Synthesis, Characterization and Solid State Structure of a Neutral Gallium(III) Amino Thiolate Complex: A Potential Radiopharmaceutical for PET Imaging

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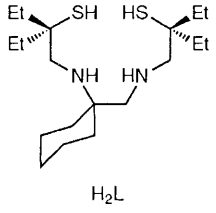
The neutral gallium complex of a bisaminoethanethiol ligand has a square pyramidal coordination geometry with Ga–N and Ga–S bonds.

We are investigating gallium(III) complexes of bisaminoethanethiol ligands (e.g. H_2L) as potential myocardial perfusion imaging agents for positron emission tomography (PET).[1] The commercially available $^{68}Ge/^{68}Ga$ generator[2] can conveniently provide a source of ^{68}Ga, a positron-emitting radioisotope. Radiopharmaceuticals based on ^{68}Ga are in routine use for human studies;[3] however, development of lipophilic^{68} Ga tracers for perfusion imaging of the brain and heart has not been successful.[4] We report here the synthesis, X-ray crystal structure and preliminary spectral characterization of a gallium(III) complex which, when prepared with ^{68}Ga, shows excellent myocardial uptake and high quality PET images in animals; these details will be reported elsewhere.[1] This complex is one of a few examples of monomeric, five-coordinate, neutral gallium(III) complexes[5,6] and it is very stable to air and moisture. The tracer complex is stable to saline solution and *in vivo*. Gallium–sulphur bonding is unusual;[6,7] this is one of few gallium–sulphur complexes to be isolated and characterized and the first with square pyramidal coordination geometry containing Ga–N and Ga–S bonds.

Reaction of $GaCl_3$ with an aqueous, methanolic solution of the dihydrochloride of ligand L[8] results in the formation of the complex [GaCl(L)] **1**. The complex formation is assisted by the addition of ammonium hydroxide solution to neutralize two equivalents of hydrogen ions released during the S–Ga bond formation. The neutral Ga complex [Λ_M, 10^{-3} mol dm^{-3} in MeCN: 0.423 Ω^{-1} cm^2 dm^3 mol^{-1}; *m/z* (electron ionization): 464 for **1**, 427 for **1** − Cl$^-$] is soluble in organic solvents but insoluble in water. The complex is stable in air as well as in solution.

Colourless crystals of **1** were grown from dimethylformamide (DMF)–dilute HCl solution.† Both hydrogens bonded to N(1) and N(2) were located in the difference Fourier map. The oxygen of DMF, which crystallized with the complex, is involved in hydrogen bonding with the N(1) amine proton [O · · · H(N1) 2.048 Å; O · · · N(1) 2.934 Å]. The N(2) amine proton is hydrogen bonded to the Cl of another molecule [Cl · · · H(N2) 2.671 Å; Cl · · · N(2) 3.452 Å]. An ORTEP drawing of complex **1** is shown in Fig. 1. The coordination geometry about the gallium is a distorted square pyramid; the base plane consists of N(1), N(2), S(2) and Cl and the axial ligand, S(1), is bent by about 10° towards N(1), away from S(2). Atoms in the base plane are coplanar within < 0.05 Å. The cyclohexyl moiety is in the chair conformation. The Ga–S bond distances in **1** are appreciably less than in other Ga–S compounds reported in the literature.[9,10] Ga–N and Ga–Cl bond distances fall within ranges of 2.034(7)–2.433(6) and 2.235(3)–2.440(3) Å, respectively, in for five- and six-coordinate complexes reported in the literature.[9–12]

The complex retains its integrity in solution; its ^1H NMR spectrum in $CDCl_3$ (room temperature) shows resonances for the eight diastereotopic protons on the backbone of the ligand [protons on C(2), N(1), C(5), N(2) and C(4)], and the methyl and methylene protons of the cyclohexane and ethyl groups [δ, multiplicity, integration, assignment: 3.08, dd, 2, N(2)–H and H on C(5) or C(4); 2.94 dd, 2, H on C(2) and on C(4) or C(5); 2.69, t, 1, H on C(4) or C(5); 2.52, t, 1, H on C(5) or C(4); 2.31 br m, 1, N(1)–H; 2.11, t, 1, H on C(2); 1.59, br m, 18, CH_2 of cyclohexane and tetraethyl groups; 0.96, m, 12, CH_3]. The ^{13}C NMR spectrum shows 19 resonances corresponding to the 19 unique carbon atoms. Resonances of low intensity (<5% for ^1H) are observed close to the major resonances in the ^1H and ^{13}C spectra, indicating that a small percentage of a separate species may exist in solution. NMR data taken in DMF and DMF–H_2O show that two Ga(L) species in close to equal amounts are present in these solvent



H_2L

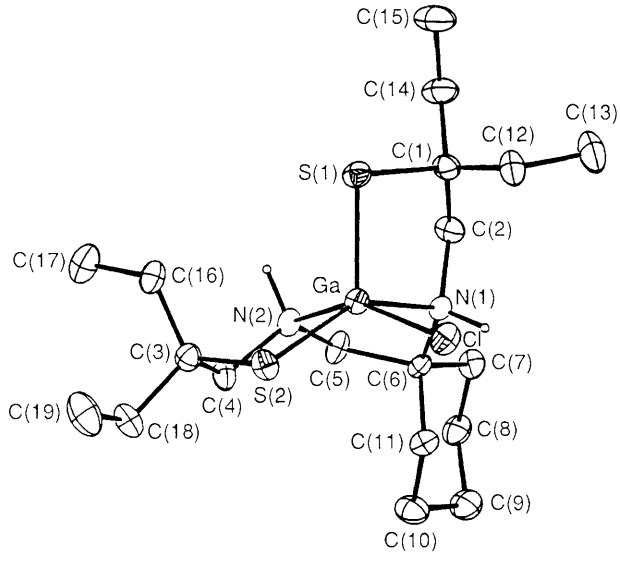


Fig. 1 ORTEP diagram of the complex [GaCl(L)] **1**. Selected interatomic distances (Å) and angles (°) are as follows: Ga–Cl 2.365(1), Ga–N(1) 2.078(3), Ga–N(2) 2.204(3), Ga–S(1) 2.247(1), Ga–S(2) 2.256(1), Cl–Ga–N(2) 151.92(8), Cl–Ga–N(1) 90.75(8), Cl–Ga–S(1) 106.79(4); Cl–Ga–S(2) 89.90(4), S(1)–Ga–S(2) 121.25(4), N(1)–Ga–S(1) 91.60(8), N(1)–Ga–S(2) 145.32(8), N(2)–Ga–N(1) 78.3(1), N(2)–Ga–S(1) 99.36(8), N(2)–Ga–S(2) 85.08 (9).

† The crystal system is monoclinic, space group $P2_1/n$ with a = 10.703(1), b = 12.616(1), c = 21.429(2) Å, β = 102.54(2)°, V = 2825 Å^3, Z = 4. The structure was solved by standard heavy atom techniques and refined by full-matrix least-squares methods using 4780 reflections with $I > 3\,\sigma(I)$ to a final R = 0.043 and R_w = 0.070. Hydrogen atoms were found from difference Fourier synthesis and all non-hydrogen atoms were refined anisotropically. Data were collected on an Enraf-Nonius CAD4 diffractometer at ambient temperature. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

systems [species 1 (δ, multiplicity, integration, assignment): 4.7, br m, 1, N(2)H; 3.13, m, 3, N(1)–H, H on C(5) and H on C(4); 2.9, m, 1, C(1)H; 2.83, dd, 1, C(5)–H; 2.40, t, 1 C(4)–H; 2.25, t, 1, C(1)–H; species 2: 4.50–4.42, br m, 1, NH; 4.3, br d, 1, NH; 3.26, dd, 1, CH; 2.11, t, 1 CH; 2.9, m, 1, CH; 2.5, br m, 1, CH; 2.1, br m, 2 CH]. The structures and stabilities of the aqueous solution species are of significance in the biochemistry of this class of compounds and the design of future radiopharmaceuticals and are being further investigated.

The chemistry and biology of the tracer complex can be probed with ^{67}Ga ($t_{\frac{1}{2}}$ 78 h, γ energies 238 and 161 keV). The tracer complex may be prepared by reaction of the ligand with [^{67}Ga]gallium citrate at pH 3–5. The radiochemical purity of the complex is >95%, determined by TLC (silica gel, 75:25 acetone–acetic acid, R_f 0.8, free Ga is found at origin) and reverse phase HPLC [Hamilton PRP^{-1} column, MeCN–5 mmol dm^{-3} dimethyl glutarate (90:10); pH 7; flow rate 1 cm^3 min^{-1}; retention time 6.5 min, free Ga retention time 2 min]. Ion exchange experiments[13] with the tracer [^{67}Ga]-**1** complex indicate that a monocation exists in aqueous solution and, possibly, *in vivo*.[1] Biodistribution studies in rats show significant heart uptake with low blood activity over a period of one hour.[1] This is quite remarkable for a five-coordinate gallium(III) complex with a tetradentate ligand. It suggests that the complex is kinetically inert and does not decompose and subsequently exchange with serum proteins such as transferrin (log K, Ga-transferrin 20.3) to an appreciable extent. This stability may reflect the strong bonding associated with the Ga–S bonds. Other gallium(III) complexes examined to date for potential radiopharmaceutical application have six-coordinate N_3O_3, N_3S_3, N_2O_4, or O_6 ligand systems to provide the requisite stability.[3,9,12,14]

The unique *in vivo* stability of this class of complexes may lead to further development of Ga complexes containing sulphur ligand atoms. The N_2S_2 ligands reported here can easily be modified to alter lipophilicity and charge, properties which are important in heart and brain uptake of small molecules.[15]

This work is partially supported by a grant awarded by National Institutes of Health (NS-18509) (H. F. K.). The authors thank C. Cartwright for her assistance in preparing this paper. The authors are grateful to Drs. S. Burgmayer, S. Jurisson and S. Wehrli for helpful comments.

Received, 21st August 1990; Com. 0/03819I

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