

Aqueous chemistry of Al(III) with carboxy-phosphonate and phosphonate substrates

V. Georgantas, A. Salifoglou

Department of Chemical Engineering, Aristotle University of Thessaloniki, Thessaloniki
54124, Greece

Abstract

The reactions of $\text{Al}(\text{NO}_3)_3$ with N-(phosphonomethyl)iminodiacetic acid and with N-nitrilo-tris(methylene-phosphonic acid) in aqueous solution at various pH values afforded crystalline materials, which represent new Al(III)-organophosphate species. The isolated crystalline materials were characterized by elemental analysis, spectroscopic techniques (FTIR, NMR) and X-ray crystallography. The new species contain aluminum ions in an octahedral environment and reflect chemical reactivity of that metal ion with phosphonate-containing substrates in biologically relevant fluids.

Keywords: Al(III), N-(phosphonomethyl)iminodiacetic acid, N-nitrilo-tris(methylenephosphonic acid)

Introduction

Aluminum is widely present in the earth's crust in the form of variably formulated ores and minerals. Albeit fixed in insoluble formations of inorganic materials in nature, acidification of the environment led to its solubilization and its increasing infiltration of living organisms across the spectrum of evolutionary hierarchy of species, including plants and humans. It has since long been recognized that aluminum is a metallotoxin [1, 2]. Aluminum excess in sensitive areas of the brain has been linked to neurodegenerative diseases such as Alzheimer's disease (AD) [3]. In the latter case, elevated aluminum levels in the brains of AD patients have been associated with the densities of the pathologic anatomical hallmarks, i.e. the senile plaques (SP) and neurofibrillary tangles (NFTs) [4]. Formation of such aggregate species promotes apoptosis of hippocampal neuronal cells and contributes inevitably to Alzheimer's disease. Particularly worth noting is the association between the principal component of NFT, hyperphosphorylated protein tau, and aluminum.

This idea led to the employment of the phosphonate ligands N-phosphonomethyliminodiacetic acid (NTAP), and nitrilo-tris(phosphonomethyl) acid (NTA3P). Concurrently, phosphonate ligands are appropriate substrates to simulate the hyperphosphorylated environment in aluminum-protein tau interactions. Cognizant of the significance of the interactions developing between Al(III) and the phosphorylated sites on the aberrant protein tau, research efforts were launched in our labs to a) comprehend the chemical reactivity between the neurotoxic Al(III) and tau - relevant substrates in a biological setting, and b) delineate the physicochemical features that render the developing Al(III)-tau interactions and the ensuing biochemical processes toxic to brain neurons.

Experimental Section

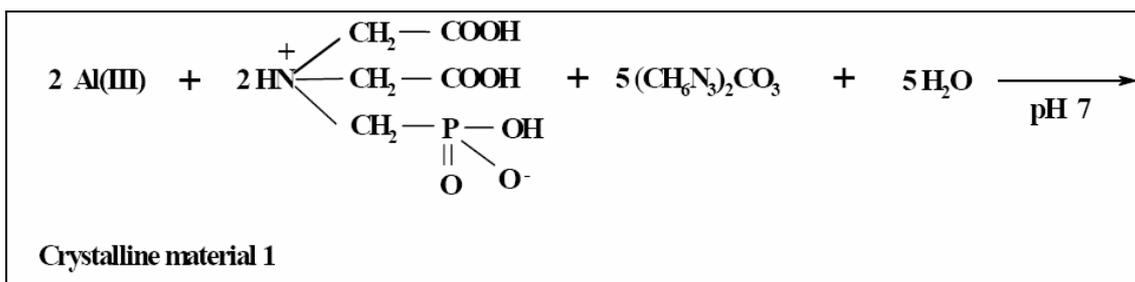
In the framework of this work, the binary system of Al(III)-NTAP was investigated synthetically in aqueous media. Under specific stoichiometric and pH conditions, and in the presence of the appropriate base,

* Corresponding author: *e-mail address:* salif@chemistry.ucl.ac.uk

Al(III) reacted with NTAP and NTA3P, respectively, leading to the isolation of colorless crystals of two new species.

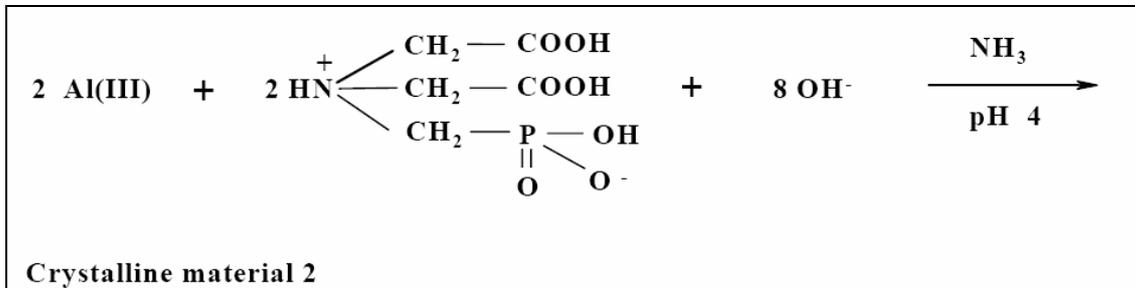
The synthesis of the crystalline material 1 took place in aqueous media (the water used was of nano-pure quality).

The pH value was adjusted to a value of ~7 by the addition of guanidine carbonate. The reaction mixture was stirred in a round flask and was subsequently placed in the refrigerator at 4°C. The stoichiometric reaction for the synthesis of complex 1 is shown below:



The synthesis of the crystalline material 2 took place in aqueous media (the water used was of nano-pure quality). The pH value and the base had a significant role for the isolation of 2. Therefore, the pH was adjusted to a value of ~4 by the addition of

aqueous ammonia. The reaction mixture was stirred in a round flask and was subsequently placed in the refrigerator at 4°C. The stoichiometric reaction for the synthesis of complex 2 is shown below:



The characterization of the newly isolated species was accomplished with the use of analytical chemistry, crystallographic and spectroscopic techniques, such as FT-IR. The FT-Infrared spectra of 1 and 2 in KBr revealed the presence of vibrationally active carboxylate and phosphonate groups. Thus, antisymmetric as well as symmetric vibrations for the carboxylate groups in the coordinated organophosphonates ligand were present in the spectra of 1 and 2. Specifically, symmetric stretching vibrations $\nu_s(\text{COO}^-)$ for the carboxylate carbonyls emerged around 1405 cm^{-1} for 1. Antisymmetric vibrations $\nu_{as}(\text{COO}^-)$ for

the same groups appeared between 1702 cm^{-1} and 1600 cm^{-1} . The symmetric stretching vibrations for the carboxylate carbonyls for compound 2 appeared between 1381 cm^{-1} and 1434 cm^{-1} and antisymmetric between 1600 cm^{-1} and 1680 cm^{-1} . The difference between the symmetric and antisymmetric stretches, $\Delta(\nu_{as}(\text{COO}^-) - \nu_s(\text{COO}^-))$, is greater than 200 cm^{-1} in both cases, indicating that the carboxylate groups of the carboxyphosphonate ligand are coordinated to Al(III) in a monodentate fashion. The $\nu(\text{P-O})$ stretching vibration appears between 927 cm^{-1} and 1106 cm^{-1} for compound 1, in the range 910 cm^{-1} - 1155 cm^{-1} for compound 2.

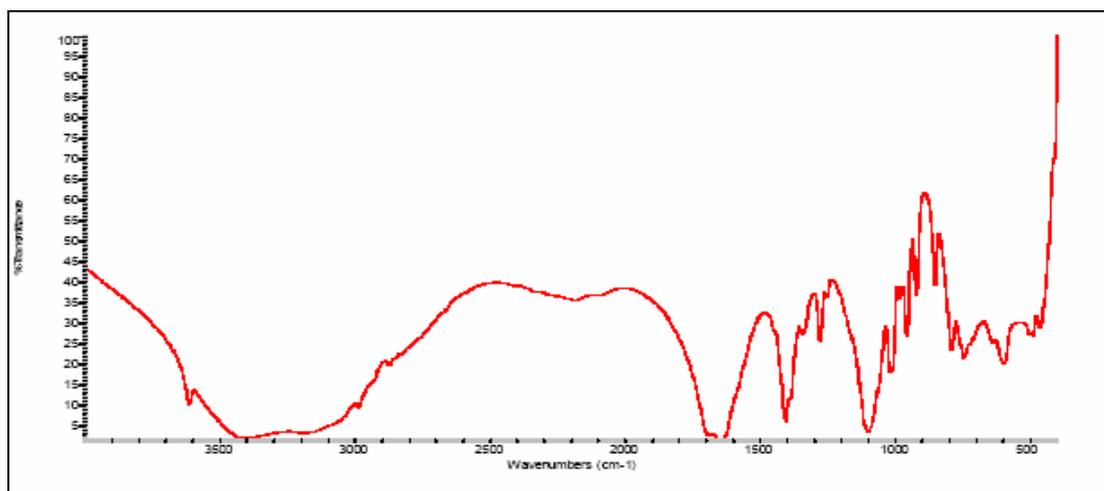


Figure 1: FTIR spectrum of crystalline material 1

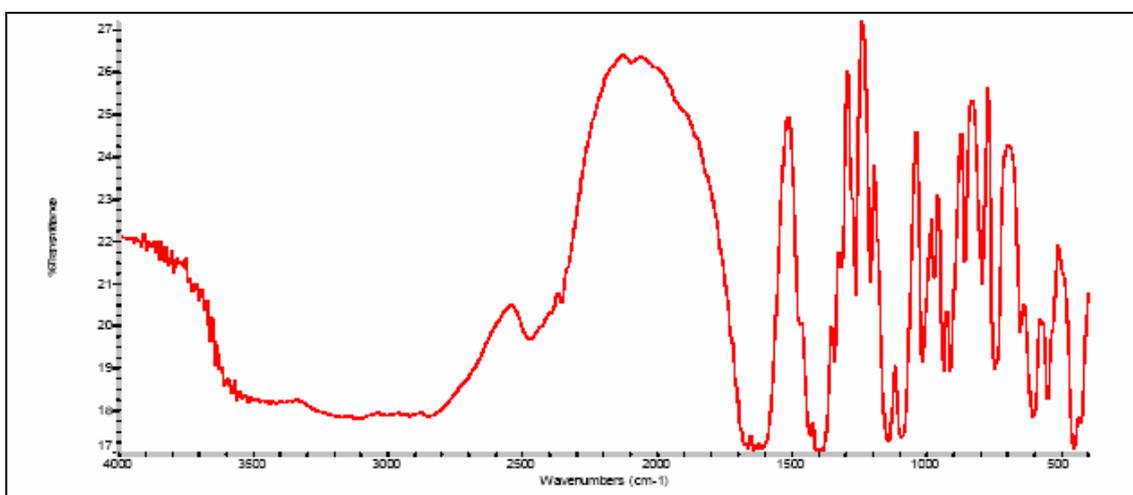


Figure 2: FTIR spectrum of crystalline material 2

X-Ray crystallography measurements provided the three dimensional structure of the investigated molecule. Complexes 1 and 2 consists of a dinuclear assembly with two aluminium centers bearing two N-(phosphonomethyl)iminodiacetic acid (NTAP) ligands. Each Al(III) ion coordinates to one NTAP. Each N-(phosphonomethyl)iminodiacetic acid is fully deprotonated and is coordinated with four binding sites of Al, respectively. Furthermore, for complex 1, aluminum coordinates with two hydroxyl bridges, and for complex 2, with one molecule of water and the oxygen of the phosphonate group of the other NTAP molecule. Thus, Al(III) and NTAP are coordinated in a distorted

octahedral environment. In both cases, the base has a twofold role in this reaction. Firstly, it adjusts the pH of the reaction mixture to deprotonate the NTAP in order to bind Al(III), and secondly it balances the charge of the arising complex.

Further characterization of the isolated complexes 1 and 2 was accomplished through ^1H -, ^{13}C -, ^{31}P -solution NMR and ^{13}C -, ^{31}P - solid state NMR.

Conclusions

The aqueous synthetic chemistry of the binary system Al(III)-organophosphonate ligand was investigated in an effort to comprehend the interaction of Al(III) with

mixed carboxy-phosphonate substrates. The data collected from the physicochemical and spectroscopic measurements project a relevance between the chemistry of the system above and the aqueous chemistry of Al(III) coordinated to low mass carboxy-phosphonate molecules, encountered in proteins and peptides relevant to key biological functions in sensitive loci. The analysis of aluminum interactions with this type of targets, suggests crucial clues on the speciation of that metal ion with carboxy-phosphonate substrates and its relevance to biotoxic effects relevant to processes involved in the formation of NFTs in Alzheimer's disease.

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