Bioinorganic Chemistry

Stable, Soluble Beryllium Aluminum Citrate Complexes Inspired by the Emerald Mineral Structure**

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Despite its high toxicity, beryllium is widely used because of its unique properties. Beryllium is toxic both as a carcinogen and as the agent that initiates chronic beryllium disease (CBD). CBD, a granulomatous lung disease, is a cell-mediated immune response to inhaled beryllium in 6–20 % of exposed individuals. Considerable invesitagations into the nature and effects of CBD have been conducted[1] but the role of beryllium in triggering CBD is still not well understood.[2,3] Most research has focused on the biological[4] and environmental[5] effects of beryllium with far less emphasis on the speciation and interactions of beryllium under physiological conditions.[6–8] The natural forms of beryllium, beryl and emerald, have not been reported to cause CBD unlike processed forms of beryllium metal and BeO.[9] The beryl structure [$Be_3Al_2(SiO_3)_6$] (Figure 1) is interesting in two

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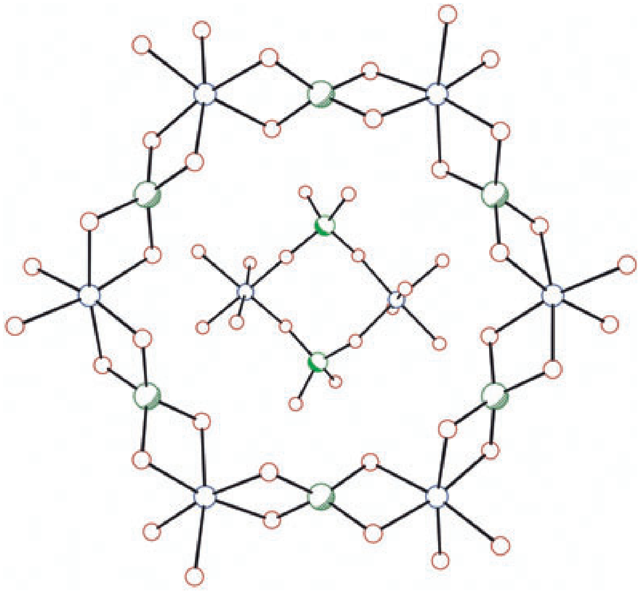

Figure 1. Overlay of the core (Al-O-Be-O)$_n$ structures of beryl [$Be_3Al_2(SiO_3)_6$] and **1**. The outer ring is beryl and the inner ring is **1**: Be = green, Al = blue, and O = Red.

aspects: it has no Be-O-Be linkage despite the propensity of beryllium to form clusters and all of the beryllium-bound oxygen atoms are Si–O units that bridge the aluminum and beryllium atoms. Although this mineral structure occurs in nature, there are no organic-based structures containing aluminum and beryllium. A few citrate-type aqueous complexes containing C–O units bridging two beryllium atoms are known[10,11] and very stable complexes with Be-O-Be linkages with phenolic species acting as bridging oxygen atoms have been recently reported.[12] We report here on the synthesis of a new stable citrate complex containing beryllium and aluminum atoms with a Be-O-Al linkage similar to that of beryl and a related aluminum beryllium citrate structure with bridging phosphate units that is highly soluble (1 M) in aqueous phosphate solution (0.5 M). The mixed-metal citrate complex in both cases is the single dominant species in solution with no evidence of dissociation or rearrangement to Al citrate and Be citrate species.

The complex $(NH_4)_6[Be_2Al_2(\text{citrate})_4]$ (**1**) was formed in quantitative yield by neutralizing an acidic solution containing $Al(NO_3)_3$, $Be(NO_3)_2$, and citric acid with aqueous NH_3. Complex **1** is highly soluble in water (approximately 3 M) between pH 3.5 and 10.5. There is one signal at $\delta = 1.84$ ppm in the ^{9}Be NMR spectrum, thus indicating that the Be center resides in the six-membered citrate chelate ring (Figure 2). The ^{9}Be NMR spectrum of the 2:1 Be citrate complex in solution has been previously reported as having two signals at $\delta = 3.5$ and 1.9 ppm, which have been assigned to Be atoms in five- and six-membered rings of citric acid, respectively.[10,12] A broad singlet at $\delta = 14.0$ ppm in the ^{27}Al NMR spectrum is in stark contrast to the ^{27}Al NMR spectrum of the 1:1 aluminum citrate complex, which comprises four peaks that suggest the presence of many different species in solution.[13] The ^{13}C NMR spectrum has only one resonance for each carbon atom from citric acid, and the pH value of the solution (pH 4–9) does not significantly affect the chemical shift of the signals in the NMR spectra, although the line broadening is influenced slightly. The NMR spectroscopic analysis indicates that there is one dominant species in solution: a Be Al citric acid complex in a ratio of 1:1:2 with beryllium in a six-membered ring.

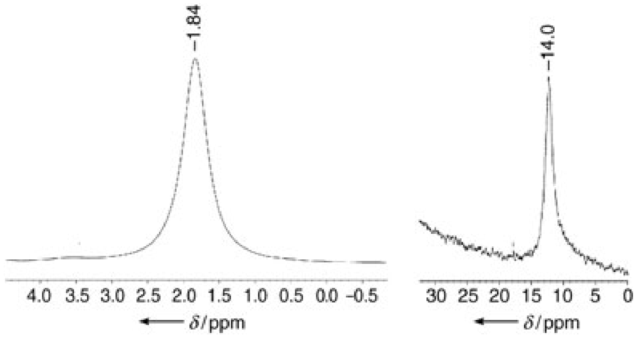

Figure 2. Left: ^{9}Be NMR spectrum of **1**. Right: ^{27}Al NMR spectrum of **1**.

An X-ray diffraction study of **1** confirms the observations from the NMR spectroscopic analysis of **1** in solution and reveals an interesting four-metal species with a core of two Al atoms and two Be atoms with four bridging O atoms in an eight-membered ring (Figure 3). This core structure is similar to the larger core of the beryl structure that contains six Al and six Be atoms in an alternating pattern bridged by O atoms from Si–O units in the mineral. The four bridging O atoms in the core structure of **1** come from the α-hydroxy group of the four bound citrate ligands. The deprotonation of the α-hydroxy group of citric acid is unusual but has been previously reported for Al citrate complexes.[11,14] The bridging hydroxy group has been shown to be vital for the stability of beryllium citrate type complexes[10,12] but has not been characterized by X-ray diffraction studies to date. Aluminum citrate complexes have been shown to bridge through the α-hydroxy group; however, bridging hydroxy groups or water molecules were also bound to the Al atom in all but one of these cases.[13–16] The aluminum atom is encased by the citrate ligand in complex **1** with two bridging R–O units and two carboxylate groups from each of the two bound citrate ligands. The Al–O (1.864(2)–1.922(3) Å) and Be–O (1.610(4)–1.646(4) Å) bond lengths are within the expected values for octahedral Al centers and tetrahedral Be centers.

One complication of studying the speciation of beryllium in the body is its low solubility in a phosphate media above pH 3. Beryllium precipitates in the presence of a phosphate buffer even in the presence of excellent chelating ligands, such as 2,3-dihydroxybenzoic acid ($k = 18.3$).[12] No stable beryllium complexes have been isolated from a phosphate medium to our knowledge. Although, a few structures of hydrothermally synthesized beryllophosphates[17,18] and beryllium phosphinate complexes[6] are known. Herein, we also report the isolation of a unique beryllium phosphate complex, $(NH_4)_{18}[Al_6Be_6(\text{citrate})_6(PO_4)_8]$ (**2**), which was prepared from a combination of beryllium, aluminum, and citric acid compounds in the presence of phosphate. Complex **2** is highly

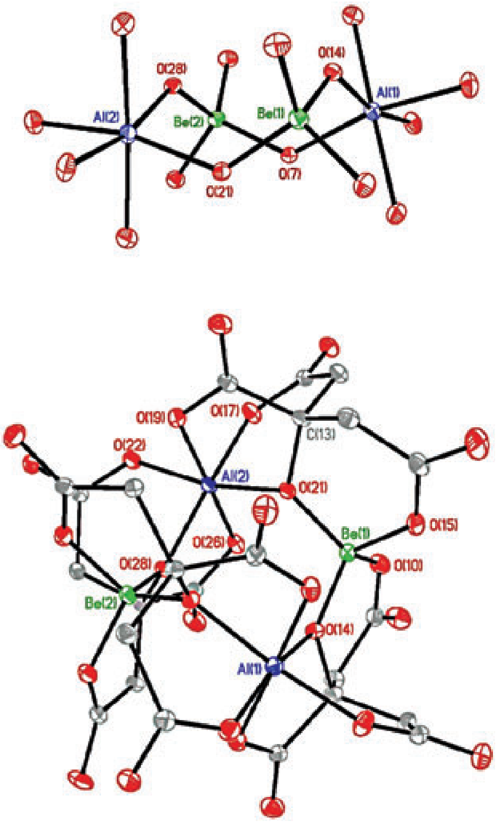

Figure 3. The crystal structure of **1**. Top: ORTEP diagram drawn at the 30% probability level. Bottom: core structure with aluminum, beryllium, and bound-oxygen atoms only. Selected bond lengths [Å] and bond angles [°]: Al(1)-O(12) 1.864(2), Al(1)-O(5) 1.886(3), Al(1)-O(8) 1.887(2), Al(1)-O(14) 1.890(3), Al(1)-O(7) 1.898(2), Al(1)-O(1) 1.922(3), Al(2)-O(26) 1.882(3), Al(2)-O(21) 1.889(2), Al(2)-O(28) 1.893(2), Al(2)-O(19) 1.896(3), Al(2)-O(22) 1.903(2), Al(2)-O(17) 1.908(3), Be(1)-O(14) 1.614(5), Be(1)-O(15) 1.618(5), Be(1)-O(21) 1.624(4), Be(1)-O(10) 1.628(5), Be(2)-O(24) 1.610(4), Be(2)-O(28) 1.622(5), Be(2)-O(7) 1.631(4), Be(2)-O(3) 1.646(4), C(13)-O(21) 1.425(4); O(14)-Al(1)-O(7) 96.75(11), O(21)-Al(2)-O(28) 97.67(10), O(14)-Be(1)-O(21) 108.7(3), O(28)-Be(2)-O(7) 109.5(2), Be(2)-O(7)-Al(1) 130.56(19), Be(1)-O(14)-Al(1) 131.6(2), Be(1)-O(21)-Al(2) 130.2(2), Be(2)-O(28)-Al(2) 132.12(19).

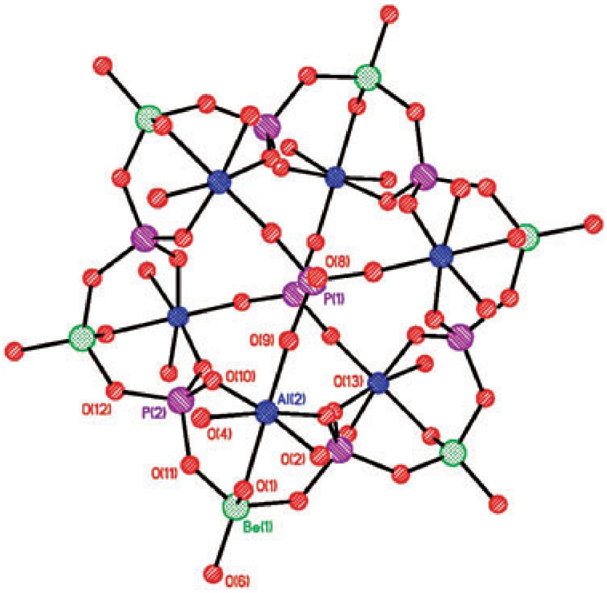

Figure 4. The crystal structure of **2** (ball and stick representation with ellipsoids set at 30% probability; citrates have been omitted for clarity with the exception of the aluminum- and beryllium-bound oxygen atoms). Selected bond lengths [Å] and bond angles [°]: Al(2)-O(9) 1.766(6), Al(2)-O(10) 1.837(6), Al(2)-O(1) 1.850(5), Al(2)-O(13) 1.880(5), Al(2)-O(2) 1.960(6), Al(2)-O(4) 1.985(6), P(1)-O(9) 1.460(6), P(1)-O(8) 1.527(8), P(2)-O(13)′ 1.513(5), P(2)-O(10) 1.520(6), P(2)-O(11) 1.542(5), P(2)-O(12) 1.543(5), Be(1)-O(1) 1.603(11), Be(1)-O(6) 1.624(10), Be(1)-O(11) 1.595(10), Be(1)-O(12)′ 1.630(11); O(9)-Al(2)-O(10) 94.6(4), O(9)-Al(2)-O(1) 169.9(3), O(10)-Al(2)-O(13) 93.8(3), O(9)-Al(2)-O(2) 90.3(4), O(9)-P(1)-O(9)′ 109.6(3), O(9)-P(1)-O(8) 109.3(3), O(10)-P(2)-O(11) 109.7(3), O(10)-P(2)-O(12) 109.9(3), O(11)-P(2)-O(12) 107.3(3), Be(1)-O(1)-Al(2) 120.0(4), P(1)-O(9)-Al(2) 174.8(7), P(2)-O(10)-Al(2) 137.3(3), P(2)-O(11)-Be(1) 127.2(5), O(11)-Be(1)-O(1) 109.3(6), O(11)-Be(1)-O(6) 109.9(6), O(1)-Be(2)-O(6) 107.1(6).

soluble at pH 7 (>1 M) and stable in the presence of a phosphate media (0.5 M).

Complex **2** was characterized by X-ray diffraction studies, and it was seen that the α-hydroxy groups from the citrate ligands bridge the aluminum and beryllium atoms in a similar manner to that observed in structure **1** (Figure 4). The structure of **2** reveals a large cluster with six Be-O-Al units linked by phosphate groups, which is in contrast to the core structure of **1** where two Be-O-Al units are linked by α-hydroxy groups in a ring structure. The structure is templated by two additional phosphate groups in the center of the molecule with each phosphate group binding three aluminum atoms with one unbound P$-$O$_{\text{free}}$ bond aligned on the c_3 axis of the molecule. The Al$-$O bond lengths (1.766(6)–1.985(6) Å) in **2** have a wider range than complex **1**: The Al$-$O$_{\text{citrate}}$ bonds are longer by 0.08 Å(avg), the Al$-$O$_{\text{Be}}$ bonds are marginally shorter by about 0.04 Å, and the Al$-$O$_{\text{P1}}$ bond is the shortest at 1.766(6) Å. The Be$-$O bond lengths (1.595(10)–1.630(11) Å) are similar to the expected values for the Be$-$O bonds and show no significant changes. The center P(1) atom has shorter P(1)$-$O$_{\text{Al}}$ bonds (1.460(6) Å) than the bridging P(2)$-$O$_{\text{metal}}$ bonds (1.513(5)–1.542(5) Å). The shortening of the P$-$O bond is presumably because the P(1) center is bonded to three aluminum atoms instead of four aluminum atoms as in the P(2) center, thus providing more electron density at the P(1) center. The ^{27}Al NMR spectrum of **2** in solution shows a relatively narrow signal at $\delta = 12.2$ ppm, which indicates that the structure around the aluminum center is symmetric and stable in solution. There are two signals in the ^{9}Be NMR spectrum of **2** in solution at $\delta = 1.01$ and 2.19 ppm in an approximate 1:3 ratio, respectively. Presumably, one of the oxygen atoms bound to the beryllium center is laible in solution, thus causing the two resonances to appear in the ^{9}Be NMR spectrum. The strong thermodynamic stability of the complex is demonstrated by the aluminum citrate solubilizing the precipitated beryllium phosphate and forming the same species as that of **2** in solution. The addition of aluminum citrate (pH 7) to a solution containing precipitated beryllium phosphate (pH 7) dissolves 74% (149 mM Be) of the precipitated beryllium phosphate (initially, 200 mM), which is relative to beryllium phosphate at pH 7 having a solubility of 19 μM Be.

We have structurally characterized a new class of beryllium aluminum compounds based on a Be-O-Al motif similar to beryl where the bridging R−O unit comes from the α-hydroxy group of citric acid. These complexes are remarkably stable, are highly soluble in aqueous solution, and do not appear to dissociate to any appreciable degree in solution. These results suggest a potentially rich new area of beryllium solution chemistry based on a Be-O-Al species that is highly stable and soluble in a phosphate media. Current investigations are underway to determine if the stability and high solubility of the mixed-metal species is driven by electronic factors or geometric considerations (namely, the presence of tetrahedral and octahedral metal sites). Such complexes could offer significant insight into how beryllium becomes mobile in a physiological, phosphate-rich medium and how it interacts within the human body.

Experimental Section

1: Citric acid (432 mg) was dissolved in $Al(NO_3)_3$ (2.25 mL, 1M) and $Be(NO_3)_2$ (2.03 mL, 1.11M) in a 20-mL vial. The pH value was increased to 7 by the addition of NH_4OH. Diffusion of ethanol into the aqueous solution afforded crystals suitable for X-ray diffraction studies. ^{13}C NMR (100.6 MHz, D_2O, 25 °C): $\delta = 40.47$ (CH_2), 43.08 (CH_2), 74.27 (CH), 176.33 (COO), 176.89 (COO), 182.26 ppm (COO); ^{9}Be NMR (56.2 MHz, D_2O, 25 °C, $Be(H_2O)_4^{3+}$): $\delta = 1.84$ ppm ($w_{1/2} = 26$ Hz); ^{27}Al NMR (104.2 MHz, D_2O, 25 °C, $Al(H_2O)_6^{3+}$): $\delta = 14.0$ ppm ($w_{1/2=}1560$ Hz).

2: Citric acid (216 mg) was dissolved in $Al(NO_3)_3$ (1.125 mL 1M) and $Be(NO_3)_2$ (1.015 mL, 1.11M) in a 20-mL vial. The pH value was increased to 7 by the addition of NH_4OH and then ammonium phosphate buffer (2.5 mL, 0.5M, pH 7) was added. Slow diffusion of ethanol into the aqueous solution afforded crystals of suitable quality for X-ray diffraction studies. ^{9}Be NMR (56.2 MHz, D_2O, 25 °C, $Be(H_2O)_4^{2+}$): $\delta = 1.01$ ($w_{1/2=}48$ Hz), 2.19 ppm ($w_{1/2=}35$ Hz); ^{27}Al NMR (104.2 MHz, D_2O, 25 °C, $Al(H_2O)_6^{3+}$): $\delta = 12.2$ ppm ($w_{1/2} = 156$ Hz).

Solubilization of beryllium phosphate with aluminum citrate: $Be(NO_3)_2$ (1.015 mL, 1.11M) was added to ammonium phosphate (2.5 mL, 0.5M) in a 20-mL vial. The pH value was increased to 7 by addition of NH_4OH, and beryllium phosphate began to precipitate above pH 2.7. Citric acid (432 mg) and $Al(NO_3)_3$ (1.125 mL, 1M) were added to H_2O (1 mL) in a separate 20-mL vial. The pH value was increased to 7 by addition of NH_4OH, and then the aluminum citrate solution was added to the beryllium phosphate solution. The mixture was stirred for 3 days, and then filtered (0.45-μm frit). Inductively coupled plasma analysis indicated that 74% of the beryllium had dissolved in the aluminum citrate solution (149 mM Be). A solution of beryllium phosphate (pH 7) was filtered and 0.1% (19 μM Be) of the beryllium was retained.

Crystal data for **1**·7 H_2O: $C_{24}H_{54}Al_2Be_2N_6O_{35}$, $M_r = 1058.74$, triclinic, space group $P\bar{1}$, $a = 10.734(2)$, $b = 11.857(2)$, $c = 17.443(4)$ Å, $\alpha = 86.554(4)$, $\beta = 81.216(4)$, $\chi = 76.273(3)°$, $V = 2130.7(7)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.650$ g cm^{-3}, $0.46 \times 0.42 \times 0.40$ mm^3, $2\theta = 56.1°$, $F(000) = 1108$, $\mu(Mo_{K\alpha}) = 0.191$ mm^{-1}, 203(2) K, 8176 unique reflections ($R_{int} = 0.0789$), R (on F) 0.0694, wR (on F^2) 0.2366 ($I > 2\sigma(I)$). Crystal data for **2**·15 H_2O: $C_{36}H_{126}Al_6Be_6N_{18}O_{89}P_8$, $M_r = 2699.25$, hexagonal, $R\bar{3}$, $a = 19.5096(19)$, $c = 23.774(5)$ Å, $V = 7836.6(19)$ Å^3, $Z = 3$, $\rho_{calcd} = 1.716$ g cm^{-3}, $0.20 \times 0.12 \times 0.10$ mm^3, $2\theta = 50.68°$, F(000) = 4206, $\mu(Mo_{K\alpha}) = 0.322$ mm^{-1}, 203(2) K, 3197 unique reflections ($R_{int} = 0.1598$), R (on F) 0.0883, wR (on F^2) 0.2407 ($I > 2\sigma(I)$). CCDC 253433 and -253432 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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