Rigid and Compact Binuclear Bis-hydrated Gd-complexes as High Relaxivity MRI Agents

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Abstract: The first binuclear Gd-complex of the 12-membered pyridine-based polyaminocarboxylate macrocyclic ligand PCTA was synthesized by C–C connection of the pyridine units through two different synthetic procedures. A dimeric AAZTA-ligand was also synthesized with the aim to compare the relaxometric results or the two ditopic Gd-complexes. Thus, the ^1H relaxometric study on $[Gd_2PCTA_2(H_2O)_4]$ and on $[Gd_2AAZTA_2(H_2O)_4]^{2-}$ highlighted the remarkable rigidity and compactness of the two binuclear complexes, which results in molar relaxivities (per Gd), at 1.5 T and 298 K of ca. 12–12.6 mM^{-1}s^{-1} with an increase of ca. 80% at 1.5 T and 298 K (+70% at 310 K) with respect to the corresponding mononuclear complexes.

A large fraction (~40%) of clinical magnetic resonance imaging (MRI) examinations requires the use of exogenous contrast agents (CAs) that allow remarkable improvements in clinical diagnosis in terms of higher specificity, better tissue characterization, reduction of image artefacts and functional information. Paramagnetic Gd^{III} complexes were early recognized as the candidates of choice for the design of MRI CAs because of their favourable magnetic properties associated with the presence of seven unpaired electrons and relatively long electronic relaxation times.[1,2] The CAs approved for clinical use are monohydrated ($q = 1$), low molecular weight Gd^{III} complexes capable of shortening the proton longitudinal relaxation times ($T_1 = 1/R_1$) of neighbouring H$_2$O molecules, thus increasing their signal intensity in T_1-weighted (T_{1w}) MR images. This ability to induce

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relaxation is called relaxivity ($r_{1,2}$) and measures the relaxation rate enhancement of water proton nuclei normalized to a 1 mM concentration of the paramagnetic ion. At the magnetic fields used in clinical (1.5 and 3 T) and preclinical scanners (up to 9.4 T) the relaxivity is mainly controlled by three parameters: the exchange rate ($k_{ex} = 1/\tau_M$) and the number (q) of water molecules coordinated to the metal centre and the rotational correlation time (τ_R).[3] The increase of the hydration state q of the metal ion can be obtained by reducing the number of donor atoms of the chelating ligand, which, however, may result in a decreased stability of the complex. This latter is assessed by measuring the thermodynamic stability and kinetic inertness toward dissociation/ transmetallation reactions of a Gd-complex that aims for in vivo applications. However, certain macrocyclic and mesocyclic bis-hydrated complexes such as GdPCTA (PCTA = 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid, Scheme 1)[4] or GdAAZTA (AAZTA = 6-amino-6-methylperhydro-1,4-diazepinetetraacetic acid, Scheme 1)[5] were found to be characterized by excellent inertness in physiological conditions, even better than that of some non-macrocyclic $q = 1$ complexes. In particular, it has been recently shown that among the $q = 2$ Gd-complexes, those that show the highest kinetic inertness are GdPCTA and the bicyclic AAZTA derivative GdCyAAZTA, with half-lives ($t_{1/2}$) at pH 7.4 of 4.4×10^6 and 8×10^5 h, respectively.[6]

Although no $q = 2$ Gd^{III}-complexes have been approved so far for clinical use, the interest in these bis-hydrated complexes is shown by the recent development by the pharmaceutical industry Guerbet of a novel functionalized tris-serinolamido PCTA derivative (Gadopiclenol, Scheme 1)[7] that exploits the excellent stability and kinetic inertness of GdPCTA-like complexes. Gadopiclenol shows remarkable relaxivity values due to its large molecular weight, the position of the Gd ion located almost at the barycentre of the molecule and the presence of hydrophilic polyalcohol pendants that favour the additional contribution of second sphere water molecules (SS) to r_1. Although the molecule does not possess the high symmetry typical of the GdDOTA-derivatives reported in early 2000,[8] the combination of the SS water molecules contribution and of a longer rotational correlation time provides high relaxivities over a broad range of magnetic field strengths.
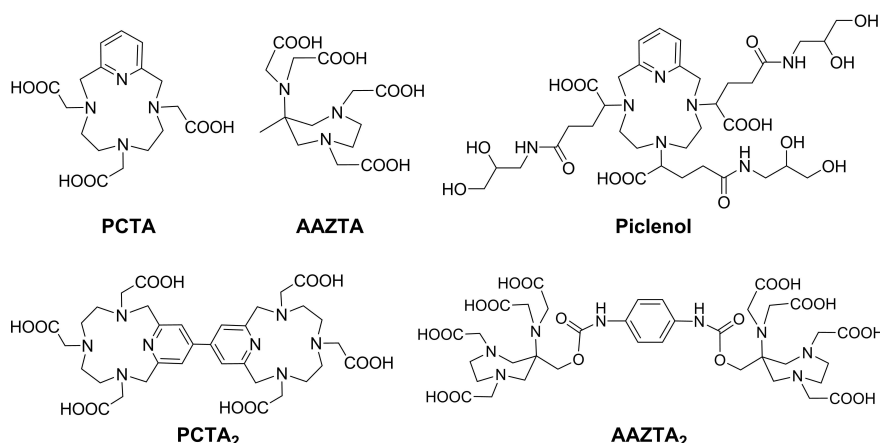
A further approach to increase the relaxivity of a Gd-complex at clinically relevant magnetic fields (1.5–3 T) is the use of multimeric Gd^{III}-agents of medium molecular weight (1-4 kDa), roughly corresponding to bi-, tri- or tetranuclear complexes. These systems allow to attain high ionic relaxivities (per Gd) which reach maximum values precisely in the range of

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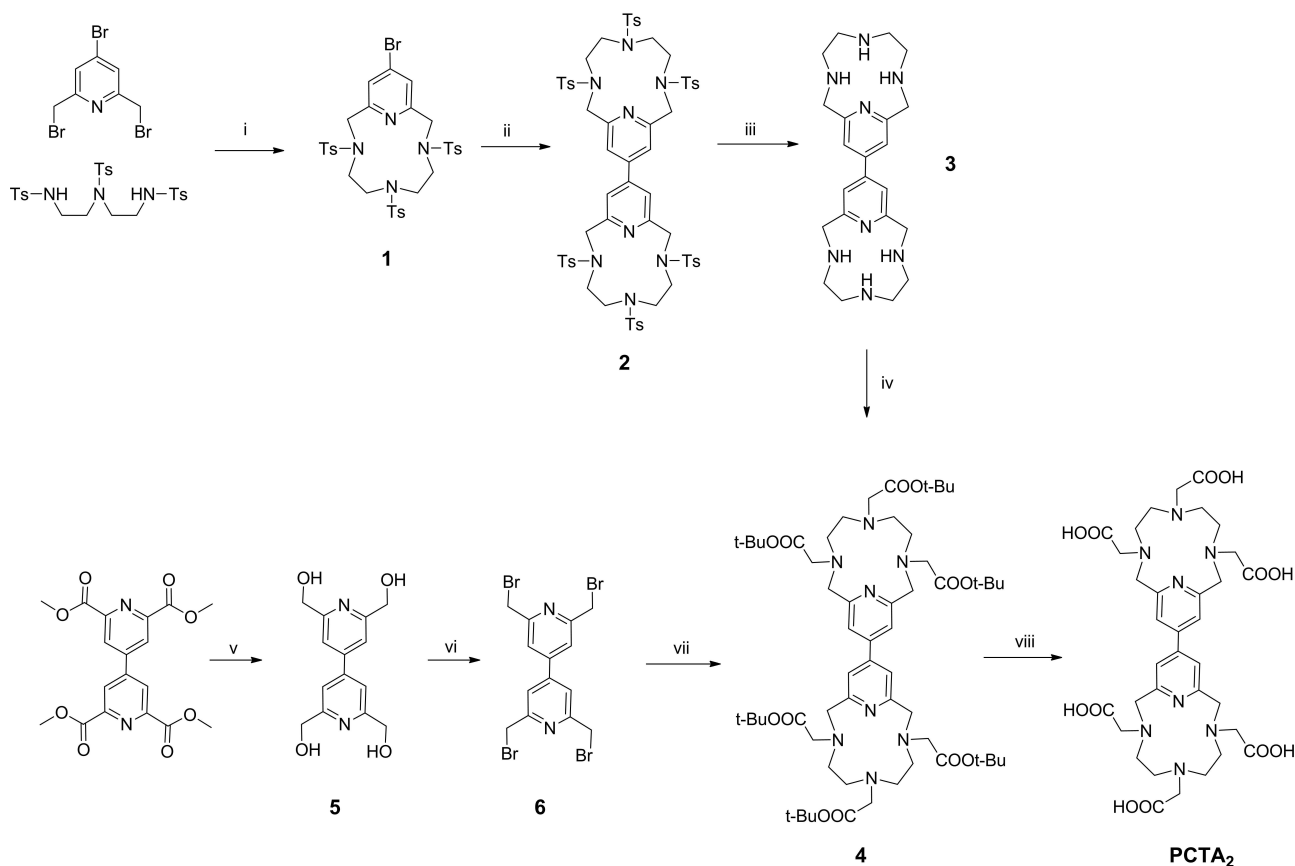Societies Publishing

Scheme 1. Ligands discussed in the text.

approx. 1–5 T.[9] Therefore, oligomeric systems (e.g. 2–4 chelates rigidly linked together) with τ_R values between ca. 150–500 ps show relaxivity peaks at high proton Larmor frequencies ($>$40 MHz).[9] Several oligomeric contrast agents have been reported in the literature based on both $q=1$ (DOTA-like) and $q=2$ (AAZTA-like) Gd-complexes. Remarkable results have been obtained when the advantages of the slower rotational dynamics are combined with fast water exchange rates and second hydration sphere contributions.[10,11] Notably, no examples of multimeric systems based on PCTA ligand have been reported in the literature. The synthesis of binuclear Gd-complexes has also been recently pursued by another contrast media company, that patented a series of ditopic GdHPDO3A-like systems linked by polyaminoalcohol groups to increase the SS contribution.[12] In this regard, it should be noted that the linker between the paramagnetic units in an oligomeric agent plays a key role for the attainment of high relaxivities. The linker needs to be as rigid as possible to favour an optimal motional coupling between the discrete interconnected chelates and, possibly, hydrophilic to enable the formation of strong hydrogen bonds with SS water molecules.

In this contribution, we combined the two approaches by synthesising a PCTA dimer in which the two units are directly connected through the pyridine moieties (PCTA$_2$, Scheme 1) to minimize local rotational motions. The synthesis of such a dimeric molecule is quite challenging and we followed two different strategies. The first involves the Ni(0)-catalysed homo-coupling of the bromopyridine-functionalized macrocycle, whereas the second is based on the synthesis of the tetrabromomethyl-bipyridine derivative (**6** in Scheme 2) to be used for bis-macrocyclization. For a comparison, a dimeric GdAAZTA-complex was also synthesized by linking together two AAZTA-OH moieties.[13] The Gd-complexes of these ditopic ligands were then investigated in detail through ^{1}H NMR relaxometry to assess their structural and dynamic properties in solution and their relaxation efficiency.

Design and synthesis

The design of a dimeric Gd-complex requires the rational choice of the monomeric chelate and of the linker connecting the two units. We have already discussed the choice of a stable $q=2$ Gd-complex, such as GdPCTA or GdAAZTA, to achieve a higher inner sphere contribution to the relaxivity. In addition, it is important to avoid the easy rotation around the linker because this implies a poor correlation between the motions of the single chelates and the global molecular reorientation.[14] A poor motional coupling invariably results in decreased relaxivity. As noted above, a further important contribution to r_1 arises from the presence of H-bonded water molecules in the proximity of the paramagnetic centres either by interaction with the linker or with the hydrophilic moieties of the chelates. Several examples of ditopic Gd-complexes have been designed to obtain improved relaxivity enhancement with respect to the monomeric units following these approaches.[15] Nonetheless, the advantage of PCTA as compared to the other polyamino-carboxylate ligands such as DOTA or AAZTA is related to the presence of a pyridine unit within the bis-macrocyclic structure that can be used to connect two ligands together. Thus, by directly linking two pyridine moieties in position 4 through a metal-catalysed homocoupling reaction a rigid and compact dimeric system with a zero-length cross linker can be obtained. In a structure of this type, the local motions of the single units should be minimized relative to the global molecular tumbling and therefore the increase in the molecular mass of the binuclear complex should translate into a corresponding increase in τ_R and therefore in relaxivity (per Gd).

In a first synthetic approach of PCTA$_2$, the key step was the Ni(0)-catalysed homocoupling reaction[16] between two units of the *N*-tosyl-protected *p*-bromo-pyclen derivative (Scheme 2). First of all, the diethyl ester of dipicolinic acid incorporating a bromo group in the para position, was obtained from chelidamic acid by bromination with PBr$_5$ and esterification, following the literature procedure.[17] Then, the cyclization reaction was carried out using the procedure optimized for PCTA,[18] i.e. reaction of 4-bromo-2,6-bis-bromomethylpyridine

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Scheme 2. Synthesis of PCTA$_2$. i. K$_2$CO$_3$, CH$_3$CN; ii. NiCl$_2$, PPh$_3$, Zn, DMF; iii. HBr 33% in AcOH; iv. BrAcO*t*Bu, NEt$_3$, *N*-methylpyrrolidone; v. NaBH$_4$, CaCl$_2$, EtOH; vi. SOBr$_2$; vii. diethylentriamine-*N*,*N*′,*N*″-tris-*tert*butyl acetate, Na$_2$CO$_3$, CH$_3$CN; viii. TFA/DCM 1:1.

and 1,4,7-tritosyl-1,4,7-triazaeptane in anhydrous acetonitrile in the presence of potassium carbonate.

The homocoupling reaction was carried out in DMF in the presence of NiCl$_2$, triphenilphosphine and Zn dust obtaining the ditopic ligand in good yield after column chromatography. Hydrolysis of the tosylate groups was accomplished with HBr 33% in acetic acid followed by alkylation of the six secondary amines with *tert*-butylbromoacetate. Deprotection of the *tert*-butyl esters with a 1:1 mixture of CH$_2$Cl$_2$ and trifluoroacetic acid resulted in the final ligand PCTA$_2$ in good yield.

In the literature there are no examples of the formation of ditopic or multimeric macrocyclic ligands linked together through homo- or cross-coupling reactions, although coupling reactions are used for the synthesis of large macrocycles or of porphyrin systems.[19] On the other hand, pyridine-based ditopic chelators are reported in the literature, but their synthesis starts from the formation of functionalized 4,4′-bipyridine. In one case, 4,4′-bipyridine was acetylated in the 2,2′,6,6′ positions using pyruvic acid, AgNO$_3$ e ammonium persulfate;[20] the tetraacetylated bipyridine was then used to form a bis-pentaaza macrocycle by Mn(II) template imine formation. In other examples,[21] the 2,2′,6,6′-tetramethyl-4,4′bipyridine was synthesized using Hunig's method by reductive coupling of 2,6-lutidine with Na in THF followed by oxidation with SO$_2$.[22]

In the second synthetic path, we followed the same procedure to obtain the bis-PCTA macrocycle. Thus, the tetramethyl derivative, obtained by Hunig's approach,[22] was oxidized with CrO$_3$ and esterified passing through the tetraacyl chloride derivative. Then, reduction of the esters followed by treatment of the tetraol **5** with thionyl bromide produced the tetrabromomethyl bipyridine **6** in good yield.[21]

In this case, the cyclization was carried out by using the diethylentriamine-*N*,*N*′,*N*″-triacetic acid in the presence of Na$_2$CO$_3$ in acetonitrile at reflux following the method reported by Picard and colleagues.[23] With this approach, the macrocyclization reaction is carried out in diluted conditions (concentration 2×10^{-3} M) and controlled by a sodium template effect. No sign of oligomerization or other by-product formation were detected by HPLC-MS analysis. Finally, the *tert*-butyl ester groups in the bis-macrocycle **4** were deprotected to obtain the final dimeric ligand PCTA$_2$ in reasonable yield.

To compare the data on the Gd-complex of PCTA$_2$, another fairly rigid $q = 2$ dimeric AAZTA-based ligand was synthesized by reaction of 1,4-phenylene diisocyanate with AAZTA-OH,[13] followed by deprotection of the *tert*-butyl esters with a 1:1 mixture of CH$_2$Cl$_2$ and trifluoroacetic acid (Scheme 3). In this case, although the linker is much longer than that used for PCTA$_2$, it contains only two sp^3 carbon atoms and the aromatic
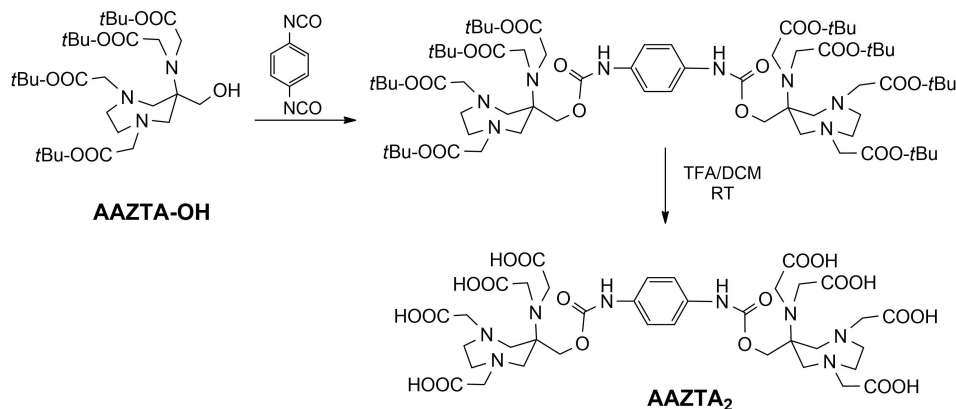
Scheme 3. Synthesis of AAZTA$_2$.

ring and the carbamate moieties should substantially hinder the local flexibility of the monomeric units.

Complexation reactions were carried out at pH = 6.5 by mixing at room temperature two molar equivalents of GdCl$_3$ with one equivalent of the dimeric ligand and the formation of the complexes were supported by ESI MS analysis and HPLC method (Supporting Information Figure S1–S5).

^{1}H NMR relaxometric study

The ionic (per Gd) relaxivity (r_1) values of the dimeric complexes [Gd$_2$PCTA$_2$(H$_2$O)$_4$] and [Gd$_2$AAZTA$_2$(H$_2$O)$_4$]$^{2-}$, measured at pH 7, 20 MHz (0.47 T) and 298 K, are 12.1 and 12.6 mM^{-1} s^{-1}, respectively (8.8 and 8.6 mM^{-1} s^{-1} at 310 K). The corresponding mononuclear complexes [GdPCTA(H$_2$O)$_2$][24] and [GdAAZTA-OH-(H$_2$O)$_2$]$^{-}$[25] show r_1 values of 6.9 and 7.6 mM^{-1} s^{-1}, respectively, measured under identical experimental conditions. Therefore, the binuclear Gd-complexes exhibit a relaxivity gain of +76% ([Gd$_2$PCTA$_2$(H$_2$O)$_4$]) and +66% ([Gd$_2$AAZTA$_2$(H$_2$O)$_4$]$^{2-}$), easily attributed to a longer value of the rotational correlation time associated with the increased molecular size, while the state of hydration remains unchanged ($q = 2$). Thus, since only the inner-sphere contribution to relaxivity depends on τ_R, whereas the outer-sphere contribution remains essentially unaffected, we can infer that the binuclear complexes are remarkably rigid and compact, hence their tumbling motion is largely isotropic as expected, in both cases, by the nature of the linkers connecting the two coordination cages.

The pH dependence of r_1 was measured for both complexes in the 4–11 pH range, at 20 MHz and 298 K as it provides useful insights into their solution behaviour and stability. The data reported in Figure 1A shows r_1 values constant over the entire pH range for [Gd$_2$AAZTA$_2$(H$_2$O)$_4$]$^{2-}$ to indicate that the coordinated water molecules are not displaced by CO$_3^{2-}$ anions, even when present at relatively high concentration as in the basic pH region. In the case of [Gd$_2$PCTA$_2$(H$_2$O)$_4$], r_1 remains constant up to ca. pH 8.5 where it begins to decrease until it reaches the value of 8.5 mM^{-1} s^{-1} at pH 11.2 (−32%), likely as a result of a partial water displacement by carbonate anions present in the
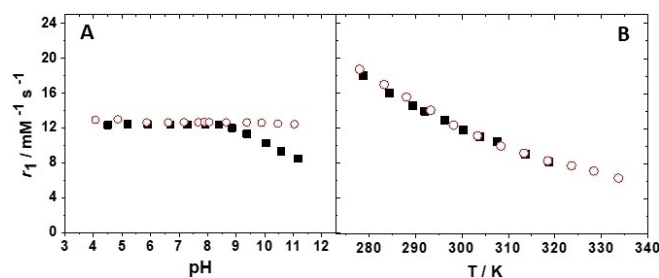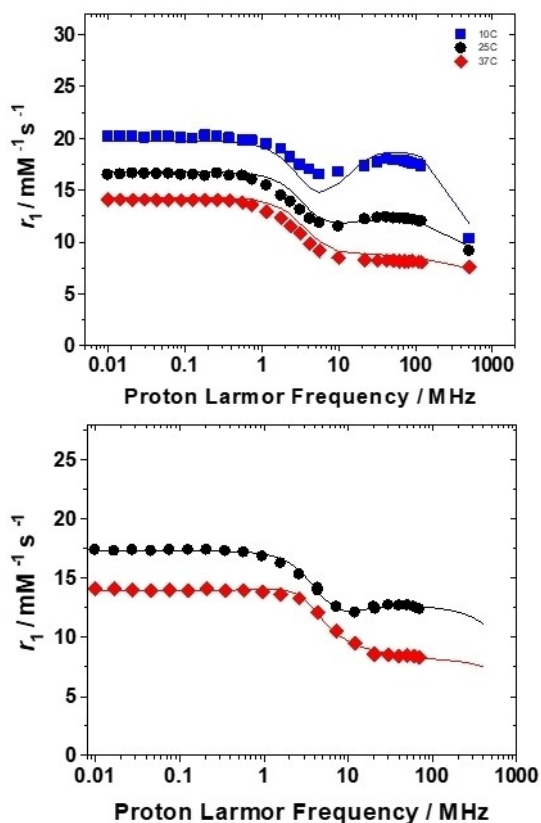

Figure 1. Plots of the ^{1}H relaxivity for [Gd$_2$PCTA$_2$(H$_2$O)$_4$] (black squares) and for [Gd$_2$AAZTA$_2$(H$_2$O)$_4$]$^{2-}$ (red circles) as a function of pH (A, 20 MHz and 298 K) and temperature (B, 20 MHz, pH 7).

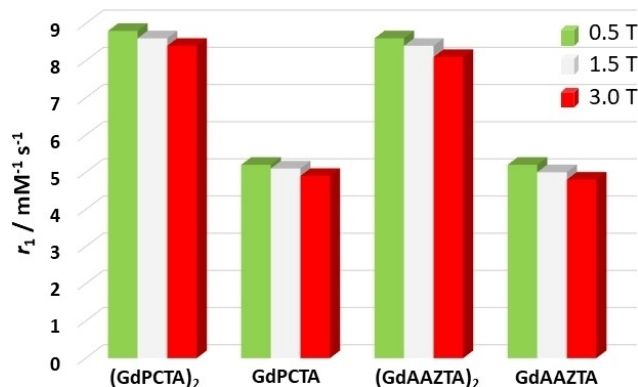aerated solution. This behaviour is rather common for $q > 1$ Gd-complexes, such as GdDO3A or GdEDTA.[24]

The magnetic field dependence of the relaxivity, the so-called NMRD (nuclear magnetic relaxation dispersion) profile, has been measured at 25 and 37 °C (for [Gd$_2$PCTA$_2$(H$_2$O)$_4$] also at 10 °C) over the proton Larmor frequency range 0.01 to 500 MHz, corresponding to magnetic field strengths varying between 2.34 × 10^{-4} T and 11.7 T (Figure 2). The temperature dependence of r_1 was also measured for both complexes at 20 MHz over the range 274–340 K and is shown in Figure 1B. The shape of the NMRD profiles and their temperature dependence (r_1 decreases with increasing temperature) reproduce the general behaviour of low molecular weight Gd-complexes, for which r_1 is not limited by the water exchange rate (fast exchange regime) but rather by the rotational motion, as for the related monomeric complexes.

The NMRD profiles were fitted in terms of the established theory of paramagnetic relaxation expressed by the Solomon-Bloembergen-Morgan (SBM)[26] and Freed's[27] equations for the inner- (IS) and outer sphere (OS) proton relaxation mechanisms, respectively. Some of the parameters (q, r_{GdH}, a, D) were fixed to known or reasonable values as indicated in Table 1. The residence lifetime of the coordinated water molecules, τ_M, does not affect the relaxivity of the systems under the regime of fast exchange and their values were fixed to those reported for the mononuclear GdPCTA and GdAAZTA complexes (70 and 90 ns,

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Figure 2. $1/T_1$ ^{1}H NMRD relaxivity data for $[Gd_2PCTA_2(H_2O)_4]$ (top) and for $[Gd_2AAZTA_2(H_2O)_4]^{2-}$ (bottom) at pH = 7.0: 283 K (blue squares); 298 K (black circles); 310 K (red diamonds). The solid lines represent the best results of the fitting to the experimental points (see Table 1).

Figure 3. Plot of the ionic relaxivity values of $[Gd_2PCTA_2(H_2O)_4]$ and $[Gd_2AAZTA_2(H_2O)_4]^{2-}$ at 0.5, 1.5 and 3.0 T and at 310 K compared to the corresponding mononuclear complexes.

respectively).[24,25] The fit was performed using as adjustable parameters τ_R and the electronic relaxation parameters Δ^2 (trace of the squared zero-field splitting, ZFS, tensor) and τ_V (correlation time for the modulation of the transient ZFS). The NMRD profiles are well reproduced with the set of parameters reported in Table 1, which clearly show that the improved r_1 values of the dimeric complexes and their frequency dependence can be well accounted for by the longer τ_R values, i.e. slower molecular tumbling. For the neutral dimer $[Gd_2PCTA_2(H_2O)_4]$, the τ_R value is more than double that reported for GdPCTA, confirming the almost total absence of

local rotational motions superimposed on the global molecular reorientation. This makes it possible to effectively translate the increase in molecular mass into a corresponding increase in τ_R. This is not entirely true for the other dimeric complex, $[Gd_2AAZTA_2(H_2O)_4]^{2-}$, where the increments of the molecular mass and τ_R are not entirely proportional. This suggests the occurrence of some degree of internal mobility through the CH_2 groups connecting the phenyl-bis-carbamate unit. Noteworthy, the values reported in Table 1 are the ionic relaxivities (per Gd^{3+}). The molecular relaxivities correspond to double values that, at 20 MHz and 298 K, are equivalent to ca. 24–25 mM^{-1}s^{-1}. It is also important to highlight that for these dimeric systems the r_1 values per Gd at the clinical fields of 1.5 and 3 T are significantly higher than those of the mononuclear complexes (at 310 K ca. 70% for $[Gd_2PCTA_2(H_2O)_4]$ and 68% for $[Gd_2AAZTA_2(H_2O)_4]^{2-}$) (Figure 3).

It is worth noting that, unlike the binuclear complexes herein reported, other binuclear GdDO3A-like complexes with xylene group as spacers were reported to form large supramolecular aggregates. The aggregates show high relaxivity values at low field (ca. 12 mM^{-1}s^{-1} at 20 MHz and 298 K), which drop down at higher field (>1 T) due to τ_R values in the order of 0.5–1 ns.[28]

In conclusion, we have reported the synthesis of the first binuclear Gd-complex of the 12-membered pyridine-based polyaminocarboxylate macrocyclic ligand PCTA by connecting

Table 1. Parameters obtained from the simultaneous analysis of ^{1}H NMRD profiles for $[Gd_2PCTA_2(H_2O)_4]$ and for $[Gd_2AAZTA_2(H_2O)_4]^{2-}$ compared to the related monomeric complexes.

Parameters	$[Gd_2PCTA_2(H_2O)_4]$	$[GdPCTA(H_2O)_2]$[a]	$[Gd_2AAZTA_2(H_2O)_4]^{2-}$	$[GdAAZTA(H_2O)_2]^{-}$[b]
$^{20}r_1^{298/310}$ (mM^{-1}s^{-1})	12.0/8.8	6.9/5.2	12.5/8.6	7.1/5.2
Δ^2 (10^{19} s^{-2})	2.6±0.2	5.9	3.1±0.1	2.2
τ_V^{298} (ps)	30.7±0.7	15	29.5±0.9	31
k_{ex}^{298} (10^6 s^{-1})	14.3	14.3	11.1	11.1
τ_R^{298} (ps)	163±2	70	145±1	74
r (Å)	3.1	3.1	3.1	3.1

[a] Ref. 24; [b] Ref. 25; * Values fixed in the fitting: the hydration number q; the distance between Gd^{3+} and the protons of the bound water molecule, r; the distance of closest approach, a, of the outer sphere water molecules to Gd^{3+} was set to 4.0 Å and for the relative diffusion coefficient D standard value of 1.7, 2.24 and 3.1×10^{-5} cm^{2}s^{-1} (at 283, 298 and 310 K, respectively).

two pyridine units via a simple C–C bond. This was achieved through two distinct synthetic procedures: 1) by synthesizing first the *p*-bromopyridine moiety already included in a protected pyclen macrocycle, followed by the Ni(0) catalysed homocoupling; 2) by synthesizing the 2,2′,6,6′-bromomethyl-substituted bis-pyridine by a multistep procedure, followed by the cyclization with a triaminotris-*t*Butylcarboxylate moiety. A dimeric AAZTA-ligand was also successfully synthesized with the purpose of collecting relaxometric data in parallel for two binuclear complexes of similar size but different molecular structure and thus be able to make a useful comparison.

The ^{1}H relaxometric study on $[Gd_2PCTA_2(H_2O)_4]$ and for $[Gd_2AAZTA_2(H_2O)_4]^{2-}$ highlighted the remarkable rigidity and compactness of the two binuclear complexes, which results in r_1 increases of ca. 80% at 1.5 T and 298 K ($+70\%$ at 310 K). In particular, $[Gd_2PCTA_2(H_2O)_4]$ showed a rotational correlation time more than doubled with respect to the monomeric GdPCTA complex, as a consequence of the zero-length linker between the two GdPCTA units. In the case of the binuclear AAZTA-like complex the relaxometric performance are in line with other dimeric AAZTA systems previously reported in the literature.[15e, 29]

It is also interesting to note that these binuclear complexes have a relaxivity about three times higher than commercial contrast agents ($q=1$), allowing the injection of lower doses of Gd^{III} and thus mitigating potential toxicity problems.

These data further confirm that the design and synthesis of binuclear Gd-complexes with high stereochemical rigidity represents an effective and simple strategy to achieve remarkable relaxivity enhancement at the magnetic field strengths useful for clinical applications (1.5–3). In the case of GdAAZTA systems, it has been highlighted that the kinetic inertness is much higher than that of linear GdDTPA or GdDTPA-bisamide complexes and can be highly improved by increasing the stereochemical rigidity with the inclusion of a cyclohexyl ring in the structure of the ligand.[6] On the other hand, being GdPCTA the most inert $q=2$ Gd-complex so far reported in the literature, a possible additional contribution from the presence of a well-defined second hydration sphere may further increase the relaxivity of this type of binuclear complex making it a valid alternative to the Gd-based CAs applied in clinics.

Finally, we would like to emphasize that pyclen-diacetates (PC2A) has been recently investigated as highly efficient ligands for Mn^{II}-based MRI contrast agents.[30] Thus the dimerization approach reported for Gd_2PCTA_2 can have further application also in the field of Mn^{II} agents.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

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