

Interactions of β -cyclodextrin with nonpolar and aromatic amino acids in water

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Three possible types of interactions of β -cyclodextrin with nonpolar and aromatic amino acids in water have been distinguished on the basis of enthalpic interaction coefficients data; these are weak solvent-governed interactions; entropy driven association and enthalpy driven complexation because of specific forces.

Cyclodextrins are frequently considered as appropriate models for enzymes. They are smaller than the enzymes, structurally simpler however, they possess the characteristic features responsible for biological activity. The cyclodextrin molecule has a nonflexible toroid structure with hydrophilic hydroxyl groups placed outside the macrocycle ring, whereas the interior of the cavity is hydrophobic. It is known that the nonpolar and aromatic side groups of polypeptide chains take part in different biochemical processes and can bind to the cyclodextrins.^{1,2} Therefore the amino acids chosen are good models for studying the mechanism and energetics of molecular recognition occurring in biological systems.

The enthalpies of dissolution of β -cyclodextrin (β -CD) in aqueous solutions of glycine, L-alanine, L-valine, L-leucine, L-proline, L-methionine, L-phenylalanine, L-histidine, L-tyrosine and L-tryptophan[†] at $25 \pm 0.005^\circ\text{C}$ were performed using an isothermal calorimeter with a cell volume of 17 ml. The error in the heat effect measurements was not greater than 0.03 J.

The samples of β -CD were dissolved in aqueous solutions of amino acids of different concentrations ($0.005\text{--}0.5\text{ mol kg}^{-1}$) in order to obtain the enthalpic coefficients of pair interactions, according to refs. 3, 4. In the cases where complexation takes place, the related thermodynamic characteristics have been calculated as well (Table 2).

The pH values of solutions investigated show that they are mainly the same, within uncertainty limits, and are close to their pI values. Only L-leucine and L-histidine show significant differences from their pI. Taking into account that for L-leucine pI = 5.98, the ionic equilibrium in solution shifts so that $\text{NH}_3^+-\text{CHR}-\text{COOH}$ (about 15%) is present together with the zwitterionic form of the amino acid. In the case of L-histidine about 20% of the molecules exist in solution in the form $\text{NH}_2-\text{CHR}-\text{COO}^-$. Of course, these effects result in some uncertainty in the interpretation of h_{xy} values for these

Table 1 The heterotactic enthalpic coefficients h_{xy} for the interaction of β -cyclodextrin (x) with amino acids (y) in water at 25°C .^a

Solute (y)	$h_{xy}/\text{J kg mol}^{-1}$	pH
Glycine	3778(435)	5.48(0.05)
L-Alanine	-1868(930)	6.02(0.1)
L-Valine	4192(1587)	5.97(0.05)
L-Proline	1482(339)	6.02(0.1)
L-Methionine	6393(1735)	6.00(0.05)
L-Leucine	43300(3465)	4.46(0.1)
L-Phenylalanine	72470(4409)	5.95(0.05)
L-Histidine	18328(1632)	7.6-7.9
L-Tryptophan	-111035(3012)	6.08(0.1)
L-Tyrosine	-326033(49000)	6.06(0.15)

^a The 95% confidence range is presented in parentheses.

[†] β -Cyclodextrin (β -CD) was obtained from Sigma. The amino acids used were purchased from Sigma (USA) and Reanal (Hungary) and were additionally purified by recrystallization from water-ethanol mixtures. All chemicals were dried *in vacuo* at 60°C for four days before use.

solutions. However, the aim of this work was to study the interactions between β -CD and a wide range of amino acids.

The magnitudes of the enthalpic coefficients h_{xy} for the interaction of β -cyclodextrin (β -CD) with amino acids (Table 1) allows one to separate three groups of compounds in water with different interaction characteristics. The first type is distinguished by the interaction between β -CD and glycine, L-alanine, L-valine and L-proline. For these systems the h_{xy} coefficients have comparatively small positive and negative magnitudes caused by a weak interaction which is accompanied by partial dehydration of the solutes (endothermic effect) without strong specific binding. In this case the solute-solute interaction is governed by the solvation effect.⁵

The systems for which the magnitudes of h_{xy} are abnormally high and positive (L-leucine, L-phenylalanine and L-histidine) form a second group. These peculiarities can be explained by the additional extra contribution of β -CD dehydration recovering the possible exothermic effect from specific interactions. Besides, the endothermic effect of proton dissociation of L-leucine⁶ can contribute to the positive h_{xy} magnitudes because of the presence of different charged forms of this amino acid in solution discussed above. Also, an additional endothermic contribution can appear upon the interaction of the large hydrophobic side group of the amino acids mentioned with the hydrophobic cavity of β -CD. In the case of L-phenylalanine and L-histidine the formation of weak associates with β -CD becomes possible because of the favourable entropy contribution (Table 2). They are typically entropy stabilized associates.^{7,8}

The interaction of β -CD with L-tryptophan and L-tyrosine is different, because the respective h_{xy} magnitudes are large and negative (Table 1). It is accompanied by the complexation and exothermic effect from specific (hydrogen bonds, ion-dipole *etc.*) forces (Table 2). To our mind the complexation is favoured due to the weaker hydration of L-tryptophan ($\Delta_{\text{hydr}}H = -117\text{ kJ mol}^{-1}$) and L-tyrosine ($\Delta H = -121\text{ kJ mol}^{-1}$) in comparison to the more strongly hydrated L-phenylalanine (-146 kJ mol^{-1}) and L-histidine (-170 kJ mol^{-1}). Therefore the process of complexation with L-tryptophan and L-tyrosine is promoted by the favourable enthalpic contribution and their dehydration is easier. Generally, as we see from our data, the interaction of β -CD with amino acids is mainly governed by the hydration state of host and guest; this is also reflected in the linear enthalpy-entropy compensation effect^{9,10} (Figure 1).

Table 2 The equilibrium constants (K_s), free energies (ΔG), enthalpies (ΔH) and entropies (ΔS) of complexation of β -cyclodextrin with some amino acids in water at 25°C .^a

Amino acid	K_s $/\text{kg mol}^{-1}$	ΔG $/\text{kJ mol}^{-1}$	ΔH $/\text{kJ mol}^{-1}$	ΔS $/\text{J mol}^{-1} \text{ K}^{-1}$
L-Phenylalanine	7.4(4.7)	-4.9(3.2)	25.4(3)	101.8(65)
L-Histidine	30.5(8)	-8.5(1.1)	2.1(0.2)	35.4(4.7)
L-Tryptophan	42.0(14)	-9.3(3)	-6.9(0.6)	7.9(2.6)
L-Tyrosine	184.5(92)	-12.9(6.5)	-3.9(1.4)	30.1(24)

^a Measurements were performed at the pH given in Table 1.

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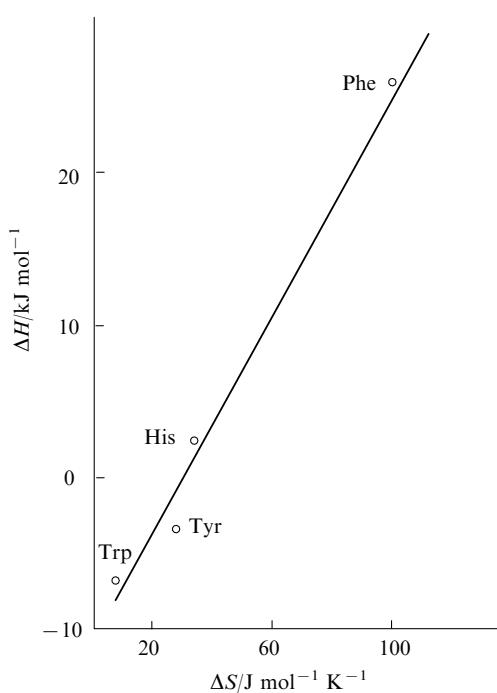


Figure 1 Enthalpy-entropy compensation effect for complexation of β -cyclodextrin with aromatic amino acids.

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