



Effects of L- α -amino acids side chains on their interparticle interactions with the dissociated potassium chloride in aqueous solutions

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ABSTRACT

Dissolution enthalpies of several natural amino acids (L- α -asparagine, L- α -glutamine, L- α -aspartic acid, L- α -glutamic acid, L- α -arginine, L- α -lysine and L- α -histidine) were measured in aqueous solutions of potassium chloride at $T = 298.15$ K. Based on the resulting data the standard dissolution enthalpy of amino acids in aqueous solutions of potassium chloride have been determined. The standard dissolution enthalpy values were subsequently used to calculate the heterogeneous enthalpic pair interaction coefficients (h_{A-KCl}) between zwitterions of L- α -amino acids and dissociated potassium chloride in water. Interparticle interactions in system (amino acid + dissociated KCl + water) were interpreted in terms of the hydrophobic - hydrophilic effects of the side chains of the tested encoded amino acids.

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1. Introduction

Natural amino acids constitute the building blocks of polypeptide chains. They are present in tissue fluids of living organisms in the form of free zwitterions ($R-C^{\alpha}HNH_3^+COO^-$) and interact with all components of these fluids. The molecules of L- α -amino acids feature an invariable fragment, a “zwitterionic head” ($-C^{\alpha}HNH_3^+COO^-$) and differentiating amino acid substituent (side chain). Natural amino acids in cellular fluids encounter a high concentration of potassium cations (K^+) and chloride anions (Cl^-). Interaction between natural amino acid zwitterions with potassium and chloride ions depends on the type of the side substituents. Side substituents of amino acid segments, forming the building blocks of polypeptide chains, interact differently with surrounding water molecules and other components of the cellular fluid, depending on their non-polar, polar or ionic properties. The specific properties of amino acid side chains play a key role in formation of the tertiary and quaternary spatial structures of proteins. Therefore, in many scientific centers [1–4], the researches on the interactions between amino acids and potassium chloride are conducted to precisely characterize these interactions.

The aim of this work, which is a continuation of studies regarding the interactions between the natural amino acids and ions [5–7], is the determination of the interaction effects between the selected zwitterions of encoded L- α -amino acids with dissociated potassium chloride in aqueous solutions with particular focus on the effects of the amino acid side chains on these interactions. The obtained results of

calorimetric enthalpy measurements of dissolution of L- α -amino acids in aqueous solutions of potassium chloride were used to calculate the heterogeneous enthalpic pair interaction coefficients [7, 8] between amino acid zwitterions and dissociated potassium chloride. Interaction coefficients derived from a modified [9, 10] McMillan–Mayer's theory [11] describe the thermodynamic effects of interaction between two molecules [12], occurring with the competitive participation of water molecules. Enthalpic coefficients [7] differentiate both the interactions occurring between amino acid zwitterions and dissociated potassium chloride, as well as the affinity of dissolved molecules for water, and thus the hydrophobic-hydrophilic character of amino acid side substituents [13].

2. Materials and methods

2.1. Materials

L- α -Asparagine (Asn), L- α -glutamine (Gln), L- α -aspartic acid (Asp), L- α -glutamic acid (Glu), L- α -arginine (Arg), L- α -lysine (Lys) and L- α -histidine (His) (all Fluka, Table 1) were crystallized with aqueous ethanol solutions and dried under reduced pressure at 333 K for 72 h. All ampoules with amino acids were prepared in a nitrogen atmosphere. The water used to prepare all solutions was deionized, distilled twice, and degassed. Potassium chloride (KCl) (Fluka) was dried under reduced pressure at $T = 373$ K for 72 h. Masses of the tested substances were measured using a Mettler AE 240 balance, ampoules of analyzed L- α -amino acids for calorimetric measurements were weighed with an accuracy of $\pm 10^{-5}$ g, and the aqueous KCl solutions with an accuracy of $\pm 10^{-4}$ g.

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Table 1

Substances used in this study including chemical abstracts service (CAS) registry numbers, empirical formulae, suppliers (F = Fluka), and approximate mass-fraction purities as given by the suppliers.

Substance	CAS-no.	Formula	Supplier	Purity	Purification method
L- α -Asparagine	70-47-3	C ₄ H ₈ N ₂ O ₃	F	>99.0%	Crystallisation ^a
L- α -Glutamine	56-85-9	C ₅ H ₁₀ N ₂ O ₃	F	>99.5%	None
L- α -Aspartic acid	56-84-8	C ₄ H ₇ NO ₄	F	>98.0%	Crystallisation ^a
L- α -Glutamic acid	56-86-0	C ₅ H ₉ NO ₄	F	>99.5%	None
L- α -Arginine	74-79-3	C ₆ H ₁₄ N ₄ O ₂	F	>99.5%	None
L- α -Lysine	56-87-1	C ₆ H ₁₄ N ₂ O ₂	F	>98.0%	Crystallisation ^a
L- α -Histidine	71-00-1	C ₆ H ₉ N ₃ O ₂	F	>99.5%	None
Potassium chloride	7447-40-7	KCl	F	>99.5%	None

^a Information in this text.

2.2. Calorimetric measurements

The dissolution enthalpies of investigated amino acids in aqueous solutions of potassium chloride were measured using an isoperibol calorimeter described previously [14]. The calorimeter was tested by measuring (twelve experiments) the standard enthalpy of solution at infinite dilution of urea in water at $T = 298.15$ K. Obtained value of 15.32 ± 0.04 kJ mol⁻¹ is in excellent agreement with literature values: 15.30 kJ mol⁻¹ [15], 15.29 kJ mol⁻¹ [16]. The calorimetric dissolution enthalpy measurements were performed with a repeatability of $\pm 0.5\%$. In total, 6–8 independent measurements of molar dissolution enthalpy ($\Delta_{sol}H_{W+KCl}$) of tested L- α -amino acids (A) were made in the concentration range from 0.001 to 0.005 mol of (A)/kg (solvent) in aqueous solutions of KCl at concentrations from 0.5 to 3.0 mol (KCl)/kg (water).

3. Results and discussion

The standard dissolution enthalpies ($\Delta_{sol}H_{W+KCl}^0$) of the investigated natural amino acids (L- α -asparagine, L- α -glutamine, L- α -aspartic acid, L- α -glutamic acid, L- α -arginine, L- α -lysine and L- α -histidine) in aqueous potassium chloride solution were calculated as the average values of molar dissolution enthalpies $\Delta_{sol}H_{W+KCl}$. The values of $\Delta_{sol}H_{W+KCl}^0$ where $\Delta_{sol}H_{W+KCl}^0$ is the standard dissolution enthalpies of L- α -amino acids in aqueous potassium chloride solution, $\Delta_{sol}H_{W}^0$ is the standard dissolution enthalpies of natural amino acids in water, m_{KCl} denotes the molality concentration of KCl in water (mol KCl/kg H₂O), h_{A-KCl} (Table 3) is the heterogeneous enthalpic pair interaction coefficient between zwitterions of amino acids and dissociated potassium chloride [19]:

The values of standard dissolution enthalpies $\Delta_{sol}H_{W+KCl}^0$ differ for investigated L- α -asparagine, L- α -glutamine, L- α -aspartic acid, L- α -glutamic acid, L- α -arginine, L- α -lysine and L- α -histidine. Dissolution enthalpies are endothermic for L- α -Arg, L- α -His, L- α -Asn, L- α -Gln, L- α -Asp and L- α -Glu, whereas only for L- α -Lys is exothermic. This

Table 2

Standard enthalpies of solution of natural amino acids in water and aqueous potassium chloride solutions at temperature $T = 298.15$ K and pressure $p = 0.1$ MPa^a.

$m_{KCl}/(\text{mol} \cdot \text{kg}^{-1})$	$\Delta_{sol}H_{W+KCl}^0/(\text{kJ} \cdot \text{mol}^{-1})$						
	Asn	Gln	Asp	Glu	Lys	Arg	His
0	21.64 ^b	22.50 ^b	25.82 ^c	27.85 ^c	-15.84 ^c	6.68 ^c	14.32 ^c
0.50	20.65	21.99	24.71	26.74	-16.68	5.62	13.75
1.00	19.88	21.21	23.73	26.11	-17.44	4.65	13.14
1.50	19.16	20.57	22.95	25.50	-18.03	3.80	12.61
2.00	18.58	20.06	22.42	24.97	-18.62	3.30	12.08
2.50	18.19	19.58	21.98	24.56	-19.12	2.80	11.64
3.00	17.77	19.56	21.44	24.44	-19.65	2.54	10.95

^a Standard uncertainties u are $u(T) = 0.0002$ K, $u(p) = 10$ kPa, $u(m_{KCl}) = 0.01\%$, $u(\Delta_{sol}H_{W+KCl}^0) = 1.5\%$, and the combined expanded uncertainty U_c is $U_c(\Delta_{sol}H_{W+KCl}^0) = 3.8\%$ with 0.95 level of confidence ($k \approx 2$).

^b Reference [17].

^c Reference [18].

phenomenon for L- α -Lys could reflect the less stable orientation of its molecules in crystalline state and as consequence the smaller amount of energy needed to release them to the aqueous solution in comparison with the other studied amino acids. The experimental data reported in Table 2 neither suggest any reliable interpretation of the observed order of standard dissolution enthalpies $\Delta_{sol}H_{W+KCl}^0$, nor allow any explanation of the different behavior of studied amino acids. Particularly there is no correlation (or even weak tendency) between standard dissolution enthalpies $\Delta_{sol}H_{W+KCl}^0$ for investigated amino acids and hydrophobic – hydrophilic properties of amino acids described by the parameter P [12]. This lack of correlation stems from the complex nature of the dissolution phenomenon which comprises at least three effects: (i) the destruction of amino acid crystalline lattice, (ii) the reorganization of solvent (water) structure to form the cavity in which the amino acid and ions interact and (iii) the enthalpy of direct interactions between amino acid molecules and dissociated potassium chloride. Therefore we used McMillan–Mayer's theory [11] to separate from enthalpies of dissolutions of amino acids (measured as a function of electrolyte molality) *only* the enthalpic effects of interaction between two (and not three, four *et cetera*) molecules, namely zwitterion of amino acid and dissociated potassium chloride in aqueous solution.

The values of standard dissolution enthalpies $\Delta_{sol}H_{W+KCl}^0$ of investigated amino acids decrease with increasing concentration of potassium chloride in aqueous solution for all investigated amino acids (Table 2). These amino acids possess the polar or ionic side chains. The increase in electrolyte concentration triggers the increase of exothermic interparticle interactions between amino acid zwitterions and dissociated electrolyte ions (K⁺ and Cl⁻) in studied solutions. These exothermic interparticle interactions comprise electrostatic attraction between opposite charged ions between K⁺ and carboxylate group (–COO⁻) of amino acid as well as Cl⁻ and ammonium group (–NH₃⁺) of amino acid.

The data of Table 2 were used to determine the enthalpic interaction coefficient of heterogeneous pairs amino acid zwitterion - dissociated electrolyte, as in our previous reports [7, 8], using the procedure of non-linear regression with Eq. (1) proposed by Desnoyers [15]:

$$\Delta_{sol}H_{W+KCl}^0 = \Delta_{sol}H_{W}^0 + 2m_{KCl}h_{A-KCl} + 3m_{KCl}^2h_{A-KCl,KCl} + \dots \quad (1)$$

where $\Delta_{sol}H_{W+KCl}^0$ is the standard dissolution enthalpies of L- α -amino acids in aqueous potassium chloride solution, $\Delta_{sol}H_{W}^0$ is the standard dissolution enthalpies of natural amino acids in water, m_{KCl} denotes the molality concentration of KCl in water (mol KCl/kg H₂O), h_{A-KCl} (Table 3) is the heterogeneous enthalpic pair interaction coefficient between zwitterions of amino acids and dissociated potassium chloride [19]:

$$2h_{A-KCl} = \left(\frac{\partial [\Delta_{sol}H_{W+KCl}^0]}{\partial m_{KCl}} \right)_{m_{KCl} \rightarrow 0} \quad (2)$$

and $h_{A-KCl,KCl}$ is the enthalpic triplet interaction coefficient. The enthalpic interaction coefficients for three molecules ($h_{A-KCl,KCl}$) were not discussed in this work, since they describe not only the interactions of three molecules but also include combinations of interactions of two molecules.

The enthalpic pair interaction coefficients h_{A-KCl} between the amino acid zwitterion and the dissociated electrolyte (KCl) of the 1:1 type, are the sum of interaction effect between the amino acids, the cation K⁺ and the anion Cl⁻ [8]:

$$h_{A-KCl} = (h_{A-K^+} + h_{A-Cl^-}) \quad (3)$$

The determined enthalpic interaction coefficient values of heterogeneous pairs (h_{A-KCl}) describe the energetic effects of interactions between hydrated zwitterions of the investigated natural amino acids

Table 3

Enthalpic pair interaction coefficients (h_{A-KCl}) between amino acid zwitterions and dissociated KCl in water solution, quantitative contribution of ($\Delta h_{A-KCl(R)}$) amino acids side chains to (h_{A-KCl}) of *R*-amino acids, enthalpic pair interaction coefficients for amino acids zwitterions with urea in water solution (h_{A-U}) and averaged hydrophobic parameters ($P_{\text{hydro-pho}}$) [12] at temperature $T = 298.15$ K and pressure $p = 0.1$ MPa^a.

Amino acid	h_{A-KCl} [J kg mol ⁻²]	Δh_{R-KCl} [J kg mol ⁻²]	$P_{\text{hydro-pho}}$	h_{A-U} [J kg mol ⁻²]
Gly	-470 ^b	0	0	-390.2 ^e
Ala	-109.1 ± 5.5 ^c	360.9	46	-238.2 ^e
Aba	132 ± 9.0 ^d	602.0		-185 ^f
Val	246 ± 8.0 ^d	716.0	123	-116 ^e
Leu	278 ± 24.0 ^d	748.0	165	-98 ^e
Ile	303 ± 37.0 ^d	773.0	172	-95 ^e
Ser	-612 ± 25.0 ^c	-142.0	-57	-511 ^e
Thr	-207.5 ± 8.0 ^c	262.5	-9	-350 ^e
Cys	-349.0 ± 24.0 ^d	121.0	78	-358 ^e
Asn	-999.0 ± 25.7	-529.0	-110	-819 ^e
Gln	-831.1 ± 93.3	-361.1	-81	-690 ^e
Asp	-1138.4 ± 57.1	-668.0	-123	-831 ^e
Glu	-1006.3 ± 54.8	-536.3	-106	-820.8 ^e
Arg	-1195.4 ± 30.3	-725.4	-130	-892 ^e
Lys	-826.5 ± 28.9	-356.5	-100	-721 ^e
His	-571.1 ± 42.2	-101.1	-34	-518 ^e

^a Standard uncertainties u are $u(T) = 0.0002$, $u(p) = 10$ kPa, and $u(h)$ are stated as \pm values for enthalpic coefficients.

^b Values from ref. [5].

^c Values from ref. [8].

^d Values from ref. [7].

^e Values from ref. [18].

^f Values from ref. [17].

and hydrated ions of dissociated potassium chloride in water. The global effect of interactions is the sum of co-competitive processes:

- interactions between “zwitterionic head” ($-\text{CHNH}_3^+\text{COO}^-$) and polar or ionic side chain groups of amino acids with dissociated potassium chloride (as the sum of contributions of the cation and anion) - exothermic effects
- for the direct interaction between the polar or ionic groups to occur, some water molecules from the hydration layers of interacting groups (ions) must be removed - endothermic effects of partial dehydration
- in case of amino acids with non-polar side substituents ($-\text{CH}_2-$), the phenomenon of hydrophobic hydration - enhanced interaction between the water molecules surrounding the non-polar group - is transferred to water molecules hydrating “zwitterionic head” and polar or ionic group, as a result of hydrogen bonds cooperation. Due to this process, the removal of some of the water molecules

from the hydration layers of interacting groups requires more energy, thereby increase participation of the endothermic effects in the global process of the discussed interactions.

The values of heterogeneous enthalpic interaction coefficients of the tested amino acids with potassium chloride (Table 3) were supplemented by data acquired and published previously by our group [5, 7, 8].

To evaluate the influence of the structure of the side chains (*R*) of the studied amino acids on the value of h_{A-KCl} , we calculated the enthalpy contributions of *R*-side chains $\Delta h_{A-KCl(R)}$ to the size h_{A-KCl} of according to Eq. (4) [2]:

$$\Delta h_{A-KCl(R)} = h_{A-KCl(R)} - h_{A-KCl(\text{Gly})} \quad (4)$$

where $h_{A-KCl(\text{Gly})}$ is the enthalpic coefficient of the pairwise interaction of L-amino acid with the side chain $R = -\text{CH}$ [5], and $h_{A-KCl(R)}$ - is the enthalpic coefficient of the pairwise interaction of amino acid with the side chain $R = -\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CHCH}_3\text{OH}$, $-(\text{CH}_2)_2\text{CONH}_2$ and so on. Calculated contributions from the *R*-side chain of amino acid to interparticle interactions with the dissociated KCl ($\Delta h_{A-KCl(R)}$) are listed in Table 3.

Amino acids possessing non-polar side substituents have positive values of Δh_{R-KCl} which increase with the increase in predominating hydrophobic effects for their side chains in the following order: Cys < Thr < Ala < Aba < Val < Leu < Ile.

Amino acids possessing polar or ionic side chains have negative values of Δh_{R-KCl} which decrease with the increase in polarity (ionic character) of their chains:

His > Ser > Lys > Gln > Asn > Glu > Asp > Arg.

The values of h_{A-KCl} (Table 3) indicate, that the exothermic contribution of polar or ionic groups in amino acid molecules to the total effect of interactions with dissociated potassium chloride outweighs the endothermic dehydrating effects. The values of h_{A-KCl} for amino acids with carboxyl group in the side chain: L- α -aspartic acid (Asp), L- α -glutamic acid (Glu) are lower than the values for L- α -asparagine (Asn) and L- α -glutamine (Gln) possessing amide side substituents (Table 3). This indicates a stronger interactions between ionic carboxyl groups and dissociated potassium chloride than in case of the amide groups.

By comparing the heterogeneous enthalpic pair interaction coefficient values between the L- α -aspartic acid and L- α -glutamic acid, as well as between the L- α -asparagine and L- α -glutamine, one can note

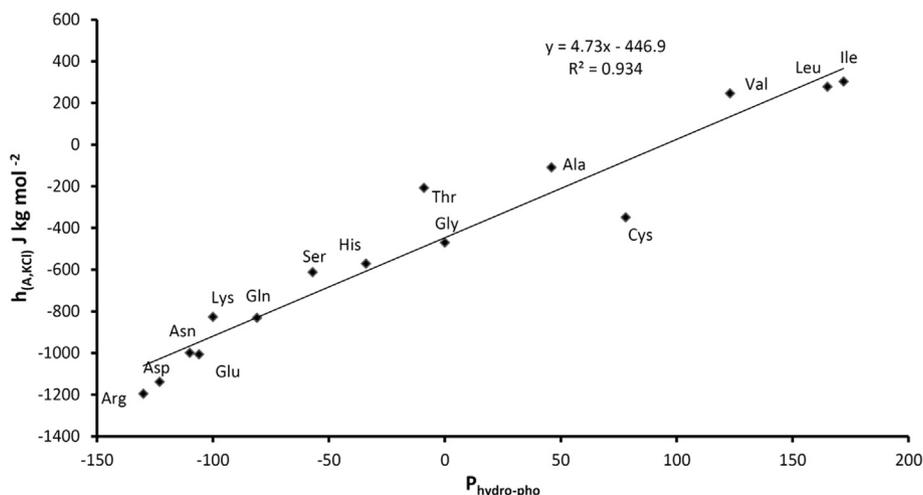


Fig. 1. Correlation between the enthalpic heterogeneous pair interaction coefficients (h_{A-KCl}) of amino acid zwitterions - potassium chloride and $P_{\text{hydro-pho}}$ in water.

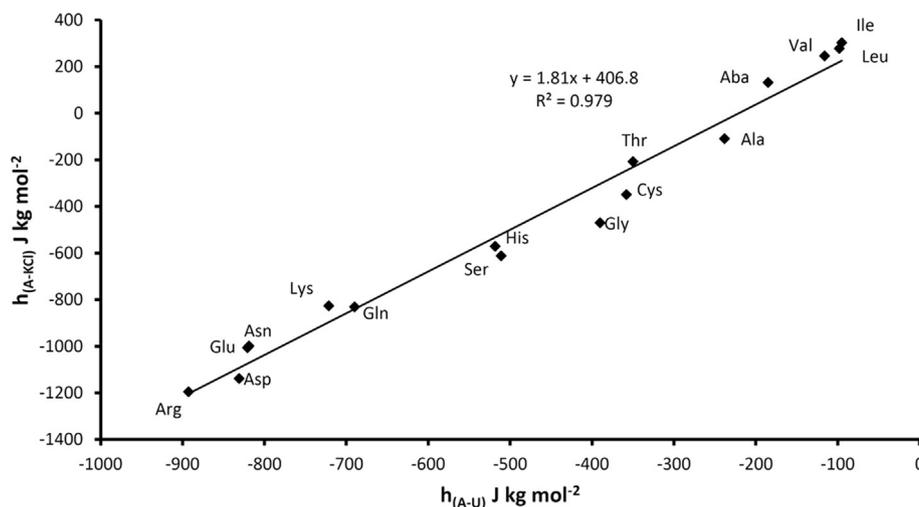


Fig. 2. Correlation between the enthalpic heterogeneous pair interaction coefficients (h_{A-KCl}) of amino acid zwitterions - potassium chloride in water and the enthalpic heterogeneous pair interaction coefficients (h_{A-U}) of amino acid zwitterions - urea molecule in water.

the increase in the endothermicity of the interaction process, due to the presence of additional hydrophobic $-\text{CH}_2-$ group in amino acid side chain:

$$h_{Asn-KCl} < h_{Gln-KCl}; h_{Asp-KCl} < h_{Glu-KCl}$$

The analysis of the h_{A-KCl} values between dissociated potassium chloride and zwitterions of natural amino acids having basic side substituents (Table 3) revealed, that L- α -arginine interacts the strongest with dissociated potassium chloride, L- α -lysine interacts weaker, while, L- α -histidine interacts the weakest. The values of h_{A-KCl} depend on the amount of both hydrophobic $-\text{CH}_2-$ groups and polar groups in the side substituents of dibasic natural amino acids. The negative (exothermic) values for enthalpy of L- α -lysine dissolution in KCl aqueous solutions show that the enthalpy of direct interactions between amino acid molecule and dissociated potassium chloride dominate over the enthalpy needed for the destruction of amino acid crystalline lattice and the reorganization of water structure to form the cavity in which the amino acid and ions interact. Only for L- α -lysine and L- α -proline the measured values of enthalpy of dissolution in aqueous solution are exothermic, which reflect the orientation and interactions between these amino acids molecules in the crystalline structure.

For the estimating of the influence of hydrophobicity of L-amino acid side-chains on the (h_{A-KCl}) values, we used the scale of hydrophobicity with a parameter ($P_{\text{hydro-pho}}$) [12]. The obtained correlation (Fig. 1) indicates that the enhancement of hydrophobicity of the side chains of L-amino acids in the series Arg < Asp < Asn \approx Glu < Gln \approx Lys < Ser < His < Gly \approx Thr < Ala < Val < Leu \approx Ile leads to an increase in the endothermicity of the coefficient value (h_{A-KCl}) in the same order. In other words, this leads to a weakening of the interactions between the zwitterions of these amino acids and the dissociated KCl. Because, the parameters of hydrophobicity ($P_{\text{hydro-pho}}$) have been successfully used by us in paper [18] for correlating the coefficients of pair-wise interactions (h_{A-U}) of L-amino acids with the urea in aqueous solution, it was interesting to check existence such interrelation between these coefficients and the coefficients of (h_{A-KCl}). It can be seen from Fig. 2 that the correlation h_{A-KCl} with h_{A-U} is linear. That is, the studied amino acids have a comparable effect on the energy of interparticle interactions with both the polar urea molecules and with the dissociated KCl. This effect and its value depend on the structure of the side chains of L-amino acids (the presence in them of hydrophobic or hydrophilic groups, their number and location relative to the polar head of zwitterion).

4. Conclusion

The analysis of the experimental and calculated data shows that the energy of intermolecular interactions of zwitterions of L-amino acids with the dissociated KCl in aqueous solution will depend not only on the concentration KCl but on structure of the side chains of studied L-amino acids. The linear correlation $h_{A-KCl} = f(P_{\text{hydro-pho}})$ established by us shows that the enhancement of the hydrophobicity of the side chains of the studied L-amino acids weakens the energy of interparticle interactions between the zwitterions of these amino acids and the dissociated (KCl) in the aqueous solution. Another linear correlation $h_{A-KCl} = f(h_{A-U})$ indicates a similar effect of analogous side chains on the energy of interparticle interactions of L-amino acids with the dissociated KCl and urea in aqueous solutions.

Notes

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