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THERMODYNAMICS OF THE INTERACTIONS OF PEPTIDES WITH α- AND β-CYCLODEXTRINS

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Abstract

The enthalpies of solution of α- and β-cyclodextrins is aqueous peptide solutions were determined experimentally at 298.15 K. The obtained results were used to calculate pair cross interaction parameters between solutes. The results are discussed in terms of the likely solute–solute interactions. For systems α-cyclodextrin+peptide and β-cyclodextrin+peptide the diametrically opposite character of interaction defined by structure and solvation of the molecules is observed.

Keywords: cyclodextrin, enthalpic cross coefficient, peptide, thermodynamics

Introduction

In the recent years native macrocyclic ligands such as cyclodextrins are often considered as appropriate models of enzymes [1, 2]. That is why the investigation of cyclodextrin–peptide interactions is important for biochemistry. The choice of guest molecules (in our case – peptides) is based on their biological meaning.

In the present work the enthalpy effects of the interactions of α- and β-cyclodextrins with glycine, diglycine, triglycine, glycyl-*L*-α-alanine, *L*-α-alanyl-glycine and *L*-α-alanyl-*L*-α-alanine in water at 298.15 K have been reported. The purpose of our study was analyzing the influence of the cyclodextrin cavity size, peptide structure and solvation of the reagents on the thermodynamics of their interactions in solutions.

Experimental

Materials

α- and β-cyclodextrins 'Sigma' were used as received. The peptides were purchased from 'Reanal' and were additionally purified by recrystallization from water–ethanol

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mixtures and dried under vacuum over several days at 343 K. The solutions were prepared by mass using doubly-distilled, degassed water.

Calorimetry

Measurements of the enthalpy of cyclodextrin dissolution in pure water and in aqueous peptide solutions of changed concentration (from 0.05 to 0.20 mol kg^{-1}) were performed using an isothermal calorimeter (with a cell volume of 17 mL) at 298.15 K in order to obtain the enthalpic virial coefficients (h_{xy}) according to [3, 4].

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

where $\Delta_{tr}H_x(w \rightarrow w+y)$ is the enthalpy of transfer of cyclodextrin (x) from water (w) to the aqueous solutions of peptide (y); m_x and m_y are the molalities of x and y solutes in ternary solutions respectively; h_{xy}, h_{xxy} and h_{xyy} are the enthalpic heterotactic coefficients of pair and triplet interactions. Since we used very low m_x (~$8 \cdot 10^{-4}$ mol kg^{-1}), i.e. $m_x \rightarrow 0$, the respective term in Eq. (1) may be neglected. The values of h_{xy} coefficients were determined by least-square method. The results are listed in Table 1.

Table 1 The enthalpic virial coefficients h_{xy} for the interaction of α- and β-cyclodextrins with peptides in water at 298.15 K

Peptide	h_{xy}/kJ kg mol^{-2}	
	α-cyclodextrin	β-cyclodextrin
Glycine	–10.43±0.50	3.78±0.44
Diglycine	–7.29±0.52	0.80±1.53
Triglycine	12.23±0.98	–10.46±2.95
Glycyl-*L*-α-alanine	4.72±0.59	–10.88±1.49
L-α-alanyl-glycine	–5.22±0.78	–12.98±2.85
L-α-alanyl-*L*-α-alanine	–17.48±1.58	12.88±1.43

The error in the heat effect measurement was not greater than 0.03 J.

Results and discussion

The evaluated coefficients of pair interactions for systems α-cyclodextrin+peptide and β-cyclodextrin+peptide are both positive and negative (Table 1).

For systems α-cyclodextrin/peptide it was found that lengthening the peptide framework from glycine to triglycine leads to the increase of h_{xy} values (Fig. 1). In this case, lengthening the peptide molecule makes α-cyclodextrin/peptide interactions less enthalpically favourable according to the rise of the enthalpy of the peptide dehydration (endothermic effect) [5].

The influence of the position of the methyl side residue in the peptide molecule on the interaction with α-cyclodextrin was defined. The possible contributions of CH_3-group to magnitude of h_{xy} can be evaluated as follows:

$$h_{xy}(–CH_3)=h_{xy}(\text{GlyAla})–h_{xy}(\text{GlyGly})=6.00 \text{ kJ kg mol}^{–2}$$

$$h_{xy}(–CH_3)=h_{xy}(\text{AlaGly})–h_{xy}(\text{GlyGly})=2.07 \text{ kJ kg mol}^{–2}$$

$$h_{xy}(2–CH_3)=h_{xy}(\text{AlaAla})–h_{xy}(\text{GlyGly})= –10.19 \text{ kJ kg mol}^{–2}$$

The results of the above calculations show the enthalpically favourable influence of the side CH_3-group only for system α-cyclodextrin+dialanine. Probably, CH_3-groups are able to screen from the solvent molecules the peptide end NH^{3+}- and COO^--groups that become less hydrated [6] and can participate in the interactions with hydroxyls surrounding the α-cyclodextrin cavity. In the case of GlyAla and AlaGly only one end group ($–COO^-$ and NH^{3+} accordingly) is screened from the water molecules and the influence of CH_3-group on the hydration state of NH^{3+} group is stronger [6]. Therefore, the contribution from the enthalpically favourable interactions is decreased and is recovered by dehydration effects. Our supposition is confirmed by experimental results: values of the enthalpic coefficients for systems α-cyclodextrin/AlaGly and α-cyclodextrin/GlyAla are relatively small compared to system α-cyclodextrin/AlaAla.

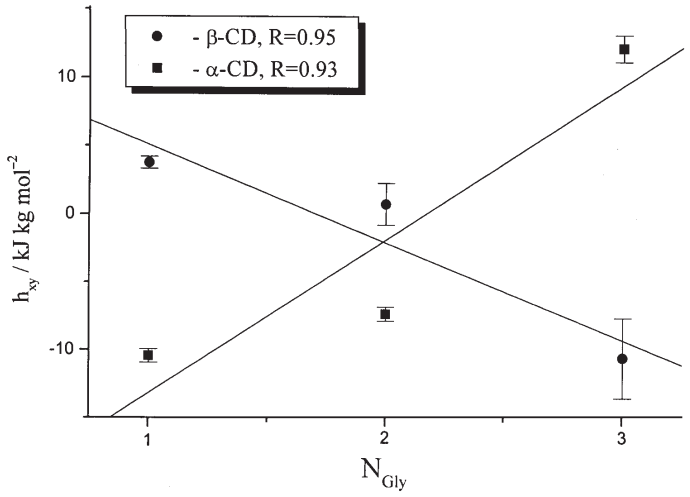

Fig. 1 Enthalpic coefficients for interactions of α- and β-cyclodextrins with peptides *vs*. the number of glycyl residues in the peptide molecule

Quite another situation is observed for β-cyclodextrin. As can be seen from Fig. 1, the values of h_{xy} are more negative and decreased with increasing of the number of glycyl residues. It allows to suppose that endothermic effects from dehydration of peptide molecules are recovered by exothermic effects from following probable interactions. Firstly, β-cyclodextrin consists of seven glucopyranose rings thus the

number of OH-groups surrounding macrocyclic cavity is larger than those in α-cyclodextrin. Therefore, we assume the possibility of formation of greater H-bonds between β-cyclodextrin and peptide molecules. Secondary, β-cyclodextrin and peptides are destructuring solutes [7, 8]. The cosphere overlap model is used for the description of the interactions of the examined compounds. According to this model overlapping the hydration cospheres of β-cyclodextrin and peptides leads to the release of water molecules from the β-cyclodextrin cosphere to solvent bulk. This process is exothermic and leads to the negative contribution to h_{xy} [7].

The influence of the position of side methyl group in the peptide molecule on the energetics of its interaction with β-cyclodextrin can be evaluated using an equations:

$$h_{xy}(-CH_3)=h_{xy}(\text{GlyAla})-h_{xy}(\text{GlyGly})= -11.68 \text{ kJ kg mol}^{-2}$$

$$h_{xy}(-CH_3)=h_{xy}(\text{AlaGly})-h_{xy}(\text{GlyGly})= -13.78 \text{ kJ kg mol}^{-2}$$

$$h_{xy}(2-CH_3)=h_{xy}(\text{AlaAla})-h_{xy}(\text{GlyGly})= 12.08 \text{ kJ kg mol}^{-2}$$

The calculation results and their combination with literature data [7] show that the side methyl group relaxes the hydration state of the peptide end groups promoting the energetically favourable peptide interactions with β-cyclodextrin. The interaction between dialanine and β-cyclodextrin is characterized by the greatest enthalpic coefficient. The end groups of dialanine molecule break the solvation spheres of the side CH_3-substitutes [9], which can participate in the hydrophobic interactions with apolar β-cyclodextrin cavity. In this case the geometrical factor may play a considerable role. β-cyclodextrin cavity size is greater on 1.4 Å compared to α-cyclodextrin [10], therefore, more favourable conditions arose for partial penetration of CH_3-groups into macrocyclic cavity. It is known from literature that one of the driving forces of the interactions of β-cyclodextrin with guest molecules is a hydrophobic interaction, and besides the more hydrophobic substitute the better binding [11]. In our case side CH_3-groups have relatively small dimensions, therefore strong binding leading to the complex formation is absent.

Conclusions

In conclusion of our investigation of the systems α-cyclodextrin+peptide and β-cyclodextrin+peptide, we would like to underline that the solvation of reagents, the differences in the cyclodextrin dimensions and in the geometry of the peptide molecules have an influence on the thermodynamics of their interactions in aqueous solutions.

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