Stability, ^{71}Ga NMR, and Crystal Structure of a Neutral Gallium(III) Complex of 1,4,7-Triazacyclononanetriacetate: a Potential Radiopharmaceutical?

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The gallium complex of 1,4,7-triazacyclononanetriacetate is C_3-symmetric both in solution and in the solid state and may be observed by ^{71}Ga NMR in aqueous solution in the pH range −0.8 to +12.

The importance of complexes of gallium and indium in diagnostic nuclear medicine has led to a resurgence of interest in their co-ordination chemistry.[1,2] The positron emitting radioisotope ^{68}Ga ($t_{1/2}$ 68 min) is an important isotope for positron emission tomography (PET),[3] while ^{67}Ga ($t_{1/2}$ 3.25 days) and ^{111}In ($t_{1/2}$ 2.81 days) are useful imaging agents in immunoscintigraphy.[4,5] A prerequisite for the use of these isotopes *in vivo* is that their complexes should be kinetically inert, resisting acid or cation mediated decomplexation and subsequent exchange with serum proteins such as transferrin (*e.g.* log K, Ga-transferrin 20.3).[6] In addition, neutral, low molecular weight and lipophilic complexes that will cross the blood-brain barrier, and hence may serve as brain scanning agents, are sought.

The development of a set of *C*-functionalised macrocyclic ligands that may be attached to a monoclonal antibody and radiolabelled with ^{64}Cu, ^{111}In, and ^{90}Y has been reported.[7,8,9] The indium macrocycle used was 1,4,7-triazacyclononanetriacetic acid (**1**) and we have recently reported the structure of its seven co-ordinate indium hydrochloride complex.[10] The hexadentate ligand also forms a neutral complex with gallium which is remarkably inert with respect to acid-promoted dissociation.

Reaction of (**1**) with $Ga(NO_3)_3$ in 40 mM aqueous nitric acid led to formation of a colourless complex [m/z (FAB): 372, 370 (M^+ + 1)], crystals of which were obtained by slow evaporation of the aqueous solution (pH ~2). The co-ordination geometry of the gallium atom is approximately octahedral with the three nitrogens of the macrocycle occupying a facial set of sites (Figure 1). All three *trans* N–Ga–O angles are approximately 167° due to the intrinsically small bite angle of the adjacent 5-ring chelates. This has led to a relative twist of the N_3 and O_3 planes of donor atoms by 13° away from a symmetrically staggered conformation. The two symmetrically occupied triangular faces are parallel (0.6°) but that comprising the oxygen atoms is enlarged while the face including the three nitrogen atoms is smaller. Thus the angles between the oxygen atoms average 95° whereas the angles between the nitrogen atoms average 84°. The whole molecule has approximately C_3 symmetry which is not crystallographically imposed.† There is no evidence for hydrogen-bonding in the structure.

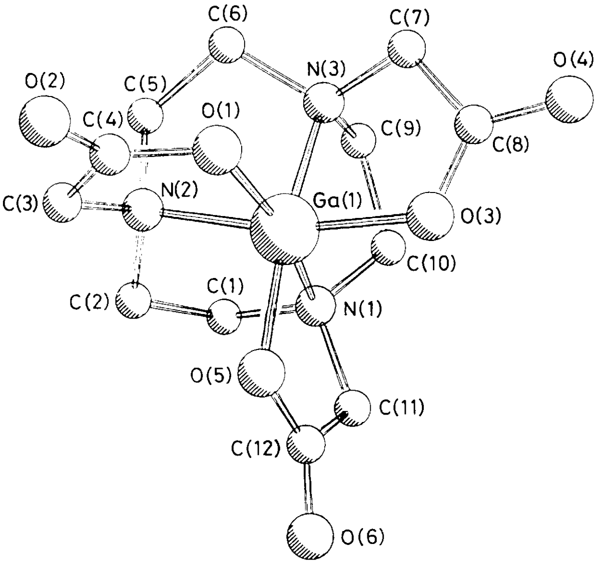

Figure 1. Perspective (ORTEP) drawing of the molecule. Selected bond lengths and bond angles: Ga–O(5) 1.940(5), Ga–O(3) 1.933(6), Ga–N(2) 2.102(6), Ga–N(1) 2.104(6) Å; O(3)–Ga–O(5) 95.0(2), O(3)–Ga–N(2) 167.7, O(1)–Ga–N(2) 83.5(2), N(2)–Ga–N(3) 84.3(2)°.

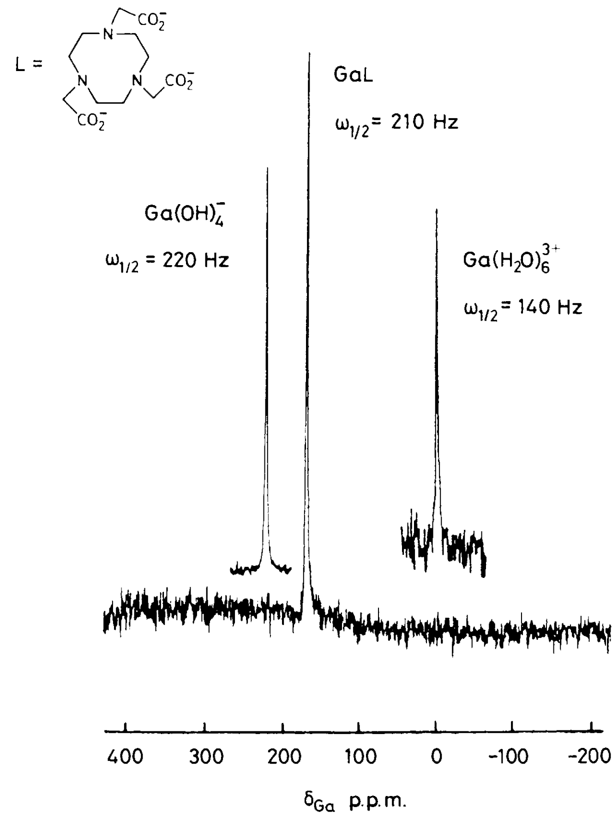

Figure 2. ^{71}Ga NMR spectra of aqueous gallium complexes (298 K, D_2O, 76.3 MHz, μ = 72°).

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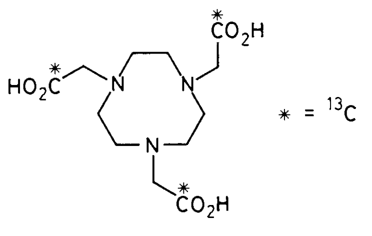
† *Crystal data* for [Ga·(**1**)]: [$C_{12}H_{18}GaN_3O_6$], M = 370.01, monoclinic, space group $P2_1/n$, a = 8.927(10), b = 13.646(15), c = 12.086(10) Å, β = 105.36(7)°, U = 1419.6(25) Å^3, Z, = 4, D_c = 1.731 g cm^{-3}, μ(Mo-K_α) = 19.62 cm^{-1}, F(000) = 759.78; room temperature X-ray data (3.5 < 2θ < 50°) were recorded on a Nicolet R3 4-circle diffractometer by a ω-scan method, yielding 1491 independent reflections with $|F|r(|F|)$ > 3.0, which were corrected for absorption, Lorentz and polarisation effects and refinement converged at R = 0.0627. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



(1)

The Ga–O and Ga–N bond lengths are similar to those reported for related complexes of gallium comprising N_3O_3 co-ordination[1,2] but these other complexes had twist angles of 52° for a salicylaldimine complex (*i.e.* nearly trigonal prismatic)[2] and *ca.* 12° for a protonated tris-phenolic derivative of triazacyclononane.[1] The gallium complex is similar in structure to the related neutral chromium(III) and nickel(III) complexes of (**1**) for which nearly regular octahedral co-ordinations have been defined with twist angles of 11 and 7°, respectively.[11,12]

The gallium complex of (**1**) has been characterised in solution using ^1H and ^{71}Ga NMR. The proton spectrum (298 K, pD 5, D_2O) revealed diastereotopic CH_2N protons resonating as multiplets centred at δ 3.51 and 3.23 with the methylene CH_2CO groups resonating as a singlet at δ 3.88 consistent with local C_3 symmetry. The ^{71}Ga spectrum (298 K, 76.3 MHz, 0.01 M, 2000 scans acquired in 200 s) gave a single resonance at δ +171 p.p.m. [to higher frequency of $Ga(H_2O)_6{}^{3+}$ at δ 0 p.p.m.] with a line-width of 210 Hz (Figure 2). Previously only the highly symmetric $Ga(OH)_4{}^-$ and $Ga(H_2O)_6{}^{3+}$ species had been observed by ^{71}Ga NMR in aqueous solution.[13] Moreover the gallium complex of (**1**) was observed unchanged by ^{71}Ga NMR after 60 days in HNO_3 (6 M) or LiOH (0.01 M). Line broadening in ^{71}Ga NMR may be ascribed either to ligand exchange processes or more commonly to interaction of the quadrupole moment (0.112) with the electric field gradient at the nucleus. Evidently in the observed gallium complex of (**1**), the electric field gradient in the planes orthogonal to the 'N_3–O_3 axis' is minimised; a testimony to the C_3-symmetry of the complex in solution. The corresponding indium complex of (**1**) is also resistant to acid-catalysed dissociation. Using ^{13}C-labelled (**1**) (prepared by reaction of triazacyclononane with $BrCH_2{}^{13}CO_2H$), free and complexed ligand are easily distinguished by ^{13}C NMR in D_2O [$\Delta\delta_C$ (carbonyl) 4 p.p.m.] and the rate of dissociation was first order in acid and complex with an observed rate constant (296 K) of 1.8 (±0.3) $\times$ 10^{-4} dm^3 mol^{-1} s^{-1}. Dissociation at pD −0.4 was essentially complete in 90 min.

The high stability in acid solution of the gallium complex of (**1**) is striking. It has a low molecular weight (370), is electrically neutral, and may be observed by ^{71}Ga NMR in aqueous media. Such properties augur well for its use as a radiopharmaceutical.

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