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Synthetic, structural, spectroscopic and solution speciation studies of the binary Al(III)–quinic acid system. Relevance of soluble Al(III)–hydroxycarboxylate species to molecular toxicity

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ABSTRACT

Efforts to delineate the interactions of Al(III), a known metallotoxin, with low molecular mass physiological substrates involved in cellular processes led to the investigation of the structural speciation of the binary Al(III)–quinic acid system. Reaction of $Al(NO_3)_3 \cdot 9H_2O$ with D-(−)-quinic acid at a specific pH (4.0) afforded a colorless crystalline material $K[Al(C_7H_{11}O_6)_3] \cdot (OH) \cdot 4H_2O$ (**1**). Complex **1** was characterized by elemental analysis, FT-IR, DSC–TGA, ^{13}C-MAS NMR, solution ^{1}H and ^{13}C NMR, and X-ray crystallography. The structure of **1** reveals a mononuclear octahedral complex of Al(III) with three singly ionized quinate ligands bound to it. The three ligand alcoholic side chains do not participate in metal binding and dangle away from the complex. The concurrent study of the aqueous speciation of the binary Al(III)–quinic acid system projects a number of species complementing the synthetic studies on the binary system Al(III)–quinic acid. The structural and spectroscopic data of **1** in the solid state and in solution emphasize its physicochemical properties emanating from the projections of the aqueous structural speciation scheme of the Al(III)–quinic acid system. The employed pH-specific synthetic work (a) exemplifies essential structural and chemical attributes of soluble aqueous species, arising from biologically relevant interactions of Al(III) with natural α-hydroxycarboxylate substrates, and (b) provides a potential linkage to the chemical reactivity of Al(III) toward O-containing molecular targets influencing physiological processes and/or toxicity events.

1. Introduction

Aluminum is an abundant element on the earth's crust with an ostensible presence in a number of abiotic materials. It has long since been recognized, however, as a metallotoxin associated with a number of aberrant cellular processes [1–6]. In humans, its presence has been shown to be linked with neurodegenerative diseases (Alzheimer's disease, microcytic anaemia, encephalopathies, etc.) albeit not through a cause and effect relationship [7–16]. This association is further enhanced by the fact that in an environment progressively being acidified, Al(III) gains access to aquifers and through them to plants, animals and humans.

Once in a cellular milieu, Al(III) interacts with a diverse spectrum of molecular targets varying in size, shape, structure and chemical reactivity. In such a competitive environment, binary and ternary interactions of Al(III) with low and high molecular mass substrates influence its toxicity profile. Among the low molecular mass biotargets of Al(III) are α-hydroxycarboxylic organic acids such as citric acid, malic acid and D-(−)-quinic acid. The latter (a) possesses antimicrobial effects [17], and (b) is an active participant in plant cell metabolism, being a key precursor in the shikimic pathway [18–20]. Through this pathway, essential aromatic amino acids are synthesized, contributing to the maintenance of cell physiology in the plant structure. It also occurs widely in fruit, other than grapes. There, the ester of quinic acid with caffeic acid (chlorogenic acid) is the first line of defense against fungal invasion. Quinic acid is also used as a raw material or building block in the synthesis of new pharmaceuticals currently undergoing clinical trials. It also participates in the photosynthetic process, where the presence of metal ions, in

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the form of coordination compounds, modulates the effect of the ligand itself [21]. The structure of quinic acid is that of a polyfunctional natural ligand containing an α-hydroxycarboxylic acid moiety on one side of the molecule and three alcoholic moieties on the other side. Hence, its chemical structure provides efficient anchors to metal ionic targets, exemplified through variable binding modes in a diverse spectrum of metal ionic geometries.

In view of the known accumulation [22–24] and toxicity of Al(III) in plants, animals and humans, its toxic manifestations entail a deep knowledge of its chemistry at the molecular level. Therefore, the aqueous speciation of this metallotoxin in binary and ternary systems, containing readily available cellular targets, is a valuable source of information. Through the aqueous speciation of such Al(III) binary and ternary systems, soluble and potentially bioavailable forms of the metal ion arise with suitable substrate ligands. It is likely that such Al(III) forms participate in molecular processes linked to that metal ion's toxicity. Poised to delineate the molecular chemistry involved in the establishment of Al(III) toxicity in cellular fluids, we launched efforts targeting the interactions of Al(III) with the natural binder D-(−)-quinic acid. To this end, we herein report on (a) the aqueous speciation of the binary Al(III)–quinic acid system, (b) pH-specific synthetic efforts to characterize species projected through the aqueous speciation of the binary Al(III)–quinic acid system, and (c) the association of the physicochemical profile of specific soluble and potentially bioavailable forms of Al(III)–quinate species, with the biological activity of that metal ion.

2. Experimental

2.1. Materials and methods

All experiments were carried out under aerobic conditions. Nanopure quality water was used for all the reactions. $Al(NO_3)_3 \cdot 9H_2O$, $AlCl_3 \cdot 6H_2O$ and quinic acid were purchased from Aldrich. Potassium hydroxide was supplied by Fluka. The Al(III) stock solution used for potentiometric measurements was prepared from recrystallized $AlCl_3 \cdot 6H_2O$ and its metal ion concentration was determined gravimetrically through its oxinate. The stock solution contained 0.1 M HCl to prevent hydrolysis of the metal ion. The exact concentrations of the ligand solution were determined by potentiometric titration, using the Gran method [25].

2.2. Physical measurements

FT-Infrared spectra were recorded on a Perkin Elmer 1760X FT-infrared spectrometer. A ThermoFinnigan Flash EA 1112 CHNS elemental analyser was used for the simultaneous determination of carbon, and hydrogen (%). The analyser is based on the dynamic flash combustion of the sample (at 1800 °C) followed by reduction, trapping, complete GC separation and detection of the products. The instrument is (a) fully automated and controlled by a PC via the Eager 300 dedicated software, and (b) capable of handling solid, liquid or gaseous substances.

A TA Instruments, model Q 600, system was used to run the simultaneous TGA–DSC experiments. The instrument mass precision is 0.1 μg. About 20 mg of sample was placed in an open alumina sample pan for each experiment. High purity helium and air (80/20 in N_2/O_2) were used at a constant flow rate of 100 mL/min, depending on the conditions required for running the experiment(s). During the experiments, the sample weight loss and rate of weight loss were recorded continuously under dynamic conditions, as a function of time or temperature, in the range 30–1000 °C. Prior to activating the heating routine program, the entire system was purged with the appropriate gas for 10 min, at a rate of 400 mL/min, to ensure that the desired environment was established.

2.3. Solid-state NMR

High resolution solid-state ^{13}C magic angle spinning (MAS) NMR spectra were measured at 100.63 MHz on a Bruker MSL400 NMR spectrometer, capable of high power ^{1}H-decoupling. The spinning rate used for the ^{1}H–^{13}C cross polarization and magic angle spinning experiments was 5 kHz at ambient temperature (25 °C). Each solid-state spectrum was the result of the accumulation of 200 scans. The recycle delay used was 4 s, the 90° pulse was 5 μs and the contact time was 1 ms. All the solid-state spectra were referenced to adamantane, which showed two peaks at 26.5 and 37.6 ppm, respectively, and to the external reference of TMS.

2.4. Solution NMR

The samples for solution NMR studies were prepared by dissolving the crystalline complex in D_2O, at concentrations in the range 0.02–0.10 M. The NMR spectra were recorded on a Bruker AM360 (^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm relative to the internal reference, TMS.

2.5. pH-potentiometric measurements

The stability constants of the proton and Al(III) complexes of the title ligand were determined by pH-potentiometric titrations of 25 mL samples in the pH range 2–9 or until precipitation occurred, under a purified argon atmosphere. Care was taken to ensure that titrimetric data were recorded and collected under conditions taking into consideration the kinetically sluggish Al(III). Duplicate titrations were performed. The reproducibility of the titrations was within 0.005 pH units. Titration points obtained when 5 min was not enough to attain pH equilibrium were omitted from the evaluation. The ionic strength was adjusted to 0.2 M with KCl. The temperature was maintained during the measurements at 25 ± 0.1 °C. The titrations were performed with a carbonate-free KOH solution of known concentration (ca. 0.2 M). The ligand concentration was 0.002, 0.004 or 0.008 M and the metal:ligand ratios were 0:1, 1:1, 1:2 or 1:4. All other experimental conditions were the same as in earlier studies [26,27].

The pH was measured with a computer-controlled Molspin titration system elaborated for titrations at low concentrations and a Metrohm 6.0234.100 combined glass electrode, calibrated for hydrogen ion concentration according to Irving et al. [28]. The concentration stability constants $\beta_{pqr} = [M_pA_qH_r]/[M]^p[A]^q[H]^r$ were calculated with the PSEQUAD computer program [29,30]. The uncertainties (3SD values) of the stability constants are given in the parentheses in Table 3. The stability constants used for the hydroxo species of Al(III) were taken from Ref. 30 and are corrected to $I = 0.2$ M using the Davies equation: −5.49 for $[AlH_{-1}]^{2+}$, −13.54 for $[Al_3H_{-4}]^{5+}$, −108.62 for $[Al_{13}H_{-32}]^{7+}$ and −23.40 for $[AlH_{-4}]^{-}$.

2.6. Preparation of the complex $K[Al(C_7H_{11}O_6)_3] \cdot (OH) \cdot 4H_2O$

A quantity of $Al(NO_3)_3 \cdot 9H_2O$ (0.25 g, 0.68 mmol) was placed in a flask and dissolved in 5.5 mL of H_2O. Subsequently, quinic acid (0.39 g, 2.0 mmol) was added slowly with continuous stirring. The solution was heated to 50 °C for 1 h until all of the reagents dissolved, and then it was cooled. Aqueous KOH was then added slowly to adjust the pH to a final value of 4.0. The resulting solution was stirred overnight. The following morning, addition of cold ethanol at 4 °C resulted, after a couple of weeks, in the deposition of a colorless crystalline material. The crystals were isolated by filtration and dried in vacuo. The yield was 0.34 g (~70%). *Anal.* Calc. for **1**, $K[Al(C_7H_{11}O_6)_3] \cdot (OH) \cdot 4H_2O$, $AlC_{21}H_{42}KO_{23}$, M.W. 728.63: C, 34.58; H, 5.76. Found: C, 34.41; H, 5.87%.