Equilibrium and Structural Studies of Silicon(IV) and Aluminium(III) in Aqueous Solution. 19. Composition and Stability of Aluminium Complexes with Kojic Acid and Maltol

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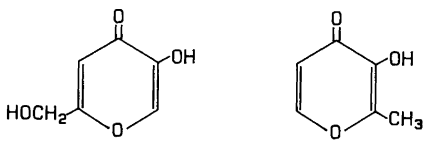
Equilibria in the title systems were studied in 0.6 M Na(Cl) medium at 25 °C using potentiometric (glass electrode) measurements. For ratios $C/B>3$, where B and C represent the total concentrations of aluminium and ligand, respectively, aluminium complexation is characterized by the formation of binary species AlL_n^{3-n} (n = 1, 2, 3). At lower ratios, a dinuclear mixed hydroxo species $Al_2(OH)_2L_2^{2+}$ is formed at $-\log[H^+]>4$. Equilibrium constants, defined according to the reaction $pH^+ + qAl^{3+} + rHL \rightleftharpoons H_pAl_q(HL)_r^{p+3q}$ are $\log\beta_{-1,0,1} = -7.609\pm0.002$, $\log\beta_{-1,1,1} = -0.37\pm0.011$, $\log\beta_{-2,1,2} = -1.50\pm0.013$, $\log\beta_{-3,1,3} = -3.56\pm0.021$ and $\log\beta_{-4,2,2} = -7.66\pm0.070$ in the $H^+-Al^{3+}-$Kojic acid system. In the H^+-Al^{3+}-Maltol system, corresponding data are: $\log\beta_{-1,0,1} = -8.381\pm0.002$, $\log\beta_{-1,1,1} = -0.130\pm0.006$; $\log\beta_{-2,1,2} = -0.956\pm0.007$, $\log\beta_{-3,1,3} = -2.67\pm0.014$ and $\log\beta_{-4,2,2} = -7.20\pm0.024$. The dissociation constants for the ligands (i.e. $\log\beta_{-1,0,1}$) were determined in separate experiments, and all standard deviations given are $3\sigma(\log\beta_{p,q,r})$. Data were analyzed using the least-squares computer program LETAGROPVRID.

In a series of model calculations, the significance of these complexes with regard to conditions prevailing in natural waters and with regard to bio-uptake in man is illustrated and discussed.

In an ongoing project at this department, the ability of Al^{3+} to form complexes with naturally occurring ligands is being investigated. Predominantly, these ligands have been chosen as to be of relevance for the behaviour of aluminium in natural waters; e.g. several probable binding sites in the naturally occurring high molecular weight organics, the humic substances, have been investigated.[1-3] The goal of these investigations is to gain a better understanding of processes affecting the mobility and toxicity of aluminium in natural waters. Through these studies, the common occurrence of ternary polynuclear Al-OH-ligand complexes in near-neutral solutions containing low ligand excesses have been clearly demonstrated. Also, the occurrence of ternary solid phases has been demonstrated in several of the systems studied.[3-5]

During the last decade, the Al^{3+} ion has also become of concern in relation to several human neurological dysfunctions (e.g. Alzheimer's disease,[6,7] dialysis encephalopathy,[8] amyotrophic lateral sclerosis[9]) and bone disorders (e.g. osteoporosis,[10] osteomalacia[11]). A key question in this field is in what form or forms the aluminium ion can be transported from the gastrointestinal tract over to the brain or bone tissue. In a recent series of papers,[12,13] Slanina *et al.* have shown that rats fed an aluminium-rich diet accumulate aluminium in brain and bone when it is administered together with citrate. Furthermore, in man,[14] the concomitant supply of lemon juice and an Al-containing antacid suspension resulted in elevated aluminium concentrations in blood. This ability of citrate to enhance absorption of Al is, according to Martin,[15] probably due to the occur-



Scheme 1.

rence of significant amounts of a water-soluble, net electrically neutral Al(Cit)° species[16,17] in the pH-range of 2–5.

The title ligands kojic and maltol (Scheme 1), both containing the 3-hydroxy-4-pyronate group as metal coordinating center, can be regarded as of relevance with regard both to human bio-uptake and to natural water. Thus, one of the ligands, maltol, is a commonly used flavoring additive in bread, malted beverages and chocolate milk, and at the same time, the positioning of a hydroxy group in an α-position relative to a keto oxygen is not at all improbable in the humic substances.

Furthermore, in the title systems the formation of net neutral, water-soluble species AlL_3^0 has recently been reported.[18] These species are, in addition, reported[18] to be highly neurotoxic when administered intracranially in rabbits.

Previous investigations concerning stoichiometry and stability of species occurring in the two systems[19–21] are based on relatively few experimental data with small variations in Al^{3+}/ligand quotient and in total concentrations. Furthermore, no unbiased search for complex model has been applied in these papers. Therefore we have considered it important to perform a careful and unbiased reinvestigation of these systems.

Experimental

Chemicals and analysis. Kojic acid [3-hydroxy-6(hydroxymethyl)-4*H*-pyran-4-one] (Sigma) and maltol (3-hydroxy-2-methyl-4*H*-pyran-4-one) (Fluka AG) were purified by repeated recrystallization from hot water before use. Stock solutions were prepared by dissolving the solids in boiled distilled water, and the HL content was determined potentiometrically using the Gran extrapolation method.[22] The amounts determined by titration were in both cases somewhat lower (≈0.4 %) than expected from weighing and the titration values were assumed to be correct.

The preparation of other solutions, the cell arrangement and the experimental details of the em*f* measurements are fully described elsewhere.[23]

Method

In the present investigation series of potentiometric titrations were carried out at 25 °C in a constant ionic medium of 0.6M Na(Cl). The titration procedures, the calibration and the assumptions made in connection with the use of the glass electrode were the same as described earlier.[23]

The acidity constants for the ligands were determined in separate experiments within the concentration range 0.002-0.030M and with $-\log[H^+]<9$.

During the three-component titrations, the ratio between the total concentration of aluminium, *B*, and total ligand, *C*, was held constant. In the Al-kojic acid system, *B* and *C* were varied within the limits $0.001M \leq B \leq 0.005M$ and $0.002M \leq C \leq 0.023M$, with C/B = 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12 and 20, and $2 \leq -\log[H^+] \leq 8$. Corresponding data for the Al-maltol system are: $0.0005B \leq 0.030M$, $0.001M \leq C \leq 0.030M$, C/B = 1, 2, 3, 4, 5 and 10, and $2.4 \leq \log[H^+] \leq 7$.

Data treatment. In the evaluation of data we will assume the presence of three-component equilibria of the general form (1), together with the two-component equilibria (2) and (3):

$$pH^+ + qAl^{3+} + r(HL) \rightleftharpoons H_pAl_q(HL)_r^{p+3q} \quad , \beta_{pqr} \tag{1}$$

$$HL \rightleftharpoons H^+ + L^- \quad , \beta_{-101} \tag{2}$$

$$pH^+ + qAl^{3+} \rightleftharpoons H_pAl_q^{p+3q} \quad , \beta_{pq0} \tag{3}$$

In these equations, HL stands for kojic acid and maltol, respectively. By applying the law of mass action to these equations, the conditions for the total concentrations give eqns. (4)–(6), in which $h = [H^+]$, $b = [Al^{3+}]$ and $c = [HL]$.

$$H = h - \beta_{-101}h^{-1}c + \Sigma p\cdot\beta_{pq0}\cdot h^p b^q + \Sigma p\cdot\beta_{pqr}\cdot h^p b^q c^r - k_w h^{-1} \quad (4)$$

$$B = b + \Sigma q\cdot\beta_{pqo}\cdot h^p b^q + \Sigma q\cdot\beta_{pqr}\cdot h^p b^q c^r \quad (5)$$

$$C = c + \beta_{-101}h^{-1}\,c + \Sigma r\cdot\beta_{pqr}\cdot h^p b^q c^r \quad (6)$$

For the binary hydrolysis equilibria according to eqn. (3), we have used results from earlier parts of this series[24,25] for the formation of: $AlOH^{2+}$ ($\log\beta_{-1,1,0} = -5.52$), $Al_3(OH)_4^{5+}$ ($\log\beta_{-4,3,0} = -13.57$), $Al_{13}O_4(OH)_{24}^{7+}$ ($\log\beta_{-32,13,0} = -109.2$) and $Al(OH)_4^-$ ($\log\beta_{-4,1,0} = -23.46$).

In the evaluation of experimental data, the least-squares computer program LETAGROP-VRID,[26] version ETITR;[27,28] was used. *pqr*-triplets and corresponding equilibrium constants that gave "best" fit to the experimental data were determined by minimizing the error-squares sum $U = \Sigma(H_{calc}-H_{exp})^2$. The LETAGROP program also gives standard deviations $\sigma(H)$, $\sigma(\beta_{pqr})$ and $3\sigma(\log\beta_{pqr})$, defined according to Sillén.[29,30] The computations were performed on a CD Cyber 850 computer.

Data, calculations and results

The H^+-kojic acid system. The data used to evaluate the acidity constant for kojic acid were based on 9 titrations with 138 experimental points within the concentration range $0.003 \le C \le 0.030$M and $-\log h \le 9$. A LETAGROP calculation using these data gave $\log(\beta_{-101}\pm 3\sigma) = -7.609\pm 0.002$ with $\sigma(H) = 0.08$mM.

The H^+-Al^{3+}-kojic acid system. The analysis of three-component data, based on 11 titrations with 187 experimental data, was started by constructing a Bjerrum plot, $\bar{n}$ ($\log[L^-]$), shown in Fig. 1. From this figure it can be concluded that, for $C/B \ge 3$, data can be explained by the formation of a series of AlL_n^{3-n} species. Since $\bar{n}$ reaches a limiting value of three, it can also be concluded that the last step in complex formation (for $-\log h \le 7.8$) is the formation of the uncharged species AlL_3^0.

For $C/B < 3$, where data were restricted to $-\log h \le 5$–6 due to slow equilibration above this limit, the experimental data deviate from this theoretical mononuclear species $\bar{n}$-curve (shown as a solid line in Fig. 1). This indicates that at low C/B ratios, mixed aluminium-hydroxo-ligand complexes are being formed. The LETAGROP calculations were therefore started with a calculation on data with $C/B \ge 3$, in which the formation constants for AlL^{2+}, AlL_2^+ and AlL_3^0 were evaluated. This calculation ended at $\sigma(H) = 0.06$mM and the equilibrium constants obtained were: $\log\beta_{-1,1,1} = -0.37\pm 0.027$, $\log\beta_{-2,1,2} = -1.51\pm 0.025$ and $\log\beta_{-3,1,3} = -3.58\pm 0.040$.

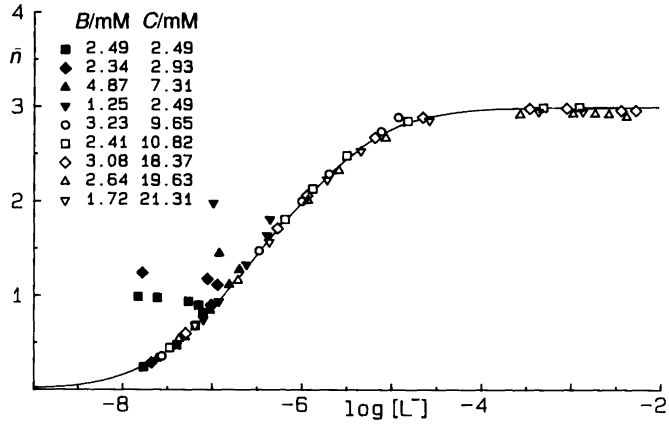


Fig. 1. Part of the experimental data in the $H^+ - Al^{3+}$–kojic acid system plotted as curves $\bar{n}(\log[L^-])$. The full curve was calculated with $\log\beta_{-1,1,1}$, $\log\beta_{-2,1,2}$ and $\log\beta_{-3,1,3}$ according to Table 1.

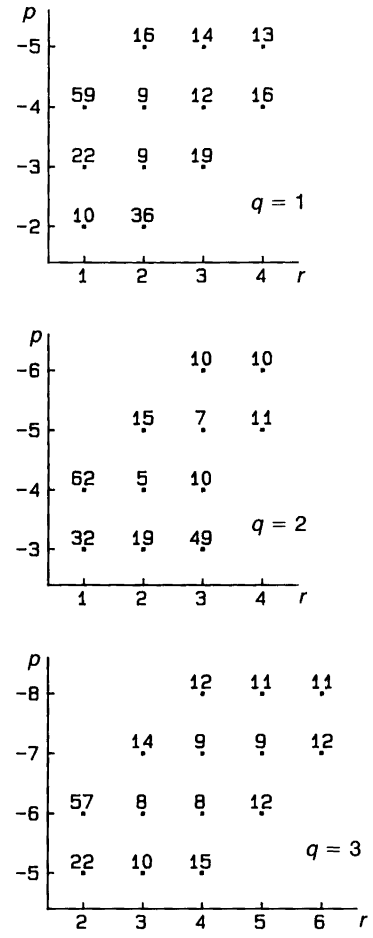


Fig. 2. Result of a *p,q,r* analysis on data for $C/B < 3$ in the system H^+-Al^{3+}–kojic acid. The figures give error-squares sums $U_H(pr)_q \cdot 10^2$ assuming one new complex. The calculations are based on 83 points giving $U_H(00)_0 = 72 \cdot 10^{-2}$.

Considering these values as known, we now introduced data for $C/B < 3$ and performed an unbiased search for the species that could "best" explain experimental data.

This analysis was performed as a *pqr* analysis [systematic testing of different *p,q,r* compositions according to eqn. (1)] with the simple hypothesis that only one new complex $H_pAl_q(HL)_r^{p+3q}$ was present. The result of this search is shown in Fig. 2, and as seen in the figure, the lowest value of U is obtained for the species $H_{-4}Al_2(HL)_2^{2+}$ with $\log(\beta_{-4,2,2} \pm 3\sigma) = -7.65 \pm 0.08$.

With these species, AlL^{2+}, AlL_2^+, AlL_3^0 and $H_{-4}Al_2(HL)_2^{2+}$, a final LETAGROP calculation was performed in which the formation constants for all four species were co-varied on the whole data material, $1 \leq C/B \leq 20$ and $-\log h \leq 7.8$. This calculation ended at $\sigma(H) = 0.04$mM, and the resulting $\log \beta_{p,q,r}$ values are given in Table 1.

The H^+-maltol system. For the evaluation of the binary system, data derived from 6 titrations with 98 experimental points within the limits $0.002 \leq C \leq 0.020$M and $-\log h \leq 9.4$ were used. The result of a LETAGROP calculation on these data ended at $\sigma(H) = 0.02$mM with $\log(\beta_{-101} \pm 3\sigma) = -8.381 \pm 0.002$.

The H^+-Al^{3+}-maltol system. The data used for the evaluation of the ternary system were based on 10 titrations with 174 experimental points within the limits $0.0005 \leq B \leq 0.003$M; $0.001 \leq C \leq 0.005$M and $-\log h \leq 7$.

The Bjerrum plot (Fig. 3) shows that the complexation behaviour in this system is quite similar to that in the aluminium-kojic acid system described above. Therefore, the mathematical evaluation of data followed the same protocol,

Table 1. Binary and ternary complexes in the H^+-Al^{3+}-kojic acid/maltol (HL) systems. The equilibrium constants (β_{pqr}) are defined according to the reaction $pH^+ + qAl^{3+} + rHL \rightleftarrows H_pAl_q(HL)_r^{p+3q}$.

H^+-Al^{3+}-kojic acid		Proposed formula	H^+-Al^{3+}-maltol	
p,q,r	$\log(\beta_{pqr} \pm 3\sigma)$		*p,q,r*	$\log(\beta_{pqr} \pm 3\sigma)$
(−1,0,1)	−7.609±0.002	L^-	(−1,0,1)	−8.381±0.002
(−1,1,1)	−0.371±0.011	AlL^{2+}	(−1,1,1)	−0.130±0.006
(−2,1,2)	−1.499±0.013	AlL_2^+	(−2,1,2)	−0.956±0.007
(−3,1,3)	−3.564±0.021	AlL_3	(−3,1,3)	−2.669±0.014
(−4,2,2)	−7.656±0.070	$Al_2(OH)_2L_2^{2+}$	(−4,2,2)	−7.203±0.024

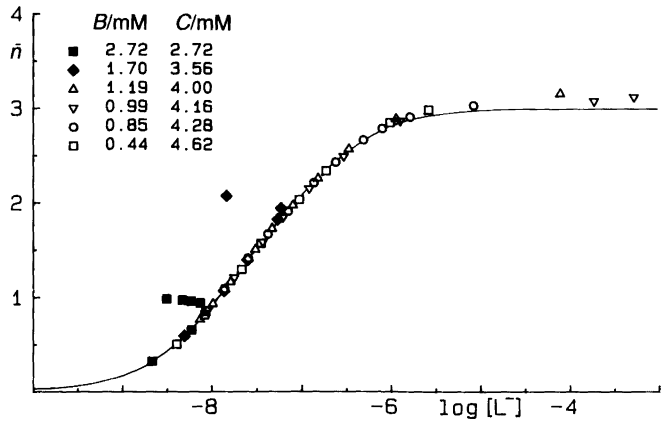


Fig. 3. Part of the experimental data in the $H^+-Al^{3+}-$maltol system plotted as curves $\bar{n}(\log[L^-])$. The full curve was calculated with $\log\beta_{-1,1,1}$, $\log\beta_{-2,1,2}$ and $\log\beta_{-3,1,3}$ according to Table 1.

ing with a determination of binary AlL_n^{3-n} constants, followed by a *pqr* analysis on data for low *C*/*B* ratios and ending with a final covariation of all constants on the whole data set.

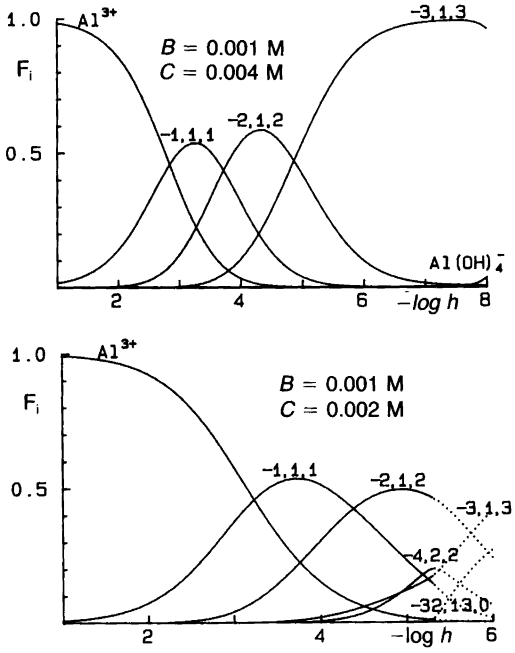


Fig. 4. Distribution diagrams $F_i(-\log h)_{B,C}$ in the system $H^+-Al^{3+}-$kojic acid. F_i is defined as the ratio of aluminium(III) in a given species to total aluminium (III). The calculations were performed using the computer program SOLGASWATER[31] with equilibrium constants given in Table 1. The broken lines denote a range where no measurements were performed.

In these calculations, it turned out that data could be explained with the same speciation scheme as in the Al-kojic acid system, i.e. with species AlL^{2+}, AlL_2^+, AlL_3^0 and $H_{-4}Al_2(HL)_2^{2+}$. In this system the calculations ended at $\sigma(H) = 0.01$mM and with equilibrium constants as given in Table 1.

The composition and stability of the minor di-

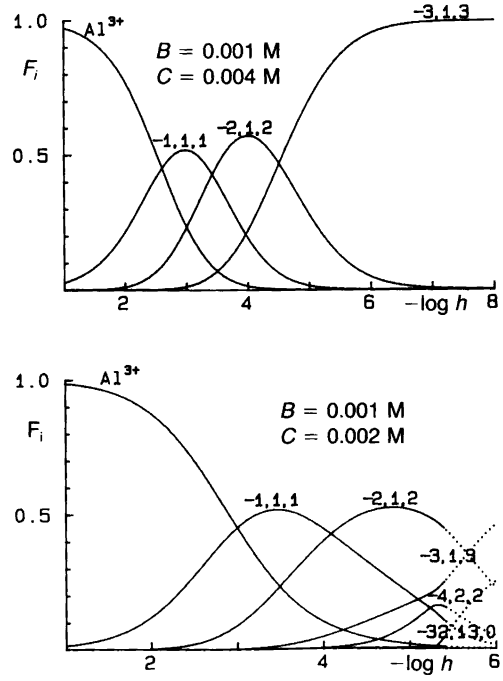


Fig. 5. Distribution diagrams $F_i(-\log h)_{B,C}$ in the system $H^+-Al^{3+}-$maltol.

nuclear species was finally validated through a titration at much higher total concentrations, $B = C = 0.030$M, with $-\log h < 4.1$. The data were fully consistent with the proposed model.

In order to visualize the amounts of different species in the two systems, the computer program SOLGASWATER[31] which comprises plotting procedures was used to calculate some distribution diagrams. These are presented in Figs. 4 and 5.

Discussion

Speciation and equilibria. The present study has confirmed that Al^{3+} forms a series of highly stable AlL_n^{3-n} complexes (n = 1–3) with the 3-hydroxy-4-pyronate group. The stabilities of these species are much higher than expected from simple monodentate coordination of hydroxy groups. This, together with the fact that the fully coordinated Al species is AlL_3^0, points to the 3-hydroxy-4-pyronate ligands acting as monobasic, bidentate ligands with the keto oxygen double bond being delocalized in the complexes formed.

A comparison between the two systems investigated reveals that the acidity of maltol (pK_a = 8.38) is significantly lower than that of kojic acid (pK_a = 7.61). This is a difference caused by the inductive effects of the methyl group in maltol. Due to the low electronegativity of this group, there will be less electron withdrawal from the -OH bond, and consequently a higher pK will result.

Another effect of the higher electron density in the maltol–OH bond than in the kojic acid–OH bond can be seen in the stability of the Al species formed. Thus, the stepwise constants for maltol ($\log K_1$ = 8.25, $\log K_2$ = 7.56 and $\log K_3$ = 6.67) are approximately one order of magnitude higher than those for kojic acid ($\log K_1$ = 7.24, $\log K_2$ = 6.48 and $\log K_3$ = 5.54).

Thus, when the complexation strength of maltol is compared to that of kojic acid at a given $-\log h$ value (cf. Figs. 4 and 5), the effect of the methyl group is to a large extent levelled off. However, as the increase in complexation strength ($\Delta\log K_n \geq 1$) does exceed the decrease in acidity ($\Delta pK_a = 0.77$), a small net increase will result. This is also illustrated in the figures, where it can be noted that the curves are somewhat shifted to lower $-\log h$ values in the maltol system and also that the tris complex of maltol is more stable towards hydrolysis (i.e. formation of $Al(OH)_4^-$) than the tris complex of kojic acid. Thus, maltol is a somewhat stronger complex-former for Al^{3+} than kojic acid.

The present study has also provided evidence for the existence of a dinuclear species, $H_{-4}Al_2(HL)_2^{2+}$, in both systems. As the maximum number of ionizable protons in the ligands is exceeded in this species, it must be a mixed hydroxo complex. As seen from Figs. 4 and 5, significant amounts of this species occurs only in near-neutral solutions ($-\log h \geq 4$) containing low ligand excesses ($C/B < 3$), and it may be tentatively assigned as a dihydroxo-bridged species, $Al_2(OH)_2L_2^{2+}$. Also in this species, the maltol anions are bound one order of magnitude more strongly than the kojic acid anions ($2Al^{3+} + 2L^- + 2H_2O \rightleftharpoons Al_2(OH)_2L_2^{2+} + 2H^+$; $\log K$ (maltol) = 9.56, $\log K$ (kojic acid) = 7.56).

Modelling calculations. The widespread occurrence of aluminium in the earth's crust, in combination with the low solubility of secondary formed hydroxo phases, implies that the behaviour of Al(III) in natural waters must be modelled with reference to a solubility-regulating solid. The presence of a complex-forming substance will, under such conditions, raise the total solu-

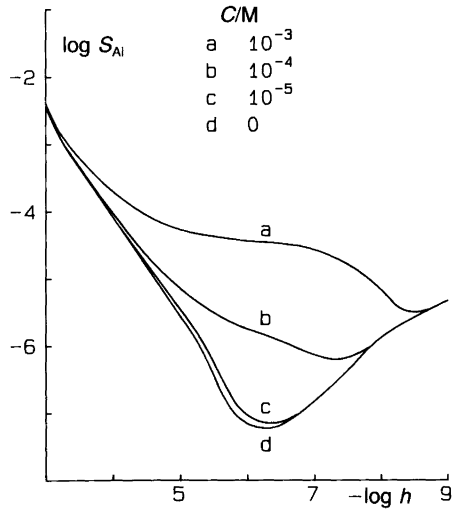


Fig. 6. The solubility (with respect to Al) of kaolinite expressed as $\log S_{Al}$ vs. $-\log h$ for different total concentrations C of kojic acid.

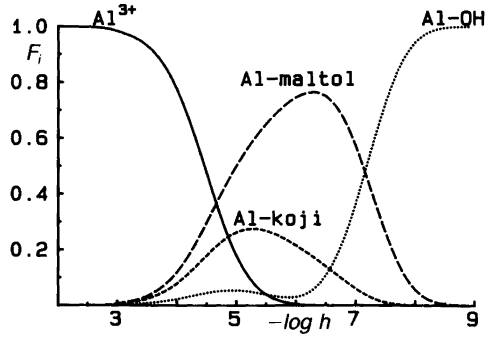


Fig. 7. Diagram showing the sum of distribution coefficients, ΣF_i, for Al-kojic acid complexes (Al-koji), Al-maltol complexes (Al-maltol), Al hydrolysis (Al-OH) as well as $F_{Al^{3+}}$. The total concentrations of kojic acid and maltol are both equal to 30 μM, and kaolinite is the regulating solid phase.

bility of the solid phase but leave concentrations of Al^{3+} and hydrolytic species unaffected.

Fig. 6 shows the calculated potential ability of kojic acid to raise the solubility of the clay mineral kaolinite [$Al_2(OH)_4Si_2O_5$; $\log K_{so} = 7.63$[32]] at various ligand concentrations. From this figure it can be concluded that the presence of 3-hydroxy-4-pyronates could be expected to cause a solubilization of kaolinite in the range $4 \leq -\log h \leq 8$, i.e. the range applying in the case of most natural waters.

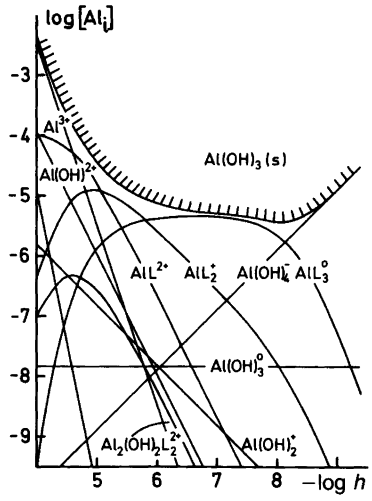


Fig. 8. Logarithmic diagram for the H^+-Al^{3+}-maltol system at $C = 10^{-4}$M. The aqueous aluminium concentration is regulated by crystalline gibbsite.

From Figs. 4 and 5 it was concluded that maltol forms somewhat stronger complexes with Al^{3+} than kojic acid. This is shown clearly in Fig. 7, which is the result of a calculation in which kaolinite has been equilibrated with equal amounts (30 μM) of kojic acid and maltol. This calculation also points out the importance of taking hydrolysis reactions into consideration.

In human bio-uptake considerations, the charge of the various species formed is of vital importance, since neutral complexes of low enough molecular weight (≤650) can cross cell membranes via a passive diffusion mechanism.[33] Fig. 8 shows the results of an equilibrium speciation calculation on the system $H^+-Al^{3+}-$maltol in which 10^{-4}M maltol has been equilibrated with crystalline gibbsite [$Al(OH)_3$; $\log K_{so} = 9.6$[34]]. This calculation shows that even small amounts of maltol are able to solubilize significant amounts of aluminium from the stable gibbsite, and that, significantly, the dominant species under neutral conditions is the uncharged neurotoxic tris complex. Thus, it can be concluded that maltol may cause maximum bioavailability of aluminium in the lower regions of the gastrointestinal tract.

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