

Synthesis and Crystal Structure of a Novel Hexaaza Macrocylic Ligand with 2-Hydroxy-3,5-dimethylbenzyl Pendant Arms and its Gadolinium(III) Complex

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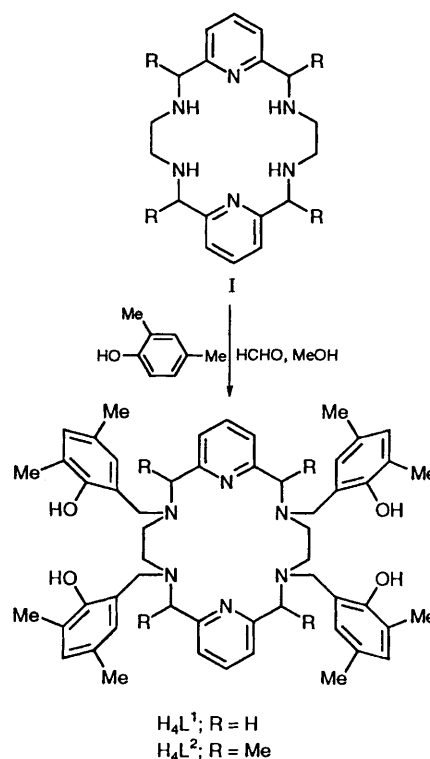
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Two new hexaaza macrocycles H_4L^1 and H_4L^2 substituted with 2-hydroxy-3,5-dimethylbenzyl groups on the secondary amine nitrogens have been synthesized; the crystal structure of H_4L^2 shows that the six nitrogen donor atoms adopt a chair conformation in the solid state, and the gadolinium(III) complex of monodeprotonated H_4L^1 , $[Gd(H_3L^1)(NO_3)]NO_3 \cdot 3H_2O$, has a nine-co-ordinate gadolinium bound to one phenolic oxygen atom, two oxygen atoms from one nitrate and six nitrogen donors from the macrocyclic ligand.

The application of chelating agents used in biology and medicine has progressed dramatically over the last decade.¹ Macrocycles functionalized with co-ordinating pendant arms have received much attention recently as a result of their enhanced stability and their favourable kinetics for the overall formation process.² We have therefore succeeded in preparing two novel potentially decadentate macrocyclic ligands H_4L^1 and H_4L^2 each possessing a N_6O_4 donor set based on the hexaaza macrocycles I. The additional donor groups, one on each arm, should provide extra co-ordination to entrap the cation within the macrocyclic cavity thus enhancing complex stability. A wide variety of pendant arms containing hydroxyl functional groups, such as 2-hydroxyethyl,³ 2-hydroxybenzyl,⁴ 3-*tert*-butyl-2-hydroxybenzyl⁴ or 2-hydroxy-3,5-dimethylbenzyl,⁵ have previously been attached to the secondary amine nitrogen but only on tetraaza or triaza macrocycles, so that the ligands H_4L^1 and H_4L^2 reported here are the first examples of hydroxyl functional groups as pendant arms on hexaaza macrocycles. The new gadolinium(III) complex with H_4L^1 has proved to have a relaxivity better than that with *N,N,N',N'',N''*-diethylenetriaminepentaacetic acid (H_5dtpa), $[Gd(dtpa)(H_2O)]^{2-}$, which is currently used in clinics as a contrast agent in magnetic resonance imaging.

The synthesis of the substituted derivatives H_4L^1 and H_4L^2 followed a Mannich-type reaction of I [2.8 g ($R = H$), 3.6 g ($R = Me$); 9×10^{-3} mol] with 2,4-dimethylphenol (9.5 cm³, 8×10^{-2} mol) in the presence of methanal (8.1 cm³, 0.11 mol) in a methanolic solution. Elemental analyses of these ligands were satisfactory, the absence of NH bands in the IR spectra at 3285 and 1595 cm⁻¹ indicating that all the amino hydrogens had been substituted. Liquid secondary ion mass spectroscopy (LSIMS) resulted in molecular ions of $[H_4L^1 + H]^+$ at m/z 864,



$[H_4L^2 + H]^+$ at m/z 920, and the loss of whole pendant arms consecutively on fragmentation. The ¹H NMR spectrum of H_4L^1 showed well defined peaks † which can be assigned to the proposed compound thus confirming that the four ethylenediamine nitrogens are fully substituted. In contrast, the ¹H NMR spectrum of H_4L^2 gave a broad band at δ 10.2 which is typical of a phenolic OH group and complex multiplets for the

† ¹H NMR data for H_4L^1 (250 MHz, CDCl₃, SiMe₄): δ 2.16 (12 H, s, 4Me), 2.20 (12 H, s, 4Me), 2.87 (8 H, s, 4 benzylic CH₂), 3.66 (8 H, s, 2CH₂CH₂), 3.74 (8 H, s, 4 pyridyl CH₂), 6.57 (4 H, d, ³J 1.63, 4 phenolic CH), 6.84 (4 H, d, ³J 1.63, 4 phenolic CH), 7.06 (4 H, d, ³J 7.71, 4 pyridine CH), 7.55 (2 H, t, ³J 7.71 Hz, 2 pyridine CH) and 10.38 (4 H, s, 4OH).

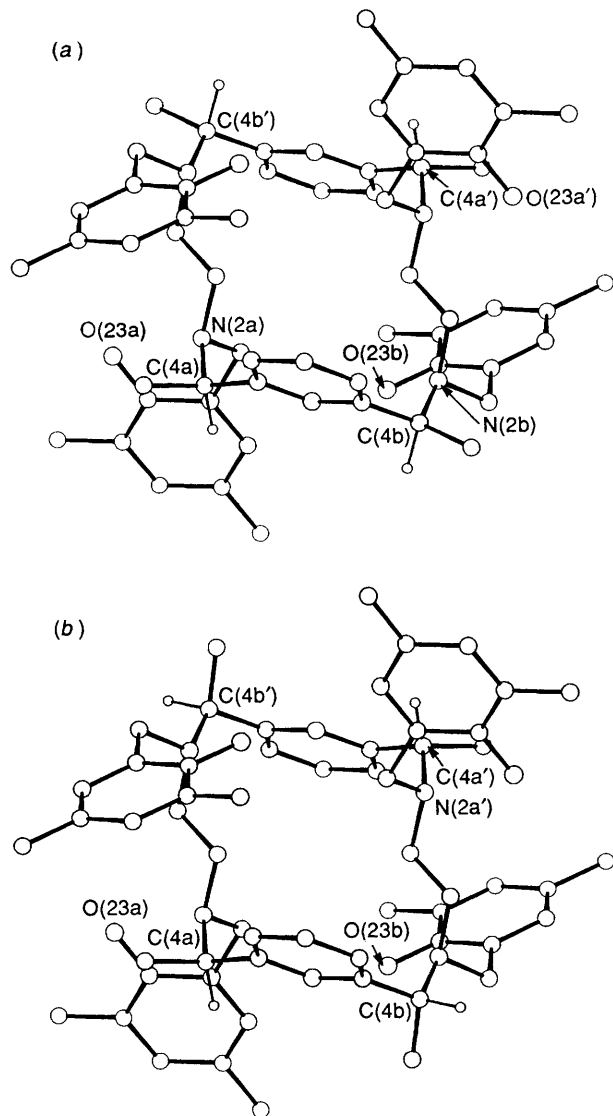


Fig. 1 The two centrosymmetric diastereoisomers observed in the solid-state structure of H_4L^2 showing the configurations at the chiral carbon atoms C(4a), C(4b), C(4a') and C(4b'): (a) *RSSR* and (b) *RRSS*

corresponding proton bands, indicating the presence of diastereoisomers. The crystal structure* of H_4L^2 shows the presence of two independent, exactly centrosymmetric, ligand molecules in the crystal and confirms the presence of two different diastereoisomers. These may be deduced from the *ca.* 60:40 disorder of the terminal methyl group, C(6a), and the hydrogen atom, H(4a), attached to the chiral carbon, C(4a), which are explained by the presence at one site in the crystal of isomers with configurations *RSSR* and *RRSS* at the four chiral carbon atoms C(4a), C(4b), C(4a') and C(4b') respectively as shown in Figs. 1(a) and 1(b) respectively for the first independent molecule. The second independent molecule is virtually identical to the first, apart from the disorder being closer to 50:50 between the two superimposed diastereoisomers.

The gadolinium(III) complex of H_4L^1 (20% yield) was isolated

* Crystal data. H_4L^2 , $C_{58}H_{74}N_6O_4$, $M = 919.26$, triclinic, space group $P\bar{1}$ (no. 2), $a = 12.320(3)$, $b = 22.594(3)$, $c = 10.591(3)$ Å, $\alpha = 98.82(2)$, $\beta = 104.81(2)$, $\gamma = 102.57(2)^\circ$, $U = 2712.77$ Å³, $Z = 2$, $F(000) = 992$, $D_c = 1.125$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.7$ cm⁻¹, $\lambda = 0.710$ 69 Å. Full-matrix least-squares refinement, converged at $R = 0.0972$ and $R' = 0.1035$ with $w = 1/[\sigma^2(F) + 0.000094F^2]$ assigned to 2098 unique reflections with $I/\sigma(I) > 3$. Structure solved using SHELX 76.⁶

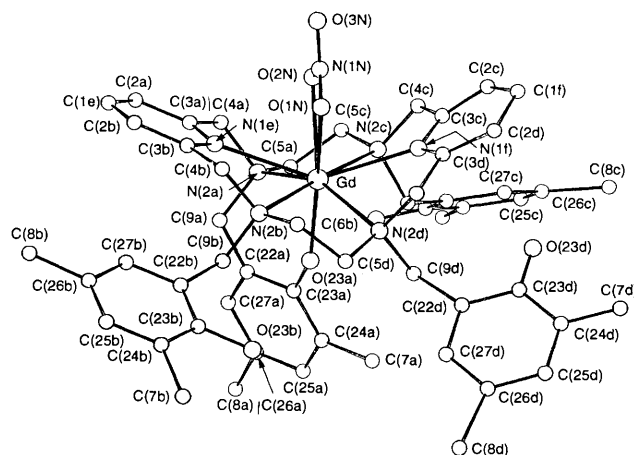


Fig. 2 The irregular nine-co-ordinate structure of the cation $[Gd(H_3L^1)(NO_3)]^+$ showing the co-ordination of one of the four pendant arms. Selected bond lengths (Å): Gd–N(2a) 2.615(13), Gd–N(2b) 2.718(11), Gd–N(2c) 2.694(10), Gd–N(2d) 2.639(12), Gd–N(1e) 2.559(11), Gd–N(1f) 2.548(12), Gd–O(1N) 2.501(11), Gd–O(2N) 2.460(11), Gd–O(23a) 2.138(10)

as pure well defined crystals when a methanolic solution of excess gadolinium nitrate (0.2 g, 4.5×10^{-4} mol) was added to a refluxing suspension of the ligand in methanol. The complex was formulated as $Gd(H_3L^1)(NO_3)_2(H_2O)_3$ from elemental analysis and by LSIMS which gave a base peak corresponding to $[Gd(H_3L^1)]^+$. The fragmentation of the complex follows the same pattern as the ligands. The IR stretching frequencies of the nitrate groups at 1481, 1384 and 1270 cm⁻¹ indicated the nitrate ions were possibly bidentate ligands. The crystal structure† (Fig. 2) shows the presence of a cationic complex $[Gd(H_3L^1)(NO_3)]^+$ in which the ligand adopts a boat conformation, in contrast to the chair conformation observed in the analogous ligand H_4L^2 in the solid state, with all the nitrogen donors being co-ordinated (Gd–N 2.548–2.718 Å). The gadolinium(III) ion has an irregular nine-co-ordinated geometry completed by a bidentate nitrate ligand [Gd–O(1N) 2.501(11) and Gd–O(2N) 2.460(11) Å] and the phenolic oxygen atom, O(23a), of one pendant arm, which forms the shortest metal–ligand bond in the structure [Gd–O(23a) 2.138(10) Å]. The remaining three pendant arms radiate out away from the metal showing no sign of co-ordination (Gd...O 5.390–5.626 Å).

The magnetic moment of $[Gd(H_3L^1)(NO_3)]NO_3 \cdot 3H_2O$ was found to be 6.5 μ_B at 303 K, lower than the typical value expected for gadolinium(III), and we have no simple explanation for this. The relaxivity, R_1 , of $[Gd(H_3L^1)(NO_3)]^+$ was 8.2×10^{-3} dm³ mol⁻¹ s⁻¹ (28 °C, 10 MHz), which is comparable to the relaxivity of $[Gd(\text{dota})]^-$ (7.2×10^{-3} dm³ mol⁻¹ s⁻¹ at 23 °C, 10 MHz, $H_4\text{dota} = 1,4,7,10$ -tetraazacyclodecane-1,4,7,10-tetraacetic acid) and better than that of $[Gd(\text{dtpa})$ -

† Crystal data. $[Gd(H_3L^1)(NO_3)]NO_3 \cdot 3H_2O$, $C_{54}H_{71}GdN_8O_{13}$, $M = 1197.5$, triclinic, space group $P\bar{1}$ (no. 2), $a = 14.220(3)$, $b = 16.699(3)$, $c = 13.553(3)$ Å, $\alpha = 104.850(2)$, $\beta = 110.261(2)$, $\gamma = 68.746(2)^\circ$, $U = 2782.16$ Å³, $Z = 2$, $F(000) = 1238$, $D_c = 1.429$ g cm⁻³, $\mu(\text{Mo-K}\alpha) = 12.1$ cm⁻¹, $\lambda = 0.710$ 69 Å. Full-matrix least-squares refinement with $w = 1/\sigma^2(F)$ applied to all reflections converged at $R = 0.0709$ ($R' = 0.0766$) for 3526 absorption corrected⁷ data with $I/\sigma(I) > 3$. Structure solved using SHELX 76.⁶ Two unco-ordinated pendant arms showed a 50:50 rotational disorder, so that the sites of O(23c) and O(23d) were interchanged with H(27c) and H(27d) respectively; there was also severe disorder of the NO_3^- counter ion and the solvent water molecules; the final difference-Fourier synthesis showed no maxima greater than $1 e^{-3}$. Atomic coordinates, thermal parameters and bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, pp. xxiii–xxviii.

$(\text{H}_2\text{O})]^{2-}$ ($5.6 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 23°C , 10 MHz, $\text{H}_5\text{dtpa} = N,N,N',N'',N''$ -diethylenetriaminepentaacetic acid).⁸ The good relaxivity of $[\text{Gd}(\text{H}_3\text{L}^1)(\text{NO}_3)]^+$ can be explained by the fairly exposed Gd^{III} ion, the co-ordinating phenolic oxygen being on the opposite side to the co-ordinating nitrate ion, which allows its easy access to water molecules. However R_1 was reduced dramatically to $2.8 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ when the gadolinium(III) complex was in phosphate buffer (pH 6).

Acknowledgements

We thank the SERC (E. G. E) and PCFC (N. C.) for studentships, Amersham International plc for financial support, and the SERC for access to the Chemical Database Service at Daresbury.

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Received 13th October 1993; Communication 3/06123J