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PAPER

A new metallostar complex based on an aluminum(III) 8-hydroxyquinoline core as a potential bimodal contrast agent†

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A ditopic DTPA monoamide derivative containing an 8-hydroxyquinoline moiety was synthesized and the corresponding gadolinium(III) complex ($[Gd(H\mathbf{5})(H_2O)]^-$) was prepared. After adding aluminum(III), the 8-hydroxyquinoline part self-assembled into a heteropolymetallic triscomplex $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$. The magnetic and optical properties of this metallostar compound were investigated in order to classify it as a potential *in vitro* bimodal contrast agent. The proton nuclear magnetic relaxation dispersion measurements indicated that the relaxivity r_1 of $[Gd(H\mathbf{5})(H_2O)]^-$ and $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ at 20 MHz and 310 K equaled 6.17 s^{-1} mM^{-1} and 10.9 s^{-1} mM^{-1} per Gd(III) ion respectively. This corresponds to a relaxivity value of 32.7 s^{-1} mM^{-1} for the supramolecular complex containing three Gd(III) ions. The high relaxivity value is prominently caused by an increase of the rotational tumbling time τ_R by a factor of 2.7 and 5.5 respectively, in comparison with the commercially used MRI contrast agent Gd(III)–DTPA (Magnevist®). Furthermore, upon UV irradiation, $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ exposes green broad-band emission with a maximum at 543 nm. Regarding the high relaxivity and the photophysical properties of the $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ metallostar compound, it can be considered as a lead compound for *in vitro* bimodal applications.

Introduction

Magnetic resonance imaging (MRI) plays a key role in medical diagnostics as it combines good spatial resolution with deep tissue penetration so that a true three-dimensional image can be obtained. Moreover, during the clinical investigation no ionizing radiation has to be used. Contrast agents increase the water proton relaxation rate ($1/T_1$) so that the image contrast with surrounding tissue is improved. The relaxivity, r_1, or the enhancement of $1/T_1$ per mM of currently used gadolinium(III)-based contrast agents is too low to monitor molecular processes and the efficiency of these contrast agents dramatically drops at higher magnetic field strength. It is common knowledge that the low sensitivity is a major drawback of the MRI technique. An approach to overcome these problems is to lower the molecular tumbling rate of the contrast agent or to concentrate several paramagnetic Gd(III) ions in a small volume by organizing them in a supramolecular complex.[1–5] The rotational motion can be reduced after a non-covalent interaction of the ligand with proteins, for instance with human serum albumin (HSA).[6–9] Contrast agents have also been covalently linked to macromolecular carriers like linear polymers or dendrimers.[10–15] Another way to achieve higher proton relaxivities is the incorporation of amphiphilic Gd(III) complexes into slowly tumbling micelles or liposomes.[16–19] More recently, paramagnetic complexes were assembled in a rigid heteropolymetallic structure with a central transition metal ion, the so-called *metallostars*.[20,21] On the other hand, optical imaging is a diagnostic tool which offers high sensitivity, although no high-resolution images can be recorded and the technique is restricted to thin tissue samples.[22–25] The development of a bimodal reporter with optical as well as magnetic properties can lead to a more detailed diagnostic method, because the advantages of both imaging techniques (optical imaging and MRI) are assembled in one molecule.[26–29] Several approaches were maintained to create bimodal agents. Derivatives of DTPA or DOTA were functionalized with organic fluorophores,[30–32] transition metal complexes[33–35] or a lanthanide sensitizer.[36–39] Also liposomal structures[40–42] and nanoparticles based on iron(III) oxide,[43–46] silica[47] or a polymer core[48–50] were designed.

Aluminum(III) is known to form highly stable complexes with the bidentate chelating 8-hydroxyquinoline. In aqueous solutions, three metal–ligand complexes Alq (log $\beta \sim 8.9$), Alq_2 (log $\beta \sim 17.4$) and Alq_3 (log $\beta \sim 24.6$) are formed with Alq_3 being the predominant metal species in a very wide range of pH.

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†Electronic supplementary information (ESI) available: ^1H (Fig. S1) and 2D COSY (Fig. S2) NMR spectra of ligand $H_4\mathbf{4}$, ESI mass spectrum of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ (Fig. S3), absorption spectra of $[Gd(H\mathbf{5})(H_2O)]^-$ and $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ (Fig. S4). See DOI: 10.1039/c2dt30605k

In the presence of a fully formed complex, only a small amount of free ligand is produced by complex dissociation, having a kinetic constant estimated to be 0.2 s^{-1}.[51–53] Tris-(8-quinolinate) aluminum(III) complexes and numerous derivatives have been intensively investigated for their strong green luminescence.[54–56] Devices with strong electroluminescent properties for OLED applications were already successfully prepared. For this purpose, the high complex stability was assured by dissolving the Alq_3 derivatives in dichloromethane and toluene, avoiding moisture.[55,56] In this work, benzyl protected 5-amino-8-hydroxyquinoline was coupled to diethylenetriamine-pentaacetic acid (DTPA) *via* a glycine linker to form H_4**4**. This ditopic ligand is able to strongly coordinate to a lanthanide ion with the DTPA unit, while after deprotection, the 8-hydroxyquinoline self-assembled around Al(III) ions, resulting in a new metallostar compound $[(Ln\mathbf{5})_3Al(H_2O)_3]^{3-}$. The synthesis of the ligand was confirmed by mass spectrometry, NMR and IR measurements. Complexation to the diamagnetic La(III) ion allowed recording the ^{1}H NMR spectrum of $[(La\mathbf{5})_3Al(H_2O)_3]^{3-}$. Finally, the magnetic as well as the photophysical properties of both monomeric $[Gd(H\mathbf{5})(H_2O)]^-$ and metallostar $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ complexes were investigated.

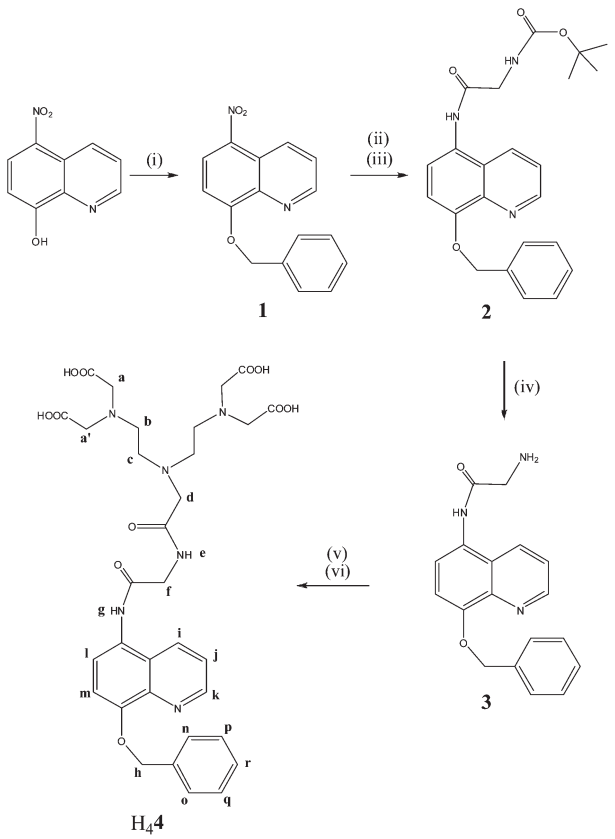
Results and discussion

Synthesis of ligand and complexes

The synthesis of the 8-hydroxyquinoline DTPA-based ligand started with the protection of the hydroxyl group of 5-nitro-8-hydroxyquinoline by a benzyl protecting group, resulting in 5-nitro-8-benzyloxyquinoline (**1**).

The nitro group of compound **1** was reduced by tin(II) chloride dihydrate in ethanol. Because of the low stability of this aromatic amine functional group, the product was immediately coupled with *t*Boc-glycine in the presence of *ortho*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) yielding compound **2**. After deprotection by trifluoroacetic acid (TFA), a more stable amine group was obtained (**3**) and coupled further with *N*,*N*-bis{*N*,*N*-bis[(*tert*-butoxycarbonyl)methyl]-ethylamine}-glycine to yield the benzyl- and *tert*butyl-protected 8-hydroxyquinoline derivative **4**. After removal of the *tert*butyl protecting groups, ligand H_4**4** was obtained as a yellow-brownish solid (Scheme 1). The benzyl protecting group was maintained to prevent coordination of the lanthanide(III) ion to the 8-hydroxyquinoline moiety.[57,58]

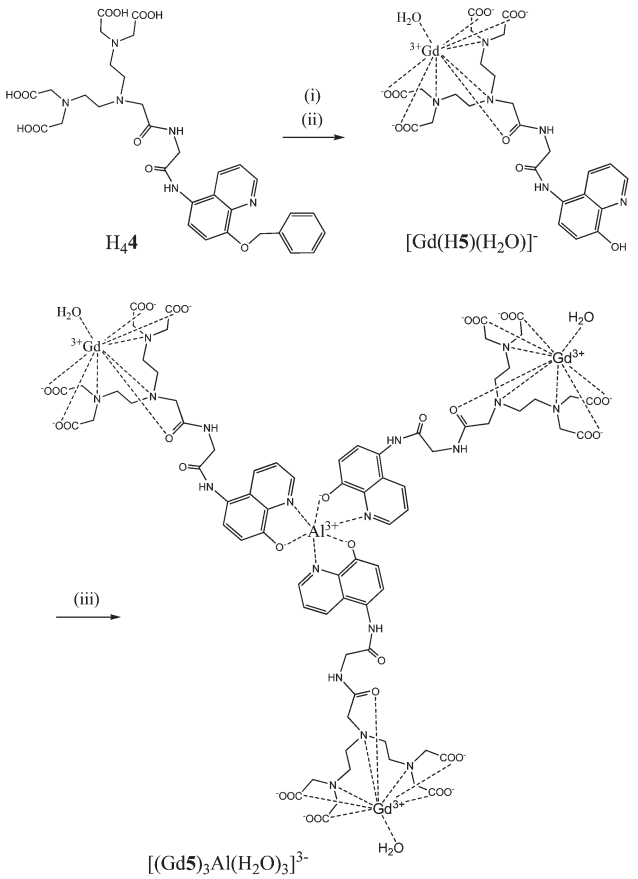
A proton NMR spectrum of ligand H_4**4** was recorded in D_2O and the observed peaks correspond to the proposed structure of the molecule (Fig. S1 in the ESI†). Further, the ligand was characterized by a two-dimensional COSY experiment (Fig. S2 in the ESI†), ^{13}C NMR, and CHN analysis. The electrospray mass spectrum (ESI-MS) in the positive mode showed molecular peaks $[M + H]^+$ and $[M + Na]^+$ at m/z = 683.4 and 705.2, respectively. Lanthanide(III) complexes were obtained by reacting ligand H_4**4** with the corresponding lanthanide(III) chlorides (Ln = La, Gd) under slightly alkaline conditions (pH = 8). After complexation, the benzyl protecting group was removed by hydrogenation, resulting in the formation of $[Ln(H\mathbf{5})(H_2O)]^-$. All complexes were purified by Chelex® 100, in order to remove the free lanthanide ions. The purity of the complexes was verified



Scheme 1 Synthesis of ligand H_4**4**. Conditions: (i) benzyl bromide, K_2CO_3, dry DMF; (ii) $SnCl_2{\cdot}2H_2O$, EtOH; (iii) *t*Boc-glycine, HATU, DIPEA, dry DCM; (iv) CF_3COOH–DCM (2 : 1, v/v); (v) DTPA-precursor, TBTU, DIPEA, dry DMF; (vi) HCl 6 N.

with a test with an arsenazo indicator solution.[59] Positive mode ESI-MS of the complexes showed molecular peaks $[M + 2H]^+$, $[M + 2Na]^+$ and $[M + 2Na + H_2O]^+$ at m/z = 729.4, 773.3 and 791.3 corresponding to the La(III) complex and at m/z = 747.8, 791.6 and 809.6 corresponding to the Gd(III) complex. The final complexes, $[(Ln\mathbf{5})_3Al(H_2O)_3]^{3-}$ (Ln = La, Gd), were obtained by reacting $[Ln(H\mathbf{5})(H_2O)]^-$ with anhydrous $AlCl_3$ under slightly alkaline conditions (pH = 8) (Scheme 2). Positive mode ESI-MS showed a molecular peak $[M + 4Na + 2H + 2H_2O]^{3+}$ at m/z = 778.2 and 796.4, corresponding to the La(III) and Gd(III) complexes (see Fig. S3 in the ESI†). Inductively coupled plasma optical emission spectrometry (ICP-OES) confirmed a 3 : 1 ratio of Gd(III) *versus* Al(III).

Fig. 1 shows the ^{1}H NMR spectra of H_4**4** and the corresponding La(III)–Al(III) complex, $[(La\mathbf{5})_3Al(H_2O)_3]^{3-}$. The spectrum shows a significant change in the aliphatic region, indicating complexation of H_4**4** to La(III). All aliphatic protons, except for proton f, show line broadening and an increase of proton resonances which is consistent with the occurrence of several interconverting isomers characteristic for lanthanide(III) complexes with DTPA ligands.[60] The aluminum(III) ion can coordinate to three 8-hydroxyquinolinate entities *via* the oxygen and nitrogen donor atoms of the ligand. Hereby, $[(La\mathbf{5})_3Al(H_2O)_3]^{3-}$ can exist as two different isomers with different chirality, *i.e.* the facial and meridional isomers.[52,61–63] Because of the higher stability of



Scheme 2 Formation of the $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ complex: (i) $GdCl_3 \cdot 6H_2O$, pyridine; (ii) Pd/C 5%, H_2 gas; (iii) anhydrous $AlCl_3$, pyridine.

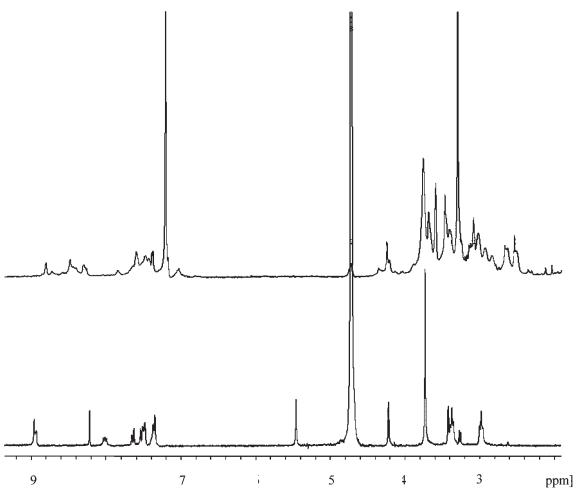


Fig. 1 ^{1}H NMR spectra of ligand H_4**4** (bottom) and $[(La\mathbf{5})_3Al(H_2O)_3]^{3-}$ (top) in D_2O at 298 K.

the meridional isomer, this form predominates in solution.[61,64] The broadening of proton signals, which can be seen in the aromatic region, indicates the occurrence of the two isomers after coordination of 8-hydroxyquinoline to the aluminum(III) ion.

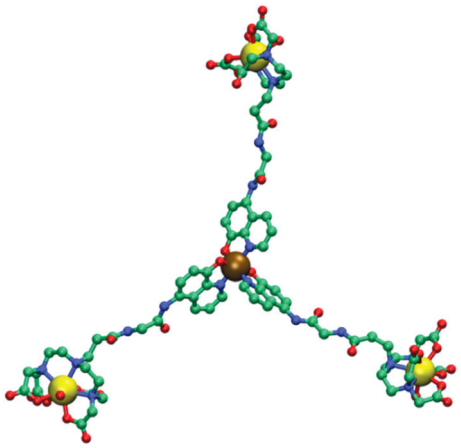


Fig. 2 Framework molecular model of the complex $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$. Hydrogen atoms have been omitted for clarity.

IR spectral data show a strong absorption at 1636 cm^{-1} due to the asymmetric C═O stretching vibration of the deprotonated acid. A shift of approximately 42 cm^{-1} to lower energy is observed for $[Ln(H\mathbf{5})(H_2O)]^-$, confirming complexation of the lanthanide ion by the ligand. Upon complexation of the 8-hydroxyquinoline moiety to aluminum(III), the asymmetric C═O stretching vibration remained unaltered, indicating that the local environment of the lanthanide(III) ion was not changed. Although no single crystals suitable for X-ray diffraction analysis could be grown, the data obtained from IR, ESI-MS and NMR are consistent with the formation of a supramolecular complex with three lanthanide(III) ions and one central aluminum(III) ion (Fig. 2).

Photophysical properties

The absorption spectrum of $[Gd(H\mathbf{5})(H_2O)]^-$ shows an intense band at 242 nm (ε = 28 100 cm^{-1} M^{-1}) which is attributed to a $\pi \rightarrow \pi^*$ transition (see Fig. S4 in the ESI†). At lower energy, a less intense and broader $\pi \rightarrow \pi^*$ band is situated at 305 nm (ε = 4100 cm^{-1} M^{-1}) and can be ascribed to the protonated quinolinate moiety.[65] After coordination with aluminum, the absorption of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ shows a red shift to 255 nm of the highest energy band (ε = 65 900 cm^{-1} M^{-1}). The lowest energy band also red-shifts to 367 nm (ε = 9100 cm^{-1} M^{-1}). The position of the bands is typical for aluminum(III) complexes of 8-hydroxyquinoline.[54]

In order to investigate the feasibility of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ to act as a bimodal agent, its luminescent properties were further investigated. 8-Hydroxyquinoline and the aluminum quinolinate complex are known to exhibit intensive green-blue broad-band luminescence.[54–56] Upon excitation into the $\pi \rightarrow \pi^*$ transition band at 305 nm, $[Gd(H\mathbf{5})(H_2O)]^-$ shows a blue broad-band emission in the range of 400–700 nm with a maximum of 454 nm (Fig. 3). After coordination with Al(III), the broad-band emission of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ red-shifts from blue to green with an emission maximum of 543 nm upon excitation at 367 nm.

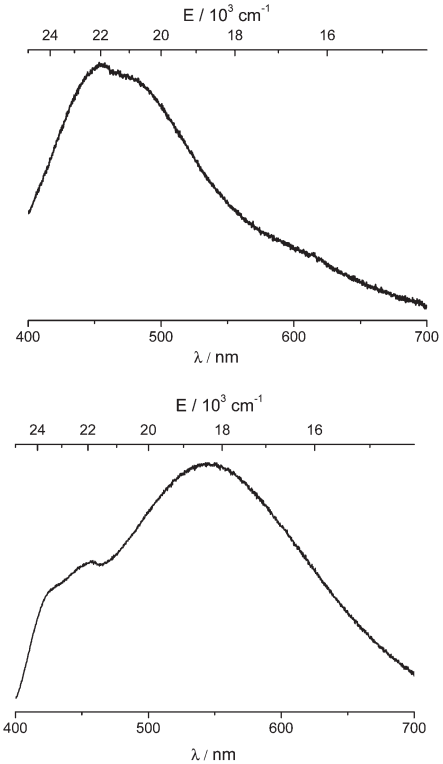


Fig. 3 Emission spectrum (λ_{ex} = 305 nm) of $[Gd(H\mathbf{5})(H_2O)]^-$ (top) and emission spectrum (λ_{ex} = 367 nm) of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ (bottom), 1×10^{-4} M in H_2O.

The emission spectrum of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ also shows a shoulder at 456 nm which can be attributed to $[Gd(H\mathbf{5})(H_2O)]^-$, most likely occurring as a result of a change in equilibrium at low concentrations. The band situated around 425 nm can be ascribed to a Raman band of water due to excitation at 367 nm.

The emission maximum of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ shows a red-shift of 18 nm compared to Alq_3 ($\lambda_{max\ em}$ = 525 nm) upon derivatization with DTPA. This effect is caused by the amide group situated on the 5-position of the quinolinate ligand because electron-donating groups located on the 5-position of 8-hydroxyquinoline decrease the HOMO–LUMO energy gap of the ligand and hereby show emission at higher wavelengths.[56] The quantum yield of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ was determined with quinine sulfate in 0.05 M H_2SO_4 as a standard and equals 0.52%.

Relaxometric studies

The relaxivity of a Gd(III) complex is defined as the efficiency to enhance the relaxation rate of the neighbouring water protons and is expressed in s^{-1} mM^{-1}. It arises from the contributions of short distance interactions between the paramagnetic Gd(III) ion and the coordinated water molecules exchanging with bulk water, the so-called inner sphere interaction,[66,67] and from the long distance interactions related to the diffusion of water molecules near the paramagnetic Gd(III) center, *i.e.* the outer sphere interaction.[68] Inner sphere interactions can be described by several parameters, such as the number of water molecules coordinated in the first hydration sphere of the complexed ion (q), the electronic relaxation times of Gd(III) (τ_{S1} and τ_{S2}), the rotational correlation time (τ_R) and the residence time of the coordinated water molecules (τ_M). A fixed τ_M value of 200 ns was used to perform the fitting because this value is in good agreement with other mono-amide derivatives of DTPA–gadolinium(III) complexes.[69]

The proton nuclear magnetic relaxation dispersion (NMRD) profiles of $[Gd(H\mathbf{5})(H_2O)]^-$ and $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ are shown in Fig. 4. An enhanced r_1 relaxivity up to 10.9 s^{-1} mM^{-1} per Gd(III) ion at 20 MHz and 310 K corresponding to 32.7 s^{-1} mM^{-1} per metallostar molecule is obtained. The theoretical fitting of the NMRD profiles takes into account the inner and outer sphere contributions to the paramagnetic relaxation rate. Some parameters were fixed during the fitting procedure: the distance (d) of closest approach for the outer sphere contribution was set at 0.36 nm, τ_M was set to 200 ns as described above, the number of coordinated water molecules was set to one (q = 1), the relative diffusion constant ($D = 3.3 \times 10^{-9}$ m^2 s^{-1})[70] and r, the distance between the Gd(III) ion and the proton nuclei of water (r = 0.31 nm). The results of these fittings are shown in Table 1. The plain lines in Fig. 4 correspond to the theoretical

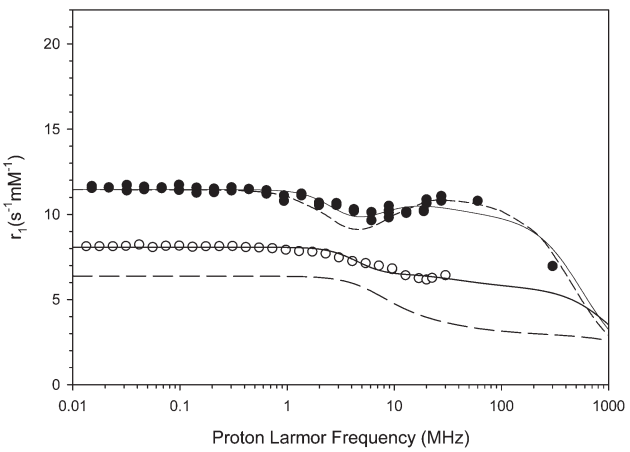


Fig. 4 ^1H NMRD profiles of $[Gd(H\mathbf{5})(H_2O)]^-$ (open circles), $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ (closed circles) and Gd–DTPA (dashed line) in water at 310 K. The plain line through the experimental data is the result of the classical fitting of the data. The dashed line corresponds to the fitting using the Lipari–Szabo approach.

Table 1 Parameters obtained by the theoretical adjustment of the proton NMRD data in water at 310 K

Parameter	Gd–DTPA[a]	$[Gd(H\mathbf{5})(H_2O)]^-$	$[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$
τ_M^{310} [ns]	143	200[b]	200[b]
τ_R^{310} [ps]	54 ± 1	147 ± 3	295 ± 3 (τ_{Rg} = 305 ± 1, τ_{Rl} = 104 ± 46)[c]
τ_{SO}^{310} [ps]	87 ± 3	80 ± 1	117 ± 1 (120 ± 2)[c]
τ_V^{310} [ps]	25 ± 3	35 ± 2	53 ± 2 (40 ± 0.1)[c]
r_1 [s^{-1} mM^{-1}] at 20 MHz	3.8 ± 0.2	6.17	10.9

[a] From ref. 71. [b] Fixed value. [c] Fit using the Lipari–Szabo approach.

fittings of the data points. The dashed line corresponds to the fitting of the Gd–DTPA data. The profile of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ shows increased values compared to the profile of $[Gd(H\mathbf{5})(H_2O)]^-$ and Gd–DTPA as a result of its higher molecular weight. The τ_R value of $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ agrees well with the size of a supramolecular complex but the agreement between the experimental data and the fit at high magnetic fields is quite poor. A better fit of the high field data could be obtained by using the Lipari–Szabo approach (Fig. 4). This fit results in a global τ_R value of 350 ± 1 ps, a local τ_R of 104 ± 46 ps and S^2 equal to 0.86 ± 0.02 showing that this metallostar is quite rigid. These data are in agreement with the values reported for a larger metallostar $\{Fe[Gd_2bpy(DTTA)_2(H_2O)_4]_3\}^{4-}$ (global τ_R = 930 ± 50 ps, local τ_R = 190 ± 15 ps and S^2 = 0.6 ± 0.04 at 298 K).[21]

Conclusions

A supramolecular metallostar $[(Ln\mathbf{5})_3Al(H_2O)_3]^{3-}$ was synthesized starting from a ditopic ligand with a DTPA and an 8-hydroxyquinoline moiety. The DTPA unit coordinates to a Gd(III) ion, forming the complex $[Gd(H\mathbf{5})(H_2O)]^-$. The rotational tumbling time τ_R of this complex is a factor of 2.7 higher in comparison with that of Gd–DTPA (Magnevist®). This enhances the relaxivity r_1 at 20 MHz and 310 K up to 6.17 s^{-1} mM^{-1}, compared to a value of 3.8 s^{-1} mM^{-1} for Gd–DTPA. The 8-hydroxyquinoline moiety, in turn, self-assembles around an Al(III) ion, leading to the formation of the metallostar compound $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$. This further increases the rotational tumbling time τ_R by a factor of 5.5 and results in the relaxivity r_1 at 20 MHz and 310 K up to 10.9 s^{-1} mM^{-1} per Gd(III) ion, which corresponds to 32.7 s^{-1} mM^{-1} per heteropolymetallic complex. In addition to the high relaxivity values, $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$ exhibits green broad-band emission luminescence upon excitation at 367 nm. The favorable relaxometric and photophysical properties of this metallostar make it an interesting compound for the further development of bimodal (optical/MR) imaging agents.

Experimental

Materials

Reagents were obtained from Aldrich Chemical (Bornem, Belgium) and Acros Organics (Geel, Belgium), and were used without further purification. Gadolinium(III) chloride hexahydrate was obtained from GFS Chemicals (Powell, Ohio, USA).

Instruments

Elemental analysis was performed by using a CE Instruments EA-1110 elemental analyzer. ^1H and ^{13}C NMR spectra were recorded by using a Bruker Avance 300 spectrometer (Bruker, Karlsruhe, Germany), operating at 300 MHz for ^1H and 75 MHz for ^{13}C, or on a Bruker Avance 400 spectrometer, operating at 400 MHz for ^1H and 100 MHz for ^{13}C. IR spectra were measured by using a Bruker Alpha-T FT-IR spectrometer (Bruker, Ettlingen, Germany). Mass spectra were obtained by using a Thermo Finnigan LCQ Advantage mass spectrometer. Samples for the mass spectrometry were prepared by dissolving the product (2 mg) in methanol (1 mL), then adding 200 μL of this solution to a water–methanol mixture (50 : 50, 800 μL). The resulting solution was injected at a flow rate of 5 μL min^{-1}. The metal contents were detected on a Varian 720-ES ICP optical emission spectrometer with reference to Chem-Lab gadolinium and aluminum standard solutions (1000 μg mL^{-1}, 2–5% HNO_3). Absorption spectra were measured on a Varian Cary 5000 spectrophotometer on freshly prepared aqua solutions in quartz Suprasil® cells (115F-QS) with an optical path-length of 0.2 cm. Emission data were recorded on an Edinburgh Instruments FS920 steady state spectrofluorimeter. This instrument is equipped with a 450W xenon arc lamp, a high energy microsecond flashlamp μF900H and an extended red-sensitive photomultiplier (185–1010 nm, Hamamatsu R 2658P). All spectra are corrected for the instrumental functions. Quantum yields were determined by a comparative method using a solution of quinine sulfate (Fluka) in 1 N H_2SO_4 (Q = 54.6%) as a standard; estimated error ±20%.[72]

Model

The model was built using Avogadro, an open-source molecular builder and visualization tool, version 1.00. The central part containing Al(III) and three 8-hydroxyquinoline molecules and the arms including Gd(III) were first optimized separately with the Universal Force Field (UFF).[73] The 8-hydroxyquinoline parts of the central unit and the arms were overlaid and the entire complex was re-optimized with UFF using Open Babel.

Proton NMRD

Proton nuclear magnetic relaxation dispersion (NMRD) profiles were measured on a Stelar Spinmaster FFC, fast field cycling NMR relaxometer (Stelar, Mede (PV), Italy) over a magnetic field strength range extending from 0.24 mT to 0.7 T. Measurements were performed on 0.6 mL samples contained in 10 mm o.d. pyrex tubes. Additional relaxation rates at 20, 60 and 300 MHz were respectively obtained on a Minispec mq20, a Minispec mq60, and a Bruker Avance 300 spectrometer (Bruker, Karlsruhe, Germany). The proton NMRD curves were fitted using data-processing software,[74,75] including different theoretical models describing the nuclear relaxation phenomena (Minuit, CERN Library).[66–68]

Synthesis

5-Nitro-8-benzyloxyquinoline (1). Compound (**1**) was prepared according to a modified literature procedure.[76] To a solution of 5-nitro-8-hydroxyquinoline (10 g, 52.6 mmol) in dry DMF (220 mL) was added benzyl bromide (15.68 mL, 132 mmol) and K_2CO_3 (22 g, 159 mmol) and the solution was stirred for 7 h at 70–80 °C until a brownish red precipitate was formed. The solvent was removed *in vacuo* and the solid residue was triturated three times with diethyl ether. The organic layers were combined, washed with an aqueous sodium hydroxide solution (1 M), dried over $MgSO_4$ and evaporated again. The crude product was purified by column chromatography [silica

gel, DCM–petroleum ether (2 : 1)] resulting in a yellow-orange solid (10 g, 35.7 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.55 (s, 2 H, benzyl CH_2), 7.05 (d, 1 H, quinoline C*H*), 7.33–7.40 (m, 3 H, benzyl C*H*), 7.50 (d, 2 H, benzyl C*H*), 7.69 (dd, 1 H, quinoline C*H*), 8.42 (d, 1 H, quinoline C*H*), 9.07 (d, 1 H, quinoline C*H*), 9.22 (d, 1 H, quinoline C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 71.5 (benzyl *C*H_2), 107.3 (quinoline *C*H), 123.1 (quinoline *C*), 124.6, 125.0 (quinoline *C*H), 127.3, 127.8, 129.1 (benzyl *C*H), 132.6 (quinoline *C*H), 136.9 (benzyl *C*), 139.7, 142.5 (quinoline *C*), 150.3 (quinoline *C*H), 160.8 (quinoline *C*). ESI-MS ($C_{16}H_{12}N_2O_3$ [M]): *m*/*z* calcd 281.3 ([M + H]$^+$); found 281.3 ([M + H]$^+$). Elemental analysis calculated (%) for $C_{16}H_{12}N_2O_3$ (280.3): C 68.56, H 4.32, N 9.99; found: C 68.87, H 4.35, N 9.75.

***N*-(*N*-*tert*-Butoxycarbonylglycine)-5-amino-8-benzyloxy-quinoline (2).** To a solution of (**1**) (2 g, 7 mmol) in ethanol (80 mL) was added tin(II) chloride dihydrate (6.44 g, 28.5 mmol) and the mixture was refluxed under an argon atmosphere for 3 h. The solution was cooled to room temperature and an aqueous solution of sodium hydrogen carbonate was added dropwise until pH 10 was reached. The reduced product was extracted with DCM, the combined organic layers were dried over $MgSO_4$ and evaporated to give a dark red oil (1.43 g, 5.7 mmol, 82%). Because of the low stability of the reduced 5-amino-8-benzyloxyquinoline, it was immediately redissolved in dry DCM (25 mL) and diisopropylethylamine (DIPEA) (1.33 mL, 7.8 mmol) was added under an argon atmosphere. To a stirred solution of *t*Boc-glycine (0.91 g, 5.2 mmol) and *o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) (2.96 g, 7.8 mmol) in dry DCM under an argon atmosphere was added dropwise DIPEA (0.89 mL, 5.2 mmol) in a second flask. The solution of the second flask was added to the first flask over 10 min and the mixture was stirred overnight. The suspension was washed with an aqueous solution of sodium hydrogen carbonate, a saturated sodium chloride solution and dried over $MgSO_4$. After evaporation, the crude product was purified by column chromatography [silica gel, DCM–MeOH (100 : 5)] resulting in a yellow oil (**2**) (1.68 g, 4.1 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.50 (s, 9 H, *tert*-butyl CH_3), 4.02 (s, 2 H, C(O)CH_2NH), 5.44 (s, 2 H, benzyl CH_2), 6.98 (d, 1 H, quinoline C*H*), 7.36 (t, 2 H, benzyl C*H*), 7.43 (m, 1 H, benzyl C*H*), 7.50 (d, 2 H, benzyl C*H*), 7.60 (d, 1 H, quinoline C*H*), 8.22 (d, 1 H, quinoline C*H*), 8.66 (d, 1 H, quinoline C*H*), 8.98 (d, 1 H, quinoline C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 28.3 (*tert*-butyl *C*H_3), 44.1 (C(O)*C*H_2NH), 70.9 (benzyl *C*H_2), 81.0 (*tert*-butyl *C*), 109.4, 117.1, 121.7 (quinoline *C*H), 124.6 (quinoline *C*), 127.2, 127.9, 128.7 (benzyl *C*H), 130.4 (quinoline *C*H), 134.1 (quinoline *C*), 136.7 (benzyl *C*), 140.4, 147.2 (quinoline *C*), 149.3 (quinoline *C*H), 156.4 (*C*(O)O), 169.0 (*C*(O)-CH_2NH). ESI-MS ($C_{23}H_{25}N_3O_4$ [M]): *m*/*z* calcd 408.5 ([M + H]$^+$) and 430.5 ([M + Na]$^+$); found 408.7 ([M + H]$^+$) and 430.7 ([M + Na]$^+$).

***N*-Glycine-5-amino-8-benzyloxyquinoline (3).** To a mixture of CF_3COOH–DCM 2 : 1 (12 mL) was added dropwise a solution of (**2**) (1.68 g, 4.1 mmol) dissolved in DCM (7 mL). The solvent was removed *in vacuo* after 2 h and the product was redissolved three times in DCM and three times in MeOH to obtain trifluoroacetic acid free *N*-glycine-5-amino-8-benzyloxy-quinoline (1.1 g, 3.6 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.06 (s, 2 H, C(O)CH_2NH$_2$), 5.33 (s, 2 H, benzyl CH_2), 7.16 (d, 1 H, quinoline C*H*), 7.35 (m, 3 H, benzyl C*H*), 7.46 (d, 2 H, benzyl C*H*), 7.55 (m, 1 H, quinoline C*H*), 8.31 (d, 1 H, quinoline C*H*), 8.37 (d, 1 H, quinoline C*H*), 8.74 (d, 1 H, quinoline C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 42.8 (C(O)*C*H_2NH), 70.5 (benzyl *C*H_2), 108.9, 117.4, 122.6 (quinoline *C*H), 123.5 (quinoline *C*), 127.3, 127.9, 128.8 (benzyl *C*H), 131.4 (quinoline *C*H), 135.0 (quinoline *C*), 137.1 (benzyl *C*), 140.2, 146.7 (quinoline *C*), 149.4 (quinoline *C*H), 168.5 (*C*(O)CH_2NH). ESI-MS ($C_{18}H_{17}N_3O_2$ [M]): *m*/*z* calcd 308.3 ([M + H]$^+$) and 637.6 ([2M + Na]$^+$); found 308.7 ([M + H]$^+$) and 637.5 ([2M + Na]$^+$).

Benzyl and *tert*-butyl protected 8-hydroxyquinoline derivative. To a stirred solution of (**3**) (1.68 g, 5.5 mmol) in dry DMF (70 mL), DIPEA (1.29 mL, 7.5 mmol) was added dropwise under an argon atmosphere in a first flask. A mixture of *N*,*N*-bis{*N*,*N*-bis[(*tert*-butoxycarbonyl)methyl]-ethylamine}-glycine[69] (3.1 g, 5.0 mmol), *o*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) (2.39 g, 7.5 mmol) and DIPEA (0.86 mL, 5.0 mmol) was also prepared in dry DMF (60 mL) under an argon atmosphere in a second flask. The solution of the first flask was added dropwise over a period of 10 min to the second flask. After 24 h, the DMF was evaporated and the mixture was redissolved in DCM. The suspension was washed with a saturated bicarbonate solution (2×), brine (2×) and dried over $MgSO_4$. After evaporation, the crude brown oil was purified by MPLC [silica gel, DCM–MeOH (100 : 0) → DCM–MeOH (100 : 7) over 2 h] resulting in the benzyl and *tert*-butyl protected 8-hydroxyquinoline derivative (2.66 g, 2.93 mmol, 59%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.36 (s, 36 H, *tert*-butyl CH_3), 2.60 (t, 8 H, NCH_2CH_2N), 3.29 (s, 2 H, C(O)CH_2N), 3.37 (s, 8 H, NCH_2C(O)O), 4.22 (s, 2 H, C(O)CH_2NH), 5.43 (s, 2 H, benzyl CH_2), 6.96 (d, 1 H, quinoline C*H*), 7.34–7.55 (m, 5 H, benzyl C*H*), 7.66 (dd, 1 H, quinoline C*H*), 8.35 (d, 2 H, quinoline C*H*), 8.87 (d, 1 H, quinoline C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 28.1 (*tert*-butyl *C*H_3), 43.9 (C(O)*C*H_2NH), 51.9 (N*C*H_2CH$_2$N), 54.1 (NCH$_2$*C*H_2N), 58.3 (N*C*H_2C(O)O), 58.7 (C(O)*C*H_2N), 70.9 (benzyl *C*H_2), 81.6 (*tert*-butyl *C*), 108.5, 117.8, 122.0 (quinoline *C*H), 122.9 (quinoline *C*), 127.3, 127.8, 128.7 (benzyl *C*H), 131.3 (quinoline *C*H), 133.6 (quinoline *C*), 137.0 (benzyl *C*), 140.1, 147.3 (quinoline *C*), 151.7 (quinoline *C*H), 168.9 (NH *C*(O)CH_2NH), 170.6 (*C*(O)O), 172.3 (*C*(O)-CH_2N). ESI-MS ($C_{48}H_{70}N_6O_{11}$ [M]): *m*/*z* calcd 908.1 ([M + H]$^+$) and 930.1 ([M + Na]$^+$); found 907.6 ([M + H]$^+$) and 929.5 ([M + Na]$^+$).

Benzyl protected 8-hydroxyquinoline derivative ($H_4$4). The benzyl and *tert*-butyl protected 8-hydroxyquinoline derivative (2.66 g, 2.93 mmol) was dissolved in a 6 N HCl (80 mL) solution. The mixture was stirred at room temperature for 1 h and then washed with CH_2Cl_2 (2×). The deprotected product was then purified by HPLC (water–acetonitrile) to give $H_4$4 as a yellow-brownish solid (360 mg, 0.53 mmol, 18%). ^{1}H NMR (400 MHz, D_2O, ppm): δ 2.67 (t, 4 H, NCH_2CH$_2$N), 2.94 (t, 4 H, NCH$_2$CH_2N), 3.42 (s, 2 H, C(O)CH_2N), 3.49 (s, 8 H, NCH_2C(O)OH), 4.21 (s, 2 H, C(O)CH_2NH), 5.35 (s, 2 H, benzyl CH_2), 6.97 (d, 1 H, quinoline C*H*), 7.35 (m, 3 H, benzyl C*H*), 7.51 (m, 2 H, benzyl C*H*), 7.62 (dd, 1 H, quinoline C*H*),

8.01 (t, 1 H, C(O)CH_2NH), 8.37 (d, 2 H, quinoline C*H*), 8.92 (d, 1 H, quinoline C*H*). ^{13}C NMR (100 MHz, D_2O, ppm): δ 42.9 (C(O)CH_2NH), 52.1 (NCH_2CH_2N), 54.2 (NCH_2CH_2N), 58.3 (C(O)CH_2N), 60.9 (NCH_2C(O)OH), 71.5 (benzyl CH_2), 107.8, 116.7, 121.1 (quinoline *C*H), 122.6 (quinoline *C*), 127.6, 128.3, 129.9 (benzyl *C*H), 131.0 (quinoline *C*H), 134.9 (quinoline *C*), 137.7 (benzyl *C*), 140.2, 146.6 (quinoline *C*), 149.1 (quinoline *C*H), 166.8 (NH *C*(O)CH_2NH), 169.8 (*C*(O)CH_2N), 173.7 (*C*OOH). ESI-MS: ($C_{32}H_{38}N_6O_{11}$ [M]): *m*/*z* calcd 683.7 ($[M + H]^+$) and 705.7 ($[M + Na]^+$); found 683.4 ($[M + H]^+$) and 705.2 ($[M + Na]^+$). IR (KBr): ν = 1636 (COO^- asym. stretch), 1534 (amide II), 1393 (COO^- sym. stretch) cm^{-1}. Elemental analysis calculated (%) for $C_{32}H_{38}N_6O_{11}\cdot 2H_2O$ (718.7): C 53.48, H 5.89, N 11.59; found: C 53.42, H 5.83, N 11.48.

Lanthanide complexes. To prevent coordination of the lanthanides to the 8-hydroxyquinoline moiety of the ligand,[57,58] the lanthanide(III) complexes were developed starting from the benzyl protected 8-hydroxyquinoline derivative H_4**4** according to a general procedure: a solution of hydrated $LnCl_3$ salt (1.05 mmol) in H_2O was added to ligand H_4**4** (1 mmol) dissolved in pyridine, and the mixture was heated at 70 °C for 3 h. The solvent was evaporated under reduced pressure and the crude product was then refluxed in ethanol for 1 h. After cooling to room temperature, the complex was filtered off and dried *in vacuo*. To allow further complexation with aluminum(III), the benzyl group was removed according to the following procedure: the lanthanide(III) complex was dissolved in a mixture of water–methanol (1 : 1, v/v) and Pd/C 5% was added. The suspension was stirred over 20 h under a hydrogen atmosphere at room temperature. The mixture was filtered over Celite and evaporated to yield the benzyl deprotected lanthanide(III) complex $[Ln(H\mathbf{5})(H_2O)]^-$. The absence of free lanthanide ions was checked by using an arsenazo indicator.[59]

La(III) complex $[La(H\mathbf{5})(H_2O)]^-$: Yield: 59%. ESI-MS ($C_{25}H_{28}LaN_6O_{11}$ [M]): *m*/*z* calcd 729.4 ($[M + 2H]^+$), 773.4 ($[M + 2Na]^+$) and 791.4 ($[M + 2Na + H_2O]^+$); found 729.4 ($[M + 2H]^+$), 773.3 ($[M + 2Na]^+$) and 791.3 ($[M + 2Na + H_2O]^+$). IR (KBr): ν = 1594 (COO^- asym. stretch), 1478 (amide II), 1393 (COO^- sym. stretch) cm^{-1}.

Gd(III) complex $[Gd(H5)(H_2O)]^-$: Yield: 66%. ESI-MS ($C_{25}H_{28}GdN_6O_{11}$ [M]): *m*/*z* calcd 747.8 ($[M + 2H]^+$), 791.8 ($[M + 2Na]^+$) and 809.8 ($[M + 2Na + H_2O]^+$); found 747.8 ($[M + 2H]^+$), 791.6 ($[M + 2Na]^+$) and 809.6 ($[M + 2Na + H_2O]^+$). IR (KBr): ν = 1594 (COO^- asym. stretch), 1479 (amide II), 1394 (COO^- sym. stretch) cm^{-1}.

Lanthanide(III)–aluminum(III) complexes. Anhydrous $AlCl_3$ (1 mmol) was added to a solution of $[Ln(H\mathbf{5})(H_2O)]^-$ (3 mmol) in a H_2O–pyridine (1 : 1, v/v) mixture and stirred at 70 °C for 3 h. The solution was concentrated under reduced pressure and the crude product was refluxed in ethanol for 1 h. After cooling to room temperature, the complex was filtered off and dried *in vacuo*. The product was purified by dialysis to remove the remaining salts.

Al(III)–La(III) complex $[(La\mathbf{5})_3Al(H_2O)_3]^{3-}$: Yield: 63%. ESI-MS ($C_{75}H_{81}AlLa_3N_{18}O_{33}$ [M]): *m*/*z* calcd 778.7 ($[M + 4Na + 2H + 2H_2O]^{3+}$); found 778.2 ($[M + 4Na + 2H + 2H_2O]^{3+}$). IR (KBr): ν = 1594 (COO^- asym. stretch), 1472 (amide II), 1396 (COO^- sym. stretch) cm^{-1}.

Al(III)–Gd(III) complex $[(Gd\mathbf{5})_3Al(H_2O)_3]^{3-}$: Yield: 66%. ESI-MS ($C_{75}H_{81}AlGd_3N_{18}O_{33}$ [M]): *m*/*z* calcd 797.3 ($[M + 4Na + 2H + 2H_2O]^{3+}$); found 796.4 ($[M + 4Na + 2H + 2H_2O]^{3+}$). IR (KBr): ν = 1593 (COO^- asym. stretch), 1475 (amide II), 1397 (COO^- sym. stretch) cm^{-1}. ICP-OES ratio (Gd/Al): 2.91.

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