The X-ray Single Crystal Structure of a Gallium Citrate Complex $(NH_4)_3[Ga(C_6H_5O_7)_2]\cdot 4H_2O$

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Gallium complexes are important in nuclear medicine,[1,2] and citrates are of particular interest.[3,4] However no definitive structural studies have been reported. There are reports of some related compounds such as dimethyl-gallium citrate triester[5] and of related tri-[6] or dinuclear complexes of trivalent metals[7] and of a chromium (III) complex.[8] These structures throw some light on the coordination modes that might be adopted in gallium citrates; however, in this note we report the preparation, and the first single-crystal X-ray diffraction structure (Figure 1), of a gallium citrate complex $(NH_4)_3[Ga(C_6H_5O_7)_2]\cdot 4H_2O$.

The title compound was synthesized from a mixture of gallium nitrate (0.66 g, 2.6 mmol) and citric acid (0.49 g, 2.6 mmol) dissolved in water (20 mL, 40 °C), NH_4OH was added until the mixture equilibrated at pH 9 and stirred at ca 80 °C for 1 h, and no special precautions were taken to exclude the atmosphere. After cooling and leaving to stand for 336 h, the reaction mixture was heated to 80 °C and filtered. On cooling prismatic crystals formed.

The solvent was removed, and the solid was filtered, washed with distilled water and acetone, and dried at room temperature. The structure was determined as described in earlier publications.[9] All hydrogen atoms were located in difference Fourier maps and refined isotropically. The crystallographic identification of H_2O and NH_4^+ was assigned on the basis of the atom thermal parameters in conjunction with the elemental analysis and the number of peaks refined satisfactorily as hydrogen positions. [The compound $C_{12}H_{30}GaN_3O_{18}$ comprises colorless crystals and the structure was determined on a single crystal measuring 0.5 × 0.5 × 0.3 mm. The structural determination was carried out using SHELXL 93. Crystallographic parameters: monoclinic, 12/*a*, $a = 19.265$ (4), $b = 9.956$ (2) $c = 23.452$ (5) Å, $\beta = 100.66$ (3), $Z = 8$,$R[F>4$,R[F>4σ $(F)] = 0.0272$.]

The structure of the title complex (Figure 1) resembles quite closely that of the related chromium(III) compound[8] as each citrate acts as a tripodal ligand with two deprotonated carboxylate donors and one alcoholate group which is coordinated to the gallium center.

The two pendent carboxylate groups are protonated. Overall each molecular unit of the complex carries a three minus charge counter balanced by three ammonium ions in the lattice. The pendent protonated carboxylates are stabilized by H-bonding to the same group in an adjacent molecule and to an ammonium ion. There is also a significant interaction between an ammonium ion and one of the other carboxylates. Bond lengths and angles are all in the normal range and are summarized in Table 1.

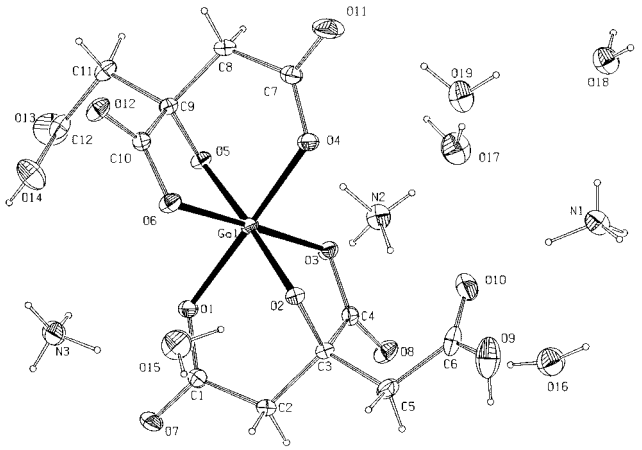

Figure 1. View of the $[Ga(Cit)_2]^{3-}$ anion showing the atom-labeling scheme. Thermal ellipsoids show 50% probability levels

Table 1. Bond Lengths (Å) and Angles (deg) in the $Ga(Cit)_2^{3-}$ Anion

Ga(1)−O(2)	1.900(2)	Ga(1)−O(5)	1.890(2)
Ga(1)−O(3)	1.983(2)	Ga(1)−O(6)	1.976(2)
Ga(1)−O(1)	2.054(2)	Ga(1)−O(4)	2.020(2)
O(1)−C(1)	1.282(3)	O(2)−C(3)	1.415(3)
O(3)−C(4)	1.282(3)	O(4)−C(7)	1.272(3)
O(5)−C(9)	1.409(3)	O(6)−C(10)	1.280(3)
O(7)−C(1)	1.233(3)	O(8)−C(4)	1.233(3)
O(9)−C(6)	1.261(3)	O(10)−C(6)	1.231(3)
O(11)−C(7)	1.245(3)	O(12)−C(10)	1.228(3)
O(13)−C(12)	1.202(3)	O(14)−C(12)	1.313(3)
O(5)−Ga(1)−O(2)	176.63(6)	O(5)−Ga(1)−O(6)	84.48(7)
O(2)−Ga(1)−O(6)	95.36(6)	O(5)−Ga(1)−O(3)	95.65(6)
O(2)−Ga(1)−O(3)	84.43(6)	O(6)−Ga(1)−O(3)	178.65(6)
O(5)−Ga(1)−O(4)	90.13(7)	O(2)−Ga(1)−O(4)	93.23(7)
O(6)−Ga(1)−O(4)	89.43(7)	O(3)−Ga(1)−O(4)	91.91(7)
O(5)−Ga(1)−O(1)	88.60(6)	O(2)−Ga(1)−O(1)	88.04(6)
O(6)−Ga(1)−O(1)	89.79(7)	O(3)−Ga(1)−O(1)	88.87(7)
O(4)−Ga(1)−O(1)	178.56(6)	C(1)−O(1)−Ga(1)	129.46(14)
C(3)−O(2)−Ga(1)	107.34(12)	C(4)−O(3)−Ga(1)	109.43(13)
C(7)−O(4)−Ga(1)	127.4(2)	C(9)−O(5)−Ga(1)	107.20(12)
C(10)−)(6)−Ga(1)	110.53(13)		

We have made some preliminary studies of solutions of this well-defined complex.

The ^{13}C NMR spectrum of the crystalline compound dissolved in D_2O at values of pH between 6 and 9.4 is broadly similar to those reported on related mixtures of citrate and gallium by Glickson et al.[10] The principal peaks in the ^{13}C NMR are observed at (DSS as external reference) 182.4, 179.6, 76.7, 63.4, 46.8, and 46.2 ppm. Although equilibria in these solutions are likely to be complex, the 2:1 molecular species suggested to be present in solution by Glickson probably has a similar structure to that reported for our complex in the solid state. A more detailed NMR study involving the use of ^1H and ^{71}Ga NMR spectroscopies is in hand at present; preliminary results are in line with those reported by Glickson et al.[11] The isolation of the $[Ga(Cit)_2]^{3-}$ anion represents the first direct proof of the

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existence of a mononuclear complex as previously proposed by Glickson and co-workers[11] and more recently suggested to be the major species in blood plasma.[3]

^{67}Ga-citrate is one of the more widely employed radiopharmaceutical agents[12,13] in current use; the clinical procedure employed uses of an injection to prevent hydrolysis on ingestion. There is still much controversy surrounding the mechanism by which ^{67}Ga accumulates in different tumors, since the rates of uptake can vary.[14,15] Citrate plays a significant role in the speciation observed in serum and the transport of this metal to the tumor site. Hence this definitive structural study on the chemistry of gallium citrate will help in understanding ^{67}Ga-citrate imaging in nuclear oncology.[16,17] Iron citrates are also important in medicine, the present complex being labile may be a better model for such species than inert complexes such as those of chromium(III).

Supporting Information Available: Tables of experimental data, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters (8 pages). See any current masthead page for ordering and Internet access information.

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