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# Interaction of Nonaromatic Amino Acids with Cyclodextrins in Aqueous Solution

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**Abstract**—Weak interactions of nonaromatic amino acids with α- and β-cyclodextrins in aqueous solutions at 298.15 K were studied calorimetrically. The structure and solvation of these compounds noticeably affect the thermodynamic characteristics of interparticle interactions.

The most remarkable feature of natural cyclic oligosaccharides, cyclodextrins, is their capability for selective interaction with various guest molecules to form inclusion compounds. This property of cyclodextrins makes them suitable as enzyme models [1, 2] and encapsulating materials [3, 4].

Previously we studied complexation of α-cyclodextrins with biologically active compounds, e.g., with amino acids [5, 6]. However, these data are incomplete, since only aromatic amino acids were considered. Previously we obtained the thermodynamic characteristics of weak interactions of β-cyclodextrin with amino acids [7]. In this work, our goal was to study calorimetrially the interaction of α-cyclodextrin with nonaromatic amino acids (Gly, Ala, Val, Leu, Pro, Asn, Thr, Ser) in aqueous solution and to reveal the effect of structure and solvation of reacting molecules on the thermodynamic characteristics of the interaction.

We found experimentally that interactions of α-cyclodextrin with nonaromatic amino acids in aqueous solutions are weak and are not accompanied by complexation; their description was based on analysis of the enthalpy virial coefficients $h_{xy}$ (see table).

Interaction of two solvated species in solution involves two steps: desolvation and intermolecular interaction proper. The quantity $h_{xy}$ includes contributions from both steps [8]. The resulting enthalpy coefficients (see table) are negative for almost all the considered systems α-cyclodextrin–amino acid. This means that the exothermic effect of amino acid interaction with α-cyclodextrin prevails over endothermic effect of molecule dehydration. Indeed, desolvation of amino acid does not play a major role, as suggested by approximately horizontal plot of $h_{xy}$ vs. enthalpy of hydration of amino acid molecules (see figure).

Enthalpy coefficients of pair interactions of α- and β-cyclodextrins with nonaromatic amino acids in aqueous solution at 298.15 K

| Amino acid | α-Cyclodextrin | | β-Cyclodextrin[a] | | p*I* |
|---|---|---|---|---|---|
| | $h_{xy}$, kJ kg mol$^{-2}$ | pH | $h_{xy}$, kJ kg mol$^{-2}$ | pH | |
| Glycine (Gly) | –10.43 (0.50)[b] | 5.47 | 3.78 (0.44) | 5.48 | 5.97 |
| *L*-α-Alanine (Ala) | –5.07 (0.47) | 5.93 | –1.87 (0.93) | 6.02 | 6.00 |
| *L*-Valine (Val) | –6.45 (0.76) | 5.92 | 4.19 (1.59) | 5.97 | 5.96 |
| *L*-Leucine (Leu) | –8.11 (1.20) | 5.26 | 43.30 (3.47) | 4.46 | 5.98 |
| *L*-Proline (Pro) | –2.95 (0.35) | 6.21 | 1.48 (0.34) | 6.02 | 6.30 |
| *L*-Asparagine (Asn) | –4.45 (0.99) | 4.28 | – | – | 5.41 |
| *L*-Serine (Ser) | –10.15 (0.58) | 5.79 | – | – | 5.68 |
| *L*-Threonine (Thr) | 6.40 (0.25) | 5.85 | – | – | 5.60 |

[a] Data of [7]. [b] The confidence ranges $\pm t_{0.95}\sigma$ are given in parentheses.

We believe that a major negative contribution to the enthalpy coefficients can be made by the following factors. First, a weak hydrogen bond is formed by a purely physical mechanism, without complex formation [10]. Second, the interaction involves release of water molecules from the solvation shell of α-cyclodextrin, which is confirmed by published data. The solvation shell of monomeric cyclodextrin units is formed by "distorted areas" [11]. A zwitterionic amino acid molecule (specifically this species is present in solution, because the solution pH was close to the isoelectric point p*I* of amino acids [12]) partially breaks the hydration shell of the macroring; water molecules are mainly released from the "distorted areas" of the solvation cosphere of α-cyclodextrin to the bulk of solution. This process is characterized by negative $h_{xy}$. Similar effects were observed in interactions of monosaccharides with glycine in aqueous solution [11]. Third, dispersion interactions can take place [13].

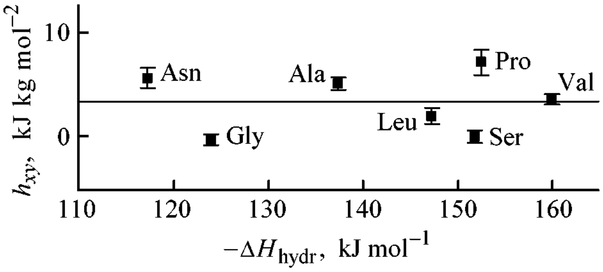
We compared the thermodynamic characteristics obtained for the same amino acids with different cyclodextrins. As compared to α-cyclodextrin, β-cyclodextrin has a larger molecular size [14]. Also, α-cyclodextrin stabilizes the structure of the solvent [15], whereas β-cyclodextrin breaks it [16]. We found that all these differences noticeably affect the interaction of these macrocyclic compounds with amino acids. For the α-cyclodextrin–amino acid systems, the exothermic interactions prevail ($h_{xy} < 0$, see table), whereas in the β-cyclodextrin–amino acid systems the prevailing contribution is made by dehydration of the interacting molecules ($h_{xy} > 0$, see table) [7]. Hence, the structure and properties of the macrorings can determine the character of their interaction with guest molecules.

Thus, our study showed that interactions of α-cyclodextrin with nonaromatic amino acids in aqueous solutions are weak; the structure and hydration state of the interacting molecules affect the thermodynamic characteristics of interparticle interaction.

## EXPERIMENTAL

Amino acids (Reanal, Hungary) were recrystallized from aqueous alcohol and dried in a vacuum oven at 350 K to constant weight (3 days).

α-Cyclodextrin (Sigma, the United States) was used without additional purification. The water content in α-cyclodextrin was 4 mol mol$^{-1}$, which was taken into account when calculating its concentration in solution.



Enthalpy coefficients of pair interaction of α-cyclodextrin with amino acids in aqueous solution at 298.15 K vs. enthalpy of hydration of amino acid molecules [9].

The thermal effects of solution of α-cyclodextrin [sample weight $(1.10 \pm 0.01) \times 10^{-2}$ g] in water [$\Delta H_s(H_2O)$] and in aqueous amino acid solutions [$\Delta H_s(AA)$] of various concentrations (0.05–0.25 mol kg$^{-1}$) were determined on a calorimeter with an isothermal jacket at 298.15 K and were subsequently used for calculating the enthalpies of transfer ($\Delta H_{tr}$) of the macrocycle from water to aqueous amino acid solutions [Eq. (1)]:

$$\Delta H_{tr} = \Delta H_s(AA) - \Delta H_s(H_2O). \quad (1)$$

The relative error in determination of the thermal effects did not exceed 0.6%. For more detailed description of the calorimeter design and experimental procedure, see [17].

The dependence of the enthalpy of transfer on the molal concentration of amino acid solutions is linear, indicating that the interactions are weak and are not accompanied by complex formation.

The weak interactions of α-cyclodextrin with nonaromatic amino acids were described on the basis of the enthalpy virial coefficients calculated by the least-squares method from expression (2) of the McMillan–Mayer theory [18, 19]:

$$\Delta H_{tr}/m_y = 2h_{xy} + 3m_y h_{xyy} + 3m_x h_{xxy} + \ldots \quad (2)$$

Here $h_{xy}$, $h_{xyy}$, and $h_{xxy}$ are the enthalpy coefficients of pair and ternary interactions, and $m_y$ and $m_x$ are the molal concentrations of amino acid ($y$) and α-cyclodextrin ($x$), respectively. Because we used dilute solutions with a constant and infinitely low concentration of α-cyclodextrin, the last term in (2) can be neglected.

The pH of solutions was measured with an I-130 pH meter with an accuracy of 0.10.

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