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Preparation and *in vitro* evaluation of a novel amphiphilic GdPCTA-[12] derivative; a micellar MRI contrast agent

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A novel amphiphilic GdPCTA-[12] derivative has been prepared. The complex formed micelles in aqueous solution with a relatively low CMC, 0.15 mM (25 °C). The concentration dependent T_1-relaxivity (r_1) of the system has been described. The maximum T_1-relaxivity, 29.2 s^{-1} mM^{-1} (20 MHz, 25 °C), was higher than for previously described micellar MRI contrast agents. This high T_1-relaxivity is a consequence of the favourable water residence time (τ_M) and the fact that the complex is heptadentate allowing two water molecules to coordinate to the gadolinium ion ($q = 2$).

Introduction

Paramagnetic materials have been investigated as MRI contrast agents (CAs) for more than two decades.[1] These materials enhance the contrast of the image indirectly by lowering the magnetic relaxation time of the water protons in the surrounding tissues.[2,3] The most frequently used CAs are stable gadolinium(III) (Gd) complexes with hydrophilic poly-(aminocarboxylate) ligands resulting in rapid extracellular distribution and renal elimination. Gd(III) is preferred because of its favourable magnetic properties (seven unpaired electrons). Depending on the denticity of the ligand one or more water molecules might be directly coordinated to the paramagnetic centre.

Gd complexes with amphiphilic properties have previously been prepared and evaluated as blood-pool and liver imaging agents. Long chain amides and esters of GdDTPA (gadolinium diethylenetriamine pentaacetic acid) are the most common.[4] More recently amphiphilic gadolinium complexes based on the DO3A (1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane) ligand have been reported.[5–7] In an aqueous environment these complexes are able to form supramolecular systems such as micelles, or in the presence of surfactants and phospholipids, mixed micelles and liposomes. The formation of these systems increases the efficacy (T_1-relaxivity) of the contrast agent due to an increase in the rotational correlation time (τ_R) of the Gd complex.

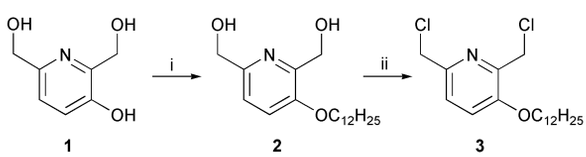
However, the increase in T_1-relaxivity of these octadentate complexes is partly quenched by the long residence time (τ_M) of the coordinated water molecule. These high τ_M values, 300 ns (25 °C) for GdDTPA, are related to the dissociative exchange mechanism of the water molecule from the coordination site to the bulk.[8] Being a heptadentate complex with two coordinated water molecules (q = 2), GdPCTA-[12] (gadolinium 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetate) is reported to have a considerably lower water residence time, 70 ns (25 °C).[9] The complex is also reported to have an acceptable stability, in order not to release highly toxic gadolinium ions *in vivo*.[10]

By introducing a lipophilic moiety onto the GdPCTA-[12] structure, preferably on the pyridine unit, one would obtain a Gd complex able to form micelles in aqueous solution. This micellar MRI contrast agent would obtain a higher T_1-relaxivity above the CMC than the previously reported $q = 1$ complexes.[5,11,12]

Results and discussion

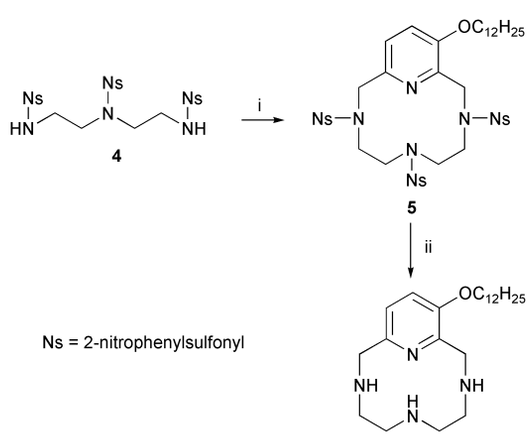
Synthesis

The synthetic strategy was a slight modification of the procedure described by Aime *et al.*[13] The trisubstituted pyridine **1**[14] was selectively alkylated at the aromatic hydroxyl functionality by dodecyl bromide in DMF in the presence of potassium carbonate. The resulting dialcohol **2** was converted to the dichloride **3** by treatment with thionyl chloride. The total yield of this reaction sequence was 54% (Scheme 1).



Scheme 1 *Reagents and conditions*: i, dodecyl bromide, K_2CO_3, DMF, 95 °C; ii, thionyl chloride, 40 °C.

The ring-forming reaction between the dichloride **3** and the sulfonamide **4**[15] was carried out under heterogeneous conditions in acetonitrile in the presence of potassium carbonate. The resulting macrocycle **5** was deprotected with thiophenol in DMF to obtain the macrocycle **6**. The total yield of these reactions was 42% from the dichloride **3** (Scheme 2). Attempts to



Scheme 2 *Reagents and conditions*: i, **3**, K_2CO_3, CH_3CN, reflux; ii, thiophenol, K_2CO_3, DMF, rt.

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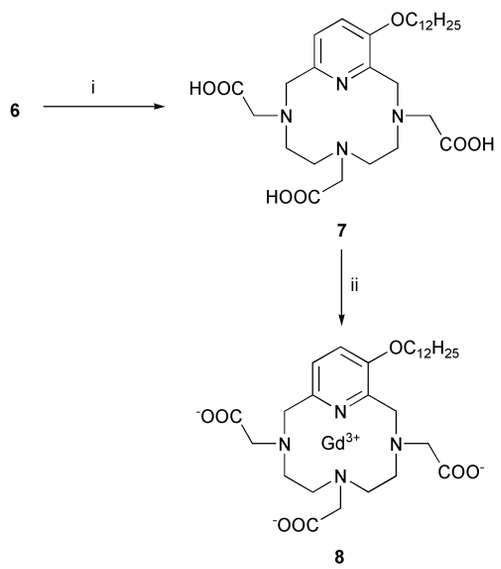
prepare the macrocycle **6** by using the corresponding tosylated intermediate was not successful. All methods employed for the hydrolysis of the tosyl groups failed, because of incomplete hydrolysis and/or cleavage of the ether bond.

Carboxymethylation was achieved in low yield (21%) by reacting macrocycle **6** with sodium chloroacetate in water–ethanol at pH 10 (Scheme 3). Purification of the resulting PCTA-[12] derivative **7** was accomplished by flash chromatography on silica gel, yielding the substance in a pure state. The structure was confirmed by NMR (^{1}H and ^{13}C) and electrospray MS.



Scheme 3 *Reagents and conditions*: i, $ClCH_2COONa$, $EtOH–H_2O$, pH 10, 70 °C; ii, Gd_2O_3, H_2O, 100 °C.

The corresponding Gd complex **8** was prepared by heating the ligand with Gd_2O_3 in water at 100 °C. Purification was achieved by continuous extraction of an alkaline (pH 9) aqueous solution with chloroform. The electrospray MS data confirmed the presence of the Gd complex **8**.

Relaxometric characterisation of the Gd complex

Because of the amphiphilic structure of the Gd complex it was thought to form micelles in aqueous solution. The formation of micelles would ideally result in a longer rotational correlation time (τ_R) and thus higher T_1-relaxivity. Earlier studies on amphiphilic gadolinium 1,4,7,10-tetraazacyclododecane-1,4,7, 10-tetraacetate (GdDOTA)- and gadolinium 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate (GdHPDO3A) derivatives have shown an increase in the T_1-relaxivity explained by the formation of micelles.[5,11,12] The increase was, however, not large (r_1 = 10–22 s^{-1} mM^{-1}, 20 or 60 MHz, 25 °C).

A plot of the T_1-relaxivity (20 MHz, pH 7) of the GdPCTA-[12] derivative **8** as a function of the concentration at two different temperatures (25 °C and 37 °C) is shown in Fig. 1.

At 25 °C the lowest T_1-relaxivity, 11.9 s^{-1} mM^{-1}, was reached at concentrations below 0.05 mM. This value was somewhat higher than reported for a monomeric GdPCTA-[12] derivative (r_1 = 8.3 s^{-1} mM^{-1}) with about the same molecular weight.[13] The reason for this might have been that the complex was not entirely in the monomeric form, even in diluted aqueous solutions. Small clusters or dimers might have formed, resulting in a slightly increased τ_R. Above this concentration the T_1-relaxivity increased until it reached a plateau of 29.2 s^{-1} mM^{-1} at about 1.50 mM. As expected, the favourable τ_M of the coordinated water molecules in GdPCTA-[12] derivatives yielded a higher T_1-relaxivity than the corresponding GdDOTA and GdHPDO3A derivatives.

Table 1 The CMC value of the GdPCTA-[12] derivative **8** compared to other relevant paramagnetic Gd complexes (25 °C)

Complex	CMC/mM
8	0.15
GdHDDDO3A[5]	2.0
GdHHDDO3A[5]	0.10
GdDOTAC12[12]	4.45
GdDOTASAC18[12]	0.06

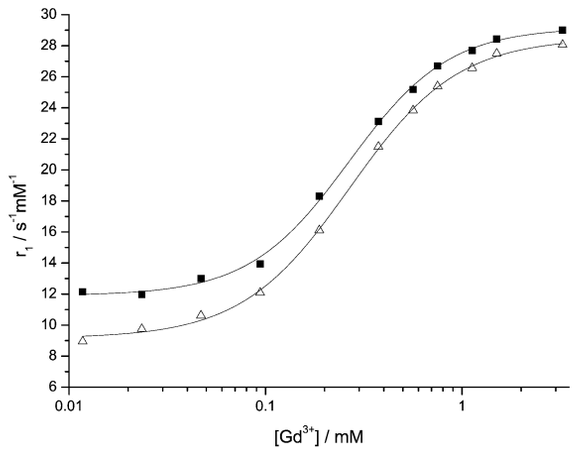


Fig. 1 The concentration dependence of the T_1-relaxivity (r_1) of the GdPCTA-[12] derivative **8** (20 MHz, pH 7). ■ 25 °C, △ 37 °C.

At 37 °C the minimum T_1-relaxivity was 9.2 s^{-1} mM^{-1}. The maximum T_1-relaxivity was 28.5 mM^{-1} s^{-1}. The shapes of the two curves were very alike, with the data for 37 °C shifted somewhat towards lower T_1-relaxivity values, as expected from the temperature dependence of τ_R.

From the data in Fig. 1 it is also apparent that the CMC of the substance is quite low. The exact values were determined by the method developed for paramagnetic compounds by Gäelle *et al.*[12] At 25 °C the value was determined to 0.15 mM, and at 37 °C it was 0.16 mM. These values were considerably lower than for earlier reported GdHPDO3A and GdDOTA complexes with lipophilic side chains of about the same length (C_{12}).[5,12] An explanation for this might be that the effective chain length for the GdPCTA-[12] derivative **8** is larger because of the hydrophobic character of the pyridine unit. In Table 1 the CMC values are compared to the values for other relevant amphiphilic Gd complexes.

A Nuclear Magnetic Resonance Dispersion (NMRD) profile of the GdPCTA-[12] derivative **8** (0.48 mM) is shown in Fig. 2. The data were fitted, and the parameters obtained are presented in Table 2. The value of τ_M was set to 100 ns, supposing that the introduction of a lipophilic chain did not alter the water

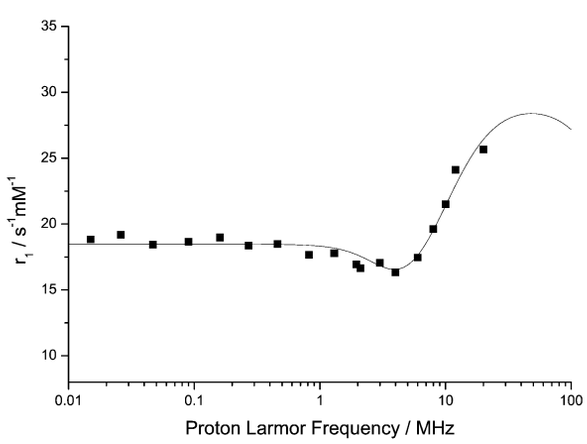


Fig. 2 NMRD profile of GdPCTA-[12] derivative **8** (0.48 mM, 25 °C). The line represents the best fit.

Table 2 Relaxation parameters for the GdPCTA-[12] derivative **8** obtained by the fitting of the NMRD profile, compared to the values for GdPCTA-[12]. The values in bold were fixed in the fitting procedure

Complex	q	$\Delta^2/s^{-2} \times 10^{19}$	τ_v/ps	τ_R/ps	r/Å
8	**2**	2.3 ± 0.1	43 ± 2	473 ± 18	**3.10**
GdPCTA-[12]	2	2.8	28	70	3.10

exchange rate to a great extent. This value could have been determined by performing variable temperature O^{17} NMR measurements. Unfortunately it was not possible to dissolve the complex in the required concentration for this experiment.

The profile showed the expected T_1-relaxivity peak around 20 MHz typical of complexes with an increased τ_R. The value obtained for τ_R by fitting of the curve was 473 ps. This value is nearly seven times the value for GdPCTA-[12], 70 ps.[9]

Experimental

Synthesis

Reagents were obtained from Aldrich Chemical Co. Inc., USA or Fluka Chemie AG, Switzerland and used as received.

NMR spectra were obtained on a Bruker Spectrospin Avance DPX300 (Bruker GmbH, Germany). Electron impact (EI) mass spectra were obtained using a Fisons VG ProSpec (70 eV and 220 °C) (Micromass Ltd., England). Electrospray (ES) FTICRMS mass spectra were recorded on a Bruker BioApex 4.7 T (Bruker GmbH, Germany). Elemental analyses were carried out by Ilse Beetz Microanalytisches Laboratorium (Germany).

3-Dodecyloxy-2,6-bis(hydroxymethyl)pyridine (2)

To a suspension of 3-hydroxy-2,6-bis(hydroxymethyl)pyridine (**1**) hydrochloride (4.79 g, 25 mmol) and potassium carbonate in ethanol (100 ml) were added a few drops of water. The mixture was stirred for 3 h at room temperature and filtered. The filtrate was evaporated *in vacuo* and dodecyl bromide (6.23 g, 25 mmol), potassium carbonate (6.90 g, 50 mmol) and DMF (100 ml) were added to the residue. The mixture was stirred at 95 °C under an argon atmosphere for 16 h, cooled to room temperature and filtered. Water (50 ml) was added to the filtrate and the solution was extracted with diethyl ether (3 × 80 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallised from cyclohexane to yield 4.84 g (60%) of a colourless solid. Mass spectrum (EI): *m*/*z* (relative intensity) 323 (100) [M^+, $C_{19}H_{33}NO_3$], 292 (38), 155 (89). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, 6.7 Hz, 3H), 1.20–1.25 (m, 16H), 1.27–1.45 (m, 2H), 1.74 (quin., 6.5 Hz, 2H), 3.93 (t, 6.5 Hz, 2H), 4.06 (s, 2H), 4.64 (s, 2H), 4.70 (s, 2H), 7.07 (d, 8.4 Hz, 1H), 7.15 (d, 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.01, 22.58, 25.90, 28.93, 29.24, 29.46, 29.49, 29.53, 29.56, 31.82, 59.92, 64.36, 68.32, 118.31, 119.90, 147.65, 149.37, 150.92.

3-Dodecyloxy-2,6-bis(chloromethyl)pyridine (3)

Thionyl chloride (10 ml) was added dropwise to 3-dodecyloxy-2,6-bis(hydroxymethyl)pyridine (**2**) (3.88 g, 12 mmol) at 0 °C. After complete addition the temperature was raised to 40 °C. After 4 h the mixture was cooled to room temperature and evaporated *in vacuo*. Water (20 ml) was added to the residue and the solution was neutralised by addition of aqueous sodium carbonate (10%). This solution was extracted with dichloromethane (3 × 40 ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Yield: 3.89 g (90%) of a slightly yellow solid. Mass spectrum (EI): *m*/*z* (relative intensity) 359 (89) [M^+, $C_{19}H_{31}Cl_2NO$], 191 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, 6.7 Hz, 3H), 1.20–1.35 (m, 16H), 1.40–1.50 (m, 2H), 1.81 (quin., 6.5 Hz, 2H), 4.00 (t, 6.4 Hz, 2H), 4.61 (s, 2H), 4.69 (s, 2H), 7.17 (d, 8.5 Hz, 1H), 7.36 (d, 8.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.04, 22.62, 25.87, 28.91, 29.20, 29.27, 29.47, 29.50, 29.57, 29.58, 31.84, 42.08, 46.26, 68.66, 119.57, 124.09, 145.53, 147.28, 152.92.

12-Dodecyloxy-3,6,9-tris(2-nitrophenylsulfonyl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (5)

Potassium carbonate (3.32 g, 24 mmol) was added to a solution of 3-dodecyloxy-2,6-bis(chloromethyl)pyridine (**3**) (2.16 g, 6 mmol) and 1,4,7-tris(2-nitrophenylsulfonyl)-1,4,7-triazaheptane (**4**) (3.95 g, 6 mmol) in acetonitrile (15 ml). The mixture was refluxed for 5 h, cooled to room temperature and evaporated *in vacuo*. The residue was partitioned between water (100 ml) and dichloromethane (50 ml). The aqueous phase was extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed with water (100 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was submitted to flash chromatography (SiO_2, *n*-hexane–ethyl acetate 2 : 3) to yield 2.89 g (51%) of a colourless solid. Mass spectrum (ES): *m*/*z* 946 [[M + H]$^+$, $C_{41}H_{52}N_7O_{13}S_3$]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, 6.6 Hz, 3H), 1.15–1.25 (m, 16H), 1.25–1.40 (m, 2H), 1.73 (quin., 6.9 Hz, 2H), 3.05–3.25 (m, 2H), 3.25–3.40 (m, 4H), 3.40–3.50 (m, 2H), 3.94 (t, 6.6 Hz, 2H), 4.50 (s, 2H), 4.68 (s, 2H), 7.21 (d, 8.5 Hz, 1H), 7.40 (d, 8.4 Hz, 1H), 7.50–7.75 (m, 9H), 7.80–8.10 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.04, 22.60, 25.73, 28.72, 29.26, 29.44, 29.53, 29.56, 31.83, 45.61, 46.32, 49.61, 54.22, 68.79, 120.00, 124.18, 124.21, 124.29, 130.79, 131.01, 131.18, 131.80, 132.05, 132.12, 132.18, 133.68, 133.79, 133.89, 143.50 145.50, 147.96, 148.13, 153.73.

12-Dodecyloxy-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (6)

Thiophenol (1.13 g, 10.3 mmol) was added to a suspension of 12-dodecyloxy-3,6,9-tris(2-nitrophenylsulfonyl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**5**) (2.70 g, 2.9 mmol) and potassium carbonate (3.94 g, 28.5 mmol) in DMF (30 ml). The mixture was stirred at room temperature under argon. Hydrochloric acid (2 M, 100 ml) was added after 5 h, and the solution was extracted with dichloromethane (3 × 50 ml). The pH of the aqueous phase was adjusted to 11 by the addition of solid sodium hydroxide. The alkaline solution was extracted with chloroform (5 × 60 ml). The combined chloroform extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield 0.91 g (82%) of a yellow oil. Mass spectrum (EI): *m*/*z* (relative intensity) 390 (15) [M^+, $C_{23}H_{42}N_4O$], 334 (68), 322 (65), 149 (60), 122 (63), 43 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (t, 6.5 Hz, 3H), 1.10–1.20 (m, 16H), 1.20–1.40 (m, 2H), 1.70 (quin., 6.8 Hz, 2H), 2.45–2.60 (m, 4H), 2.80–3.00 (m, 4H), 3.83 (t, 6.5 Hz, 2H), 3.89 (s, 2H), 3.94 (s, 2H), 4.60–5.20 (m, 3H), 6.88 (d, 8.3 Hz, 1H), 6.97 (d, 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.92, 22.47, 25.85, 28.89, 29.13, 29.35, 29.39, 29.42, 29.44, 31.69, 47.07, 47.37, 47.46, 47.87, 48.25, 52.16, 68.16, 118.17, 119.70, 148.78, 149.51, 151.06.

12-Dodecyloxy-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (7)

12-Dodecyloxy-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**6**) (0.85 g, 2.2 mmol) in ethanol (20 ml) was added to a solution of sodium chloroacetate (1.52 g, 13.1 mmol) in water (20 ml). The pH was adjusted to 10 by the addition of sodium hydroxide (1 M). The solution was heated at 70 °C for 48 h, maintaining a pH of 10. The solution was evaporated *in vacuo* and the residue was submitted to flash chromatography (SiO_2, $CHCl_3$–CH_3OH–NH_3 (25%) 9 : 6 : 1) yielding 265 mg (21%) of a slightly yellow solid. Mass spectrum (ES): *m*/*z* 565 [[M + H]$^+$, $C_{29}H_{49}N_4O_7$]. ^{1}H NMR (300 MHz, CD_3OD): δ 0.89 (t, 6.2 Hz, 3H), 1.20–1.40 (m, 16H), 1.45–1.60 (m, 2H), 1.75–1.90 (m, 2H), 1.90–2.20 (m, 2H), 2.21–2.50 (m, 3H), 2.51–2.65

(m, 2H), 2.66–2.80 (m, 1H), 2.90–3.05 (m, 1H), 3.10–3.27 (m, 2H), 3.35–3.50 (m, 3H), 3.55–3.70 (m, 1H), 3.90–4.20 (m, 5H), 7.23 (d, 8.3 Hz, 1H), 7.45 (d, 8.4 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 14.53, 23.73, 27.19, 30.13, 30.48, 30.73, 30.76, 30.79, 33.06, 55.03, 55.58, 56.40, 57.04, 59.39, 61.14, 62.11, 62.74, 63.32, 64.73, 69.94, 121.89, 122.86, 149.40, 150.05, 153.10, 179.91.

Gadolinium(III) 12-dodecyloxy-3,6,9,15-tetraazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene-3,6,9-triacetate (8)

Gadolinium(III)oxide (36 mg, 0.1 mmol) was added to a solution of 12-dodecyloxy-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (**7**) (113 mg, 0.2 mmol) in water (10 ml), and the pH was adjusted to 4 by addition of acetic acid. The suspension was heated to 100 °C for 24 h. The resulting clear solution was cooled to room temperature and the pH adjusted to about 9 by addition of aqueous sodium hydroxide (1 M). The solution was then continuously extracted with chloroform for 16 h. The chloroform extract was dried ($MgSO_4$) and evaporated *in vacuo* to yield 100 mg (69%) of a colourless solid. Mass spectrum (ES): *m*/*z* 780 $[M + CH_3COOH + H]^+$, 720 $[[M + H]^+$, $C_{29}H_{46}N_4O_7Gd]$. Anal. Calcd. (found) for $C_{29}H_{45}N_4O_7Gd{\cdot}9H_2O$: C, 39.50 (39.18); H, 7.15 (6.88); N, 6.35 (6.10)%.

Relaxometric characterisation of the Gd complex

The relaxation measurements were performed at 20 MHz on a Bruker Minispec mq 20 NMR Analyzer (Bruker Analytik GmbH, Rheinstetten, Germany). The temperature was controlled with a HAAKE DC10 circulator (Gebrüder HAAKE GmbH, Karlsruhe, Germany). The T_1-relaxation times were obtained by the inversion recovery method, and the T_1-relaxivity (r_1) was calculated using eqns. (1) and (2),

$$R_1^{obs} = \frac{1}{T_1} \quad (1)$$

$$r_1 = \frac{R_1^{obs} - R_1^{m}}{C} \quad (2)$$

where R_1^{obs} and R_1^{m} are the relaxation rates in s^{-1} of the sample and the matrix, respectively, and C is the Gd concentration in mM.

A stock solution of 1.50 mM was prepared by dissolving the complex in water and adjusting the pH to 7.0. The other solutions were prepared by diluting the stock solution. In addition a solution of 3.25 mM was prepared.

The r_1 values were plotted against the concentration as shown in Fig. 1. Analyses were performed in triplicate at each concentration.

The Gd concentrations were determined by mineralisation with hydrochloric acid (37%), followed by T_1-measurements. The T_1-relaxivity of Gd(III) under these conditions is 13.5 s^{-1} mM^{-1}.

The NMRD profile was recorded at 25 °C by a Spinmaster FFC, fast field cycling relaxometer (Stelar, Mede (PV), Italy) installed at the LIMA laboratory (Bioindustry Park, Ivrea (TO), Italy). The relaxation parameters obtained from the experimental NMRD data were calculated using a programme written by E. Terreno (University of Turin, Italy) and the computer software Origin (Microcal™ Origin, Northampton, MA).

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