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COMPLEXATION OF L-HISTIDINE WITH PYRIDINE CARBOXYLIC ACID ISOMERS IN AQUEOUS BUFFER SOLUTION AT 298.15 K: A CALORIMETRIC STUDY

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Abstract. The peculiarities of interaction of heterocyclic amino acid of L-histidine (His) with structural isomers of pyridine carboxylic acid: picolinic (PA), nicotinic (NA), and isonicotinic (INA) acids in the phosphate buffer, pH 7.4 at $T = 298.15$ K, are studied by the method of solution calorimetry. Thermodynamic parameters, viz. binding constants, enthalpies of complexation, Gibbs energies and entropies, are determined. For His and pyridine monocarboxylic acids, the formation of hydrogen bonds and electrostatic interactions is found to be the main force determining the formation of complexes between them in the buffer solution, as evidenced by large negative enthalpy values and positive entropy values. The stability of the obtained complexes depends on the structural isomerism of pyridine carboxylic acid and increases in the series: PA < NA < INA. The main contribution to the stabilization of the formed complexes is shown to be made by the enthalpic component of the Gibbs free energy of complexation.

Keywords: *enthalpy of solution, histidine, pyridine monocarboxylic acid isomers, buffer solution, thermodynamic characteristics*

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INTRODUCTION

In recent years, the attention of researchers has been attracted to interactions between model protein compounds and pharmacologically active substances, which underlie the processes of their transfer in the human body, and are also important in the development of new biotechnologies for the production of innovative dosage forms. The studies devoted to such interactions most often record changes in various physicochemical properties (viscosity, density, ultrasonic velocity, etc.) of solutions containing mainly aliphatic amino acids upon addition of drugs, without considering the possibility of intermolecular complexes to be formed [1–3]. There is a lack of studies on the thermodynamics of interaction of amino acids containing polar or charged side chains with biologically active compounds (ligands) in liquid media with physiological pH values.

L-Histidine, His (or 2-amino-3-(4-imidazolyl) propionic acid) is one of the 20 most abundant natural amino acids in living organisms. Unlike aliphatic amino acids, which have no polar side groups, the His molecule contains an imidazole ring in the side chain that can potentially interact with a ligand, along with terminal α-amino and a-carboxyl groups. Histidine plays a vital role in the prevention of various diseases such as asthma, liver cirrhosis, chronic kidney disease, cardiovascular diseases [4, 5]. The structure and chemical composition of histidine serve as the basis for many enzyme active centers, ion channels, and metalloproteins [5].

The three isomeric molecules of picolinic (pyridine-2-carboxylic) acid, nicotinic (pyridine-3-carboxylic) acid, and isonicotinic (pyridine-4-carboxylic) acid are pyridine derivatives and are pharmacologically important due to their chemical and biological properties. Pyridine carboxylic acids (PyCOOH) and their derivatives are widely used as B vitamins, chemotherapeutic agents to improve metabolism, antihyperlipidemic agents to reduce cholesterol levels, antituberculosis drugs, etc. [6–8]. The results of published studies [9–12] of interaction of pyridine derivatives with various metals and organic compounds have shown that the reactivity of the carboxyl group depends on its location in the pyridine ring. Previously, we studied [13–15] thermodynamics of the interaction of pyridine monocarboxylic acid isomers with such amino acids as L-aspartic acid (Asp) and L-asparagine (Asn) in aqueous solutions, and L-lysine (Lys) in the buffer solution, which contain acidic, neutral, and basic polar groups in the alkyl side chain, respectively. This work

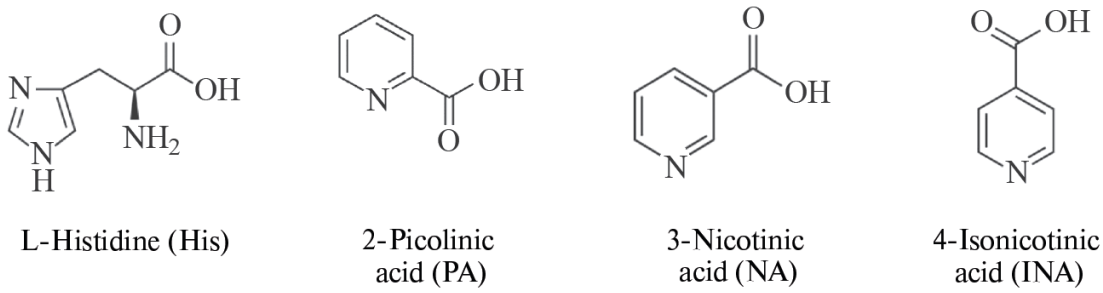

Fig. 1. Structure of the studied compounds.

is aimed at further studies of the factors determining the formation of complexes between PyCOOH isomers and the heterocyclic amino acid L-histidine in the aqueous buffer solution. The structures of the studied compounds are shown in Fig. 1.

We use the solution calorimetry method to study interaction of the reagents at $T = 298.15$ K in the phosphate buffer, pH 7.4. Under these conditions, dissociation of the a-COOH group and protonation of the a-NH_2 group of the L-histidine molecule are observed, and the imidazole ring in its side chain is deprotonated [16], and, consequently, His exists predominantly in the zwitterionic form ($HL^{\pm}$), with the probability of presence of the cationic form (H_2L^+) being less than 5%. As previously shown [14, 17], the nicotinic (NA), picolinic (PA), and isonicotinic (INA) acids take the form of anions (L^-) in the buffer solution with pH 7.4. To analyze the role of the imidazole group in the His side chain, we compare the results obtained with data on the complexation of Lys with the same PyCOOH isomers in the buffer solution [15]. We also study the change in the ability of His to interact with PyCOOH when the carboxyl group is located at the 2-, 3-, 4-positions in the pyridine ring. We determine the thermodynamic characteristics of complexation ($\lg K_c$, $\Delta_c G^o$, $\Delta_c H^o$, $\Delta_c S^o$), which will allow us to discuss the driving forces involved in the interaction of His with the studied pyridine monocarboxylic acid molecules in the buffer solution.

EXPERIMENTAL PART

We used L-histidine (Sigma-Aldrich, Japan, CAS 63-91-2, >0.99), nicotinic acid (Sigma-Aldrich, Germany, CAS 59-67-6, ≥ 0.98), picolinic acid (Aldrich, CAS 98-98-6, ≥ 0.99), and isonicotinic acid (Aldrich, CAS 55-22-1, 0.99). We dried the amino acid and pyridine carboxylic acid isomers at 356 K in a vacuum dryer for 48 h immediately before use. The studies were carried out in the aqueous buffer solution at pH 7.4, which approximates the environment to the conditions of real biological systems. We recorded the pH values of the solutions with a Mettler Toledo digital pH meter, Five-Easy model. All solutions were prepared by the weight method using Sartorius-ME215S scales (with weighing accuracy of 1×10^{-5}g). The preparation error for the solutions of the desired concentration did not exceed $\pm 2 \times 10^{-4}$ mol kg^{-1}.

The solution enthalpies of crystalline L-histidine (fixed portion) in buffer solutions containing different concentrations of pyridine carboxylic acid were measured on an isothermal-shell calorimeter and a reaction glass capacity of 60 cm^3 at 298.15 ± 0.01 K. The scheme of the experimental setup and description of the thermometric procedure are given in [18, 19]. For the calibration data of the calorimeter and calculation of the measurement error, see Supplementary Materials to [20]. The relative standard error in the measurements of the solution enthalpies was not more than 0.7%.

The calorimeter was tested by measuring the solution enthalpy of potassium chloride (KCl) (Sigma-Aldrich, CAS 7447-40-7, purity 99.5 wt%) in H_2O at $T = 298.15$ K, recommended as a standard in [21–23]. Our values ($\Delta_{sol}H^\circ = 17.23 \pm 0.07$ kJ mol^{-1}) at infinite dilution are in good agreement with the recommended published data ($\Delta_{sol}H^\circ = 17.25 \pm \pm 0.04$ kJ mol^{-1} [23] and (17.22 ± 0.04) kJ mol^{-1} [21, 22]). In addition, comparison of our previously obtained values of solution enthalpies of some amino acids in water with the data of other authors showed that our values $\Delta_{sol}H^\circ = 14.25 \pm 0.06$ kJ mol^{-1} for glycine [24], $\Delta_{sol}H^\circ = -3.22 \pm 0.02$ kJ·mol^{-1} for L-proline [20], and $\Delta_{sol}H^\circ = 14.30 \pm 0.08$ kJ mol^{-1} for L-histidine [25] at infinite dilution in water agree with the published values (14.23 ± 0.02 kJ mol^{-1}) [26], (−3.25 ± 0.03 kJ mol^{-1}) [27], and (14.32 ± 0.06 kJ mol^{-1}) [27], respectively, which further confirms the validity of our results obtained with this calorimeter.

DISCUSSION OF RESULTS

The experimental values of enthalpy of histidine dissolution in buffer solutions containing isonicotinic and picolinic acids of variable concentration are

Table 1. Dissolution enthalpies of L-histidine (His) in aqueous buffer solutions of pyridine carboxylic acids (NA, INA, PA) at 298.15 K

His [a] – NA – buffer [25]		His [a] – INA – buffer		His [a] – PA– buffer	
m_{NA}, mol kg^{-1}	$\Delta_{sol}H_m(s + L)$, kJ mol^{-1}	m_{INA}, mol kg^{-1}	$\Delta_{sol}H_m(s + L)$, kJ mol^{-1}	m_{PA}, mol kg^{-1}	$\Delta_{sol}H_m(s + L)$, kJ mol^{-1}
0.000	8.68	0.000	8.68	0.000	8.68
0.0032	7.74	0.0038	5.25	0.0064	6.61
0.0064	6.83	0.0057	3.34	0.0129	5.29
0.0096	6.10	0.0095	2.41	0.0193	4.36
0.0161	4.86	0.0133	1.05	0.0321	2.42
0.0224	3.35	0.0211	−1.14	0.0448	0.59
0.0288	2.04	0.0284	−2.25	0.0576	−0.81
0.0321	1.39	0.0354	−3.41	0.064	−1.25
0.0416	−0.10	0.0438	−4.69	0.0832	−2.54
0.0520	−1.82	0.0521	−5.31	0.104	−3.26
0.0640	−3.40	0.064	−5.62	–	–
0.0768	−3.77	–	–	–	–

[a] $m_{His} = 0.0064$ mol kg^{-1}.

given in Table 1, with the earlier obtained data for nicotinic acid [25] given there for comparison. As we can see from Table 1, the endothermicity of the amino acid dissolution process decreases as the concentration of pyridinmonocarboxylic acid in the buffer solution grows.

Based on the experimental values of the solution enthalpies of His in buffer, $\Delta_{sol}H_m(s)$, and in the buffer solution with a ligand added, $\Delta_{sol}H_m(s + L)$, (where L is PyCOOH), the transfer enthalpies, $D_{tr}H$, of the amino acid from the buffer to the ligand buffer solution were determined by the ratio

$$\Delta_{tr}H = \Delta_{sol}H_m(s + L) - \Delta_{sol}H_m(s). \quad (1)$$

The obtained value of enthalpy difference ($D_{tr}H$) can be considered as the enthalpy proportional to the enthalpy of complexation of His with PyCOOH isomers. The formation of His complex with NA, PA, INA can be judged upon by the dependence of the values of $D_{tr}H$ on the concentration of pyridine carboxylic acid (PA, INA). As we can see from Fig. 2, the concentration dependences of the transfer enthalpies $D_{tr}H = f(m_L)$ have a nonlinear character. For comparison, Fig. 2 also shows the results obtained for the system (His + NA + buffer) in the previous work [25]. For the systems studied, the transfer enthalpies decrease as the concentration of pyridine carboxylic acid grows until reaching almost constant values. This behavior results from binding of ligands (NA, PA, INA) by histidine and allows suggesting the existence of interactions leading to complex formation in the studied systems.

The obtained calorimetric data ($\Delta_{sol}H_m$, $\Delta_{sol}H_m$) were processed using the HEAT computer program [28], in which the search for unknown parameters ($\lg K_c$, DH_c^0) is reduced to the numerical minimization of the functional F with respect to the sought parameters

$$F = \sum_{i=1}^{n} w_i \left(\Delta H_i^{exp} - \Delta H_i^{theor}\right)^2, \quad (2)$$

where DH_i is the heat effect of the ith reaction, n is the number of experiments, w_i is the weighting factors calculated as $w_i = A/(d\Delta H_i)^2$ (where A is the coefficient chosen from the condition $\sum w_i = n$, i.e., the sum of weights equals the number of experiments, $d\Delta H_i$ is the absolute error of measurement DH_i). Since acid-base equilibria, in which reagents in solutions participate, can make a certain contribution to the values of the sought value ($\lg K_c$ and D_cH^o), the heat effects and equilibrium constants of the reagents [17, 29–33] were

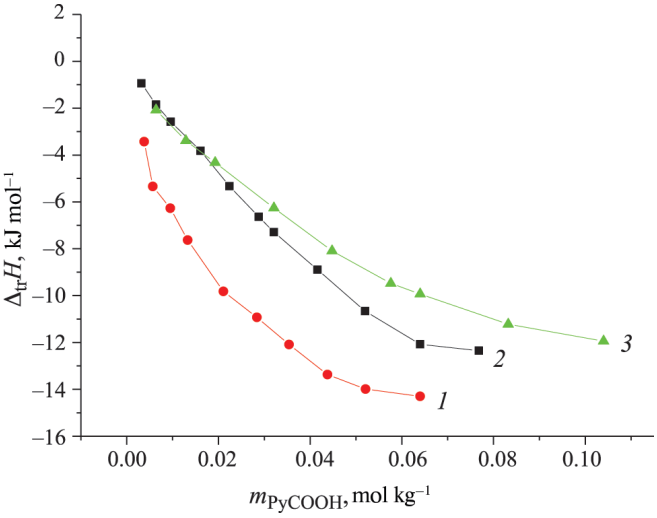

Fig. 2. Dependences of transfer enthalpies of L-histidine (His) from buffer to the buffer solution of pyridine carboxylic acid isomers (*1* INA, *2* NA, *3* PA) on the PyCOOH concentration at $T = 298.15$ K. Molality of the amino acid is $m_{His} = 0.0064$ mol kg^{-1}.

additionally introduced into the computational program when calculating the thermodynamic parameters of complexation.

Calculation of the equilibrium composition for the studied systems taking into account different stoichiometric schemes of interaction showed the best compliance with the minimization condition of relation (2) when the complex of composition His/2L is formed, where L = NA, INA, PA. The process of complexation between His ($HX^{\pm}$) zwitterion and the anionic form of the ligand (A^-) can be represented by the scheme

$$HX^{\pm} + 2A^- = HX^{\pm} \cdot 2A^-$$
$$K_c = [HX^{\pm} \cdot 2A^-]/[HX^{\pm}] \cdot [A^-]^2. \quad (3)$$

The Gibbs energy and entropy of complexation are calculated using the thermodynamic relations

$$\Delta_c G^o = -RT\ln K_c, \quad (4)$$

$$\Delta_c G^o = \Delta_c H^o - T\Delta_c S^o. \quad (5)$$

Table 2 presents thermodynamic parameters ($\lg K_c$, D_cG^o, D_cH^o, TD_cS^o), which were obtained under standard conditions ($p = 1.01 \times 10^5$ Pa, $T = 298.15$ K) and refer to the interaction process of the reactants taken presumably in the standard state, i.e., having properties as in an infinitely dilute solution. Taking into account the low molar concentrations of the reagents used in the experiments, as well as their organic nature, the indicated thermodynamic parameters can be considered as corresponding to those for the standard state. The data in Table 2 indicate that, in the buffer solution (pH 7.4), the heterocyclic amino acid His forms molecular complexes with pyridine carboxylic acid isomers of 1 : 2 composition with binding constants of medium strength.

Analysis of the obtained results shows that the values Δ_cG^o are negative for all systems. The $\lg K_c$ values of the formed His/2PyCOOH complexes increase in the series of isomers PA→NA→INA. A similar sequence is observed for the obtained values $T\Delta_cS^o$ (the increasing trend) and Δ_cG^o (the decreasing trend). A more stable His/2INA complex is formed when the carboxyl group (COO^-) is located at the 4-position in the pyridine ring, and its displacement to the 3- and 2-positions leads to a decreased ability of the NA and PA isomers to form complexes with His. Note that when pyridine carboxylic acids are dissolved in the buffer (pH 7.4), the anions ($PyCOO^-$) formed during deprotonation at the 2- and 4-position of the (COO^-) group in the pyridine ring are stabilized by delocalization of the negative charge along the conjugated system that includes the heteroatom (N), unlike 3-pyridine carboxylic acid in which the COO^- group is not conjugated to the heteroatom [9]. His and NA, PA, INA isomers interact through overlapping of their hydrate spheres, which is accompanied by dehydration of the starting substances. Obviously, the location of the negatively charged carboxyl group closer to the nitrogen atom with an unshared pair of electrons leads to changes in the hydrate states as well as acidic properties of the above PyCOOH isomers, which leads to changes in the reactivity of the substances.

The values of the enthalpy D_cH^o and entropy Δ_cS^o include contributions from the processes of complexation between reactants due to noncovalent interactions, from dehydration of dissolved substances during their interaction, from hydration of formed complexes and solvent reorganization. The prevalence of these or other processes causes negative or positive values of enthalpy and the complexation entropy [34, 35]. The molecules of the studied compounds His, NA, PA, INA contain charge centers (COO^-/NH_3^+, COO^-), hydrophilic (> C = O, > N, –NH), and hydrophobic groups. Interactions such as van der Waals forces, hydrogen bonding, electrostatic and hydrophobic interactions may be involved in complexation. In buffer solutions (pH 7.4), the negatively charged carboxyl group COO^- in PyCOOH isomer molecules participates in electrostatic interactions with the end charge (COO^-, NH_3^+) groups of the zwitterionic form of His. Polar groups of the main chain, as well as two nitrogen atoms in the imidazole ring of the histidine side chain and polar (C = O, N_{pyr}) groups of pyridine carboxylic acids can participate in the formation of hydrogen bonds, and the available nonpolar hydrocarbon groups in their

Table 2. Thermodynamic characteristics of complexation of L-histidine (His) with picolinic (PA), nicotinic (NA), and isonicotinic (INA) acids in the aqueous buffer solution, pH 7.4, $T = 298.15$ K

Complex	$\lg K_c$	$\Delta_c G^o$, kJ/mol	$\Delta_c H^o$, kJ mol^{-1}	$T\Delta_c S^o$, kJ mol^{-1}K^{-1}
His:2PA	3.03 ± 0.01	−17.27 ± 0.12	−16.05 ± 0.23	1.23 ± 0.29
His:2NA*	3.16 ± 0.01*	−18.02 ± 0.06*	−14.32 ± 0.25*	3.69 ± 0.42*
His:2INA	4.14 ± 0.01	−23.60 ± 0.10	−15.27 ± 0.21	8.33 ± 0.31

* Data taken from [25].

molecules can participate in hydrophobic and van der Waals interactions. In addition, the studied His, NA, PA, and INA reagents contain imidazole and pyridine rings, which can interact via π-stacking. The obtained large negative values of $\Delta_c H^o$ and positive values of $\Delta_c S^o$ indicate that the main contribution to the stabilization of His/2PyCOOH complexes in solutions with pH 7.4 is made by electrostatic forces and hydrogen bonds along with the existing hydrophobic and possibly stacking interactions [34].

The exothermic effect of interaction of the studied amino acid with pyridine carboxylic acid isomers is shown to prevail over the endothermic effect of their dehydration. The influence of the position of the carboxyl group in the pyridine ring of PyCOOH isomers on the values of $\Delta_c H^o$ is revealed. A decrease in the exothermicity of the complexation of His with PyCOOH in the sequence PA > INA > NA symbathic to a decrease in the dissociation constant $K_{a,1}$ of the COOH-group (an increase in $pK_{a,1}$) of the indicated pyridine carboxylic acid isomers, is established. This seems to be due to the predominance of the positive contribution due to the dehydration of dissolved substances and hydrophobic interactions [34].

The enthalpic contribution favors the formation of His complexes with pyridinmonocarboxylic acids. The enthalpy value $\Delta_c H^o$ is determined by several effects, among which are the breakage of hydrogen bonds between water molecules during the dissolution of the reactant (solvent reorganization), dehydration of the initial molecules during the interaction, and hydration of the formed complex. The first two effects give endothermic contributions while the third one gives an exothermic contribution to the value $\Delta_c H^o$. Note that the hydrated state of the dissolved substances affects the ability to bind the amino acid to PyCOOH isomers. It was of interest to compare the enthalpies of solvation of PyCOOH isomers in the aqueous solution (in the absence of data for the buffer solution). Using available published data on solution enthalpies ($D_{sol}H_m\infty$) of nicotinic, picolinic, and isonicotinic acids in aqueous solutions [36-38] and sublimation enthalpies ($D_{sub}H_m^o$) [39], the enthalpies of their solvation at 298.15 K were determined using the ratio

$$\Delta_{solv}H_m^{\infty} = \Delta_{sol}H_m^{\infty} - \Delta_{sub}H_m^{o}. \quad (6)$$

The obtained values of the molar solvation enthalpy at infinite dilution ($D_{solv}H_m\infty$) for PA, NA, INA in water are negative (Table 3) and become less exothermic in the series INA > NA > PA. The constant ($\lg K_c$) of His/2PyCOOH complexation decreases in the same sequence (Table 2).

Obviously, although the dehydration energy cost to form a His complex with PA is less than with the other two isomers and the process itself is more enthalpically favorable, the entropic contribution and the configurational packing of the complex are apparently unfavorable factors that lead to the least stability of the His/2PA complex. Moreover, the picolinic acid molecule has three most stable conformers (one with intramolecular hydrogen bonding and two without hydrogen bonding), nicotinic acid can exist in two conformations differing in the orientation of the carboxyl group, and only one stable conformer has been described for isonicotinic acid [40]. Apparently, all these factors determine the different ability of the above PyCOOH isomers to form complexes with His.

The obtained positive values $\Delta_c S^o$ are usually regarded as evidence of the presence of hydrophobic interactions, the existence of different configurations of the complex and dehydration of dissolved substances in the complexation process [34, 41]. As can be seen from Table 2, the values $T\Delta_c S^o$ increase in the series PA < NA < INA. Hence, the complexation entropy becomes more positive when the carboxyl group "moves" from 2- (PA) to 3-(NA) and 4-(INA) positions relative to the nitrogen atom of the pyridine ring, which is probably due to the weakening of steric hindrances and the effect of relaxation into the volume of water molecules from the hydrate shells of the reagents. The results obtained indicate an increase in the contribution of the entropic factor to the stabilization of the formed His/2PyCOOH complexes in the indicated sequence.

Table 3. Values of standard molar sublimation enthalpy ($\Delta_{sub}H_m^o$), molar solution enthalpy ($\Delta_{sol}H_m^\infty$), and molar solvation enthalpy $\Delta_{solv}H_m^\infty$) at infinite dilution in the aqueous solution of picolinic (PA), nicotinic (NA), and isonicotinic (INA) acids at $T = 298.15$ K

PyCOOH	$\Delta_{sub}H_m^o$ [a], kJ mol^{-1}	$\Delta_{sol}H_m^\infty$, kJ mol^{-1}	$\Delta_{solv}H_m^\infty$, kJ mol^{-1}
PA	92.7 ± 0.5	16.02 ± 0.25 [b]	–76.68 ± 0.76
NA	105.2 ± 0.6	14.27 ± 0.39 [c]	–90.93 ± 0.94
INA	111.3 ± 0.6	15.18 ± 0.25 [d]	–96.12 ± 0.86

[a] Data from [39]; [b] Data from [37]; [c] Data from [36]; [d] Data from [38]

Comparison of the results on complexation of L-histidine and L-lysine [15] with PyCOOH isomers showed that stability of the formed amino acid/PyCOOH complexes depends on the structure of the side radicals of amino acid molecules and their ionic state in the buffer solution. Lysine (Lys), due to the presence of an ionogenic amino group in the side chain, has more pronounced basic properties than His, whose imidazole group is also basic due to resonance delocalization of charge during protonation in aqueous solutions. Note that in the buffer solution, pH 7.4, Lys exists predominantly in the cationic form (H_2L^+), and the probability of the presence of the zwitterionic form ($HL^\pm$) is less than 4% [15].

His and Lys molecular complexes with isomers (NA, INA, PA) with stoichiometry of 1:2 and 1:1, respectively, were found to be formed in the buffer solution, which is accompanied by negative enthalpy changes and positive entropy values. The trends of thermodynamic parameters ($\lg K_c$, $\Delta_c H^o$, $T\Delta_c S^o$) are maintained during the formation of His and Lys complexes in the series of pyridine carboxylic acid isomers. At the same time, the value of reagent binding constants is larger for histidine than for lysine: $\lg K_c$(His) > $\lg K_c$(Lys). The cationic form of lysine forms less stable complexes with the anionic form of PyCOOH isomers than the zwitterionic form of His. The exothermicity of the formation of Lys/PyCOOH complexes is significantly reduced [15] as compared to His/2PyCOOH complexes. In specific binding, complementarity in the interaction between the active groups of amino acids and pyridine carboxylic acids plays a major role. Apparently, in the buffer solution, the structural correspondence between PyCOOH isomers and the heterocyclic His molecule is more pronounced than that of lysine, whose molecule has a linear side chain (NH_2-CH_2-CH_2-CH_2-CH_2-). This is also confirmed by more positive entropy changes in the case of formation of Lys/L complexes as compared to His/2L (where L is NA, PA, INA). It is shown that molecular complexes of His with NA, INA and PA are stabilized mainly by enthalpic contribution, and molecular complexes of Lys with NA and INA are stabilized by entropic contribution to the Gibbs free energy of complexation. The stability of the Lys complex with PA is determined by the balance between enthalpic and entropic components of the Gibbs energy [15]. The results obtained confirm the dominance of electrostatic interactions and the formation of hydrogen bonds among other types of interactions (hydrophobic, van der Waals, π-stacking) during the binding of the above amino acids with pyridine carboxylic acid isomers to the complex under the buffer solution conditions, pH 7.4.

CONCLUSIONS

The solution enthalpies of heterocyclic amino acid L-histidine in aqueous buffer solutions (pH 7.4) containing structural 2-, 3- and 4-isomers of pyridine carboxylic acid (PyCOOH) at 298.15 K are determined by calorimetry at 298.15 K; thermodynamic functions ($\lg K_c$, D_cG^o, D_cH^o, TD_cS^o) of the complexation process between the reagents are calculated. His complexes with isomers (NA, INA, PA) of medium strength with 1 : 2 stoichiometry are established to be formed in the buffer solution. The influence of the structural isomerism of pyridine carboxylic acid on the stability of the formed complexes with histidine is shown; the values of stability constants ($\lg K_c$) increase in the series of PyCOOH isomers: PA < NA < INA. The entropy of complexation becomes more favorable (more positive) when the carboxyl group "shifts" from *ortho*- (RA) to *meta*- (NA) and *para*- (INA) positions relative to the nitrogen atom of the pyridine ring. It is found that the exothermic effect of interaction of His with PyCOOH isomers prevails over the endothermic effect of their dehydration in the buffer solution. Molecular complexes of His with NA, INA, and PA are stabilized predominantly by enthalpic contribution to the Gibbs energy of complexation. The main driving forces for the formation of His/2PyCOOH complexes are electrostatic interactions and formation of hydrogen bonds between zwitterions of L-histidine and anionic forms of NA, PA, and INA isomers under the phosphate buffer solution conditions of, pH 7.4.

REFERENCES

1. *Zhang J., Zhu C., Ma Y.* // J. Chem. Thermodynamics. 2017. Vol. 111. P. 52. http://dx.doi.org/10.1016/j.jct.2017.02.024
2. *Chauhan S., Singh K., Kumar K. et al.* // J. Chem. Eng. Data. 2016. Vol. 61. P. 788. https://doi.org/10.1021/acs.jced.5b00549
3. *Sawhney N., Kumar M., Sharma A.K. et al.* // J. Chem. Thermodynamics. 2017. Vol. 115. P. 156. https://doi.org/10.1016/j.jct.2017.07.040
4. *Tavallali H., Espergham O., Deilamy-Rad G. et al.* // Anal. Biochem. 2020. Vol. 604. P. 113811. https://doi.org/10.1016/j.ab.2020.113811
5. *Li Sh., Hong M.* // J. Am. Chem. Soc. 2011. Vol. 133. P. 1534. dx.doi.org/10.1021/ja108943n
6. *Gille A., Bodor E.T., Ahmed K. et al.* // Annu. Rev. Pharmacol. Toxicol. 2008. Vol. 48. P. 79. https://doi.org/10.1146/annurev.pharmtox.48.113006.094746
7. *Zhang Y.* // Annu. Rev. Pharmacol. Toxicol. 2005. Vol. 45. P. 529. https://doi.org/10.1146/annurev.pharmtox.45.120403.100120
8. *El-Dean A.M.K., Abd-Ella A.A., Hassanien R. et al.* // ACS Omega. 2019. Vol. 4. P. 8406. https://doi.org/10.1021/acsomega.9b00932
9. *Marinković A.D., Drmanić S.Ž., Jovanović B.Ž. et al.* // J. Serb. Chem. Soc. 2005. Vol. 70. P. 557.
10. *Gamov G.A., Kiselev A.N., Alexsandriiskii V.V. et al.* // J. Mol. Liq. 2017. Vol. 242. P. 1148. http://dx.doi.org/10.1016/j.molliq.2017.07.106
11. *Al-Saif F.A., Al-Humaidi J.Y., Binjawhar D.N. et al.* // J. Mol. Struct. 2020. Vol. 1218. P. 128547. https://doi.org/10.1016/j.molstruc.2020.128547
12. *Lugo M.L., Lubes V.R.* // J. Chem. Eng. Data. 2007. Vol. 52. P. 1217. https://doi.org/10.1021/je6005295
13. *Tyunina E.Yu., Krutova O.N., Lytkin A.I.* // Thermochimica Acta 2020. Vol. 690. P. 178704. https://doi.org/10.1016/j.tca.2020.178704
14. *Tyunina E.Yu., Krutova O.N., Lytkin A.I. et al.* // J. Chem. Thermodynamics. 2022. Vol. 171. P. 106809. https://doi.org/10.1016/j.jct.2022.106809
15. *Tyunina E.Yu., Mezhevoi I.N.* // J. Chem. Thermodynamics. 2023. Vol. 180. P. 107020. https://doi.org/10.1016/j.jct.2023.107020
16. *Chernova R.K., Varygina O.V., Berezkina N.S.* // Izv. of Saratov Univ. Nov. Ser. Ser. Chemistry. Biology. Ecology. 2015. Vol. 15. No. 4. P. 15. DOI:10.18500/1816-9775-2015-15-4-15-21
17. *Lytkin A.I., Badelin V.G., Krutova O.N. et al.* // Russ. J. Gen. Chem. 2019. Vol. 89. P. 2235 DOI:10.1134/S1070363219110124.
18. *Badelin V.G., Tyunina E.Yu., Mezhevoi I.N.* // Russ. J. Appl. Chem. 2007. Vol. 80. P. 711. Doi: 10.1134/S1070427207050047
19. *Tyunina E.Yu., Mezhevoi I.N., Dunaeva V.V.* // J. Chem. Thermodynamics. 2020. Vol. 150. P. 106206. Doi:10.1016/j.jct.2020.106206
20. *Smirnov V.I., Badelin V.G.* // Thermochim. Acta. 2015. Vol. 606. P. 41. http://dx.doi.org/10.1016/j.tca.2015.03.007
21. *Wadsö I., Goldberg R.N.* // Pure Appl. Chem. 2001. Vol. 73. P. 1625.
22. *Parker V.B.* Thermal properties of univalent electrolytes, vol. 2, Nat. Stand. Ref. Data Ser. Nat. Bur. Stand., US Gov., Washington, DC 2, 1965, pp. 66.
23. *Archer D.G.* // Phys. Chem. Ref. Data. 1999. Vol. 28. P. 1. Doi:10.1063/1.556034
24. *Badelin V.G., Smirnov V.I., Mezhevoi I.N.* // Zh. fiz. khim. 2002. Vol. 76. No. 7. P. 1299.
25. *Tyunina E.Yu., Badelin V.G., Mezhevoi I.N.* // J. Mol. Liq. 2019. Vol. 278. P. 505. Doi: 10.1016/j.molliq.2019.01.092
26. *Palecz B.* // J. Therm. Anal. Calorim. 1998. Vol. 54. P. 257.
27. *Palecz B.* // J. Am. Chem. Soc. 2005. Vol. 127. P. 17768.
28. *V.A. Borodin, E.V. Kozlovsky, V.P. Vasil'ev.* // Russ. J. Inorg. Chem. 1982. Vol. 27. Pp. 2169–2172.
29. Chemistry and biochemistry of the amino acids. / Ed. By G.C. Barret, Chapman and Hall, London-N.Y.; 1985.
30. *Pettit L.D.* // Pure Appl. Chem. 1984. Vol. 56. P. 247.
31. *V.P. Vasil'ev, L.A. Kochergina, V.Yu. Garavin.* // Russ. J. Gen. Chem. 1985. Vol. 55. P. 2780.
32. *Nagal H., Kuwabara K., Carta G.* // J. Chem. Eng. Data. 2008. Vol. 53. P. 619. https://doi.org/10.1021/je700067a
33. *Ashton L.A., Bullock J.* // J. Chem. Soc. Faraday Trans. Part 1. 1982. Vol. 78. P. 1177.
34. *Ross P.D., Subramanian S.* // Biochemistry. 1981. Vol. 20. P. 3096. https://doi.org/10.1021/bi00514a017
35. *Castronuovo G., Niccoli M., Varriale L.* // Tetrahedron. 2007. Vol. 63. P. 7047. Doi:10.1016/j.tet.2007.05.014
36. *Kuranova N.N.* Complexation and acid-base equilibria in water-organic solutions of Cu^{2+}, Fe^{3+} and nicotinic acid: Author's abstract of dissertation for a Candidate of Chemical Sciences degree. Ivanovo: Ivanovo State University of Chemistry and Technology. 2019. 16 p.
37. *Lytkin A.I., Chernikov V.V., Krutova O.N., Krutova E.D.* // Russ. J. Phys. Chem. A. 2020. Vol. 94. P. 2569. DOI:10.1134/S003602442012016X

38. *Lytkin A.I., Chernikov V.V., Krutova O.N., Krutova E.D.* // Ibid. A. 2020. Vol. 94. P. 1342. DOI:10.1134/S0036024420070213

39. *Sabbah R., Ider S.* // Can. J. Chem. 1999. Vol. 77. P. 249. https://doi.org/10.1139/cjc-77-2-249

40. *Koczoń P., Dobrowolski J.Cz., Lewandowski W.* // J. Molec. Struct. 2003. Vol. 655. P. 89. https://doi.org/10.1016/S0022-2860(03)00247-3

41. *Haj-Zaroubi M., Schmidtchen F.P.* // Chem. Phys. Chem. 2005. Vol. 6. P. 1181. DOI: 10.1002/cphc.200400559