Solution Study, Crystal Structure and Relaxivity Properties of a Gd^{3+} Complex with an Uncharged Macrocyclic Ligand Bearing Four Amidic Side Arms

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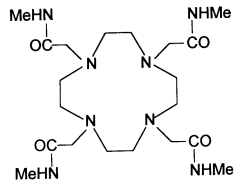
Received April 6, 1998

Keywords: Gadolinium complexes / Gadolinium / Magnetic Resonance Imaging (MRI) / Contrast agents / Polyaminopolycarboxylic ligands

Equilibrium data on the interaction of DTMA [(DTMA = DOTA tetrakis(methylammide)] with Gd^{3+} in aqueous solution, properties of the complexes formed in the pH range 0.6–11.8, water proton relaxation rate enhancement, and the crystal structure analysis of the $[Gd(DTMA)H_2O]^{3+}$ complex are reported. In the crystal structure the metal ion is bound to the nitrogen atoms of the tetraazamacrocyclic moiety, to the amidic oxygen atoms, and to an oxygen atom of a water molecule. The nine donors are located at the vertices of a distorted square antiprism, which is capped by the coordinated water oxygen atom in the axial position. In solution $[Gd(DTMA)]^{3+}$ is not very stable [$\log K_{ML}$ = 12.8(1)] and gives rise to the formation of $[Gd(DTMA)OH]^{2+}$ [pK_a = 7.9(1)] and $[Gd(HDTMA)]^{4+}$ [$\log K_{(ML+H)}$ = 3.4(1)]. The proton solvent relaxivity of aqueous complex solutions assumes a constant value in the pH range 3–8, increasing at higher and lower pH. For pH > 3 the data are in good agreement with a previous study on the same compound. For pH < 3 a new interpretation is presented, based on the formation of $[Gd(HDTMA)]^{4+}$ and the release of Gd^{3+}.

A recent communication by Aime et al.[1] reported the interesting observations of the enhancement of the nuclear relaxation rate of water protons brought about by the $[Gd(DTMA)]^{3+}$ complex [(DTMA = DOTA tetrakis-(methylammide)] in aqueous solution. This presented for the first time a distinct evaluation of the water and prototropic exchange rates for a Gd^{3+}-coordinated solvent molecule. The uncharged DTMA ligand was selected in order to assess the contribution of prototropic exchange to the overall water exchange between the complex and the bulk solvent, as it had been observed that the exchange lifetime of Gd^{3+}-coordinated water molecules increases with decreasing negative charge of the Gd^{3+} complex. Actually, the nuclear transverse relaxation rate of ^{17}O nuclei of the solvent observed for the $[Gd(DTMA)]^{3+}$ complex is the slowest water exchange rate so far reported for a lanthanide(III) complex[1].

Aqueous solutions containing the triflate salt of $[Gd(DTMA)]^{3+}$ revealed a peculiar pH dependence of the longitudinal solvent relaxivity[2] (R_{1p}): R_{1p} assumes a constant value (ca. 2.6 $mM^{-1}s^{-1}$) in the pH range 2−8, increasing at higher and lower pH ($R_{1p} \approx 5.8$ $mM^{-1}s^{-1}$ at pH = 11−12 and $R_{1p} \approx 5.4$ $mM^{-1}s^{-1}$ at pH = 0.5). In the pH range 2−8 the low relaxivity values are consistent with a purely outer-sphere contribution[3]. ^{19}F-NMR measurements performed in this pH range were indicative of strong ion pairing between the complex $[Gd(DTMA)]^{3+}$ and the counterions $CF_3SO_3^-$[1]. The increase in relaxivity for pH > 8 was attributed to the additional contribution to ^1H-R_{1p} deriving from a prototropic exchange caused by the presence of the hydroxo species $[Gd(DTMA)OH]^{2+}$, while the increase in relaxivity in very acidic solutions was attributed to the acid-catalyzed dissociation of the ion pairs formed by $[Gd(DTMA)]^{3+}$ with the counterions[1]. The interpretation of the relaxivity behavior in acidic solutions was



DTMA

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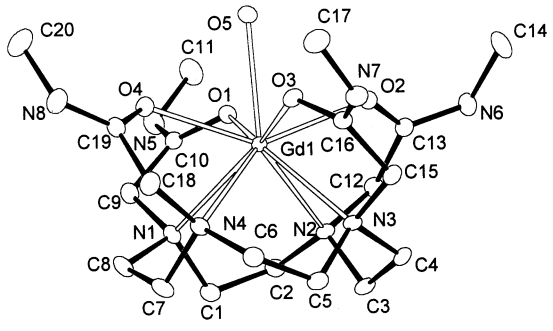
based on the assumption that the complex $[Gd(DTMA)]^{3+}$ is the only species present in such media, as suggested by the ^1H- and ^{13}C-NMR spectra of the analogous $[Eu(DTMA)]^{3+}$ complex.

Results and Discussion

A parallel but independent study performed in our laboratories on the same compound led to the determination of the crystal structure[4][5][6][7][8] of the $[Gd(DTMA)H_2O]^{3+}$ cation, to the identification of the Gd^{3+} complexes formed in solution by DTMA in the pH range 2.5−10, and to the determination of equilibrium constants of these complexes[9]. This elucidated some aspects of the system and completed the picture outlined by the previous work[1].

DTMA actually acts as an octadentate ligand toward Gd^{3+}, forming a tight structure where a water molecule is accommodated in the ninth position. Crystals of $[Gd(DTMA)H_2O](ClO_4)_3 \cdot NaClO_4 \cdot 3\ H_2O$[10] are composed of $[Gd(DTMA)H_2O]^{3+}$ cations, sodium ions, perchlorate counterions and water of crystallization. The metal ion is bound to the nitrogen atoms of the tetraazamacrocyclic moiety and to the amidic oxygen atoms provided by the four side arms, and finally to an oxygen atom of a water molecule (Figure 1).

Figure 1. Molecular structure (ORTEP[11] draw) of the $[Gd(DTMA)H_2O]^{3+}$ cation[a]



[a] Selected interatomic distances [Å] and angles [°]: Gd(1)−O(2) 2.351(5), Gd(1)−O(3) 2.351(4), Gd(1)−O(4) 2.393(5), Gd(1)−O(1) 2.455(5), Gd(1)−O(5) 2.461(5), Gd(1)−N(4) 2.621(6), Gd(1)−N(1) 2.626(5), Gd(1)−N(3) 2.648(5), Gd(1)−N(2) 2.649(5); O(2)−Gd(1)−O(3) 84.1(2), O(5)−Gd(1)−N(1) 123.1(2), O(2)−Gd(1)−O(4) 142.3(2), N(4)−Gd(1)−N(1) 69.2(2), O(3)−Gd(1)−O(4) 83.7(2), O(2)−Gd(1)−N(3) 74.9(2), O(2)−Gd(1)−O(1) 81.8(2), O(3)−Gd(1)−N(3) 66.1(2), O(3)−Gd(1)−O(1) 145.1(2), O(4)−Gd(1)−N(3) 130.4(2), O(4)−Gd(1)−O(1) 88.3(2), O(1)−Gd(1)−N(3) 138.3(2), O(2)−Gd(1)−O(5) 73.4(2), O(5)−Gd(1)−N(3) 130.9(2), O(3)−Gd(1)−O(5) 74.1(2), N(4)−Gd(1)−N(3) 68.5(2), O(4)−Gd(1)−O(5) 69.0(2), N(1)−Gd(1)−N(3) 106.0(2), O(1)−Gd(1)−O(5) 71.3(2), O(2)−Gd(1)−N(2) 66.7(2), O(2)−Gd(1)−N(4) 142.5(2), O(3)−Gd(1)−N(2) 130.7(2), O(3)−Gd(1)−N(4) 74.0(2), O(4)−Gd(1)−N(2) 142.6(2), O(4)−Gd(1)−N(4) 65.7(2), O(1)−Gd(1)−N(2) 70.9(2), O(1)−Gd(1)−N(4) 132.3(2), O(5)−Gd(1)−N(2) 127.8(2), O(5)−Gd(1)−N(4) 126.5(2), N(4)−Gd(1)−N(2) 105.6(2), O(2)−Gd(1)−N(1) 131.1(2), N(1)−Gd(1)−N(2) 68.6(2), O(3)−Gd(1)−N(1) 142.4(2), N(3)−Gd(1)−N(2) 68.3(2), O(4)−Gd(1)−N(1) 74.5(2), O(1)−Gd(1)−N(1) 65.4(2).

The nine donors are located at the vertices of a distorted square antiprism, capped by the coordinated water oxygen atom in the axial position. Similar coordination spheres were found for other Gd^{3+} complexes with analogous ligands derived from the 1,4,7,10-tetraazacyclododecane macrocycle[12]. The four nitrogen atoms supplied by the macrocyclic ligand are in a well-defined plane, while the maximum deviation from the mean plane formed by the four amidic oxygen atoms is 0.025(5) Å. The oxygen atom of the water molecule is ca. 1.7 Å away from the mean O1−O2−O3−O4 plane, with the Gd−O5 bond direction almost perpendicular to this plane (87°). The metal ion is significantly shifted towards the mean plane of the oxygen donors with respect to the plane described by the four nitrogen atoms (0.74 vs. 1.59 Å, respectively). The Gd−N bond lengths [2.621(5)−2.649(6) Å], the Gd−O amidic bond lengths [2.351(5)−2.455(5) Å], as well as the Gd−O water distance [2.461(5) Å, see Figure 1] compare well with those previously reported for analogous gadolinium(III) complexes[12]. Concerning the ligand, the tetraaza ring adopts the [3333] C corners conformation[13], with the four side arms, which are folded towards the macrocyclic cavity, in a head-to-tail arrangement. The four amidic nitrogen atoms have a significant sp^2 character, thus the usual π conjugation takes place in each amidic functional group enhancing the donor capability of the carbonylic oxygen atoms.

The molecular packing reveals a large number of H-bond contacts (< 3.0 Å) involving the water of crystallization, the oxygen atoms of the perchlorate anions and various hydrogen and nitrogen atoms of the ligand, while the sodium ion is six-coordinated [Na−O bond lengths range from 2.413(9) to 2.80(1) Å] by four perchlorate oxygen atoms and two water molecules of crystallization. It is worth noting that the oxygen atom O5 of the Gd^{3+}-coordinated water molecule is very close [2.92(1) Å] to an oxygen atom of a perchlorate ion. This suggests the presence of a strong hydrogen bond between $[Gd(DTMA)H_2O]^{3+}$ and a counterion, offering a model for the ion pairing occurring in solution[1] between the complex and $CF_3SO_3^-$.

Gd^{3+} complexation by DTMA is very slow; solutions containing the metal ion and the ligand in the pH range 2.5−8 require several days to equilibrate at 298.1 K. For this reason the speciation of the system was performed by using an out-of-cell batch technique in which 40 solutions corresponding to different points in a conventional potentiometric titration were allowed to equilibrate at 298.1 K[9]. The same procedure was adopted to study the Eu^{3+}/DTMA system. The formation constants[9] determined for the complexes formed at equilibrium (0.1 mol dm^{-3} Me_4NNO_3, 298.1 ± 0.1 K) are listed in Table 1, which also contains the ligand protonation constants determined under the same experimental conditions.

The $[Gd(DTMA)]^{3+}$ complex is not very stable [$\log K$ = 12.8(1)] if compared with the analogous complex with DOTA ($\log K = 24.67$)[14], demonstrating the lower coordinating ability toward Gd^{3+} of amidic groups with respect to carboxylate groups[15]. Starting from neutral pH the metal-bound water molecules in $[Gd(DTMA)H_2O]^{3+}$ dissociate

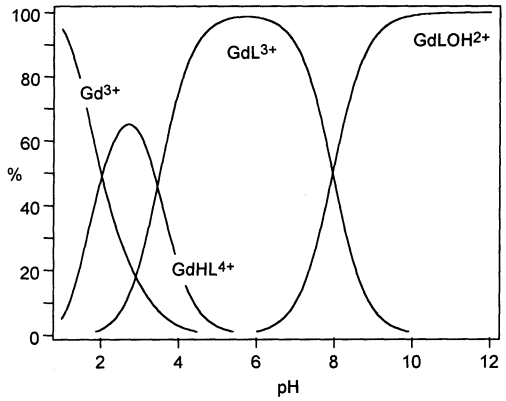
Table 1. Logarithms of the equilibrium constants of the Gd^{3+} and Eu^{3+} complexation reactions with DTMA, determined in 0.1 mol dm^{-3} Me_4NNO_3 at 298.1 ± 0.1 K[a]

reaction	log *K*
$DTMA + H^+ \rightleftharpoons HDTMA^+$	9.27(1)
$HDTMA^+ + H^+ \rightleftharpoons H_2DTMA^{2+}$	5.55(2)
$H_2DTMA^{2+} + H^+ \rightleftharpoons H_3DTMA^{3+}$	1.56(7)
$Gd^{3+} + DTMA \rightleftharpoons [Gd(DTMA)]^{3+}$	12.8(1)
$[Gd(DTMA)]^{3+} + H^+ \rightleftharpoons [Gd(HDTMA)]^{4+}$	3.4(1)
$[Gd(DTMA)]^{3+} + OH^- \rightleftharpoons [Gd(DTMA)OH]^{2+}$	5.8(1)
$Eu^{3+} + DTMA \rightleftharpoons [Eu(DTMA)]^{3+}$	13.17(4)
$[Eu(DTMA)]^{3+} + OH^- \rightleftharpoons [Eu(DTMA)OH]^{2+}$	6.83(5)

[a] Values in parentheses are standard deviations on the last significant figure

[pK_a = 7.9(1)] giving rise to the hydroxo complex $[Gd(DTMA)OH]^{2+}$, while for pH < 5 $[Gd(DTMA)]^{3+}$ undergoes protonation to produce the species $[Gd(HDTMA)]^{4+}$. Due to the reduced coordinating ability of DTMA toward Gd^{3+}, the uncoordinated metal ion is present in acidic media at pH < 4 (Figure 2).

Figure 2. Distribution diagram of the complexed species formed by DTMA with Gd^{3+} as a function of pH in 0.1 mol dm^{-3} Me_4NNO_3 solution at 298.1 K; [DTMA] = $[Gd^{3+}] = 1 \times 10^{-3}$ mol dm^{-3}



As can be seen in Table 1, DTMA displays almost the same tendency to bind Gd^{3+} and Eu^{3+}, but $[Eu(DTMA)H_2O]^{3+}$ demonstrates a higher propensity than $[Gd(DTMA)H_2O]^{3+}$ to form the hydroxylated complex [pK_a = 7.0(1)], and does not form protonated species.

Hence, the use of the Eu^{3+} complex with DTMA as a model for the Gd^{3+}/DTMA system led Aime et al. to ignore the formation of $[Gd(HDTMA)]^{4+}$ in their interpretation of the relaxivity properties in acidic media.

Measurement of water relaxation times in the presence of the gadolinium complex, performed with 0.1 mol dm^{-3} Me_4NNO_3 solutions after equilibration in the pH range 0.6−11.8, confirmed the pH dependence of relaxivity found by Aime et al.[1] in the presence of $CF_3SO_3^-$ at pH > 3. This accounts for similar properties of NO_3^- and $CF_3SO_3^-$ in the formation of ion pairs with the complex. However for pH values < 3 the relaxivity increases with decreasing pH more rapidly than previously reported[1] for measurements performed shortly after solution acidification. The equilibrium data obtained for the Gd^{3+}/DTMA system (Table 1) confirm the role played by $[Gd(DTMA)]^{3+}$ and $[Gd(DTMA)OH]^{2+}$ in determining the relaxivity properties of solutions at pH > 3 containing the complex, offering a new interpretation of the relaxivity behavior observed at pH < 3. Actually, in acidic solutions at equilibrium the relaxivity increases with increasing concentration of free Gd^{3+} (released by the complex upon acid-catalyzed dissociation), and at pH ≈ 0.5, where complete complex dissociation occurs (Figure 2), approaches the value expected (ca. 11 $mM^{-1}s^{-1}$) at such pH for a solution of Gd^{3+} in the ionic medium employed.

On the other hand, potentiometric measurements performed on $[Gd(DTMA)]^{3+}$ in acidic solutions indicate that the monoprotonated complex is formed after rather short equilibration times (2−3 h), while complex dissociation is expected[1] to produce significant concentrations of uncoordinated Gd^{3+} only after many hours.

Complex protonation produces a more open structure around Gd^{3+}, which means either an increase in the metal-ion hydration number or a wider diffusion of water molecules in proximity of the paramagnetic centre; both phenomena are expected[3] to imply an enhancement of the relaxation rate of water protons.

Therefore, the Gd^{3+}/DTMA system gives different relaxivity responses in acidic media, depending on the equilibration times of the complex; relaxivity increases with decreasing pH due to: i) the formation of the monoprotonated $[Gd(HDTMA)]^{4+}$ complex, after short equilibration times, ii) the presence of uncoordinated Gd^{3+} ion after long equilibration times. Both effects can be present simultaneously.

We believe that the relaxation properties of $[Gd(DTMA)]^{3+}$ observed by Aime et al. in acidic solutions are principally connected with the first factor.

Indeed, the results on the Gd^{3+}/DTMA system have a direct impact in the research about paramagnetic contrast agents for magnetic resonance imaging, suggesting that modulation of water proton relaxivity can be achieved by tuning the solution pH under kinetic control of the Gd^{3+}/ligand complexation reaction. Furthermore, the results described here demonstrate the necessity to be very prudent in the use of Eu^{3+} complexes as models for the corresponding Gd^{3+} systems.

We are grateful to Mr. *Massimo Foresti*, Dr. *Palma Mariani*, Mrs. *Lucia Monti*, and Dr. *Stefano Seniori Costantini* for technical assistance

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[2] Relaxivity is defined as the nuclear magnetic relaxation rate increase of water nuclei per unit concentration of the paramagnetic complex.
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[4] Crystal data: $[Gd(DTMA)H_2O](ClO_4)_3 \cdot NaClO_4 \cdot 3\ H_2O$, triclinic, *P*1, *a* = 11.558(6), *b* = 13.251(9), *c* = 14.713(9)Å, α = 94.29(9), β = 109.65(8), γ = 102.97(6)°, *V* = 2040(4) $Å^3$, *Z* =

2, $D_{calcd.}$ = 1.80 g cm^{-3}, T = 298 K, graphite-monochromated Mo-K_α radiation, λ = 0.71069 A, μ = 19.9 cm^{-1}; data collection with an Enraf Nonius CAD4 automatic diffractometer, $\theta-2\theta$ scan, $2\theta \leq 50°$, 7622 reflections, 6377 observed [$I > 2\sigma(I)$] data, absorption correction by DIFABS[5]. The structure, solved by direct methods of SIR92[6] and refined[7] by full-matrix least squares against F^2 (non-H atoms anisotropic, the hydrogen atoms of the macrocyclic ligand were placed in calculated positions and treated with an overall temperature factor refined to 0.053 A^2, 528 variables/7111 data) to $wR2$ = 0.139, goodness-of-fit 1.06, $R(F,$ obs. data) = 0.050. The Fourier difference map did not allow us to localize the hydrogen atoms of the Gd-coordinated water molecule. Geometrical parameters were obtained by using PARST93[8]. Further information on the crystal-structure determination has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101378 and may be obtained from CCDB, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336033; e-mail: deposit@ccdc.cam.ac.uk]

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[9] Equilibrium constants were obtained by means of potentiometric titrations in 0.1 mol dm^{-3} Me_4NNO_3 at 298.1 ± 0.1 K. Under such conditions pK_w = 13.83(1). Out-of-cell experiments were performed by employing individual solutions equilibrated at 298.1 ± 0.1 K. The pH of these solution was recorded at intervals until no further pH drift was observed. E.m.f. data were processed by using the HYPERQUAD program (P. Gans, A. Sabatini, A. Vacca, *Talanta* **1996**, *43*, 1739−1753).

[10] Crystals of $[Gd(DTMA)H_2O](ClO_4)_3 \cdot NaClO_4 \cdot 3\,H_2O$ were obtained by slow concentration at room temp. of aqueous solutions containing equimolar quantities of DTMA and $GdCl_3$ in the presence of a tenfold excess of $NaClO_4$. Satisfactory elemental analyses were obtained for the various samples prepared.

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