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The Role of Weak and Specific Forces in the Interaction of Amino Acids with Cytosine, Uracil and Caffeine

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It is shown that the interactions of amino acids with nucleic acid bases and caffeine can, depending on the nature of the amino acids, be characterized as either *weak*, *i.e*. accompanied by partial molecular dehydration, or as *specific*, resulting in the formation of associates (dimers) by means of hydrogen bonding or π-π-interactions (stacking interactions).

The study of interactions between peptides and nucleic acids and their monomer units – amino acids and nucleic acid bases – is a fundamental problem in biology. It is known that biosynthesis of the protein molecule proceeds with participation of the specific sRNA molecules fixing the positions of the corresponding amino acids.[1] The molecular recognition of every amino acid is determined by the peculiar sequence of the nucleotides in sRNA. Thermodynamic investigations elucidate the nature and driving forces of these processes.

In this paper the enthalpies of solution of caffeine, cytosine and uracil have been measured in aqueous solutions of the following amino acids: glycine, L-α-alanine, L-β-phenylalanine, L-proline, DL-threonine and L-tryptophan at different concentrations. The amino acids mentioned contain polar, apolar and aromatic side chains and have a zwitterionic structure. This allows the study of a wide spectrum of possible interactions in biological systems. Cytosine and uracil are the components of nucleic acids and caffeine has a

Table 1 Enthalpic cross interaction coefficients and binding constants (K_B) for nucleic acid bases (x) and amino acids (y) in water at 298.15 K.[a]

Solutes (x + y)	h_{xy}/J kg mol^{-2}	h_{xyy}/J kg^2 mol^{-3}	K_B/kg mol^{-1}	R^b
Glycine + glycine	−439(5)[c]			
L-α-Alanine + L-α-alanine	217(0.4)[c]			
Caffeine + caffeine	−108860(886)[d]		10.2[e]	
Cytosine + glycine	−1839(669)			
Cytosine + L-α-alanine	10743(1937)	−10590(2667)		0.89
Cytosine + DL-threonine	5762(2301)	18345(7695)		0.77
Cytosine + L-proline	2469(192)	−701(385)		0.72
Cytosine + L-β-phenylalanine	27977(9408)			
Cytosine + L-tryptophan	37807(12801)			
Caffeine + glycine	378(287)			
Caffeine + L-α-alanine	493(453)	2280(681)		0.96
Caffeine + DL-threonine	−793(222)	2328(379)		0.95
Caffeine + L-proline	3112(298)	−1993(372)		0.94
Caffeine + L-β-phenylalanine	−21340(3115)	39294(17851)	10.0	0.74
Caffeine + L-tryptophan	−248260(7053)	1319690(157252)	14.9	0.95
Uracil + glycine	−2734(789)	3633(922)		0.91
Uracil + L-α-alanine	−9604(603)			
Uracil + DL-threonine	−584(720)	−18088(1939)		0.98
Uracil + L-proline	−8516(355)	8896(1134)	4.8	0.97
Uracil + L-β-phenylalanine	−3645(902)	−52730(5115)		0.99

[a]The number in parentheses represents the 95% confidence range. [b]Correlation coefficient. [c]Data from ref. 9. [d]Data from ref. 10. [e]Data from ref. 7.

similar structure to those of purine bases.

The amino acids were produced by "Reanal" (Hungary) and were additionally purified by recrystallization from water/ethanol mixtures. Nucleic acid bases and caffeine produced by "Sigma" were used without additional purification. All chemicals were dried *in vacuo* at 60 °C for four days before use.

The measurements of enthalpies of solution were performed using an isothermal calorimeter with cell volume 70 ml at 25 ± 0.005 °C. The solute mass was constant for every system. The solute molalities were as follows: M(caffeine) = 0.0032–0.0039 mol kg^{-1}; M(cytosine) = 0.0026–0.0043 mol kg^{-1}; M(uracil) = 0.0019–0.002 mol kg^{-1}. The error in the heat effect measurements was not greater than 0.08 J.

The samples of caffeine, cytosine and uracil were dissolved in aqueous solutions of amino acids of differing concentrations (from 0.05–0.9 mol kg^{-1}) in order to obtain the enthalpic coefficients of pair interactions, according to ref. 2.

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

In equation (1), ${}_{tr}H_x(w \rightarrow w + y)$ is the enthalpy of transfer of nucleic acid base (x) from water to aqueous solutions of amino acids (y). This equation is based on the virial expansion of McMillan–Mayer[3] for the excess enthalpies of solution. The quantities m_x and m_y are the molalities of x and y solutes in ternary solutions, respectively; and h_{xy}, h_{xyy} and h_{xxy} are the enthalpic heterotactic coefficients of pair and triplet interactions.

Since we used very low m_x concentrations, *i.e.* $m_x \rightarrow 0$ (standard state), the respective term in equation (1) may be neglected. The values of h_{xy} and h_{xyy} coefficients were obtained by a least-squares method. The results of the calculations are listed in Table 1.

The evaluated coefficients of pair interactions between amino acids and cytosine and caffeine, h_{xy}, are generally positive (Table 1). They are negative only for cytosine + glycine, caffeine + DL-threonine, caffeine + L-β-phenylalanine and caffeine + L-tryptophan pairs. The positive h_{xy} values suggest that there is probably a weak interaction between solute molecules accompanied by partial dehydration but without association due to specific interactions (H-bonding, electrostatic interactions, *etc.*). This fact is supported by the linear relationships found between h_{xy} and the enthalpy of hydration of the corresponding amino acids ΔH_{hydr}[4] (Fig. 1). The abnormally negative h_{xy} values for caffeine + L-β-phenylalanine and caffeine + L-tryptophan systems can be explained by the formation of associates between heterocycles of the molecules due to π-π-electronic interactions. It is usually considered that the structure of these associates is sandwich-like[5–7] and their formation is accompanied by a considerable *exo*-effect.[6–8] Such a mechanism of caffeine interaction with aromatic amino acids

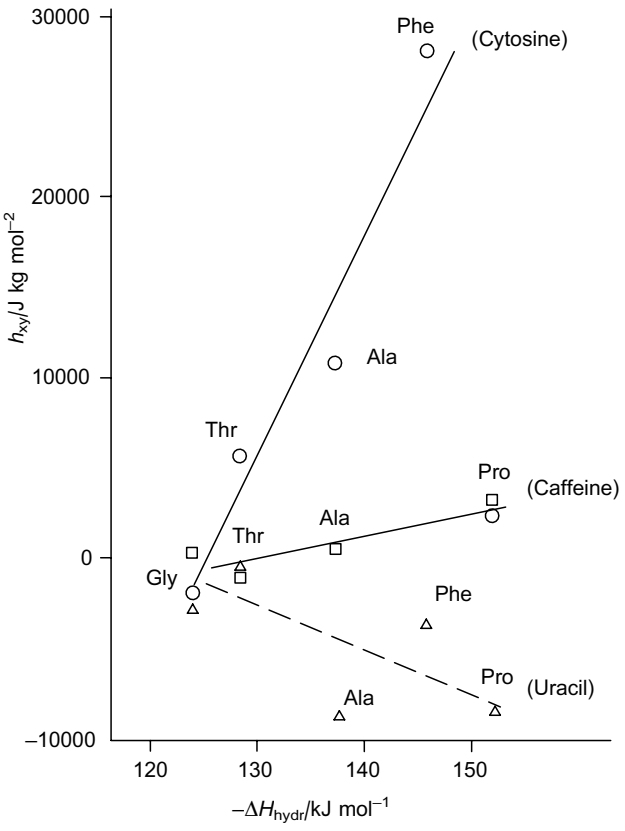

Fig. 1 Enthalpic coefficients for interaction of nucleic acid bases with amino acids *versus* the enthalpies of hydration of amino acids.

(L-β-phenylalanine and L-tryptophan) is confirmed by the fact that in the interaction with L-proline possessing an apolar cyclic side chain (the possibility of π-π-electronic interaction is absent) no associate formation has been found.

Negative h_{xy} values have been found for the interaction of amino acids with uracil (Table 1). Taking into account the competing effects of hydration and solute-solute interactions, the more negative h_{xy} values are explained by the more specific interaction of uracil with amino acids. Evidently, the endothermic effect of dehydration will be smaller in comparison with the exothermic effect of uracil interaction with amino acid. The appearance of a non-additive specific contribution to h_{xy} explains the absence of a linear dependence between h_{xy} and ΔH_{hydr} and the negativity of h_{xy} values. The uracil hydrogen bond formation (specific interaction) with amino acids leads to a specific association with L-proline (Table 1). In this case the binding between the zwitterion and the uracil side groups (NH, CO) becomes possible due to their favourable configurations.

Thus, the interaction of amino acids with nucleic acid bases and caffeine in water strongly depends on the hydration and specific properties of both. Cytosine and caffeine do not form complexes with aliphatic amino acids, but caffeine forms weak complexes with aromatic amino acids. Uracil is able to form associates with L-proline.

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