Figure S1**); 300 MHz ^{1}H NMR spectra of the $[Sm(\mathbf{1})(H_2O)_2]^-$ and $[Sm(\mathbf{2})(H_2O)]^{2-}$ complexes in D_2O (30 mM, pH 7.0, 298 K) (**Figure S2**); 500 MHz ^{1}H DQF-COSY spectrum of $[Sm(\mathbf{1})(H_2O)_2]^-$ in D_2O (30 mM, pH 7.0, 298 K) (**Figure S3**); 500 MHz ^{1}H NMR spectrum of $[Eu(\mathbf{1})(H_2O)_2]^-$ (5 mM, pH 7.35, 298 K), in the absence and presence of 50 mM phosphate (**Figure S4)**. Tables containing the frequency dependence of the water proton relaxivities of $[Gd(\mathbf{1})(H_2O)_2]^-$ (**Table S1**) and of $[Gd(\mathbf{2})(H_2O)]^{2-}$ (**Table S2**) complexes in aqueous solutions at two temperatures; Table containing the frequency dependence of the water proton relaxation rates of 1.5 mM $[Gd(\mathbf{1})(H_2O)_2]^-$ dissolved in 4% aqueous HSA at two temperatures (**Table S3**); Tables containing the variable temperature reduced transverse and longitudinal ^{17}O relaxation rates and chemical shifts of $[Gd(\mathbf{1})(H_2O)_2]^-$ and $[Gd(\mathbf{2})(H_2O)]^{2-}$ aqueous solutions at 4.7 T (**Table S4** and **Table S5**, respectively).

Equations used for the analysis of NMRD and ^{17}O NMR data

NMRD and ^{17}O NMR data have been analysed within the framework of Solomon-Bloembergen-Morgan theory.

^{17}O NMR spectroscopy

From the measured ^{17}O NMR relaxation rates and angular frequencies of the paramagnetic solutions, $1/T_1$, $1/T_2$ and ω, and of the acidified water reference, $1/T_{1A}$, $1/T_{2A}$ and ω_A, one can calculate the reduced relaxation rates and chemical shift, $1/T_{1r}$, $1/T_{2r}$ and $\Delta\omega_r$, which may be written as in Equations (A1)-(A3), where $1/T_{1m}$, $1/T_{2m}$ are the relaxation rates of the bound water and $\Delta\omega_m$ is the chemical shift difference between bound and bulk water, τ_m is the mean residence time or the inverse of the water exchange rate k_{ex} and P_m is the mole fraction of the bound water. [1, 2]

$$\frac{1}{T_{1r}} = \frac{1}{P_m}\left[\frac{1}{T_1} - \frac{1}{T_{1A}}\right] = \frac{1}{T_{1m} + \tau_m} + \frac{1}{T_{1os}} \qquad \text{(A1)}$$

$$\frac{1}{T_{2r}} = \frac{1}{P_m}\left[\frac{1}{T_2} - \frac{1}{T_{2A}}\right] = \frac{1}{\tau_m}\frac{T_{2m}^{-2} + \tau_m^{-1}T_{2m}^{-1} + \Delta\omega_m^2}{(\tau_m^{-1} + T_{2m}^{-1})^2 + \Delta\omega_m^2} + \frac{1}{T_{2os}} \qquad \text{(A2)}$$

$$\Delta\omega_r = \frac{1}{P_m}(\omega - \omega_A) = \frac{\Delta\omega_m}{(1 + \tau_m T_{2m}^{-1})^2 + \tau_m^2\Delta\omega_m^2} + \Delta\omega_{os} \qquad \text{(A3)}$$

Previous studies have shown that outer sphere contributions to the ^{17}O relaxation rates are negligible. [3]

In equation (A3) the chemical shift of the bound water molecule, $\Delta\omega_m$, depends on the hyperfine interaction between the Gd^{III} electron spin and the ^{17}O nucleus and is directly proportional to the scalar coupling constant, $\frac{A}{\hbar}$, as expressed in Equation (A4). [4]

$$\Delta\omega_m = \frac{g_L\mu_B S(S+1)B}{3k_B T}\frac{A}{\hbar} \qquad \text{(A4)}$$

The isotopic Landé g factor is equal to 2.0 for the Gd^{III}, B represents the magnetic field, and k_B is the Boltzmann constant.

The outer-sphere contribution to the chemical shift is assumed to be linearly related to $\Delta\omega_m$ by a constant C_{os} [Equation (A5)]. [5]

$$\Delta\omega_{os} = C_{os}\Delta\omega_m \qquad \text{(A5)}$$

^{17}O longitudinal relaxation rates are given by Equation (A6) where γ_S is the electron and γ_I is the nuclear gyromagnetic ratio ($\gamma_S = 1.76\times10^{11}$ rad s^{-1} T^{-1}, $\gamma_I = -3.626\times10^{7}$ rad s^{-1} T^{-1}), r_{GdO} is the effective distance between the electron charge and the ^{17}O nucleus, I is the nuclear spin (5/2 for ^{17}O), χ is the quadrupolar coupling constant and η is an asymmetry parameter:

$$\frac{1}{T_{1m}} = \left[\frac{1}{15}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2\gamma_I^2\gamma_S^2}{r_{GdO}^6} S(S+1)\right] \times \left[6\tau_{d1} + 14\frac{\tau_{d2}}{1+\omega_S^2\tau_{d2}^2}\right] + \frac{3\pi^2}{10}\frac{2I+3}{I^2(2I-1)}\chi^2\left(1+\eta^2/3\right)\tau_{RO} \quad \text{(A6)}$$

where:

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_m} + \frac{1}{\tau_{RO}} + \frac{1}{T_{ie}} \quad \text{for } i = 1,2 \quad \text{(A7)}$$

The τ_{RO} overall rotational correlation time is assumed to have simple exponential temperature dependence with an E_R activation energy as given in equation (A8).

$$\tau_{RO} = \tau_{RO}^{298} \exp\left[\frac{E_R}{R}\left(\frac{1}{T} - \frac{1}{298.15}\right)\right] \quad \text{(A8)}$$

In the transverse relaxation the scalar contribution, $1/T_{2sc}$, is the most important [Equation (A9)]. $1/\tau_{s1}$ is the sum of the exchange rate constant and the electron spin relaxation rate.

$$\frac{1}{T_{2m}} \cong \frac{1}{T_{2sc}} = \frac{S(S+1)}{3}\left(\frac{A}{\hbar}\right)^2 \tau_{s1} \quad \text{(A9)}$$

$$\frac{1}{\tau_{s1}} = \frac{1}{\tau_m} + \frac{1}{T_{1e}} \quad \text{(A10)}$$

The exchange rate is supposed to assume to obey the Eyring equation. In equation (A11) $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ are the entropy and enthalpy of activation for the water exchange process, and k_{ex}^{298} is the exchange rate at 298.15 K.

$$\frac{1}{\tau_m} = k_{ex} = \frac{k_B T}{h} exp\left\{\frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H^{\ddagger}}{RT}\right\} = \frac{k_{ex}^{298} T}{298.15} exp\left\{\frac{\Delta H^{\ddagger}}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \quad \text{(A11)}$$

NMRD

The measured longitudinal proton relaxation rate, $R_1^{obs} = 1/T_1^{obs}$, is the sum of a paramagnetic and a diamagnetic contribution as expressed in Equation (A12), where r_1 is the proton relaxivity:

$$R_1^{obs} = R_1^d + R_1^p = R_1^d + r_1 [Gd^{3+}] \quad \text{(A12)}$$

The relaxivity can be divided into an inner and an outer sphere term as follows:

$$r_1 = r_{1is} + r_{1os} \quad \text{(A13)}$$

The inner sphere term is given in Equation (A14), where q is the number of inner sphere water molecules. [6]

$$r_{1is} = \frac{1}{1000} \times \frac{q}{55.55} \times \frac{1}{T_{1m}^H + \tau_m} \quad \text{(A14)}$$

The longitudinal relaxation rate of inner sphere protons, $1/T_{1m}^H$ is expressed by Equation (A15), where r_{GdH} is the effective distance between the electron charge and the ^{1}H nucleus, ω_I is the proton resonance frequency and ω_S is the Larmor frequency of the Gd^{III} electron spin.

$$\frac{1}{T_{1m}^H} = \frac{2}{15}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{r_{GdH}^6} S(S+1) \times \left[3J(\omega_I ; \tau_{d1}) + 7J(\omega_S ; \tau_{d2})\right] \quad \text{(A15)}$$

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_m} + \frac{1}{\tau_{RH}} + \frac{1}{T_{ie}} \qquad \text{for } i = 1,2 \tag{A16}$$

where τ_{RH} is the rotational correlation time of the Gd-H_{water} vector. This rotational correlation time is linked to the τ_{RO} by $0.65 \le \tau_{RH}/\tau_{RO} \le 1$. [7]

The outer-sphere contribution can be described by Equation (A17) where N_A is the Avogadro constant, and J_{os} is its associated spectral density function as given by Equation (A18). [8, 9]

$$r_{1os} = \frac{32N_A\pi}{405}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2\gamma_S^2\gamma_I^2}{a_{GdH}D_{GdH}} S(S+1)\left[3J_{os}(\omega_I, T_{1e}) + 7J_{os}(\omega_S, T_{2e})\right] \tag{A17}$$

$$J_{os}(\omega, T_{je}) = \mathrm{Re}\left[\frac{1 + \frac{1}{4}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{1/2}}{1 + \left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{1/2} + \frac{4}{9}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right) + \frac{1}{9}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{3/2}}\right] \tag{A18}$$

$j = 1,2$

The longitudinal and transverse electronic relaxation rates, $1/T_{1e}$ and $1/T_{2e}$ are expressed by Equation (A19)-(A20), where τ_v is the electronic correlation time for the modulation of the zero-field-splitting interaction, E_v the corresponding activation energy and Δ^2 is the mean square zero-field-splitting energy. We assumed a simple exponential dependence of τ_v versus $1/T$ as written in Equation (A21).

$$\left(\frac{1}{T_{1e}}\right)^{ZFS} = \frac{1}{25}\Delta^2\tau_v\left\{4S(S+1) - 3\right\}\left(\frac{1}{1+\omega_S^2\tau_v^2} + \frac{4}{1+4\omega_S^2\tau_v^2}\right) \tag{A19}$$

$$\left(\frac{1}{T_{2e}}\right)^{ZFS} = \Delta^2 \tau_v \left(\frac{5.26}{1+0.372\omega_S^2 \tau_v^2} + \frac{7.18}{1+1.24\omega_S \tau_v} \right) \quad \text{(A20)}$$

$$\tau_v = \tau_v^{298} \exp\left[\frac{E_v}{R} \left(\frac{1}{T} - \frac{1}{298.15} \right) \right] \quad \text{(A21)}$$

The diffusion coefficient for the diffusion of a water proton away from a Gd^{III} complex, D_{GdH}, is assumed to obey an exponential law versus the inverse of the temperature, with an activation energy $E_{DGdH,}$ as given in Equation (A22). D_{GdH}^{298} is the diffusion coefficient at 298.15K.

$$D_{\mathrm{GdH}} = D_{\mathrm{GdH}}^{298} \exp\left\{ \frac{E_{\mathrm{GdH}}}{R} \left(\frac{1}{298.15} - \frac{1}{T} \right) \right\} \quad \text{(A22)}$$

References for Equations

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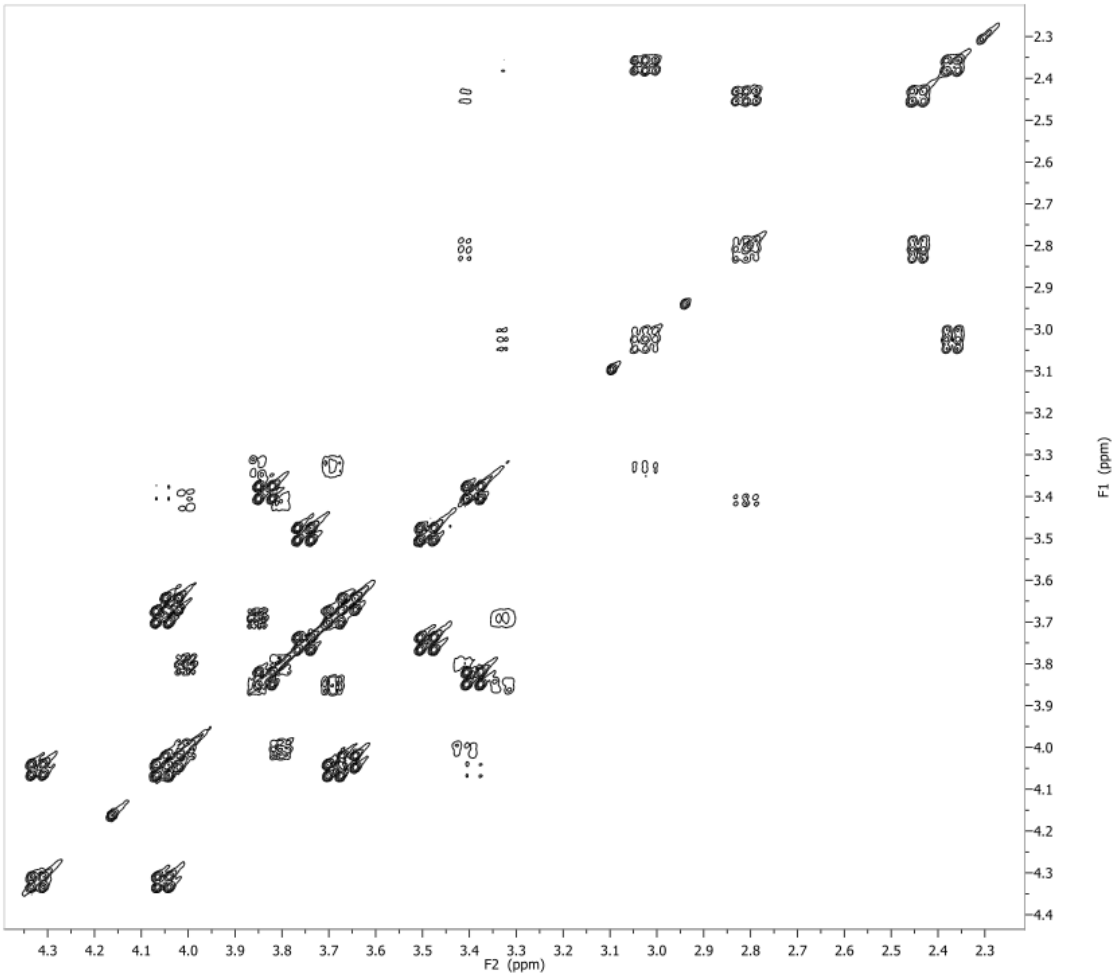

Figure S1: 600 MHz ^{1}H g-COSY spectrum of the [La(**1**)$(H_2O)_2$]$^{-}$ complex in D_2O (30 mM, pH 7.0, 298 K).

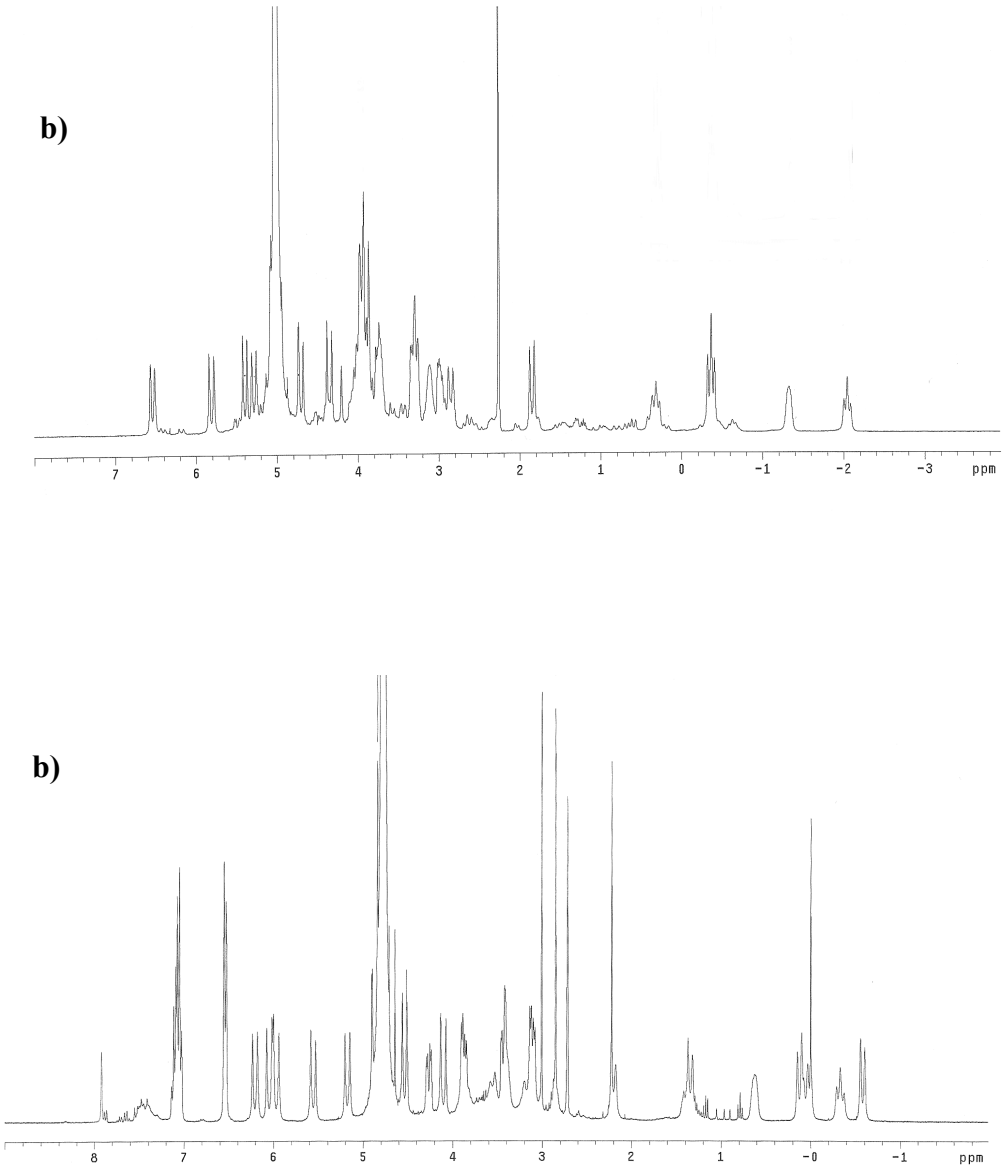

Figure S2: 300 MHz ^{1}H NMR spectra of the Sm^{3+} complexes in D_2O (30 mM, pH 7.0, 298 K): a) $[Sm(\mathbf{1})(H_2O)_2]^-$; b) $[Sm(\mathbf{2})(H_2O)]^{2-}$.

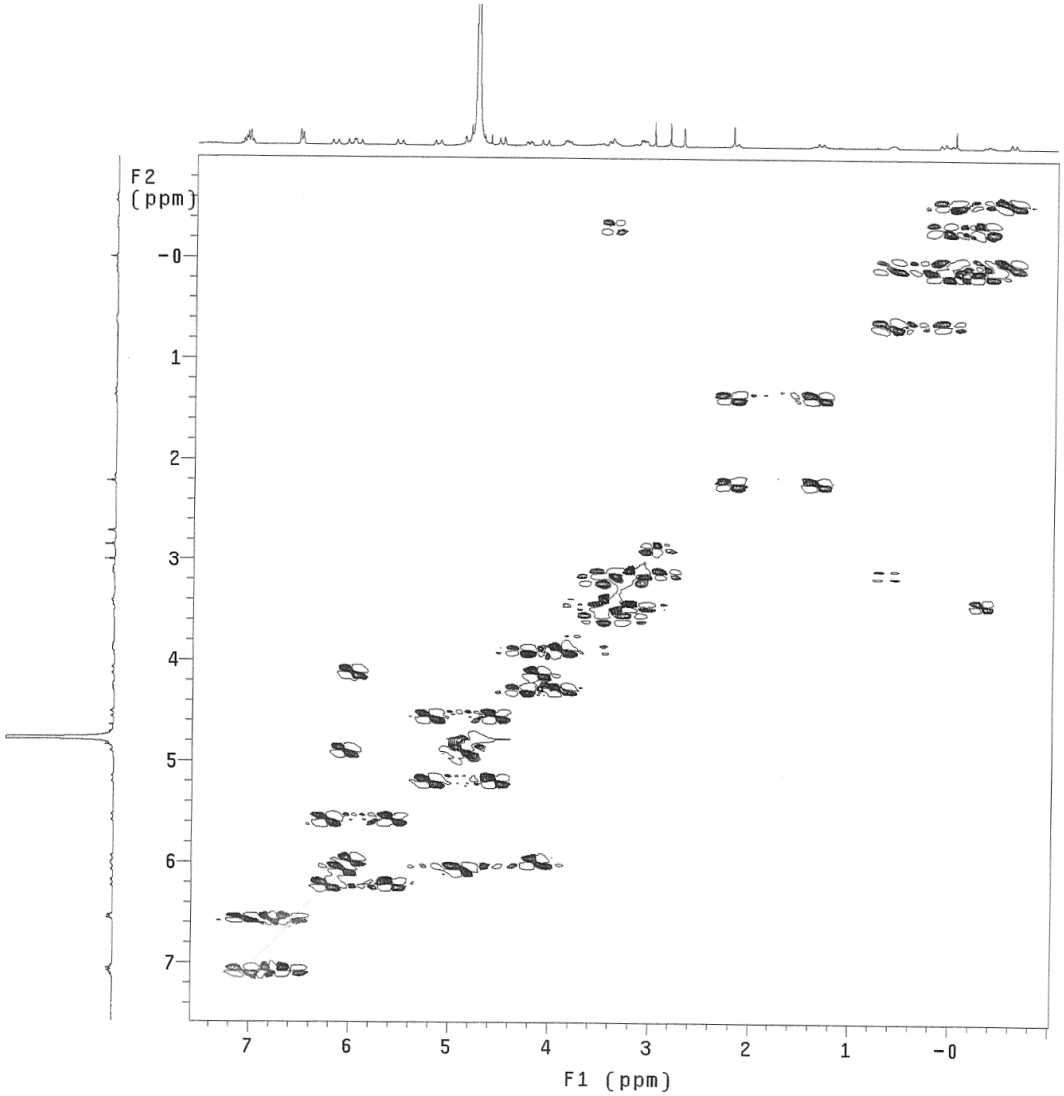

Figure S3: 500 MHz ^{1}H DQF-COSY spectrum of the [Sm(**1**)$(H_2O)_2$]$^{-}$ complex in D_2O (30 mM, pH 7.0, 298 K).

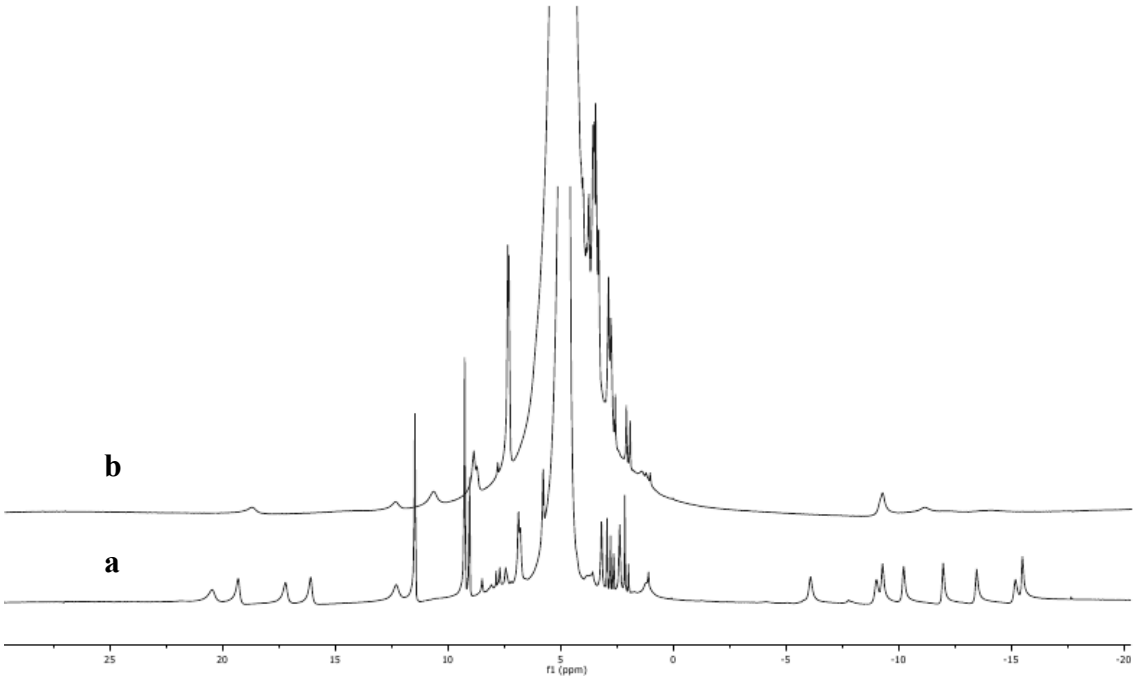

Figure S4: 500 MHz ^{1}H NMR spectrum of $[Eu(\mathbf{1})(H_2O)_2]^-$ in D_2O (5 mM, pH 7.35, 298 K), a) in D_2O; b) in the presence of 50 mM phosphate.

Table S1: Variable temperature proton relaxivities (r_1; $mM^{-1}s^{-1}$) of [Gd(N'-Bz-C4,4'-$(CH_2OH)_2$DTTA)$(H_2O)_2$]$^-$ ($c_{Gd(III)}$ = 5.55 mM; pH = 6.18)

	r_1/$mM^{-1}s^{-1}$	
Frequency/MHz	**298 K**	**310 K**
0.0100	19.105	14.890
0.0144	19.035	14.946
0.0208	19.087	15.088
0.0298	18.768	15.041
0.0428	19.017	15.056
0.0616	18.970	14.867
0.0887	18.889	15.007
0.1273	18.959	14.982
0.1834	19.006	14.968
0.2637	18.979	14.922
0.3792	18.952	14.993
0.5458	18.820	15.083
0.7845	18.6764	14.913
1.1287	18.505	14.605
1.6244	17.822	15.139
2.3360	17.284	13.679
3.3605	16.248	13.270
4.8335	14.734	11.690
6.9512	14.051	11.067
10.0020	12.606	9.973
11.9990	12.572	9.503
14.0010	12.168	9.229
16.0020	12.026	9.059
18.0000	12.071	8.912
19.9980	11.925	8.713
30.0000	12.109	8.962
40.0000	12.067	8.837
60.0000	12.157	8.780

Table S2: Variable temperature proton relaxivities (r_1; $mM^{-1}s^{-1}$) of $[Gd(C4,4'\text{-}(CH_2OH)_2DTPA)(H_2O)]^{2-}$ ($c_{Gd(III)}$ = 5.06 mM; pH = 6.39)

	$r_1/mM^{-1}s^{-1}$	
Frequency/MHz	**298 K**	**310 K**
0.0100	8.564	7.066
0.0144	8.674	7.059
0.0208	8.624	7.081
0.0298	8.591	7.033
0.0428	8.658	7.033
0.0616	8.667	7.004
0.0887	8.615	7.017
0.1273	8.551	7.019
0.1834	8.624	6.995
0.2637	8.582	7.109
0.3792	8.612	7.013
0.5458	8.657	7.013
0.7845	8.487	6.976
1.1287	8.363	6.864
1.6244	8.237	6.793
2.3360	8.003	6.628
3.3605	7.698	6.439
4.8335	7.238	5.970
6.9512	6.738	5.707
10.0020	6.125	5.032
11.9990	5.898	4.752
14.0010	5.623	4.522
16.0020	5.469	4.279
18.0000	5.357	4.218
19.9980	5.291	4.240
30.0000	5.488	4.264
40.0000	5.389	4.143
60.0000	5.250	4.038

Table S3: Variable temperature proton relaxation rates (R_1; s^{-1}) of [Gd(N'-Bz-C4,4'-$(CH_2OH)_2$DTTA)$(H_2O)_2$]$^-$ dissolved in 4% aqueous HSA ($c_{Gd(III)}$ = 1.5 mM; pH = 7.0)

	R_1/s^{-1}	
Frequency/MHz	**298 K**	**310 K**
0.010012	32.14	28.25
0.014693	32.59	28.41
0.021426	32.32	28.16
0.031418	32.29	27.97
0.045976	32.36	28.45
0.067387	32.51	28.10
0.09854	32.16	28.13
0.14415	32.22	27.75
0.21134	32.15	27.97
0.30953	31.53	27.51
0.45292	31.15	27.35
0.66296	30.52	26.85
0.9706	29.65	26.12
1.4213	28.97	25.17
2.0812	27.58	24.20
3.0474	26.49	22.85
4.4613	24.96	22.55
6.5297	24.66	21.96
9.5619	25.08	21.94
10	26.09	22.74
12	26.91	23.35
14	27.83	23.41
16	28.90	23.87
18	29.74	24.08
20	29.90	24.13

Table S4: Variable temperature reduced transverse and longitudinal ^{17}O relaxation rates and chemical shifts of $[Gd(N'\text{-Bz-C4,4'-}(CH_2OH)_2DTTA)(H_2O)_2]^-$ solution at 4.7 T. c_{Gd} = 26.53 mmol/Kg; $P_m = 9.56\times10^{-4}$; pH= 6.70

T/K	1000/T	T_1/s(ref)	T_1/s	ln(1/T_{1r})	T_2/s (ref)	T_2/s	ln(1/T_{2r})	ν/Hz	ν/Hz (ref)	$\Delta\omega_r$(rads^{-1})×10^{-5}
297	3.36	0.0069	0.0058	10.2	0.0068	0.0011	13.4	-638.8	-580.6	-3.82
304	3.29	0.0082	0.0066	10.3	0.0081	0.0012	13.5	-648.6	-590.4	-3.81
306	3.26	0.0087	0.0072	10.1	0.0086	0.0013	13.4	-649.5	-593.7	-3.66
315	3.17	0.0104	0.0087	9.88	0.0099	0.0015	13.3	-657.7	-601.9	-3.66
288	3.47	0.0056	0.0046	10.5	0.0055	0.0010	13.7	-624.0	-571.5	-3.44
276	3.62	0.0038	0.0032	10.8	0.0038	0.0009	13.7	-614.2	-559.2	-3.60
326	3.07	0.0128	0.0108	9.59	0.0121	0.0015	13.5	-665.1	-615.8	-3.23
336	2.97	0.0152	0.0128	9.45	0.0151	0.0024	12.8	-679.8	-626.5	-3.49
348	2.88	0.0179	0.0155	9.07	0.0173	0.0032	12.4	-689.7	-638.0	-3.39
359	2.79	0.0196	0.0171	8.96	0.0196	0.0038	12.3	-694.6	-645.4	-3.22

Table S5: Variable temperature reduced transverse and longitudinal ^{17}O relaxation rates and chemical shifts of $[Gd(C4,4'\text{-}(CH_2OH)_2DTPA)(H_2O)]^{2-}$ solution at 4.7 T. c_{Gd} = 25.12 mmol/Kg; $P_m = 4.53\times10^{-4}$; pH= 6.89.

T/K	1000/T	T_1/s(ref)	T_1/s	$\ln(1/T_{1r})$	T_2/s (ref)	T_2/s	$\ln(1/T_{2r})$	ν/Hz	ν/Hz (ref)	$\Delta\omega_r(rads^{-1})\times10^{-5}$
348	2.88	0.0179	0.0165	9.25 (8.57)	0.0173	0.0034	13.2 (12.5)	-673.3	-638.0	-4.90 (-2.45)
359	2.78	0.0196	0.0176	9.46 (8.77)	0.0196	0.0038	13.0 (12.3)	-677.4	-645.4	-4.44 (-2.22)
336	2.97	0.0152	0.0138	9.60 (8.95)	0.0151	0.0025	13.5 (12.8)	-655.2	-626.5	-3.98 (-1.99)
326	3.07	0.0128	0.0116	9.79 (9.08)	0.0121	0.0020	13.7 (13.0)	-647.8	-615.8	-4.44 (-2.22)
315	3.17	0.0104	0.0093	10.1 (9.50)	0.0099	0.0015	14.0 (13.3)	-639.6	-601.9	-5.23 (-2.62)
306	3.26	0.0088	0.0078	10.4 (9.65)	0.0086	0.0015	14.0 (13.3)	-631.4	-593.7	-5.23 (-2.62)
297	3.36	0.0069	0.0062	10.5 (9.73)	0.0068	0.0014	14.0 (13.2)	-601.1	-580.6	-2.84 (-1.42)
304	3.29	0.0082	0.0071	10.6 (9.90)	0.0081	0.0014	14.1 (13.4)	-625.7	-590.4	-4.90 (-2.45)
288	3.47	0.0055	0.0050	10.6 (9.91)	0.0055	0.0015	13.9 (13.2)	-587.9	-571.5	-2.27 (-1.14)
276	3.62	0.0038	0.0035	10.8 (9.99)	0.0038	0.0015	13.7 (13.0)	-577.3	-559.2	-2.51 (-1.26)