Supplementary Materials: Electronic Effects of the Substituents on Relaxometric and CEST Behaviour of Ln(III)-DOTA-Tetraanilides

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Equations Used for the Analysis of ¹⁷O NMR and NMRD Data

¹⁷O NMR Spectroscopy

From the measured ^{17}O NMR transversal 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, $1/T_{1r}$, $1/T_{2r}$ and reduced chemical shifts (Eq. (1) – (2)), 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.[i,ii]

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

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

The outer sphere contributions to the ^{17}O relaxation rates and chemical shifts have been considered negligible in the present study. $\Delta\omega_m$ is determined by the hyperfine or scalar coupling constant, $A/\hbar$, according to Equation (3), where B represents the magnetic field, S is the electron spin (S = 7/2 for high-spin Gd(III) complexes) and g_L is the isotropic Landé g factor.[iii]

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

The exchange rate is supposed to assume the Eyring equation. In Eq. (4) $\Delta S^{\ddagger}$ 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.

$$\frac{1}{\tau_m} = k_{ex} = \frac{k_B T}{h}\exp\left\{\frac{\Delta S^{\ddagger}}{R} - \frac{\Delta H}{RT}\right\} = \frac{k_{ex}^{298}T}{298.15}\exp\left\{\frac{\Delta H^{\ddagger}}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \tag{4}$$

In the transverse relaxation the scalar contribution, $1/T_{2sc}$, is the most important, Eq. (5). $1/\tau_{s1}$ is the sum of the exchange rate constant and the electron spin relaxation rate.

$$\frac{1}{T_{2m}} \cong \frac{1}{T_{2SC}} = \frac{S(S+1)}{3}\left(\frac{A}{\hbar}\right)^2 \tau_{S1} \tag{5}$$

$$\frac{1}{\tau_{S1}} = \frac{1}{\tau_m} + \frac{1}{T_{1e}} \tag{6}$$

¹H NMRD

The measured longitudinal proton relaxation rate, R_1^{obs} is the sum of a paramagnetic and a diamagnetic contribution as expressed in Eq. (7), where r_{1p} is the proton relaxivity:

$$R_1^{obs} = R_1^d + R_1^p = R_1^d + r_{1p}[Gd(III)] \tag{7}$$

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

$$r_1 = r_{1is} + r_{1os} \tag{8}$$

The inner sphere term is given in Eq. (9), where q is the number of inner sphere water molecules.[iv]

$$r_{1is} = \frac{1}{1000} \times \frac{q}{55.55} \times \frac{1}{T_{1m}^H + \tau_m} \tag{9}$$

The longitudinal relaxation rate of inner sphere protons, $1/T_{1m}^H$ is expressed by Eq. (10):

$$\frac{1}{T_{1m}^H} = \frac{2}{15}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\gamma_I^2 g^2 \mu_B^2}{r_{GdH}^6} S(S+1)\left[\frac{3\tau_{d1}}{1+\omega_I^2\tau_{d1}^2} + \frac{7\tau_{d2}}{1+\omega_S^2\tau_{d2}^2}\right] \tag{10}$$

where r_{GdH} is the effective distance between the electron charge and the ¹H nucleus, ω_I is the proton resonance frequency and ω_S is the Larmor frequency of the Gd(III) electron spin.

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_m} + \frac{1}{\tau_R} + \frac{1}{T_{ie}} \qquad i = 1, 2 \tag{11}$$

The longitudinal and transverse electronic relaxation rates, $1/T_{1e}$ and $1/T_{2e}$ are expressed by Eqs. (12)-(14),[v] 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 Eq. (14).

$$\frac{1}{T_{1e}} = \frac{1}{25}\Delta^2\tau_V \{4S(S+1)-3\}\left(\frac{1}{1+\omega_s^2\tau_v^2} + \frac{4}{1+4\omega_s^2\tau_v^2}\right) \tag{12}$$

$$\frac{1}{T_{2e}} = \left(\left(0.02\times(4S^2+4S-3)\times\tau_V\times\Delta^2\times\left(\left(\frac{5}{1+\omega_s^2\tau_V^2}\right)\right)\right) + \left(\frac{2}{1+4\omega_s^2\tau_V^2}\right)+3\right) \tag{13}$$

$$\tau_v = \tau_v^{298} \exp\left\{\frac{E_v}{R}\left(\frac{1}{T} - \frac{1}{298.15}\right)\right\} \tag{14}$$

The outer-sphere contribution can be described by Eq. (15) where N_A is the Avogadro constant, and J_{os} is its associated spectral density function.[vi,vii]

$$r_{1os} = \frac{32 N_A \pi}{405}\left(\frac{\mu_0}{4\pi}\right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{a_{GdH} D_{GdH}} S(S+1)\left[3 J_{os}(\omega_I;T_{1e}) + 7 J_{os}(\omega_I;T_{2e})\right] \tag{15}$$

$$J^{os}(\omega, T_{je}) = \mathrm{Re}\left[\frac{1 + \frac{1}{4}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{\frac{1}{2}}}{1 + \left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{\frac{1}{2}} + \frac{4}{9}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right) + \frac{1}{9}\left(i\omega\tau_{GdH} + \frac{\tau_{GdH}}{T_{je}}\right)^{\frac{3}{2}}}\right] \tag{16}$$

where $j = 1,2$, $\tau_{GdH} = \dfrac{a_{GdH}^2}{D_{GdH}}$.

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_{GdH}, as given in Eq. (17). D_{GdH}^{298} is the diffusion coefficient at 298.15 K.

$$D_{GdH} = D_{GdH}^{298} \exp\left\{\frac{E_{GdH}}{R}\left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \tag{17}$$

Table S1. Emission lifetimes and hydration numbers determined for $[EuL1]^{3+}$ complex.

	$\tau(H_2O)$ [ms]	$\tau(D_2O)$ [ms]	q[a]
[EuL1]$^{3+}$	0.30	0.45	1.03

[a] Obtained using the method proposed by A. Beeby, I. M. Clarkson, R. S. Dickins, S. Faulkner, D. Parker, L. Royle, A. S. de Sousa, J. A. G. Williams, M. Woods, J. Chem. Soc. Perkin Trans. 2 1999, 493– 503. A correction of -0.25 ms^{-1} has been applied for the determination of q, to allow for the effect of closely diffusing OH oscillators.

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