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Interactions of aluminum(III) with the biologically relevant ligand D-ribose

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Contents

Abstract

Aluminum(III) can be absorbed when it is appropriately complexed. There are several plasma components which can bind weakly Al(III). Many proteins bind Al(III) in solution quite strongly. Carbohydrates bearing an abundance of electronegative functional groups can interact with metal cations. In solution, D-ribose exists as a mixture at equilibrium of many isomers and only a few of them bear a 'complexing' sequence of the hydroxyl groups. The presence of D-ribose in an Al(III) solution experiences a decrease of its Brönsted-acid sites. The lowering of the Brönsted acidity of an Al(III)–D-ribose mixture suggests the existence of attractive interactions ('association') between Al(III) ion and the complexing sequence of the hydroxyls of D-ribose. There is enhancement in the stability of the interaction complexes between Al(III) and D-ribose through strong intramolecular hydrogen bonding, which offers the possibility to investigate the kinetics of the subsequent proton release reactions. On the basis of the kinetic results, it may be concluded that proton release reactions, which are associated with the complexation reactions, are associatively activated. The complexes $(Al(H_2O)_{6-n}(D\text{-ribose}_{-n\,H})^{(3-n)+})$ resulting from the various 'complexing' forms of D-ribose are formed at mainly acidic pH. As the pH increases, the values of the activation enthalpy, $\Delta H^{\neq}$, are changing, because of the formation of mixed hydroxo-complexes $(Al(H_2O)_{6-n-m}(OH)_m(D\text{-ribose}_{-n\,H})^{(3-n-m)+})$; finally, OH^- displaces D-ribose from the coordination sphere of Al(III) in a rather slow process, i.e. with high values of $\Delta H^{\neq}$; the activation enthalpy values,

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$\Delta H^{\neq}$, decrease with the progression of the displacement, becoming finally very small due to the formation of a precipitate. Chelate coordination of D-ribose with some divalent and trivalent metal ions has been also reported.

Keywords: Aluminum interactions; Aluminum association; Aluminum complexation; D-Ribose association; D-Ribose complexation

1. Introduction

Aluminum can be found in small amounts in all organisms [1,2] and in measurable amounts in air, water, soil and food [3]. Alumina deposits are found in certain trees, especially in tropical areas and high levels of aluminum are found in tea plants [4]. The complexation of anthocyanins (which are widespread in flowers) with Al(III) has been known for a long time [5] and the ion could be of biological relevance in the expression of the blue colour in flowers. Aluminum has not been proven to be essential in biological processes by playing any functional role. Even at low levels, aluminum is known to be toxic to plant and animal life [3], primarily in some inorganic soluble form. It may also be involved in human diseases [6].

Biological systems cannot reduce Al(III) ions to the metal state [7]. If organisms had found Al(III) to be useful they could have developed mechanisms to extract it from $Al(OH)_3$, which is formed at pH 4–10, just as they did with Fe(III), which is also hydrolysed [8]. There is evidence however, that Al(III) can be absorbed when it is appropriately complexed [9]. Organic substances readily complex and, if in the solid form, adsorb Al(III) species [10–13].

Aluminum(III) prefers to bind to groups such as the phosphates in membranes, DNA and ATP, causing toxicity in the brain, the bones and the hematopoietic system [14]. Many aspects of aluminum toxicity, including its ability to contribute to Alzheimer's disease and other neurodegenerative diseases [15–17], are questionable.

Anthropogenic introduced sulphur and nitrogen oxides from coal burning power plants, internal combustion engines etc. can lower the pH of rain striking the earth's surface [18–20]. Acidic rain falling contacts rocks, vegetation and soils. Falling directly into forests and especially, cultivated crops, causes release of Al(III) upon reaction with minerals or organic materials containing aluminum, causing aluminum intoxication to the plants [21]. Particularly toxic to plants is the polynuclear form of aluminum [22].

Silicon species are thought to be involved in an evolutionary mechanism to protect against aluminum poisoning [23]. The formation of hydroxyaluminosilicates significantly reduces the bioavailability of aluminum [14]. The balance of these two elements is important [24]. A displacement of this balance in favour of an increased exposure to aluminum was caused by some human activities, for example the introduction of aluminum into foodstuffs, pharmaceuticals, the burning of fossil fuels etc. This increased bioavailability of aluminum is manifested as toxicity [25].

1.1. Some aspects of the aqueous chemistry of aluminum

The aqueous chemistry of Al(III) is complicated because of the tendency of oxygen to form bridges between different Al(III) ions [26]. As a typical hard metal ion, aluminum interacts most strongly with hard donors, i.e. oxygen donors. Being small with a quite high charge-to-radius ratio, $z/r = 134\ \mathrm{nm}^{-1}$ [8], ligands for complexing should contain negatively charged oxygen donors and the selectivity increases by an increase in the number and the basicity of the charged oxygen groups [27]. The chemistry of aluminum in biology is predominated by its ligation by oxygen-containing functional groups.

Solutions of $Al(H_2O)_6^{3+}$ salts are acidic (Brönsted acidity)

$$Al(H_2O)_6^{3+} + H_2O \rightleftharpoons Al(H_2O)_5OH^{2+} + H_3O^+ \quad (1)$$

and the situation is complicated by the dimerisation [28–30]

$$2Al(H_2O)_5OH^{2+} \rightleftharpoons (H_2O)_4Al(OH)_2Al(H_2O)_4^{4+} + 2H_2O \quad (2)$$

and further polymerisation [31]. The hydroxy complexes could be of various different forms [12,13,32]. Monomeric and polynuclear aluminum can adsorb or complex with various organic ligands [33]. Organic aluminum is less toxic to aquatic life than inorganic aluminum [34].

The concentration of the free species Al_{aq}^{3+}, and not the total aluminum concentration, is currently identified as the critical determinant to the toxicity of aluminum [35,36].

The ligand exchange rates of the various Al(III) complexes cover a wide range of reaction rates [9]. Al(III)-complexation reactions are rather slow when oligonuclear and/or mixed hydroxo complexes are involved in the complex formation.

The higher binding strengths and the slower reaction kinetics of aluminum compared to the ions calcium and magnesium makes aluminum an inhibitor of many biological processes dependent on these universally important cations [37].

In aqueous solutions Al(III) ions have a high affinity for a variety of anions [7]. There are also several plasma components which can bind weakly Al(III) [9]. Many

proteins can bind Al(III) and the surprising feature is that Al(III) binding to such proteins in solution is quite strong [7].

1.2. Interactions between carbohydrates and metal cations

Complexes of metal cations with carbohydrates play an important biological role in the transport phenomena of metal ions across cell membranes [38]. Angyal's pioneering work initiated their more detailed study [39]. Extensive reviews have been published on the metal–carbohydrate interactions [40–43], though this area has been little studied due to the complexity of carbohydrate chemistry.

Carbohydrates can interact with metal cations [43], because they bear an abundance of electronegative functional groups. Angyal [44] has derived rules for predicting metal complexation abilities of neutral sugars. These stereochemical rules serve only as guidelines, since metals are all unique and factors such as bond lengths and coordination geometries need also to be considered. The interaction between sugars and metal cations is weak: only those sugars (or isomers) with hydroxyl groups in a specific arrangement can form stable complexes with metal cations in aqueous solutions competing with water molecules [41]. The competition between sugar and metal ion solvation is a decisive factor for the aqueous solutions of carbohydrates [45]. Strong complexation to the sugar residues has been established only with metals that form oxocations, such as vanadium and molybdenum [46].

An important aspect of metal binding to carbohydrates is the ionic radii of the metals, which presumably will influence their ability to be accommodated by the ligand [45]. Ions that are either too small or too large or only weakly interacting will not bind well. Thus, transition metals can be used to assemble sugars in novel structures. The oxygen-rich periphery of the sugar–metal complexes may act as a binding region for metal ions, hydrogen bonding or electrostatic complexation; such complexes may have an important use as functionalisable species in organometallic chemistry [47]. Also, the existence of many functional groups on carbohydrates allows for the manipulation of sites away from the binding ones, so that other useful capacities may be imparted to the molecules [43].

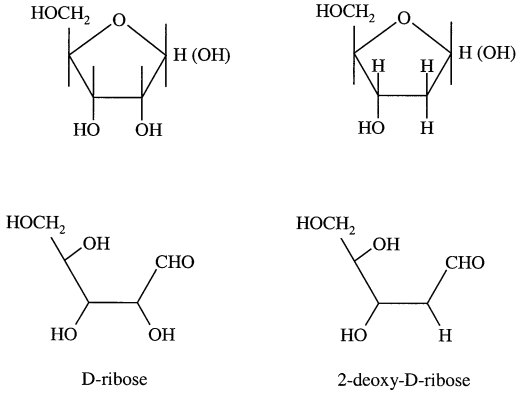

Fig. 1. Chemical structures of D-ribose and 2-deoxy-D-ribose.

It should also be noted that complexation of metals to sugars depends very much on pH, metal-to-sugar ratio, total metal and sugar concentrations, ionic strength and temperature [43].

1.3. D-Ribose and its 'complexing' forms

D-Ribose and 2-deoxy-D-ribose (Fig. 1) are among the simplest class of building blocks of RNA and DNA [48,49].

In solution, D-ribose exists as a mixture at equilibrium of many isomers (mainly six): 59% of the $^1C_4$ and $^4C_1$ conformers of β-pyranose, 21% of the $^1C_4$ and $^4C_1$ conformers of α-pyranose, 14% of β-furanose and 6% of α-furanose [41]. Only a few of these isomers bear a 'complexing' sequence of the hydroxyl groups, i.e. the $^1C_4$ and $^4C_1$ conformers of the α-anomer and the $^1C_4$ conformer of the β-anomer among the ribopyranose forms, and the α-anomer among the ribofuranose forms [50].

Studies [50–53] of the composition of the aqueous mixtures at equilibrium have shown that the various 'complexing' forms of ribose exist in solution with the following composition at 304 K [50]: 21.5% ($\alpha P^1C_4 + \alpha P^4C_1$) + 15% ($\beta P^1C_4$) + 6.5% (αF) = 43%.

However, the kinetic studies that are presented in Section 3 do not discriminate amongst the various complexes formed between Al(III) and the various isomers. The treatment of the kinetic data is limited to a 'global' phenomenon, considering only one type, averaged, of complexed sites, assuming that all complexes with the same empirical formula had the same kinetic behaviour and thus the same activation parameters. In all those complexes the local geometries around the metal cation, $Al^{3+}_{(aq)}$, are expected to be very similar; thus the above assumption seems reasonable.

Therefore, the activation parameters (Section 3) are overall values for all ribose isomers present in solution, as in other studies in the determination of the values of various parameters of ribose solutions has been already assumed [54].

2. Attractive interactions between aluminum(III) and D-ribose: 'association' complexes

2.1. Decrease of Brönsted-acid sites

Complexation of water to a transition metal results in an increase of its Brönsted acidity [32,55–57].

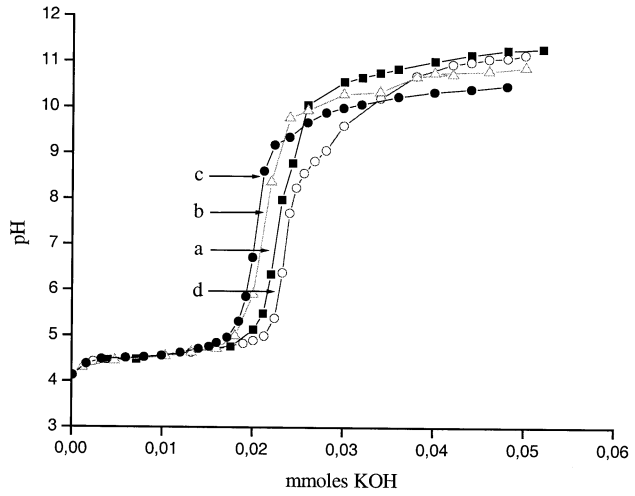

Fig. 2. Decrease of the acidity caused by $Al(III)_{aq}$ 0.001 M (curve d) in solutions containing Al(III): D-ribose 1:1 (0.001:0.001 M) (curve a), Al(III): D-ribose 1:10 (0.001:0.01 M) (curve b), Al(III): D-ribose 1:100 (0.001:0.1 M) (curve c). From Refs. [58,59].

It is also observed that the addition of aqueous solution of D-ribose to Al(III) solution causes decrease in its Brönsted acidity [58,59]. The more concentrated the solutions of D-ribose are, the more the acidity is restricted (Fig. 2). Preferential solvation of $Al(III)_{aq}$ by D-ribose reduces the number of $Al(III)_{aq}\cdots OH$ interactions with water and the remaining D-ribose hydroxy groups.

The changes in the concentration of 'free' hydroxy and lone-pair groups in coordinated water must play a part in governing the observed shifts in the pH curves. Such changes are taken as evidence for the existence of 'weak' association between $Al(III)_{aq}$ and the D-ribose molecules [58,59]. The protons embedded in the intramolecular ($Al(III)_{aq}\cdots$D-ribose)–OH···OH– structural fragments are not free to dissociate and thus the Brönsted acidity is affected. Hence the presence of D-ribose in the Al(III) solution experiences the decrease of Brönsted-acid sites [58,59].

2.2. Stabilisation through strong intramolecular hydrogen bonding

There is enhancement in the stability of the interaction complexes between Al(III) and D-ribose, through strong *intramolecular* hydrogen bonding which offers the possibility to investigate the *subsequent kinetics* of the proton release reactions following the association procedure [60,61].

The differences observed in the stabilities of the 'association complexes' between Al(III) and other trivalent metal-cations (Fe(III), Cr(III) [58,59]) with D-ribose (Fig. 3) could be attributed to sterically controlled differences in hydrogen bonding interactions between D-ribose and coordinated oxygen atoms in the respective complexes.

It has been shown [62] that the hydrogen-bonded hydrogen resembles an aluminum centre with regard to observed electronegativity about oxygen. This may also contribute to the stability of the Al(III) 'association' complexes [61]. A negative value of $\Delta S^{\neq}$ (see Section 3) is consistent with the formation of a hydrogen-bonded intermediate, which then undergoes proton elimination through an *associatively activated complex* to yield the chelated Al(III)–D-ribose complexes.

2.3. Chemical equilibrium of association

Carbohydrates containing an axial–equatorial–axial sequence of three hydroxyl groups in a six-membered ring or a *cis–cis* sequence in a five-membered ring can interact in solution specifically with some metal ions [39].

The previously described lowering of the Brönsted acidity of an Al(III)–D-ribose mixture suggested that interactions between Al(III) ion and D-ribose exist, as in the case of other metal ions [63] has been reported. The solutions of D-ribose present anomeric and conformational equilibria and only some of the isomers (Fig. 4) contain suitably positioned sequences of hydroxyl groups (axial–equatorial–axial in the pyranose forms and *cis–cis* in the furanose forms) to interact with Al(III) [61] as they do with other metal ions [63].

The existence in solution of the many anomers is one of the great difficulties of the thermodynamic, hence global approach to the problem [64]. Thermodynamic parameters such as $\Delta H^{\neq}$ are discussed in Section 3.

All the active isomers of D-ribose are assumed to form with Al(III), as they do with other metal ions, i.e. Ca(II) [65], 'complexes' of comparable stabilities. The stability constants are of the order of unity in the case of the rather weak interactions between D-ribose and some cations. Calcium, because of its great biological importance, is probably the cation that has been studied most [39,63–70]

The couple Al(III)/(axial–equatorial–axial sequence and Al(III))/(*cis–cis* sequence) of oxygen atoms of the D-ribose isomers exist at equilibrium (Fig. 5) with an association constant K_{ass} (Eq. (3)).

$$K_{ass} = \frac{(LAl^{3+})}{(Al^{3+})(L)} \quad (3)$$

The various anomeric and conformational equilibria which are established in the D-ribose solutions may be shifted because of the complexation of some of the isomers. For example, the $^1C_4$ conformer of β-pyranose is active and, when Al(III) is associated with it, the equilibrium between the (two) conformers is expected to be displaced in favour of the $^1C_4$ form.

The overall equilibrium constant may be written:

$$K_{ass} = \frac{\sum_i (L_i Al^{3+})}{(Al^{3+})(L)} \quad (4)$$

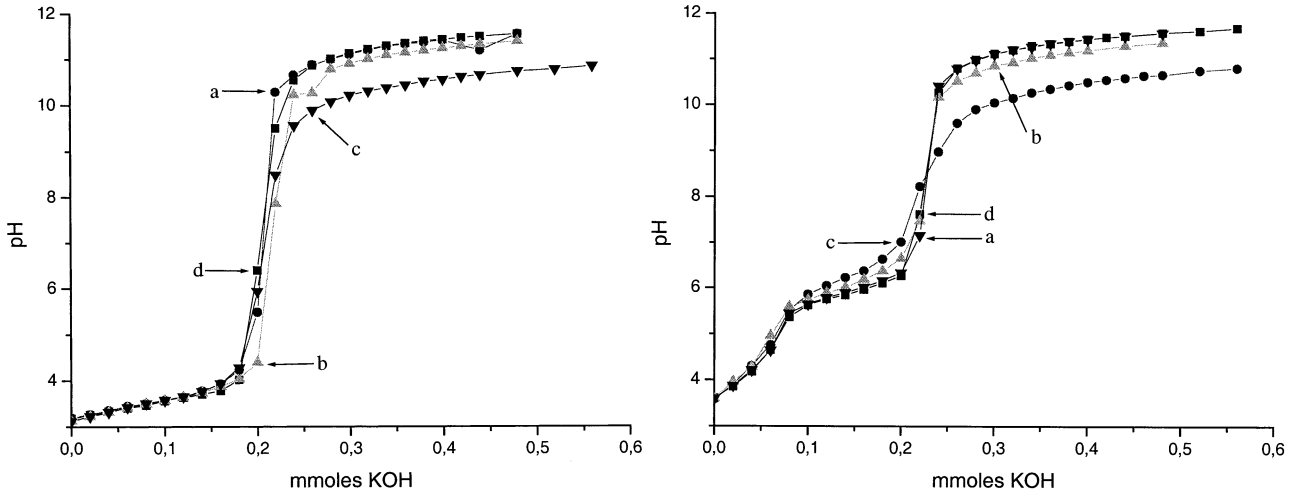

Fig. 3. The 'association' complexes between the trivalent cations Fe(III) (left) and Cr(III) (right) with D-ribose differ in stability from the corresponding Al(III) (Fig. 2) complexes. From Refs. [58,59].

It was also found that some divalent alkaline-earth cations [39,71] and some trivalent cations like La(III) [66,71,72] are notably associated with D-ribose in aqueous solutions.

Parameters of the association of D-ribose with Ca(II), Sr(II), Ba(II), La(III) and Gd(III) have been determined in aqueous solutions at 25 °C [65]. It was also reported that the enthalpy of dilution of D-ribose is not very much concentration dependent [65].

The activation parameters of the reactions of association leading to complexation of Al(III) with the complexing forms of D-ribose have been globally estimated [60,61] (Section 3).

2.4. Thermodynamic parameters of the reaction of association

The weak cation–D-ribose association is a result of a large compensation between a favourable enthalpic contribution and a very large unfavourable entropic contribution of the reaction [50,64,65].

The association phenomenon is essentially controlled by the hydration of the various species involved in the process, during which reorganisation of the hydration spheres of both the cation and the sugar takes place [65].

The fact that 'association' is favoured suggests negative ΔG for the reaction. The 'association' leads to a loss of degrees of freedom (internal and external) by the sugar, which gives a negative contribution to ΔS (and hence a positive $-T\Delta S$ term). The three hydroxyls involved in the 'association' complex lose their rotational freedom and the lone pairs of the oxygen atoms cannot participate anymore in the hydrogen bonds of the various hydration structures of the free D-ribose [65]. Since the enthalpy of hydration of Al(III) is large and the molecule of D-ribose is hydrophilic, the negative energetic balance for the association process indicates that the Al(III)–D-ribose 'complex' is itself strongly hydrated.

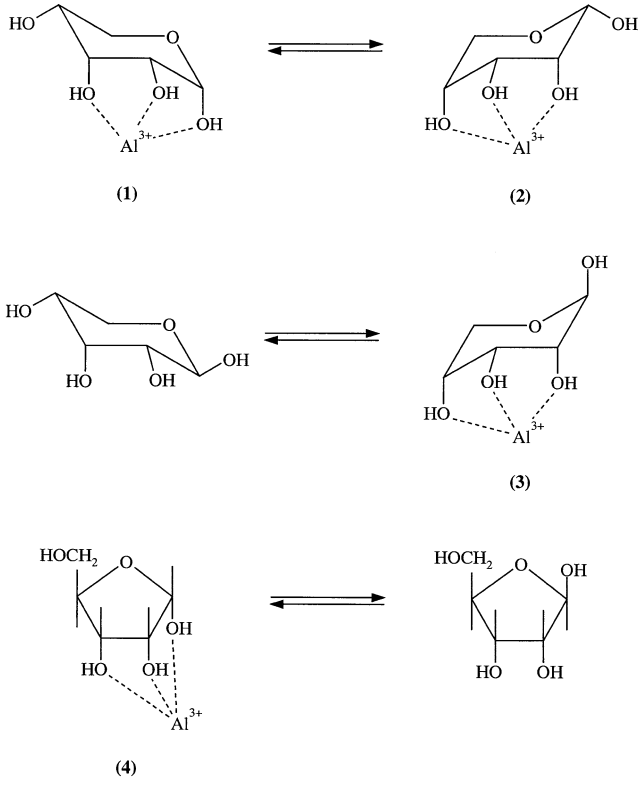

Fig. 4. 'Complexing' forms of D-ribose: The αP^4C_1 (**1**), αP^1C_4 (**2**) and βP^1C_4 (**3**) forms possess an axial–equatorial–axial sequence of hydroxyl groups, and the αF form (**4**) has hydroxyl groups in a *cis–cis* position [61].

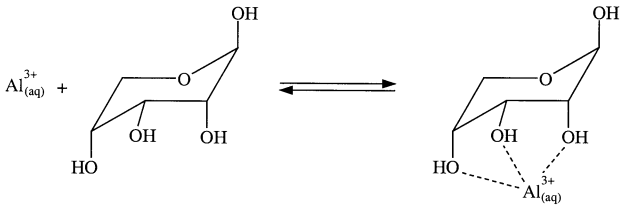

Fig. 5. Chemical equilibrium of association between $Al^{3+}_{(aq)}$ and an isomer bearing suitably positioned hydroxyl groups [61].

Generally, depending on the structure of the sugar and on the nature of the hydration particular to this structure, these types of interaction can either be attractive, leading to association, or repulsive, leading to salting-out. This points out that the interactions in dilute aqueous solutions differ from those in concentrated solutions or in the solid state [53].

2.5. Comparison between aluminum(III), iron(III) and chromium(III)–D-ribose interactions

In view of the similarities between Fe(III) and Al(III) complexes [73], the behaviour of the Al(III), Fe(III) and Cr(III) complexes with D-ribose is compared [58,59].

Although weak, the extent of association varies from one cation to the other (Figs. 2 and 3). Neither the charge nor the size of the cation is important in determining the value of the association constant [65]; in fact it appears that the extent of association of cations with similar size is not proportional to their charge, and also the extent of association of ions with the same valence is not clearly related to their size. For example, the thermodynamic properties of association of D-ribose with the 'complexed' cations Sr(II), Ba(II), La(III) and Gd(III) are not related to the size of the cations or to their charge in a simple way [65].

However, the complexes of Al(III), Fe(III) and Cr(III) ions are expected to show different sensitivities to solvation environment due to the difference in their size. The differences observed in the stabilities of their 'association' complexes have been attributed mainly to sterically controlled differences in hydrogen bonding interactions (Section 2.2).

3. Al(III)–D-ribose complexation

3.1. Processes leading to proton release

The formation of $Al(H_2O)_{6-n}(\text{D-ribose}_{-nH})^{(3-n)+}$ complexes was studied [58–61] and the following mechanism was proposed based on kinetic data:

$$Al(H_2O)_6^{3+} + \text{D-ribose} \overset{\text{fast}}{\rightleftharpoons} Al(H_2O)_6^{3+} \cdot \text{D-ribose},\ K_{ass}\ (\Delta H_1^\circ, \Delta S_1^\circ) \quad (5)$$

$$Al(H_2O)_6^{3+} \cdot \text{D-ribose} \xrightarrow{k} [Al(H_2O)_{6-n}(\text{D-ribose}_{-nH})]^{(3-n)+} + nH_3O^+ \quad (6)$$

Since the pK_a values of D-ribose change upon coordination to aluminum and in the presence of an intramolecular OH_2, a strong hydrogen bond–proton transfer to the OH_2 results in H_3O^+ [58–61]. Thus, the protons can be liberated either from the –OH groups of D-ribose, as stated previously, accompanied by concomitant coordination of the –OH groups or from water molecules in the coordination sphere of the Al(III). It is likely that these two processes take place in parallel, and hence formation of binding isomers is probable.

For a mechanism described by Eqs. (5) and (6), the apparent activation enthalpy, $\Delta H^{\neq}$, is the sum of ΔH_1° and $\Delta H_2^{\neq}$, where ΔH_1° is the enthalpy for the equilibrium (association) step described by Eq. (5) and $\Delta H_2^{\neq}$ is the enthalpy of activation for the rate-determining step described by Eq. (6) [74]. If ΔH_1° for the equilibrium is negative, the observed activation enthalpy ($\Delta H^{\neq}$) will be lower than the value of activation enthalpy for the rate-determining step ($\Delta H_2^{\neq}$).

The above formalism does not indicate whether the rate-determining step is associative, dissociative or concerted.

The reaction of association (Eq. (5)) has been previously discussed (Section 2). The subsequent proton release step (Eq. (6)) has been investigated [58–61] by following the rate of pH decrease caused by the increase of the proton concentration.

3.2. Activation enthalpy–Activated complex(es)–I_a mechanism

The proton release reactions follow both the Arrhenius and Eyring equations [60,61], leading to the apparent (associated with k_{obs}) activation parameters, activation enthalpy ($\Delta H^{\neq}$) and activation entropy ($\Delta S^{\neq}$). Given the apparent character of these activation parameters, they must be considered as valid only for the experimental conditions under which they have been deduced. The variation of the conditions, for example the ratio of (ionised) ligand to aluminum, the pH of the solution, the concentrations of ligand and aluminum etc. is the reason for the observed variation of the values of the activation parameters [60,61].

As mentioned earlier (Section 1.3), our method does not allow differentiation between the various isomers, but gives an overall rate constant and overall activation parameters, characteristic of the complexation of all the complexing forms of D-ribose.

At more acidic pH, $\Delta H^{\neq}$ is increasing with addition of base, hence the rate of the proton release reactions is decreasing; the appropriate Arrhenius and Eyring plots are linear [60,61]. The continuous addition of base, and hence the increase of the solution pH, results in conditions causing deviation from the Arrhenius law [60,61].

The appropriate plots are curved downwards, suggesting [74] a mechanism consisting of successive steps in which a steady-state intermediate, proposed to be the $Al(H_2O)_{6-m}(OH)_m \cdot (D\text{-ribose})^{(3-m)+}$, is present [60,61].

Large $\Delta H^{\neq}$ values are accompanied by low activity and are consistent with breaking of the intramolecular hydrogen bonds during the transition state. The hydrogen-bonded hydrogen resembles an aluminum centre with regard to observed electronegativity about oxygen [75]. This also explains the slowness of the proton-release reaction(s). Coordination of D-ribose to aluminum via oxygen suggests that the D-ribose hydrogen atom is a stronger Lewis acid than the aluminum.

Given the negative value of ΔH_1° (Section 2.4), it is concluded that the apparent activation enthalpy ($\Delta H^{\neq}$) becomes smaller than $\Delta H_2^{\neq}$, which corresponds to the rate-determining step, i.e. the breaking of hydrogen bonding. This is the reason for values of $\Delta H^{\neq}$ ranging between ca. 80 and 120 kJ mol^{-1} [60,61].

The kinetic investigation of the Al(III)–D-ribose system which was conducted in aqueous solution under various conditions of pH, concentration, ionic strength and temperature, has led to the values of the activation parameters [60,61] and, on the basis of the kinetic results, it may be concluded that proton release reactions, which are associated with the complexation reactions, are *associatively activated* (negative $\Delta S^{\neq}$) [60,61]. A similar mechanism has been proposed for the fluoride exchange reactions of the Al(III)–F^- system, where it was also concluded from ^{19}F-NMR studies that fluoride exchange reactions are associatively activated [76].

An associative (I_a) mechanism has been supported by Plankey and Patterson [77] for the formation of the complex $AlF(H_2O)_5^{2+}$, though the ligand substitution processes of Al(III) in aqueous solution are known to follow the I_d mechanism [76]. However, the occurrence of an I_a mechanism for the complexation reactions of Al(III) is unusual, since it is generally known that all substitution processes for octahedral M(III) species are I_a unless r(M(III)) < 0.6 Å [78], when it is not possible to have sufficient space in the coordination sphere of M(III) to accommodate an extra incoming ligand molecule, in our case a D-ribose molecule (Fig. 6). In the case, however, of Al(III), this may not be strictly valid, since the ion is only slightly smaller than 0.6 Å (Fig. 6).

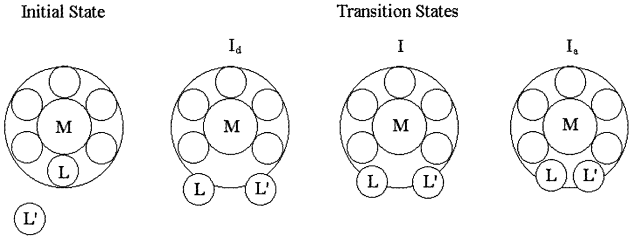

Fig. 6. Schematic representation of an exchange reaction proceeding by the Interchange (I) mechanisms. The circle in the middle of the idealised 'flat' octahedral complex represents the metal ion (in our case Al(III)). The small circles represent the bound and free ligands. In an I mechanism an outer-sphere complex is formed first, and then the leaving group moves from the inner to the outer coordination sphere and simultaneously the entering group moves from the outer to the inner coordination sphere. During the critical concerted I step, in a dissociative-like (I_d) mechanism there is only weak bonding to the entering and leaving groups, whereas in an associative-like (I_a) mechanism the bonding is stronger. In this figure bonding is symbolised by placing the leaving and incoming groups at different distances from the central metal ion.

Angyal [52] has pointed out that the composition of sugars in solution varies considerably with variations in temperature, and in particular the proportion of furanose forms which increases considerably as the temperature is increased. This is not a problem in the kinetic studies, since all the compositions are not known at the same temperature and, moreover, are not known at the applied temperatures, and thus affect all the values as incalculable uncertainty. In spite of that, the thermodynamic parameters of the reaction appear to be similar for the various forms of D-ribose, which is a result of the fact that the interaction between the suitably positioned hydroxyl groups of D-ribose and the cation Al(III) is approximately the same for all the complexing forms.

3.3. Aluminum(III) complexes of D-ribose

The formation of the various $Al(H_2O)_{6-n}(D\text{-ribose}_{-n\mathrm{H}})^{(3-n)+}$ and $Al(H_2O)_{6-n-m}(OH)_m(D\text{-ribose}_{-n\mathrm{H}})^{(3-n-m)+}$ species can be followed by the values of $\Delta H^{\neq}$.

The complexes resulting from the various complexing forms of D-ribose are formed at the mainly acidic pH values. There is no need to invoke mixed hydroxo complexes at these acidic pH values.

The kinetics are dominated by the formation of complexes and only procedures which result in altering the solution pH, i.e. in proton release are observed. Exchange processes could not be detected, since they do not cause pH changes. Our kinetic measurements do not provide direct information on the geometry of the complexes. Nevertheless, the intensity of the ^{27}Al-NMR signals [60,61] at various conditions support an octahedral geometry. The complexation is accompanied by a downfield shift in the characteristic $Al_{(aq)}^{3+}$ peak [60,61]. As the various isomeric Al(III) complexes of D-ribose should give separate resonances, the broad signal at around ca. 70 ppm is the weight-averaged signal of the many complexes [60,61]. The metal cation NMR spectra provide information directly related to the cation coordination sphere and thus permits the study of the inner-sphere complexes [79,80]. Obviously, ^{27}Al-NMR spectroscopy is particularly appropriate for the study of the interactions of Al(III) with polyols in solution.

It is, though, observed that, as the pH increases, the values of $\Delta H^{\neq}$ are changing due to the formation of ternary $Al(H_2O)_{6-n-m}(OH)_m(\text{D-ribose}_{-n}H)^{(3-n-m)+}$ species. The formation of such species is favoured at higher pH and modest D-ribose concentrations. On increasing the pH of the solution by addition of KOH, OH^- displaces D-ribose from the coordination sphere of Al(III) in a rather slow process (high values of $\Delta H^{\neq}$); this displacement reaction is governed primarily by the progression of the oligomerisation processes of the mononuclear Al(III)–D-ribose complex. Also, the equilibrium between the D-ribose isomers present in solution may be shifted by the presence of a large quantity of salt (KNO_3) resulting from the continuous addition of base (KOH); this, of course, creates a problem in comparing the various results [54]. The values of $\Delta H^{\neq}$ start to decrease and finally (may) become very small (ca. 30 kJ mol^{-1}) [60,61]. This phenomenon was also reported by Tóth and co-workers [76] and Martinez et al. [81], who observed that the NMR signals disappeared. The existence of a fine, colourless precipitate was indicated [76], the analysis of which accounted for all the 'missing' Al(III). Finally, formation of the tetrahedral [82] $Al(OH)^-_{4(aq)}$ results. That is, there is a change in geometry from octahedral ($Al(H_2O)^{3+}_{6(aq)}$) to tetrahedral. It is not known where this change takes place, because of experimental difficulties associated with solubility and polymerisation [76].

The reactions described are largely suppressed in the concentration range of μmolar level; this may alter the Al(III) binding abilities of D-ribose.

Finally, the fact that the reaction is expected to be extremely slow at very low concentrations suggests that under ordinary physiological conditions the complexation by D-ribose and, probably, by other sugars and their derivatives might represent only a minor contribution to the intracellular metabolism of Al(III).

3.3.1. Chelate coordination of D-ribose

It was stated that no detection had been made by any structural investigation method of any significant interaction between Al(III) and the alcoholic hydroxyl(s) at the ribose or deoxy-ribose units of nucleotides [9]. The system Al(III)–D-ribose is actually not simple: it should be represented by a formation of a series of complexes. The investigations described here give a lot of information about the system, especially about the types of complexes formed and the activation parameters of their formation reactions. All the data led to suggestions about chelate coordination. Chelate coordination of D-ribose has been also suggested in many other cases: in the Cu(II)–D-ribose complex, two species at equilibrium are proposed in an 1:1 complex [83], which are suggested to differ from each other in the number of hydroxide ions coordinated to the Cu(II) ion [83]. A chelate ring is proposed, formed through the binding of two deprotonated alcoholic oxygen atoms. Similar structures in aqueous solution are reported for Fe(III)–sugar complexes [83].

Also, in solid vanadyl(IV) complexes of D-ribose interaction takes place through pairs of deprotonated *cis*-diol groups of the ribose units [84].

Chelate coordination of D-ribose to La(III) [54] and Ca(II) [50,53,65,85] has been reported. The reaction between Cr(VI) and D-ribose was also studied, because it was found that only ribonucleotides and not deoxyribonucleotides reduce Cr(VI) to an intermediate Cr(V) [86], which is believed to participate in the mechanism of chromium-induced carcinogenesis [87–89].

The orientation of the hydroxyl groups on the ribose ring is suggested to govern the absolute chirality of the Co(II) complexes, as demonstrated by CD studies [90].

An intermediate *bidentate complex* coordinated with hydroxy groups at carbon atoms 1 and 2 of the hydrated aldopentoses is supposed to be involved in the reactions of a macrocyclic Cr(III) complex (of the optically active 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane tetraamine ligand), and in favour of the *chelate coordination* is the finding that a similar reactivity between the same Cr(III) complex and 2-deoxy-ribose has not been detected [91].

3.3.2. Extended (complex) structures

The structural variety of polyols (diols, triols) and sugar alcohols, as well as low molecular weight carbohydrates, oligo- and polysaccharides-, makes them suitable building blocks for the synthesis of *complex structures*. Coordination polymers can be created through combination of metal ions with the polyolato ligands, in which *extended structures* are produced. In the presence of Cu(II) or Pd(II) ions, polyols are multiply deprotonated in aqueous solution and chelate to the metal ion [92–94]. When the metal building blocks used are bifunctional, polymer chains are expected [95].

Al(III) reacting over a period of up to about 2 h leads to polynuclear species [21]. Thus, complexes formed during such a period of reaction time may be considered to be polymeric.

4. Conclusions

An aqueous solution of D-ribose added to Al(III) solution causes a decrease in its Brönsted acidity, and the more concentrated the solutions of D-ribose are, the more the acidity is restricted. This reveals that the presence of D-ribose in the Al(III) solution experiences a decrease of Brönsted-acid sites. Such effect is taken as evidence for the existence of 'weak' association between Al(III) and the D-ribose molecules. The association complexes between Al(III) and D-ribose are stabilised by intramolecular hydrogen bonding, which makes it

possible to investigate the kinetics of the subsequent complexation by proton liberating reactions. The association reaction of Al(III) with the 'complexing' forms of D-ribose and the subsequent proton release leading to complexation have been globally studied and activation parameters have been calculated. A mechanism is supported according to which a fast equilibrium step (association step) is followed by the rate-determining step (proton release step). The complexation reactions, which are associated with the proton release reactions, are *associatively activated*. At the more acidic pH values, where the appropriate Arrhenius and Eyring plots are linear, complexes of the type $Al(H_2O)_{6-n}$(D-ribose$_{-n\mathrm{H}}$)$^{(3-n)+}$ are formed. The continuous increase of the solution pH results in conditions causing deviation from the Arrhenius law. The appropriate plots are curved downwards, suggesting a mechanism with successive steps, in which a steady-state intermediate bearing hydroxide group(s) in the coordination sphere of Al(III), $Al(H_2O)_{6-n-m}(OH)_m$(D-ribose$_{-n\mathrm{H}}$)$^{(3-n-m)+}$, is present. The apparent activation enthalpy $\Delta H^{\neq}$ becomes smaller than the activation enthalpy ($\Delta H_2^{\neq}$), which corresponds to the rate-determining step (breaking of hydrogen bonding), because of the negative value of ΔH_1° (equilibrium of the association reaction). The ^{27}Al-NMR signals at different conditions support octahedral geometries of the various complexes. The fact that the reactions are expected to be extremely slow at very low concentrations suggests that, under ordinary physiological conditions, the complexation by D-ribose, and probably by other sugars and their derivatives, might represent only a minor contribution to the intracellular metabolism of Al(III). However, the fact of the existence of association between Al(III) and D-ribose, stabilisation of the 'association' complex through hydrogen bonding and subsequent complexation through proton release could suggest a significant (new) important role of Al(III) ions in biological systems.

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