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

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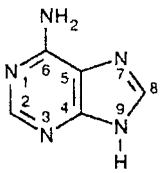
Two groups of amino acids, which react differently with adenine, are distinguished. In the case of nonpolar and aliphatic amino acids, the endothermic effect of dehydration plays a decisive role, while in the case of aromatic, polar, and charged amino acids the exothermic effect of interaction with adenine is dominant. Associates of Ade with Lys · HCl, His, Trp, Asp, and Glu were found. It was demonstrated that the complex-forming ability of purines (Ade and Caf) is higher than that of pyrimidines. Based on the linear enthalpy-entropy compensation effect for complexes of amino acids with adenine, it was suggested that the hydration state of interacting molecules contributes significantly to interactions of Ade with amino acids.

Key words: amino acid, nucleic acids bases, thermodynamics of interactions, complexation.

As part of continuing studies of thermodynamic characteristics of molecular recognition and interactions between nucleic acid bases and amino acids,[1–4] in the present work we studied the thermodynamics of interactions of adenine (purine base) with amino acids in water.



Experimental

The enthalpies of dissolution of adenine (Ade) in aqueous solutions of the following acids were measured at 25 °C with the use of an isothermic-shell calorimeter equipped with a 17-mL cell: glycine (Gly), L-a-alanine (L-Ala), L-proline (L-Pro), L-valine (L-Val), L-leucine (L-Leu), DL-methionine (DL-Met), L-phenylalanine (L-Phe), L-histidine (L-His), L-tryptophan (L-Trp), DL-threonine (DL-Thr), L-asparagine (L-Asn), L-glutamine (L-Gln), L-lysine hydrochloride (L-Lys HCl), L-glutamic acid (L-Glu), and L-aspartic acid (L-Asp). The error in measurements of thermal effects did not exceed 0.03 J.

Weighed samples of Ade (Sigma) were dissolved in aqueous solutions of amino acids with different concentrations (0.005—0.5 mol kg^{-1}) with the aim of determining enthalpy coefficients of pairwise interactions using the following equation:

$$\Delta_{tr}H_x(w \to w + y)/m_y = 2h_{xy} + 3m_yh_{xyy} + 3m_yh_{xxy},$$

where $D_{tr}H_x(w \to w + y)$ is the enthalpy of transfer of Ade (x) from water to aqueous solutions of amino acids (y); m_x and m_y are molalities of the corresponding compounds x and y of a three-component solution; and h_{xy}, h_{xyy}, and h_{xxy} are the enthalpy heterotactic coefficients of pairwise and three-body interactions. The values of the coefficients h_{xy} and h_{xyy} were calculated by the linear least-squares method.[5–6]

The amino acids were purchased from Sigma and Reanal. The latter were additionally purified by recrystallization from

Table 1. Enthalpy coefficients (h) of pairwise and three-body interactions of Ade (x) with amino acids (y) in water at 298.15 K

Solution x+y	h_{xy} /J kg mol^{-2}	h_{xyy} /J kg^2 mol^{-3}
Ade+Gly	1144 (1737)	
Ade+L-Ala	1859 (211)	−1.9 (0.5)
Ade+L-Leu	2678 (148)	8.1 (5.3)
Ade+L-Val	2123 (1257)	
Ade+L-Pro	1928 (1313)	20.0 (4.0)
Ade+DL-Met	2529 (936)	−2.7 (1.8)
Ade+L-Lys · HCl	−30563 (831)	344.0 (24.0)
Ade+L-Thr	−2176 (1027)	
Ade+L-His	−46892 (7861)	
Ade+L-Phe	−4703 (3507)	
Ade+L-Trp	−61373 (1997)	12.3 (141.0)
Ade+L-Asn	−16242 (3006)	
Ade+L-Gln	−6683 (398)	22.6 (11.2)
Ade+L-Asp	−83452 (2800)	1407.0 (150.0)
Ade+L-Glu	−69074 (6295)	1324.0 (306.0)

Note. The values of the 95% confidence interval are given in parentheses.

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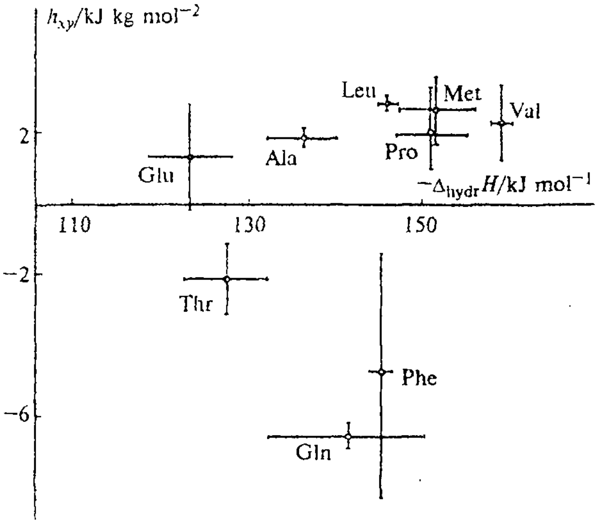

Fig. 1. Enthalpy coefficients of pairwise interactions of Ade with amino acids as a function of the enthalpy of hydration of amino acids.

an aqueous-ethanolic solution. All reagents were dried *in vacuo* at 60 °C for 4 days.

Results and Discussion

The calculated coefficients of pairwise and three-body interactions are given in Table 1. Two groups of amino acids, which react differently with adenine (Fig. 2), can be distinguished. The first group includes nonpolar (Gly, Pro, and Met) and aliphatic (Ala, Leu, and Val) amino acids with small positive values of h_{xy}. The second group consists of aromatic (Phe, His, and Trp), polar (Asn and Gln), and charged (Lys · HCl, Asp, and Glu) amino acids with negative values of h_{xy}. When the thermodynamics of interactions of molecules of different kinds in water is considered, the following competing processes are generally taken into account: interactions between dissolved molecules (exothermic effect), dehydration (endothermic effect), and water—water interactions (structural effects). It is believed that in the first group the effect of dehydration of Ade and amino acids dominates over the effect of interactions between amino acids. For amino acids of the second group, the exothermic effect of interactions of Ade with amino acids has a dominant role. No relationship between Δh_{xy} and ΔH_{dis} of the terminal groups (NH_3^+ and COO^-) of amino acids was found.[7] Therefore, the conclusion can be made that interactions of amino acids with adenine occur *via* side groups of amino acids, while terminal carboxy and amino groups virtually are not involved in interactions, as in the case of Ura.[3,4]

Associates of Ade with Lys · HCl, His, Trp, Asp, and Glu were found in aqueous solutions under study. The thermodynamic characteristics of this association are given in Table 2. Taking into account the thermodynamics of interactions of pyrimidine bases (Ura, Cyt, and Thy) with amino acids in water, it can be concluded that the complex-forming ability of purines (Ade and Caf [2]) is higher than that of pyrimidines.

Association of Ade with His can be explained by the interaction between the electron-donating indole system of His and the purine ring *via* the π—π overlap with a partial charge transfer. According to the crystallographic data,[8] no stacking interactions exist in the Ade+Trp system. Complexation between molecules is attributable to N_{Ind}—H...N_{Ade} hydrogen bonding distinguished by the N_{Ade} atom that acts as an acceptor of the H bond a second time.[9] An alternative explanation involves the charge-transfer interaction and the formation of the n—π complex. In the latter case, the amino group of Trp possessing the lone electron pair should act as a donor.[10] The absence of association with aromatic acid Phe may be related to the sterically hindered interaction between the aromatic and purine rings. In the case of the Ade+Lys · HCl, Ade+Asp, and Ade+Glu systems, association is most likely to occur through the acid-base interaction of the carboxy COO^- group with the N(1) and N(3) atoms of adenine, which are its active centers.[11] Although this mechanism of interaction is not ruled out for Asn and Gln, complexation was not observed for these amino acids, apparently due to the

Table 2. Thermodynamic functions of complexation of Ade with selected amino acids in water at 298.15 K

Compound	K_{as}	ΔH	ΔG	ΔS
	/kg mol^{-1}	kJ mol^{-1}		/J mol^{-1} K
L-Lys · HCl	17.1 (5.7)	−6.16 (2.05)	−7.04 (2.35)	2.94 (0.98)
L-His	24.2 (8.1)	−7.28 (2.43)	−7.89 (2.63)	2.04 (0.79)
L-Trp	27.4 (9.1)	−7.78 (2.59)	−8.20 (2.74)	1.44 (0.48)
L-Asp	4.2 (8.0)	−34.63 (11.60)	−3.57 (1.19)	−104.0 (35.0)
L-Glu	62.7 (21.3)	−4.32 (1.43)	−10.25 (3.42)	19.90 (6.60)

Note. K_{as} is the constant of complexation of Ade with amino acids. The values of the 95% confidence interval are given in parentheses.

neutralizing effect of the NH_3^+ group on the carboxy groups of amino acids.

Many authors noted an important role of the solvent in the process of complexation. The contribution of the solvent is reflected in the existence of the linear enthalpy-entropy compensation effect.[12–15] Actually, we found that ΔH_c and ΔS_c are related by the following correlation equation:

$$\Delta H_c(\mathrm{J\ mol^{-1}}) = -8161 + 235\ \Delta S_c\ (\mathrm{J\ mol^{-1}\ K^{-1}}).$$

The isokinetic temperature corresponding to this effect is 235 K.

When considering the nature of the compensation effect, the process of rearrangement of hydrogen bonds should be taken into account because water is a strong solvating solvent possessing an extensive network of hydrogen bonds. It is known that changes due to the presence of H bonds are approximately an order of magnitude larger then changes caused by weak interactions.[15]

Evidently, the existence of the enthalpy-entropy compensation effect proves that the hydration state of interacting molecules makes a substantial contribution to the reactions of Ade with amino acids.

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