Thermodynamics and the mechanism of interaction of uracil with amino acids in water

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Interaction of most of the side groups of amino acids with uracil and their dehydration do not contribute significantly to the pair interaction coefficients. It has been suggested that the interaction between the terminal groups of amino acids and the side groups of uracil (NH, CO) occurs by the acid-base mechanism. The possibility was found of formation of uracil + L-proline associates, owing to favorable configurations of the components, uracil + L-tryptophan associates, owing to π—π electronic interaction between their aromatic rings, and uracil + L-lysine · HCl, owing to the side ammonium group in amino acid.

Key words: amino acids, uracil, interaction, thermodynamics; complex formation.

Elucidation of the mechanism of interaction and molecular recognition between amino acids (AA) and nucleic bases (NB) is one of the most important problems in modern biophysical chemistry. These compounds participate in many processes occurring in living organisms.[1—5]

The reactions of NB with AA have been studied in a number of papers in connection with studies of the mechanisms of action of enzymes, hallucinogens, medicines and other biologically active substances.[5—7] A common drawback of these studies is that the authors attempted to elucidate the mechanism based on the investigation of individual NB with particular AA. In our opinion, to understand the general principles of the interaction and molecular recognition in the NB—AA system, it is necessary to carry out a complex study using various methods.

To continue the preliminary studies along this line,[8] in the present work, we investigated the thermodynamics of the reaction of uracil (a pyrimidine NB) with a wide range of AA containing aliphatic, nonpolar, aromatic, polar, and charged groups.

Experimental

Enthalpies of dissolution of uracil (Ura) in aqueous solutions of glycine (Gly), L-α-alanine (L-Ala), L-proline (L-Pro), L-valine (L-Val), L-leucine (L-Leu), L-methionine (L-Met), L-phenylalanine (L-Phe), L-histidine (L-His), L-tryptophan (L-Trp), DL-threonine (DL-Thr), L-asparagine (L-Asn), L-lysine hydrochloride (L-His · HCl), L-arginine hydrochloride (L-Arg · HCl), L-glutamic acid (L-Glu), and L-aspartic acid (L-Asp) were studied. Amino acids produced by the Sigma and Reanal companies were used; the latter were purified by recrystallization from aqueous ethanol. All the reactants were dried *in vacuo* at 60 °C for 4 days. The measurements were carried out at 25 °C using an isothermal calorimeter with a 17 mL-cell. The error in determining the enthalpies did not exceed ±0.03 J.

Weighed portions of Ura (Sigma) were dissolved in aqueous solutions of amino acids of various concentrations (0.005—0.500 mol kg^{-1}), and the enthalpy coefficients of pair interactions were found from the equation

$$\Delta_{tr}H_x(w \rightarrow w + y)/m_y = 2h_{xy} + 3m_y h_{xyy} + 3m_x h_{xxy}, \quad (1)$$

where $\Delta_{tr}H_x(w \rightarrow w + y)$ is the enthalpy of transfer of Ura (x) from water to aqueous solutions of amino acids (y); m_x and m_y are molalities of the corresponding components, x and y, of the solution; and the coefficients h_{xy}, h_{xyy}, and h_{xxy} are enthalpy heterotactic coefficients of pair and triple interactions. The values of h_{xy} were determined by the least-squares method as has been described previously.[9,10]

Results and Discussion

The calculated coefficients h_{xy} of the pair interactions of Ura with AA are listed in Table 1. For three pairs of compounds, they are abnormally large and negative: −8516 J kg mol^{-2} for Ura + L-Pro, −49331 J kg mol^{-2} for Ura + L-Trp, and −18708 J kg mol^{-2} for Ura + L-Liz · HCl. These h_{xy} values for the above pairs of compounds can be explained by the formation of associates between the AA and Ura molecules, accompanied by a marked exothermal effect, due to specific forces (π—π-electron interactions, H-bonds, ion-dipole interactions, *etc.*). It is generally believed that associates of this type incorporating aromatic molecules have sandwich-like structures,[11—13] and their formation is accompanied by exothermal effects.[12—14] The association of these molecules in solution found by us is also confirmed by the data of X-ray diffraction[15] and crystallographic[16] analysis, according to which in the case of

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Table 1. Enthalpy coefficients of the pair interactions of Ura (x) with amino acids (y) in water at 298.15 K

$x + y$	h_{xy} /J kg mol^{-2}	pH
Ura + Gly[a]	3297 (449)[b]	5.48 (0.05)[b]
Ura + L-Ala[a]	−9604 (603)	6.02 (0.1)
Ura + L-Val	2768 (448)	5.97 (0.05)
Ura + L-Leu	2852 (1855)	4.46 (0.15)
Ura + L-Pro[a]	−8516 (355)	6.02 (0.1)
Ura + DL-Met	14491 (876)	6.34 (0.2)
Ura + L-His	5676 (1874)	7.6—7.9
Ura + L-Phe[a]	−3645 (902)	5.95 (0.05)
Ura + L-Trp	−49331 (1989)	6.08 (0.15)
Ura + DL-Thr[a]	−584 (720)	5.44 (0.15)
Ura + L-Asn	7872 (1883)	4.05 (0.05)
Ura + L-Lis · HCl	−18708 (1622)	5.40 (0.2)
Ura + L-Arg · HCl	5692 (974)	5.47—5.14
Ura + L-Asp	135112 (7531)	2.83 (0.2)
Ura + L-Glu	31995 (2549)	2.96 (0.05)

[a] Lit. data.[8]
[b] The magnitudes of 95% confidence interval are given in parentheses.

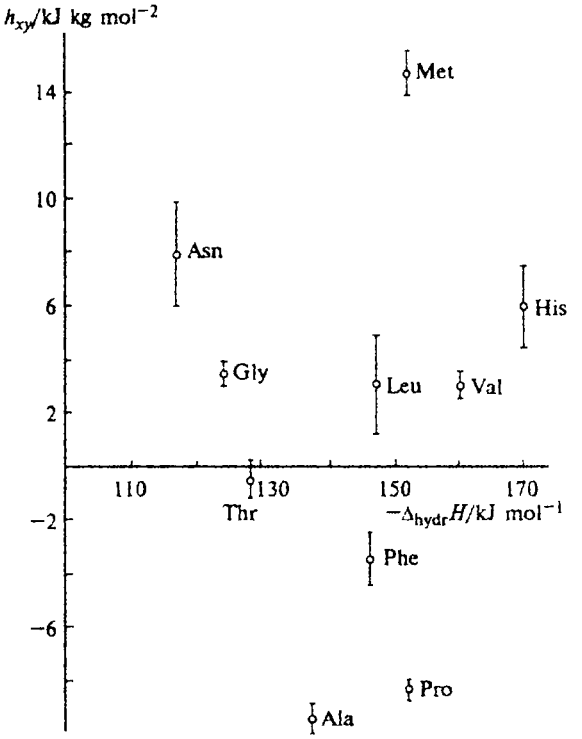
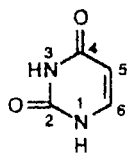


Fig. 1. Dependence of the coefficients of pair interactions (h_{xy}) of AA with uracil on the enthalpy of hydration ($\Delta_{hydr}H$) of AA.

L-Trp derivatives, electron-donating indole systems undergo association with the pyrimidine rings of the NB through π—π-overlap with partial charge transfer. In the case of the Ura + L-Liz · HCl system, acid-base interaction of the side NH_3^+ group of lysine with the O atoms of uracil is the most likely.

According to published data,[17] the O(2) and O(4) atoms are active centers in the uracil molecule, but the interaction with O(4) is more favorable than that with O(2). For the Ura + L-Pro system, the coefficient of pair interaction is abnormally negative; however, it is relatively low compared to those for the Ura + L-Trp and Ura + L-Liz · HCl systems. Therefore, it can be assumed that weak associates are formed through binding of the zwitterion to the side groups of Ura (NH, CO) and this is made possible by favorable configurations of the molecules. Thermodynamic characteristics of the complex formation for these compounds are listed in Table 2.



For other systems consisting of Ura and an aromatic AA (Ura + L-His, Ura + L-Phe), no association was observed. No tendency to form complexes was found in the case of the Ura + L-Ala system, for which h_{xy} is also abnormally negative. Unusually high positive h_{xy} coefficients were found for the Ura + Asp and Ura + Glu systems (135112 and 31995 J kg mol^{-2}, respectively). At the pH values studied (2.83 for Ura + Asp and 2.96 for Ura + Glu), amino acids exist in the H_3N^+—CHR—COOH form. The high positive h_{xy} values found for these systems can be regarded as being due to the endothermal effect of the dissociation of the carboxyl group in an AA.[18]

For the rest of the systems considered, the coefficients of pair interactions (see Table 1) take small posi-

Table 2. Thermodynamic characteristics of complex formation of Ura with some amino acids in water at 298.15 K

Compound	K_{as}[a] /kg mol^{-1}	$-\Delta G$ kJ mol^{-1}	$-\Delta H$ kJ mol^{-1}	ΔS /J · mol^{-1} K
L-Pro	4.8 (1.6)[b]	3.89 (1.29)[b]	5.31 (1.50)[b]	−4.77 (1.59)[b]
L-Trp	26.9 (9.8)	8.16 (2.72)	3.54 (1.20)	15.48 (5.16)
L-Liz · HCl	32.2 (10.9)	8.60 (2.87)	2.46 (0.86)	20.60 (6.87)

[a] K_{as} is the constant of complex formation of Ura with AA.
[b] The magnitudes of 95% confidence interval are given in parentheses.

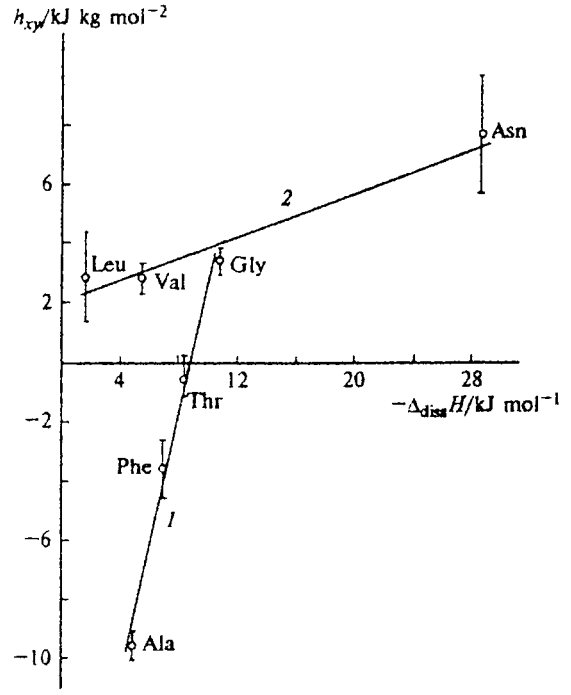


Fig. 2. Dependence of the coefficients of pair interactions (h_{xy}) of AA with uracil on the enthalpy of dissociation ($\Delta_{diss}H$) of the carboxyl group of AA for the series Ala—Phe—Thr—Gly (*1*) and Leu—Val—Gly—Asn (*2*).

tive or negative values; this rules out the possibility of complex formation. As can be seen from Fig. 1, no correlation can be followed between the enthalpy of hydration of an AA ($\Delta_{hydr}H$) and the h_{xy} value. In the study of thermodynamics of the interaction of molecules of various types in water, one should take into account the competing processes of their interaction (exothermal effect) and dehydration (endothermal effect). The linear dependence between h_{xy} and $\Delta_{hydr}H$ attest to weak interaction between the molecules of the dissolved substance accompanied by their partial dehydration.[19] The absence of linear dependence between the h_{xy} and $\Delta_{hydr}H$, which is observed in our case, can be explained by the competition between the two above processes without predominance of either of them and indicates that the effect of the solvent on the interaction is not a crucial factor.

Since for most of the AA, no interaction of the basic side groups with uracil was found, it can be assumed that the acid-base interaction of the terminal groups of AA with the side groups of uracil (NH, CO) plays an important role. To verify this assumption, we considered the dependences between the h_{xy} and $\Delta_{diss}H$ values[18] for the terminal groups of amino acids (NH_3^+, COO^-). Linear correlations were found for the dependence between h_{xy} and $\Delta_{diss}H$ for the carboxyl groups in AA. Two of these dependences are presented in Fig. 2. It can be seen that the slope of straight line *1* is larger than that of straight line *2*. Both dependences indicate that as the acid properties of the COO^- group increase, the exo-effect of this interaction increases.

Thus, it can be concluded that the interaction of AA with uracil is mostly an acid-base interaction, determined by the end groups of AA and by the side groups of uracil. The interaction of the side groups of most of the amino acids with uracil and their dehydration do not make crucial contributions to the coefficients of pair interactions.

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