

## Study of Aluminum binary systems with phosphonate substrates and their relevance to neurodegeneration

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Received: 15 April 2011; Accepted: 30 May 2011

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### Abstract

The interest to delineate the interactions between aluminum and phosphonate substrates and their relevance to Alzheimer's Disease, led to the investigation of the pH-specific synthetic chemistry of the binary Al(III)-[N-(phosphonomethyl) iminodiacetic acid] (Al-NTAP) and Al(III)-[nitrilotris(methylene-phosphonic acid)] (Al-NTA3P) systems, in correlation with solution speciation studies. Investigation of the binary Al(III)-NTAP system afforded two new species  $(\text{CH}_6\text{N}_3)_4[\text{Al}_2(\text{C}_5\text{H}_6\text{NPO}_7)_2(\text{OH})_2] \cdot 8\text{H}_2\text{O}$  (**1**) and  $(\text{NH}_4)_2[\text{Al}_2(\text{C}_5\text{H}_6\text{NPO}_7)_2(\text{H}_2\text{O})_2] \cdot 4\text{H}_2\text{O}$  (**2**). A third compound emerged from the binary system of Al(III) with NTA3P,  $\text{K}_8[\text{Al}_2(\text{C}_3\text{H}_6\text{NP}_3\text{O}_9)_2(\text{OH})_2] \cdot 20\text{H}_2\text{O}$  (**3**). Complexes **1**, **2** and **3** were characterized by elemental analysis, FT-IR,  $^{13}\text{C}$ -,  $^{31}\text{P}$ -,  $^1\text{H}$ -NMR, and X-ray crystallography. The structures of **1**, **2** and **3** reveal the presence of dinuclear complexes of octahedral Al(III). Each Al(III) center is bound to a fully deprotonated phosphonate ligand, water and hydroxo moieties. The species emerging in solution from the dissolution of **1-3** reflect the aqueous speciation of the respective systems and suggest chemical reactivities consistent with the involvement of biotoxic Al(III) in neurodegenerative diseases.

**Keywords:** aluminum, phosphonate substrates, Alzheimer's Disease, metallotoxin.

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### 1. Introduction

Aluminum is one of the metals that can be found in the earth's crust, in excessively high amounts. The abundance of aluminum reflects the presence of that metal in insoluble forms (primarily ores). Unfortunately, anthropogenic activities in the environment and the acidification of the soil convert these insoluble forms to soluble ones. Therefore, the fact that the arising soluble forms can easily penetrate the human body, through water, [1] respiration and the food chain, is amply attested to. Previous studies have pointed strongly toward a correlation between aluminum concentration in the human body and neurodegenerative diseases, such as encephalopathy, microcytic anemia and Alzheimer's disease (AD) [2].

The neurofibrillary tangles and the senile plaques are the principal pathologic anatomical hallmarks of Alzheimer's disease [3]. One of the reasons pointing to the involvement of aluminum, leading to the formation of neurofibrillary tangles, is the interaction between that hard Lewis acid and the aberrantly hyperphosphorylated form of protein tau [4]. The investigation of this interaction has not been easy to carry out over the years, even though such knowledge would undoubtedly shed light on the aqueous chemistry of aluminum and its contribution to the onset and progress of dementia and ultimately AD. In order to delineate this problem, we focused our attention on the study of the interaction between the phosphonate and carboxylate groups present in tau, thereby using biomimetic organo-phosphonate substrates and organo-phosphonic-carboxylate substrates, with aluminum in aqueous media of variable molecular stoichiometry and pH.

The work carried out led to the development of two new crystalline materials emerging from synthetic processes as part of the structural speciation approach employed; the first compound arose through the reaction of  $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  with N-phosphonomethyliminodiacetic acid (NTAP) at specific pH (7.0 and 4.0).

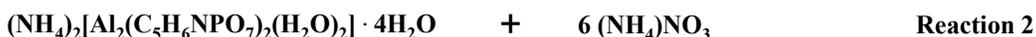
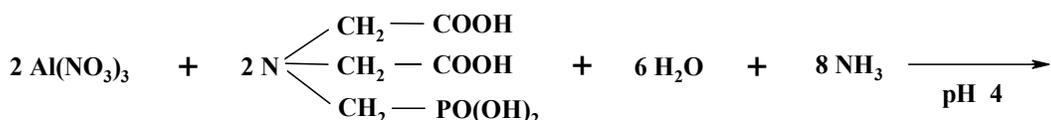
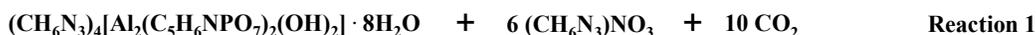
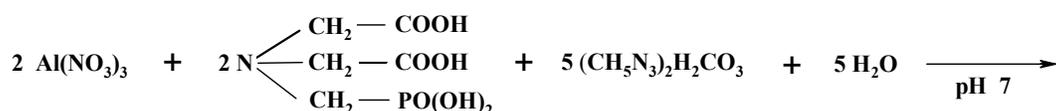
The two compounds were characterized by elemental analysis, FT-IR,  $^{31}\text{P}$ -,  $^{13}\text{C}$ -MAS-solid state-NMR and solution  $^1\text{H}$ -,  $^{31}\text{P}$ - and  $^{13}\text{C}$ -NMR, and X-ray crystallography. The collective data shed ample light on the intricate interactions of aluminum with carboxy-phosphonate substrates, thereby establishing the basis for the development of appropriate organic substrates targeting solubilization of Al-phospho bioprecipitates in biologically sensitive loci, not unlike those in the brains of AD patients.

## 2. Materials and methods

All experiments were carried out under aerobic conditions. Nanopure quality water was used for all reactions.  $\text{Al}(\text{NO}_3)_3$ , NTAP, NTA3P and  $\text{H}_2\text{O}_2$  30% were purchased from Aldrich. Ammonia and guanidine carbonate were supplied by Fluka.

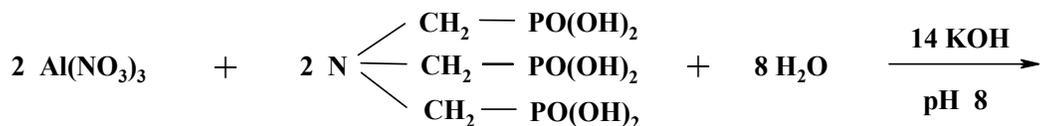
## 3. Results and Discussion

The synthetic efforts afforded compounds **1**, **2** and **3** under pH-dependent conditions. Compounds **1** and **2** resulted from the binary system of Al(III) with NTAP at pH values of 7.0 and 4.0, respectively. The pH was adjusted after heating and stirring overnight by the addition of guanidine carbonate for compound **1** and ammonia for compound **2**. The overall stoichiometric reaction leading to compounds **1** and **2** are shown schematically below:



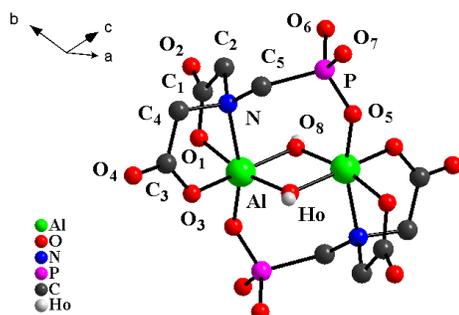
Compounds **3** resulted from the binary system of Al(III) with NTA3P. The solution was heated overnight under continuous stirring. The pH was adjusted at 8.0 through the addition of aqueous

potassium hydroxide. The overall stoichiometric reaction leading to compounds **3** are shown schematically below:



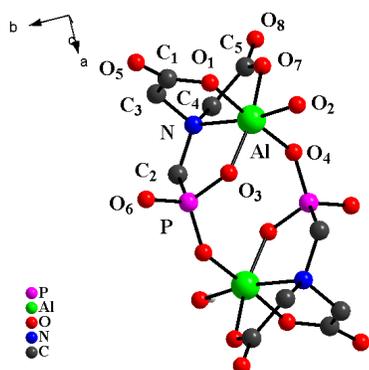
In all cases, addition of base not only helped adjust the pH of the reaction mixture, but also provided the necessary counter ions to balance the arisen complex charge. All three compounds were isolated in a pure crystalline form upon addition of alcohol to the reaction mixture at 4 °C.

**Synthesis.** The X-ray crystal structure of **1** reveals the presence of a lattice comprised of  $[\text{Al}_2(\text{C}_5\text{H}_6\text{NPO}_7)_2(\text{OH})_2]^{4-}$  units counterbalanced by guanidinium ions. The compound crystallizes in the triclinic space group  $P\bar{1}$ . The crystal structure diagram of **1** is shown in **Fig. 1**.



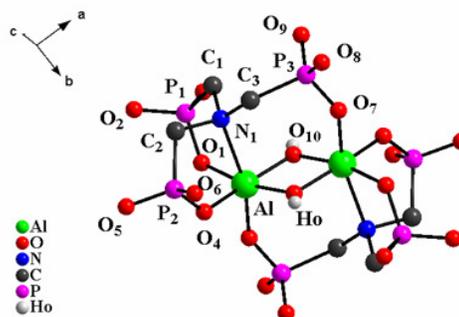
**Figure 1.** Structural diagram of the anion  $[\text{Al}_2(\text{C}_5\text{H}_6\text{NPO}_7)_2(\text{OH})_2]^{4-}$ .

Compound **2** crystallizes in the monoclinic space group  $P2_1/n$ . The centrosymmetric dinuclear structure contains Al(III) ions, with each one being bound to one NTAP ligand through the two carboxylates, phosphonate and nitrogen moieties. The NTAP ligand present in this assembly is fully deprotonated, with the sites of deprotonation being the two carboxylates and the terminal phosphonate groups. As a result, the charge of the assembly in the anion of **2**  $[\text{Al}_2(\text{C}_5\text{H}_6\text{NPO}_7)_2(\text{H}_2\text{O})_2]^{2-}$  is -2. This charge is counteracted by two  $\text{NH}_4^+$  ions. The crystal structure diagram of **2** is shown in **Fig. 2**.



**Figure 2.** Structural diagram of the anion  $[\text{Al}_2(\text{C}_5\text{H}_6\text{NPO}_7)_2(\text{H}_2\text{O})_2]^{2-}$ .

Compound **3** crystallizes in the monoclinic space group  $P2_1/n$ . The anionic centrosymmetric structure contains a dinuclear  $[\text{Al}_2(\text{OH})_2]^{4+}$  core bound to two NTA3P ligands. Charge balance consideration indicates that the NTA3P ligand is fully deprotonated, with the sites of deprotonation being the three terminal phosphonate groups. Due to the high charge of the dinuclear  $[\text{Al}_2(\text{C}_3\text{H}_6\text{N}-\text{P}_3\text{O}_9)_2(\text{OH})_2]^{8-}$  eight potassium ions act as counter ions. The crystal structure diagram of **3** is shown in **Fig. 3**.



**Figure 3.** Structural diagram of the anion  $[\text{Al}_2(\text{C}_3\text{H}_6\text{NP}_3\text{O}_9)_2(\text{OH})_2]^{8-}$ .

#### 4. Conclusion

In all cases the structural assembly formulating the coordination sphere of Al(III) is characterized by the presence of five-membered metallacyclic rings involving the carboxylate groups (compounds **1** and **2**), the carboxylate and phosphonate groups (compound **2**), and the phosphonate groups in compound **3**. Phosphonate groups, by virtue of their dual deprotonated hydroxo moieties giving rise to O-anchors, can participate in those metallacyclic rings both in the presence and absence of hydroxo bridges. Undoubtedly, therefore, the contribution of those five-membered rings is expected to be significant in the stabilization of the Al(III) centers and the  $\text{Al}_2$  dinuclear core in the solid state. At low pH (synthesis of compound **2**), the dinuclear species contains a dimetallic core displaying no hydroxo bridges between the two Al(III) centers. As the pH of the reaction mixture rises, the products isolated (compounds **1** and **3**) exhibit hydroxo-bridged dinuclear  $\text{Al}_2$  cores. Apparently, the hydroxo bridges stabilize the dinuclear  $\text{Al}_2$  core, fulfilling the octahedral coordination requirements of the respective Al(III) centers in the presence of fully deprotonated NTAP and NTA3P ligands.

In doing so, they bring the Al(III) centers closer to each other, thus reducing the intermetallic distance in the compound (vide infra).

The aqueous speciation in the binary Al(III)–NTAP acid system can be described satisfactorily by considering the presence of various 1:1 Al(III)–NTAP complexes [5]. Based on the existing literature, it is logical to juxtapose the results of the aqueous speciation with the solid-state structure of Al(III)–phosphonate compounds reported herein and their physicochemical properties in the solid state and in solution.

The chemical propensity of Al(III) to interact with oxygen- and nitrogen-containing substrates at the abiotic and biological level governs the wide chemical reactivity of that metal ion toward a diverse spectrum of organic substrates in nature (including plants, animals and humans). It is likely that Al(III), participating in such biosystems, ultimately delivers itself into processes involving molecular targets contributing to neurotoxicity.

Given that soluble and bioavailable Al(III) is a hard Lewis acid seeking interactions with hard Lewis bases, not unlikely those of phosphorylated sites on tau protein, Al(III) stands as a good reagent to promote binding to that protein locus. The phosphonate ligands employed in this work, project biomimetic analogs of phosphorylated sites albeit not identical with them. The fundamental PO<sub>3</sub> moiety in both phosphonated and phosphorylated substrates is there to promote interactions with Al(III).

In this sense, the chemical interactions of Al(III) with low molecular mass congener phosphonate and carboxy-phosphonate substrates provide the first well-characterized binary model system reflecting Al(III)–phosphosubstrate chemical reactivity.

#### Acknowledgements

This work was supported by a “Heraklitos II” grant financed by the Greek Ministry of Education, Lifelong Learning and Religious Affairs.

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