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The gadolinium(III) chelate of 1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid. Formation of polymeric chains in the solid state and relaxivity properties

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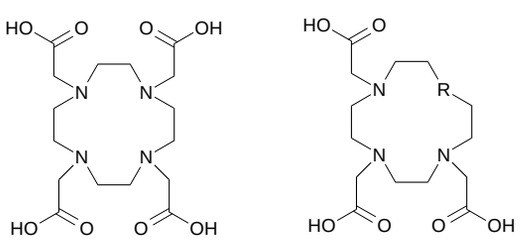
The crystal structure of the gadolinium(III) chelate of the macrocyclic ligand odotra (1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetate) was determined by X-ray single-crystal analysis: [Gd(odotra)(H_2O)$_5$] crystallizes in the orthorhombic space group *Pbca*, with a = 12.84(8), b = 21.53(4), c = 15.30(7) Å and Z = 8. The metal ion is at the centre of a square antiprism capped with one water molecule. The chelate units are linked by bridging carboxylic groups and form linear polymeric chains. The macrocycle adopts its preferred square [3333] conformation. Nuclear magnetic resonance dispersion studies indicate that [Gd(odotra)] and its analogue [Gd(dotra)] (dotra = 1,4,7,10-tetraazacyclododecane-4,7,10-triacetate) exhibit the same relaxivity behaviour but are not as effective magnetic resonance imaging contrast agents as expected presumably because of their low symmetry.

Several gadolinium(III) polyaminopolycarboxylic chelates are currently used as contrast agents because these paramagnetic compounds can highlight lesions that might otherwise be missed on magnetic resonance images. The chelates must be thermodynamically highly stable and kinetically inert to ensure complete excretion from the body within a few hours. This goal has been achieved with twelve-membered macrocyclic polyaza polycarboxylic ligands which impart their steric constraints on lanthanide complexes. The preferred square [3333] conformation of cyclododecane is adopted in the solid state[1] and in solution[2] by the chelates formed by its 1,4,7,10-tetraaza-substituted derivatives such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, (H_4dota). This [3333] arrangement favours the formation of a highly rigid nine-co-ordinated capped square-antiprismatic geometry with four nitrogen atoms defining one square face, four carboxylic oxygen atoms delimiting the other square face and one water molecule on the C_4 axis. It will be shown here that this conformational preference is maintained in the solid-state structure of the gadolinium(III) chelate of H_3odotra (1-oxa-4,7,10-triazacyclododecane-1,4,7-triacetic acid) although this features an oxatriaza cycle and only three carboxylic groups. A second objective of the present study is an analysis of the relaxivity properties of this chelate and of its fully nitrogenated analogue H_3dotra (1,4,7,10-triazacyclododecane-1,4,7-triacetic acid).

Experimental

The compounds H_3dotra[3] and H_3odotra[4,5] and their gadolinium(III) chelates[1] were synthesized according to previously outlined procedures. The purity of the chelates was checked by HPLC according to the method of Kumar *et al.*[6] Proton-relaxation dispersion profiles (NMRD curves) were recorded as reported earlier[7] on an IBM research field-cycling relaxometer over the field range 2×10^{-4} to 1.2 T (corresponding proton Larmor frequencies ranging from 0.01 to 50 MHz). The NMRD curves of at least two different samples of [Gd(odotra)] and [Gd(dotra)] originating from different syntheses were recorded at 25 ± 0.1 and 37 ± 0.1 °C and the gadolinium content of the solutions used for the measurements was measured by inductively coupled plasma (ICP) atomic emission on a Bausch and Lomb 3510 spectrometer.



H_4dota

H_3odotra R = O
H_3dotra R = NH

Crystallography

Crystals (white, prismatic) suitable for X-ray analysis were obtained after dissolving the hydrated [Gd(odotra)] complex in the minimum volume of methanol, adding a layer of acetone and allowing the two solutions to mix slowly by diffusion. A selected specimen (0.25 × 0.20 × 0.25 mm) was mounted on a glass fibre. X-Ray diffraction data were obtained with an Enraf-Nonius CAD-4 four-circle computer-controlled diffractometer (using graphite-monochromated Mo-Kα radiation, λ = 0.710 73 Å) at 293 K. The unit-cell parameters and standard deviations were calculated for the setting angles of 25 reflections with $5 < 2\theta < 30°$. The space group was established from systematic absences.

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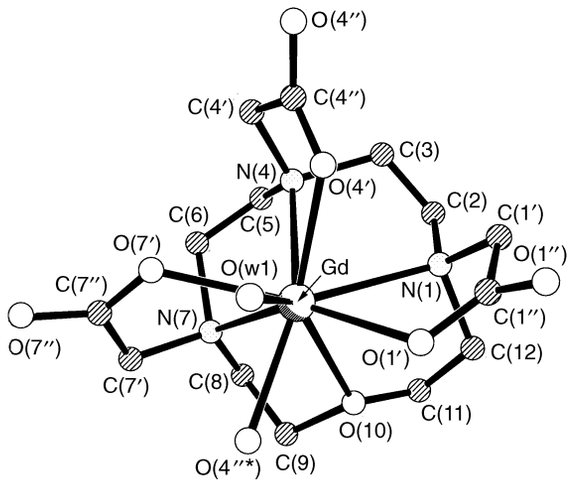

Fig. 1 Molecular structure of [Gd(odotra)]. Selected bond distances (Å) and angles (°): Gd–N(1) 2.674(9), Gd–N(4) 2.644(9), Gd–N(7) 2.674(9), Gd–O(10) 2.574(7), Gd–O(1′) 2.327(7), Gd–O(4′) 2.351(7), Gd–O(7′) 2.357(7), Gd–O(w1) 2.559(7) and Gd–O(4″*) 2.328(6); N(1)–Gd–N(4) 66.3(3), N(1)–Gd–N(7) 102.7(3), N(1)–Gd–O(10) 64.1(3), N(1)–Gd–O(4′) 78.3(3), N(1)–Gd–O(7′) 148.6(3), N(1)–Gd–O(4″*) 127.0(3), N(1)–Gd–O(1′) 63.5(3) and N(1)–Gd–O(w1) 127.0(2)

Crystal data and data-collection parameters. $C_{14}H_{32}GdN_3O_{12}$, $M_r = 591.67$, orthorhombic, space group *Pbca*, $a = 12.84(8)$, $b = 21.53(4)$, $c = 15.30(7)$ Å, $U = 4231(6)$ Å^3, $Z = 8$, $D_c = 1.858$ Mg m^{-3}, μ(Mo-Kα) = 3.2129 mm^{-1}, $F(000) = 2376$. The intensities of 4507 [$I > \sigma(I)$] reflections were measured by the ω–2θ scan technique in the range $4 < 2\theta < 45°$ (index ranges: $16 \leqslant h \leqslant 0$, $-18 \leqslant k \leqslant 0$, $-25 \leqslant l \leqslant 25$). They corresponded to 2304 independent reflections ($R_{int} = 0.025$). Three standard reflections were monitored at 30 min intervals to check crystal stability. No significant decrease in intensity during data collection was observed. Data were corrected for Lorentz-polarization and absorption effects, the latter by a semiempirical method.[8] The transmission factors ranged from 0.79 to 1.00.

Structure solution and refinement. The structure was solved by direct methods and Fourier techniques and refined by full-matrix least squares minimizing $\Sigma w(|F_o| - |F_c|)^2$. A weighting scheme based on counting statistics was used: $w = 1/[\sigma(F_o)]^2$. Refinement was carried out on 1925 reflections (based on F_o) with $F > 3\sigma(F)$. The non-hydrogen atoms were treated anisotropically. Hydrogen atoms placed in calculated positions (C–H 0.95 Å) were included in the final structure-factor calculation with $B_{iso} = 1.30B_{iso}$ of the attached C atom. A secondary extinction coefficient was refined to a value of $g = 3.83 \times 10^{-8}$ {$F_c = F_c/[1 + g(F_c)^2L_p]$}. The final agreement factors for the observed data were $R = 0.037$ and $R' = 0.058$ {$R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R' = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}$}. Number of parameters refined 272, goodness of fit $S = 1.53$, data-to-parameter ratio 7.08 : 1, maximum shift/e.s.d. in final cycle 0.02. The highest peak in the final Fourier-difference map, 1.45 e Å^{-3}, was located near the Gd atom. Calculations were performed with the SDP-plus package.[9]

Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/356.

Results

The molecular structure of the [Gd(odotra)] complex together with the atomic numbering scheme is shown in Fig. 1. Selected bond distances and angles are summarized in the legend. The

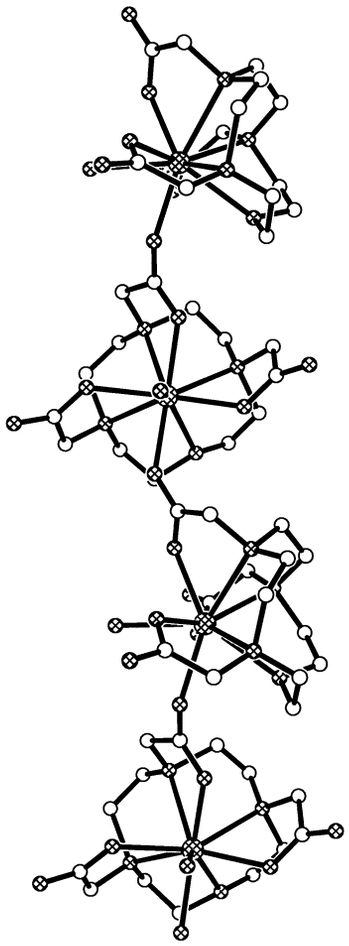

Fig. 2 The polymeric structure of [Gd(odotra)]. The non-carbon atoms are cross-hatched and hydrogen atoms are omitted for clarity

gadolinium(III) ion lies in a slightly distorted monocapped square-antiprismatic environment of nitrogen and oxygen atoms provided by the four heteroatoms of the twelve-membered ring (N_3O face), by four acetate oxygen atoms (O_4 face) and by one water molecule. This co-ordination geometry is achieved by sharing carboxylic groups between adjacent chelates in infinite polymeric chains as shown in Fig. 2. The two square faces of the chelate are quasi-parallel (angle 3.43°) and the heteroatoms form exact planar arrays (average displacements of 0.03 and 0.01 Å for the N_3O and O_4 faces respectively). The metal ion lies 0.720 Å above the O_4 face and 1.633 Å below the N_3O face. The Gd–O_{water} bond is nearly at right angles with the O_4 face (angle 80.1°) and the water molecule is located at a distance of 2.559(7) Å from the metal ion {corresponding value[10] in the case of $[Gd(dota)]^-$ is 2.447 Å}. The average Gd–N distance in [Gd(odotra)] [2.654(9) Å] is very similar to the value[10] for $[Gd(dota)]^-$ (2.663 Å) and is slightly longer than the Gd–O_{ring} distance as indicated in the legend of Fig. 1. All the distances between the gadolinium ion and the acetate oxygen atoms [mean 2.345(7) Å] are very similar to the values reported[10] for $[Gd(dota)]^-$ (mean 2.364 Å). The oxygen atom O(4″*) which completes the square-antiprismatic co-ordination sphere of each [Gd(odotra)] unit belongs to a carboxylic group from an adjacent molecule in the polymeric chain. The Gd–O(4″*) distance is identical to the other Gd–O distances and the formation of a polymer has no influence on the geometry of the chelate. The interatomic distances in the ligand fall within the range documented for similar bonds[2,10] and the macrocycle is in the expected square [3333] conformation with torsion angles close to the usual $g^{\pm}g^{\pm}a$ or ∓60, ∓80, ±165° sequence[11] previously found in $[Gd(dota)]^{-}$[10] and $[Eu(dota)]^{-}$[2] {mean torsion angles in [Gd(odotra)]: −58(1), −80(1) and

160(1)°}. Despite their structural differences, the ligands odotra and dota thus form nearly identical co-ordination spheres around the gadolinium ion. One difference between the two chelates should however be pointed out: the macrocycle in [Gd(odotra)] and $[Gd(dota)]^-$ adopts the same conformation but the acetate substituents are arranged around the central metal ion with opposite chiralities in a propeller-like manner that is counterclockwise for the former chelate and clockwise for the latter. Moreover, the angles between two vectors defined respectively by N atom–centroid of the N_3O face and O atom–centroid of the O_4 face in the same $NCH_2CO_2^-$ group are somewhat smaller in [Gd(odotra)] (30.3 and 31.2°) than in $[Gd(dota)]^-$ (37.6 and 39.6°). Therefore, [Gd(odotra)] is a slightly more distorted square antiprism (ideal angle 45°) and is slightly more elongated than $[Gd(dota)]^-$ (distance between the two square faces: 2.488 and 2.353 Å respectively).

The presence of diastereoisomers in crystals of various derivatives of the lanthanide dota chelates featuring asymmetric centres has been reported[12–14] and seems to be a general rule for these complexes. The [Gd(odotra)] polymeric chain itself is made up of alternating enantiomers, *i.e.* the conformations of both the macrocyclic ring and the acetate arms are inverted along the chain. The mean N_4 planes of two successive chelates make an angle of ±99.9° and the stacking of the crystals results from a three-dimensional network of hydrogen bonds involving the carboxylate oxygens and five water oxygen atoms. To our knowledge this is the first example of a polymeric chain formed by a chelate of the dota family. However, the structure of smaller aggregates has been described. A dimeric structure with a bridging carboxyl group between the two metal ions has been reported for the gadolinium(III) complex of (1*R*,4*R*,7*R*)-α,α′,α″-trimethyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid[13] and [Gd(dotra)] is known[14,15] to form a trimer with a bridging carbonate ion when it crystallizes in the presence of Na_2CO_3. The stereochemical preferences of the twelve-membered tetraaza macrocycles are so pronounced that a square-antiprismatic geometry with a [3333] arrangement is formed even if the chelate ring contains different heteroatoms, features only three substituting arms and is part of a di-, tri- or poly-meric structure.

The proton-relaxation dispersion profiles of [Gd(odotra)] and [Gd(dotra)] at 25 and 37 °C are reproduced in Fig. 3. The NMRD curves of at least two samples of each chelate prepared from Gd_2O_3 or $Gd(OH)_3$ with macrocycles obtained from different syntheses were found to be identical within the experimental errors. The relaxivity curves of [Gd(odotra)] and [Gd(dotra)] are nearly identical at all frequencies and can be interpreted by a best-fit approach based on the Solomon–Bloembergen–Morgan equation.[17] The complex $[Gd(ttha)]^{3-}$ was used for estimating the outer-sphere contribution to the relaxivity since ttha completely encapsulates the Gd^{3+} ion and prevents its co-ordination to a water molecule[18] {H_6ttha = $[CH_2N(CH_2CO_2H)CH_2CH_2N(CH_2CO_2H)_2]_2$}. Moreover, the exchange lifetime τ_m of a hydration water molecule in the first co-ordination sphere of [Gd(odotra)] and [Gd(dotra)] was fixed at 10 ns. This parameter has little or no influence on the relaxivity properties provided it is much smaller than the longitudinal relaxation time of the water protons as shown earlier for $[Gd(dota)]^-$.[19] It was assumed that the Gd^{3+} ion is co-ordinated to two water molecules and the water proton–Gd^{3+} distance was fixed at 3.13 Å, a mean value found in the present crystallographic study and in earlier investigations.[2,10] A good agreement between the experimental and calculated relaxivities of [Gd(odotra)] and [Gd(dotra)] was obtained with the following mean parameters (in ps): τ_{s0} (electronic relaxation time at zero field) = 120 ± 15, τ_v (correlation time of the modulation of the zero-field splitting) = 55 ± 14, τ_r (rotational correlation time) = 81 ± 13 at 25 °C and τ_{s0} = 134 ± 10, τ_v = 16 ± 2, τ_r = 45 ± 3 at 37 °C. The errors are standard deviations on the mean of the parameters calculated for each chelate. The τ_v and τ_r values are in the ranges found[17] for other small rapidly rotating chelates. These correlation times and the absence of a maximum in relaxivity around 20 MHz clearly indicate that, as expected, [Gd(odotra)] loses its polymeric structure on dissolution in water. The τ_{s0} correlation time is significantly shorter than the values reported for $[Gd(dota)]^-$ (460 ps at 25 °C[20] and 650 ps or higher at 37 °C[21]). This difference can be assigned to the lower symmetry and/or the reduced rigidity of the triacetic ligands which causes a larger zero-field splitting and thus a reduction in τ_{s0}.[22] Symmetry effects have already been noted for dota derivatives with identical substituents in different arrangements[20] and for a triacetic monoamide dota derivative,[23] although unusually small τ_0 values have been reported in the case of highly symmetric unhydrated polyphosphinate macrocyclic chelates.[24] Surprisingly, replacing an oxygen atom in the tetraaza ring by a NH group does not seem to modify significantly τ_{s0}. This insensitivity to ligand-field effects could arise because [Gd(odotra)] and [Gd(dotra)] have the same symmetry and similar rigidity, but it cannot be ruled out that a compensation of the effect of the $Gd\cdots H_{water}$ distance, of the hydration number and of the various correlation times of these two chelates was not revealed by the best-fit computations.

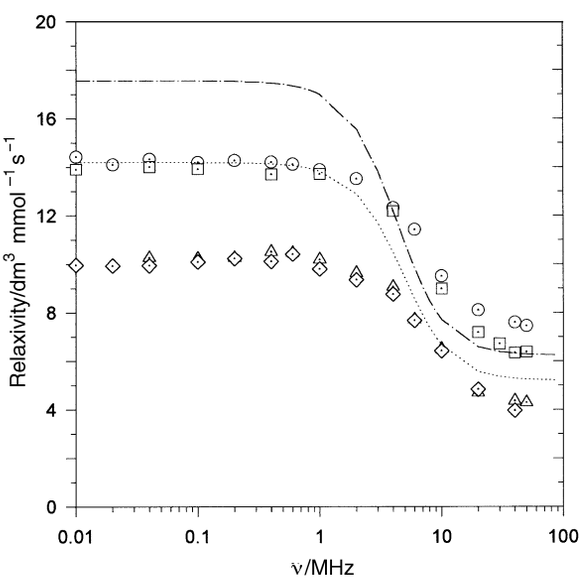

Fig. 3 Proton-relaxation dispersion curves of [Gd(odotra)] (⊙, ◇) and [Gd(dotra)] (⊡, △) at 25 (upper curves) and 37 °C (lower curves). These data are compared with the corresponding curves calculated for $[Gd(dota)]^-$[16] with a hydration number of two at 25 (—·—·—) and 37 °C (·····)

On the more practical side, [Gd(odotra)] is not expected to be a useful magnetic resonance imaging contrast agent because of its probable low stability. However, our measurements confirm that designing contrast agents with a higher number of exchangeable water molecules does not necessarily lead to the expected increase in relaxivity at low and medium fields presumably because of the lower symmetry and rigidity of the ligands. Should $[Gd(dota)]^-$ contain two hydration water molecules instead of one, one would expect[16] a relaxivity at 0.1 MHz close to 17.9 and 14.1 $dm^3\ mmol^{-1}\ s^{-1}$ at 25 and 37 °C respectively, *i.e.* significantly higher than the values obtained for [Gd(odotra)] and [Gd(dotra)] as shown in Fig. 3.

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