Synthesis, Structural Characterization, and Solution Behavior of the First Mononuclear, Aqueous Aluminum Citrate Complex

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Aluminum has been widely distributed in nature,[1] yet its role in biological systems remains a subject of considerable debate. In numerous clinical and biological studies over the recent years, aluminum's accumulation and biotoxicity[2−4] have been linked with (a) its detection in neuritic deposits of Alzheimer's disease patients,[5−7] (b) other human pathological conditions[8,9] such as renal dialysis related encephalopathy, osteomalacia, and endemic amyotrophic lateral sclerosis, and (c) have been strongly associated with toxic processes emerging from the increasing acidification of the environment.[1,10] The involvement of citric acid, the main small molecule metal ion binder in plasma, in promoting Al^{3+} absorption by and facilitating Al^{3+} accumulation and biotoxicity in biological tissues has been well documented.[11] Solution studies carried out in an attempt to delineate the speciation of Al in the presence of citrate under varying conditions have provided useful information on the proposed species, but no definitive synthetic and structural details.[12] The scarcity of crystallographically characterized, low molecular weight Al-citrate complexes, reflecting physiologically relevant chemical entities in biological fluids, has prompted us to pursue pertinent aqueous synthetic studies. Herein, we report on the synthesis, isolation and crystallographic characterization of the first such mononuclear aluminum citrate complex.

Reaction between Al^{3+} and citric acid (eq 1) with a ratio of 1:2 in aqueous solution at pH ∼ 8 yielded colorless crystalline material, the composition of which was consistent with the formula $[(NH_4)_5\{Al(C_6H_4O_7)_2\}\cdot 2H_2O]$ (**1**).

The X-ray crystal structure[13] determination of **1** revealed a centrosymmetric elongated octahedral complex of two citrate ligands bound to Al^{3+} ion. Each citrate ligand is fully deprotonated, and as such it is coordinated to aluminum through its central hydroxyl and carboxylate groups in the equatorial plane

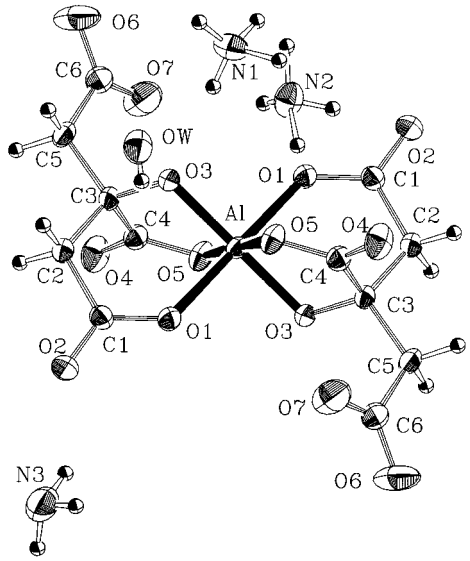
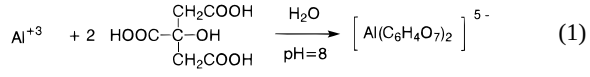


Figure 1. Structure of anion **1** with the atom labeling scheme. Thermal ellipsoids are drawn by ORTEP and represent 50% probability surfaces. Citrate hydrogen atoms have been omitted for clarity. Al−O(1), 1.961-(3) Å; Al−O(3), 1.844(3) Å; Al−O(5), 1.884(3) Å; O(1)−Al−O(3), 89.70(11)°; O(3)−Al−O(5), 85.64(13)°; O(1)−Al−O(5), 89.45(10)°; O(1)−C(1), 1.280(4) Å; O(2)−C(1), 1.240(4) Å; O(3)−C(3), 1.417(3) Å; O(5)−C(4), 1.290(4) Å; O(4)−C(4), 1.233(4) Å; O(6)−C(6), 1.259-(4) Å; O(7)−C(6), 1.235(4) Å; C(1)−C(2), 1.526(4) Å; C(2)−C(3), 1.534-(4) Å; C(3)−C(4), 1.545(4) Å; C(3)−C(5), 1.529(4) Å; C(5)−C(6), 1.525(4) Å.



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(1) Martin, R. B. *Acc. Chem. Res.* **1994**, *27*, 204−210.
(2) Forbes, W. F.; Agwani, N. *J. Theor. Biol.* **1994**, *171*, 207−214.
(3) Flaten, T. P.; Garruto, R. M. *J. Theor. Biol.* **1992**, *156*, 129−132.
(4) Exley, C.; Birchall, J. D. *J. Theor. Biol.* **1992**, *159*, 83−98.
(5) Clauberg, M.; Joshi, J. G. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1009−1012.
(6) Fasman, G. D.; Moore, C. D. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11232−11235.
(7) Vyas, S. B.; Duffy, L. K. *Biochem. Biophys. Res. Commun.* **1995**, *206*, 718−723.
(8) Van der Voet, G. B.; Van Ginkel, M. F.; de Wolff, F. A. *Toxicol. Appl. Pharmacol.* **1989**, *99*, 90.
(9) Kerr, D. N. S.; Ward, M. K. *Met. Ions Biol. Syst.* **1988**, *24*, 217−258.
(10) van Breemen, N. *Nature* **1985**, *315*, 16.
(11) (a) Domingo, J. L.; Gomez, M.; Llobet, J. M.; del Castillo, D.; Corbella, J. *Nephron* **1994**, *66*, 108−109. (b) Öhman, L.-O.; Martin, R. B. *Clin. Chem.* **1994**, *40*, 598−601.
(12) (a) Öhman, L.-O.; Sjöberg, S. J. *J. Chem. Soc., Dalton Trans.* **1983**, 2513−2517. (b) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1984**, *23*, 18−23. (c) Gregor, J. E.; Powell, H. K. J. *Aust. J. Chem.* **1986**, *39*, 1854−1864. (d) Karlik, S. J.; Tarien, E.; Elgavish, G. A.; Eichhorn, G. L. *Inorg. Chem.* **1983**, *22*, 525−529.

(13) X-ray-quality crystals of $(NH_4)_5Al(C_6H_4O_7)_2\cdot 2H_2O$ were grown from water−ethanol mixtures. Crystal dimensions 0.10 × 0.20 × 0.35 mm, triclinic, space group $P\bar{1}$, $a = 9.638(5)$ Å, $b = 9.715(5)$ Å, $c = 7.237(4)$ Å, $\alpha = 90.96(1)$, $\beta = 105.72(1)$, $\gamma = 119.74(1)°$, $V = 557.1(3)$ Å^3, $Z = 1$, $\rho_{calc} = 1.578$ g/cm^3, $2\theta_{max} = 50°$, Mo Kα radiation ($\lambda = 0.710\ 73$ Å), $T = 298$ K, θ-2θ scan, 3914 measured reflections, 1957 independent reflections ($R_{int} = 0.0279$) all included in the refinement. Lorentzian, polarization corrections were made, $\mu = 0.180$ mm^{-1}, $[\Delta/\sigma]_{max} = 0.030$, 225 parameters refined, $R_1 = 0.0498$ (for 1494 reflections with $I > 2\sigma(I)$), $wR_2 = 0.1477$ (on F^2). Max/min residual peaks in the final difference map 0.510/−0.328 e A^{-3}. Diffraction data were collected at room temperature on a Crystal Logic Dual Goniometer diffractometer. The structure was solved by direct methods using SHELXS-86 and refined by full-matrix least-squares techniques on F^2 by using SHELXL93. All non-H atoms were refined anisotropically. All H-atoms were located by difference maps and refined isotropically. In the crystal structure, N3 occupies a center of symmetry. Therefore, the ammonium ion is disordered. Only three of the four hydrogen atoms were located in the difference Fourier map. Full details on the structure can be found in the Supporting Information.

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and a terminal carboxylate in the axial position. The remaining terminal carboxylate group, albeit deprotonated, remains uncoordinated. In addition, the Al−O (carboxylate) axial distance of 1.961(3) Å is slightly longer than both equatorial distances of 1.844(3) Å (hydroxyl) and 1.884(3) Å (central carboxylate), respectively (Figure 1). Overall, the Al−O distances in **1** are similar with the corresponding distances in [{$Al_3(H_{-1}Cit)_3(OH)(H_2O)$}$^{4-}$] (range: 1.832(5)−1.935(5) Å) (**2**). **2** is a trinuclear cluster, in which each aluminum displays a distorted octahedral coordination.[14] Moreover, the Al−O distances in **1** compare favorably with those observed in the octahedral mononuclear $[Al\{ox\}_3]^{3-}$ (**3**) (range: 1.886(2)−1.909(1) Å).[15] The angles around aluminum in **1** range from 85.64(13)° to 94.36(13)° and are closer to ideal octahedral angles than and well within the range of those in the octahedrally distorted complexes **2** (range: 78.7(2)−100.8(2)°) and **3** (range: 83.9(1)−96.8(1)°). An extensive network of hydrogen bonds connects the complex anion with the NH_4^+ cations through mediating water molecules in the lattice.

The FT-infrared spectrum of **1** (in KBr) exhibits strong absorptions for the carbonyls of the citrate carboxylates. Asymmetric stretching vibrations $\nu_{as}(COO^-)$ appear between 1627 and 1588 cm^{-1}, whereas the symmetric ones $\nu_s(COO^-)$ appear between 1436 and 1380 cm^{-1}. All of the bands are shifted to lower frequencies compared to the free citric acid. The difference, $\Delta(\nu_{as}(COO^-)-\nu_s(COO^-))$,[16] is greater than 200 cm^{-1} indicating the presence of deprotonated carboxylate groups free or coordinated to the metal in a monodentate fashion, in agreement with the observed features in the X-ray crystal structure of **1**.

The behavior of **1** in aqueous solution is best described by the ^{13}C NMR spectrum in D_2O at pH ∼ 8.6, where peaks at 182.4, 179.7, 75.7, 46.2 and at 187.5, 179.6, 74.7, 46.0 ppm are observed (vs TMS as external standard) and attributed to free and Al(III)-bound citrate, respectively. Similar ^{13}C NMR results were obtained by Gregor and Powell[12c] at 4-fold excess of citrate over Al(III) in the pH range 2−8. There, the relatively broad structure of the resonances observed for coordinated citrate was explained by an equilibrium of coordination isomers and/or the presence of both Al^{3+} mono- and bis-citrate complexes. Two AB quartets dominate the ^1H NMR spectrum of **1**: one with sharp resonances at 2.68, 2.64, 2.56, and 2.52 ppm for the free citrate and another one with significantly broader resonances at 2.67, 2.62, 2.55, and 2.50 ppm attributed to citrate bound in the bis-citrate complex. Similar AB quartets were observed for a citrate-titrated aqueous Ga(III) system investigated under similar experimental conditions.[17] Based on these results we propose a symmetrical coordination (via the terminal carboxylates and the central alkoxy group) of the ligands around Al^{3+} in solution, rather than a nonsymmetrical one occurring in the solid state. The above NMR features of **1** may suggest either coordination isomerization of the complex upon dissolution or fluxional behavior of bound citrates. Over time (∼24 h), the ^1H NMR spectrum of **1** in D_2O slowly assumes a more complicated pattern, in which, aside from the aforementioned AB quartets, some of the characteristic resonances of the asymmetric $[Al_3(H_{-1}Cit)_3(OH)(H_2O)]^{4-}$ trinuclear species[14] (at 2.86, 2.84, 2.82, 2.80, 2.77, 2.74, 2.72 ppm) can also be recognized. The ^{27}Al NMR spectrum of **1** recorded (in H_2O) in equilibrium solutions shows a broad ($w_{1/2}$ = 560 Hz) asymmetric signal with a maximum at 11.84 ppm (vs $AlCl_3$) and a shoulder at a higher field. In addition, the relatively limited change of the ^{27}Al NMR spectra of the major components of an Al(III)-citrate (1:1) system, observed over time, at neutral pH suggests no significant alteration in coordination number and/or geometry of the predominant complex(es) involved. Overall, the preliminary NMR data at hand suggest the presence of equilibria (eqs 2) involving trinuclear Al(III) species in addition to the mononuclear Al(III)-bound citrate(s) upon dissolution of **1** in water.

$$[Al(H_{-1}\,Cit)_2]^{5-} + H_2O \rightleftharpoons [Al(H_{-1}\,Cit)(OH)]^{2-} + Cit^{3-}$$

$$3[Al(H_{-1}\,Cit)(OH)]^{2-} + H_2O \rightleftharpoons [Al_3(H_{-1}\,Cit)_3(OH)(H_2O)]^{4-} + 2OH^- \quad (2)$$

Taken together, these results are in line with those of previous solution speciation studies of Öhman and Sjöberg[12,18] projecting viable models of discrete molecular Al-Cit species in aqueous solution. In those studies, mononuclear as well as oligonuclear Al-citrate complexes had been proposed to exist in Al-citrate solutions. Among those included are mononuclear Al-citrate species such as $AlCit^0$, $AlHCit^+$, $Al(OH)(H_{-1}Cit)^{2-}$, etc.[12,18] Moreover, the distinct possibility of other low MW complexes, not as yet isolated, present in aqueous solutions at specified stoichiometric and pH conditions should not be discounted. Research efforts targeting the above entities,[19] those originating from physiologically relevant conditions ([Al^{3+}]:[cit] = 1:10), as well as their detailed solid and solution (multinuclear NMR) state properties, are expected to aid in understanding the chemistry of Al^{3+} ion with biological ligands and likely its link to absorption and biotoxicity. Such studies are currently underway in our laboratories.

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Supporting Information Available: Tables of X-ray crystal structure refinement data, positional and thermal parameters, ORTEP drawings, analytical data, and text giving preparative details for $(NH_4)_5Al(C_6H_4O_7)_2\cdot 2H_2O$. A crystallographic file, in CIF format, is also available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Feng, T. L.; Gurian, P. L.; Healy, M. D.; Barron, A. R. *Inorg. Chem.* **1990**, *29*, 408−411.
(15) Bulc, N.; Golic, L.; Siftar, J. *Acta Crystallogr.* **1984**, *C40*, 1829−1831.
(16) (a) Djordjevic, C.; Lee, M.; Sinn, E. *Inorg. Chem.* **1989**, *28*, 719−723. (b) Deacon, G. B.; Philips, R. *J. Coord. Chem. Rev.* **1980**, *33*, 227−250.
(17) Chang, C. H. F.; Pitner, T. P.; Lenkinski, R. E.; Glickson, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 5858−5863.
(18) Öhman, L.-O. *Inorg. Chem.* **1988**, *27*, 2565−2570.
(19) Attempts to isolate new species under the experimental reaction conditions employed herein and Al-citrate stoichiometry of 1:1 yielded again crystalline compound **1** (by FT-infrared data).