Electronic Supplementary Information

for

Underlining the importance of peripheral protic functional groups to enhance the proton exchange of Gd-based MRI contrast agents.

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1. Protonation and complexation equilibria of L1 and L2:

The protonation constants of H₄L₂, defined by Eq. (S1), were determined by pH-potentiometry.

\[ K_i^H = \frac{[H_iL]}{[H_{i-1}L][H^+]} \]  

(S1)

where \( i=1, 2...6 \). The log\( K_i^H \) values of L2 obtained by pH-potentiometry are listed and compared with those of H₃HPADO3A, H₃HPDO3A, H₃BT-DO3A and H₄DOTA (Scheme S1) in Table S1. Standard deviations (3\( \sigma \)) are shown in parentheses. By taking into account the protonation sequence of the macrocyclic DOTA-like ligands determined by spectroscopy and potentiometry methods,¹⁻³ it is assumed that the first and second protonation of L2 occur at two opposite ring nitrogen atoms, whereas the third protonation process takes place at one of the carboxylate groups attached to the non-protonated ring nitrogen atoms. Fourth proton is localized on the carboxylate group of the 2-hydroxypropanoic side chain, whereas further protonation of L2 occurs at the non-protonated carboxylate pendant arms. Comparison of the protonation constants (Table S1) reveals that the log\( K_i^H \) and log\( K_2^H \) values of L2, HPADO3A and BT-DO3A are comparable and significantly lower than that of HPDO3A and DOTA. In fact, equilibrium data characterizing the protonation of L1, L2, HPADO3A and BT-DO3A ligands were measured in the presence of 0.15 M and 0.1 M NaCl ionic strength, whereas those of HPDO3A and DOTA complexes were obtained in 0.1 M Me₄NCl and 0.1 M KCl solution, respectively. It is well known that DOTA derivatives form complexes with Na⁺ ion (log\( K_{Na(DOTA)}=4.38 \); log\( K_{Na(BT-DO3A)}=2.32 \)),⁴,⁵ which are clearly responsible for the lower log\( K_1^H \) and log\( K_2^H \) values of L2, HPADO3A and BT-DO3A ligands.

![Scheme S1. Macrocyclic ligands discussed in the present work.](image-url)
The stability and protonation constants of Ca\(^{II}\), Zn\(^{II}\), Cu\(^{II}\) and Gd\(^{III}\)-complexes of L2, expressed by Eqs. (S2) and (S3), were determined by pH-potentiometry and spectrophotometry at 25 °C in 0.15 M NaCl solution.

$$K_{ML} = \frac{[ML]}{[M][L]} \quad (S2)$$

$$K_{MH,L} = \frac{[MH,L]}{[MH_{i+1,L}][H^+]^i} \quad (S3)$$

where i=0, 1, 2, 3. The $K_{ML}$ and $K_{MH,L}$ values of Ca\(^{II}\), Zn\(^{II}\) and Cu\(^{II}\)-L2 complexes were calculated from the pH-potentiometric titration data obtained at 1:1 metal to ligand concentration ratios. In the calculations, the best fitting of the mL NaOH – pH data was obtained by assuming the formation of ML, MHL, MH\(_2\)L and MH\(_3\)L species. The stability constant of GdL2 was calculated from the equilibrium data obtained by the “out-of-cell” technique due to the slow complexation reaction.

The formation of lanthanide\(^{III}\)-complexes with DOTA and DOTA derivatives takes place via the diprotonated “out-of-cage” intermediate species (e.g. $^{*}$Ln(H\(_2\)DOTA)), in which the Ln\(^{III}\)-ion is coordinated by the carboxylate groups, whereas two opposite ring nitrogens are protonated.\(^6\)\(^-\)\(^10\)

Typically, the formation of the “in cage” Ln(DOTA)\(^{+}\) and LnDOTA-like complexes occurs by the slow deprotonation of the ring nitrogens, which is followed by the penetration of the Ln\(^{III}\)-ion into the N and O donors coordination cage of the ligand. In order to calculate reliable equilibrium constants, the presence of the Ln(H\(_2\)DOTA)\(^{+}\) intermediate, the free Ln\(^{3+}\) ion and the final Ln(DOTA)\(^{+}\) complex should be considered in the equilibrium Ln\(^{III}\) - DOTA system.\(^11\),\(^12\)

The formation and stability constant of the $^{*}$Ln(H\(_2\)L) intermediate is expressed by Eqs (S4) and (S5).

$$\text{Ln}^{3+} + \text{H}_2\text{L} \rightleftharpoons ^{*}\text{Ln(H}_2\text{L)} \quad (S4)$$

$$^{*}K_{Ln(H_2L)} = \frac{[Ln(H_2L)]}{[Ln^{3+}][H_2L]} \quad (S5)$$

Since this out-of-cage intermediate is formed rapidly, the $^{*}K_{Gd(H_2L)}$ stability constant of the intermediate $^{*}$Gd(H\(_2\)L2) was calculated from the equilibrium data obtained by the direct pH-potentiometric titration of Gd\(^{3+}\) - L2 systems at 1:1 metal to ligand concentration ratios in the pH range 1.7 – 4.0. On the other hand, the stability constant of GdL2 was calculated from the mL NaOH – pH data of the “out-of-cell” samples, which had equilibrium pH values in the range of 2.0 – 4.0.

For the complete characterization of the Gd\(^{3+}\)-L2 system, the GdL2 complex (which is formed completely at about pH=3.5) was titrated with 0.2 M NaOH solution in the pH range 3.5 – 12.0.
During these titrations, base consumption was observed at about pH > 3.5 and pH > 8.0, which indicated the deprotonation of the Gd(HL) and GdL species, respectively. These processes correspond the dissociation of H⁺ ion from the carboxylate and the alcoholic -OH group of the 2-hydroxypropanoic pendant arm (Eqs. (S3) and (S4)). A pH-potentiometric titration of GdL1 complex with 0.2 M NaOH solution was also performed to determine the deprotonation constant of the hydroxyl group in the methyl 2-hydroxypropanoate pendant arm (log K\(_{\text{Gd(L)H-1}}\), Table S1).

By taking into account the protonation constants of the ligand L2, the stability constant of the *Gd(H2L2) intermediate and the stability and protonation constant of the GdL2 complex, the species distribution of the Gd\(^{3+}\) - L2 system was calculated (Figure S1).

![Species distribution diagram of the Gd\(^{3+}\)-L2 system (\([\text{Gd}^{3+}]=[\text{L2}]=1.0\: \text{mM}, 0.15\: \text{M} \: \text{NaCl}, 298\: \text{K})\) ](image)

**Figure S1.** Species distribution diagram of the Gd\(^{3+}\)-L2 system ([Gd\(^{3+}\)]=[L2]=1.0 mM, 0.15 M NaCl, 298K)

Then, the stability and protonation constants of CuL2 were determined by spectrophotometry. The equilibrium reaction (Eq. (S6)) was studied in the [H\(^+\)] range of 0.01 – 1.0 M. The ionic strength of these samples was not constant at [H\(^+\)] > 0.15 M ([H\(^+\)] ≤ 0.15 M, I=[Na\(^+\)] + [H\(^+\)] = 0.15 M). In these sample the formation of Cu\(^{2+}\), Cu(H2L), Cu(H3L) and H\(_x\)L species was assumed.

\[
\text{Cu}^{2+} + \text{H}_x\text{L} \rightleftharpoons [\text{Cu(H}_{x-y}\text{L})] + y\text{H}^+ \quad (S6)
\]

where x=5 and 6; y=3 and 4. Some characteristic absorption spectra are shown in Figure S2.
**Figure S2.** Absorption spectra of Cu\textsuperscript{2+}–L\textsubscript{2} system. The solid lines and the open symbols represent the experimental and the calculated absorbance values, respectively. ([Cu\textsuperscript{2+}]=[L2]=0.72 mM, [H\textsuperscript{+}]=1.0 (□), 0.60 (◇), 0.31 (△), 0.10 (○), 0.043 (◇), 0.023 (□) and 0.011 M (△). [Cu\textsuperscript{2+}]=0.72 mM, I=[Na\textsuperscript{+}]+[H\textsuperscript{+}]=0.15, [H\textsuperscript{+}]\leq0.15 M, l=0.2 cm, 25\textdegree C).

The stability and protonation constants of the Ca\textsuperscript{II}, Zn\textsuperscript{II}, Cu\textsuperscript{II} and Gd\textsuperscript{III}–L\textsubscript{2} complexes are shown and compared with those of HPADO3A, HPDO3A, DOTA and BT-DO3A complexes in Table S1. The stability constants of the Ca\textsuperscript{II}, Zn\textsuperscript{II}, Cu\textsuperscript{II} and Gd\textsuperscript{III} complexes formed with L\textsubscript{2}, HPADO3A and BT-DO3A (Table S1) are very similar and about 1 – 5 orders of magnitude lower than those of the corresponding DOTA and HPDO3A complexes, which might be explained by the lower log\textit{K}\textsubscript{1\textsuperscript{H}} and log\textit{K}\textsubscript{2\textsuperscript{H}} values of L\textsubscript{2}, HPADO3A and BT-DO3A ligands due to the formation of the Na\textsuperscript{1}-complexes. Although the stability constants obtained for CuL\textsubscript{2} and Cu(HPADO3A) are significantly higher than that of Cu(BT-DO3A) published earlier in literature,\textsuperscript{5} it can be assumed that pH-potentiometric method used for the determination of the stability constant of Cu(BT-DO3A) cannot provide reliable information for the estimation of the log\textit{K}\textsubscript{CuL} value due to complete formation of Cu(H\textsubscript{2}L) species and the negligible amount of free Cu\textsuperscript{2+} ion at pH>1.7.

The equilibrium constants characterizing the protonation of the carboxylate group in the 2-hydroxypropanoic pendant arm of ZnL\textsubscript{2} (ZnH\textsubscript{2}L\textsubscript{2}), CuL\textsubscript{2} (CuH\textsubscript{2}L\textsubscript{2}) and GdL\textsubscript{2} (GdHL\textsubscript{2}) complexes are very similar to that of the free L\textsubscript{2} ligand (log\textit{K}\textsubscript{4\textsuperscript{H}}), which indicate that the extra carboxylate group does not coordinate the metal ions. Interestingly, the stability constant of the diprotonated *Gd(H\textsubscript{2}L\textsubscript{2}) intermediate (log\textit{K}\textsubscript{Gd(H2L2)}) is similar to that of *Gd(H\textsubscript{2}DOTA) and about 1.5 – 2 log\textit{K} unit higher than that of *Gd(H\textsubscript{2}HPADO3A) and *Gd(H\textsubscript{2}HPDO3A), which might be interpreted by the coordination of the Gd\textsuperscript{III} ion by the four carboxylate groups of L\textsubscript{2} resulting in the formation of *Gd(H\textsubscript{2}L\textsubscript{1}) intermediate similar to *Gd(H\textsubscript{2}DOTA).
Table S1. Protonation constants of L2, HPADO3A, HPDO3A, DOTA and BT-DO3A ligand, the stability and protonation constants of CaII-, ZnII-, CuII- and GdIII-complexes at 25°C

|      | L2 | HPADO3Aa | HPDO3Ab,c | DOTAf | BT-DO3Ad |
|------|----|----------|-----------|-------|---------|
| I    |    | 0.15 M NaCl | 0.1 M Me₄NCl | 0.1 M NaCl | 0.1 M NaCl |
| logK₁H | 8.95 (3) | 8.96 | 11.96 | 9.37 | 9.46 |
| logK₂H | 8.95 (2) | 9.07 | 9.43 | 9.14 | 9.36 |
| logK₃H | 4.22 (3) | 4.22 | 4.30 | 4.63 | 4.17 |
| logK₄H | 3.74 (3) | 2.64 | 3.26 | 3.91 | 3.02 |
| logK₅H | 2.47 (4) | 1.25 | – | – | – |
| logK₆H | 1.75 (4) | – | – | – | – |
| CaL  | 11.63 (1) | 12.13 | 14.83 | 16.37e | 12.1 |
| CaHL | 5.20 (5) | 4.67 | – | 3.60e | – |
| Ca(L)H₁ | – | 11.50 | – | – | – |
| ZnL  | 17.81 (6) | 17.18 | 19.37 | 18.7e | 17.0 |
| ZnHL | 3.86 (5) | 3.67 | 3.7 | 3.53e | 4.3 |
| ZnH₂L | 3.32 (3) | 2.87 | – | 3.96e | – |
| ZnH₃L | 2.29 (5) | – | – | – | – |
| Zn(L)H₁ | – | 10.79 (5) | – | 10.62e | – |
| *CuL | 21.87 (6) | 21.53 | 22.84 | 22.72e | 19.1 |
| CuHL | 3.84 (2) | 4.00 | 3.72 | 4.45e | 3.8 |
| CuH₂L | 3.36 (2) | 1.24 | 2.3 | 3.92e | 2.4 |
| CuH₃L | 1.36 (8) | – | – | – | – |
| Cu(L)H₁ | – | 10.55 | – | – | – |
| GdL  | 19.26 (3) | 18.41 | 23.8 | 24.7 | 18.7 |
| GdHL | 3.36 (3) | – | – | – | – |
| **GdH₂L | 6.73 (3) | 5.72 | 5.10 | 6.07 | 4.53 |
| Gd(L)H₁ | 9.58 (3) | 6.73 | 11.36d | – | 9.48 |

a Ref. [11]; b Ref. [13]; c Ref. [14]; d Ref. [5]; e Ref. [15]; f Ref. [16]; GdL1: logK_{Gd(L)H₁}=9.36 (6); *obtained by spectrophotometry; **stability constants of the protonated *Gd(H₂L) out-of-cage complex (intermediate): K_{Gd(H₂L)}=[Gd(H₂L)]/[Gd^{3+}][H₂L], 0.15 M NaCl, 25°C

The protonation constant of the alkoxide-O⁻ donor atom (logK_{Gd(L)H₁}) in GdL1 and GdL2 complexes are about 2 orders of magnitude lower than that of Gd(HPDO3A) due to the electron withdrawing effect of the carboxylate and ester pendants of the 2-hydroxypropanoic/ate side chain in GdL1 and GdL2. On the other hand, these values are about 3 orders of magnitude higher than that of
Gd(HPADO3A) \( (\log K_{Ga(\text{H})L^{-1}}=6.73) \), due to the significantly higher electron withdrawing effect of the amide functional group in the 2-hydroxypropanamide side chain of Gd(HPADO3A).

2. Kinetic inertness of GdL2

In order to investigate the kinetic inertness of GdL2, the dissociation reactions of GdL2 were followed by \(^1\)H-NMR relaxometry in the presence of large acid excess ([HCl]= 0.01 – 1.0 M) to guarantee the pseudo-first-order kinetic conditions. The \( R_{1}^{\text{obs}} \) values as a function of time for the dissociation reactions of GdL1 are shown in Figure S3.

![Figure S3. \( R_{1}^{\text{obs}} \) values of GdL2 as a function of time in the presence of 0.70 (◆), 0.29 ( ■), 0.16 (▲), 0.06 (●), 0.025 (★) and 0.010 (◆) M HCl, ([GdL2]=1.0 mM, [H\(^+\)]=0.15 M→[Na\(^+\)]+[H\(^+\)]=0.15 M, 25°C)](image)

![Figure S4. Pseudo-first-order rate constant \( (k_d) \) characterizing the dissociation of GdL2 as a function of [H\(^+\)] ([GdL2]=1.0 mM, [H\(^+\)]=0.15 M→[Na\(^+\)]+[H\(^+\)]=0.15 M, 25°C).](image)
In the presence of HCl excess, the dissociation of GdL2 can be treated as a pseudo-first-order process and the rate of the reaction can be expressed by Eq. (S7)

\[
- \frac{d[GdL]}{dt} = k_d[GdL]_{\text{tot}} \tag{S7}
\]

where \( k_d \) is a pseudo-first-order rate constant, \([GdL]_t\) and \([GdL]_{\text{tot}}\) are the concentrations of the GdL species at time \( t \) and the total concentration of the complex, respectively. The rates of the dissociation reactions were determined at different concentrations of HCl ([HCl]=0.01 – 1.0 M). The \( k_d \) values as a function of \([H^+]\) are shown in Figure S4.

As it is shown in Figure S4, \( k_d \) pseudo-first order rate constants increase with the concentration of \( H^+ \), which can be explained by the proton assisted dissociation of GdL2. The proton assisted dissociation of GdL2 might occur by the equilibrium formation of a protonated \(*\text{Gd}(\text{H}_2\text{L}_2)\) intermediate (Eq. (S8)), which dissociates spontaneously (Eq. (S9)).

\[
\text{Gd}(\text{HL}_2) + H^+ \rightleftharpoons \text{Gd}(\text{H}_2\text{L}_2) \tag{S8}
\]

\[ K^H_{\text{Gd(HL)}} = \frac{[\text{Gd}(\text{H}_2\text{L})]}{[\text{Gd}(\text{HL})][H^+]} \]

\[ *\text{Gd}(\text{H}_2\text{L}_2) \xrightarrow{k_{\text{GdH}_2\text{L}_2}} \text{Gd}^{3+} + \text{H}_3\text{L}_2 \tag{S9} \]

\( k_{\text{GdH}_2\text{L}_2} \) is the rate constant characterizing the dissociation of \(*\text{Gd}(\text{H}_2\text{L}_2)\) intermediate. The \( K^H_{\text{GdHL}} \) is the protonation constant of the protonated Gd(HL2) species, which predominates at pH<3.0 (Figure S1). By considering the dissociation of the \(*\text{Gd}(\text{H}_2\text{L}_2)\) intermediate (Eq. (S8)) and the rate of dissociation of GdL2 (Eq. (7)), the pseudo-first-order rate constant \( (k_d) \) can be expressed by Eq. (10).

\[ - \frac{d[GdL]}{dt} = k_{\text{GdH}_2\text{L}_2}[\text{Gd}(\text{H}_2\text{L})] \tag{S10} \]

By taking into account the total concentration of the complex ([GdL2]_{\text{tot}}=[Gd(HL2)]+[*Gd(H2L2)]), the protonation constants of Gd(HL2) \( K^H_{\text{GdhL}}, \text{Eq. (8)} \) and Eq. (10), the pseudo-first-order rate constant \( (k_d) \) can be expressed as follows:

\[ k_d = \frac{k_1[H^+]}{1 + k^H_{\text{GdHL}}[H^+]} \tag{S11} \]

where \( k_1 = k_{\text{GdH}_2\text{L}_2} \times K^H_{\text{GdHL}} \) are the rate constants characterizing the proton assisted dissociation of Gd(HL2). \( k_1 \) value of Gd(HL2) were calculated by fitting of the kinetic data (Figure S12) to Eq. (S11).
3. X-ray diffraction studies of $[\text{Gd}(L2)\text{H}_1(\text{OH}^-)]^{3-}$ complex

**Figure S5.** Ellipsoids representation of crystallographic asymmetric unit content (ASU) for dimeric $[\text{Gd}(L2)\text{H}_1(\text{OH}^-)]^{3-}$ (50% probability): A) complete ASU content; B) solvent water molecules omitted for clarity. Naming scheme used for Gd$^{III}$-ion coordination spheres is reported.
Figure S6. Sticks representation of dimeric [Gd(L2)H_{1}(OH^{−})]^3−. Hydrogen bonded water molecules surrounds the capsule (omitted for clarity). Naming scheme used for Gadolinium coordination spheres is reported. A crystallographic inversion center lies on dimeric [Gd(L2)H_{1}(OH^{−})]^3− barycenter.
**Figure S7.** Crystal packing of dimeric $[\text{Gd(L2)H}_4(\text{OH}^-)]^3^-$ along crystallographic $a$, $b$ and $c$ axis.
Table S2. Crystallographic data and refinement details for dimeric [Gd(L2)H·(OH')]\(^3^{-}\).  

| Property                                      | Value                                                                 |
|-----------------------------------------------|----------------------------------------------------------------------|
| CCDC Number                                   | 2087813                                                             |
| Chemical Formula                              | C\(_{34}\)H\(_{100}\)Gd\(_4\)N\(_8\)O\(_{44}\)                      |
| Formula weight (g/mol)                        | 1954.21                                                             |
| Temperature (K)                               | 100(2)                                                              |
| Wavelength (Å)                                | 0.700                                                               |
| Crystal system                                | Triclinic                                                           |
| Space Group                                   | P-1                                                                 |
| Unit cell dimensions                          |                                                                      |
| \(a\) = 10.541(2) Å                          |                                                                      |
| \(b\) = 11.172(2) Å                          |                                                                      |
| \(c\) = 14.209(3) Å                          |                                                                      |
| \(\alpha\) = 78.78(3)°                      |                                                                      |
| \(\beta\) = 80.23(3)°                       |                                                                      |
| \(\gamma\) = 86.89(3)°                      |                                                                      |
| Volume (Å\(^3\))                             | 1617.1(6)                                                           |
| Z                                             | 1                                                                   |
| Density (calculated) (g·cm\(^{-3}\))         | 2.007                                                               |
| Absorption coefficient (mm\(^{-1}\))         | 3.979                                                               |
| F(000)                                        | 968                                                                 |
| Crystal size (mm\(^3\))                      | 0.12 x 0.08 x 0.05                                                  |
| Crystal habit                                 | Colorless rods                                                      |
| Theta range for data collection               | 2.11° to 30.00°                                                     |
| Resolution (Å)                                | 0.70                                                                |
| Index ranges                                  |                                                                      |
| -14 ≤ h ≤ 13                                  |                                                                      |
| -15 ≤ k ≤ 15                                  |                                                                      |
| -20 ≤ l ≤ 20                                  |                                                                      |
| Reflections collected                         | 49466                                                               |
| Independent reflections (data with I>2σ(I))   | 9571 (9542)                                                         |
| Data multiplicity (max resln)                 | 5.02 (4.38)                                                        |
| I/σ(I) (max resln)                            | 27.64 (25.43)                                                      |
| R\(_{merge}\) (max resln)                     | 0.0485 (0.0502)                                                    |
| Data completeness (max resln)                 | 97.2% (93.6%)                                                      |
| Refinement method                             | Full-matrix least-squares on F\(^2\)                               |
| Data / restraints / parameters                | 9571 / 37 / 485                                                     |
| Goodness-of-fit on F\(^2\)                    | 1.063                                                               |
| \(\Delta/\sigma_{max}\)                      | 0.002                                                               |
| Final R indices [I>2σ(I)]\(^a\)              | R\(_1\) = 0.0207, wR\(_2\) = 0.0540                                |
| R indices (all data)\(^a\)                    | R\(_1\) = 0.0207, wR\(_2\) = 0.0542                                |
| Largest diff. peak and hole (e·Å\(^{-3}\))   | 0.898 and -1.654                                                   |
| R.M.S.D. from mean (e·Å\(^{-3}\))            | 0.126                                                               |

\(^a\) R\(_1\) = \(\Sigma |F_{o}|-|F_{c}|\) / \(\Sigma |F_{o}|\), wR\(_2\) = \(\Sigma [w(F_{o}^2 - F_{c}^2)] / \Sigma [w(F_{o}^2)]\)\(^{1/2}\)
Table S3. Selected bond distances and angles (Å and degrees) for coordination spheres of the crystallographically independent Gd\textsuperscript{III} centers in dimeric [Gd(L2)\textsubscript{2}(OH\textsubscript{3})\textsuperscript{3-}]. (Gd\textsubscript{12} and Gd\textsubscript{13}). Naming scheme is reported in Figure S6.

### Gd\textsubscript{12} - diGdHPDO4A

| Distances (Å) | Angles (°) | Distances (Å) | Angles (°) |
|---------------|------------|---------------|------------|
| Gd\textsubscript{12}-O\textsubscript{11} | 2.38(2) | O\textsubscript{11}-Gd\textsubscript{12}-O\textsubscript{11} | 94.35(6) |
| Gd\textsubscript{12}-O\textsubscript{12} | 2.40(2) | O\textsubscript{12}-Gd\textsubscript{12}-O\textsubscript{12} | 130.73(5) |
| Gd\textsubscript{12}-O\textsubscript{13} | 2.35(2) | O\textsubscript{13}-Gd\textsubscript{12}-O\textsubscript{13} | 69.69(5) |
| Gd\textsubscript{12}-O\textsubscript{14} | 2.44(2) | O\textsubscript{14}-Gd\textsubscript{12}-O\textsubscript{14} | 67.72(6) |
| Gd\textsubscript{12}-O\textsubscript{15} | 2.65(2) | O\textsubscript{15}-Gd\textsubscript{12}-O\textsubscript{15} | 102.20(6) |
| Gd\textsubscript{12}-O\textsubscript{16} | 2.66(2) | O\textsubscript{16}-Gd\textsubscript{12}-O\textsubscript{16} | 167.47(5) |
| Gd\textsubscript{12}-N\textsubscript{1} | 2.74(2) | N\textsubscript{1}-Gd\textsubscript{12}-N\textsubscript{1} | 114.22(6) |
| Gd\textsubscript{12}-N\textsubscript{2} | 2.70(2) | N\textsubscript{2}-Gd\textsubscript{12}-N\textsubscript{2} | 67.88(5) |
| Gd\textsubscript{12}-O\textsubscript{17} | 4.06(1) | O\textsubscript{17}-Gd\textsubscript{12}-O\textsubscript{17} | 3.968(3) |
| Gd\textsubscript{12}-Gd\textsubscript{13} | 3.62(1) | Gd\textsubscript{12}-Gd\textsubscript{13} | 98.75(6) |
| Gd\textsubscript{12}-Gd\textsubscript{14} | 4.06(1) | Gd\textsubscript{12}-Gd\textsubscript{14} | 63.37(5) |
| Gd\textsubscript{12}-Gd\textsubscript{15} | 4.06(1) | Gd\textsubscript{12}-Gd\textsubscript{15} | 110.59(6) |
| Gd\textsubscript{12}-Gd\textsubscript{16} | 4.06(1) | Gd\textsubscript{12}-Gd\textsubscript{16} | 119.28(6) |

Symmetry transformations used to generate equivalent atoms: #1 - x+1, y+1, z+1

### Gd\textsubscript{13} - diGdHPDO4A

| Distances (Å) | Angles (°) | Distances (Å) | Angles (°) |
|---------------|------------|---------------|------------|
| Gd\textsubscript{13}-O\textsubscript{11} | 2.59(2) | O\textsubscript{11}-Gd\textsubscript{13}-O\textsubscript{11} | 146.82(5) |
| Gd\textsubscript{13}-O\textsubscript{12} | 2.47(2) | O\textsubscript{12}-Gd\textsubscript{13}-O\textsubscript{12} | 124.75(5) |
| Gd\textsubscript{13}-O\textsubscript{13} | 2.82(2) | O\textsubscript{13}-Gd\textsubscript{13}-O\textsubscript{13} | 67.47(5) |
| Gd\textsubscript{13}-O\textsubscript{14} | 2.48(2) | O\textsubscript{14}-Gd\textsubscript{13}-O\textsubscript{14} | 67.74(5) |
| Gd\textsubscript{13}-O\textsubscript{15} | 2.40(2) | O\textsubscript{15}-Gd\textsubscript{13}-O\textsubscript{15} | 68.19(5) |
| Gd\textsubscript{13}-O\textsubscript{16} | 2.54(2) | O\textsubscript{16}-Gd\textsubscript{13}-O\textsubscript{16} | 138.19(6) |
| Gd\textsubscript{13}-O\textsubscript{17} | 2.38(2) | O\textsubscript{17}-Gd\textsubscript{13}-O\textsubscript{17} | 138.12(6) |
| Gd\textsubscript{13}-O\textsubscript{18} | 2.47(2) | O\textsubscript{18}-Gd\textsubscript{13}-O\textsubscript{18} | 128.65(5) |
| Gd\textsubscript{13}-Gd\textsubscript{13} | 3.20(1) | Gd\textsubscript{13}-Gd\textsubscript{13} | 99.31(4) |
| Gd\textsubscript{13}-Gd\textsubscript{14} | 3.20(1) | Gd\textsubscript{13}-Gd\textsubscript{14} | 72.24(5) |
| Gd\textsubscript{13}-Gd\textsubscript{15} | 3.20(1) | Gd\textsubscript{13}-Gd\textsubscript{15} | 79.27(5) |
| Gd\textsubscript{13}-Gd\textsubscript{15} | 3.20(1) | Gd\textsubscript{13}-Gd\textsubscript{15} | 65.92(5) |
| Gd\textsubscript{13}-Gd\textsubscript{13} | 3.20(1) | Gd\textsubscript{13}-Gd\textsubscript{13} | 142.01(2) |
| Gd\textsubscript{13}-Gd\textsubscript{13} | 3.20(1) | Gd\textsubscript{13}-Gd\textsubscript{13} | 81.42(4) |

Symmetry transformations used to generate equivalent atoms: #1 - x+1, y+1, z+1
Table S4. Geometrical parameters of polar contacts found in dimeric \([\text{Gd(L2)H}_{1+}(\text{OH}^-)]^3^-\) crystal packing. Naming scheme is reported in Figure S8.

| D-H⋯A        | d(D-H) (Å) | d(H⋯A) (Å) | d(D⋯A) (Å) | <(DHA) (°) |
|--------------|------------|------------|------------|-----------|
| O\(_{14}\)-H\(_{1+}\)...O\(_{11}\) | 0.73(3) | 2.35(3) | 2.715(2) | 113(3) |
| O\(_{15}\)-H\(_{1+}\)...O\(_{24}\)#1 | 0.869(5) | 1.912(7) | 2.778(2) | 174(3) |
| O\(_{16}\)-H\(_{1+}\)...O\(_{31}\) | 0.869(5) | 1.875(9) | 2.729(2) | 167(3) |
| O\(_{17}\)-H\(_{1+}\)...O\(_{40}\) | 0.869(5) | 2.52(4) | 3.137(3) | 129(5) |
| O\(_{18}\)-H\(_{1+}\)...O\(_{49}\) | 0.99(5) | 2.50(4) | 3.521(3) | 171.4 |
| O\(_{19}\)-H\(_{1+}\...O\(_{58}\) | 0.99(5) | 2.53(4) | 3.509(3) | 170.5 |
| O\(_{20}\)-H\(_{1+}\)...O\(_{67}\) | 0.99(5) | 2.63(4) | 3.531(3) | 150.7 |

Symmetry transformations used to generate equivalent atoms:
- #1 -x+1,-y+1,-z+1
- #2 -x+2,-y+1,-z+2
- #3 x,y,z
- #4 -x+1,-y,-z+1
- #5 x+1,y,z
- #6 -x+1,-y+1,-z+2
- #7 x+1,y+1,z
- #8 -x+1,-y+2,-z+2

Figure S8. Naming scheme for the geometrical parameters of polar contacts found in dimeric \([\text{Gd(L2)H}_{1+}(\text{OH}^-)]^3^-\) crystal packing.
4. $^1$H and $^{13}$C NMR spectra of protected and deprotected ligands

Fig. S9a $^1$H NMR spectrum of L1(OtBu)$_3$
Fig. S9b $^{13}$C NMR spectrum of $\text{L1(OrBu)}_3$

Fig. S10a $^1$H NMR spectrum of $\text{L2(OrBu)}_3$

Fig. S10b $^{13}$C NMR spectrum of $\text{L2(OrBu)}_3$
Fig. S11a $^1$H NMR spectrum of L1

Fig. S11b $^{13}$C NMR spectrum of L1
**Fig. S12a** $^1$H NMR spectrum of L2

**Fig. S12b** $^{13}$C NMR spectrum of L2
Fig. S13a HPLC-MS chromatogram of L1

Fig. S13b ESI-MS spectrum of L1
Fig. S14a HPLC-MS chromatogram of L2

Fig. S14b ESI-MS spectrum of L2
Fig. S15a HPLC-MS chromatogram of GdL1.

Fig. S15b ESI-MS spectrum of GdL1
Fig. S16a HPLC-MS chromatogram of GdL2

Fig. S16b ESI-MS spectrum of GdL2
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