Pergamon

Polyhedron Vol. 14, No. 4, pp. 567 569, 1995
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0277 5387/95 $9.50 + 0.00

0277-5387(94)00318-1

COMMUNICATION

NEUTRAL GADOLINIUM(III) COMPLEXES OF BULKY OCTADENTATE dtpa DERIVATIVES AS POTENTIAL CONTRAST AGENTS FOR MAGNETIC RESONANCE IMAGING

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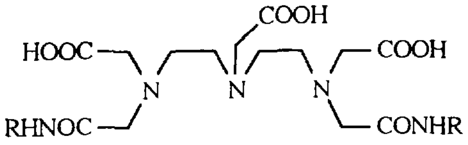
(*Received* 13 *July* 1994; *accepted* 8 *August* 1994)

Abstract—A series of bulky and neutral gadolinium complexes of [bis(R-amide)dtpaH_3] (where R = Pr^i, Bu^i, Bz and phenylethyl, L^1–L^4) with potential application as contrast agents for magnetic resonance imaging has been prepared and characterized; the relaxivity of these complexes is comparable to the contrast agent $[Gd(dtpa)(H_2O)]^{2-}$ which is currently used in clinics; the X-ray structure analysis of the gadolinium(III) complex of L^3 reveals a neutral nine-coordinate complex featuring a water molecule in the tricapped trigonal prismatic metal coordination sphere.

Progress in the development of neutral paramagnetic magnetic resonance imaging (MRI) contrast agents has been focused on the derivatives of diethylenetriaminepentaacetic acid (dtpaH_5) and 1, 4, 7, 10 - tetrakis (carboxymethyl) - 1, 4, 7, 10 - tetraazacyclododecanoic acid (dotaH_4). At present two neutral gadolinium(III) complexes, [Gd(bis(methylamide)dtpa)][1] and [Gd(hp-do3a)][2] where hp-do3a is 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate, are currently being used in human studies. A comparative study of the neutral $[Gd(bis(methylamide)dtpa)(H_2O)]$ and the dianionic MRI contrast agent, currently in clinical use, $[Gd(dtpa)(H_2O)]^{2-}$ has shown that the neutral complex not only has advantageous osmolarity but also better LD_{50} properties.[1] Despite this *in vivo* targeting ability, the bis(methylamide) dtpa–gadolinium(III) complex is restricted to the extracellular compartment, a behaviour similar to that of the dtpa complex. However the partial lipophilic bis(R-amide)dtpaH_3 ligand (R = undecanoic acid, Puchel) does have intracellular activity and has been studied extensively as a complexing agent for removing deposited radionuclides such as plutonium.[3] Systematic variation of the amide substituents of the dtpaH_3 ligand is being studied with the aim of balancing control of solubility and targeting properties of the resulting gadolinium complexes thus allowing fine tuning of potential MRI agents.

The bis(amide)dtpaH_3 ligands L^1–L^4 were pre-



	R
L^1	Pr^i
L^2	Bu^i
L^3	Bz
L^4	phenylethyl

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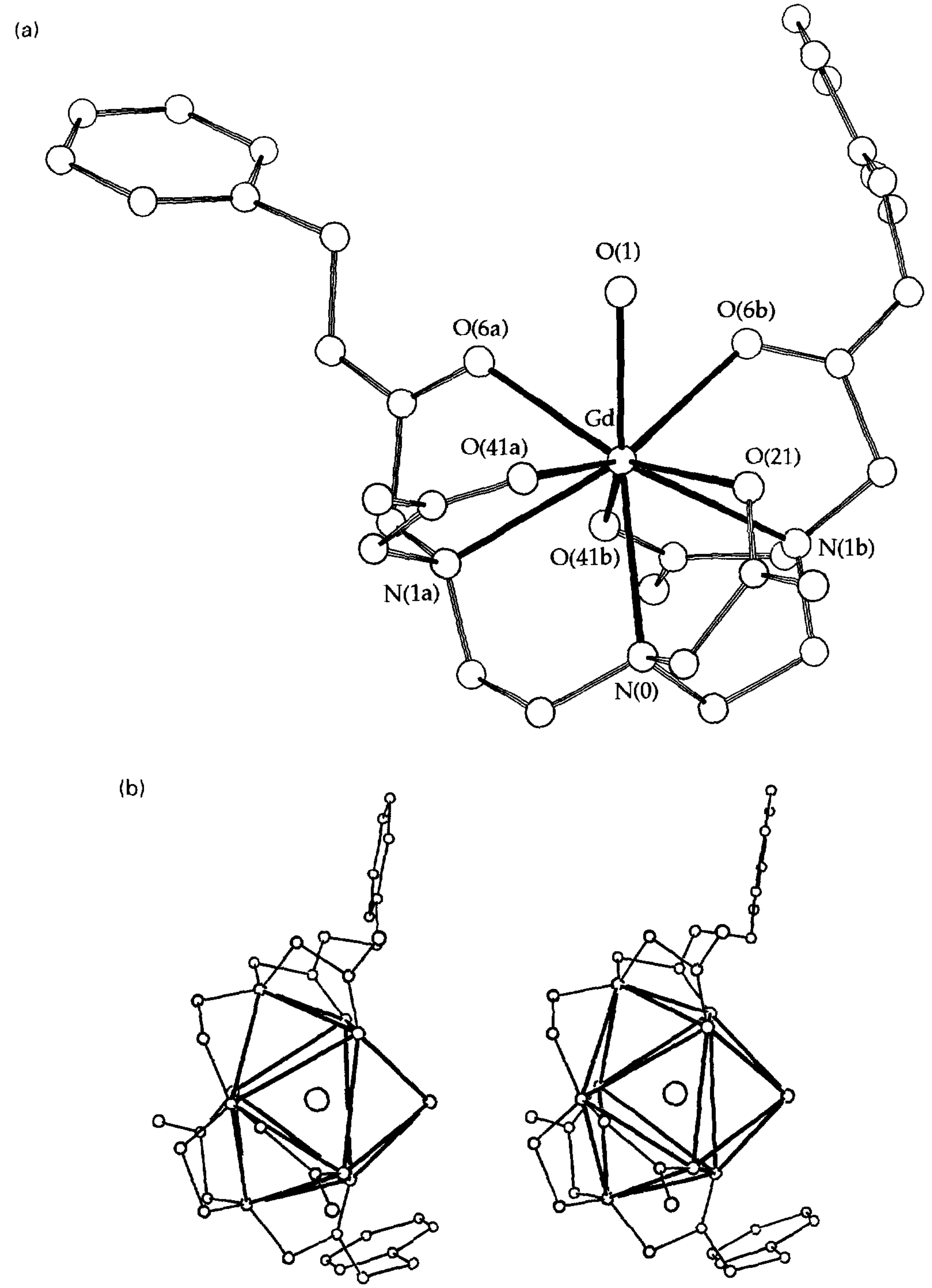

Fig. 1. The molecular structure of $[GdL^3(H_2O)]$: (a) Gd—N(0) 2.600(7), Gd—N(1a) 2.665(7), Gd—N(1b) 2.751(8), Gd—O(41a) 2.371(7), Gd—O(41b) 2.368(6), Gd—O(6a) 2.455(7), Gd—O(6b) 2.427(7), Gd—O(21) 2.384(7), Gd—O(1) 2.442(7) Å; (b) Stereoview of the tricapped trigonal prismatic metal coordination polyhedron.

pared by adapting the published method for the synthesis of bis(ethylamide)dtpaH_3[4] and their gadolinium(III) complexes by refluxing aqueous solutions with gadolinium oxide. The ligands L^1, L^2 and L^3 have not been isolated before, but the structure of the ligand L^3,[5] and of its yttrium(III) complex[6] have been reported recently. Although the complexes are neutral, they are readily soluble in cold water, with the exception of $[Gd(L^3)(H_2O)]$ which solubilizes only on heating. Shifts of *ca* 20–90 cm^{-1} to lower energy were observed for the carbonyl stretching frequencies on gadolinium complexation indicating amide oxygen coordination. The magnetic moments in the range 7.2–7.8 B.M. are consistent with seven unpaired electrons in each gadolinium complex.

The compounds are efflorescent making exact assignment of the water content difficult. X-ray structural analysis† of the L^3 complex established the presence of one coordinated water and eight waters of crystallization per molecule. Figure 1(a) shows the neutral molecular structure of $[GdL^3(H_2O)]$ in which the dtpa unit of the ligand effectively "cups" the metal ion in a hydrophilic cleft leaving the ninth site available to coordinate water. The metal coordination polyhedron most closely resembles a tricapped trigonal prism [Fig. 1(b)]; the two trigonal faces of the prism are described by N(0), O(41a), O(21) and O(6a), O(6b), O(41b), respectively, while N(1a), N(1b) and the oxygen of the coordinated water [O(1)] cap the three rectangular faces. The metal coordination geometry in $[GdL^3(H_2O)]$ resembles the gadolinium(III) coordination geometry in the complex derived from the related bis(ethylamide) ligand[4] but, interestingly, contrasts with the square antiprismatic coordination reported for yttrium(III) in $[YL^3(H_2O)]$.[6] In common with other lanthanide polyaminocarboxylate complexes,[4,6,7] $[GdL^3(H_2O)]$ features relatively long metal–amine bond lengths [2.600(7)–2.751(8) Å] and short metal–carboxylate bonds [2.368(6)–2.384(7) Å], consistent with the hard character of the trivalent lanthanides. There is a total of 16 uncoordinated water molecules in the unit cell which form a complicated three-dimensional network of hydrogen bonds involving all the potential hydrogen-bonding donors of the complex.

The R_1 proton relaxivity at 298 K of the gadolinium(III) complex of L^1–L^4 are 4.27, 5.09, 4.50 and 4.86 $dm^3\ mmol^{-1}\ s^{-1}$ respectively. These are comparable with the proton relaxivities of $[Gd(dtpa)(H_2O)]^{2-}$ and $[Gd(bis(ethylamide)dtpa)(H_2O)]$ and indicate the presence of one coordinated water in each complex, giving an overall formulation $[GdL^{1-4}(H_2O)] \cdot xH_2O$; in the case of the L^3 complex, X-ray structural analysis shows that $x = 8$. The distribution coefficient of $[NdL^4(H_2O)]$ in octanol/water measured by UV/vis spectroscopy is 0.24, and from this the potential of the gadolinium(III) complex of L^4 as intracellular agent may be deduced. The advantage of these bulky complexes being water soluble and yet neutral is of great significance in the design of MRI contrast agents.

Acknowledgements—We thank the S.E.R.C. for financial support (I.J.S.) and access to the Chemical Database Service at Daresbury, and Dr Orla Ni Dhubhghaill (Institut de Chimie Minerale et Analytique, Lausanne) for the relaxivity measurements.

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† *Crystal data*: $[GdL^3(H_2O)] \cdot 8H_2O$, $(C_{28}H_{36}N_5O_9Gd)(H_2O)_8$, $M = 888.0$, triclinic, space group $P\bar{1}$ (No. 2), $a = 12.651(3)$, $b = 14.140(3)$, $c = 12.649(3)$ Å, $\alpha = 91.74(2)$, $\beta = 114.77(3)$, $\gamma = 68.33(2)^\circ$. $U = 1888.56$ Å^3, $Z = 2$, $F(000) = 910$, $D_c = 1.562$ g cm^{-3}, μ(Mo-$K\alpha$) = 17.5 cm^{-1}, $\lambda = 0.71069$ Å. A colourless crystal with dimensions $0.54 \times 0.29 \times 0.22$ mm^3 was mounted in a Lindemann tube under solvent and used for data collection. Data were collected on a Philips PW1100 four-circle diffractometer in the θ-range 3–21° using a scan width of 0.9° and a scan speed of 0.05 deg s^{-1} with the method described previously.[8] Refinement[9] converged at $R = 0.0455$ and $Rw = 0.0450$ for 3235 absorbance corrected[10] data $[I/\sigma(I) \geq 3]$ and 461 parameters.