Electronic Supplementary Information for Chemical Communications

Supporting information

Gd(DO3A-N-α-aminopropionate): a versatile and easily available synthon with optimized water exchange for the synthesis of high relaxivity, targeted MRI contrast agents[#]

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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, $1/T_2$ and ω, and of the acidified water reference, $1/T_{2A}$ and ω_A, one can calculate the reduced relaxation rates and chemical shifts, $1/T_{2r}$ and $\Delta\omega_r$, which may be written as in Equations (A1)-(A2), where, $1/T_{2m}$ is the relaxation rate 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]

$$\frac{1}{T_{2r}} = \frac{1}{P_m}\left[\frac{1}{T_2} - \frac{1}{T_{2A}}\right] = \frac{1}{\tau_m}\frac{T_{2m}^{-2} + \tau_m^{-1}T_{2m-1} + \Delta\omega_m^2}{(\tau_m^{-1} + T_{2m}^{-1})^2 + \Delta\omega_m^2} + \frac{1}{T_{2os}} \qquad \text{(A1)}$$

$$\Delta\omega_r = \frac{1}{P_m}(\omega - \omega_A) = \frac{\Delta\omega_m}{(1+\tau_m T_{2m}^{-1})^2 + \tau_m^2 \Delta\omega_m^2} + \Delta\omega_{os} \quad \text{(A2)}$$

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

In equation (A2) 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 (A3). [4]

$$\Delta\omega_m = \frac{g_L \mu_B S(S+1)B}{3k_B T}\frac{A}{\hbar} \quad \text{(A3)}$$

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 (A4)]. [5]

$$\Delta\omega_{os} = C_{os}\Delta\omega_m \quad \text{(A4)}$$

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.

$$\frac{1}{T_{2m}} = \frac{1}{T_{2sc}} = \frac{S(S+1)}{3}\left(\frac{A}{\hbar}\right)^2 \tau_{s1} \quad \text{(A5)}$$

$$\frac{1}{\tau_{s1}} = \frac{1}{\tau_m} + \frac{1}{T_{1e}} \quad \text{(A6)}$$

The exchange rate is supposed to obey the Eyring equation. In equation (A7) $\Delta S^{\ddagger}$ 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.

$$\frac{1}{\tau_m} = k_{ex} = \frac{k_B T}{h}\exp\left\{\frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H^{\ddagger}}{RT}\right\} = \frac{k_{ex}^{298} T}{298.15}\exp\left\{\frac{\Delta H^{\ddagger}}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \quad \text{(A7)}$$

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:

$$R_1^{obs} = R_1^d + R_1^p = R_1^d + r_1[Gd^{3+}] \quad \text{(A8)}$$

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

$$r_1 = r_{1is} + r_{1os} \quad \text{(A9)}$$

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

$$r_{1is} = \frac{1}{1000} \times \frac{q}{55.55} \times \frac{1}{T_{1m}^H + \tau_m} \quad \text{(A10)}$$

The longitudinal relaxation rate of inner sphere protons, $1/T_{1m}{}^H$ is expressed by Equation (A11), 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.

$$\frac{1}{T_{1m}^H} = \frac{2}{15}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{r_{GdH}^6} S(S+1) \times \left[3J(\omega_I; \tau_{d1}) + 7J(\omega_S; \tau_{d2})\right] \quad \text{(A11)}$$

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_m} + \frac{1}{\tau_{RH}} + \frac{1}{T_{ie}} \qquad \text{for } i = 1,2 \quad \text{(A12)}$$

where τ_{RH} is the rotational correlation time of the Gd-H_{water} vector.

The rotational correlation time, τ_{RH} is assumed to have simple exponential temperature dependence with an E_R activation energy as given in equation (A13).

$$\tau_{RO} = \tau_{RO}^{298} \exp\left[\frac{E_R}{R}\left(\frac{1}{T} - \frac{1}{298.15}\right)\right] \quad \text{(A13)}$$

The outer-sphere contribution can be described by Equation (A14) where N_A is the Avogadro constant, and J_{os} is its associated spectral density function as given by Equation (A15). [8, 9]

$$r_{1os} = \frac{32 N_A \pi}{405}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{a_{GdH} D_{GdH}} S(S+1)\left[3J_{os}(\omega_I, T_{1e}) + 7J_{os}(\omega_S, T_{2e})\right] \quad \text{(A14)}$$

$$J_{\mathrm{os}}\left(\omega,T_{je}\right)=\mathrm{Re}\left[\frac{1+14\left(i\omega\omega_{GdH}+\frac{\tau_{\mathrm{GdH}}}{T_{je}}\right)^{1/2}}{1+\left(i\omega\omega_{GdH}+\frac{\tau_{\mathrm{GdH}}}{T_{je}}\right)^{1/2}+49\left(i\omega\omega_{GdH}+\frac{\tau_{\mathrm{GdH}}}{T_{je}}\right)+19\left(i\omega\omega_{GdH}+\frac{\tau_{\mathrm{GdH}}}{T_{je}}\right)^{3/2}}\right] \qquad \text{(A15)}$$

$j=1,2$

The longitudinal and transverse electronic relaxation rates, $1/T_{1e}$ and $1/T_{2e}$ are expressed by Equation (A16)-(A17), 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 (A18).

$$\left(\frac{1}{T_{1e}}\right)^{\mathrm{ZFS}}=\frac{1}{25}\Delta^2\tau_v\left\{4S(S+1)-3\right\}\left(\frac{1}{1+\omega_S^2\tau_v^2}+\frac{4}{1+4\omega_S^2\tau_v^2}\right) \qquad \text{(A16)}$$

$$\left(\frac{1}{T_{2e}}\right)^{\mathrm{ZFS}}=\Delta^2\tau_v\left(\frac{5.26}{1+0.372\omega_S^2\tau_v^2}+\frac{7.18}{1+1.24\omega_S\tau_v}\right) \qquad \text{(A17)}$$

$$\tau_v=\tau_v^{298}\exp\left[\frac{E_v}{R}\left(\frac{1}{T}-\frac{1}{298.15}\right)\right] \qquad \text{(A18)}$$

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 (A19). D_{GdH}^{298} is the diffusion coefficient at 298.15K.

$$D_{\mathrm{GdH}}=D_{\mathrm{GdH}}^{298}\exp\left\{\frac{E_{\mathrm{GdH}}}{R}\left(\frac{1}{298.15}-\frac{1}{T}\right)\right\} \qquad \text{(A19)}$$

References for Equations

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Experimental Section

Materials and Equipment: Chemicals were purchased from Sigma-Aldrich and used without further purification. Analytical grade solvents were used and not further purified unless specified. Reactions were monitored by TLC on *Kieselgel* 60 F_{254} (Merck) on aluminium support, with detection by examination under UV light (254 nm), by adsorption of iodine vapour and by spraying with ninhydrin. Flash chromatography was performed on Kieselgel 60 (Merck, mesh 230-400). Ion exchage chromatograpy was performed on Dowex 1X2-OH^- resin (Sigma Aldrich). The resin was purchase as the Cl^- form and converted to the OH^- form by the standard procedure. The relevant fractions from chromatography were pooled and concentrated under reduced pressure, T <40 ^oC. ^1H and ^{13}C NMR spectra (assigned by 2D DQF-COSY and HMQC techniques) were run on a Varian Unity Plus 300 NMR spectrometer, operating at 299.938 MHz and 75.428 MHz, for ^1H and ^{13}C, respectively. Chemical shifts (δ) are given in ppm relative to the $CDCl_3$ solvent (^1H, δ 7.27; ^{13}C 77.36) as internal standard. For ^1H and ^{13}C NMR spectra recorded in D_2O, chemical shifts (δ) are given in ppm, respectively, relative to TSP as internal reference (^1H, δ 0.0) and *tert*-butanol as external reference (^{13}C, CH_3 δ 30.29). Mass spectrometry was performed at CACTI- Vigo, Spain.

Synthesis of monoalkylated cyclen (3): K_2CO_3 (1.47 g, 10.6 mmol) was added to a solution of cyclen (0.920 g, 5.34 mmol) in MeCN (40 cm^3). To this solution was added Boc_2-Δ-AlaOMe (**2)** (1.07 g, 3.55 mmol). The suspension was vigorously stirred at room temperature for 4 hrs. The suspended solid was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (100% CH_2Cl_2→ CH_2Cl_2/EtOH/NH_3/H_2O (50:50:1:1)) to the afford compound **3** as a viscous light yellow oil (1.29 g, 77.0%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 18H, Boc), 2.50-2.80 (m, 16H, N(CH_2)$_2$N), 3.78 (dd, *J*= 14.4 and 5.4 Hz, 1 H, N$CH_a$$H_b$CH), 3.49 (dd, *J*= 14.4 and 5.4 Hz, 1 H, N$CH_a$$H_b$CH), 3.69 (s, 3H, OMe), 5.00 (t, *J*= 5.4 Hz, 1H, NCH$_a$H$_b$*CH*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ= 27.92 (C(CH_3)$_3$), 44.74 (CH_2), 45.89 (CH_2), 46.72 (CH_2), 50.76 (CH_2), 52.20 (OCH_3), 55.52 (NCH_2CH), 56.08 (*C*H), 83.29 (*C*(CH_3)$_3$), 151.87 (N*C*(O)O), 170.80 (*C*(O)OCH_3). HRMS (ESI): m/z: cacd for $C_{22}H_{44}N_5O_6$: 474.3292, found: 474.3286

Synthesis of fully alkylated cyclen (4): K_2CO_3 (1.17 g, 8.46 mmol) was added to a solution of monoalkylated cyclen **3** (0.880 g, 1.86 mmol) in MeCN (40 cm^3). To this suspension was added *tert*-butyl bromoacetate (0.763 cm^3, 6.14 mmol). The suspension was vigorously stirred at room temperature for 4 hrs. The suspended solid was removed by filtration, the solvent was evaporated under reduce pressure and the residue was purified by flash chromatography (100% CH_2Cl_2 → CH_2Cl_2/EtOH (1:1)) to afford compound **4** (0.754 g, 50 %) as a white foam. ^1H NMR (300 MHz, $CDCl_3$): δ= 1.47 (s,

45 H, *tert*-Bu), 2.00-3.70 (broad, overlapped signals with a integration corresponding to, 20 H, N(CH_2)$_2$N and NCH_aH_bCH), 3.79 (s, 3H, OMe), 4.93 (m (br), 1H, NCH$_a$H$_b$*CH*). ^{13}C NMR (75.4 MHz, $CDCl_3$): 27.81, 27.94 and 28.03 (C(CH_3)$_3$), 52.66 (1C, CH$\underline{C}$H$_2$), 51.640 (4C, $\underline{C}$H$_2$), 51.89 (1C, $\underline{C}$H$_2$), 52.13 (OCH_3), 52.60 (CH_2), 56.25, 56.20 and 56.46 (NCH_2C(O)), 81.96 , 82.42 and 83.80 (C(CH$_3$)$_3$) (151. 8 (NC(O)O), 172.8 (C(O)), 173.6 (C(O)). HRMS (ESI): m/z: cacd for $C_{40}H_{74}N_5O_{12}$: 816.5334, found: 816.5328.

Synthesis of orthogonal protected cyclen (5): K_2CO_3 (2.79 g, 20.2 mmol) was added to a solution of monoalkylated cyclen **3** (1.59 g, 3.36 mmol) in MeCN (60 cm^3). To this suspension was added ethyl bromoacetate (1.50 cm^3, 13.4 mmol). The suspension was vigorously stirred at room temperature for 4 hrs. The suspended solid was removed by filtration, the solvent was evaporated under reduce pressure and the residue was purified by flash chromatography (100% CH_2Cl_2 → CH_2Cl_2/EtOH (1:1)) to afford compound **4** (1.74 g, 71 %) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.26 (m, 9 H, OCH_2), 1.46 (set of sharp singulets, C$(CH_3)_3$), 2.2-3.60 (broad, overlapped signals with a integration corresponding to, 20 H, N(CH_2)$_2$N and NCH_aH_bCH), 3.72 (s, 3H, C(O)OCH_3), 4.84 (m (br), 1H, NCH$_a$H$_b$*CH*). ^{13}C NMR (75.4 MHz, $CDCl_3$): selected signals: 14.07 (OCH$_2$$CH_3$), 27.89 (C($CH_3$)$_3$), 50.85 (cluster of unresolved signals, CH$_2$), 52.57 (OCH_3), 55.01 (CH_2), 55.58 (CH_2), 55.88 (*CH*), 56.43 (CH_2), 57.00 (CH_2), 58.26 (CH_2), 60.52 (CH_2) 61.14, 61.27, 61.52 (OCH_2) 83.81 (C(CH$_3$)$_3$), 152.01 (NC(O)O), 173.60 (C(O)). HRMS (ESI): m/z: cacd for $C_{34}H_{62}N_5O_{12}$: 732.4395, found: 732.4398.

Synthesis of selectively deprotected amine (7): A solution of orthogonally protected cyclen (**5**) (1.50 g, 2.05 mmol) in trifluoroacetic acid in dichlorometane (10%, 40 cm^3) was stirred overnight at room temperature. The solvent was evaporated at reduced pressure and the residue was redissolved in dichlorometane. The solvent was evaporated, and this procedure was repeated several times to give a light yellow thick oil. ^{1}H NMR spectroscopy ($CDCl_3$) revealed the disappearance of the signals assigned to the *Boc* groups in the precursor compound **5**. The ratio of integration between the methine proton NCH$_2$*CH* and the methyl or methylene protons (from the ethyl ester groups) indicated that no deprotection of the ethyl ester groups had occurred during the deprotection with TFA.

Synthesis of DO3A-N-α-amionopropionate (6): Fully protected cyclen (**4**) (0.822 g, 1.01 mmol) was dissolved in a mixture ethanol (10 cm^3) / hydrochloric acid (6M, 10 cm^3) and stirred at room temperature overnight. The solvent was evaporated at reduced pressure (temperature ~25 ºC), the residue was redissolved in water and evaporated again. This procedure was repeated several times. The remaining thick oil was dissolved in water (30 cm^3) and the solution was adjusted to pH 10-11 (pH paper) by addition of small portions of Dowex-1X2-100 OH$^-$ resin (~ 40 cm^3 wet resin). The reaction mixture was stirred for 4 hrs at room temperature. The resin was transferred into a column, washed with water and eluted with hydrochloric acid (0.1 M). The relevant fractions were pooled together and the solvent was removed under reduced pressure (temperature < 40 ºC) to give compound **6** as the hydochloride (0.380 g, 61 %). ^{1}H NMR (600 MHz, D_2O): acetate arms C$\underline{H}_2$ (AB systems): 3.98 (d), 3.78 (d); 3.92 (d), 3.68 (d); 3.22 (d), 2.90 (d); aminopropionate arm C$\underline{H}_2$ (ABX system): 3.61 (dd), 3.25 (m), 2.80 (m); macrocyclic ring C$\underline{H}_2$: 4.10 (m), 4.06 (d), 3.85 (m), 3.56 (m), 3.53 (m), 3.50 (m), 3.33 (m), 3.30 (m), 3.18 (m), 3.15 (m), 3.10 (m), 2.97 (m), 2.87 (m), 2.75 (m), 2.70 (m), 2.60 (m). ^{13}C NMR (75.4 MHz, $CDCl_3$): 46.57 (CH_2), 48.08 (CH_2), 49.16 (CH_2), 49.68 (CH_2), 50.20 (CH_2), 51.19 (CH_2), 5.92 (CH_2), 52.51 (CH), 53.32 (CH_2), 54.26 (CH_2), 55.36 (CH_2), 57.11 (CH_2), 58.19 (CH_2), 170.45 (C(O)), 170.79 (C(O)), 172.67 (C(O)), 178.36 (CHC(O)). HRMS (ESI): m/z: cacd for $C_{17}H_{32}N_5O_8$: 434.2251, found: 434.2245.

1D and gCOSY 2D ^{1}H NMR spectra of ligand L and 1D ^{1}H NMR spectra of the EuL and SmL complexes were run at 600.14 MHz, on a Varian VNMRS 600 NMR spectrometer.

^{17}O NMR and ^{1}H NMRD experiments

Sample Preparation.

The [Gd(DO3A-N-alpha-aminopropionate)(H_2O)]$^-$ complex for ^{17}O NMR and ^{1}H NMRD was prepared by mixing equimolar amounts of $GdCl_3$ and the respective ligand. A slight excess (5%) of ligand was used and the pH of the stock solution was adjusted by adding aqueous NaOH (0.1 mM). The solution was allowed to react for 24 hours at 333K. The absence of free metal was checked in each sample by testing with xylenol orange [1,2]. O- enriched water (^{17}O: 11.4%) was added to the solutions for the ^{17}O measurements to improve the sensitivity. The final solution concentration was 30.01 mmol kg^{-1} at pH = 6.75. For the NMRD experiments a 1.0 mM solution at pH 7.1 was used for complex [Gd(DO3A-N-alpha-aminopropionate)(H_2O)]$^-$.

^{1}H NMR of [Ln(1)(H_2O)$_2$]$^-$ and [Ln(2)(H_2O)]$^{2-}$.

To an aqueous solution of the ligand (pH = 5.0) was added dropwise an aqueous solution of the corresponding $LnCl_3$ in the 1:1 mole ratio. The pH was kept around 5.7 by the addition of aqueous KOH and the solution was stirred at room temperature over 1 hour. The solution was concentrated under reduced pressure. The solutions for NMR measurements were obtained by dissolution in D_2O (V = 1 cm^3) of the solid complexes prepared previously to obtain 20 mM concentrations. Proton 1D and 2D g-COSY spectra of the solutions of the paramagnetic (Sm^{3+} and Eu^{3+}) and diamagnetic (La^{3+}) complexes were obtained at 298 K on a Varian VNMRS 600 (14.09 T, 600.14 MHz) NMR spectrometer.

^{17}O NMR experiments.

Variable-temperature ^{17}O NMR measurements were performed on a Bruker Avance-500 (11.7 T) spectrometer and a BVT-3000 temperature control unit were used to stabilize the temperature, measured by a substitution technique. The samples were sealed in glass spheres that fitted into 10 mm o.d. NMR tubes, to eliminate susceptibility corrections to the chemical shifts [3,4]. Longitudinal relaxation rates $1/T_1$ were obtained by the inversion recovery method and transverse relaxation rates $1/T_2$ by the Carr-Purcell-Meiboom-Gill spin-echo technique. As an external reference, acidified water of pH 3.4 was used.

NMRD measurements.

The measurements were performed by using a Stelar Spinmaster FFC NMR relaxometer (0.01-20 MHz) equipped with a VTC90 temperature control unit. At higher fields, the ^{1}H relaxivity measurements were performed on a Bruker Electromagnet at the frequencies of 20MHz, 40MHz, 60MHz and 80MHz. In each case, the temperature was measured by a substitution technique. Variable temperature measurements were performed at 25 and 37ºC.

Transmetallation studies with Zn^{2+}.

The transmetallation reaction of [Gd(DO3A-N-alpha-aminopropionate)(H_2O)]$^-$ with Zn^{2+} was studied by the time dependent decrease of the water proton longitudinal relaxation rate, R_1, measured on a Bruker Minispec mq20 (20 MHz, 25, 310K), of a phosphate-buffered saline solution (PBS, pH 7.1, 10 mM) containing 0.75 mM of [Gd(DO3A-alpha-aminopropionate)(H_2O)]$^-$ after addition of an equimolar amount of $ZnCl_2$, while the sample was vigorously stirred [5]. The water longitudinal relaxation rate was also measured as a function of time on the PBS buffered solution (pH 7.1, 10 mM) containing 0.75 mM [Gd(DO3A-N-alpha-aminopropionate)(H_2O)]$^-$ [6].

References for experimental section

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Supplementary Results.

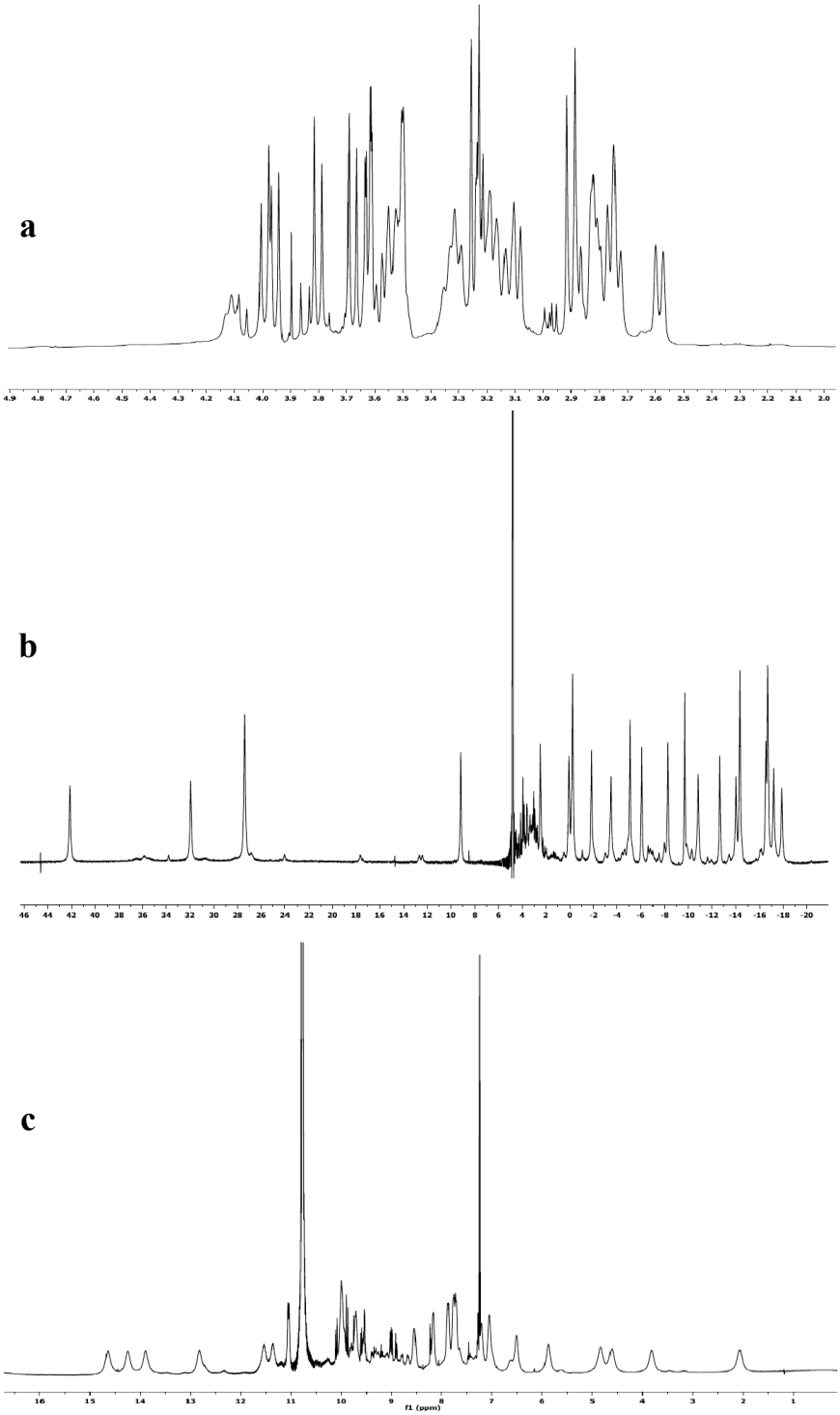

Figure 1S. ^{1}H NMR spectra of Ln^{3+} complexes in D_2O and its ligand (20 mM, pH 7.0, 298 K); **a)** DO3A-N- α -aminopropionate at 600 MHz (expansion); **b)** [Eu(DO3A-N- α -aminopropionate)$(H_2O)]^-$ at 600 MHz; **c)** [Sm(DO3A-N- α -aminopropionate)$(H_2O)]^-$ complex at 600 MHz.

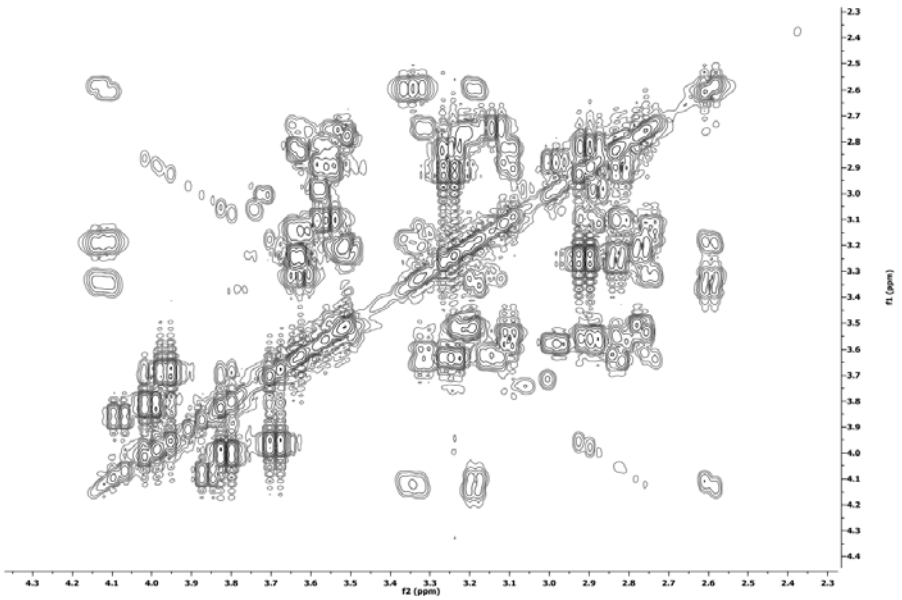

Figure 2S. ^{1}H NMR 2D gCOSY spectra of the ligand DO3A-N- α -aminopropionate in D_2O 20 mM, pH 7.0, 298 K).

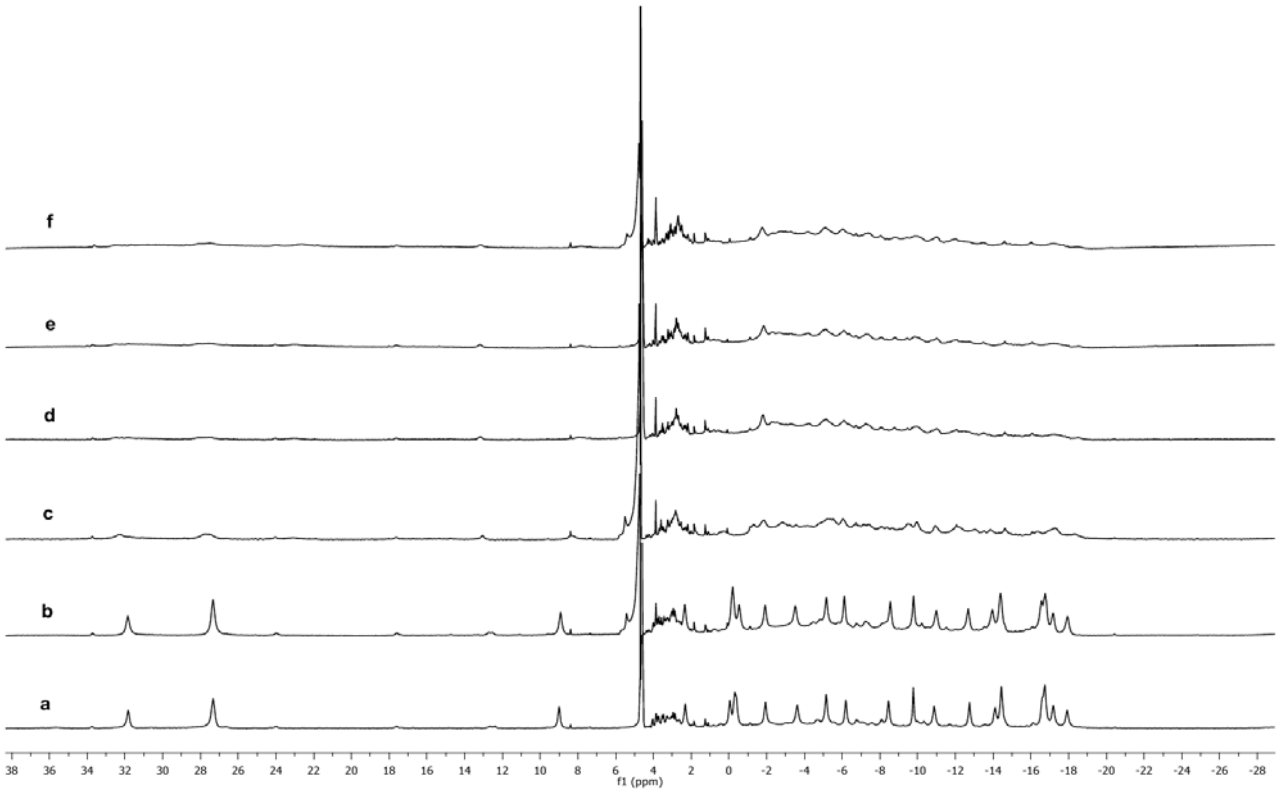

Figure 3S. pH dependence of the ^{1}H NMR spectrum of the [Eu(DO3A-N- α -aminopropionate)(H_2O)] complex in D_2O (600 MHz, 20 mM, 298 K): a – f correspond to pH 7.0, 8.0, 9.0, 10.0, 11.0 and 12.0, respectively.

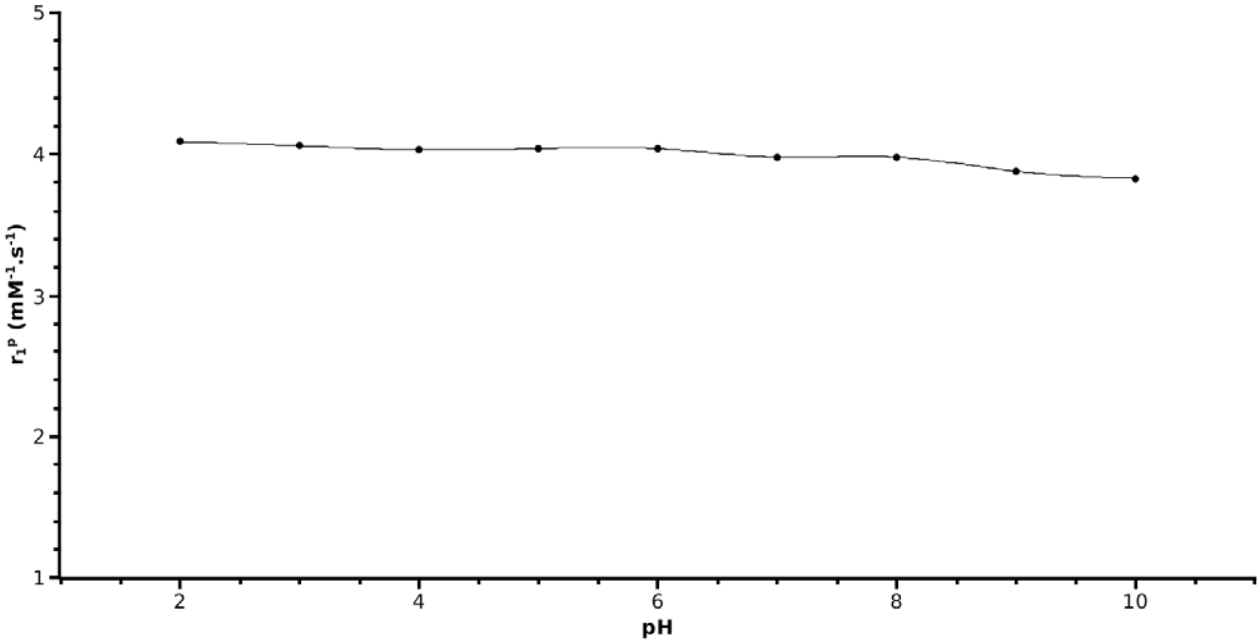

Figure 4S. Proton longitudinal paramagnetic relaxation rates (R_1^p) dependency with the pH of aqueous solutions containing 1mM of Gd-DO3A-N- α -aminopropionate at 20MHz (pH 7.1, T = 310K).

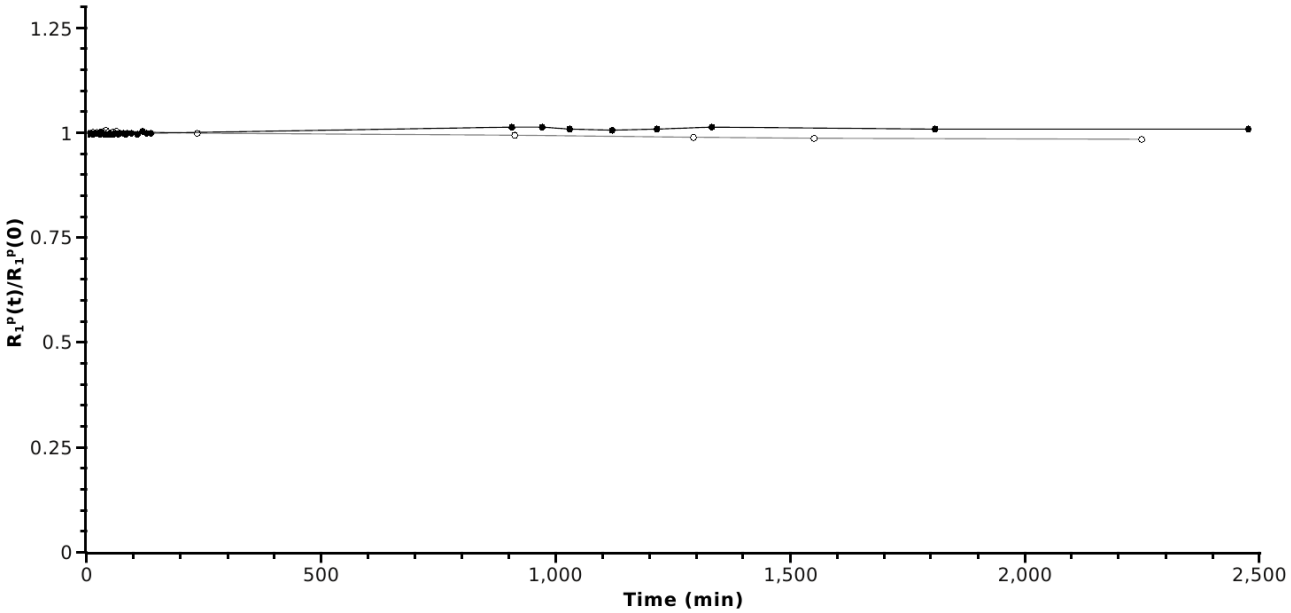

Figure 5S. Evolution of the relative water proton paramagnetic relaxation rate R_1^p (t)/R_1^p(0) (20 MHz, pH 7.1, 310 K) versus time for 0.75 mM Gd-DO3A-N- α -aminopropionate in the presence of equimolar amounts of Zn^{2+} ions, in 10 mM phosphate solution (empty circles). Evolution of R_1^p (t)/R_0^p(0) in 10 mM phosphate solution without Zn^{2+} ions (full circles). The lines are only guides for the eye.

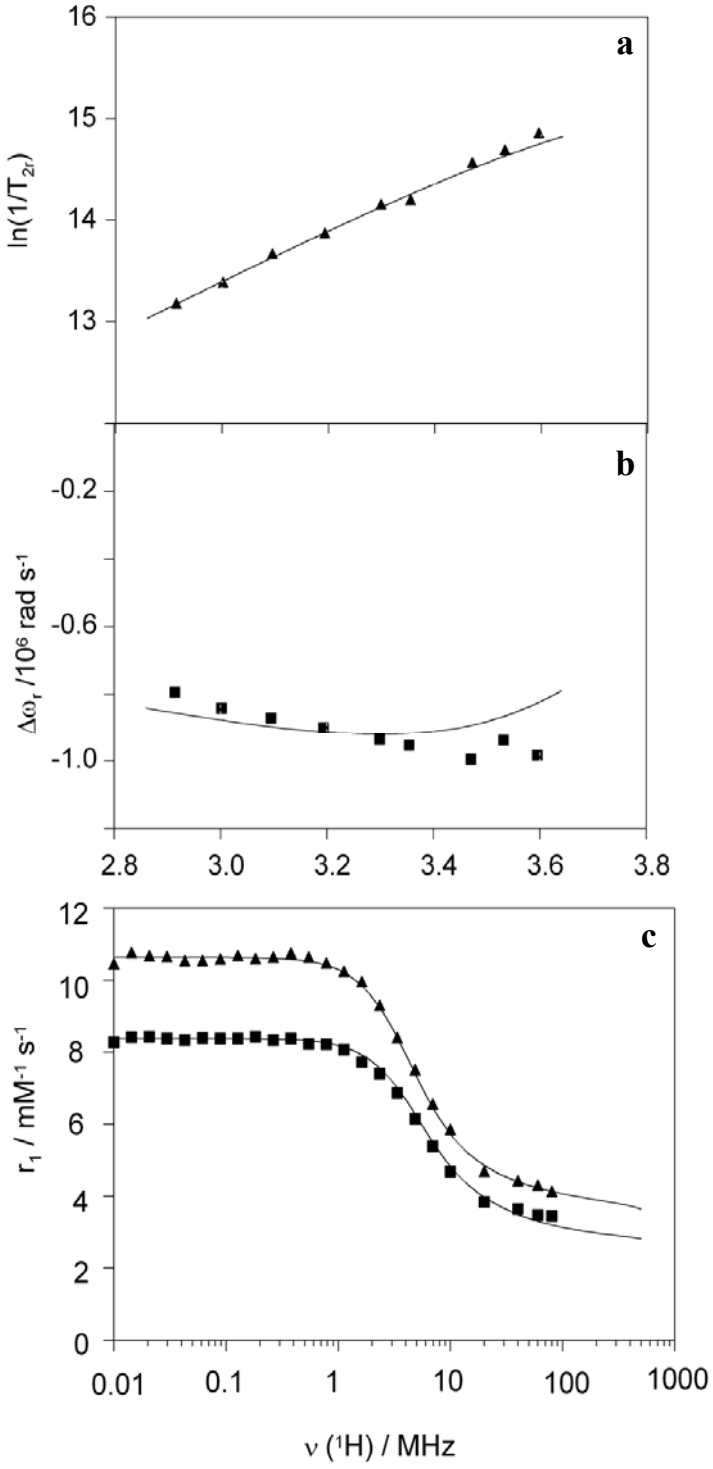

Figure 6S. Temperature dependence of the **a**) reduced ^{17}O transverse relaxation rates (triangles) and **b)** reduced ^{17}O chemical shifts (squares) at B=11.7T. **c**) ^{1}H NMRD profiles at 25ºC (triangles) and 37ºC (squares) for the Gd-DO3A-alpha-aminopropionate complex. The lines show a simultaneous fit of the ^{17}O NMR and NMRD data.

Table 1S. Best fit parameters obtained for [Gd(DO3A-N-α-aminopropionate)(H_2O)] from the analysis of ^{17}O NMR and ^{1}H NMRD data.

Parameters	DO3A-N-α-aminopropionate
$q(H_2O)$	1
$\Delta H^{\ddagger}$ [J/K/mol]	19.1±1.6
$\Delta S^{\ddagger}$ [kJ/mol]	-35±6
k_{ex}^{298} [10^7 s^{-1}]	4±0.4
E_R [kJ/mol]	17±1
τ_{RH}^{298}[ps]	71±6
E_V [kJ/mol]	1
τ_V^{298} [ps]	11±1
Δ^2 [10^{20} s^{-2}]	0.25±0.02
A/ħ [10^6 rad/s]	-3.6±0.3
D_{GdH}^{298} [10^{-10} m^2s^{-1}]	26
E_{DGdH}^{298} [kJ/mol]	20