

Isolation of a Unique Hexanuclear $[Bi_6O_4OH(cit)_3(H_2O)_3]^{3-}$ Cluster from the Bismuth-Containing Ulcer Healing Agent "Colloidal Bismuth Subcitrate (CBS)"

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An active ingredient of peptic ulcer healing agent "Colloidal Bismuth Subcitrate (CBS)" has been isolated by crystallization from a solution containing bismuth citrate and ammonia. The single-crystal X-ray structure analysis has demonstrated that it consists of unique anionic hexanuclear bismuth oxo-hydroxo-citrate clusters connected by ammonium ions and weak citrate bridges.

Bismuth compounds have since long been used in medicine for treatment of a variety of gastrointestinal disorders, because of their demulcent properties.¹⁾ Among the modern bismuth-based ethical pharmaceuticals, colloidal bismuth subcitrate (CBS) is widely used in many countries to treat peptic ulcers. Because the significantly reduced relapse rates for the patients of ulcer treated with CBS has been reported to be due to the bactericidal action of CBS against *Helicobacter pylori*,^{2,3)} a pathogenic factor in the etiology of chronic gastritis and of the peptic ulcer, isolation and structure determination^{4,5)} of CBS have attracted much attention.

According to the most recent Merck index,⁶⁾ CBS is thought to have the approximate formula $K_3(NH_4)_2Bi_6O_3(OH)(Hcit)_4$, where Hcit stands for the trionized citrate anion. The compound has been thought to be a complex polynuclear bismuth citrate salt, co-precipitated with potassium and/or ammonium citrate. Our interest⁴⁾ in Bi-citrate chemistry caused us to try isolating polynuclear species containing bismuth citrate units, with the final aim to determine the crystal structure. In this communication we report the first example of a three-dimensional structure of a unique polymeric bismuth citrate, consisting of hexanuclear bismuth citrate $[Bi_6O_4OH(cit)_3(H_2O)_3]^{3-}$ (A^{3-}) building blocks.

The polymeric bismuth citrate complex $(NH_4)_6A \cdot (Hcit) \cdot 2H_2O$ was isolated as follows. To an aqueous suspension (20 ml) of bismuth citrate BiHcit (10 g, 0.025 mol) was added a 25% ammonia solution (10 ml). The solution was filtered to remove a small amount of insoluble material. Very slow evaporation of the filtrate gave colorless cubic crystals. Since the crystals very easily loose lattice water in air, a single crystal was mounted into a capillary with a small amount of solvent (water:methanol = 15:85). Elemental analysis⁷⁾ of the compound was fully satisfactory with the formula $(NH_4)_6[Bi_6O_4(OH)_4(Hcit)_4] \cdot 2H_2O$, which is very close to that cited in the Merck index,⁶⁾ suggesting that in fact it could be an active ingredient of CBS.

The crystal structure determination⁸⁾ confirmed that the compound indeed contains hexanuclear units, however, with the composition $[Bi_6O_4OH(cit)_3(H_2O)_3]^{3-}$, A^{3-} (see Fig. 1) and not $[Bi_6O_4(OH)_4(Hcit)_4]^{6-}$; in addition, these hexanuclear units link together through citrate-bridging, water molecules and ammonium cations, yielding a complicated polymeric structure.

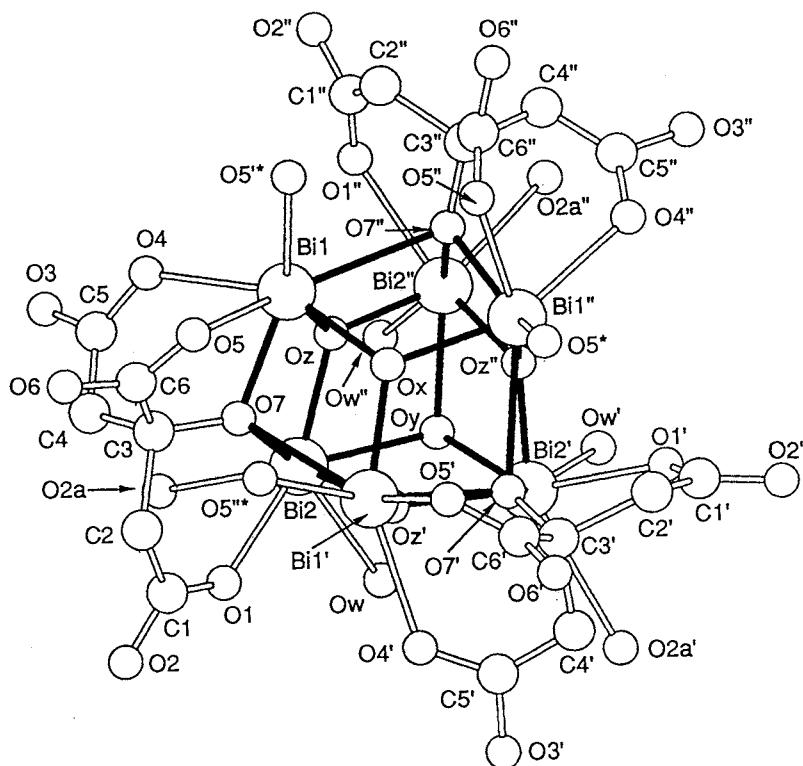


Fig.1. Projection of the hexanuclear unit \mathbf{A}^{3-} as present in $(\text{NH}_4)_3\mathbf{A} \cdot (\text{NH}_4)_3\text{Hcit} \cdot 2\text{H}_2\text{O}$.

Relevant atomic distances (Å) are: Bi1-Ox 2.186(9), Bi1-O7 2.22(3), Bi1-O7" 2.80(2), Bi1-Oz 2.19(3), Bi1-O4 2.52(3), Bi1-O5 2.36(3), Bi1-O5'* 2.84(3), Bi1-Bi1' 3.731(2), Bi2-Oy 2.49(2), Bi2-Oz 2.26(3), Bi2-Oz' 2.10(2), Bi2-O7 2.47(3), Bi2-O1 2.46(4), Bi2-Ow 3.16(8), Bi2-O2a 3.05(3), Bi2-Bi2' 3.707(3), Bi1-Bi2 3.750(3), Bi1-Bi2" 3.727(2). Relevant angles (°) are: Bi1-Ox-Bi1' 117.1(7), Bi1-O7-Bi1' 95.3(7), O7-Bi1-O7" 129.3(8), Bi1-O7-Bi2 106(1), Bi1-Oz-Bi2 115(1), O7-Bi1-Oz 72(1), O7-Bi2-Oz 67(1), Bi2-Oy-Bi2' 96(1), Bi2-Oz-Bi2" 117(1), Oz-Bi2-Oz' 89.4(9), Oz-Bi1-O7" 70.1(8), O7-Bi2-Oz' 78.8(9), Bi1'-O7-Bi2 89.8(7), Bi1-Oz-Bi2" 121(1), Bi1'-Bi1-Bi1" 60.00(5), Bi2'-Bi2-Bi2" 60.00(5). Symmetry codes: ' (-y, x-y, z), " (y-x, -x, z), a (1/3-x, 2/3-y, 2/3-z), * (-x, -y, -z).

For better understanding the structure **A**³⁻, a schematic comparison of the structural units of **A**³⁻ and that of an earlier reported⁹⁾ hexanuclear cationic bismuth complex $[\text{Bi}_6\text{O}_4(\text{OH})_4](\text{ClO}_4)_6 \cdot 7\text{H}_2\text{O}$, **B**(ClO_4)₆ · 7H₂O, is shown in Fig. 2. The cluster unit **A**³⁻ with C₃ symmetry has a three-fold axis on an imaginary line made by an apical μ_3 -hydroxo oxygen (Oy) and a μ_3 -oxo atom (Ox) in the opposite apical position. Each of three bismuth atoms (i.e. Bi2) close to the coordinated hydroxo side is further coordinated by an oxo (O²⁻) ligand (Oz; μ_3 -bridging), H₂O ligand (Ow), a terminal carboxylate in citrate (O1), and the hydroxo atom of the citrate (O7; μ_3 -bridging). Each of the other three equivalent bismuth atoms (i.e. Bi1, Bi1', and Bi1'') close to the apical μ_3 -oxo is coordinated by the central carboxylate (O5), the other carboxylate (O4), and the μ_3 -hydroxo atom (O7) of the citrate.

Compared with the structure of **B**⁶⁺, three of the four hydroxides in **B**⁶⁺ are substituted by the hydroxy oxygen of each citrate in **A**³⁻. Three of six bismuth atoms (Bi2) are coordinated by water. However, the two frameworks forming hexanuclear Bi₆ in **B**⁶⁺ and **A**³⁻ are nearly the same. Structural data on Bi(III) compounds with oxygen ligands remain scarce,^{10,11)} but most mixed Bi(III) oxides have only five or six neighbors at distances from 2.1 to 2.7 Å and a small number of additional neighbors.¹¹⁾

When the sum of the van der Waals radii for bismuth(III) and O^{2-} is considered (3.47 Å), two other long bismuth oxygen contacts are present on the title compound, i.e. Bi1---O5* (2.84 Å) and Bi2---O2a (3.05 Å), with O5* and O2a coming from neighboring clusters. Thus, the present compound could be regarded as having a polymeric structure and all the bismuth atoms exhibit a coordination number of 7.

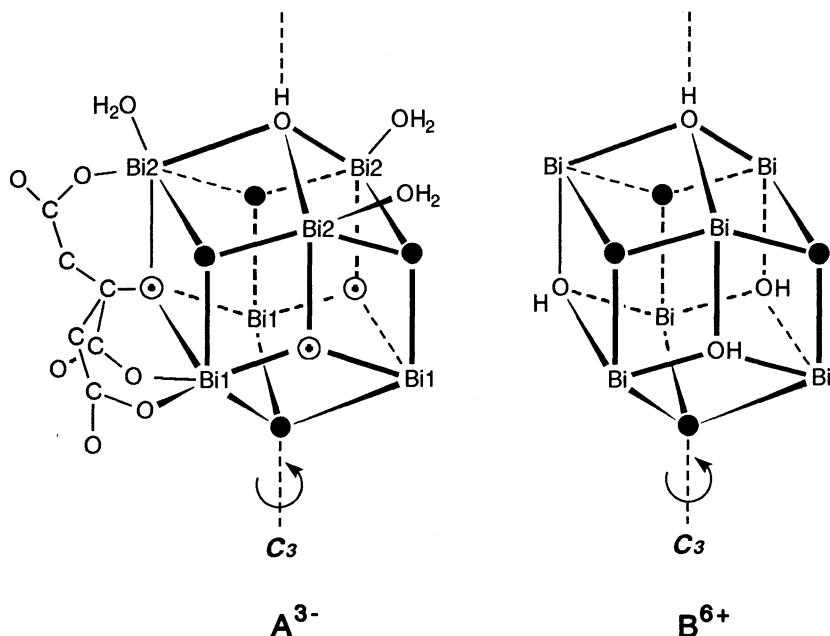


Fig.2. Comparison of (part of) the hexanuclear units in A^{3-} and B^{6+} ; only part of the citrates are shown for the compound. ● = μ_3 -oxo(2-); ○ = μ_3 -O7(1-); (from citrato).

Although the title compound should include 6 ammonium ions, 2 non-coordinating water molecules, and one citrate $Hcit^{3-}$ per hexanuclear unit, based on the elemental analyses, only 3 ammonium ions could be located so far. The other small molecules and the citrate could not be detected by the X-ray analysis under the present data collection conditions. To detect the missing citrate ^{13}C NMR spectra¹²⁾ have been recorded. In fact, the ^{13}C NMR spectrum of the title compound shows several signals in the solid state and in solutions, depending on the used concentrations. In addition to the several signals for coordinated citrates, one set of signals would agree to non-coordinating citrate (with chemical shifts close to those of ammonium citrate measured at the same pH). The most plausible explanation for the missing citrate in the lattice is that this citrate(3-) is located on the three crystallographically equivalent positions with a occupancy factor of 1/3 around the hexanuclear cluster having a three-fold axis to result in blurring toward detection by X-ray. Since the single crystals are very sensitive toward X-ray at room temperature, low-temperature data collection is scheduled, to obtain detailed information about the "lattice citrate" and to fully interpret the NMR data.

Contrary to B^{6+} , that undergoes hydrolytic decompositions⁹⁾ above pH 5 in aqueous solutions, the present compound can persists the hexanuclear unit structure up to pH 8⁴⁾ as result of the rigid chelation by the citrate ligands. Under acidic conditions (<pH 4), however, it is hydrolyzed by hydrochloric acid to form a precipitate (white finely divided powder), which appears to be a mixture of bismuth citrate and bismuth oxychloride.¹³⁾

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- 7) Anal. Found: C, 12.61; H, 2.29; N, 3.68; Bi, 54.84%. Calcd for $C_{24}H_{52}N_6O_{38}Bi_6$ as $(NH_4)_6[Bi_6O_4(OH)_4(Hcit)_4] \cdot 2H_2O$ and $(NH_4)_6[Bi_6O_4OH(cit)_3(H_2O)_3] \cdot (Hcit) \cdot 2H_2O$: C, 12.60; H, 2.31; N, 3.60; Bi, 54.0%.
- 8) Crystal data for \mathbf{A}^3 : $C_{24}H_{52}N_6O_{38}Bi_6$, $M=2286.6$, rhombohedral (hexagonal axis), $R\bar{3}$, $a=b=17.864(2)$, $c=31.317(3)$, $U=8655.1 \text{ \AA}^3$, $Z=6$, $D_c=2.59 \text{ gcm}^{-3}$, Monochromatized Mo-K α radiation, $\lambda=0.7107 \text{ \AA}$, $\mu=183.1 \text{ cm}^{-1}$, $T=298 \text{ K}$, analytical absorption correction (max./min. transmission factors: 0.998, 0.304, respectively). Total of 2017 reflections measured ($0.5 < \theta < 20.0^\circ$) on a CAD4 diffractometer; 1551 were unique and 1183 satisfied $I > 3.0\sigma(I)$. The structure solved by direct methods and refined by full-matrix least squares refinement (MolEN). Anisotropic thermal parameters for only Bi atoms. Refinement converged with $R=0.060$ and $R_w=0.080$ for weighting scheme $w=[\sigma F^2+(0.02F)^2+1]^{-1}$.
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- 12) A ^{13}C NMR spectrum of the present compound in aqueous solution (pH 6.96) was recorded at a Bruker 400 MHz spectrometer, using DSS as an external standard. Major chemical shifts for 0.25 mol/dm 3 solution (in ppm from DSS) are: 48.5, 53.0, 77.5-80.5 (multiplet), 178.5, 179.6, 188-193 (multiplet).
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