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Inorganic Chemistry Communications 7 (2004) 69–72

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The first metal complex of 5-hydroxyorotic acid: dimethylammonium bis(*N*,*N*-dimethylformamide) bis(5-hydroxyorotato(-2))gallate(III)

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Received 18 July 2003; accepted 11 October 2003

Abstract

Reaction of $Ga(acac)_3$ with 5-hydroxyorotic acid dihydrate (5-hydroxy-2,6-dioxo-1,2,3,6-tetrahydropyridimine-4-carboxylic acid dihydrate, $LH_4 \cdot 2H_2O$) in DMF yields the mononuclear complex $(CH_3)_2NH_2[Ga(LH_2)_2(DMF)_2] \cdot H_2O \cdot 0.4DMF$ (**1**). X-ray crystallographic analysis showed that the octahedral anion $[Ga(LH_2)_2(DMF)_2]^-$ self-assembles through hydrogen bonds to form a 2D anionic framework; the cation $(CH_3)_2NH_2^+$ derives from the hydrolysis of the solvent. Complex **1** is the first crystallographically characterized 5-hydroxyorotate complex of any metal, and also the first Ga(III) complex with an orotate-type ligand.

Keywords: Bioinorganic chemistry; Crystal structure; Gallium complexes; 5-hydroxyorotic acid; Metal orotate complexes

The coordination chemistry of orotic acid (2,6-dioxo-1,2,3,6-tetrahydropyridimine-4-carboxylic acid, vitamin B_{13}, orH_3, Scheme 1) continues to attract attention, research in this area ranging from bioinorganic [1] to medicinal [2,3] and materials chemistry [4,5]. Orotic acid occupies a special position in biology by being the only effective precursor in the biosynthesis of pyrimidine bases of nucleic acids in living organisms [6]; the presence of metal ions (especially Mg^{2+}) is essential during this process [7]. A Zn^{2+} ion is also present in the active site of dihydroorotase, the enzyme that catalyses the conversion of *N*-carbamyl-L-aspartate to L-dihydroorotate in the third reaction of the de novo biosynthesis of pyrimidine nucleotides [8]. Metal orotates are also widely applied in medicine; they have been used for enhancement of uric acid excretion, for electrolyte substitution (in heart and liver protection) and screened as therapeutic agents for cancer [2,3]. Moreover, interest has been focused on the proposed biological carrier function of orH_2^- for metal ions, which is held responsible for the successful application of orotate complexes in curing syndromes associated with a deficiency of a variety of metals such as calcium, magnesium, zinc or iron [2]. Mingos, Williams and co-workers [5] have demonstrated that the in-built triple hydrogen-bonding functionality of the coordinated dianion orH^{2-} is able to recognize at a molecular level organic molecules, which have complementary hydrogen-bonding groups; such interactions have potential implications for materials chemistry and for metallo-drug design.

Despite the interest in orotate metal complexes, the coordination chemistry of the derivatives of orotic acid has received scant attention [1]. One of these derivatives is 5-hydroxyorotic acid (LH_4, Scheme 1), which has completely unknown coordination chemistry. LH_4 is an interesting ligand since it is potentially polydentate; especially above the deprotonation pH values, coordination may occur through the carboxylate group, the heterocyclic N atoms, the two exocyclic carbonyl O atoms and the hydroxy O atom.

Gallium has been found to accumulate in biological tissues of tumorous nature, thus raising the possibility of

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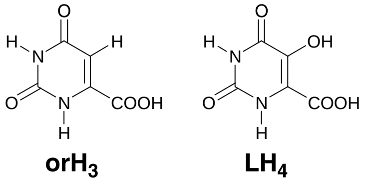
doi:10.1016/j.inoche.2003.10.007



orH_3 LH_4

Scheme 1. Orotic acid (orH_3) and 5-hydroxyorotic acid (LH_4) in their neutral forms.

its use in radiodiagnostic medicine for the localization, imaging and treatment of aberrant soft tissue [9]. Today the biomedical interest of gallium(III) complexes originates from the incorporation of its radionuclides ($^{67}Ga^{3+}$, $^{68}Ga^{3+}$) into diagnostic radiopharmaceuticals [10], the strong antitumour activity of $GaCl_3$ and $Ga(NO_3)_3$ which have been tested in cancer patients [11], and from the moderate in vitro anti-HIV activity of $Ga(NO_3)_3$ and some $GaCl_3$/L complexes (L = various azoles) [12].

The above considerations prompted us to initiate studies for the preparation, structural and physical characterization, and evaluation of the biological activity of Ga(III) complexes with orotate-type ligands. Herein we describe the synthesis, single-crystal X-ray structure and IR characterization of the product isolated from the reaction between a Ga(III) source and LH_4. This product is the first structurally characterized Ga(III) complex with an orotate-type ligand, and also the first 5-hydroxyorotate complex of any metal. The present work can be regarded as a continuation of our efforts in the bioinorganic chemistry of Ga(III) [13].

Reaction of [Ga(acac)$_3$] (0.06 g, 0.16 mmol) with two equivalents of $LH_4 \cdot 2H_2O$ (0.07 g, 0.32 mmol) [1] in DMF (11 ml) under gentle heating resulted in a light green solution. The solution was allowed to slowly concentrate at room temperature for a period of two weeks. Upon slow evaporation, X-ray quality crystals of $(CH_3)_2NH_2[Ga(LH_2)_2(DMF)_2] \cdot H_2O \cdot 0.4DMF$ (**1**) formed in 55% yield, which were collected by filtration, washed with Et_2O and dried in air. [2] The preparation of the complex is summarized in Eq. (1):

$$\begin{aligned}&[Ga(acac)_3] + 2LH_4 \cdot 2H_2O + 3.4HCON(CH_3)_2\\ &\underset{T}{\overset{DMF}{\rightarrow}} \underset{\mathbf{1}}{(CH_3)_2NH_2[Ga(LH_2)_2\{HCON(CH_3)_2\}_2]}\\ &\quad \cdot H_2O \cdot 0.4HCON(CH_3)_2 + 3acacH\\ &\quad + HCOOH + 2H_2O \qquad (1)\end{aligned}$$

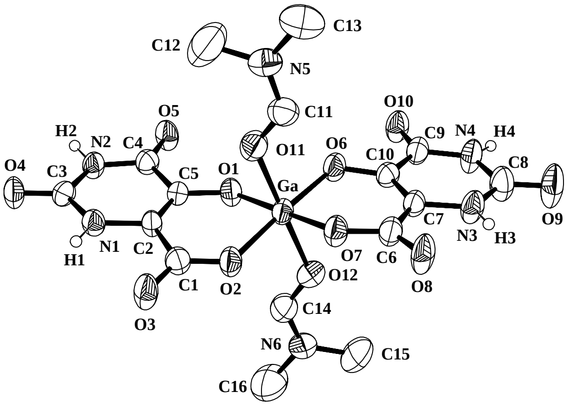


Fig. 1. An ORTEP representation of the anion of complex **1**. Selected bond lengths (Å) and angles (°): Ga–O(6) 1.922(6), Ga–O(1) 1.928(5), Ga–O(2) 1.941(6), Ga–O(7) 1.943(6), Ga–O(11) 2.019(6), Ga–O(12) 2.026(6), O(2)-Ga–O(6) 177.1(2), O(1)–Ga–O(7) 177.2(2), O(11)–Ga–O(12) 179.5(3).

The double deprotonation of 5-hydroxyorotic acid is a consequence of the relatively high $acac^-$ to LH_4 ratio (3:2) used in the reaction. The dimethylammonium cation in **1** originates from the decomposition of DMF. Such decomposition has a precedent in coordination chemistry [15]. The hydrolysis of the DMF solvate molecule which gives $(CH_3)_2NH_2^+$ most likely involves direct polarization of its C=O bond as the result of coordination of the oxygen atom to Ga^{III}, activation of the carbonyl carbon atom to undergo nucleophilic attack and, finally, cleavage of the C–N bond of DMF.

The crystal structure [3] of **1** consists of $(CH_3)_2NH_2^+$ cations, $[Ga(LH_2)_2(DMF)_2]^-$ anions (Fig. 1) and DMF and H_2O solvate molecules. The Ga^{III} atom displays a slightly distorted octahedral coordination. The *cis* octahedral angles are in the 86.0–93.6° range, while the *trans* ones in the narrow 177.1–179.5° range. Each LH_2^{2-}

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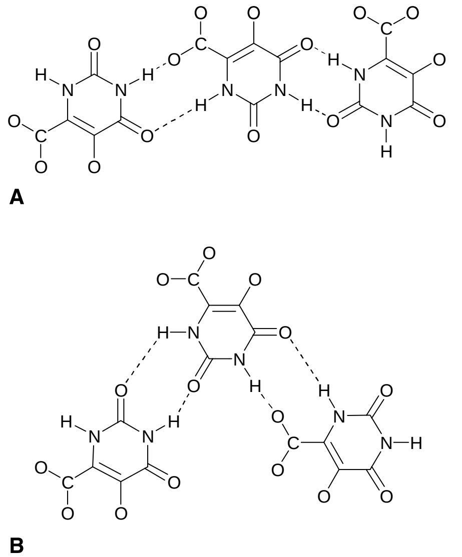
[1] 5-hydroxyorotic acid dihydrate ($LH_4 \cdot 2H_2O$) was synthesized by the peroxydisulfate oxidation of orotic acid followed by hydrolysis [14].

[2] Satisfactory C, H, N and Ga^{3+} analyses were obtained.

[3] Crystallographic data for **1**: $C_{19.2}H_{30.8}N_{7.4}GaO_{13.4}$, $M = 649.43$, monoclinic, $P2_1/n$, $a = 11.641(6)$, $b = 21.04(1)$, $c = 12.247(7)$ Å, $\beta = 94.18(2)°$, $V = 3480(3)$ Å^3, $Z = 4$, $D_c = 1.239$ g cm^{-3}, μ(Mo-Kα) = 0.853 mm^{-1}, $T = 298$ K, 4579 reflections measured, 4372 unique ($R_{int} = 0.0349$), $R1$ on F($wR2$ on F^2) = 0.0733(0.1683) for 2652 observed ($I > 2\sigma(I)$) reflections. A crystal of **1** with approximate dimensions 0.12 × 0.13 × 0.30 mm was mounted in capillary. Diffraction measurements were made on a Crystal Logic Dual Goniometer diffractometer using graphite monochromated Mo radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11 < 2\vartheta < 23°$. Intensity data were recorded using a ϑ–2ϑ scan to 2ϑ(max) = 44.6°. Lorentz and polarization corrections were applied using Crystal Logic software. The structure was solved by direct methods using SHELXS-86 and refined by full matrix least-squares techniques on F^2 with SHELXL-93. Hydrogen atoms on C(12), C(14), C(15), C(16), C(20), C(21) and N(8) were introduced at calculated positions as riding on bonded atoms; the rest were located and refined isotropically. The DMF solvate (lattice) molecule was refined isotropically with occupation factors fixed at 10.4. A H_2O solvate molecule was found disordered and refined isotropically in four positions with occupation factors fixed at 10.25. All the rest non-hydrogen atoms were refined anisotropically.

acts as a bidentate ligand following deprotonation at the carboxylic and 5-hydroxy groups; the donor atoms are the phenolate oxygen and one of the carboxylate oxygens, thus giving one six-membered chelate ring per ligand. Two terminal, O-bonded DMF molecules complete the coordination sphere at the metal centre. The carboxylate, hydroxy and DMF oxygen atoms are in a *cis*, *cis* and *trans* arrangement, respectively. The Ga–O (DMF) distances (2.019(6), 2.026(6)Å) are slightly longer than those involving the deprotonated hydroxy and carboxylate O atoms (1.922(6)–1.943(6)Å). The Ga–O (hydroxy, carboxylate) distances are in the range of those observed in other octahedral Ga(III) complexes involving alcoholate and carboxylate donor groups [9a].



Scheme 2. The complementary double hydrogen-bonding interactions observed within $[Ga(LH_2)_2(DMF)_2]^-$ resulting in a lamellar structure.

The supramolecular structure of **1** is interesting. One of the two coordinated LH_2^- (Scheme 2, **A**) uses the two N–H groups (N(3)–H(3), N(4)–H(4)), the uncoordinated carboxylate oxygen (O(8)) and one carbonyl oxygen (O(10)), while the other (Scheme 2, **B**) uses the two N–H groups (N(1)–H(1), N(2)–H(2)) and the two carbonyl oxygens (O(4), O(5)), for hydrogen bonding. As a result, each $[Ga(LH_2)_2\ (DMF)_2]^-$ anion is bound through four double hydrogen bonds to four other complex anions to form a two-dimensional (2D) anionic framework (Fig. 2). The arrangement of the anionic complexes gives rise to the formation of elliptical cavi-

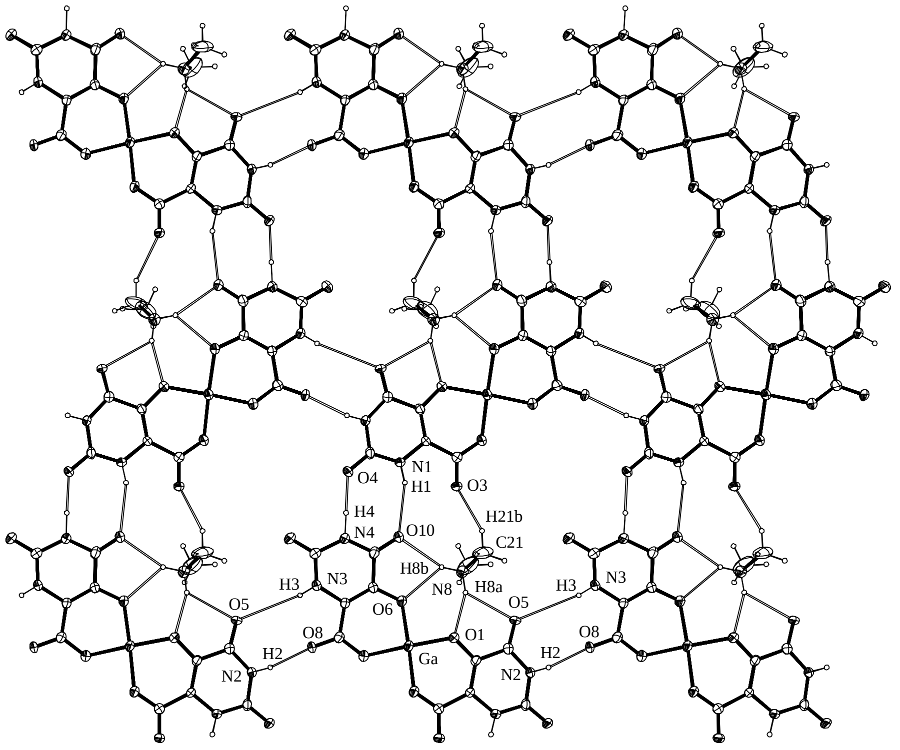


Fig. 2. The lamellar structure adopted by complex **1** illustrating the complementary double hydrogen bonding interactions (open bonds). The cation is bound to the framework through five hydrogen bonds (open bonds). The coordinated DMF molecules, and the solvate H_2O and DMF molecules have been omitted for clarity. Selected hydrogen-bonding interactions (distances in Å, angles in °): $N(1)\cdots O(10)^{i}$ 3.125(9), $H(1)\cdots O(10)^{i}$ 2.28(6), $N(1)–H(1)\cdots O(10)^{i}$ 161(4), $N(2)\cdots O(8)^{ii}$ 2.751(9), $H(2)\cdots O(8)^{ii}$ 1.93(7), $N(2)–H(2)\cdots O(8)^{ii}$ 164(5), $N(4)\cdots O(4)^{iii}$ 2.801(9), $H(4)\cdots O(4)^{iii}$ 1.75(11), $N(4)–H(4)\cdots O(4)^{iii}$ 165(8), $N(8)\cdots O(1)$ 2.840(10), $H(8a)\cdots O(1)$ 1.991(9), $N(8)–H(8a)\cdots O(1)$ 157(7), $N(8)\cdots O(10)$ 3.038(10), $H(8b)\cdots O(10)$ 2.193, $N(8)–H(8b)\cdots O(10)$ 156.0, $C(21)\cdots O(3)$ 3.228(16), $H(21b)\cdots O(3)$ 2.341, $C(21)–H(21b)\cdots O(3)$ 153.2. Symmetry operations: $^{i}0.5-x,\ -0.5+y,\ 0.5-z$, $^{ii}1+x,y,z$; $^{iii}0.5-x,\ 0.5+y,\ 0.5-z$.

ties within the framework. Each elliptical cavity is a host for binding one $(CH_3)_2NH_2^+$ cation in the solid state; the latter forms two strong bifurcated hydrogen bonds (N(8)–H(8a)···O(1), N(8)–H(8a)···O(5) and N(8)–H(8b)···O(6), N(8)–H(8b)···O(10)) with the oxygen atoms of the deprotonated hydroxy group and the adjacent carbonyl group of two LH_2^{2-} ligands belonging to the same anionic complex, and one weaker C–H···O hydrogen bond [16] with an uncoordinated oxygen atom (O(3)) of a carboxylate group from a neighboring complex (Fig. 2). Weak hydrogen bonds with C–H groups as donors are currently under intense study. Formerly considered as "unusual" or "unconventional", they are now discussed rather frequently in many fields of structural chemistry and biology [16].

In the 3500–3000 cm^{-1} region, the IR spectrum of complex **1** shows three broad bands of medium intensity at 3424, 3180 and 3020 cm^{-1} assigned [1] to $\nu(OH)_{water}$, $\nu(NH)$ and $\nu(NH_2^+)$, respectively. In the spectrum of $NaLH_3$ the bands due to the $\nu_{as}(CO_2)$ and $\nu_s(CO_2)$ vibrations appear at 1644 and 1414 cm^{-1}, respectively; in **1** the corresponding bands are at 1625 and 1418 cm^{-1}. For the monodentate carboxylate coordination observed in the structure of complex **1** we would expect the relationship $\Delta_{complex} > \Delta_{NaLH_3}$ to apply [17], where $\Delta = \nu_{as}(CO_2) - \nu_s(CO_2)$. The fact that for **1** $\Delta_{complex}(207\ cm^{-1}) < \Delta_{NaLH_3}(230\ cm^{-1})$ is presumably due to the involvement of the uncoordinated carboxylate oxygens in hydrogen-bonding linkages [17] or/and the dianionic character of the orotate ligand in the gallium(III) complex [1].

5-hydroxyorotic acid is a new ligand which can form interesting complexes and has the ability to participate in the formation of multiple hydrogen bonds. Thus, we believe that the anionic forms of LH_4 have great potential as useful new polyfunctional ligands in coordination and supramolecular chemistry, and they will prove attractive to a variety of chemists.

The chemistry of orotates with Ga(III) in aqueous solution is under intense investigation in our laboratories. Recent results have revealed that orotates can promote solubilization of Ga(III) in the physiological pH range thus offering potentiality for orotates' contribution to the accumulation of this metal ion in biological tissues and influence on its bioavailability.

Supplementary material

Crystallographic data for **1** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 215177. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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