Supporting information

For

Optimizing the relaxivity of MRI probes at high magnetic field strengths with binuclear Gd^{III} complexes

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1. Equations used for the analysis of ¹⁷O NMR and NMRD data

1.1. ¹⁷O NMR spectroscopy:

From the measured ¹⁷O 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}

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

$$\Delta \omega_{\rm r} = \frac{1}{P_{\rm m}} (\omega - \omega_{\rm A}) = \frac{\Delta \omega_{\rm m}}{\left(1 + \tau_{\rm m} T_{\rm 2m}^{-1}\right)^2 + \tau_{\rm m}^2 \Delta \omega_{\rm m}^2} + \Delta \omega_{os}$$
(2)

The outer sphere contributions to the ¹⁷O 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/η , according to Equation (3), where *B* represents the magnetic field, S is the electron spin (S = 7/2 for high-spin Gd(II) complexes) and g_L is the isotropic Landé *g* factor.ⁱⁱⁱ

$$\Delta \omega_{\rm m} = \frac{g_L \mu_{\rm B} S(S+1) B}{3k_{\rm B} T} \frac{A}{\eta}$$
(3)

The exchange rate is supposed to assume the Eyring equation. In Eq. (4) ΔS^{\ddagger} and ΔH^{\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.

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

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

$$\frac{1}{\tau_{S1}} = \frac{1}{\tau_m} + \frac{1}{T_{1e}}$$
(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:

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

$$r_{\rm lis} = \frac{1}{1000} \times \frac{q}{55.55} \times \frac{1}{T_{\rm lm}^{\rm H} + \tau_{\rm m}} \tag{9}$$

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

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

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_{m}} + \frac{1}{\tau_{R}} + \frac{1}{T_{ie}} \qquad i = 1, 2$$
(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).

$$\frac{1}{T_{1e}} = \frac{1}{25} \Delta^2 \tau_V \left\{ 4S(S+1) - 3 \right\} \left(\frac{1}{1 + \omega_s^2 \tau_v^2} + \frac{4}{1 + 4\omega_s^2 \tau_v^2} \right)$$
(12)
$$\frac{1}{T_{2e}} = \left(\left(0.02 \times \left(4S^2 + 4S - 3 \right) \times \tau_V \times \Delta^2 \times \left(\left(\frac{5}{1 + \omega_s^2 \tau_V^2} \right) \right) \right) + \left(\frac{2}{1 + 4\omega_s^2 \tau_V^2} \right) + 3 \right)$$
(13)
$$\tau_v = \tau_v^{298} \exp \left\{ \frac{E_v}{R} \left(\frac{1}{T} - \frac{1}{298.15} \right) \right\}$$
(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}

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

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

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

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.

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

2. Supplementary Figures



Fugure S1. Z-spectra of 5 mM solution of Eu_2L2 at variable pH (from pH 4 to pH 9.1, $B_1=12 \mu T$).



Figure S2. pH dependent relaxivities (r_1) of Gd₂L1 (left) and Gd₂L2 (right) measured at 20 MHz and 298 K.



Figure S3. Temperature dependence of the longitudinal water proton relaxivity for Gd_2L1 at 20 MHz and pH = 7.



Figure S4. Temperature dependence of the longitudinal water proton relaxivity for Gd_2L2 at 20 MHz and pH = 7.



Figure S5. Energy scan for the rigid rotation of Gd_2L2 in vacuo around the linker connecting the two Gd^{III} complexes.



Figure S6. Energy scan for the rigid rotation Gd_2L2 in water (9 explicit molecules + PCM for long range) around the branch connecting the two Gd^{III} complexes.

3. ¹H and ¹³C NMR spectra and LC-MS chromatogram





Figure S7. (a) 1 H NMR, (b) 13 C NMR spectra and (c) LC-MS chromatografic profile of 1,2-diacrylamidoethane



Figure S8. LC-MS chromatografic profile of Gd_2L1



Figure S9. LC-MS chromatografic profile of Eu_2L1





Figure S10. (a) ¹H NMR, (b) ¹³C NMR Spectra and (c) LC-MS chromatografic profile of *N*,*N*-(ethane-1,2-diyl)bis(oxirane-2-carboxamide)





Figure S11. (a) ¹H NMR, (b) ¹³C NMR Spectra and (c) LC-MS chromatografic profile of (HPA-DO3A)₂(tBu)₆





Figure S12. (a) ¹H NMR, (b) ¹³C NMR spectra and (c) LC-MS chromatografic profile of (HPA-DO3A)₂ (L2)



Figure S13. Chromatografic profile of Gd_2L2



Figure S14. LC-MS chromatografic profile of Eu₂L2

4. References

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