Relaxivity Studies on a Gadolinium(III) Complex of a Macrocyclic DTPA Derivative

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The dinuclear Gd^{3+} complex of the 30-membered cyclic DTPA derivative, cy(DTPA-en-DTPA-en), was studied by various NMR spectroscopic techniques in order to evaluate the parameters governing its relaxivity. The values obtained were compared with those for Gd(DTPA-BMA), which is an acyclic mononuclear analogue. Because of the increase in molecular weight the relaxivity r_1 =5.25 $s^{-1}mM^{-1}$ (20 MHz, 37 °C) is higher than that of the monomeric analogue (4.2 $s^{-1}mM^{-1}$). The rotational correlation time at 298 K, τ_R^{298} was determined to be 175–188 ps, which is significantly higher than that expected, based on the increase in the molecular volume of the acyclic compared to the cyclic compound. Possibly, the cyclic nature of the ligand induces steric constraints in Gd[cy(DTPA-en-DTPA-en)], which reduce the local mobility. The water exchange rate for this complex (k_{ex}^{298} = 2.9×10^5 s^{-1}) is somewhat smaller than that of Gd(DTPA-BMA) (k_{ex}^{298} = 4.5×10^5 s^{-1}), which suggests that the water exchange rates are different in the various isomers of acyclic Gd-DTPA-bisamides.

Introduction

Chelates of Gd^{3+} have found widespread application as contrast agents for MRI (Magnetic Resonance Imaging).[1−3] The paramagnetic Gd^{3+} ion in these compounds has an enhancing effect on the relaxation rate of the water protons in its proximity, which may lead to an increase in the quality of the images and a decrease of the recording time. The encapsulation of Gd^{3+} into a strongly chelating ligand is necessary, since the Gd^{3+} aquo ion is highly toxic, whereas the chelates are not. The currently commercially available MRI contrast agents are derivatives of either the acyclic DTPA (DTPA = diethylenetriamine-*N*,*N*,*N*′,*N*′′,*N*′′-pentaacetate) or the macrocyclic ligand DOTA (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate). Both types of Gd^{3+} complexes have been shown to be very suitable for this application, because of their high in vivo thermodynamic and kinetic stabilities. It is important that the chelating ligand leaves enough space on the Gd^{3+} ion for the coordination of a water molecule, which exchanges with the bulk to provide an overall reduction of the water proton relaxation rate.

The overwhelming success of the MRI contrast agents and the rapid development of the MRI technique have given rise to a continuing demand for new generations of contrast agents that are more effective and selective. Extensive studies in this field have shown that higher relaxivities, r_1 (enhancement of the water proton relaxation rate, expressed in $s^{-1}mM^{-1}$ Gd^{3+}), may be achieved, for example, by: (i) the design of the environment of the water coordination site, so that the water exchange rate will not limit the overall relaxivity ($\tau_m < T_{1m}$, with τ_m being the residence time of a water molecule in the first coordination sphere, and T_{1m} its proton longitudinal relaxation time), or (ii) an increase of the molecular weight of the compounds, in order to increase τ_R and thus the relaxivity, or (iii) by attaching substituents onto the ligand so that a higher tissue specificity is obtained.

Here, we report on a comprehensive study of the parameters that govern the relaxivity of the dinuclear Gd^{3+} complex of the 30-membered macrocycle cy(DTPA-en-DTPA-en),[4,5] also referred to as L (see Figure 1), using variable temperature ^{17}O and ^2H NMR spectroscopic measurements, and ^1H NMR longitudinal relaxation rate measurements at variable magnetic fields (NMRD profiles).

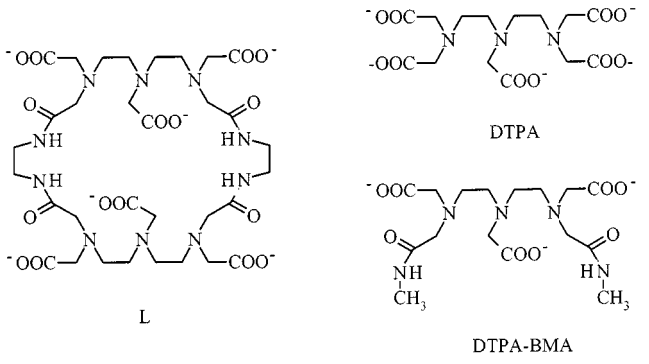

Figure 1. Chemical structure of the cy(DTPA-en-DTPA-en) ligand (L), DTPA and DTPA-BMA

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Ligand L can be considered as a cyclic dimer of DTPA-bis(methylamide) (DTPA-BMA) and features several interesting aspects which may be of relevance to its relaxivity: (i) the distance between the two Gd^{3+} ions in the dinuclear complex is relatively small (7.1 Å),[6] which might result in magnetic coupling and a concomitant effect on the electronic relaxation, (ii) Gd_2L has a higher molecular weight than Gd(DTPA-BMA), which may result in a smaller tumbling rate and (iii) intramolecular fluctuations are reduced due to the cyclic nature of the ligand. Furthermore, the number of diastereomeric pairs is reduced from 4 to 2 upon the 'cyclization' of DTPA-BMA[5] and, therefore, this compound may afford information on possible differences in water exchange rates between the various diastereomers of Gd^{3+} complexes of DTPA derivatives. Recently, it has been shown that subtle differences in the coordination geometry of the lanthanide ion in chelates, with macrocyclic derivatives of cyclen, has a profound effect on the rate of exchange between the bound water and the bulk.[7–12]

Results and Discussion

NMRD Measurements

The complex Gd_2L was investigated by water ^1H longitudinal relaxation time measurements at several temperatures (5, 15, 25, 37, and 45 °C) and magnetic field strengths varying between 2.5×10^{-4} T and 1.2 T (NMRD) in order to assess the relaxation processes in this system (see Figure 2). The profiles were fitted using the Solomon–Bloembergen–Morgan equations, to obtain the inner-sphere relaxation, along with the Freed equations for the outer-sphere contribution. Using these well-established procedures[13] may afford the values of the parameters that determine the overall relaxivity of Gd_2L. Since the NMRD curves are rather featureless and the number of parameters is large, first τ_m and τ_R were determined independently using other techniques. Previous studies have shown that variable temperature ^{17}O NMR spectroscopy is a very suitable technique for evaluating accurate values for water exchange rates.[13] Discrepancies often exist between τ_R values obtained from ^{17}O NMR spectroscopy and those obtained from NMRD. Therefore, these values were determined independently with the use of ^2H longitudinal relaxation rates. The advantage of ^2H relaxation for the determination of τ_R is that it is fully controlled by quadrupolar interactions (see below), while for the ^{17}O longitudinal relaxation, a dipole-dipole contribution also has to be taken into account.[14]

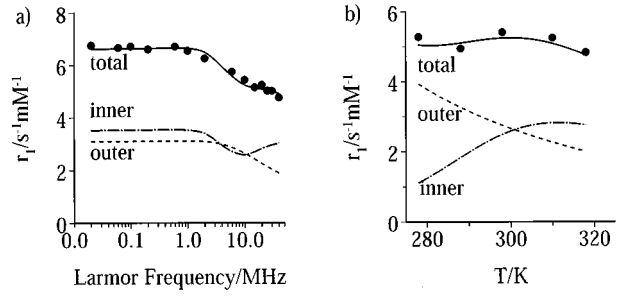

Figure 2. (a) NMRD profile of Gd_2L at 310 K. The lines are calculated using the values for the parameters as mentioned in Table 1. (b) Temperature dependence of the relaxivity of Gd_2L at 20 MHz

Variable Temperature ^2H NMR Spectroscopy

The cyclic ligand L deuterated at the methylene moieties of the acetate groups was synthesized in a similar manner to the unlabeled compound[4] which is by condensation of the bisamide of DTPA and ethylenediamine with DTPA-bisanhydride. However, deuterated DTPA was now used as the starting compound. The latter was obtained by refluxing a solution of DTPA in D_2O at pD 10.6 for 24 hours.[15] Subjecting the cyclic ligand L to similar reaction conditions leads to the hydrolysis of the amide bonds.[16]

The ^2H longitudinal relaxation time T_1 of La_2L, the diamagnetic analogue of the Gd^{3+} complex under study, was measured at different temperatures (see Figure 3). The rotational correlation time (τ_R) was calculated from the data using Equation (1), where χ is the quadrupolar coupling constant ($\chi = 1.06\times10^6$ rad s^{-1}) and η is an asymmetry factor which is negligible for the C-^2H bond. From the temperature dependence of the rotational correlation times, the values of $\tau_R^{298} = 175$ ps and an activation energy $E_R = 22.1$ kJ mol^{-1} were calculated using Equation (2).

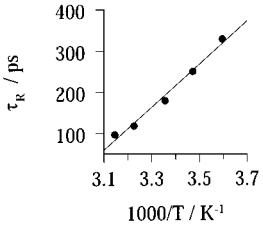

Figure 3. Temperature dependence of τ_R of La_2L, as determined from ^2H longitudinal relaxation rates as calculated from the experimental T_1 values using Equation (1)

$$\frac{1}{T_1}\left(^2H\right) = \frac{3\pi^2}{10}\frac{2I+3}{I^2(2I-1)}\chi^2\left(1+\eta^2/3\right)\tau_R \quad (1)$$

$$\tau_R = \tau_R^{298}\exp\left(\frac{E_R}{R}\left(\frac{1}{T}-\frac{1}{298.15}\right)\right) \quad (2)$$

Variable Temperature ^{17}O NMR Spectroscopy

The water exchange rate ($k_{ex} = \tau_m^{-1}$) of Gd_2L was determined from a variable temperature ^{17}O NMR spectroscopic study (chemical shifts and longitudinal and transversal relaxation rates). The total set of data (see Figure 4) enables the determination of a number of parameters including the rotational correlation time (τ_R), the hyperfine coupling constant ($A/\hbar$), and parameters concerning the electronic relaxation, τ_V (the correlation time for the zero-field splitting),

E_V (the activation energy for the latter process) and Δ^2 (the trace of the square of the zero-field splitting tensor).

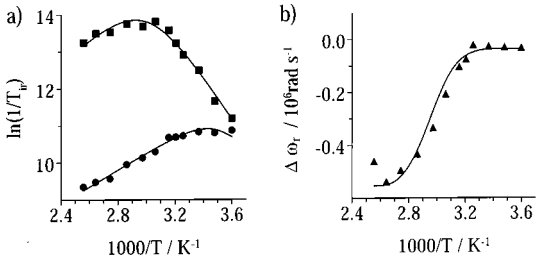

Figure 4. Temperature dependence of the reduced ^{17}O (a) transverse (filled squares) and longitudinal (filled circles) relaxation rates, expressed as $\ln(1/T_{ir})$, and (b) chemical shifts (filled triangles), $\Delta\omega_r$.

Simultaneous Fitting of NMRD and ^{17}O NMR Spectroscopic Data

The NMRD data of Gd_2L (Figure 2) together with the ^{17}O NMR spectroscopic data (Figure 4) was submitted for a least-squares fitting procedure. The advantage of a simultaneous fitting is that it puts constraints on the common parameters. Additional constraints were introduced by fixing the water hydration number (q) of each Gd^{3+} at 1, the quadrupolar coupling constant $[\chi(1 + \eta^{2/3})^{1/2}]$ at 7.58 MHz, the distance of closest approach of a water proton to a Gd^{3+} center (a_{GdH}) at 3.5 Å, and the inner sphere Gd−H distance (r_{GdH}) at 3.1 Å. In Table 1, the parameters as determined from the multiparameter fit are compared with those of the acyclic complexes $Gd(DTPA)^{2-}$ and Gd(DTPA-BMA).[17] Three parameters for the cyclic dinuclear complex Gd_2L differ significantly from those of its acyclic mononuclear counterparts, namely, $A/\hbar$, τ_R, and k_{ex}^{298}.

The relatively low value found for the scalar coupling constant ($A/\hbar = -3.2\times10^6$ rad s^{-1}, see Table 1) may indicate that there is effectively less water bound to the paramagnetic center. The hydration number, q, is an average taken over the different isomers, which are characterized by their respective lifetime in aqueous solution. Because of the crowding in the cyclic ligand, it is very well possible that the averaged value of q is smaller than one. Overestimation of the (fixed) hydration number in the fitting procedure can result in a lower value for $A/\hbar$. Assuming that $A/\hbar = -3.9\times10^6$ rad s^{-1} for a Gd^{3+}-bound ^{17}O nucleus,[13,15] the data would indicate that $q = 0.8$, which is in good agreement with previous results based on Dy^{3+} induced water ^{17}O shifts.[5]

Table 1. Comparison of parameters obtained from simultaneous fitting of ^{17}O NMR spectroscopic and NMRD data with some literature data

	DTPA[17]	DTPA-BMA[17]	L
k_{ex}^{298} (10^6 s^{-1})	3.3 ± 0.2	0.45 ± 0.01	0.29 ± 0.02
$\Delta H^{\neq}$ (kJ mol^{-1})	51.6 ± 1.4	47.6 ± 1.1	44.8 ± 2.2
τ_R (ps)	58 ± 11	66 ± 11	188 ± 9
E_R (kJ mol^{-1})	17.3 ± 0.8	21.9 ± 0.5	19.0 ± 1.3
τ_v (ps)	25 ± 1	25 ± 1	21 ± 2
E_v (kJ mol^{-1})	1.6 ± 1.8	3.9 ± 1.4	1[a]
$A/\hbar$ (10^6 rad s^{-1})	−3.8 ± 0.2	−3.8 ± 0.2	−3.2 ± 0.5
C_{os}	0.18 ± 0.04	0.11 ± 0.04	0.05 ± 0.08
Δ^2 (10^{20} s^{-2})	0.46 ± 0.02	0.41 ± 0.02	0.51 ± 0.07
δg_L^2 (10^{-2})[b]	1.2 ± 0.3	0.8 ± 0.2	2.0 ± 0.9
D_{GdH}^{298} (10^{-10} m^{2}s^{-1})	20 ± 3	23 ± 2	23 ± 1
$E_{D\ GdH}$ (kJ mol^{-1})	19.4 ± 1.8	12.9 ± 2.1	20.4 ± 1.0
r_{GdO} (Å)	2.20 ± 0.09	2.12 ± 0.04	2.09 ± 0.02
$\chi(1+\eta^2/3)^{1/2}$ (MHz)	7.58	7.58	7.58[a]

[a] Parameter fixed in fitting procedure. – [b] Parameter that determines the spin rotation contribution of the longitudinal electronic relaxation.[13]

The value of the rotational correlation time (τ_R^{298}) follows the general trend of the relative molecular masses of the complexes. The value found from the simultaneous fitting was in good agreement with the value determined by ^2H NMR spectroscopy (see above). It should be noted that the ^1H water relaxation rate of Gd_2L solutions at 200 MHz was linearly dependent on the concentration of the paramagnetic compound in solution. Over the concentration range in which the ^{17}O and ^2H NMR spectroscopic measurements and the NMRD profiles were recorded (200, 50 and 1 mM of Gd^{3+}, respectively), a correlation coefficient of 0.99 was calculated for T_1 as a function of the concentration. This justifies the use of the data that were obtained via the different techniques in a simultaneous fitting procedure.

It is surprising that the increase of τ_R^{298} upon going from Gd(DTPA-BMA) to GdL_2 is not linearly proportional with the increase in molecular weight. The molecular mass of the dimeric compound is two times higher than that of the DTPA-BMA complex, and the molar volume, as estimated from molecular mechanics using the HyperChem program on the Gd_2L complex (1857 Å^3) is 1.7 times higher than that of Gd(DTPA-BMA) (1084 Å^3). Based on these data, and the Debye−Stokes−Einstein relationship, a value for τ_R^{298}, of about 112 ps would be expected for Gd_2L. The value of 175 ps for τ_R^{298} as found by ^2H NMR spectroscopy that is in agreement with the results of the fitting of the ^{17}O NMR spectroscopic data, is significantly higher. Therefore, features other than the molar volume must be involved in the rotational correlation time of these complexes. Possibly, the τ_R^{298} value of Gd(DTPA-BMA) is not only determined by the global rotation, but has an additional contribution of relatively fast local motions. It may be expected that the mobility decreases upon going from the acyclic Gd(DTPA-BMA) to its macrocyclic dimer Gd_2L, which may explain the unexpectedly high τ_R^{298} value for the latter compound. This is in line with the ratio of the τ_R values for $Gd(DOTA)^-$ and $Gd(DTPA)^{2-}$, which is 1.3, whereas the molecular volumes of these complexes are about equal (982 Å^3 and 937 Å^3, respectively).

The water exchange rate k_{ex}^{298} for the dimeric Gd_2L ligand is somewhat smaller than for DTPA-BMA. The cyclic nature of the ligand limits the number of isomers that are existing in solution.[5] Recently, it was shown that for Ln^{3+} complexes of cyclen derivatives the water exchange rate can vary significantly for the different isomers of a complex in solution.[7−11] So, the reduction of the number of isomers

in the present case may explain a different overall water exchange rate than was observed for the acyclic monomeric counterpart.

The relatively low exchange rate of the inner sphere water molecules in Gd_2L limits the transfer of inner sphere relaxation towards the bulk solution. This effect is manifested clearly in Figure 2, b, which displays the relaxivity at 20 MHz as a function of the temperature. The inner and outer sphere contributions to the relaxivity have an opposite temperature dependence; the outer sphere term increases with a decrease in the temperature. Upon decreasing the temperature below 30 °C the relaxivity levels off, because the effect of the increase in τ_R is quenched by slow water exchange. The water exchange is slowed down (and the inner sphere relaxivity decreases) to the extent where the outer sphere relaxivity, which increases on lowering the temperature, becomes predominant.

Finally, the NMRD profile recorded from an aqueous solution of the Gd_2L compound containing 4% Human Serum Albumin (HSA), at 37 °C, was identical to the curve obtained in the absence of HSA, indicating that there is no interaction with albumin.

Conclusion

The 'cyclo-dimerisation' of Gd(DTPA-BMA) towards Gd_2L has some particular effects on the relaxivity properties. First, the increase in molar volume (with a factor of 1.7) resulted in a much higher increase in the rotational correlation time (factor of 2.7), suggesting a reduction in the local mobility of the complex as induced by the cyclic nature of the ligand. Moreover, the water exchange rate, k_{ex}^{298} is somewhat smaller for Gd_2L than for Gd(DTPA-BMA), which may be due to a difference in the isomer distribution in aqueous solution. The exchange rate of the inner sphere water molecule with the bulk, limits the relaxivity to such an extent that, at low temperature (5 °C), the outer sphere term becomes predominant. The electronic relaxation does not seem to be influenced by the cyclo-dimerization. Apparently, the interaction between the neighboring Gd^{3+} ions is negligible. Finally, it can be stated that the design of rigid cyclic ligands can lead to an increase in τ_R, which is favorable for higher relaxivity values. A drawback is that the water exchange can become so slow, that the effect of τ_R is counteracted. The challenge is to find an optimum for both parameters.

Experimental Section

General Remarks: All chemicals were purchased from ACROS Chimica, except the lanthanide chlorides that were purchased from Aldrich Chemical Co. All compounds were used without further purification.

NMR Spectroscopy: The ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-300 or a Varian VXR-400 spectrometer. *Tert*-butyl alcohol was used as an internal standard (methyl signal at $\delta = 1.2$ (^1H NMR) and $\delta = 31.2$ (^{13}C NMR). The variable temperature ^{17}O NMR spectroscopic measurements were performed with H_2O solutions at a magnetic field of 7.05 T on a Varian INOVA 300 spectrometer. The samples were enclosed in a sealed NMR tube under argon atmosphere. The ^1H signal of *tert*-butyl alcohol was used as an internal reference, to correct the ^{17}O NMR chemical shift for the Bulk Magnetic Susceptibility (BMS) shift contribution. The BMS shift had to be taken into account since the measurements were performed in an unlocked configuration.

Longitudinal relaxation rates, $1/T_1$, were measured using the inversion-recovery method, and transversal relaxation rates, $1/T_2$, were obtained via the Carr−Purcell−Meiboom−Gill spin-echo technique. At each temperature, the spectral parameters were measured for both a sample with 0.1 M dinuclear Gd^{3+} complex and a sample of acidified water (pH 5.2) under exactly the same conditions.

^2H longitudinal relaxation rates were measured at 4.7 T on a Bruker MSL-200−15 spectrometer using a broadband probe. The solvent (water) was deuterium depleted. The 90° and 180° pulse lengths were 9 and 18 μs, respectively.

The exact Gd^{3+} contents of the NMR samples were determined by ICP. The pH values of the NMR samples were measured at room temperature with a calibrated micro-combination probe (Aldrich Chemical Co.) and a Corning 125 pH meter. No corrections were made for deuterium isotope effects.

Relaxivity Measurements: The $1/T_1$ NMRD (Nuclear Magnetic Relaxation Dispersion) profiles were recorded at different temperatures on a FCS Research Relaxometer using the field cycling method, covering a continuum of magnetic fields from 2.5×10^{-4} to 1.2 T (corresponding to a proton Larmor Frequency range of 0.01−50 MHz). The absolute uncertainty in the $1/T_1$ values for the NMRD measurements was about 2%. The spin-lattice relaxation rates at 20 MHz were also measured on a Minispec Bruker PC-20 spin analyzer.

Computer Calculations: Experimental variable-temperature ^{17}O NMR spectroscopic and NMRD data were fitted with a computer program written by Dr. É. Tóth and Dr. L. Helm (University of Lausanne, Switzerland) using the Micromath Scientist program version 2.0 (Salt Lake City, UT, USA). Molecular volumes were calculated with the use of the HyperChem program (version 6.0, HyperCube Inc., Gainsville FL, USA).

Synthesis of the Ligands: The ligand L was synthesized following Carvalho et al.[4] Purification was done via ion exchange chromatography (DOWEX 1×8−200, OAc^- form, elution with a gradient of HOAc).[5] Ligand L with deuterated methylene groups in the acetate functions was synthesized in an analogous way starting from DTPA, deuterated at the corresponding positions. The latter was obtained using the procedure of Wheeler and Legg.[15] H_5DTPA (0.42 g) was dissolved in 15 mL D_2O, and the pD was adjusted to 10.6 by addition of solid K_2CO_3. The solution was refluxed for 24 h. After cooling, the reaction mixture was acidified to pD 2 using concentrated HCl. The solution obtained was concentrated under reduced pressure, and the solid KCl was filtered off. Upon addition of 2-propanol to the filtrate, the deuterated compound precipitated, and was filtered off. The yield of $[D_{10}]H_5DTPA$ was 0.27 g (67%). The degree of acetate methylene deuteration (>99%) was determined from the integrals in the ^1H NMR spectrum. The compound was converted into the bis-anhydride compound by reflux in an acetic anhydride/pyridine mixture.

Preparation of the Dinuclear Gd_2L Complex: The gadolinium complex of the macrocyclic ligand L was prepared by adding an aque-

ous solution of $GdCl_3 \cdot 6H_2O$ dropwise to a solution of the ligand in water (molar ratio $GdCl_3$:L = 2:1) while keeping the pH at about 6. Salts were removed by ultrafiltration over a UTC-60 membrane (Toray Industries, Tokyo, Japan) under a pressure of 20 bar N_2. Finally, the aqueous solution was freeze dried. The complex was tested for the absence of free lanthanides using an arsenazo III indicator.

Acknowledgments

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