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Synthetic and structural carboxylate chemistry of neurotoxic aluminum in relevance to human diseases

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Contents

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Abstract

The contact of Al(III) with biological components in human physiology has increased significantly over the years, due to a number of factors, prominent among which stands the rapid acidification of the environment and the concomitant introduction of that abundant metal ion in human biological fluids. As a result, pathophysiological aberrations in humans have arisen due to Al(III) (neuro)toxicity. Among the efforts targeting the elucidation of the factors responsible for Al(III) toxicity is the exploration of the requisite Al(III)-carboxylate chemistry in aqueous media, and its relevance to soluble, potentially bioavailable species capable of exerting toxic effects. A detailed synthetic, structural, and spectroscopic account of the Al(III)-carboxylate complexes, purported to exist as components in aqueous Al(III)–carboxylic acid speciation, is presented. The structures described are classified as mononuclear, dinuclear, trinuclear, tetranuclear, and polynuclear species, arising from various aqueous and non-aqueous Al(III)-carboxylate ligand reactions. Moreover, the solution chemistry and kinetic behavior of the so far reported complexes is given, with the specific aim of comparing their solid state and solution chemical and structural properties. In this sense, a comprehensive picture on the Al(III) speciation, in the presence of various physiological or biologically relevant carboxylate ligands, appears to emerge, which is expected to contribute to the understanding of Al(III) (neuro)toxicity and its consequence(s) in a multitude of human diseases. Carboxylate containing low and high molecular mass components stand prominent in their chemical preference to react with Al(III) in biological fluids. In this context, factors considered to influence the aqueous low molecular mass Al(III)-carboxylate chemistry, thus affecting the solubility and possibly the bioavailability of the resulting species, are discussed as potential research links to the ultimate manifestation of Al(III) toxicity at the cellular level.

Keywords: Aluminum-carboxylates; Speciation; Bioavailability; Crystal structures; (Neuro)toxicity; Disease

1. Introduction

The acidification of the environment [1,2] linked with the subsequent chemistry of solubilized Al(III) within living organisms is one of the routes for increasingly developing interactions between the abundantly present metal and biological components in nature. Such interactions could induce pathophysiological aberrations in humans, the most profound of which are argumentatively considered to be emerging from the biotoxicity [3–5] of that element. In this context, the neurotoxic effects of Al(III) [6,7] have been detected and well established over the years through in vivo and in vitro studies. Accumulation of that element in humans has been known to impart toxic effects, with severe forms of symptomatic pathologies (dialysis dementia, osteomalacia, etc.) [8–11] occurring in various vital parts of the human body. Lately, the presence of Al(III) has been associated with neurodegenerative diseases (Alzheimer's disease, etc.) [12–16], and currently constitutes an issue of considerable scientific conjecture, which has yet to be resolved.

How does Al(III), though, interact with biological components, and which species arise from such interactions? Are all of these species (forms) capable of exerting toxic effects? Which bioavailable species are in a position to influence the biochemistry of metabolic and other pathways linked (if definitively proven) with the onset and progress of human diseases? Answers to such questions could in principle be associated with the chemistry of that element with biologically related sites, represented by proteins, enzymes and enzyme active sites, as well as low molecular mass organic substrates available in biological fluids.

In an initial attempt to focus on the stated questions, a number of speciation studies [17–21] were carried out in aqueous solutions of Al(III), in the presence of small organic molecules as putative ligands to that metal ion. The reported studies provided a wide view of the number and nature of species present in the entire pH range, as a function of concentration of Al(III) and the associated ligand. Consequently, a plethora of species, potentially significant in promoting (bio)chemical reactions in human biological fluids was proposed. Among those included were Al(III)-citrate, Al(III)-succinate [22], Al(III)-malate [23], Al(III)-tartrate [24], and other complexes in aqueous solutions. Moreover, significant strides were made in proposing variable nuclearity complexes of Al(III), bearing different metal to ligand ratios and assembled through pH-dependent synthetic approaches. Thus, speciation studies were pivotal in unearthing complex forms of Al(III), potentially bioavailable toward interacting biological systems. Collectively, the invoked studies aided in the formulation of

soluble, bioavailable forms of Al(III) that could exert toxic effect(s) on human biological targets.

The emergence of speciation information was even more crucial in further advancing our understanding of the intricate chemical reactivity of Al(III) entering biological fluids (such as human plasma), and interacting with high as well as low molecular mass natural ligands. In view of the toxicity of Al(III) and the (bio)chemical significance of such interactions, the need for further researching the 'structure–toxicity' relationship of Al(III) complex species, arisen from such studies, in biologically relevant media proved to be essential.

In order to implement pertinent research plans coping with the aforementioned issues, however, it would be imperative to have the proposed Al(III) species in a pure, isolated form, and in sufficient quantities, so as to be able to launch crystallographic, spectroscopic, and solution investigations. The number of complexes, though, of Al(III) with physiological ligands, well characterized in the solid state and in solution, was limited. The lack of such information prompted the scientific community to investigate in depth the synthetic aspects of the chemistry of Al(III) with various ligands, and study their solid state and solution properties. Undoubtedly, the expected information would be invaluable in further assessing the potential of those complexes, as bioavailable forms of the metal, to exert toxic effects on vital physiological functions in humans.

Over the years, a number of Al(III) complexes with biologically relevant carboxylic acid ligands have emerged from synthetic studies carried out in aqueous solutions. These various Al(III) species are discussed here in detail, with emphasis on their solid state and solution properties. Consequently, variable nuclearity complexes (containing a variable number of Al(III) ions) are analyzed, and their chemical properties and structures in solution are directly compared with their properties and structures in the solid state. A detailed account of this structural speciation of Al(III) with carboxylate containing ligands is envisaged to set the stage for further in-depth perusal of any potential toxicity these species might be capable of exhibiting in vivo.

2. Structural chemistry of Al(III)-carboxylate complexes. An account of synthesis and characterization of Al(III) species in the solid state and in solution

Generally, simple reactions of Al(III) with various carboxylate ligands, under variable pH reaction conditions, lead to the synthesis and isolation of a number of different complexes. Examples of Al(III)-carboxylates synthesized in organic media are also reported. Detailed structural data on these complexes are listed in Table 1.

2.1. FT-IR spectroscopy in the characterization of Al(III)-carboxylate complexes

Of the various spectroscopic methods employed in the identification and characterization of Al(III) complexes, FT-IR spectroscopy is instrumental in many respects. A number of the herein-described compounds, examined by FT-IR, exhibit spectra, which are dominated by strong absorptions for the carboxylate ligands in the carbonyl region. In particular, distinct antisymmetric stretching vibrations, $\nu_{as}(COO^-)$, appear between around 1640 and 1600 cm^{-1}. The corresponding symmetric stretches, $\nu_s(COO^-)$, appear in the range between 1440 and 1380 cm^{-1}. For all FT-IR investigated compounds, the observed bands are shifted to lower frequencies compared to those belonging to the free carboxylic acid. Moreover, the difference $\Delta(\nu_{as}(COO^-)-\nu_s(COO^-))$ [25,26] is consistently greater than 200 cm^{-1} for the complexes investigated, indicating the presence of deprotonated carboxylate groups which are either free or coordinated to the metal ion in a monodentate fashion. This observation has been seen before for carboxylate complexes of other metal ions [27–29], and is in agreement with the coordination mode of the carboxylate-containing ligands in the reported X-ray crystal structures.

2.2. Mononuclear species

2.2.1. Lactic acid

Lactic acid, $CH_3CH(OH)COOH$, is a α-hydroxycarboxylic acid. A good example of its structural association with Al(III) is the mononuclear complex $Al(CH_3CH(OH)COO)_3$ (**1**). X-ray crystallography reveals that the Al(III) central ion is surrounded by three lactate ligands arranged in an octahedral fashion [30]. Therefore, Al(III) is in an oxygen donor environment, whereby the oxygens originate in the carboxylate group and the α-hydroxy oxygen of lactic acid. Lactic acid acts as a singly deprotonated moiety with the carboxylic group being the one subjected to deprotonation. It appears that in **1** the hydroxy proton is retained on the coordinated ligand(s). As a result, the charge on the complex is zero.

Complex **1** was extensively used in clinical in vivo and in vitro investigations, looking into the toxicology of the species arising upon dissolution of the compound in water and its use under physiological conditions [31]. Preferential use of **1** in such investigations was primarily due to its high solubility in water and the lack of $Al(OH)_3$ precipitation at physiological pH. In light of the aforementioned use of Al(III)-lactate, extensive work was carried out to elucidate its behavior in aqueous solutions. Key to that endeavor was potentiometry, and ^1H-, ^{13}C-, and ^{27}Al-NMR spectroscopy [32–34]. Specifically, the data for **1**, upon dissolution in

Table 1
Bond distances (Å) and angles (°) in Al(III)-carboxylate complexes

Compound	Distances (Å)		Angles (°)	
	Al–O	Al–N	$(O–Al–O)_{equatorial}$ [u]	$(O–Al–O)_{apical}$ [v]
Mononuclear				
$Al(CH_3CH(OH)COO)_3$ [a]	1.856(4)–1.908(4)		82.1(1)–96.9(1)	82.1(1)–96.0(1)
$K_3[Al(C_2O_4)_3]$ [b]	1.876(3)–1.913(3)		83.9(2)–97.3(2)	83.1(2)–100.1(2)
$Na(Et_4N)_2[Al(C_2O_4)_3]$ [c]	1.889(3)–1.908(2)		84.2(1)–95.7(1)	84.6(1)–93.5(1)
$K[Al(C_3H_2O_4)_2(H_2O)_2]\cdot 2H_2O$ [d]	1.862(2)–1.902(2)		86.3(1)–93.1(1)	87.0(1)–92.6(1)
$[Al(H_2O)_6][Al(C_4H_4O_4)_2(H_2O)_2]\cdot[Cl]_2\cdot 4H_2O$ [e]	1.840(2)–1.935(2)		87.6(1)–92.4(1)	88.9(1)–91.1(1)
$Na[Al(C_4H_4O_4)_2(CH_3OH)_2]$ [f]	1.848(3)–1.937(4)		86.9(1)–93.1(1)	88.4(2)–91.6(2)
$K[Al(C_4H_5NO_4)_2]\cdot 2.5H_2O$ [g]	1.858(2)–1.878(2)	2.048(3)–2.060(3)	83.6(1)–97.5(1) [w]	83.3(1)–100.7(1) [w]
$K[Al(C_5H_7NO_4)_2]$ [h]	1.873(1)–1.879(1)	2.031(2)	89.7–90.3 [y]	85.4–94.6 [w,y]
$[Al(C_6H_6NO_6)(H_2O)_2]\cdot(CH_3)_2CO\cdot H_2O$ [i]	1.829(3)–1.893(3)	2.086(4)	85.2(1)–95.1(1) [w]	81.8(1)–99.3(1) [w]
$(NH_4)_5[Al(C_6H_4O_7)_2]\cdot 2H_2O$ [j]	1.844(3)–1.961(3)		89.45(10)	85.64(13)–89.70(11)
$(NH_4)_4[Al(C_6H_4O_7)(C_6H_5O_7)]\cdot 3H_2O$ [j]	1.836(1)–1.959(1)		85.58(6)–94.47(6)	88.56(6)–92.49(6)
$K_4[Al(C_6H_4O_7)(C_6H_5O_7)]\cdot 4H_2O$ [j]	1.821(2)–1.954(2)		88.57(8)	85.87(7)–90.46(7)
$K[Al(C_{10}H_{12}N_2O_8)]\cdot 2H_2O$ [k]	1.859(3)–1.886(3)	2.045(3)–2.075(3)	82.8–110.4 [w,y]	83.3–95.4 [w,y]
Dinuclear				
$Na_3H_3[Al(C_2H_2O_3)_3]_2$ [l]	1.888(3)–1.889(3)		83.1(1)–98.0(1)	83.1(1)–98.0(1)
$[Al(C_4H_5NO_4)(OH)(H_2O)]_2\cdot 2H_2O$ [m]	1.847(2)–1.889(3)	2.081(3)	78.1–94.0 [y]	82.7–95.8 [w,y]
$[Al(H_2O)_2][Al_2(C_6H_6NO_6)_2(\mu\text{-}OH)_2]\cdot[OH]\cdot 3H_2O$ [i]	1.816(2)–1.909(2)	2.073(3)	79.6(1)–99.5(1) [w]	80.4(1)–100.0(1) [w]
$[Al\{C_6H_8NO_5\}(H_2O)]_2\cdot 2H_2O$ [n]	1.798–1.898 [y]	2.056 [y]	85.7–96.1 [y]	77.4–100.0 [w,y]
$[Al_2(\mu\text{-}CH_3COO)_2(\mu\text{-}OH)(CH_3COOC_2H_5)_6][AlCl_4]_3$ [o]	1.850(8)–1.980(7)		82.9(4)–93.6(4)	84.4(4)–95.8(4)
Trinuclear				
$(NH_4)_5[Al_3(C_6H_4O_7)_3(OH)(H_2O)]\cdot[NO_3]\cdot 6H_2O$ [p]	1.832(5)–1.935(5)		77.6(2)–98.2(2)	82.8(2)–100.8(2)
Tetranuclear				
$[(AlMe_2)_2(\mu\text{-}O_2C)_2\text{-}1,2\text{-}C_6H_4]_2$ [q]	1.818(1)–1.870(1)		92.64(6)–100.74(5) [x]	
Polynuclear				
$[Al_{13}(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_{12}(C_6H_8NO_5)_6(H_2O)_6](NO_3)_3$ [n]	1.894(15) [r]		84.0–96.0 [y]	84.0–96.0 [y]
	1.822(19)–2.040(24) [s]		76.9–97.3 [y]	77.9–100.7 [y]
	1.852(19)–1.951(36) [t]	2.057(25)	84.7–97.5 [y]	82.0–97.5 [w,y]

[a] Ref. [30]; $CH_3CH(OH)COO^-$ = lactate.
[b] Ref. [36–38]; $C_2O_4^{2-}$ = oxalate.
[c] Ref. [43]; $C_2O_4^{2-}$ = oxalate.
[d] Ref. [48]; $C_3H_2O_4^{2-}$ = malonate.
[e] Ref. [49]; $C_4H_4O_4^{2-}$ = methyl malonate.
[f] Ref. [50]; $C_4H_4O_4^{2-}$ = methyl malonate.
[g] Ref. [52]; $C_4H_5NO_4^{2-}$ = bis(imino)diacetate.
[h] Ref. [55]; $C_5H_7NO_4^{2-}$ = bis(methylimino)diacetate.
[i] Ref. [56]; $C_6H_6NO_6^{3-}$ = nitrilotriacetate.
[j] Ref. [57,60]; $C_6H_4O_7^{4-}$ and $C_6H_5O_7^{3-}$ = citrate.
[k] Ref. [65,66]; $C_{10}H_{12}N_2O_8^{4-}$ = ethylenediamine tetraacetate.
[l] Ref. [67,68]; $C_2H_2O_3^{2-}$ = glycolate.
[m] Ref. [69]; $C_4H_5NO_4^{2-}$ = bis(imino)diacetate.
[n] Ref. [71]; $C_6H_8NO_5^{3-}$ = *N*-(2-hydroxyethyl)iminodiacetate.
[o] Ref. [72]; CH_3COO^- = acetate, $CH_3COOC_2H_5$ = ethylacetate.
[p] Ref. [75]; $C_6H_4O_7^{4-}$ = citrate.
[q] Ref. [81]; $C_6H_4(COO)_2^{2-}$ = phthalate.
[r] Central Al.
[s] Peripheral Al.
[t] Al of the outer shell.
[u] O–Al–O angle range in the equatorial plane.
[v] O–Al–O angles between the axial and equatorial ligands.
[w] O–Al–N and N–Al–N angles included.
[x] Tetrahedral angles around Al.
[y] Standard deviations for bond distances and angles not available from the respective reference papers and the crystallographic data from the CCDC database.

water at pH 3.5, support the idea of its dissociation to free lactate and Al(III)-bound lactate species. They also indicate a rapid attainment of equilibrium, at which species such as $[Al(lact)_2(H_2O)_2]^+$, $[Al(lact)_2(OH)(H_2O)]$ and/or $[Al(lact)(H_{-1}lact)(H_2O)_2]$ ($H_{-1}lact = CH_3CH(O)COO^{2-}$) with smaller amounts

of Al(lact)$_3$ (lact = $CH_3CH(OH)COO^-$) [35] are present. At physiological pH values, most of the lactate ligand is not coordinated to Al(III), yet its presence in solution contributes significantly to the retardation of the ultimate appearance of $Al(OH)_3$. Under these conditions, the presence of (meta)stable species like $[Al(OH)_3(H_2O)_3]$ is proposed. It is such species that mainly reflect the toxicological implications of the administration of Al(III)-lactate in aqueous solutions.

2.2.2. Oxalic acid

Oxalic acid, $(COOH)_2$, is a simple dicarboxylic acid, which reacts expediently with Al(III) in aqueous solutions to yield the mononuclear anionic complex $[Al(ox)_3]^{3-}$ (ox = $C_2O_4^{2-}$) (**2**). The anionic species **2** has been isolated in a crystalline form, in the presence of a variety of counterions including potassium [36–38], sodium [39,40], ammonium [41], tetramethylammonium [42], and sodium-tetraethylammonium [43]. The trianionic complex consists of an octahedral Al(III) ion with three coordinated oxalate ligands.

The ligand upon reacting with Al(III) becomes fully deprotonated, and as a dianion it coordinates to the metal ion. Consequently, the overall charge of the complex is 3−. The structure of the mononuclear complex **2** is similar to that of the Fe(III) [44,45] and Cr(III) [36,46,47] analogues.

2.2.3. Malonic acid

Malonic acid, $CH_2(COOH)_2$, is a dicarboxylic acid, which differs from oxalic acid in that it contains an additional CH_2 group between the two carboxylic moieties. It reacts expediently with Al(III) in aqueous solutions, and under basic conditions affords the mononuclear species $K[Al(C_3H_2O_4)_2(H_2O)_2]\cdot 2H_2O$ (**3**) [48].

The X-ray crystal structure of **3** reveals the presence of an octahedral Al(III) center, to which two malonate ligands are coordinated in a bidentate fashion through their terminal carboxylates. The remaining vacant coordination sites are occupied by two water molecules. The latter ligands occupy the axial positions in the assembled octahedron, with the carboxylate oxygens of the malonate ligands lying in the equatorial plane. It appears that the dicarboxylic malonic acid is fully deprotonated and as such it coordinates to Al(III). The derived charge on the overall complex in **3** is 1−, and this charge is counterbalanced by K^+ ions. Two additional water molecules of crystallization complete the molecular assembly of the complex. In the lattice of **3** extensive interactions involving the potassium counterions with the oxygens of the coordinated water and malonate ligands as well as the water molecules of crystallization, very likely, contribute to its stability.

The solution behavior of **3** was studied by ^{13}C-, ^{1}H-, and ^{27}Al-NMR spectroscopy [48]. Based on these studies, when **3** dissolves in neutral water it undergoes partial hydrolysis to $[Al(C_3H_2O_4)_3]^{3-}$, which is considered to be the thermodynamically stable species, and non-detectable Al(III)-aqua-hydroxo species. Hydrolysis of the $[Al(C_3H_2O_4)_2(H_2O)_2]^-$ species is favored upon increasing the pH of the aqueous solution toward the physiological pH value. In this case, the $[Al(C_3H_2O_4)_3]^{3-}$ complex is the predominant species in neutral solution. Under such conditions no formation of $Al(OH)_3$ is observed.

2.2.4. Methylmalonic acid

Methylmalonic acid, $CH_3CH(COOH)_2$, is a derivative of malonic acid, exhibiting reactivity toward Al(III) in aqueous media. Two mononuclear octahedral complexes have been reported as a result of the reaction of Al(metal) + Al(III) with methylmalonic acid, namely $[Al(H_2O)_6][Al(C_4H_4O_4)_2(H_2O)_2]\cdot[Cl]_2\cdot 4H_2O$ (**4**) [49] and $Na[Al(C_4H_4O_4)_2(CH_3OH)_2]$ (**5**) [50].

Both complexes contain octahedral Al(III) ions with two methylmalonate ligands in their respective coordination spheres. The vacant coordination sites are occupied by two water molecules in one case and by two methanol molecules in the other.

As in the case of the Al(III)-malonate complex, here too, the malonate ligands are doubly deprotonated, and as such they coordinate to the metal ion through their carboxylate groups in a bidentate fashion. The overall charge of the complex is 1−. $[Al(H_2O)_6]^{3+}$ and Cl^- ions in **4**, and Na^+ ions in **5** balance the single negative charge on the respective complexes. The coordinated malonate oxygens lie in the equatorial plane of both complexes, in consonance with the analogous arrangement of the oxygens in the malonate complex (vide supra) **3**. The apical positions in each octahedron are occupied by water (**4**) or methanol (**5**) oxygens.

Speciation studies on the Al(III)-methylmalonic aqueous system were carried out by means of potentiometric measurements [51]. The derived speciation data suggest the presence of a series of complexes including $[Al(C_4H_4O_4)]^+$, $[Al(C_4H_4O_4)_2]^-$, and $[Al(C_4H_4O_4)_3]^{3-}$.

2.2.5. Bis(imino)diacetic acid

Bis(imino)diacetic acid, $NH(CH_2COOH)_2$, appears to be a potent chelator of Al(III) in aqueous solutions. An octahedral complex, $K[Al(ida)_2]\cdot 2.5H_2O$ (ida = $C_4H_5NO_4^{2-}$) (**6**), resulting from the reaction of Al(III) with ida (molar ratio Al(III)–ida ca. 1:2), in the presence of an aqueous solution of KF, has been structurally characterized [52]. The anionic structure of the complex is similar to those previously reported for Cr(III) [53] and Co(III) [54]. The central Al(III) ion is surrounded by two ida ligands (Fig. 1A). The ligands are dicarboxylic acids, and are capable of using both carboxylate groups as binding sites to Al(III).

Therefore, two ida molecules, acting as doubly deprotonated moieties, bind to the metal ion through

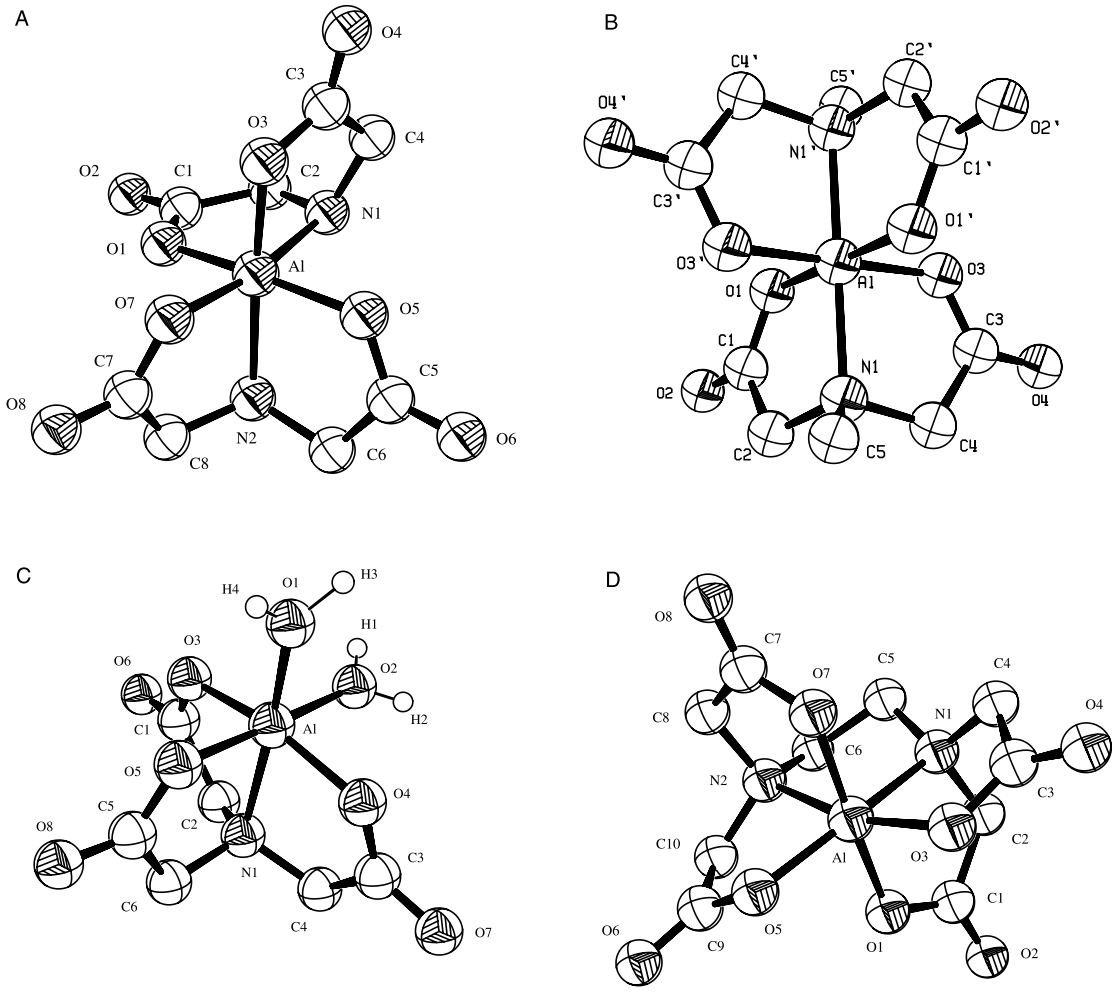


Fig. 1. (A) Structure of the anionic complex $[Al(C_4H_5NO_4)_2]^-$. (B) Structure of the anionic complex $[Al(C_5H_7NO_4)_2]^-$. (C) Structure of the mononuclear assembly $[Al(C_6H_6NO_6)(H_2O)_2]$. (D) Structure of the anionic complex $[Al(C_{10}H_{12}N_2O_8)]^-$.

the carboxylate oxygens. The two remaining sites in the octahedral environment around Al(III) are occupied by the respective ida imino nitrogen atoms. It should be emphasized that ida is the first dicarboxylic acid in this review, which binds Al(III) in a tridentate fashion. All of the previous dicarboxylic acids act as bidentate ligands in their coordination around Al(III). The X-ray structure reveals that the imino nitrogens are *cis* to each other. Overall, ida uses identical anchor sites to Al(III) (vide infra) with nta, a cognate molecule to ida, where one hydrogen has been replaced by an acetate moiety. Due to the doubly deprotonated ligands attached to Al(III), the overall charge on the complex in **6** is 1−. This anionic charge is counterbalanced by one K^+ ion. Water molecules of crystallization are also present in the lattice of this mononuclear complex.

The aqueous chemistry of Al(III) with ida appears to be quite diverse in that dinuclear complexes can also be studied and isolated from various reaction mixtures (vide infra).

2.2.6. *Bis(methylimino)diacetic acid*

Bis(methylimino)diacetic acid, $CH_3N(CH_2COOH)_2$, reacts equally well with Al(III) in water. An example of such a reaction has been reported to result in the isolation of $[Al(C_5H_7NO_4)_2]^-$ (**7**) at pH 4–5, in the presence of two different cations, namely, Na^+ and K^+ [55].

X-ray crystallographic studies reveal that complex **7** consists of an octahedral Al(III) ion, to which two Mida ($Mida = C_5H_7NO_4^{2-}$) ligands are attached (Fig. 1B). Both ligands are dicarboxylic acids, and as doubly deprotonated moieties anchor onto the metal ion.

The remaining two coordination sites around Al(III) are occupied by the methylimino nitrogen atoms, thus satisfying the coordination requirements of the octahedron. The two methylimino nitrogens are *trans* to each other, in contrast to the *cis* configuration observed in the case of the analogous ida complexes (vide supra). This difference may be due to steric hindrance arising from the methyl groups attached to the nitrogen atoms.

Here, too, the ligand acts as a tridentate binder to Al(III) in consonance with what has been reported for the congener bis(imino)diacetate ligand (ida).

2.2.7. Nitrilotriacetic acid

Nitrilotriacetic acid, $N(CH_2COOH)_3$, is a tricarboxylic acid (H_3nta) capable of offering three carboxylate groups for binding to Al(III) ions. In a characteristic reaction of Al(III) with this acid, isolation of complex $Al(nta)(H_2O)_2$ ($nta = C_6H_6NO_6^{3-}$) (**8**) has been reported as an acetone and water solvate [56].

In this mononuclear complex **8**, Al(III) sits in a distorted octahedral environment, with one nitrilotriacetic acid ligand in its coordination sphere (Fig. 1C). Nitrilotriacetic acid acts as a tetradentate ligand, which is triply deprotonated. The three carboxylates each coordinate to Al(III) in a monodentate fashion, through one of their oxygen termini. In addition, the nta nitrogen participates in the coordination environment of Al(III) occupying a fourth coordination site. The remaining vacant sites are occupied by water molecules from the reaction medium, thus satisfying the coordination requirements of the distorted octahedral Al(III). It is worth noting that the coordinated water molecules are *cis* to each other and lie in the equatorial plane of the octahedron along with one of the carboxylate oxygens and the nitrogen atom of the tetradentate ligand. The overall charge of the complex is zero.

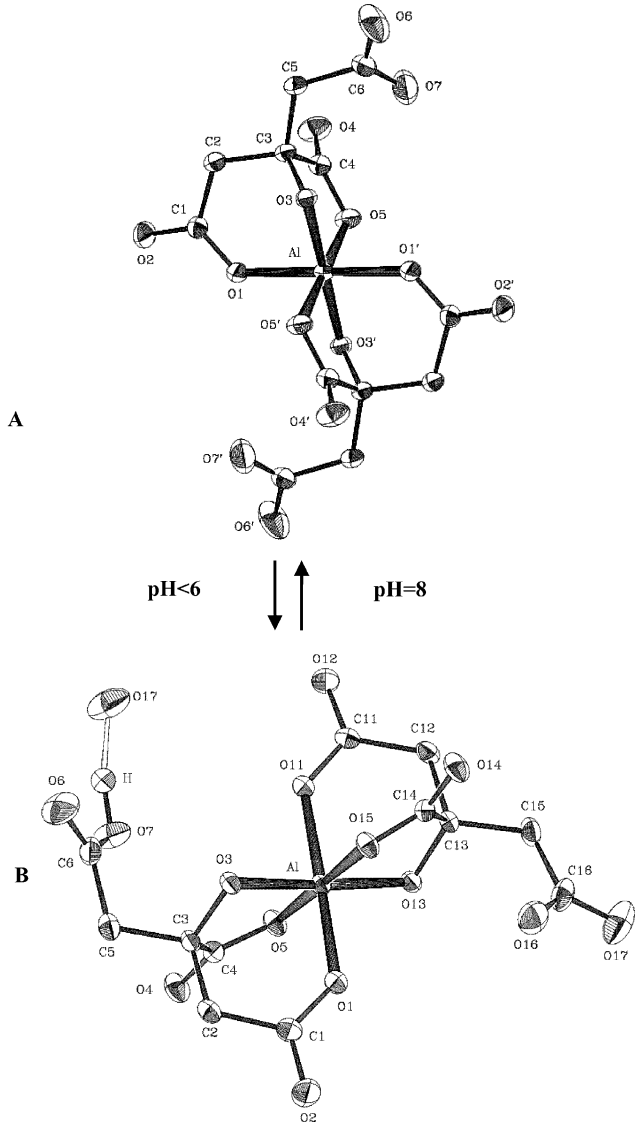


Fig. 2. pH-dependent interconversion between $(NH_4)_5[Al(C_6H_4O_7)_2]\cdot 2H_2O$ (A) and $(NH_4)_4[Al(C_6H_4O_7)(C_6H_5O_7)]\cdot 3H_2O$ (B).

2.2.8. Citric acid

The reactivity of Al(III) with citric acid, $HOOCCH_2C(COOH)(OH)CH_2COOH$, in aqueous solutions has been probed over a wide pH range. Specifically, at pH ca. 8 isolation of a mononuclear complex has been reported, bearing the molecular formula $(NH_4)_5[Al(C_6H_4O_7)_2]\cdot 2H_2O$ (**9**) [57].

X-ray crystallography reveals the presence of a mononuclear octahedral complex with Al(III) surrounded by two citrate ligands (Fig. 2A). The citrate ligands are quadruply deprotonated and as such they employ two of the three carboxylate groups as well as their central hydroxide group to coordinate to Al(III). The third carboxylate group, albeit deprotonated, does not bind to Al(III), and it dangles away from the coordination sphere of the metal ion.

The carboxylate groups each bind to Al(III) in a monodentate fashion, as seen in the case of other metal ion complexes with carboxylate bearing ligands [58,59]. As a result of the full deprotonation of the two citrate ligands bound to Al(III), the overall charge of the complex is 5−. This charge is counterbalanced by ammonium counterions.

Significant, also, is the contribution of hydrogen bonding interactions to the stabilization of the solid-state structure in **9**. Water molecules of crystallization and ammonium counterions participate in the establishment of an extended hydrogen-bonding network in the crystal lattice, which includes the involvement of oxygens of the bound citrate ligands.

In an interesting twist of the pH dependence of the synthetic chemistry of aqueous Al(III) in the presence of citrate, reactions run at lower pH values (4–6) resulted in the isolation and crystallization of mononuclear complexes as well. These complexes bear the molecular formulae $(Cat)_4[Al(C_6H_5O_7)(C_6H_4O_7)]\cdot nH_2O$ ($Cat = NH_4^+$, $n = 3$ (**10**); $Cat = K^+$, $n = 4$ (**11**)).

The central feature in the X-ray structures of such mononuclear species is their octahedral coordination environment, also observed at higher pH values. Here, too, in the lower pH range, the central Al(III) ion is surrounded by two citrate ligands, fulfilling its coordination requirements arising from an octahedral field. A small, yet significant, change in the structure of these

complexes differentiates them from their structural analogue synthesized at higher pH values. Specifically, one of the citrate ligands bound to Al(III) is quadruply deprotonated, as seen in the pH ca. 8 complex, whereas the other one is triply deprotonated (Fig. 2B). Irrespective, however, of the deprotonation status of the two ligands, the latter are attached to Al(III) in much like the same fashion as the two citrates in the pH ca. 8 complex. Further X-ray crystallographic analysis [60] reveals that the non-coordinated terminal carboxylate group in the triply deprotonated citrate is protonated, thus differentiating its nature from the analogous non-coordinated, yet deprotonated carboxylate group of the fully deprotonated citrate. The overall charge of the complexes isolated at low pH values is 4−, which is reduced by one unit from the charge of their congener species isolated at high pH.

The introduced asymmetry in the coordination environment of Al(III) in $[Al(C_6H_5O_7)(C_6H_4O_7)]^{4-}$ is important, in that it allows for further development of hydrogen bonding interactions between the protonated carboxylate group of the complex and the deprotonated terminal carboxylate group in the bound citrate ligand of an adjacent molecule in the crystal lattice. Further involvement of the counterions ammonium (**10**) and potassium (**11**) as well as water molecules of crystallization in the establishment of an extended hydrogen-bonding network contributes to the overall stability of the derived complex.

2.2.8.1. Interconversions—speciation components. A significant aspect of the chemistry of Al(III) with citrates in aqueous solutions is the interconversion of the mononuclear complexes, synthesized and isolated thus far, under the influence of pH [60]. In particular, when complex **9**, isolated at pH 8, is placed in water and the pH of the resulting solution is adjusted to 4.5, addition of alcohol yields complex **10**. Conversely, when **10** is placed in water and the pH of the resulting solution is adjusted to ca. 8, addition of alcohol affords complex **9** (Fig. 2). It appears, therefore, that beyond the synthetic utility of this interconversion, the pH of the aqueous solution emerges as a factor influencing the structural attributes of the complexes isolated. Furthermore, the pH dependence of the interconversion between the two forms of complexes proves their presence in aqueous solutions of the Al(III)-citrate system. Hence, the pH-dependent linkage of the two complexes attests to their participation as key species in Al(III) speciation in aqueous citrate media.

2.2.8.2. Solid state-solution structure correlations. The solution properties of the two classes of mononuclear complexes were probed by multinuclear NMR spectroscopy. To this end, direct comparisons with the solid state structure, as that emerged from X-ray crystallography and solid state NMR spectroscopy, are made [60].

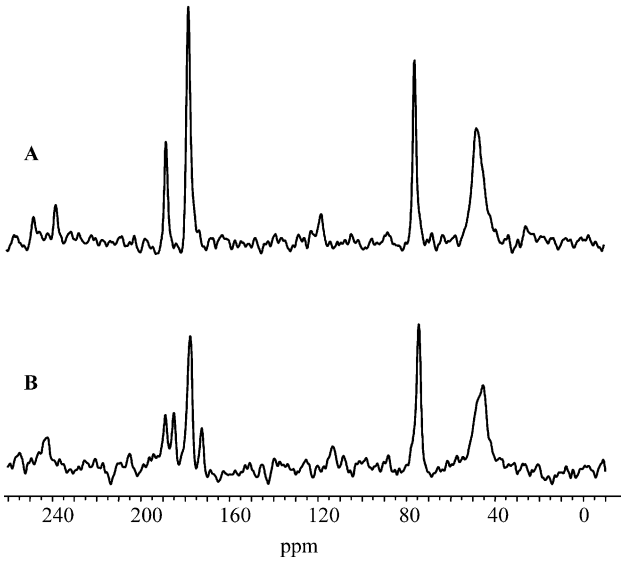


Fig. 3. ^{13}C-NMR spectra of $(NH_4)_5[Al(C_6H_4O_7)_2]\cdot 2H_2O$ (A) and $(NH_4)_4[Al(C_6H_4O_7)(C_6H_5O_7)]\cdot 3H_2O$ (B).

2.2.8.2.1. Solid state. Solid state NMR spectroscopy was instrumental in revealing binding modes of the tricarboxylic citric acid to Al(III) ions in the complexes synthesized and isolated under variable pH reaction conditions. Specifically, the MAS ^{13}C-NMR spectrum of **9** indicates the asymmetric nature of the bound citrate ligands around Al(III) (Fig. 3A). In fact, there is sufficient resolution of the observed NMR peaks to support the differentiation of the two terminal carboxylate carbons, one which is bound to Al(III) and the second one which is uncoordinated and thus removed from the coordination sphere of the metal ion. The spectral pattern observed is consistent with that previously reported for the solid state ^{13}C-NMR spectrum of $Na_2[Bi_2(CitH_{-1})_2]\cdot 7H_2O$ [61]. The overall picture is consistent with that derived from the three dimensional X-ray crystal structure determination of the aforementioned mononuclear complex.

In the case of complexes **10** or **11**, isolated at acidic pH values, the MAS ^{13}C-NMR spectrum reveals the presence of broadened or split resonances, consistent with the protonation of one of the unbound carboxylates, which for the methylene carbons of the citrate ligands attached to Al(III) are chemically distinguishable (Fig. 3B). The splitting of both terminal carboxylates, the central carboxylate carbonyl resonances as well as the bound and unbound carboxylate carbonyl peaks are indicative of the complex binding modes of the two citrates to Al(III) and the variable protonation state of one of the bound citrate ligands. The possible contribution of the hydrogen bonding interactions in the arisen solid state behavior cannot be discounted. Overall, the complex yet adequately resolved picture, un-

ravelled by solid state NMR, is consistent once again with the X-ray structural features observed in the three dimensional structure determination of these mononuclear Al(III)-citrate complexes.

Unequivocally, MAS ^{13}C-NMR spectroscopy is a powerful tool in corroborating the structural identity of both classes of mononuclear Al(III)-citrate complexes arisen from X-ray crystallography. Conceivably, building sufficient information on the NMR identity of Al(III)-citrate and other ligand systems in the solid state, will enable the technique to be used in the identification of new materials emerging from such Al(III)-ligand systems.

2.2.8.2.2. Solution. The ^{13}C-NMR spectrum of **9** in D_2O solutions exhibits peaks belonging to both free and Al(III)-bound citrate [60]. This is in consonance with previously recorded ^{13}C-NMR spectra of Al(III)-citrate systems, with a fourfold excess of citrate over Al(III) in the pH range from 2 to 8 [62]. In those studies, the observed broad resonances for bound citrate were attributed to an equilibrium of coordination isomers. An alternative explanation included the putative presence of both mono- and bis-Al(III)-citrate complexes [60].

The time dependent behavior of the complex upon dissolution in water is quite revealing. It shows that the trinuclear complex $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$ is the predominant species at the thermodynamic equilibrium state (vide infra).

The ^{1}H-NMR spectroscopy of **9** suggests the existence of a symmetrical coordination of the citrate ligands to Al(III) in solution [60]. One such possible coordination sphere around Al(III) could include the involvement of the terminal carboxylates and the central hydroxide group. In view of this formulation, the arisen structure of the complex in solution is pronouncedly different from that offered by the X-ray three-dimensional structure in the solid state. The latter, shows a rather non-symmetrical arrangement of the two citrate ligands around Al(III), with one bound and one free terminal carboxylate groups. The fact that no separate signals are observed for bound and unbound citrate CH_2COO^- moieties could also be ascribed to fast intramolecular exchange of the two moieties. That means that the citrate ligands behave fluxionally. This putative fluxionality seems to be a more likely explanation than isomerization of the complex upon dissolution in water. Furthermore, the observation of separate signals for bound and free citrates indicates slow intermolecular exchange of the citrate molecules. This behavior was also seen in the case of a Ga(III)-citrate complex [63], and it was ascribed to a significantly weaker binding of Ga(III) with the central carboxylate group than with the central hydroxide oxygen. In this sense, the central hydroxide oxygen attaches itself to Ga(III), while the metal–carboxylate bonds break and reform quite rapidly.

The time dependent behavior of the ^{1}H-NMR spectrum of **9**, in aqueous solutions, was extremely informative in elucidating the dynamic behavior of the compound. Initially, the spectrum exhibits signals consistent with the above described behavior. Concomitantly, the spectrum changes with time, ultimately leading to the signals belonging to the trinuclear complex $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$. It appears, therefore, that upon dissolution of the mononuclear species a complex set of equilibria is set up, which can be depicted by the equations given below:

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

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

where $CitH_{-1} = C_6H_4O_7^{4-}$.

The complexity of the investigated system is reflected in the difficulty of proposing the existence of various species, appearing as components of the dynamic equilibrium system described above and transforming with time to others (which have yet to be identified), ultimately giving rise to the thermodynamically stable trinuclear species.

Equally perplexing was the solution behavior of the Al(III)-citrate complex **10** (Fig. 4). Here, too, the predominant species at the thermodynamic equilibrium state is the trinuclear complex $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$. A detailed study, however, of the mononuclear complex in solution shows that 1:1 and 1:2 species can exist as participants of the dynamic behavior unfolding upon dissolution of the complex in water, and that these species may not be strictly single species, but rather assemblies of conformers and isomers. Further analysis of the observed resonances and their properties as a function of time suggests that a dinuclear complex could also be present. Such a species might serve as the precursor to the thermodynamically stable trinuclear complex $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$. 2D-COSY-NMR spectroscopy attested to this contention.

The ^{27}Al-NMR spectrum of complex **9** in equilibrium aqueous solutions shows a broad (560 Hz) asymmetric signal with a maximum at 11.84 ppm (vs. $AlCl_3$) and a shoulder at a higher field. Furthermore, experiments carried out in the Al(III)-citrate (1:1) system at neutral pH, reveal relatively limited changes in the ^{27}Al-NMR spectra of the major component over time [64]. Hence, the spectral pattern of the equilibrium sample suggests that the trinuclear complex $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$ is the predominant Al(III) species in equilibrium solutions at neutral pH either at 1:1 or 1:2 metal ion to ligand ratio.

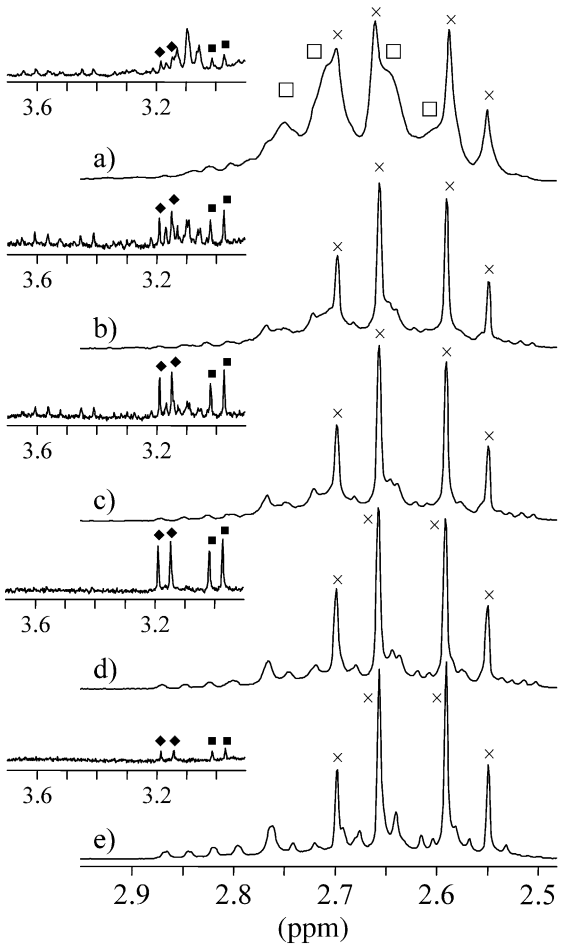


Fig. 4. ^{1}H-NMR spectrum of a 0.07 M solution of complex **10** in D_2O: (a) 10 min (pD = 6.32); (b) 25 min; (c) 2 h; (d) 20 h; and (e) 4 days (at thermodynamic equilibrium, pD = 6.06) following dissolution of the complex. Labels: (x), free citrate; (■,◆), citrate complexed in the intermediate 1:1 species; (□), citrate complexed in the 1:2 complex. In all of the spectra, the region between 3.0 and 3.6 ppm is shown as an insert (fourfold spectral enlargement).

2.2.9. Ethylenediamine tetraacetic acid

The chemistry of ethylenediamine tetraacetic acid (H_4edta) reveals its true polydentate binding character as a ligand toward Al(III). Reaction of Al(III) with edta in aqueous solutions provides easy access to the mononuclear complex $K[Al(edta)]\cdot 2H_2O$ (**12**) [65,66]. The complex contains an octahedral Al(III) ion, to which one edta (edta = $C_{10}H_{12}N_2O_8^{4-}$) ligand is coordinated through the four carboxylate groups and the two amino nitrogen atoms (Fig. 1D).

In the present case, H_4edta appears to be fully deprotonated and as such it binds Al(III) in a hexadentate fashion. Thus, four out of the six coordination sites in the octahedron are occupied by carboxylate groups. The remaining two sites are filled by the two amino nitrogens of the ligand. Due to the 4− charge of the ligand attached to Al(III), the overall charge on the complex is 1−. This charge is counterbalanced by a K^+ ion. Two water molecules of crystallization complete the lattice requirements of the structure.

2.3. Dinuclear species

2.3.1. Glycolic acid

The reported chemistry of this very simple α-hydroxycarboxylic acid with Al(III) leads to a complex with strikingly interesting structural features in the solid state. The complex has been isolated from an aqueous reaction mixture of Al(III) and HO–CH_2–COOH, at pH 4, in the form of its Na^+ salt [67,68].

The complex composition is consistent with the formulation $Na_3H_3[Al(C_2H_2O_3)_3]_2$ (**13**). X-ray crystallography reveals the presence of a dimeric species with two facially oriented mononuclear octahedral Al(III) sites, and strong hydrogen-bonding interactions mediating the close proximity of the two centers (Fig. 5A). Half of the hydroxy groups are deprotonated. Therefore, three short and symmetrical hydrogen-bonding interactions arise, each between twofold related hydroxy groups on the glycolate ligands, with O···O 2.425(4) Å, and the bridging hydrogen sitting on the twofold axis. The structural analysis, also, indicates that the carboxylate group of glycolic acid is deprotonated upon reaction with Al(III). This, in turn, facilitates its coordination to the Al(III) ion, ultimately leading to the balance of charge by three sodium counterions.

The solid state ^{13}C-CPMAS and ^{27}Al-MAS NMR data are consistent with half of the hydroxy groups on the glycolic ligands being deprotonated, thus leading to a facial geometry of the ligands in the dimeric assembly.

2.3.2. Bis(imino)diacetic acid

The ability of bis(imino)diacetic acid (H_2ida) to participate in the formation of dinuclear complexes of Al(III) is exemplified in the complex $[Al(C_4H_5NO_4)(OH)(H_2O)]_2\cdot 2H_2O$ ($C_4H_5NO_4^{2-}$ = ida) (**14**). Synthetically, the dinuclear species is isolated from a reaction mixture of Al(III), H_2ida, and KOH in water, with a molar ratio 1:1.8:4.2.

The dinuclear complex consists of two Al(III) centers, each of which is surrounded by one ida ligand, two hydroxide ions and a water molecule (Fig. 5B). The dicarboxylic acid H_2ida in **14** is doubly deprotonated and as such it offers both of its carboxylate groups as monodentate anchors to Al(III), along with its imino nitrogen atom. The hydroxides serve as μ_2-bridges to the two Al(III) centers of the dinuclear complex, thus satisfying the coordination requirements of both Al(III) ions [69]. The overall charge of the complex is zero.

The aqueous behavior of **14** upon its dissolution in water can be followed by ^{27}Al-NMR spectroscopy. The spectra of crystals of the above compound in solutions with pH 5 (the autogenous pH) show the presence of two resonances with chemical shifts at 21.4 and 37.2

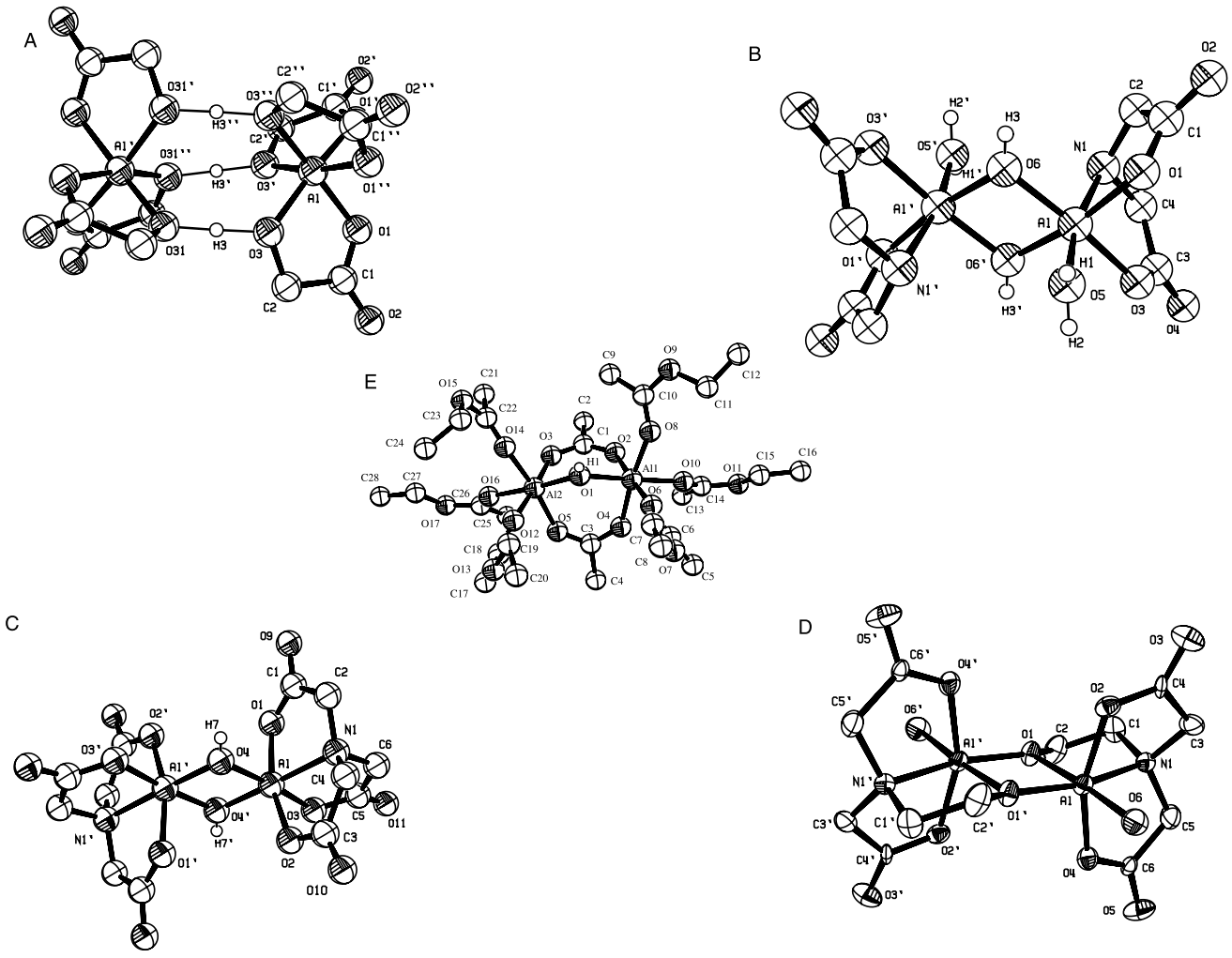


Fig. 5. (A) Structure of the Al(III)-glycolate complex $Na_3H_3[Al(C_2H_2O_3)_3]_2$. Sodium ions have been omitted. (B) Structure of the dinuclear complex $[Al(C_4H_5NO_4)(OH)(H_2O)]_2$. (C) Structure of the anionic assembly $[Al_2(C_6H_6NO_6)_2(\mu\text{-}OH)_2]^{2-}$. (D) Structure of the dinuclear complex $[Al(C_6H_8NO_5)(H_2O)]_2$. Hydrogen atoms on coordinated waters ($H_2O(6)$ and $H_2O(6')$) are not shown. (E) Structure of the cationic complex $[Al_2(\mu\text{-}CH_3COO)_2(\mu\text{-}OH)(CH_3COOC_2H_5)_6]^{3+}$.

ppm (vs. $Al(NO_3)_3$ in D_2O) with widths 100 and 300 Hz, respectively. The ratio of intensities of the two resonances is 3:1. Based on detailed spectroscopic work on the system $Al(NO_3)_3$–$C_4H_7NO_4$–OH^- in D_2O, the following equilibrium is suggested as the most likely route to the eventual appearance of the resonances in the spectrum of **14**.

$$4[Al(C_4H_5NO_4)(OH)(H_2O)]_2 + 6H_2O \rightleftarrows 6[Al(C_4H_5NO_4)(OH)(H_2O)_2] + [Al(C_4H_5NO_4)(OH)(H_2O)]_2$$

Thus, in solution, the complex dissociates into two species, with the ratio of Al(III) concentrations 3:1. These equilibrium species are tentatively assigned to $Al(C_4H_5NO_4)(OH)(H_2O)_2$ and $[Al(C_4H_5NO_4)(OH)(H_2O)]_2$, respectively. Based on the available data, the claim is made that the formation of the monomeric complex is an event preceding the ultimate assembly of the dinuclear complex [69].

2.3.3. Nitrilotriacetic acid

This tricarboxylic acid (H_3nta) supports formation of dinuclear Al(III) complexes, beyond the already known mononuclear complex **8**. A good example of such a dimer is the compound $[Al(H_2O)_2][Al_2(nta)_2(OH)_2]\cdot[OH]\cdot 3H_2O$ (**15**), easily isolated from aqueous solutions of Al(III) and H_3nta [56].

Each of the Al(III) centers is octahedral, surrounded by one nta = $C_6H_6NO_6^{3-}$ ligand and two hydroxide ion groups. The latter serve as μ_2-bridges between the two Al(III) ions. The nta ligand is potentially tetradentate. In this case, it appears to be triply deprotonated and uses its three terminal carboxylate group oxygens to coordinate to Al(III). The octahedral coordination requirements around each Al(III) are satisfied by the participation of the nta nitrogen atom in the coordina-

tion sphere of the metal ion (Fig. 5C). The overall charge of the dinuclear complex is 2−. An additional OH^-, however, raises the overall negative charge to 3−. This negative charge is neutralized by a cation, which itself is a mononuclear $[Al(O^*)_4(H_2O)_2]^+$ complex. In this mononuclear Al(III) site, the metal ion is coordinated octahedrally to four oxygens (O*), from four different anionic units $[Al_2(C_6H_6NO_6)_2(\mu\text{-}OH)_2]^{2-}$, and two water molecules *trans* to each other. Water molecules of crystallization complete the lattice requirements of the complex. Strong intermolecular hydrogen bonding interactions appear to stabilize the crystal lattice of **15**.

Comparison of complex $[Al_2(nta)_2(\mu\text{-}OH)_2]^{2-}$ with an Fe(III) analogue $[\{Fe(nta)(H_2O)\}_2O]^{2-}$ reveals equally significant structural similarities and fundamental differences. Specifically, the Fe(III)-nta complex is dinuclear in nature, just like its Al(III) analogue. The bridges in both complexes are oxygen-based, with the only one in the Fe(III) complex being oxide, O^{2-}, whereas the ones (two) in the Al(III) species being hydroxides, OH^- [70]. The observed structural differences may reflect further differentiation in the hydrolytic chemistry of the two metal ions, and may thus imply pronouncedly different biological roles for Al(III) and Fe(III), when the latter enter metallo-regulated (bio)chemical processes.

The dianionic dinuclear complex appears to be related to the mononuclear structure described previously for **8**. Conceivably, two of these mononuclear species could in principle come near each other, and one water molecule from each mononuclear species could be deprotonated. With the arisen terminal hydroxide ligand on each derived species, the dinuclear complex **15** could be assembled with the concomitant production of two protons and the removal of one water molecule from each mononuclear unit.

$$[Al(nta)(H_2O)_2] + [Al(nta)(H_2O)_2] \rightarrow [Al_2(nta)_2(\mu\text{-}OH)_2]^{2-} + 2H^+ + 2H_2O$$

2.3.4. *N*-(2-Hydroxyethyl)iminodiacetic acid

The multidentate properties of *N*-(2-hydroxyethyl)iminodiacetic acid, $N(CH_2CH_2OH)(CH_2COOH)_2$, ($H_2$heidi) as a ligand toward Al(III) arise prominently from the requisite chemistry in water. Thus, when Al(III) interacts with H_2heidi (molar ratio of Al(III)–H_2heidi = 1:2), in the presence of pyridine, in aqueous solutions at pH 4.3, the compound $[Al\{C_6H_8NO_5\}(H_2O)]_2\cdot 2H_2O$ (heidi = $C_6H_8NO_5^{3-}$) (**16**) can be easily isolated [71]. The dinuclear complex consists of two Al(III) centers, each coordinated to a triply deprotonated heidi^{3-} ligand and a water molecule (Fig. 5D). Since H_2heidi is a dicarboxylic acid with an additional *N*-(2-hydroxyethyl) moiety, it can potentially act as a tetradentate binder. It employs both terminal carboxylate group oxygens, the alkoxide oxygen and the nitrogen atom to coordinate to the Al(III) ion. The carboxylate groups are coordinated to Al(III) ions in a monodentate fashion. Moreover, the alkoxide terminal oxygen acts as a μ_2-bridge to the second Al(III) ion, thus giving rise to the dinuclear complex. Both Al(III) ions in the symmetric dimer are octahedral, with the sixth coordination site occupied by a water molecule. The overall charge on the complex is zero.

^{27}Al-NMR spectroscopy shows that complex **16** retains its dinuclear structure upon dissolution in water, at the autogenous pH 4.4, and its solutions are stable for long periods of time (ca. 2 weeks) with no significant changes [71]. pH dependent hydrolysis of aqueous solutions of **16** results in the formation of soluble species, as attested to by ^{27}Al-NMR spectroscopy. One such soluble, polynuclear cluster $[Al_{13}(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_{12}(heidi)_6(H_2O)_6](NO_3)_3$ has been isolated, and its solid state and solution properties have been probed (vide infra).

2.3.5. Ethyl acetate

Quite interesting is the chemistry of the simple organic ester ethyl acetate with Al(III). When ethyl acetate reacts with Al(III) in hexane, it yields a product $[AlCl_3(CH_3COOC_2H_5)_2]$, which upon hydrolysis results in the formation of a dinuclear complex $[Al_2(\mu\text{-}CH_3COO)_2(\mu\text{-}OH)(CH_3COOC_2H_5)_6][AlCl_4]_3$ (**17**) [72].

In the X-ray structure of this cationic dimer, the Al(III) centers are each coordinated to three ethyl acetates in a monodentate fashion (Fig. 5E). The two centers are linked through two acetates and a hydroxide ion group, all three acting as bridges. The coordination geometry around the Al(III) centers is octahedral. The nature of the bridge unit in the dimer is similar to that previously observed for iron, and proposed to be a potential mimetic model for the active site of the non-heme iron hemerythrin [73,74]. The tripositive charge on the complex is counterbalanced by three anionic $[AlCl_4]^-$ species.

2.4. Trinuclear species

2.4.1. Citric acid

The reactivity of citric acid with Al(III) extends beyond the chemistry already described for mononuclear species, and covers high nuclearity complexes as well. In this case, citric acid illustrates its multidentate character upon complexation with Al(III). A paradigm of this chemistry is the reaction between Al(III) and citric acid, with a 1:1 molar ratio, in aqueous solutions at pH 7.5, which affords upon slow evaporation a trinuclear complex, consistent with the molecular for-

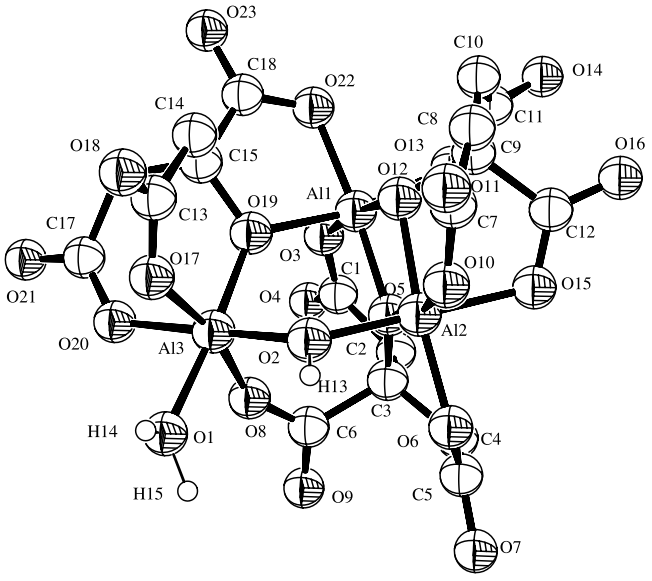


Fig. 6. Structure of the anionic complex $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$.

mula $(NH_4)_5[Al_3(C_6H_4O_7)_3(OH)(H_2O)][NO_3]\cdot 6H_2O$ (**18**) [75].

The derived X-ray crystal structure of the trinuclear complex **18** reveals the presence of three Al(III) ions surrounded by three citrate ligands. The three Al(III) centers are octahedrally coordinated to six oxygen donors originating in three citrate ligands, a hydroxide ion, and a water molecule. From the ligand point of view (Fig. 6), one of the citrate ligands binds to all three Al(III) centers through the carboxylate oxygens O(3), O(6), and O(8), while it provides a bridge to Al(1) and Al(2) through the deprotonated central hydroxy group O(5). The second citrate ligand bridges the aforementioned Al(III) ions through the central hydroxide oxygen O(12), and uses two carboxylate oxygens O(10) and O(15) to bind Al(2), and one carboxylate oxygen O(13) to bind Al(1). The third citrate serves as a bridge between Al(1) and Al(3), with the bridging atom being the central hydroxide oxygen O(19). It additionally provides two carboxylate oxygens O(17) and O(20) to bind Al(3), and one carboxylate oxygen, O(22), to bind Al(1). Two of the three Al(III) centers, Al(2) and Al(3) are linked via a hydroxide ion, HO(2). The coordination requirements of Al(3) are finally fulfilled with an oxygen donor, O(1), belonging to a bound water molecule.

The structural features of the trinuclear complex are worthy of attention, as the binding modes of citrate ligands in it are also encountered in other metal citrate complexes, like magnesium-citrate $[Mg(H_2O)_6][Mg(C_6H_5O_7)(H_2O)]_2\cdot 2H_2O$ [76] and nickel-citrate $\{[NMe_4]_5[Ni_4(C_6H_4O_7)_3(OH)(H_2O)]\cdot 18H_2O\}_2$ [77]. In the case of Mg(II), the citrates are triply deprotonated, with the carboxylate groups being the ones subjected to deprotonation. The multidenticity of citrate is reflected in its expedient coordination to octahedral Mg(II) ions and its involvement in the linkage of abutting Mg-citrate units creating a ribbon-like structure in the lattice. Columns of $[Mg(H_2O)_6]^{2+}$ units are trapped between the so assembled Mg-citrate ribbons and held in place by hydrogen bonds. In the case of octanuclear Ni-citrate, aside from the triply bridging hydroxide ion, the multidenticity of the fully deprotonated citrates bound to Ni(II) ions, three of which exhibit distorted octahedral geometry with the fourth one being approximately square pyramidal, is exemplified through the linkage of adjacent Ni(II) centers via the deprotonated central hydroxy groups acting either as μ_2- or μ_3-bridges.

The solution behavior of $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$ was studied by multinuclear NMR spectroscopy [75]. The ^{13}C-NMR spectrum of the trinuclear complex exhibits three distinct groups of resonances for the carbons on the three participating citrate ligands in the coordination sphere of the respective Al(III) ions. The ^{27}Al-NMR spectrum of $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$ consists of three singlet resonances. On the basis of the linewidth of these peaks tentative assignments, albeit difficult, can be made for the three distinct Al(III) centers in the complex. Given, therefore, that the linewidth is related to the local symmetry around each investigated Al(III) nucleus, the observed peaks at 0.2 (vs. $Al(H_2O)_6^{3+}$), 10.7, and 12.6 ppm could be tentatively assigned to Al(3), Al(1), and Al(2), respectively. Overall, the data are consistent with the retention of the integrity of the complex in aqueous solutions. This conclusion is in line with previous proposals [18,78,79] on the existence of polynuclear Al(III)-citrate complexes in aqueous solutions (pH range up to 9).

Detailed NMR studies on the nature and kinetic behavior of trinuclear Al(III)-citrate complexes (e.g. $[Al_3(C_6H_4O_7)_3(OH)(H_2O)]^{4-}$ and $[Al_3(C_6H_4O_7)_3(OH)_4]^{7-}$) in aqueous solutions and their appearance as: (a) discrete species; and (b) products of the dynamic behavior of mononuclear complexes upon dissolution in water, have been carried out and support the aforementioned description [60,64,80].

2.5. Tetranuclear species

2.5.1. Phthalic acid

The chemistry of Al(III) with carboxylic acids does extend into the organic media in an effective fashion. An example of that chemistry is seen in the tetranuclear complex $[(AlMe_2)_2(\mu\text{-}COO)_2\text{-}1,2\text{-}C_6H_4]_2$ (**19**) isolated from reaction mixtures of the organoaluminum reagent $AlMe_3$ and phthalic acid in toluene [81].

The X-ray structure reveals the presence of a centrosymmetric tetranuclear complex (Fig. 7) consisting of four Al(III) centers. The four carboxylate groups of the two phthalic rings provide for efficient bridges among the organoaluminum centers, to which they coordinate. Specifically, the two bidentate carboxylate groups of

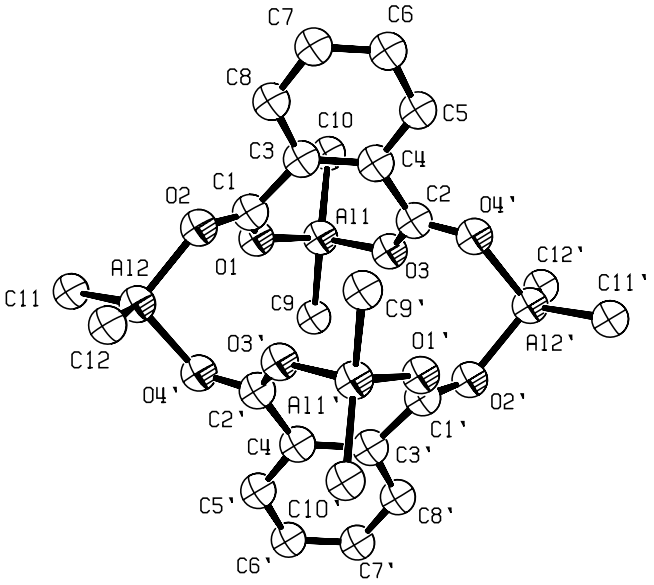
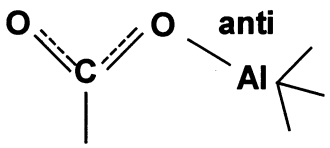
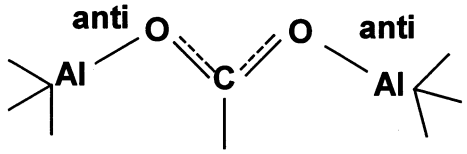


Fig. 7. Structure of the tetranuclear complex $[(AlMe_2)_2(\mu\text{-}COO)_2\text{-}1,2\text{-}C_6H_4]_2$.

each phthalate bind through one of their oxygens to two $AlMe_2$ units, thus forming a highly distorted 16-membered macrocyclic ring. Within this ring, employment of the second oxygen in each carboxylate group of phthalate leads to binding to two more $AlMe_2$ units, one for each phthalic acid ligand, thus creating two additional seven-membered heterocyclic rings facing each other. Each carboxylate group on the phthalate ligand is deprotonated and as such it coordinates to Al(III), promoting a tetrahedral coordination around it. The overall charge of the complex is zero. Of the notable structural features in **19**, likely to be of relevance to metal ion–carboxylate binding in biological systems [82,83], is the location of the Al(III) moiety bound to the oxygen atoms in the syn–syn and anti–anti direction with respect to the carboxylate groups. The indication that the anti position is the most likely location of the Al center with respect to the carboxylate group is consistent with data observed for the monodentate $[Me_3Al(OOCCH_3)]^-$ [84]



as well as the bidentate $[(Me_3Al)_2(OOCCH_3)]^-$ anions [85].



^{1}H- and ^{27}Al-NMR spectroscopies in organic solvents are consistent with the structure of the complex in the solid state.

The tetranuclear complex is the only species, of the ones reported herein, in which Al(III) displays a tetrahedral coordination geometry.

2.6. Polynuclear species

2.6.1. N-(2-Hydroxyethyl)iminodiacetic acid

The multidentate properties of H_2heidi extend beyond the already described dinuclear complex $[Al\{C_6H_8NO_5\}(H_2O)]_2\cdot 2H_2O$ (**16**). They are well reflected into the Al(III) chemistry of polynuclear cluster assembly. Evidence to this thesis comes from the reactivity of Al(III) toward the H_2heidi ligand (Al(III)–H_2heidi = 2:1) in aqueous solutions, at pH ca. 5, leading to the isolation of a tridecanuclear cluster $[Al_{13}(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_{12}(heidi)_6(H_2O)_6](NO_3)_3$ (heidi = $C_6H_8NO_5^{3-}$) (**20**) [71].

It is apparent from the X-ray structure of the cluster that the H_2heidi ligand acts efficiently as a polynucleating agent, promoting the 13 metal ion assembly. Essential components to this assembly are hydroxide ion and alkoxide ligands, which serve as μ_3- or μ_2-bridges, connecting the metal ions with the deprotonated heidi ligands. The inner core of the cluster consists of a $[Al_7(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_6]^{9+}$ unit, which serves as the scaffold for the entire assembly (Fig. 8). Through the triply and doubly bridging hydroxide ligands the core is connected to an outer shell of Al(III) bound heidi^{3-} ligands. The triply deprotonated heidi^{3-} ligand, as a potentially tetradentate binder, coordinates to one Al(III), while concurrently uses its alkoxide terminal to span over and coordinate to a second Al(III) ion in the periphery of the cluster. Thus, three different kinds of Al(III) environment are created, reflecting the location of the central Al(III), the six Al(III) ions in the periphery, and six more Al(III) ions in the outer shell of the cluster. In all of these cases, the Al(III) ions sit on octahedral sites, satisfying their coordination requirements with the variable ligand components (OH^-, heidi^{3-}, H_2O) of the structure.

^{27}Al-NMR spectroscopy indicates that the tridecanuclear Al(III) cluster **20** can be a major component in an aqueous system comprised of Al(III) and the H_2heidi ligand [71]. Moreover, the use of ^{27}Al-NMR in investigating the solution chemistry of this cluster constitutes a good example of a probe potentially useful in exploring the Al(III) environment, and through that the speciation of the metal ion in aqueous media. The potential significance of such species in aqueous media stems from the fact that the hydrolytic chemistry of Al(III) in the presence of H_2heidi leads to soluble species, in contrast to a number of analogous compounds of Fe(III) which are insoluble [86]. In turn, this observation may indicate: (a) the influence of the nature of the ligand

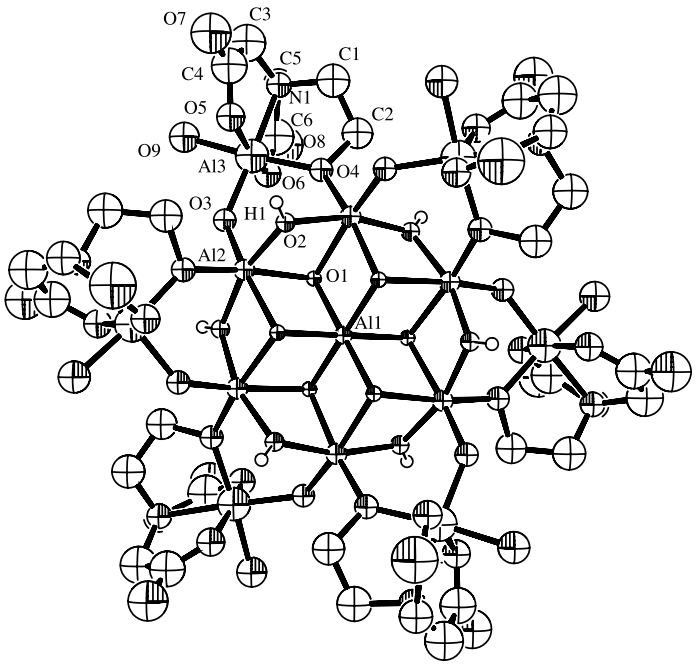


Fig. 8. Structure of the polynuclear cationic complex $[Al_{13}(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_{12}(C_6H_8NO_5)_6(H_2O)_6]^{3+}$. Due to congestion, only hydrogens on μ_2-OH groups are shown.

affecting metal ion hydrolytic chemistries in nature (e.g. biomineralization) [87,88]; and (b) the different bioavailability of the two metal ions in the presence of similar ligands in aqueous media.

3. Discussion

3.1. General comments

The need to elucidate the intricate nature of Al(III)'s involvement in toxic phenomena, related to human health and disease, has since long prompted an increase in relevant research activities. Primary attention was, then, focused on unravelling the admittedly complex nature of that metal's aqueous speciation, in the presence of natural or physiologically relevant ligands. A multitude of solution studies initiated a drive to peruse the speciation patterns of a variety of Al(III)-ligand systems, as a function of metal (and ligand) concentration and pH. Concurrently, efforts to discover soluble, bioavailable forms of Al(III) in aqueous solutions, in the presence of various physiological ligands, instigated synthetic research activities corroborating the ongoing solution studies. As a result, a number of Al(III)-ligand systems were perused synthetically, and novel Al(III) complexes were isolated and characterized. To date, these complexes present the basis of current and future attempts to understand the chemistry underscoring the potential biotoxic effects of Al(III), earth's most abundant metal [89], in organisms and especially humans.

The achieved structural characterization of the herein-presented Al(III) complexes signifies the influence of a number of factors on the chemistry of this element, in the presence of specific ligands. Some of these factors are discussed below, in a way that denotes their involvement in the synthesis and concomitant influence on the nature of species to be isolated. These same factors may ultimately play key roles in delineating dynamic (bio)chemical processes involving the metal ion.

3.1.1. Nature of the ligand interacting with Al(III)

The nature of the ligands, used in the synthesis and isolation of the herein-described complexes, encompasses a number of structural features worthy of discussion. These features are the following:

1) All the primary ligands are carboxylic acids. Therefore, their primary anchors to Al(III) are carboxylate groups.
2) The number of carboxylic groups ranges from one to four. In this context, from monocarboxylic to tetracarboxylic acids, a variable number of binding sites arises, which, depending on the reaction conditions, determines how the coordination geometry requirements of Al(III) will be satisfied.
3) The variable number of carboxylate groups in the ligands dictates the potential denticity of the ligand when reacting with the metal.
4) Potential sites for binding with Al(III) do not only include carboxylates, but also amino or imino nitrogen atoms and alkoxide-containing side chains.

When carboxylate groups are not sufficient to satisfy the coordination requirements of the metal ion, then for those ligands containing an amino or imino nitrogen further binding to that atom is promoted by Al(III). In fact, the additional nitrogen binding site raises the potential denticity of the ligand used, and contributes to the stability of the species assembled and eventually isolated.

5) Even though carboxylates are bidentate, it appears that in the case of the Al(III)-carboxylate chemistry described herein, the individual carboxylate groups bind to a specific Al(III) center in a monodentate fashion.
6) Carboxylate groups can serve as bridges to adjacent Al(III) centers.
7) When available in a specific ligand, alkoxide or carboxylate or both can serve as bridges to adjacent Al(III) centers, potentially affecting the nuclearity of the species formed (vide infra).
8) Hydroxide (OH^-) ions can also act as ligands, providing bridges to adjacently located Al(III) centers in dinuclear or polynuclear assemblies.

3.1.2. Nuclearity-structural diversity of Al(III) species

The aforementioned attributes of the ligands arise from their involvement in the synthesis, isolation, and X-ray structural characterization of a plethora of Al(III)-carboxylate complexes from aqueous and non-aqueous systems. It appears that the employed ligands lead to a multitude of structures attained in the presence of Al(III). The nuclearity of the species, achieved under the reaction conditions investigated and reported thus far, ranges from 1 to 13. In this sense, it is not surprising that, in the presence of a specific ligand, Al(III) can react to yield mononuclear and dinuclear complexes (e.g. ida) or dinuclear and polynuclear complexes (e.g. heidi). Thus, the nature of the ligand does influence the chemistry unfolding around a specific center, yet the reaction conditions, including

a) metal to ligand stoichiometry
b) starting material (organoaluminum reagents vs. Al(III) salts)
c) solvent medium
d) solubility (vide infra)
e) pH

may also play key roles in eventually dictating structural features (e.g. octahedral vs. tetrahedral Al(III) coordination geometry, ligand binding modes, etc.) of the product to be isolated in a crystalline form. Therefore, all of these factors should be considered as parameters in Al(III) chemistry.

Moreover, the diversity of structural forms in the species of Al(III), arising from its reaction(s) with various ligands, provides a pool of reference structures allowing comparisons with the species forming or being present in biological systems (e.g. Al(III)–protein adducts, Al(III)-cell membrane component adducts, analogues of active sites in proteins), natural processes (e.g. biomineralization), or neurotoxic phenomena (e.g. neurodegeneration) thought to contribute to biological aberrations in human physiology.

3.1.3. The pH factor in Al(III) chemistry

Among other factors involved in the complex Al(III)-carboxylate chemistry, pH does play a significant role in the structure of species formed, isolated and characterized. A classical paradigm is the Al(III)-citrate system, where

a) pH dependent synthesis leads to the isolation of mononuclear Al(III)-citrate complexes of distinct nature and structural features (e.g. protonation (**10**) or deprotonation (**9**) of one of the terminal carboxylates in the citrates coordinated to the Al(III) center), and
b) pH change of aqueous solutions of pure compounds leads to interconversion of species (e.g. **9** and **10**), thus attesting to their association with the aqueous Al(III)-citrate speciation.

Other pH induced structural variations could in principle exist in this or other systems that have yet to be explored and discovered. Thus, pH arises as a factor, which contributes to the formulation of the structural identity of the species forming and eventually being isolated. This is an experimental affirmation of the inherent capacity of pH to control the aqueous speciation pattern(s) of a metal ion, in this case Al(III), in the presence of a specific ligand.

3.2. Synthetic methodologies for Al(III) complexes

Simple synthetic methodologies seem to be adequate for the syntheses of the variety of Al(III)-carboxylate complexes discussed in this review. Main strategies include the use of Al(III) salts or organoaluminum starting materials with the appropriate carboxylic acid(s) in aqueous solutions or organic solvents, respectively. The preponderance of complexes synthesized reflects the reactivity of Al(III) with ligands, in the presence of a base, in aqueous solutions, from which addition of an organic solvent affords precipitation of the least soluble product. Alternatively, evaporation yields equally isolable species in several cases. Worthy of attention is the case of complexes **17** and **19**, the syntheses and isolation of which were pursued in non-aqueous media. In the case of the second complex, a tetrahedral organoaluminum reagent was used in place of a simple Al(III) salt, ordinarily employed in the aqueous syntheses mentioned above. Along similar

lines, the synthesis, isolation, and structural characterization of $Al(O_3PCH_2COO)\cdot 3H_2O$ was reported in the literature [90]. This compound, however, belongs to a class of inorganic–organic hybrid Al(III)-carboxylate–phosphonate solid materials, which are not the subject of this review.

As the synthetic exploration of Al(III) binary or even more complex systems progresses, with more than one chemical species being isolated, characterized chemically, spectroscopically and structurally, and their pH-dependent interconnectivity being confirmed in the requisite speciation patterns, the idea of interwoven equilibria set or ultimately achieved emerges dominant. Under such reaction conditions, the least soluble products appear to constitute the majority of the species isolated, leaving in solution other species to be isolated through synthetic approaches that challenge contemporary research. Overall, the simplicity of the reactions employed, thus far, may denote a similar basic reactivity for this metal ion in biological fluids, where formation of different species constitutes part of the chemistry reflecting the speciation of Al(III) in the presence of potentially complex ligands.

3.3. Linkage of Al(III)-carboxylate complexes to Al(III) speciation

A number of investigated Al(III)-carboxylate systems are good cases of model systems, from which several complexes have arisen and subsequently have been shown to be components of speciation schemes of Al(III) and the specific ligand(s). One such example is the Al(III)-citrate system, for which one trinuclear and two mononuclear complexes are known, and their spectroscopic and structural properties have been elucidated. Moreover, their solution chemistry and dynamic kinetic behavior have been thoroughly perused, with that of the trinuclear complex exhibiting the highest thermodynamic stability of the species in solution. For at least the mononuclear complexes, pH dependent interconversion has shown their linkage as components in Al(III)-citrate speciation. Despite the simplistic nature of this binary system, the progress made in the synthetic approaches leading to the isolation and subsequent structural characterization of key Al(III)-citrate complexes, signifies the contribution of the related chemistries to the elucidation of the speciation characteristics of this metal ion in biologically relevant systems. To this end, ternary or even more complex Al(III)-ligand systems are (e.g. Al(III)-citrate–phosphate) expected to be investigated synthetically, targeting the discovery of novel species closely related to the composition of biological fluids, within which the metal ion promotes interactions.

3.4. Relevance to biological systems

The potential relevance of Al(III)-carboxylate complexes, like the ones described in this review, to biological systems stems from the nature of the ligand used, and the potential chemical and structural characteristics of the species isolated and studied, both in the solid state and in solution. Since all of the reported complexes here pertain to low molecular mass species of Al(III), pertinent discussion of their properties relevant to biological conditions revolves around their distribution as a function of pH and concentration (i.e. speciation). Given that biologically relevant speciation is linked with discrete species of specific structure and chemical properties, the complexes discussed here are examples of species, for which key properties should be considered:

3.4.1. Solubility

All of the aqueous complexes examined, irrespective of their nuclearity and ligand composition, are soluble species of Al(III) and as such could conceivably be participants in the speciation of that metal ion with the respective ligand. For a number of such complexes, previously proposed to arise from potentiometric solution model studies, kinetic profiles and thermodynamic parameters (e.g. stability constants, etc.) are known [91], offering a significant amount of information as to their standing in potential biodistribution schemes of Al(III) in binary and ternary biological ligand systems. Apparently, solubility in aqueous media is a prerequisite for their potential involvement in subsequent (bio)chemical interactions and possible biological effects (e.g. toxicity). This principle is in keeping with: (a) the increasing accessibility of Al(III) to humans as a result of professional exposure and the metal's introduction to the food chain by acid rain [92–94]; and (b) the subsequent influence of the solubilized bioavailable forms of Al(III) to human health (diseases) [95].

3.4.2. Bioavailability

It is the attribute of a soluble species to elicit further (bio)chemical interactions at the molecular or cellular level. Whether or not the complexes discussed here behave as bioavailable species in biological fluids remains to be elucidated.

3.4.3. Charge

The significance of charge in a species is exemplified, among other aspects, by the potential of the latter to efficiently penetrate and traverse barriers at the cellular level (e.g. blood brain barrier—BBB). Thus, zero charged Al(III) molecules can potentially diffuse through membranes, and gain access to the cytosol of a cell and its inclusive compartments or penetrate the BBB and reach areas of the human body (e.g. brain),

where subsequent interactions might lead to toxic effects. In this regard, the complexes presented in this review contain a wide variety of species the charge of which varies from 3+ to 5−. Whether the effect of the charge on the specific complexes affects their potential biological toxicity remains to be assessed in conjunction with other factors, like hydrophilicity, size, shape, etc.

3.4.4. Potential (neuro)toxicity

Several forms of Al(III)-ligand preparations (e.g. Al(III)–citric acid) have been used in animal and other studies [96–98], investigating the potential toxicity of Al(III) and the consequences of its up-to date unknown chemical interactions leading to physiological aberrations and pathogenicity. Specifically, abnormal exposure to Al(III) has been recognized as an etiological factor in a number of human clinical aberrant conditions including aluminosis [99], encephalopathy [100], osteodystrophy [101], and non-iron deficiency microcytic anemia [102]. Al(III) has also been implicated as a neurotoxin in the neurodegenerative Alzheimer's disease, endemic amyotrophic lateral sclerosis, and Parkinsonism dementia [103–105].

In view of the above investigations, the advent of solid state and solution techniques, seeking to delineate the chemical and structural properties of well characterized Al(III) complexes in biologically relevant media, offer a first glimpse of the participation of that metal ion in biological interactions, which could reflect subsequent adverse physiological effects (e.g. neurotoxicity) [106]. In this sense, dynamic solution studies for well characterized binary Al(III)-ligand complexes known to date and more complex systems to be discovered in the future, could provide considerable insight into that metal ion's intricate nature of interactions at the biological level.

What is the future of the Al(III)-carboxylate chemistry?

a) more complex model systems relevant to biological conditions

   Inescapably, more complex systems involvingAl(III)-binary (e.g. Al(III)-novel carboxylate ligands) and ternary (e.g. Al(III)-carboxylate–phosphate) low molecular mass model systems andAl(III)-binary and ternary high molecular mass model systems (e.g. including proteins, enzymes, and/or mixed high and low molecular mass ligand systems) should be investigated. Such investigations entail concurrent synthetic and solution speciation studies, targeting the extraction of information on species-specific interactions in aqueous media. To this end, solution studies for some Al(III)-noncarboxylate ligand systems have been reported [107,108]. It remains to be seen how synthetic approaches will corroborate such studies. Furthermore, based on the fact that the hard acid character of Al(III), seeking out hard bases like the carboxylate oxygens, is a reflection not only of Al(III)-low molecular mass ligand interactions, but also of Al(III) interactions with carboxylate-containing amino acids in high molecular mass biomolecules in biological media, research efforts targeting exploration of such interactions assume high significance for biochemical events unfolding in the biological milieu. This approach covers a multitude of biological processes (biosynthetic, catalytic, etc.), in which Al(III) could be involved, and it is expected to shed light into unknown or unexplained facets of its chemistry and biology.

b) advanced techniques for deconvoluting complex systems

   Extraction of information from complex systems, such as the ones proposed above, requires data acquisition and deconvolution both at the synthetic level as well as the level of their solution study. To this end, advanced analytical techniques (HPLC, LC-MS, ESI, NMR, etc.) capable of probing complex systems in aqueous media are called for. They are useful tools for concurrent investigations of multiple parameters in specific Al(III)-ligand systems.

c) direction of the chemistry—link with biology and toxicity—toward processes and potential mechanisms related to diseases, diagnostics and therapeutics

   Since pathological symptoms, considered to have been caused by Al(III), relate to its toxicity in humans, it ensues that the toxicity of the chemical and biological interactions arisen by Al(III) should be linked with the chemical and biological research. Therefore, based on the results of research in Al(III), future efforts should be directed toward the elucidation of its chemistry, as that relates to the potential involvement of the metal ion in the biological interactions with components at both the molecular and cellular level. Consequently, well characterized complexes, emerging from synthetic studies, are prime materials for further studies (including toxicity) incorporating all of the previously mentioned factors and seeking to comprehend potential mechanistic pathways linked with Al(III) toxicity at the cellular level. Such information may further allow to continue probing distinct facets of Al(III) interjection in diseases, their diagnosis and future therapeutic trials.

4. Conclusions

In this review an attempt was made to present collectively the diverse spectrum of Al(III)-carboxylate

species arisen synthetically. To this end, key aspects of the aqueous and non-aqueous chemistry of Al(III) with a variety of ligands were discussed, and the products of such chemistries were elaborated on. X-ray crystallographic studies, pinpointing the three dimensional structures of isolable species in the solid state, showed the nature of interaction between Al(III) and the employed ligand(s). A variety of structures with varying nuclearity, structural features of bound ligands, binding modes of coordinated ligands, pH-dependent properties of ligands and associated Al(III) complexes, variable protonation state of ligands and associated charge of the assembled Al(III) complex(es), and others, are some of the attributes of the species reported. Corroborating the X-ray results were spectroscopic techniques such as FT-IR and MAS-NMR spectroscopy. Concomitantly, for some of the species synthesized, a concise account of their solution properties was given, based on evidence from multinuclear NMR solution studies, delving into the nature of the well-characterized solid state species upon their dissolution in water. Meaningful comparisons, between the solid state and solution chemical properties and structures, enrich significantly our understanding of the Al(III)-carboxylate chemistry occurring in solution.

Moreover, the kinetic behavior of some of these species, purported to be biologically related to Al(III) forms eliciting biological interactions, was presented with the goal of identifying intermediate and final thermodynamically stable products. With the aid of the aforementioned data, speciation diagrams of certain systems of Al(III) with physiological ligands (e.g. citrate) have now become easier to rationalize. Al(III)-citrate is a good example of a model system, which was investigated in depth, with tangible conclusions drawn from the recovered experimental results. In view of the fact that citrate is a physiological molecule, present in human plasma and acting as an efficient metal ion binder, considerable attention, emphasis, and coverage of its related chemistry with Al(III) was devoted in this review. It ensues, then, logically that extensive pursuit of analogous synthetic and structural characterization efforts for other model systems are further required.

Since enzymes and proteins do not function with Al(III), it is likely that intrusion of this metal ion in the requisite human biochemistry exerts toxic effects with undesired pathological symptoms. This toxicity relies heavily on the bioavailability of Al(III), which in turn requires soluble forms of that metal ion in biological fluids. To this end, the investigated and reported species reflect the products of such interactions of Al(III) with low molecular mass carboxylate components, resulting in soluble species. Which of those, however, constitute bioavailable forms of Al(III)? Which of the complexes, described in this review, possess biological properties linked to its toxicity (possibly neurodegenerative properties) in humans?

We are now starting to understand the chemical properties of various species of Al(III)-carboxylates in simple biologically relevant systems. The extent, however, to which such properties project further biological metallotoxic consequences remains to be perused. Hence, searching for bioavailable forms of Al(III) and their potential involvement in toxic events in biology lies ahead.

Acknowledgements

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