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O.A. Golovanova, I.A. Tomashevsky

F.M. Dostoevsky Omsk State University, Russia
(E-mail: ivan_tomashevsky@mail.ru)

Determination of the nature of the interaction of calcium ions with amino acids by potentiometric titration

In work on the basis of potentiometric titration, the features of interaction of Ca^{2+} calcium ions with amino acids (AC), which are involved in biochemical processes in the human body, are established. The regularities of the complexes formed in the «Ca^{2+}-AC» system are studied theoretically by the example of mixtures of calcium nitrate with isoleucine (Ile), arginine (Arg), aspartic acid (Asn), glycine (Gly), alanine (Ala). The conditions for titration are chosen, under which the destruction of the complex occurs. By results, semi-quantitative characteristics of the interaction of Ca^{2+} and the studied AC were established. It was shown that the stability of the complexes increases with increasing number of carboxyl groups –COOH and nitrogen-containing groups in the AC molecule (especially NH_2 groups in the α-position), and with the increase in the length of the carbon skeleton of the molecule and the appearance of bulky substituents — decreases. Also, on the base of insertion of the new criteria δ are established comparative rates of lability of complexes. According to their lability, complexes of Ca^{2+} with these amino acids are located in the next order: δ (Ca^{2+} – Asp) < δ (Ca^{2+} – Ile) < δ (Ca^{2+} – Ala) < δ (Ca^{2+} – Arg) < δ (Ca^{2+} – Gly).

Keywords: complexation, amino acids, bioorganic ligands, potentiometric titration, modeling, stability constants, calcuim, lability.

Nowadays, the trend that matches with the studying of the principles of processes which are happening in the alive systems, becomes one of the most leading in the current scientific reaserches. It's exactly, because actual negative factors of the technosphere (social risks, conflicts and stresses, impact of noise, vibrations, malnutrition, ecological risks, manufacture hazards, physical inactivity etc.) could disengage complex system of organic and inorganic substances that exist in the human body in a certain balance [1–7]. At the same time, the growth of the number of diseases which are linked with the formation of, for example, pathogenic organomineral aggregates (POA) in the human body is 0,5–5,5 % per year [1; 8–10].

The key role in the processes that are characteristic for the human body is allotted for the calcium ions. In the ionic forms, the content of calcium in the human body is nearly 1 %. It takes fifth place by the abundance in vivo among chemical elements after carbon, nitrogen, oxygen and hydrogen. In the human and mammalian bodies 95 % of calcium is contained in the solid tissues: bones and tooth, where he stands in the form of fluorapatite $Ca_5(PO_4)_3F$ and hydroxylapatite $Ca_5(PO_4)_3OH$; in the birds and mollusk organism prevailing type of form is calcuim carbonate. On the surface of the blood vessel wall and arteries calcium can be found in the form of calcium carbonate or in the complex with the cholesterol, and in the kidneys — in the forms of oxalate or urates (salts of uric acids) [11]. Calcium ion is primary component not only in quantitative, but even in functional relation. He takes part in the processes of the transferring of nerve impulses, provides equilibrium between processes of excitation and stopping in the cortex, participates in the regulation of contractility of skeletal muscles and heart muscle, takes influence on acid-base equilibrium in organism and on activity of some enzimes [1; 6–10].

It must be noted that in the human body Ca^{2+} stands in the continuous interaction between thw organic and inorganic constitutions of biofluids, including the amino acids. At the time of impaction of negative factors which are highlighted before, interaction between the ions of calcium and amino acids could be disrupted. In particular, researches [1, 8–10, 12–18 etc.] confirm that POA have organic constituents in their own composition. Authors [19] in their work try to find out possible conditions of dissolution of amino acids which were previously adsorbed on biological substrate. Also, interaction between Ca^{2+} with the biological enzimes, which are accelerate processes of reaction of calcium ions with the organic constituents of the human body, was researched on the molecular level [20]. We have understanding of behavior of amino acids in the solution with the organic salts of sodium, potassium and calcium [21]. However, to prevent human body from the possible repercussions which are related with the pathogenic mineral aggregation and another diseases, disturbance of musculoskeletal system, fragility of bones, weakening of immunity and increased fatigue of organism, on the first stage we should now semi-quantitative and quantitative characteristics of interaction of components which are taking part in the functioning of the vital activity, in particular, between such a components as biogenic calcium-ion and amino acid.

Because most of the POA are introduced by the salts of calcium, a lot of investigators are noting that just specificity of organic constituent, partially, Ca^{2+} and amino acid, mostly controls the process of phase formation in the human body [9, 10, 12–18 etc.]. But, nowadays there is no unified theory which could explain the nature of interaction between organic and inorganic constituents of POA.

According to this, the aim of present work is development of methodology for the establishment of the behavior of the interaction between Ca^{2+} and amino acid which are take part in the metabolism. Also, very important thing is to find out pattern between the structure of the majority of amino acids and their specific interaction with the calcium ions.

Experimental part

General issues. Quantitative criteria of the interaction of these components is overall stability constant which can be calculated by the following formula:

$$M + nL \rightleftarrows [ML_n];$$

$$\beta_n = \frac{[ML_n]}{[M][L]^n}, \quad (1)$$

where β — overall stability constant of all complexes in all existing forms; $[ML_n]$ — equilibrium concentration of the formed complex of calcium and amino acid; $[M]$ — equilibrium concentration of free metal in the ionic form in the solution; $[L]^n$ — equilibrium concentration of free ligand in the solution.

To determine its value, in the most of the cases are used spectrophotometric, ion-exchange and polarographic methods [6, 22]. But, as it was said before, the object of analysis is difficult and little-learned system, and format of interaction «Ca^{2+} – Amino acid» is not obvious as in the most cases of complexion. There must be created methods which would be sensitive, precise, quick and selective for another components of the system. Possible way of such a evaluating could become using of potentiometric titration of mixes of Ca^{2+} and amino acids by the solution of sodium hydroxide NaOH with the following decoding of experimental data.

Materials and methods. In the present study were used aminoacetic acid (glycine, Gly), aminopropanoic acid (alanine, Ala), 2-amino-3-carbamoylpropanoic acid (aspartic acid, Asn), 2-amino-5-(diamino-methylideneamino) pentanoic acid (arginine, Arg), 2-amino-3-methylpentanoic acid (isoleucine, Ile) (all are «chemically pure»), their main characteristics are introduces in the Table 1, calcium chloride $CaCl_2$ («ch.p.»). Researchment of interaction between Ca^{2+} and amino acid was conducted at the $T = 298$ K by the potentiometric titration with the ion-selective electrode *ЭЛИС-121Ca*, the possibility of its applying as a selective for calcium ions is pointed in the work [23].

Silver/silver chloride electrode *ЭСр-10103* in this work was used as a reference electrode. The measuring electrode was Ionomer *И-160-МИ*, whose precision of measuring e.m.f. is ± 0.1 mV. Precision of potentiometric titration as a method is enough (overall error of determination is 0.5–1.0 %) to define nature of interaction of amino acids and calcium ions [24].

Before and after every series of titration potentiometric unit was calibrated by dint of the standard aqua solutions of calcium nitrate ($C_{Ca(NO_3)_2} = 10^{-2}$, 10^{-3}, 10^{-4} mole per liter) under the fixed value of ionic strength $I = 0.5$ mole per litre (KNO_3 was an ionic medium).

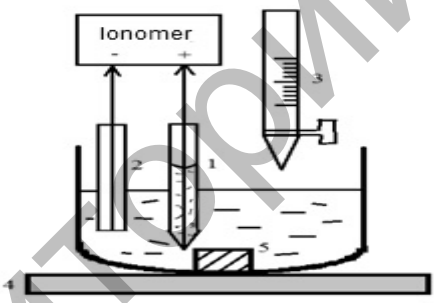
The stock solutions of amino acids and $CaCl_2$ were prepared from samples of solid substances, which were selected with the precision to 10^{-4} g; the samples were completely transferred in the volumetric flask and were dissolved, after that flask was filled by the distill water to the label. The mass of the samples were determined with a view to reach concentrations $C_{\text{amino acid}} = 10^{-2}$ mole per litre, $C_{Ca(NO_3)_2} = 10^{-3}$ mole per litre — it's optimum concentrations of salt and amino acid under which titration jumps have more obvious form. These values of concentrations were established experimentally by the authors.

In the case when solubility of amino acid in water is limited, the solution, before filling to the label, was heated till the full dissolution of precipitation.

During the titration, aliquot with the $V = 10.0$ ml of stock solutions of amino acid and $Ca(NO_3)_2$ consistently were placed in the volumetric flask with the volume $V = 100.0$ ml, then flask was filled by the distill water to the label. After that, content of the flask undergo mixing by dint of the apparatus of mixing of fluids during the 30 minutes. Finally, from the content of the flask was selected precise volume (20.0 ml) of process solution and was transferred in pure beaker. Content of the beaker was acidified to pH = 3 by dint of glass electrode.

Then, in the content of the beaker was immersed connected to ionomer И-160-МИ electrodes: calcium-selective electrode, reference electrode and temperature sensor. The first clean measure of e.m.f. of the solution was established in the range of ±0.1 mV during 3 minutes. The titration was conducted with the 0.5 ml-step from the burette, as titrant was used fresh solution of 0.10 M NaOH (its was standardized by the solution of HCl with the acid-base indicator phenolphthalein), the analytical signal was the value of e.m.f. in mV. The value of this criteria before every measure was established during 45 seconds. Titration was continued before the moment of starting of precipitation of $Ca(OH)_2$. The titration was conducted under intensive mix by dint of magnetic stirrer.

The principle scheme of potentiometric unit is depicted on Figure 1.



1 — Silver/silver chloride electrode; *2* — Glass electrode; *3* — Burette; *4* — Magnetic stirrer; *5* — Magnet

Figure 1. The principal scheme of potentiometric unit for titration aims

It was carried out 3 duplicating titrations, the values of e.m.f. were averaged [25]. Every amino acid was titrated separately from the other amino acids.

Results and discussion

According to these methodology, we have received potentiometric titration curves for highlighted amino acids (Table 1). To find out the form of amino acid in stock solution at constant pH, we have drawn ion percentage diagrams of studied amino acid, where along the abscissa is pointed pH, along the ordinate — shares of forms of amino acids (Table 2, Fig. 2).

For the aspartic acid ion diagram is drawn at the Figure 3, for the arginine — at the Figure 4. As values of $pKa_{(acid.)}$, except arginine, are standing in the range to pH < 3, amino acids in the aqua solutions before titration will stay predominantly in the form of zwitter-ion:

$$R - CH_2 - NH_2 - COOH \rightleftarrows R - CH_2 - NH_3^+ - COO^- \quad (2)$$

Arginine, besides α-NH_3^+ group, has in its composition guanidine group at the δ-carbon atom, and that's why arginine will stay predominantly in the cationic form at this pH in the aqua solutions [25]:

$$R^+ - CH_2 - NH_2 - COOH \rightleftarrows R^+ - CH_2 - NH_3^+ - COO^- \quad (3)$$

Table 1

The most common characteristics of amino acids, including the dissociation constants and the isoelectrical points

AA	Reduction	Formule	Structure
Glycine	Gly	$C_2H_5NO_2$	$H_2N–CH_2–COOH$
Alanine	Ala	$C_3H_7NO_2$	$CH_3–CH(NH_2)–COOH$
Aspartic acid	Asp	$C_4H_7NO_4$	$HOOC–CH_2–CH(NH_2)–COOH$
Isoleucine	Ile	$C_6H_{13}NO_2$	$CH_3–CH_2–CH(CH_3)–CH(NH_2)–COOH$
Arginine	Arg	$C_6H_{15}N_4O_2$	$H_2N–C(=NH)–NH–(CH_2)_3–CH(NH_2)–COOH$

Table 2

δ-values for all amino acids

Amino acid	δ
Glycine	6.3
Alanine	3.1
Aspartic acid	2.1
Isoleucine	2.2
Arginine	5.3

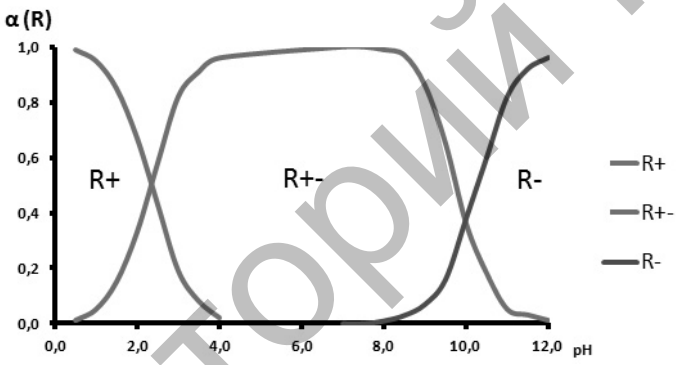


Figure 2. Ion diagram of forms at the different pH for amino acids, which don't have ionized links in the side groups (Isoleucine, Alanin, Glycine)

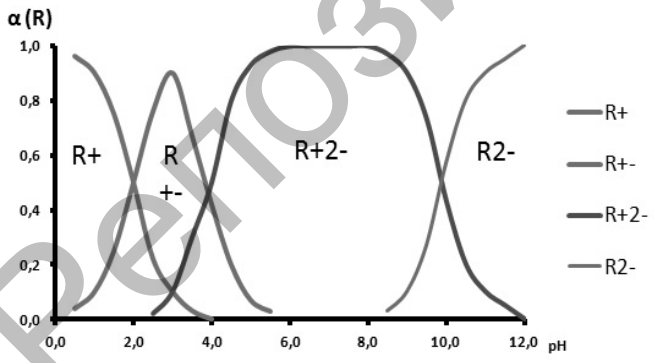


Figure 3. Ion diagram of forms of «acidic» amino acids

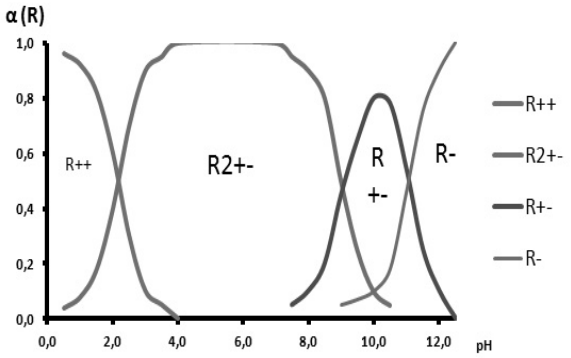


Figure 4. Ion diagram of forms of «basic» amino acids

To understand basic regularities of complexion of Ca^{2+} with amino acids, it will be needed to classify obtained curves into smaller groups which will be created by virtue of the structure of studied amino acids. Based on the experience of later researches [1, 8, 26, 27], we can predict that system in the system are formed complexes with the ratio Ca^{2+}:Amino acid — 1:1.

On the Figure 5 are introduced titration curves of $Ca(NO_3)_2$ and first group of amino acids (Isoleucine, Arginine, Aspartic Acid) by the aqua solution of sodium hydroxide.

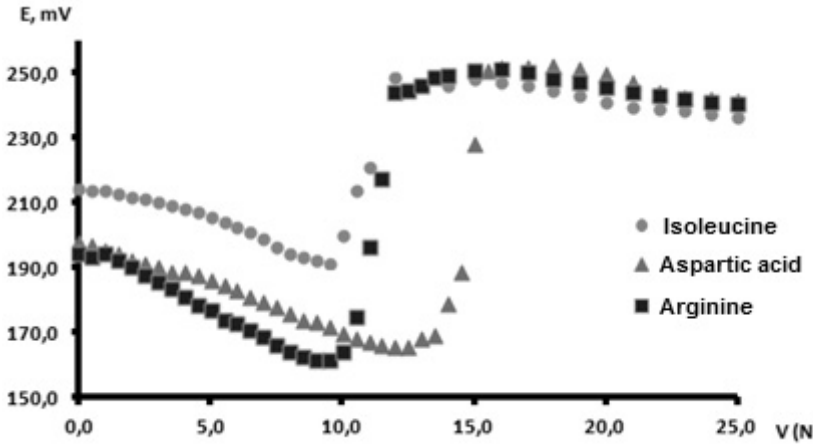


Figure 5. Potentiometric titration curves of calcium nitrate ($C_{Ca(NO_3)_2} = 10^{-3}$ mole per liter) and amino acids ($C_{\text{amino acid}} = 10^{-2}$ mole per liter)

Proceeding the form of curves, it could be predicted, that in system are flowing the following reactions:

On the first step, where is happening the mixing of solutions of $Ca(NO_3)_2$ with the solutions of the amino acids, usually form complexes, where Ca^{2+} perform a role of complexing agent and amino acids are playing a role of ligands (4, 5):

$$R - CH_2 - NH_3^+ - COO^- = L^{\pm};\ Ca^{2+} + L^{\pm} \rightleftarrows [CaL^{\pm}]^{2+} \quad (4)$$

For arginine

$$R^+ - CH_2 - NH_3^+ - COO^- = L^{\pm+};\ Ca^{2+} + L^{\pm+} \rightleftarrows [CaL^{\pm+}]^{2+} \quad (5)$$

In the start of titration adding of titrant causes small decrease of e.m.f. It is all because of the increasing of ionic strength, which reduces acivity of free ions of calcium. At the same time $[CaL^{\pm}]^{2+}$ and $[CaL^{\pm+}]^{2+}$ are staying stable.

At a certain moment, after another adding of portion of titrant, there is a sharp increase of e.m.f. It can be corresponded to the increase of concentration of unbounded calcium ions, which are releasing in the solution during the destruction of complex:

$$[CaL^{\pm}]^{2+} \rightleftarrows Ca^{2+} + L^{\pm} \quad (6)$$

For the arginine:

$$[CaL^{\pm+}]^{2+} \rightleftarrows Ca^{2+} + L^{\pm+} \quad (7)$$

It could be expected that in the equivalence point (eq.p.) 50 % of complex molecules are stable, 50 % — are destroyed, so, they have formation function $\bar{n} = 0.5$ [28].

After full destruction of the complex, e.m.f. starts to undergo small decrease again because of the increasing of ionic strength, which reduces acivity of free ions of calcium.

At a certain moment, pH of the solution increases to the 10–10.5, which leads to precipitation of insoluble calcium hydroxide (pSP = 5.26):

$$Ca^{2+} + 2OH^- \rightarrow Ca(OH)_2 \quad (8)$$

As in the eq.p. 50 % of molecules of previously formed complexes are destroying, volume of sodium hydroxide solution which was wasted on the titration to attain eq.p. can be some sort of semi-quantitative criteria of interaction between calcium ions and every of the amino acids. So, the more volume we have wasted, the more we need this to destroy complex and more stable the complex is. To explain the obtained results, we should return to the table 1. It should be noted that structural formulas of three amino acids above are differ between each other by: a) the number of carbon atoms in the structural formula; b) the nature of functional groups; c) location of the functional groups.

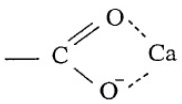
The molecule of isoleucine has 5 atoms of carbon in the main chain, contains one carboxyl (–COOH) group, one aminogroup ($–NH_2$), at α-position one methyl ($CH_3–$) group; the molecule of arginine has the same structure, but instead of methyl group, on another from carboxyl group ending of molecule is located

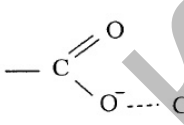
guanidine group NH_2–C(NH)–NH_2. Molecule of aspartic acid has smaller number of carbon atoms (4) in the structure and it doesn't have another group as previous two amino acids, but it contains two –COOH groups and one –NH_2 group at the same time.

On the Figure 5 seems obvious the fact that eq.p., if look on it from the side of volume of wasted titrant, eq.p. of the amino acids line up in the following row: $V_{Ile} < V_{Arg} < V_{Asn}$, what is more, V_{Ile} and V_{Arg} are slightly different from each other, and V_{Asn} is more different from previous volumes row.

According to the investigation of K.B. Yatsimirsky [29], calcium ions concerns to first group of cations for which complexing is carried out, predominantly, on account of oxygen atoms — –COOH-group of amino acid. Impaction of donor atoms of nitrogen for creating of coordinating bonds with calcium (II) is possible, although insignificant.

As values of volumes of sodium hydroxide, which are wasted on titration of complexes of Ca^{2+} with isoleucine and arginine, are approximately equal, it should be predicted that stability constants of present complexes have the similar values. At the same time, eq. p. on the titration curve of $Ca(NO_3)_2$ and aspartic acid is located far away from the origin than for first two amino acids, moreover, for the molecule of aspartic acid two –COOH groups at the same time. As it said before, coordination of hard ions of metals in reactions of complexing with the amino acids is carried out on account of oxygen atoms of carboxyl groups. Also, –COOH-group there is bidentate and forms a cyclic or bridge structures [30]:





Because the molecule have two carboxyl groups, it considered to be more strong ligand, and complex of Ca^{2+} with the aspartic acid is more stable than with previous amino acid, which is consisted with our data. In the second group of amino acids (Isoleucine, Alanine, Glycine) are observing next tendencies, which are submitted on the Figure 6.

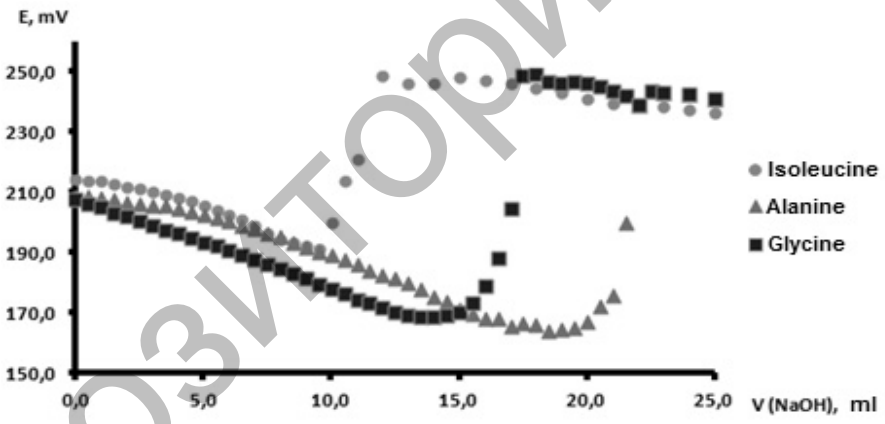


Figure 6. Potentiometric titration curves of calcium nitrate
($C_{Ca(NO_3)_2} = 10^{-3}$ mole per liter) and amino acids ($C_{\text{amino acid}} = 10^{-2}$ mole per liter)

All stages of the curves are the same as first group of amino acids. It is seen that eq. p. of titration curve of mix of Ca^{2+} and isoleucine is located significantly closer to the origin than for mixes of Ca^{2+} with alanine and glycine. In contrast to isoleucine, molecules of alanine and glycine are consisted from smaller number of atoms of carbon and they don't have big CH_3-alternates, which can come the steric obstacles for transferring of free s-orbitales of complexing agent Ca^{2+} to the electronic pairs of ligand. That's why complexes of Ca^{2+} with amino acids AK without any steric obstacles are more stable than those who have in its composition big alternates and more atoms of carbon in the main chain. Besides the investigation of titration curves of complexes, the experimental data were processed mathematically and we have obtained first and second derivatives of curves titration and derivative curves, which were described according to the Gran method.

In the Gran method eq.p. usually determines on graph in the coordinates: $V/\Delta E - V$, where ΔV is the step of titiration, ΔE — difference of the utmost points of e.m.f.; V — the volume of added titrant. Before eq. p. and after it curve of Gran is linear. Eq.p. serves as the point of the intersection of these lines. Advantages

and facilities of Gran method are especially obvious in the time of analysis of dilute solutions; they allow to obtain eq.p. with the require precise because of the linearity of the graph and in the cases, when curve isn't have a typical form [31].

As our experimental data are different from the classical potentionmetric titration curves, the Gran method was modified by the changing of criteria of axis of ordinates — there were a difference between the current e.m.f. value and the volume of the spent titrant and their values before the start of titration, respectively. This type of processing allows to avoid the misinterpretation of curves from the collateral processes, it's very convenient for analysis. For example, on the Figure 7 are illustrated differentiated titration curves for mixtures of $Ca(NO_3)_2$ with isoleucine and arginine.

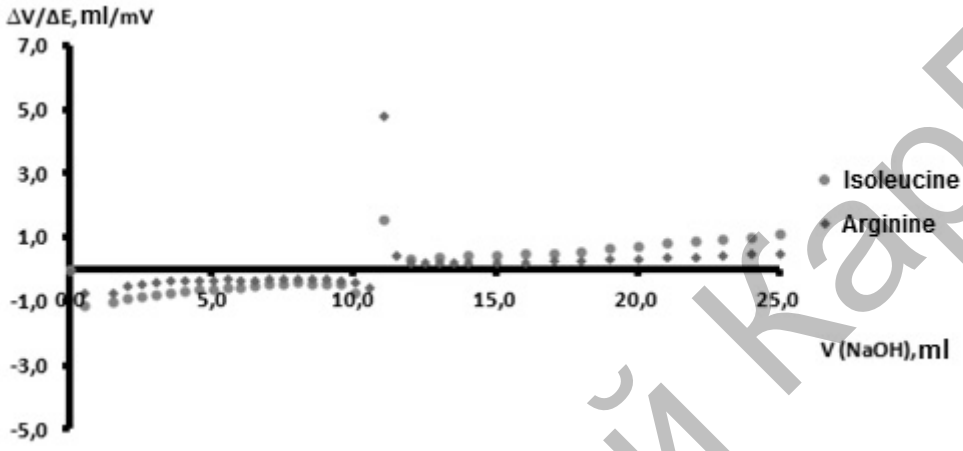


Figure 7. Differentiated titration curves, proceeded by the Gran method* of mixtures of $Ca(NO_3)_2$ ($C_{Ca(NO_3)_2} = 10^{-3}$ mole per liter) and amino acids ($C_{\text{amino acid}} = 10^{-2}$ mole per liter) by the solution of sodium hydroxide ($C_{NaOH} = 10^{-1}$ mole per liter)

The obtained curves as such could be used for semi-quantitative description of lability of complexes. To determine the degree of lability, we suggest semi-quantitative criteria, which can describe the behavior of the collapsing complex — δ, which is described by the following equation:

$$\delta = \frac{\Delta V}{\Delta E} \text{ after the eq.p.;} \quad -\frac{\Delta V}{\Delta E} \text{ before the eq.p.,} \tag{9}$$

where the first term is the relation of the above differences for the point, which is next after the eq.p., the second term — similarly for a point immediately up to the eq.p. So, the less δ is, the faster complex destroys and forms, so it's more labile, and on the turnover.

For every amino acid, according to its curve, was obtained the value of δ, all values were matched with each other. As we see, according to their lability, complexes of Ca^{2+} with these amino acid are formed the following row: δ (Ca^{2+} – Asp) < δ (Ca^{2+} – Ile) < δ (Ca^{2+} – Ala) < δ (Ca^{2+} – Arg) < δ (Ca^{2+} – Gly), so, the most labile complex is complex with the aspartic acid, with the isoleucine — the most stable.

Finally, the obtained results are in good agreement with the theoretical data of other studies [8; 25–27], which makes it possible to use this laboratory unit as a basic model for further complication and varying the experimental conditions for establishing the character of the interaction between calcium ions and amino acids.

Conclusions

1. A technique of potentiometric titration of amino acids and calcium salts is proposed.

2. The nature of all potentiometric titration curves is explained, possible processes, occurring in solutions with titrant addition, consistent with the theoretical data, are indicated.

3. On the example of solutions of calcium nitrate with a raw of amino acids (isoleucine, arginine, aspartic acid, alanine, glycine), the principal possibility of ranking by their potentiometric titration curves is shown.

4. Semiquantitative characteristics of the interaction of calcium ions and some amino acids, which can indicate: a) the stability of the complexes formed; b) their lability, are established.

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О.А. Голованова, И.А. Томашевский

Потенциометрлік титрлеу арқылы амин қышқылдары мен кальций иондарының өзара іс-қимыл сипатын құру

Мақалада потенциометрлік титрлеу негізінде адам ағзасындағы биохимиялық үрдістерге қатысатын кальций иондары (Ca^{2+}) және амин қышқылдарының (АС) өзара әрекеттесу ерекшеліктері қарастырылды. «Ca^{2+} – АС» жүйесінде пайда болатын кешен сипаты теориялық тұрғыда кальций нитраты изолейцин (Ile), аргинин (Arg), аспарагин қышқылы (Asn), глицин (Gly), аланин (Ala) қоспалары мысалында зерттелді. Кешен ыдырауына септесетін титрлеу шарттары талданды. Олардың нәтижелері бойынша зерттеліп отырған АС мен Ca^{2+} өзара әрекеттесуінің жартылай сандық сипаттары алынды. Амин қышқылы молекуласында карбоксилді топтар –COOH және азот құраушы топтар (әсіресе NH_2 тобының α-жағдайындағы) саны жоғарлаған сайын кешен тұрақтылығы артатыны, ал молекуланың көміртек қаңқасының ұзындығы артқан сайын және көлемді орынбасушылардың пайда болуынан — азаятындығы белгілі болды. Сондай-ақ δ жаңа көрсеткіштерін енгізу негізінде комплекстер тұрақсыздығының салыстырмалы көрсеткіштері белгілі болды. Олардың қозуы тұрақсыздығына байланысты Ca^{2+} мен $\delta(Ca^{2+} – Asp) < \delta(Ca^{2+} – Ile) < \delta(Ca^{2+} – Ala) < \delta(Ca^{2+} – Arg) < \delta(Ca^{2+} – Gly)$ кешендері осы тәртіп бойынша тізбектелген.

Кілт сөздер: кешендер, амин қышқылдары, биоорганикалық лигандтар, потенциометрлік титрлеу, модельдеу, тұрақтылық, кальций, қозғыштық, тұрақсыздық.

О.А. Голованова, И.А. Томашевский

Установление характера взаимодействия ионов кальция с аминокислотами с помощью потенциометрического титрования

В статье на основе потенциометрического титрования установлены особенности взаимодействия ионов кальция (Ca^{2+}) с аминокислотами (АС), которые участвуют в биохимических процессах в организме человека. Характеристики комплексов, образующихся в системе «Ca^{2+} – АС», теоретически изучаются на примере смесей нитрата кальция с изолейцином (Ile), аргинином (Arg), аспарагиновой кислотой (Asn), глицином (Gly), аланином (Ala). Выбраны условия титрования, при которых происходит разрушение комплекса. По их результатам были установлены полуколичественные характеристики взаимодействия Ca^{2+} и изучаемых АС. Было показано, что стабильность комплексов возрастает с увеличением в молекуле аминокислоты числа карбоксильных групп –COOH и азотсодержащих групп (особенно группы NH_2 в α-положении), а с увеличением длины углеродного скелета молекулы и появлением объемных заместителей — уменьшается. Кроме того, на основе введения новых критериев δ установлены сравнительные показатели лабильности комплексов. Согласно их лабильности комплексы Ca^{2+} с этими аминокислотами расположены в следующем порядке: $\delta (Ca^{2+} – Asp) < \delta (Ca^{2+} – Ile) < \delta (Ca^{2+} – Ala) < \delta (Ca^{2+} – Arg) < \delta (Ca^{2+} – Gly)$.

Ключевые слова: комплексообразование, аминокислоты, биоорганические лиганды, потенциометрическое титрование, моделирование, константы устойчивости, кальций, лабильность.

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