

**Supporting Information**

for

**Lanthanide(III) Complexes of Novel Mixed Carboxylic-Phosphorus Acid  
Derivatives of Diethylenetriamine. A Step towards More Efficient MRI  
Contrast Agents.**

By

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Table S1. The chemical shifts of the various protonated species of ligand  $H_6L^1$  as obtained by fitting of the chemical shift titration curves.<sup>a</sup>

	H(a)	H(b)	H(c)	H(d)	P
$L^{6-}$	3.105(17)	2.547(17)	2.723(17)	2.592(17)	16.50(3)
$HL^{5-}$	3.261(15)	3.053(15)	3.423(15)	2.989(15)	6.74(2)
$H_2L^{4-}$	3.82(4)	2.73(3)	3.10(30)	3.41(3)	14.9(3)
$H_3L^{3-}$	3.818(12)	2.824(12)	3.064(12)	3.402(12)	18.008(15)
$H_4L^{2-}$	3.91(6)	2.91(8)	3.154(10)	3.50(6)	16(1)
$H_5L^{1-}$	3.93(5)	3.31(5)	3.53(5)	3.47(5)	11.23(13)
$H_6L$	4.9(5)	2.9(4)	2.9(4)	4.0(4)	23(4)

<sup>a</sup> For labelling of the nuclei, see Figure 1c.

Table S2. The chemical shifts of the various protonated species of ligand  $H_5L^2$  as obtained by fitting of the chemical shift titration curves.<sup>a</sup>

	H(a)	H(b)	H(c)	H(d)	H(arom.)	P
$L^{5-}$	2.962(2)	2.884(2)	2.564(2)	2.412(2)	7.700(2)	29.017(8)
$HL^{4-}$	3.29(2)	2.937(5)	2.789(11)	2.79(2)	7.732(5)	27.34(10)
$H_2L^{3-}$	3.634(2)	2.858(1)	2.855(1)	3.033(1)	7.742(1)	28.323(7)
$H_3L^{2-}$	3.75(4)	2.93(4)	2.90(3)	3.10(2)	7.762(10)	28.90(12)
$H_4L^{1-}$	3.821(14)	3.244(8)	3.200(7)	3.181(8)	7.771(6)	26.38(10)
$H_5L$	4.25(5)	3.191(16)	3.03(3)	3.34(2)	7.816(11)	35.0(3)

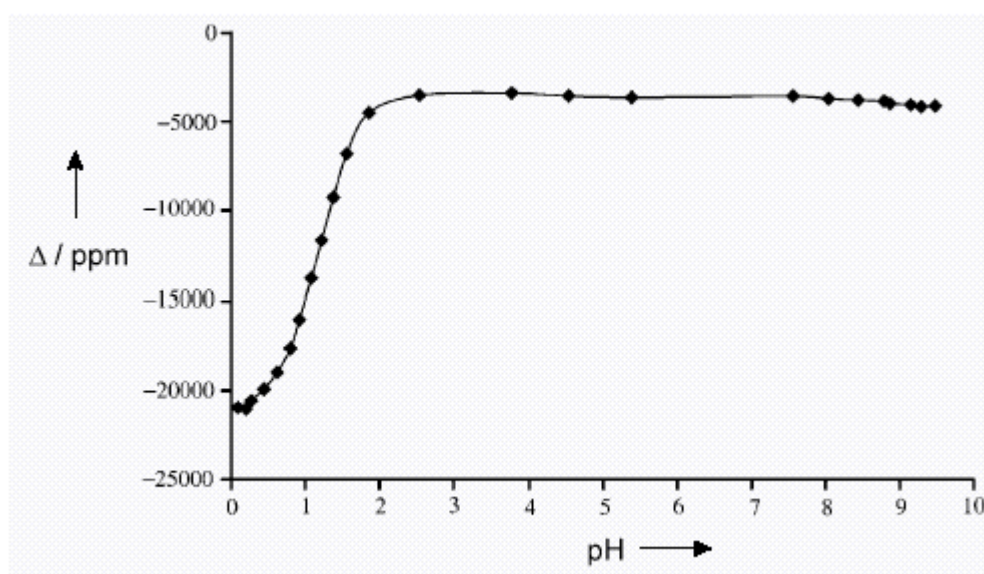
Table S3. The chemical shifts of the various protonated species of ligand  $H_5L^3$  as obtained by fitting of the chemical shift titration curves.<sup>a</sup>

	H(a)	H(b)	H(c)	H(d)	H(e)	H(f)	P
$L^{5-}$	3.10(4)	2.57(4)	2.54(4)	2.57(4)	2.57(4)	3.68(4)	36.57(3)
$HL^{4-}$	3.2(2)	2.7(1)	2.9(1)	2.7(2)	2.7(1)	3.6(1)	32.8(6)
$H_2L^{3-}$	3.65(5)	2.64(5)	2.84(5)	3.13(5)	2.67(5)	3.73(5)	34.97(9)
$H_3L^{2-}$	3.77(3)	2.59(3)	2.84(3)	3.18(3)	3.22(3)	4.45(3)	25.80(4)
$H_4L^{1-}$	4.11(6)	2.81(6)	3.12(6)	3.38(6)	3.23(6)	4.50(6)	22.8(1)

Table S4. Values of  $\Delta$  in water  $^{17}\text{O}$  NMR resonances (ppm) of the lanthanide(III) complexes of the ligands studied at 70 °C.

Ln	$\text{H}_6\text{L}^1$	$\text{H}_5\text{L}^2$	$\text{H}_5\text{L}^3$	Ln	$\text{H}_6\text{L}^1$	$\text{H}_5\text{L}^2$	$\text{H}_5\text{L}^3$
La	305.0	308.6	368.9	Tb	-1878	-2057	-2042
Ce	349.9	358.3	418.5	Dy	-1825	-1839	-1843
Pr	457.1	430.5	473.8	Ho	-1079	-1034	-1226
Nd	550.1	552.9	608.4	Er	-189.3	-214.0	-514.3
Sm	255.2	241.6	297.2	Tm	323.7	197.7	143.4
Eu	-323.0	-402.4	-383.2	Yb	331.5	281.1	334.6
Gd	-1608	-1916	- <sup>a</sup>	Lu	287.9	267.7	377.6

<sup>a</sup> not observed due to the extensive line broadening



**Figure S1.** Plot of  $\Delta$  ( $^{17}\text{O}$  NMR of water signal) versus pH for a solution of 0.2 M  $\text{DyCl}_3$  and  $\text{H}_5\text{L}^2$  in water at 25 °C.

#### *Variable temperature $^{17}\text{O}$ NMR study on gadolinium(III) complexes*

The reduced relaxation rates and chemical shifts ( $1/T_{1r}$ ,  $1/T_{2r}$  and  $\omega_r$ ) were calculated from  $^{17}\text{O}$  NMR relaxation rates and chemical shifts ( $1/T_1$ ,  $1/T_2$  and  $\omega$ ) of water signal in  $[\text{Gd}(\text{L})(\text{H}_2\text{O})]^{n-}$

solution and acidified water reference sample using Equations (1)–(3).<sup>[1-3]</sup>

$$\frac{1}{T_{1r}} = \frac{1}{P_M} \left[ \frac{1}{T_1} - \frac{1}{T_{1w}} \right] = \frac{1}{T_{1M} + \tau_M} \quad (1)$$

$$\frac{1}{T_{2r}} = \frac{1}{P_M} \left[ \frac{1}{T_2} - \frac{1}{T_{2w}} \right] = \frac{1}{\tau_M} \cdot \frac{T_{2M}^{-2} + \tau_M^{-1} T_{2M}^{-1} + \Delta\omega_M^2}{(\tau_M^{-1} + T_{2M}^{-1})^2 + \Delta\omega_M^2} \quad (2)$$

$$\Delta\omega_r = \frac{1}{P_M} (\omega - \omega_w) = \frac{\Delta\omega_M}{(1 + \tau_M T_{2M}^{-1})^2 + \tau_M^2 \Delta\omega_M^2} + \Delta\omega_{OS} \quad (3)$$

in which  $1/T_{1M}$  and  $1/T_{2M}$  are the relaxation rates for bound water molecules,  $\tau_M$  represents the residence lifetime of a bound water molecule,  $\Delta\omega_M$  stands for the chemical shift difference between the bound and bulk water and  $P_M$  is the mole fraction of bound water.  $\Delta\omega_{OS}$  represents the outer-sphere contribution to the chemical shift.

The hyperfine interaction between  $Gd^{III}$  electron spin and the  $^{17}O$  nucleus governs the chemical shift of the  $Gd^{III}$ -bound water (Equation (4)).<sup>[4]</sup>

$$\Delta\omega_M = \frac{g_L \mu_B S(S+1)B}{3k_B T} \cdot \frac{A}{\hbar} \quad (4)$$

$g_L$  is the Landé factor ( $g_L = 2.0$  for  $Gd^{III}$ ),  $S$  stands for the electron spin ( $S = 7/2$  for  $Gd^{III}$ ),  $B$  is the magnetic field,  $k_B$  is the Boltzmann constant and  $A/\hbar$  represents the hyperfine coupling constant.

While  $^{17}O$  longitudinal relaxation rates for bound water in  $Gd^{III}$  solutions are governed by dipole-dipole and quadrupolar interactions (Equation (5)),<sup>[5]</sup> the transverse relaxation rates are dominated by electron-nucleus scalar mechanisms (Equation (6), assuming extreme narrowing).<sup>[6,7]</sup>

$$\frac{1}{T_{1M}} = \left[ \frac{1}{15} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{r_{GdO}^6} \cdot S(S+1) \right] \cdot \left[ 6\tau_{d1} + 14 \left( \frac{\tau_{d2}}{1 + \omega_S^2 \tau_{d2}} \right) \right] + \frac{3\pi^2}{10} \cdot \frac{2I+3}{I^2(2I-1)} \cdot \chi^2 \left( 1 + \frac{\eta^2}{3} \right) \cdot \tau_R$$

(5)

$$\frac{1}{T_{2M}} = \frac{S(S+1)}{3} \left( \frac{A}{\hbar} \right)^2 \left[ \tau_{1S} + \frac{\tau_{2S}}{1 + \omega_s^2 \tau_{2S}^2} \right] \quad (6)$$

where  $\mu_0/4\pi$  is the magnetic permeability in vacuum,  $\gamma_I$  is the nuclear gyromagnetic ratio,  $\gamma_S$  is the electron gyromagnetic ratio,  $r_{\text{GdO}}$  is the distance between the electron charge and the  $^{17}\text{O}$  nucleus,  $\tau_{\text{di}}^{-1} = \tau_{\text{M}}^{-1} + T_{\text{ie}}^{-1} + \tau_{\text{R}}^{-1}$ .  $T_{\text{ie}}$  stands for electronic relaxation time,  $\tau_{\text{R}}$  is the rotational correlation time,  $I$  is the nuclear spin ( $I = 5/2$  for  $^{17}\text{O}$ ),  $\chi$  is the quadrupolar coupling constant and  $\eta$  is the asymmetry parameter.  $\tau_{\text{is}}^{-1} = \tau_{\text{M}}^{-1} + T_{\text{ie}}^{-1}$ .

$$\frac{1}{T_{\text{ie}}} = \left( \frac{1}{T_{\text{ie}}} \right)^{\text{ZFS}} + \left( \frac{1}{T_{\text{ie}}} \right)^{\text{SR}} \quad (7)$$

Symbols ZFS and SR mean zero field splitting interaction<sup>[8]</sup> and a spin rotation mechanism,<sup>[9-11]</sup> respectively.

The ZFS contribution to the longitudinal and transverse electronic relaxation rates may be accurately described by Equations (8) and (9).<sup>[12]</sup>

$$\left( \frac{1}{T_{1e}} \right)^{\text{ZFS}} = \frac{1}{25} \Delta^2 \tau_v [4S(S+1) - 3] \left( \frac{1}{1 + \omega_s^2 \tau_v^2} + \frac{1}{1 + 4\omega_s^2 \tau_v^2} \right) \quad (8)$$

$$\left( \frac{1}{T_{2e}} \right)^{\text{ZFS}} = \Delta^2 \tau_v \left( \frac{5.26}{1 + 0.372\omega_s^2 \tau_v^2} + \frac{7.18}{1 + 1.24\omega_s^2 \tau_v^2} \right) \quad (9)$$

Here,  $\Delta^2$  represents the mean-square ZFS energy and  $\tau_v$  is the correlation time describing the modulation of the electronic spin-state splitting. The spin rotation (SR) contribution is a magnetic field independent mechanism which may be approximated with Equation (10) where  $\delta g_L^2 = \sum_i \delta g_{Li}^2$  which refers to the deviations from the free-electron value of  $g_L$ .

$$\left(\frac{1}{T_{1e}}\right)^{SR} = \frac{\delta g_L^2}{9\tau_R} \quad (10)$$

**Variable temperature NMRD study on gadolinium(III) complexes**

The dependences of longitudinal proton relaxation upon magnetic field is commonly expressed in terms of relaxivity ( $r_1$ ) in  $s^{-1} \text{ mM}^{-1}$  or in paramagnetic relaxation rates ( $1/T_1^p$ ). Two contributions are generally considered to influence the longitudinal proton relaxation rate profile, inner-sphere and outer-sphere relaxivity (Equation (11)).

$$r_1 = r_1^{IS} + r_1^{OS} \quad (11)$$

The inner-sphere contribution ( $r_1^{IS}$ ), mainly caused by dipolar interaction, is described by Equation (12) and by the Solomon-Bloembergen equation (Equation (13)),<sup>[13,14]</sup> while the outer-sphere contribution ( $r_1^{OS}$ ), coming from the diffusion of bulk water, is described by Freed (Equations (14) and (15)).<sup>[15]</sup>

$$r_1^{IS} = \frac{q}{1000 \cdot 55.5} \cdot \frac{1}{T_{1m} + \tau_m} \quad (12)$$

where  $c$  is the Gd(III) concentration in  $\text{mol dm}^{-3}$  and  $q$  is the number of inner-sphere water molecules.

$$\frac{1}{T_{1m}} = \frac{2}{15} \left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{r_{GdH}^6} S(S+1) \cdot \left(\frac{3\tau_{d1}}{1+\omega_I^2 \tau_{d1}^2} + \frac{7\tau_{d2}}{1+\omega_S^2 \tau_{d2}^2}\right) \quad (13)$$

where  $\gamma_{S(i)}$  is the electron (proton) gyromagnetic ratio,  $r_{GdH}$  is the distance between gadolinium and water protons and  $\tau_{di}^{-1} = \tau_M^{-1} + \tau_R^{-1} + T_{ie}^{-1}$  ( $i = 1,2$ ), and the rotational correlation time ( $\tau_R$ ) describes the rotation of Gd(III)-water proton vector.

$$r_1^{OS} = \left(\frac{32\pi}{405}\right) \left(\frac{\mu_0}{4\pi}\right)^2 \gamma_I^2 \gamma_S^2 \hbar^2 S(S+1) \frac{N_A}{a_{GdH} D_{GdH}} \left[3J_{OS}(\omega_I, T_{1e}) + 7J_{OS}(\omega_S, T_{1e})\right] \quad (14)$$

$$J_{os}(\omega, T_{je}) = Re \left\{ \frac{1 + \frac{1}{4} \left[ i\omega\tau_{GdH} + \left( \frac{\tau_{GdH}}{T_{je}} \right) \right]^{\frac{1}{2}}}{1 + \left[ i\omega\tau_{GdH} + \left( \frac{\tau_{GdH}}{T_{je}} \right) \right]^{\frac{1}{2}} + \frac{4}{9} \left[ i\omega\tau_{GdH} + \left( \frac{\tau_{GdH}}{T_{je}} \right) \right] + \frac{1}{9} \left[ i\omega\tau_{GdH} + \left( \frac{\tau_{GdH}}{T_{je}} \right) \right]^{\frac{3}{2}}} \right\} \quad (15)$$

where  $N_A$  is Avogadro's number,  $a_{GdH}$  is the distance of closest approach of water molecule from Gd(III), and  $\tau_{GdH}$  is the correlation time corresponding with  $a_{GdH}^2/D_{GdH}$ . The spectral density functions,  $J_{os}(\omega, T_{je})$  ( $j = 1, 2$ ) in Equation (15) express the electronic-relaxation dependence.  $D_{GdH}$  stands for the diffusion coefficient. The temperature dependence of residence time  $\tau_R$  is assumed to be determined via the Eyring Equation (16), where  $k_{ex}$  is the exchange rate of water between the complex and the bulk. All other correlation times are assumed to obey an exponential temperature dependence (Equation (17)) where  $\tau_x^T$ , and  $\tau_x^{298}$  are the values of the concerning parameter at temperature  $T$  and 298.15 K, respectively,  $E_x$  is the associated activation energy and  $R$  is the gas constant.

$$\frac{1}{\tau_M} = k_{ex} = \frac{k_{ex}^{298} T}{298.15} \exp \left[ \frac{\Delta H^\#}{R} \left( \frac{1}{T} - \frac{1}{298.15} \right) \right] \quad (16)$$

$$\tau_x^T = \tau_x^{298} \exp \left[ \frac{E_x}{R} \left( \frac{1}{298.15} - \frac{1}{T} \right) \right] \quad (17)$$

Table S5. Reduced variables ( $T_{1r}$ ,  $T_{2r}$  and  $\omega_r$ ) obtained from  $^{17}\text{O}$  NMR measurements of  $[\text{Gd}(\text{L}^1)(\text{H}_2\text{O})]^{3-}$ .

$t$ [°C]	$\ln(1/T_{1r})$	$\ln(1/T_{2r})$	$\Delta\omega_r 10^6$ [rad s $^{-1}$ ]
4.9	10.97	13.86	-0.12689
14.9	10.84	14.15	-0.25702
25.2	10.20	14.01	-0.28648
35.8	10.01	13.60	-0.43254
46.5	9.77	13.38	-0.46885
57.1	9.62	12.93	-0.43759
67.6	9.43	12.56	-0.43524
78.4	9.24	12.20	-0.39450
89.1	8.98	11.80	-0.37386

Table S6. Reduced variables ( $T_{1r}$ ,  $T_{2r}$  and  $\omega_r$ ) obtained from  $^{17}\text{O}$  NMR measurements of  $[\text{Gd}(\text{L}^2)(\text{H}_2\text{O})]^{2-}$ .

$t$ [°C]	$\ln(1/T_{1r})$	$\ln(1/T_{2r})$	$\Delta\omega_r 10^6$ [rad s $^{-1}$ ]
4.8	11.15	14.18	-0.32518
14.8	11.22	14.12	-0.50789
25.2	10.24	14.31	-0.51918
30.4	10.05	14.09	-0.42286
35.6	10.61	13.79	-0.82664
46.1	10.14	13.53	-0.55351
56.8	9.92	13.21	-0.62785
67.4	9.69	12.92	-0.56907
77.6	9.60	12.68	-0.52950
88.4	9.42	12.29	-0.48059

Table S7. Reduced variables ( $T_{1r}$ ,  $T_{2r}$  and  $\omega_r$ ) obtained from  $^{17}\text{O}$  NMR measurements of  $[\text{Gd}(\text{L}^3)(\text{H}_2\text{O})]^{2-}$ .

$t$ [°C]	$\ln(1/T_{1r})$	$\ln(1/T_{2r})$	$t$ [°C]	$\Delta\omega_r 10^6$ [rad s $^{-1}$ ]
4.3	11.64	12.95	5.0	-0.09403
9.8	11.54	13.36	9.5	-0.00304
14.8	11.34	13.61	14.6	-0.07950
20.1	11.17	13.78	19.8	-0.09844
25.3	11.04	13.85	25.3	-0.20660
30.7	10.85	14.00	30.6	-0.25670
36.0	10.61	14.02	35.0	-0.24835
46.7	10.33	13.92	40.5	-0.40610
56.8	10.08	13.74	50.3	-0.36169
67.5	9.84	13.52	58.0	-0.37901
79.7	9.60	12.90	68.9	-0.42622
89.1	9.38	12.60	79.6	-0.41696
—	—	—	90.6	-0.42496



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