Synthesis and Relaxometric Properties of Gadolinium(III) Complexes of New Triazine-Based Polydentate Ligands

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Dedicated to Professor *Jean-Claude Bünzli* on the occasion of his 65th birthday

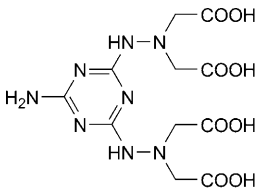
Two new derivatives based on an *s*-triazine structural motif were synthesized by attaching two 2,2′-hydrazinylidenebis[acetic acid] moieties to the triazine ring to reach an overall heptadenticity for the complexation of lanthanide(III) cations. The remaining reactive site was exploited for the substitution with a functionizable amino group (see H_4**L1**) and a lipophilic moiety (see H_4**L2**). Luminescence-lifetime determinations revealed the presence of a single H_2O molecule coordinated for [Eu(**L1**)]. A complete ^{1}H-NMR relaxometric study was carried out for the octacoordinated [Gd(**L1**)] and [Gd(**L2**)] complexes. A remarkably long H_2O residence lifetime ($^{298}\tau_M = 5.2$ μs) was found by ^{17}O-NMR in the case of [Gd(**L1**)]. Micelle formation of the lipophilic complex [Gd(**L2**)] was evidenced, the critical micellization concentration (cmc) determined, and relaxometric properties of the system investigated.

Introduction. – Chemical research in the field of contrast agents (CAs) has paralleled the rapid success of magnetic resonance imaging (MRI) as the predominant diagnostic technique in modern medicine [1–3]. To enhance the information content of an image and to shorten the time of acquisition, the use of CAs is often needed; in particular, the efforts have focused on Gd^{III} complexes because of the metal-related favorable features, among which *i*) the seven unpaired electrons, *ii*) the long electronic relaxation time, and *iii*) the high magnetic moment [4]. The evaluation of a CA is first carried out '*in vitro*' by assessing its relaxivity (r_{1p}), defined as the relaxation enhancement of the H_2O H-atoms in a solution containing the paramagnetic agent at a 1 mM concentration. Current commercial CAs consist of low-molecular-mass Gd^{III} complexes with polyaminopolycarboxylate chelates characterized by relaxivities of 4–5 mM^{-1} s^{-1} (20 MHz and 298 K) and a single coordinated H_2O molecule ($q = 1$). According to theory, the increase of the hydration state and/or H_2O exchange rate and slowing the tumbling of the complex can lead to high values of relaxivity. In fact, much

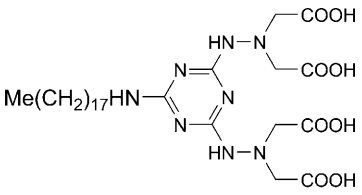
work has been done in the last decades to pursue such goals and thus to obtain optimal CAs [5].

The synthesis of ligands capable of forming Gd^{III} complexes with two (or more) H_2O molecules bound in the first (inner) coordination sphere has been an intriguing challenge as testified by the number of different approaches presented in the literature [6–11]. For this purpose, both acyclic and macrocyclic polyaminocarboxylate ligands have been thoroughly monitored to obtain Gd^{III} complexes with $q = 2$ without compromising thermodynamic and kinetic stabilities.

In this context, we designed a new series of ligands based on the common *s*-triazine (= 1,3,5-triazine) heterocyclic ring which is a well-known and tough structural motif for the construction of a large variety of interesting molecules, showing an outstanding ability in intermolecular interactions [12]. Cyanuric chloride (*i.e.*, 2,4,6-trichloro-1,3,5-triazine) is the cheap and versatile starting material for the straightforward preparation of highly structured molecules, as sequential reactivity of the three halogen atoms is easily controlled by the experimental conditions employed. Although both acyclic and cyclic pyridine-containing ligands have been reported for lanthanide ions [10][11], no examples with other heterocyclic rings involved in the coordination of the Ln^{III} ions are reported. We were then prompted to explore the possibility to employ the triazine ring as coordinating unit, relying on its structural versatility to implant auxiliary coordinating groups and tailor-made recognition moieties. The introduction of additional remote functional groups would allow conjugation of the corresponding complexes to macromolecules or biological targeting vectors. Two 2,2′-hydrazinylidenebis[acetic acid] moieties complete the overall heptadenticity of the ligand, to obtain a stable coordinating environment for lanthanide ions. Finally, the tritopic nature of *s*-triazine offers a third additional position where it is possible to locate a suitably designed R group; in the ligands H_4**L1** and H_4**L2** reported here, the variable R group is an amino group and a lipophilic amino group, respectively.



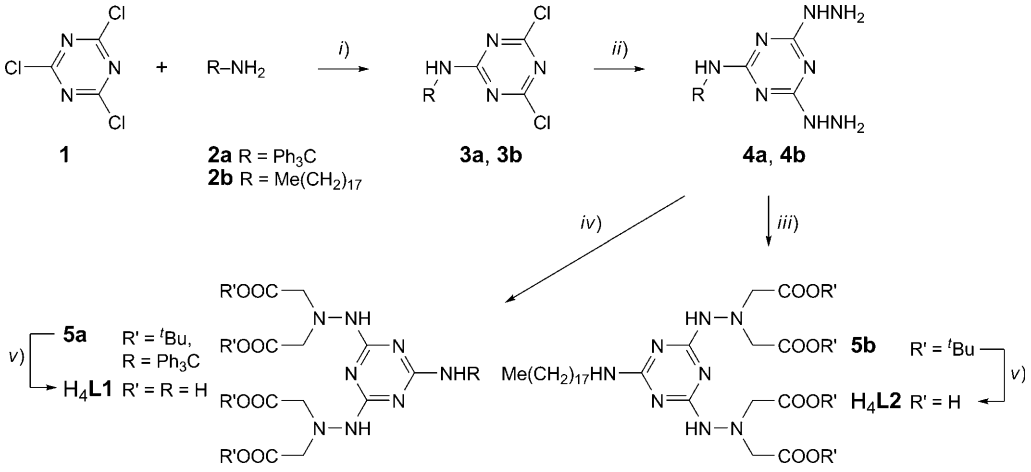
H_4**L1**



H_4**L2**

Results and Discussion. – *Synthesis.* The first step of the synthesis of H_4**L1** and H_4**L2** was accomplished, starting from cyanuric chloride (**1**), by reaction with tritylamine (**2a**) and octadecylamine(**2b**), respectively (*Scheme*). Hydrazine was then attached in both 4 and 6 positions of the triazinamines **3** (→ **4**) followed by tetraalkylation with *tert*-butyl bromoacetate (→ **5**). Deprotection of the *tert*-butyl esters (and trityl group for H_4**L1**) by acid hydrolysis with CF_3COOH gave rise to H_4**L1** and H_4**L2** in 24 and 32% overall yield respectively, starting from cyanuric chloride.

Scheme



i) Na_2CO_3, Et_2O, 0–5°, then r.t. *ii*) $NH_2NH_2 \cdot H_2O$, MeOH, r.t. or reflux. *iii*) $BrCH_2COO^tBu$, $^iPr_2NEt$, MeCN/toluene, 70–75°. *iv*) $BrCH_2COO^tBu$, K_2CO_3, MeCN, reflux. *v*) CF_3COOH/PhOMe, r.t.

Hydration-State Determination. The prepared novel free ligands H_4**L1** and H_4**L2** are heptadentate, and it was expected that they will give rise to lanthanide complexes with two inner-sphere H_2O molecules ($q = 2$). The most widely used method of assessing the hydration number of lanthanide complexes for a given ligand is based on the lifetime measurement of its respective Eu complex. Eu-Complex [Eu(**L1**)] has, therefore, been prepared to determine the hydration number q for the complexes of **L1**. The luminescence lifetimes measured in H_2O and D_2O are 0.67 and 1.92 ms, respectively. The hydration number q_{Eu} for an Eu complex is calculated with *Eqn. 1*, where τ_{H2O} and τ_{D2O} are the luminescence lifetimes in H_2O and D_2O, respectively, and the 0.25 term is the contribution of the second-sphere H_2O molecules [13]. The latter term is an estimate from previous empirical measurements [13]. Substituting the measured lifetime values in *Eqn. 1* gives a q value of 0.87 ± 0.06 for [Eu(**L1**)]. Based on this observation it should be assumed that the complex [Gd(**L1**)] is a monohydrated ($q = 1$) octadentate species, which is an unexpected result for this heptadentate ligand.

$$q_{Eu} = 1.2\ (1/\tau_{H_2O} - 1/\tau_{D_2O} - 0.25) \quad (1)$$

*Relaxometric Characterization. [Gd(**L1**)].* At 20 MHz and 298 K, the value of the water-proton relaxivity r_{1p} of [Gd(**L1**)] was measured to be 3.7 $mM^{-1}\ s^{-1}$, a value well below the expected range (4.5–6 $mM^{-1}\ s^{-1}$) for a Gd-complex endowed with one coordinated H_2O molecules ($q = 1$) [2][3]. This suggests the occurrence of a limitation of the relaxivity by a slow rate of H_2O exchange. This hypothesis is corroborated by the fact that the relaxivity at 310 K (3.9 $mM^{-1}\ s^{-1}$) is higher than at 298 K. The pH dependency of r_{1p} is shown in *Fig. 1* and provides some further useful information. The relaxivity is constant in the pH range 4 to 9, whereas it increases both at low pH and in the basic region. The observed behavior is reminiscent of a similar trend found in the

case of cationic Gd^{III} complexes with tetraamide derivatives of H_4DOTA (=1,4,7,10-tetraazacyclododecane-1,4,7-tetraacetic acid) which was accounted for in terms of a contribution of an acid- and base-catalyzed prototropic exchange to the overall H_2O exchange [14]. The prototropic contribution increases the effective H_2O exchange rate, k_{ex}, and then increases the relaxivity. Based on these observations, we can predict that [Gd(**L1**)] is characterized by a τ_M value ($\tau_M = 1/k_{ex}$ is the mean residence lifetime of the coordinated H_2O molecule) of the order of microseconds.

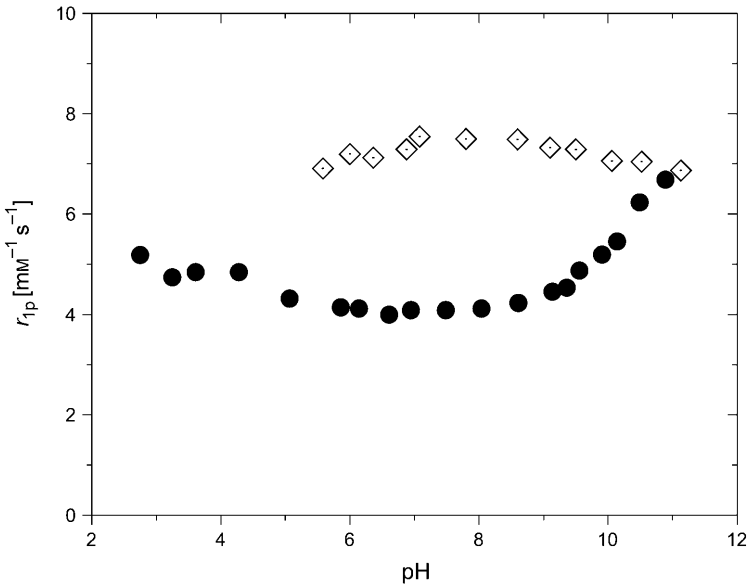


Fig. 1. *Plot of H-atom relaxivity* r_{1p} *at 20 MHz and 298 K* vs. *pH for [Gd(***L1***)]* (●) *and [Gd(***L2***)]* (◇)

The above qualitative considerations can find support in the determination and analysis of the magnetic-field dependence of the relaxivity, the so-called nuclear magnetic relaxation dispersion (NMRD) profile and in the temperature dependence of the ^{17}O-NMR transverse relaxation rate that provides direct information on the kinetic parameters of the H_2O exchange [15]. The NMRD profiles, measured at 298 and 310 K and at neutral pH are characterized by the typical shape and amplitude of monoaquo, low-molecular-mass complexes, featuring a single dispersion around 4–6 MHz (*Fig. 2*). The relaxivity is particularly low in the constant region at low fields, and it is higher at 310 than at 298 K over the entire range of the H-atom *Larmor* frequencies (0.01–70 MHz) investigated. Both these features are consistent with a slow rate of H_2O exchange. It is well known that in general, the NMRD profiles do not allow extracting accurate information on the parameters that characterize the H_2O exchange. These are conveniently evaluated through the association of variable-temperature ^{17}O-NMR study in a fairly concentrated solution of the paramagnetic complex. The R_{2p} data, measured at 9.4 T in an 10.9 mM aqueous solution of [Gd(**L1**)], show an increase when the temperature increases in the range 298–340 K (*Fig. 3*). The ^{17}O-NMR data were analyzed in terms of the *Swift–Connick* equations [15][16], whereas the NMRD

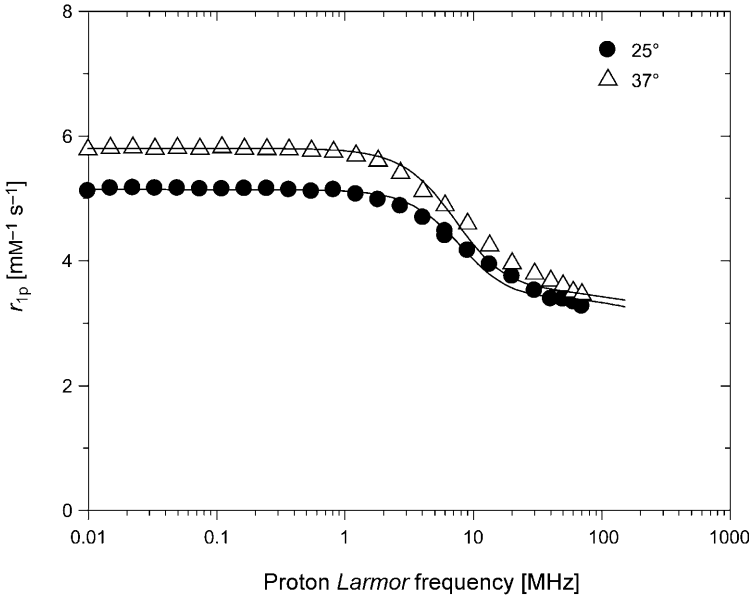


Fig. 2. *^{1}H-NMRD Relaxation data* (relaxivity r_{1p} *vs.* ^{1}H *Larmor* frequency) *for [Gd(***L1***)] at pH 7.2 and 298 K* (△) *and 310 K* (●). The solid lines represent the best results of the fitting to the experimental points (see *Table*).

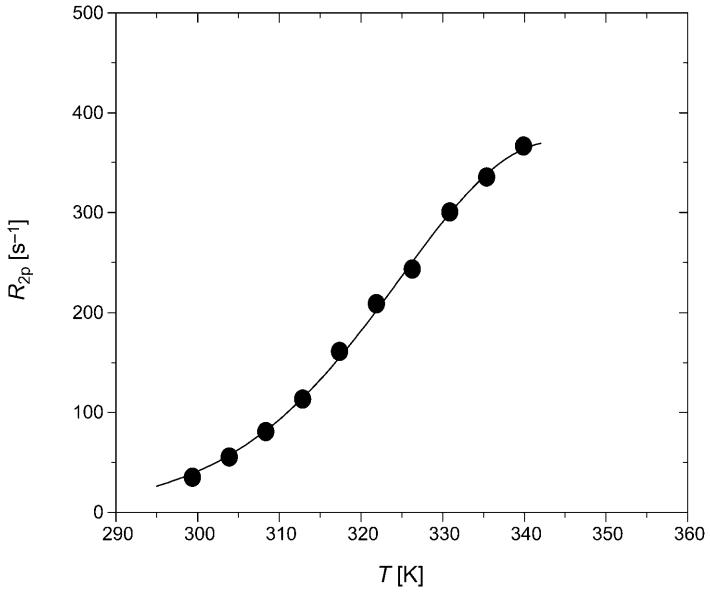


Fig. 3. *Plot of the paramagnetic contribution to the ^{17}O transverse relaxation rate* R_{2p} *as a function of temperature at 9.4 T* (12.2 MHz) *and neutral pH for a 10.9 mM aqueous solution of [Gd(***L1***)]*

profiles were fitted to the standard equations for the inner- (*IS*) and outer-sphere (*OS*)-relaxation contributions by fixing the values of the following parameters: the hydration number ($q = 1$), the Gd – H_w distance ($r = 3.0$ Å), the distance of closest approach of the bulk H_2O molecules ($a = 4.0$ Å) to the metal ion, and the relative diffusion coefficient ($D = 2.4 \cdot 10^{-5}$ cm^2 s^{-1}) for solute and solvent [1–3]. The best fit parameters are listed in the *Table* and clearly confirm the occurrence of a remarkably long residence lifetime of the bound H_2O molecule that represents a limitation to the relaxation efficacy of the complex: $^{298}\tau_M = 5.2$ μs ($^{298}k_{ex} = (1.9 \pm 0.1) \cdot 10^5$ s^{-1}). Whereas the other relaxation parameters are in the range of values typical of acyclic, low-molecular-mass Gd^{III} complexes, the H_2O-exchange rate of [Gd(**L1**)] is surprisingly slow, assuming a value which is observed for the first time in the case of an anionic, octacoordinate Gd^{III} complex for which an associative mechanism of exchange should be expected. Clearly, to find an explanation for this result, a careful elucidation of the exchange mechanism and structural information are needed. Based on the available data, we can only make the hypothesis of the presence of H-bonding interactions involving the bound H_2O molecule and the proximate NH groups, mediated by second-sphere H_2O molecules. This interaction could stabilize the bound H_2O molecule (as indicated by the high value of the enthalpy of activation, $\Delta H^{\#} = 63.6$ kJ/mol), and render more difficult the approach of a new H_2O molecule.

Table. *Selected Relaxation Parameters for [Gd(**L1**)] and [Gd(**L2**)] Derived from the Analysis of ^{17}O-NMR Data*[a]), *^1H-Relaxivity as a Function of Temperature* (20 MHz), *and Magnetic-Field Strength* (NMRD)[b])

Parameter	[Gd(**L1**)]	[Gd(**L2**)]
$^{310}r_{1p}$ [mM^{-1} s^{-1}]	4.0	44.8
$^{298}k_{ex}$ [10^6; s^{-1}]	0.19 ± 0.01	3.4 ± 0.3
ΔH_M [kJ mol^{-1}]	63.6 ± 2.8	35.0 ± 3.1
Δ^2 [10^{19}; s^{-2}]	7.8 ± 0.3	0.64 ± 0.03
$^{298}\tau_V$ [ps]	15 ± 1	45 ± 3
$^{298}\tau_{Rg}$ [ps]	74.6 ± 1.4	8200 ± 365
ΔH_{Rg} [kJ mol^{-1}]	17 ± 1	18 ± 1
$^{298}\tau_{RI}$ [ps]	–	1334 ± 108
ΔH_{RI} [kJ mol^{-1}]	–	16 ± 1
S^2	–	0.49 ± 0.01

[a]) [Gd(**L1**)]. [b]) For the parameters q, r, a, ΔH_V, and ^{298}D, the values of 1, 3.0 Å, 4.0 Å, 2.0 kJ mol^{-1}, and $2.24 \cdot 10^{-5}$ cm^2 s^{-1} were used, respectively.

The temperature dependence of the H-atom relaxivity was also measured at 20 MHz, and the data are shown in *Fig. 4*. The curve through the experimental data is the result of the analysis carried out as detailed in [17] and by using the parameters of the *Table*. The r_{1p} increases by lowering T from 335 to *ca.* 315 K, then it flattens and begins to decrease below *ca.* 300 K. A minimum is reached around 285 K, and then the relaxivity increases again with decreasing temperature. The overall behavior reflects the slow rate of exchange of the bound H_2O molecule and is the consequence of the opposite temperature dependence of the *IS* and *OS* contributions to the r_{1p} of [Gd(**L1**)], as shown in *Fig. 4* by the curves calculated with the parameters of the *Table*.

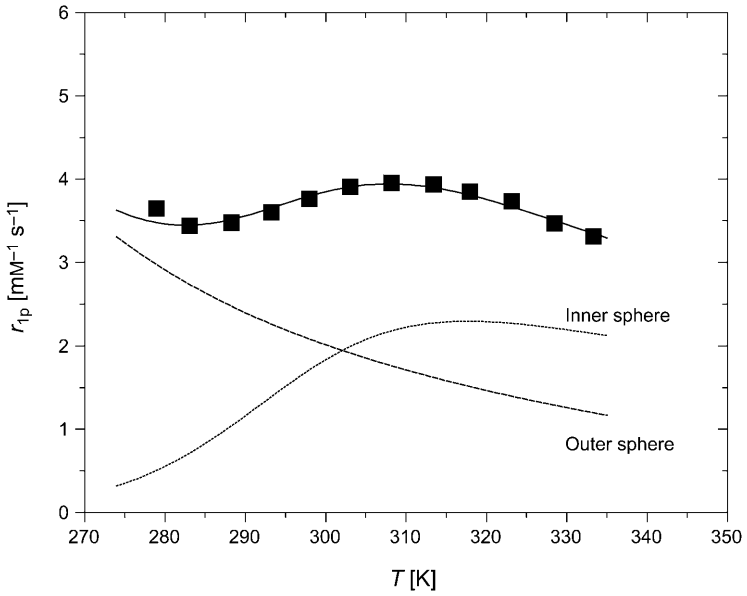


Fig. 4. *Temperature dependence of the ^{1}H relaxivity* r_{1p} *for [Gd(***L1***)] at 20 MHz and pH 7.2.* The solid line through the data points (■) represents the best result of the fitting to the experimental data (see *Table*); the calculated inner- and outer sphere contributions to the relaxivity are also represented.

*[Gd(***L2***)]*. The ability of the lipophilic analogue [Gd(**L2**)] to self-assemble into micelles was assessed by measuring the observed relaxation rate *vs.* concentration at 20 MHz and 298 K. Above the critical micellar concentration (cmc), the relaxation rate is the sum of two contributions, one arising from the monomeric complex (present at the concentration given by the cmc) and the second due to the aggregated form, *i.e.*, the micelles. Consequently, the H_2O H-atom relaxation rate of this paramagnetic system can be expressed as in *Eqn. 2* [18], where $r_1^{n.a.}$ and r_1^a are the relaxivities of the nonaggregated and aggregated forms, respectively, R_1^d is the relaxation rate of pure H_2O (0.38 s^{-1} at 20 MHz and 298 K), and C is the analytical concentration of Gd^{III}. Clearly, the relaxivity of the free complex, $r_1^{n.a.}$, is simply expressed by *Eqn. 3*. By plotting $R_1^{obs} - R_1^d$ as a function of the parameter C, $r_1^{n.a.}$, and r_1^a can be obtained by fitting *Eqns. 2* and *3*, as shown in *Fig. 5*.

$$R_1^{obs} - R_1^d = (r_1^{n.a.} - r_1^a)\,\mathrm{cmc} + r_1^a\ C \tag{2}$$

$$R_1^{obs} - R_1^d = r_1^{n.a.}\ C \tag{3}$$

At 20 MHz and 298 K, the relaxivity of [Gd(**L2**)] is 20.2 ± 0.9 mM^{-1} s^{-1} below the cmc, whereas the relaxivity of the aggregated form is 36.7 ± 0.3 mM^{-1} s^{-1}, and the cmc is 0.056 ± 0.002 mM. A scrupulous study of the micellization and relaxometric properties was previously reported for a series of [Gd(DOTA)] derivatives substituted with aliphatic chains of increasing length [19]. As expected, the cmc decreases following the lengthening of the chain from C_{10} to C_{18}, and for the latter, a cmc of 0.06 mM was found,

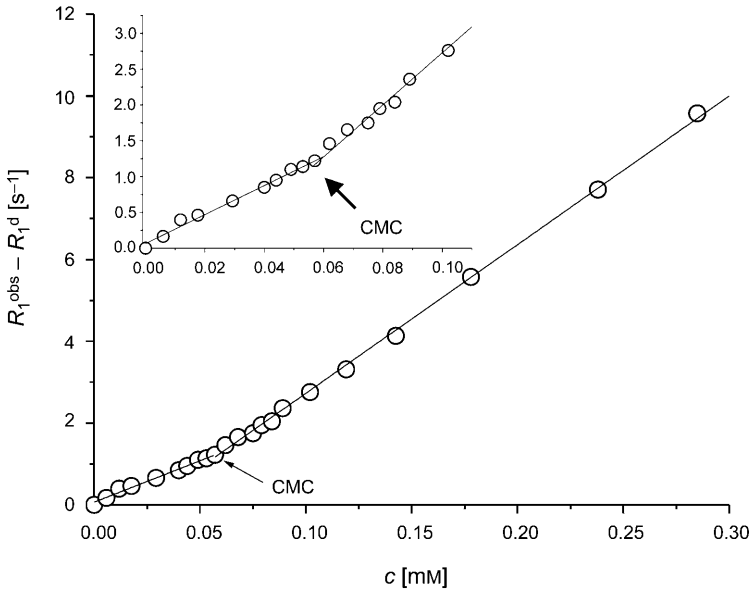


Fig. 5. *Plot of the H_2O ^1H longitudinal relaxation rate at 20 MHz and 298 K as a function the total Gd^{III} concentration for [Gd(***L2***)] and least-squares fit according to* Eqn. 2

in perfect agreement with the value found for [Gd(**L2**)], a complex functionalized with the same pendant aliphatic chain. On the other hand, the r_1^a value for [Gd(**L2**)] is sensibly higher than those found in the case of other (monoaquo) gadolinium(III) complexes bearing a ligand with an aliphatic chain of comparable length ($r_{1p}^a \approx 17-22$ mM^{-1} s^{-1}). To investigate this and other aspects, NMRD profiles were recorded in the frequency range 0.01 to 70 MHz at 298 (*Fig. 6*), 310, and 318 K. The profiles present small differences in their amplitudes but share a general shape with a broad hump centered around 20 MHz, typical of slowly tumbling macromolecular systems. Furthermore, the relaxivity values increase on passing from 298 to 318 K, indicating the occurrence of a relatively slow rate of H_2O exchange that represent a limiting factor to the relaxivity.

The analysis of the NMRD profiles requires a different approach since the presence of a relatively fast local rotation of the complex about the main axis of the aliphatic chain superimposed to the global motion of the micellar aggregate needs to be taken into account. This is possible by incorporating the description of the rotational dynamics according to the model-free *Lipari–Szabo* approach into the *Solomon–Bloembergen–Morgan* equations for the *IS* relaxation mechanism [20]. This model allows separating the contribution of the overall global rotation of the paramagnetic micelle (τ_{Rg}) from the contribution of a faster local motion (τ_{Rl}) due to the free rotation of the coordination cage about the aliphatic chain. The correlation of the two types of motions is described by the parameter S^2 whose value is comprised between zero (completely independent motions) and one (totally correlated motions). A least-square fit of the data was performed at 298 K (*Fig. 6*) by fixing the values of q, r, a, and

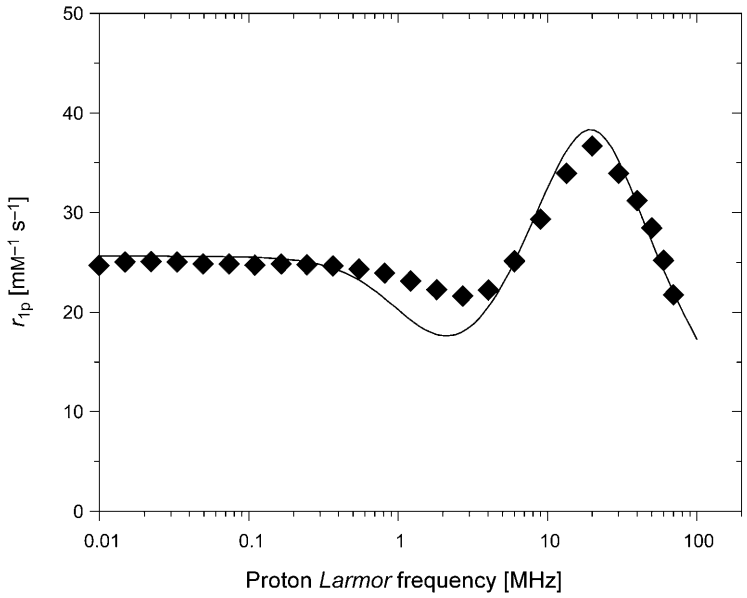


Fig. 6. *^{1}H-NMRD profile* (relaxivity r_{1p} *vs.* ^{1}H *Larmor* frequency) *of [Gd(***L2***)] at pH 7.2 and 298 K at a concentration above the cmc* (0.3 mM). The solid curve through the data points is calculated with the parameters reported in the *Table*.

D and treating as variable parameters Δ^2, τ_V, τ_M, τ_{Rg}, τ_{Rl}, and S^2. The best-fit parameters are listed in the *Table* and indicate that a significantly lower rotational dynamics of the micellar system together with a faster rate of H_2O exchange are responsible of the high relaxivity values. In fact, the global reorientational correlation time is from three to four times longer than for corresponding complexes in the aggregated form based on the DOTA chelating unit, and this suggests a larger dimension of the micelles formed by [Gd(**L2**)]. On the other hand, the value of the order parameter, $S^2 = 0.49$, is rather close to those of the related systems, indicating a similar degree of rotational flexibility about the aliphatic chain.

Since the residence lifetime of the coordinated H_2O molecule is only roughly estimated from the analysis of the NMRD profiles, we decided to obtain an independent evaluation of τ_M from the temperature dependence of the H-atom relaxivity. The data were obtained in the temperature interval 274–333 K and are reported in *Fig. 7*. The relaxivity increases with temperature up to *ca.* 320 K where a broad hump is formed, and then it starts to decrease above 330 K. Clearly, this behavior appears to be dictated by the contribution of the *IS* relaxivity that is severely limited by the slow H_2O-exchange rate and then reproduces its temperature dependence. In the fitting procedure, the relaxation parameters were fixed to the value obtained from the refinement of the NMRD profiles, with the exception of their enthalpy of activation and $^{298}\tau_M$ that were let to vary. A good fit of the data is obtained with a $^{298}\tau_M$ value of 0.3 μs. This value is in very good agreement with that estimated from NMRD data, and it is significantly shorter (one order of magnitude) than that found for [Gd(**L1**)].

Finally, it is worth observing that this result is also in agreement with the pH dependency of the relaxivity (*Fig. 1*). Unlike the behavior observed for [Gd(**L1**)], in the case of [Gd(**L2**)], the increase of the relaxation rate with pH in the basic region is sensibly attenuated, as a result of a shorter value of the H_2O residence lifetime.

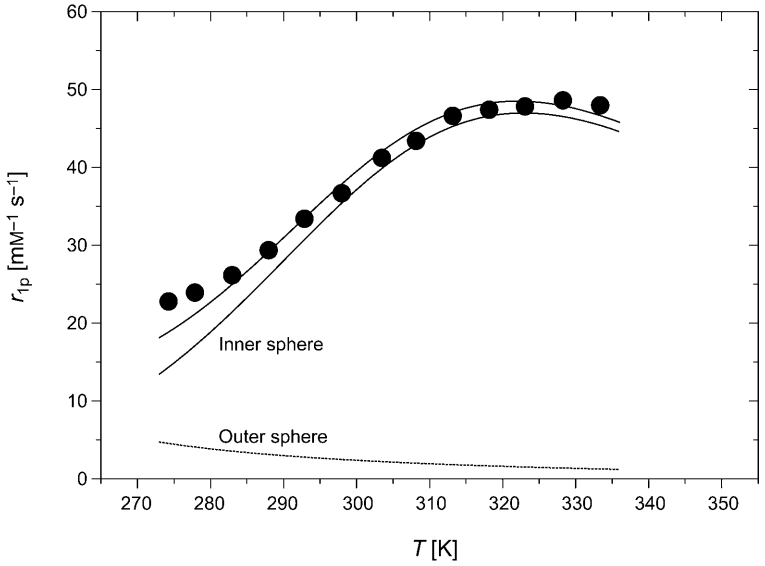


Fig. 7. *Variable-temperature ^{1}H-NMR relaxation data* (relaxivity r_{1p}) *for [Gd(***L2***)] at 20 MHz and at a concentration above the cmc* (0.25 mM), *normalized to 1 m*M *concentration of Gd.* The solid line through the data points (●) represents the best result of the fitting to the experimental data (see the *Table*); the calculated inner- and outer-sphere contributions to the relaxivity are also represented.

Conclusions. – Two novel, potentially heptadentate triazine-containing aminocarboxylic ligands were synthesized and characterized. Unexpectedly, the corresponding Gd^{III} complexes possess a single H_2O molecule in their inner coordination sphere. Thus, [Gd(**L1**)] and [Gd(**L2**)] represent rare examples of monoaquo octacoordinate Gd^{III} complexes in aqueous media. The exchange rate of the coordinated H_2O molecule is remarkably low, another unusual property for Gd^{III} chelates characterized by an octacoordinate ground state. Presumably, both electronic and structural effects are responsible for these findings that need further studies for their elucidation. In addition, for [Gd(**L2**)], only differing from [Gd(**L1**)] by the presence of a C_{18} aliphatic chain in place of an amino H-atom, the H_2O residence lifetime is significantly reduced. This lipophilic complex forms large micellar aggregates at low concentration which show high relaxivity values in spite of the presence of a high degree of flexibility due to local rotation about the aliphatic chain.

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Experimental Part

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. CC = Column chromatography.

4,6-Dichloro-N-*(triphenylmethyl)-1,3,5-triazin-2-amine* (**3a**). The 2,4,6-trichloro-1,3,5-triazine (2.84 g, 15.4 mmol) and Na_2CO_3 (1.96 g, 18.5 mmol) were suspended in Et_2O (27 ml). To the stirred and cooled (ice-bath) suspension, tritylamine (4.00 g, 15.4 mmol) was added portionwise, then the ice-bath was removed, and the mixture was stirred at r.t. for 20 h. The mixture was filtered and the solid washed with CH_2Cl_2. The combined filtrate and washings were concentrated, and the residue was recrystallized from AcOEt/petroleum ether: pure **3a** (4.00 g, 64%). White solid. M.p. 293–294°. ^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): 7.34–7.22 (*m*, 15 H); 7.13 (br. *s*, 1 H). ^{13}C-NMR (75.4 MHz, $CDCl_3$, 298 K): 170.0 (*s*); 169.6 (*s*); 165.7 (*s*); 143.2 (*s*); 128.8 (*d*); 128.2 (*d*); 127.5 (*d*); 71.9 (*s*). ESI-MS: 417.2 ($[M+Na]^+$), 419.2 ($[M+H]^+$); calc. for $C_{22}H_{16}Cl_2N_4$, 416.1 and 418.1.

4,6-Dihydrazinyl-N-*(triphenylmethyl)-1,3,5-triazin-2-amine* (**4a**). A soln. of **3a** (2.50 g, 6.14 mmol) in $NH_2NH_2 \cdot H_2O$ (3.88 ml, 80 mmol) and MeOH (15 ml) was stirred at r.t. for 48 h. The mixture was then cooled and filtered, and the solid residue was washed thoroughly with aq. MeOH and subsequently dried *in vacuo:* **4a** (2.13 g, 87%). White solid. M.p. 252–254°. ^{1}H-NMR (300 MHz, (D_6)DMSO, 298 K): 7.52 (br. *s*, 2 H); 7.38–7.12 (*m*, 15 H); 6.88 (br. *s*, 1 H); 3.18 (br. *s*, 4 H). ^{13}C-NMR (75.4 MHz, (D_6)DMSO, 363 K): 167.7 (*s*); 165.9 (*s*); 146.3 (*s*); 129.2 (*d*); 128.0 (*d*); 126.8 (*d*); 70.4 (*s*). ESI-MS: 399.3 ($[M+H]^+$), 243.5 (Ph_3C^+); calc. for $C_{22}H_{22}N_8$, 398.2.

*Tetra(*tert*-butyl) 2,2′,2″,2‴-{[6-[(Triphenylmethyl)amino]-1,3,5-triazine-2,4-diyl]dihydrazin-2-yl-1-ylidene}tetrakis[acetate]* (**5a**). Compound **4a** (2.00 g, 5.03 mmol) and powdered anh. K_2CO_3 (4.16 g, 30.2 mmol) were suspended in MeCN (15 ml). *tert*-Butyl bromoacetate (3.70 ml, 25.1 mmol) was added dropwise, and then the suspension was refluxed for 6 h. Inorg. salts were removed by filtration, and the filtrate was concentrated. The residue was then purified by CC (AcOEt/petroleum ether 3:7 → 5:5): pure **5a** (2.40 g, 57%). Off-white solid. M.p. 203–205°. ^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): 7.32–7.12 (*m*, 17 H); 3.72 (br. *s*, 8 H); 1.42 (*s*, 36 H). ^{13}C-NMR (75.4 MHz, $CDCl_3$, 298 K): 169.6 (*s*); 166.4 (*s*); 165.9 (*s*); 145.5 (*s*); 129.1 (*d*); 127.7 (*d*); 126.8 (*d*); 81.7 (*s*); 70.5 (*s*); 57.8 (*t*); 28.2 (*q*). ESI-MS: 855.3 ($[M+H]^+$), 634.2 ($[M+Na-Ph_3C]^+$), 612.4 ($[M+H-Ph_3C]^+$), 578.5 ($[M+Na-Ph_3C-{}^t\!Bu]^+$), 243.5 (Ph_3C^+); calc. for $C_{46}H_{62}N_8O_8$, 854.5.

2,2′,2″,2‴-[(6-Amino-1,3,5-triazine-2,4-diyl)dihydrazin-2-yl-1-ylidene]tetrakis[acetic Acid] (H_4**L1**). The ester **5a** (500 mg, 0.585 mmol) was dissolved in a mixture of CF_3COOH (20 ml) and anisole (5 ml) and stirred at r.t. overnight. The waxy residue obtained after vacuum evaporation was dissolved in MeOH (2 ml), and excess Et_2O was added dropwise leading to the precipitation of an off-white solid. The latter was washed thoroughly with Et_2O, then dried *in vacuo* to constant weight: H_4**L1** (172 mg, 76%). Amorphous white solid. ^{1}H-NMR (300 MHz, $D_2O + K_2CO_3$, 298 K): 3.53 (br. *s*, 8 H). ^{13}C-NMR (75.4 MHz, $D_2O + K_2CO_3$, 298 K): 177.9 (*s*); 166.0 (*s*); 165.1 (*s*); 59.2 (*t*). ESI-MS: 411.2 ($[M+Na]^+$), 389.2 ($[M+H]^+$); calc. for $C_{11}H_{16}N_8O_8$, 388.1.

4,6-Dichloro-N-*octadecyl-1,3,5-triazin-2-amine* (**3b**). As described for **3a**, with 2,4,6-trichloro-1,3,5-triazine (2.84 g, 15.4 mmol), Na_2CO_3 (1.96 g, 18.5 mmol), Et_2O (50 ml), and octadecylamine (4.16 g, 15.4 mmol; addition within 30 min); at r.t. overnight. After washing with hot AcOEt and evaporation, the residue was submitted to flash chromatography (AcOEt/petroleum ether 5:95): **3b** (5.60 g, 87%). White solid. M.p. 293–294°. ^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): 6.36 (*t*, *J* = 5.3, 1 H); 3.47 (*q*, *J* = 6.7, 2 H); 1.59 (*quint.*, *J* = 7.1, 2 H); 1.30–1.18 (*m*, 30 H); 0.86 (br. *t*, *J* = 6.6, 3 H). ^{13}C-NMR (75.4 MHz, $CDCl_3$, 298 K): 171.2 (*s*); 169.7 (*s*); 165.9 (*s*); 41.7 (*t*); 32.0 (*t*); 29.8 (8*t*); 29.7 (*t*); 29.6 (*t*); 29.5 (*t*); 29.4 (*t*); 29.2 (*t*); 29.1 (*t*); 26.7 (*t*); 22.8 (*t*); 14.2 (*q*). ESI-MS: 429.1 and 431.1 ($[M+Na]^+$), 417.3 and 419.3 ($[M+H]^+$); calc. for $C_{21}H_{38}Cl_2N_4$, 416.2 and 418.3.

4,6-Dihydrazinyl-N-*octadecyl-1,3,5-triazin-2-amine* (**4b**). As described for **4a**, with **3b** (1.10 g, 2.64 mmol), $NH_2NH_2 \cdot H_2O$ (6.0 ml, 124 mmol) and MeOH (10 ml); at 80° for 4 h. Washing with H_2O: **4b** (770 mg, 72%). White solid. M.p. 152–154°. ^{1}H-NMR (300 MHz, (D_6)DMSO, 298 K): 6.32–6.19 (*m*, 2 H); 3.38 (*m*, 4 H); 2.96 (br. *t*, *J* = 7.5, 2 H); 1.46 (br. *quint.*, 2 H); 1.32–1.15 (*m*, 30 H); 0.84 (br. *t*, *J* = 6.5, 3 H). ^{13}C-NMR (75.4 MHz, (D_6)DMSO, 298 K): 168.9 (*s*); 165.8 (*s*); 46.2 (*t*); 31.8 (*t*); 29.7 (9*t*); 29.8 (2*t*); 29.6 (*t*); 28.2 (*t*); 27.2 (*t*); 22.8 (*t*); 13.9 (*q*). ESI-MS: 409.5 ($[M+H]^+$); calc. for $C_{21}H_{44}N_8$, 408.4.

*Tetra(*tert*-butyl) 2,2′,2″,2‴-{[6-(Octadecylamino)-1,3,5-triazine-2,4-diyl]dihydrazin-2-yl-1-ylidene}-tetrakis[acetate]* (**5b**). To a suspension of **4b** (1.50 g, 3.68 mmol) in a mixture of MeCN (10 ml) and toluene (30 ml), $^{i}Pr_2NEt$ (4.45 ml, 25.7 mmol) was added, followed by dropwise addition of *tert*-butyl bromoacetate (2.71 ml, 18.40 mmol). The milky suspension was stirred and heated to 70–75° for 3.5 h. Volatiles were evaporated, then the residue was partitioned between CH_2Cl_2 and 10% aq. Na_2CO_3 soln. The org. extract was dried (Na_2SO_4) and evaporated and the residue purified by CC (AcOEt/petroleum ether 2 : 8 → 3 : 7): pure **5b** (1.96 g, 62%). Light yellow viscous oil. ^{1}H-NMR (300 MHz, $CDCl_3$, 298 K): 6.94 (br. *s*, 2 H); 3.71 (*s*, 8 H); 3.28 (*m*, 2 H); 1.43 (*m*, 2 H); 1.39 (*s*, 36 H); 1.21 (*m*, 30 H); 0.83 (br. *t*, J = 7.1, 3 H). ^{13}C-NMR (75.4 MHz, $CDCl_3$, 298 K): 169.1 (*s*); 166.6 (*s*); 166.2 (*s*); 81.4 (*s*); 60.9 (*t*); 57.9 (*t*); 40.8 (*t*); 31.9 (*t*); 29.6 (10*t*); 29.4 (*t*); 29.3 (*t*); 28.1 (*t*); 27.6 (*t*); 26.9 (*t*); 22.6 (*t*); 14.0 (*q*). ESI-MS: 887.3 ($[M+Na]^+$), 865.5 ($[M+H]^+$); calc. for $C_{45}H_{84}N_8O_8$, 864.6.

2,2′,2′,2″-{[6-(Octadecylamino)-1,3,5-triazine-2,4-diyl]dihydrazin-2-yl-1-ylidene}tetrakis[acetic acid] (H_4**L2**). As described for H_4**L1**, with **5b** (610 mg, 0.705 mmol), CF_3COOH (10 ml), and anisole (2 ml): H_4**L2** (371 mg, 82%). Off-white amorphous solid. ^{1}H-NMR (300 MHz, CD_3OD, 323 K): 3.90 (*m*, 8 H); 3.34 (*t*, J = 7.1, 2 H); 1.54 (br. *quint.*, 2 H); 1.36–1.22 (*m*, 30 H); 0.89 (*t*, J = 6.7, 3 H). ^{13}C-NMR (75.4 MHz, CD_3OD, 323 K): 171.6 (*s*); 164.1 (*s*); 157.3 (*s*); 156.6 (*s*); 57.2 (*t*); 41.0 (*t*); 31.8 (*t*); 29.4 (12*t*); 29.1 (*t*); 29.0 (*t*); 26.6 (*t*); 22.4 (*t*); 13.1 (*q*). ESI-MS: 663.3 ($[M+Na]^+$), 641.3 ($[M+H]^+$); calc. for $C_{29}H_{52}N_8O_8$, 640.4.

Gd^{III} Complexes. The Gd^{III} complexes were prepared by mixing stoichiometric amounts of the chloride salt to an aq. soln. of the corresponding ligand and monitoring the formation of the complex by measurement of the solvent H-atom relaxation rate ($1/T_1$) while keeping a constant neutral pH with 1M NaOH. The final solns. were checked with the orange xylenol test [21] and accepted for characterization when free $[Gd^{III}] < 1\%$.

Eu^{III} Complexes. The Eu^{III} complexes were prepared by mixing 10% excess of the chloride salt to an aq. soln. of the corresponding ligand, keeping a constant neutral pH with 1M NaOH. The excess of metal ions was removed by precipitation as hydroxide at basic pH followed by centrifugation.

Luminescence Lifetime Measurements. The luminescence lifetime measurements were carried out on a *Fluorolog* fluorometer with a photomultiplier tube, electronics, and software supplied by *Horiba Jobin Yvon*. *Horiba Jobin Yvon Spectraled* source was used to directly excite the Eu^{III} ion at 395 nm, as spectral measurements have not shown any significant sensitization of the Eu emission by the triazine ring. The lifetime measurement was carried out with the DataStation v2.5 software. The subsequent data analysis was performed with the DAS6 v6.4 software.

^{1}H-NMR Relaxometric Measurements. The H_2O H-atom longitudinal relaxation rates of dil. aq. solns. of complexes [Gd(**L1**)] and [Gd(**L2**)] were measured with a *Stelar-Spinmaster* spectrometer (*Mede*, Italy) operating at 0.5 T and 298 K. For the measurement of the relaxation rates, the standard inversion-recovery method was employed (16 experiments, 4 scans) with a typical 90° pulse width of 3.5 ms, and the reproducibility of the T_1 data was ±0.5%. The temp. was controlled with a *Stelar-VTC-91* air-flow heater equipped with a copper-constantan thermocouple (uncertainty ±0.1°). The H-atom $1/T_1$ NMRD profiles were measured on a fast field-cycling *Stelar-Spinmaster-FFC* relaxometer over a continuum of magnetic-field strengths from 0.00024 to 0.5 T (corresponding to 0.01–20 MHz H-atom *Larmor* frequencies). The relaxometer operates under computer control with an absolute uncertainty in $1/T_1$ of ±1%. Additional data points at 20–70 MHz were obtained on a *Stelar* relaxometer.

^{17}O-NMR. Variable-temp. ^{17}O-NMR measurements were recorded on a *Jeol-ECP-400* (9.4 T) spectrometer equipped with a 5 mm probe and a standard temp.-control unit. Aq. solns. of the complexes containing 2.8% of the ^{17}O isotope (*Cambridge Isotope*) were used. The observed transverse relaxation rates (R_2^{obs}) were calculated from the signal width at half-height ($\Delta\nu_{1/2}$): $R_2^{obs} = \pi \times \Delta\nu_{1/2}$.

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