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Complexation of Al(III) with Ampicillin and Amoxicillin

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Abstract

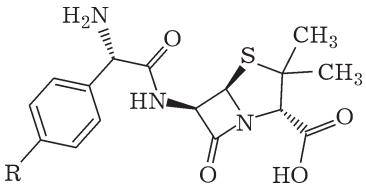
The interaction of Al(III) with ampicillin (Amp^-) and amoxicillin (Axn^-) in an aqueous solution at 25 °C and the ionic strength of 0.1 (KNO_3) was studied by means of pH-metric titration. The formation of complexes $AlAmp^{2+}$ (log β = 5.11±0.06), $AlHAmp^{3+}$ (log β = 9.63±0.07), $AlAxn^{2+}$ (log β = 4.64±0.09), $AlHAxn^{3+}$(log β = 7.95±0.09) was detected.

Key words: ampicillin, amoxicillin, aluminum complexes, antibiotic complexes

INTRODUCTION

In [1] we presented results of the study of complexation of Al^{3+} ions with two penicillins of the acidic type, viz. benzylpenicillin and carbenicillin. Amphoteric penicillins containing amino groups, as a rule, form more stable metal complexes than acidic ones [2]. And although Al^{3+} ion is not inclined to the formation of coordination bonds with amino groups, it was of interest to study Al^{3+} complexation with two most widely used amphoteric penicillins: ampicillin (HAmp) and amoxicillin (HAxn).

Due to the presence of the carboxyl-, amide and amino- groups these compounds are similar to dipeptides in terms of acid-base and ligand properties. In an aqueous solution depending on the pH value they can exist as the cation (H_2L^+), zwitter-ion ($HL^±$) or anion (L^-) [3], where L^- = Amp^- and Axn^-.



R = H – ampicillin, R = OH – amoxicillin

EXPERIMENTAL

We used ampicillin trihydrate $HAmp \cdot 3H_2O$ (Ferain JSC, Moscow) and amoxicillin trihydrate $HAmp \cdot 3H_2O$ (Hemofarm, Serbia). The procedures of the preparation and standardization of initial solutions, measurement of the pH value, calculation of equilibrium constants and computer modelling of the structure of complexes are analogous to those described in [1].

Solutions for the study of the complexation were prepared as following: 0.5 g of the antibiotic in 50 mL of 0.1 mol/L of KNO_3 solution was placed in a volumetric flask of 500 mL: the antibiotic was dissolved, the equivalent volume of 0.1 mol/L of HNO_3 solution to transfer the antibiotic into the form of the cation (H_2L^+) was added and brought up to the mark with 0.1 mol/L of KNO_3 solution.

The solution prepared in such a way in the amount of 100 mL was placed in a thermostatic cell at 25 °C, 5 mL of $Al(NO_3)_3$ solution was added and titrated with 0.0435 mol/L so-

lution of NaOH. The concentration of Al (III) in the solution titrated was $9 \cdot 10^{-4}$ mol/L, the one of the antibiotic was $2.4 \cdot 10^{-3}$ mol/L.

RESULTS AND DISCUSSION

Experimental and calculated curves of the titration of solutions containing $Al(NO_3)_3$ and H_2Amp^+ or H_2Axn^+ are presented in Fig. 1. In the calculation of mathematical models of equilibriums in the studied systems, the equilibriums of the acidic dissociation of antibiotics, hydrolysis of Al^{3+} ions and formation of mono- (Al^{2+}) and biligand (AlL^{2+}) complexes, as well as protonated ($AlHL^{3+}$) complexes and hydroxo-complexes ($Al(OH)L^+$) are taken into consideration. In this case hydrolysis constants of Al^{3+} [1] and constants of the protonation of Amp^- and Axn^-: $\log \beta(HAmp) = 7.28$, $\log \beta(H_2Amp^+) = 10.32$, $\log \beta(HAxn) = 7.66$, $\log \beta(H_2Axn^+) = 10.76$ [2] identified by us earlier are used. The introduction of the constants of Al^{3+} hydrolysis determined on the same device under the same experimental conditions into the calculation instead of the literature values allowed us to obtain more precise data in comparison with those obtained earlier [4] regarding the complexation in systems Al(III)–Amp and Al(III)–Axn.

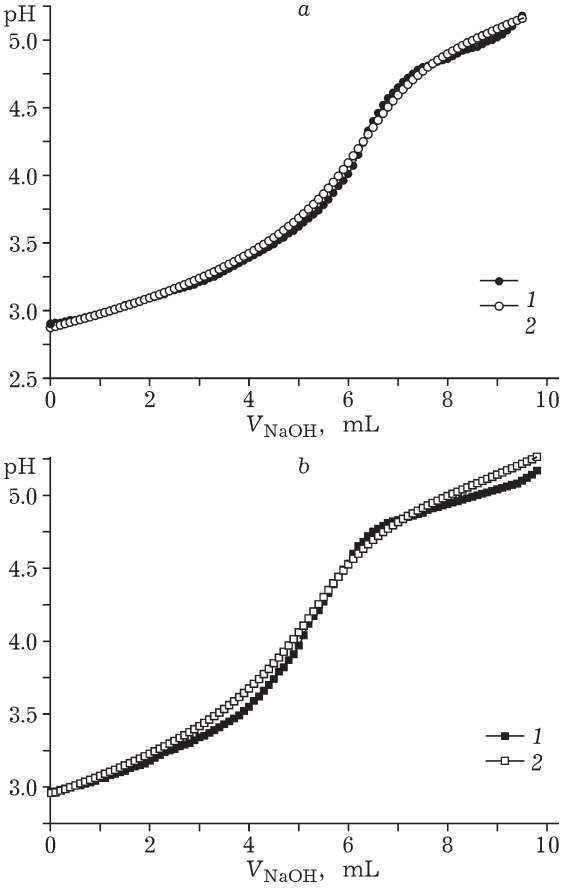


Fig. 1. Curves of pH-metric titration of H_2Amp^+ solution (*a*) and H_2Axn^+ (*b*) in the presence of Al^{3+} ions: *1* – experimental, *2* – calculated.

As a result of the calculations, the formation of monoligand medium and protonated complexes $AlAmp^{2+}$ ($\log \beta = 5.11 \pm 0.06$), $AlHAmp^{3+}$ ($\log \beta = 9.63 \pm 0.07$), $AlAxn^{2+}$ ($\log \beta = 4.64 \pm 0.09$), $AlHAxn^{3+}$ ($\log \beta = 7.95 \pm 0.09$) was established. The program estimates forms $Al(OH)L^+$ and AlL_2^+ as insignificant and excludes them. For the system Al^{3+}–Amp^- SS = 0.18, for Al^{3+}–Axn^- SS = 0.29 for curves of 96 points. Analogous results: the formation of medium complexes and complexes protonated at the amino-group, were obtained earlier during the investigation of the complexation of Al(III) by dipeptides [5] which ampicillin and amoxicillin have structural similarities with. As it was expected, Al(III) complexes with amphoteric antibiotic anions proved to be somewhat more stable, in comparison with $AlBzp^{2+}$ ($\log \beta = 3.6$) and $AlCarb^+$ ($\log \beta = 4.10$) investigated earlier.

Results of the computer modelling of the structure of complexes AlL^{2+} and $AlHL^{3+}$ show that Amp^- and Axn^- anions are coordinated analogously to Bzp^- anion as tridentate ligands through oxygen atoms of the carboxylate, β-lactam and amide groups (Fig. 2, *a*). Internuclear distances Al–O for $AlAmp^{2+}$ are 0.1695 (COO^-), 0.1851 (β-lactam) and 0.1805 nm (amide); for $AlAxn^{2+}$ they are 0.1724 (COO^-), 0.1895 (β-lactam) and 0.1947 nm (amide). Therefore, the length of Al–O bonds is greater than in the model $AlAmp^{2+}$, consequently, the strengthof bonds is smaller. This is consistent with a lower stability of the complex $AlAxn^{2+}$ determined experimentally, in comparison with $AlAmp^{2+}$. Zwitter-ions $HAmp^{\pm}$ and $HAxn^{\pm}$ are coordinated bidentately through the carboxylate group (see Fig. 2, *b*), internuclear distances are almost the same for $AlHAmp^{3+}$ and $AlHAxn^{3+}$ and equal to 0.1763 and 0.1771 nm, respectively.

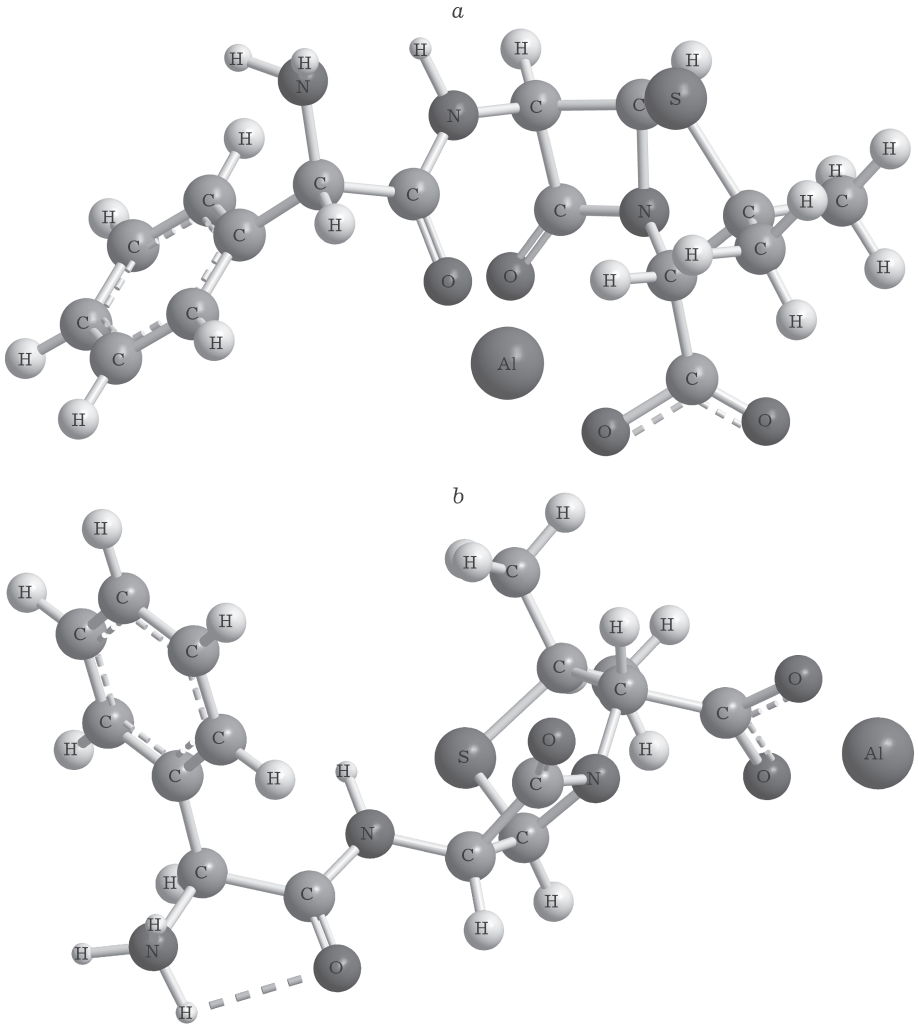


Fig. 2. Computer model of complexes $AlAmp^{2+}$ (*a*) and $AlHAmp^{3+}$ (*b*). The dashed line indicates the intramolecular hydrogen bond.

CONCLUSION

The study of the complexation of Al(III) with benzylpenicillin, carbenicillin and amoxicillin shows that these antibiotics used widely in the medical practice can bind Al^{3+} ions into stable soluble complexes and thus contribute to the removal of the excess of aluminum from an organism.

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