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Volumetric and calorimetric study on complex formation of cyclodextrins with aminobenzoic acids

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A volumetric and calorimetric study on the complex formation of α- and β-cyclodextrins with isomeric aminobenzoic acids in water at 298.15 K revealed the noticeable influence of reagent structure on the driving forces and thermodynamic parameters of binding.

Cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides consisting of six or more glucose units linked by glycosidic bond. In supramolecular chemistry, they are known as macrocyclic ligands that are able to form inclusion complexes with a variety of guest molecules *via* noncovalent interactions.[1,2] CDs are widely applied as non-toxic encapsulating materials in pharmaceutical, cosmetic and food industries in order to improve the physico-chemical properties of biologically active molecules and to prolong their biological activity.[3,4]

This work is a continuation of our previous studies[5,6] devoted to the complex formation of native and substituted CDs with *para*- and *meta*-aminobenzoic acids (pABA and mABA, respectively). In particular, the binding mode of CDs with ABAs has been proposed on the basis of ^{1}H NMR data[5] and thermodynamic parameters of mABA complexation with β-CD, and its methylated and hydroxypropylated derivatives have been obtained.[6] The choice of pABA and mABA as guest molecules was determined by the following. First, pABA possesses a biological activity and displays therapeutic effect against typhus. Moreover, it is known as vitamin H_1 and used as a UV filter in sunscreen cosmetics.[7,8] mABA is also of great importance in the synthesis of analgesics, antihypertensives and vasodilators.[9,10] Therefore, encapsulated forms of these biomolecules are of practical significance. Second, pABA and mABA are structural isomers, consequently, the opportunity to analyze the influence of position of the functional groups in the aromatic ring on the complexation process will appear. In addition, the influence of CD cavity dimensions on the complex formation can be considered.

The complex formation of CDs with ABA has been studied by different experimental techniques.[11–18] Stability constants of 1:1 inclusion complexes and other thermodynamic parameters of their formation are listed in Table 1. Our results obtained previously[5,6] are also presented here. More stable complexes are formed between α-CD and pABA. Probably, principle of structural complementarity plays an important role and favours the binding in this case. The insertion of ABA into CD cavity was observed in all systems under consideration. Binding is accompanied by negative enthalpy and entropy changes; however, the $\Delta_c H$ and $\Delta_c S$ values obtained by different authors considerably differ (Table 1). Therefore, in this work, combination of calorimetric and volumetric methods was employed for more particular description of CD complex formation with ABA. The calorimetric measurements can be useful for accurate calculation of the thermodynamic parameters of binding. The results of densimetry allow one to obtain information on the

Table 1 Published data on the complex formation of cyclodextrins with aminobenzoic acids.

Complex	lg K	$\Delta_c G$/kJ mol^{-1}	$\Delta_c H$/kJ mol^{-1}	$T\Delta_c S$/kJ mol^{-1}	Method	Ref.
α-CD/mABA	1.7	–9.9	–32.5±0.3	–22.6±0.8	circular dichroism	18
	1.8±0.4	—	—	—	^{1}H NMR	5
α-CD/pABA	2.8±0.1	–15.9±0.4	–49±2	–33	calorimetry	17
	2.8	–16.0	–43.6±0.8	–27.6±2.5	circular dichroism	18
	3.0±0.4[a] (pH 2.0)	—	—	—	fluorescence	15
	3.15±0.08[a] (pH 3.5)	—	—	—	fluorescence	15
	3.1±0.6	—	—	—	^{1}H NMR	5
β-CD/mABA	1.8	–10.3	–8.7±0.3	1.6±1.3	circular dichroism	18
	2.2[b] (pH ~1)	–12.74	–68.0	–55.26	UV-VIS	11
	2.1[b] (pH ~1)	–12.23	—	—	fluorimetry	11
	1.8[b] (pH ~7)	–10.03	–68.0	–57.97	UV-VIS	11
	2.0[b] (pH ~7)	–17.26	—	—	fluorimetry	11
	1.8±0.3	—	—	—	^{1}H NMR	5
	1.85±0.03[a]	—	—	—	UV-VIS	6
β-CD/pABA	2.7	–15.4	–23.4±0.4	–8.0±1.3	circular dichroism	18
	2.4±0.3[a] (pH 2.0)	—	—	—	fluorescence	15
	2.8±0.2[a] (pH 3.5)	—	—	—	fluorescence	15
	1.9[b] (pH ~1)	–11.31	–70.75	–59.44	UV-VIS	12
	2.3[b] (pH ~1)	–13.51	—	—	fluorimetry	12
	1.5[b] (pH ~7)	–8.81	–70.75	–61.94	UV-VIS	12
	2.4[b] (pH ~7)	–13.72	—	—	fluorimetry	12
	2.8±0.6	—	—	—	^{1}H NMR	5

[a]At 293 K. [b]At 303 K.

Table 2 Thermodynamic parameters of the complex formation of cyclodextrins with aminobenzoic acids in water at 298.15 K.

Complex	Densimetry					Calorimetry			
	lg K	$V_{\Phi,c}$(ABA)/ cm^3 mol^{-1}	$\Delta V_{\Phi,c}$(ABA)/ cm^3 mol^{-1}	$V_{\Phi,c}$(CD)/ cm^3 mol^{-1}	$\Delta V_{\Phi,c}$(CD)/ cm^3 mol^{-1}	lg K	$\Delta_c G^0$/kJ mol^{-1}	$\Delta_c H^0$/kJ mol^{-1}	$T\Delta_c S^0$/kJ mol^{-1}
α-CD/mABA	1.7±0.2	82.3±1.9	–11.5±0.9	595.0±0.5	–8.3±0.7	1.8±0.2	–10.3±1.1	–21.9±0.6	–11.6±1.5
β-CD/mABA	1.8±0.2	111.8±0.9	18.0±0.8	732.4±0.9	27.2±0.6	1.8±0.1	–10.2±0.5	–2.2±0.1	8.0±0.8
α-CD/pABA	2.8±0.2	93.7±0.8	–9.1±0.9	596.5±0.5	–6.8±0.6	3.2±0.2	–18.3±1.1	–41.0±0.4	–22.7±1.6
β-CD/pABA	2.8±0.2	117.4±0.8	14.6±0.9	728.1±1.0	22.9±0.5	2.9±0.1	–16.6±0.6	–14.2±0.2	2.4±0.1

nature of solute–solute interactions and structural rearrangements in solution occurring upon inclusion complex formation. Note that densimetry is not so common for investigation of CD complexation as spectroscopy, calorimetry, solubility and other methods. As a consequence, the number of volumetric studies of CD complex formation is limited in the literature.[19]

The densities of solutions were measured at 298.15±0.01 K using a vibrating-tube digital densimeter (DMA 4500 model, Anton Paar, Austria) with a precision of 1×10^{-5} g cm^{-3}. The densimeter was calibrated with dry air and freshly prepared twice distilled water. The operation of the densimeter was checked by measuring the density of aqueous solutions of NaCl (Fluka, > 99.99%). A good agreement with the literature data[20] was detected. All the solutions were prepared by weight using twice distilled water and commercial mABA (Aldrich), pABA (Fluka), α-CD (Fluka) and β-CD (Fluka). α-CD and β-CD were stable crystal hydrates with water contents of 10 and 12.3%, respectively.

The apparent molar volumes (V_Φ) were calculated on the basis of the following relation:

$$V_\Phi = M/d + 10^3(d - d_0)/mdd_0, \quad (1)$$

where M is the solute molar mass; m is the molality; d_0 and d are the densities of solvent and solution, respectively. For binary systems (CD + H_2O) or (ABA + H_2O), water was the reference solvent with d_0 = 0.99704 g cm^{-3}. For ternary systems (CD + + ABA + H_2O), the reference solvents were aqueous solutions of CD or ABA. The two sets of experiments were carried out. The apparent molar volumes of CDs [V_Φ(CD)] were determined at constant CD concentration (0.005 mol kg^{-1}) and variable ABA concentration (0–0.04 mol kg^{-1}) and *vice versa* the apparent molar volumes of ABA [V_Φ(ABA)] were determined at constant ABA concentration (0.005 mol kg^{-1}) and changeable CD concentration (0–0.08 mol kg^{-1}). As an example, concentration dependences of V_Φ are plotted in Figure 1.

Enthalpies of CD solution in pure water (ΔH_w) and in aqueous solutions of ABA at concentrations of 0–0.04 mol kg^{-1} (ΔH) were determined at 298.15 K using the isothermal ampule calorimeter of solution. The calorimeter was described previously.[6] Enthalpies of transfer of CDs from water to aqueous solutions of ABAs ($\Delta_{tr}H$) were get by the following way:

$$\Delta_{tr}H = \Delta H - \Delta H_w. \quad (2)$$

Concentration dependences of $\Delta_{tr}H$ are presented in Figure 2. K and $\Delta_c H$ were calculated on the basis of these dependences using a nonlinear least-squares method. Subsequently, $\Delta_c G$ and $\Delta_c S$ were evaluated from the well-known thermodynamic equations. The thermodynamic parameters of complex formation summarized in Table 2 are in a good agreement with the data reported by Lewis *et al.*[17] and Harata[18] (Table 1). The observed in the other cases discrepancy can be caused by the different experimental conditions (temperature, pH).

It was detected in our previous works[5,6] and in the literature[11–18] that 1:1 complex formation of CDs with ABA takes place. This process is described by the equation:

$$\mathrm{CD + ABA} \rightleftharpoons \mathrm{CD{\cdot}ABA}. \quad (3)$$

According to the Young rule,[21] for 1:1 complexation mode, the V_Φ, which is separately determined for each reagent, contains the contributions from volumes of free and complexed species presented in the system:

$$V_\Phi = (1 - \alpha_c)V_{\Phi,f} + \alpha_c V_{\Phi,c}, \quad (4)$$

where α_c is the fraction of the complexes; $V_{\Phi,f}$ and $V_{\Phi,c}$ are the volumes of free and fully complexed species, respectively. Contributions due to ionization/protonation of ABA were considered as negligible in the concentration ranges under study since the measured pH of solutions (pH 3.6 for pABA and pH 3.9 for mABA) corresponded to the predominant existence of neutral (or zwitterionic) structures of ABA.[22,23] CDs do not dissociate under experimental conditions.[1,2]

Some mathematical rearrangements of equation (4) result in

$$V_\Phi = (V_{\Phi,f} + KV_{\Phi,c}m)/(1 + Km), \quad (5)$$

where K is stability constant of 1:1 complexes and m is the solute concentration. Analytical solution of equation (5) by nonlinear least-squares fitting gives $V_{\Phi,c}$ for each of reagents and K, the values of which are summarized in Table 2. The values of $V_{\Phi,f}$ preliminarily determined for binary systems (CD + H_2O) and (ABA + H_2O) were 603.3, 705.2, 102.8 and 93.8 cm^3 mol^{-1} for α-CD, β-CD, pABA and mABA, respectively. They are in a good agreement with values reported by Spildo *et al.*[24] for α-CD (604±2 cm^3 mol^{-1}), Milioto *et al.*[25] for β-CD (706.5±0.3 cm^3 mol^{-1}) and Hynčica *et al.*[26] for pABA (103.61 cm^3 mol^{-1}). No partial molar volumes of mABA were found in the literature.

The change in the molar volumes ($\Delta V_{\Phi,c}$) induced by complex formation can be calculated as

$$\Delta V_{\Phi,c} = V_{\Phi,c} - V_{\Phi,f}. \quad (6)$$

According to the above experiment, the values of $\Delta V_{\Phi,c}$ were estimated for CDs and ABAs (Table 2).

It can be seen in Table 2 that transfer of mABA and pABA from water to aqueous solutions of α-CD is accompanied by

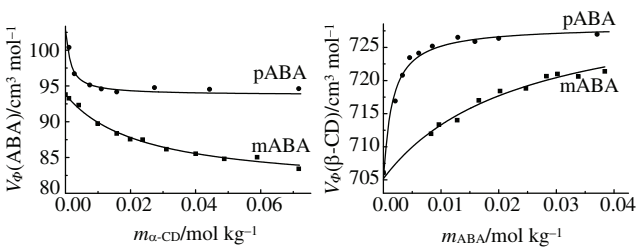

Figure 1 Concentration dependences of V_Φ.

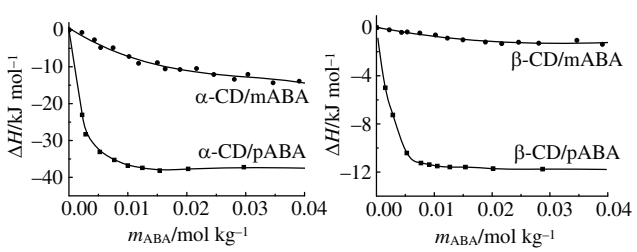

Figure 2 Isotherms of binding of ABA with CDs.

negative volume changes [$\Delta V_{\Phi,c}$(ABA) < 0]. The same character of volume changes was obtained for transfer of α-CD to aqueous solutions of both mABA and pABA [$\Delta V_{\Phi,c}$(α-CD) < 0]. The opposite behaviour of $\Delta V_{\Phi,c}$ was observed for β-CD complex formation. In these cases, an increase in the apparent molar volumes of ABA and β-CD was found (Table 2).

The $\Delta V_{\Phi,c}$ values can be interpreted on the basis of the reorganization of solvent (water) molecules during complex formation.[24,25,27–29] It is known that cavity of α-CD or β-CD contains 2 or 6.5 water molecules, respectively, which are partially or completely replaced by the guest molecules upon binding.[30,31] This process gives the positive contribution to the $\Delta V_{\Phi,c}$ values.[24,27,28] In addition, complex formation is accompanied by the partial destruction of hydration shells of ABA and CD. Restructurization of the hydration shells of the solutes can be explained using a cosphere overlap model proposed by Friedman and Krishnan.[29] According to this model, hydrophilic–hydrophilic interactions result in positive contribution to $\Delta V_{\Phi,c}$, whereas hydrophilic–hydrophobic and hydrophobic–hydrophobic interactions contribute negatively to $\Delta V_{\Phi,c}$.

Taking into account all these processes, one can suppose that negative $\Delta V_{\Phi,c}$ obtained for α-CD complexation is a result of dominant contribution from interactions occurring between polar groups of ABA and CD cavity and between aromatic ring of ABA and non-polar cavity of CD. These interactions are in agreement with the established shallow penetration of ABA in the α-CD cavity,[5] which is caused by the smaller diameter of macrocyclic cavity and characterized by negative values of enthalpy and entropy of complexation (Table 2). The partial insertion of ABA into α-CD cavity means that a part of guest molecule is outside the cavity and in contact with solvent. In this case, the contribution from dehydration is minimal, and negative $\Delta_c S$ is explained by the loss in conformation mobility of the solutes. The tight fitting of ABA into α-CD cavity is mainly governed by van der Waals interactions, which are accompanied by negative $\Delta_c H$ values (Table 2). However, the external H-binding is not excluded. Evidently, location of NH_2 group in the *para* position of an aromatic ring seems to be structurally favourable for its interactions with the OH groups of α-CD rims. The external interactions of α-CD with pABA due to their polar groups result in decreasing $\Delta_c H$ and $\Delta_c S$ and make $\Delta V_{\Phi,c}$(pABA) and $\Delta V_{\Phi,c}$(α-CD) less negative in comparison with those parameters for mABA/α-CD complexation (Table 2). Thus, more compact and less flexible complexes of higher stability are formed between pABA and α-CD.

As found previously,[5] the deeper penetration of ABA into β-CD cavity takes place. The positive $\Delta V_{\Phi,c}$ values (Table 2) observed for β-CD complex formation are related to release of more water molecules from β-CD cavity than from α-CD cavity. This fact is also confirmed by less negative $\Delta_c H$ and positive $\Delta_c S$ obtained for β-CD complexation (Table 2). Note that small negative $\Delta_c H$ and positive $\Delta_c S$ are also typical of hydrophobic interactions, which contribute negatively to $\Delta V_{\Phi,c}$, as provided by the cosphere overlap model.[29] However, the positive $\Delta V_{\Phi,c}$ values detected for β-CD complex formation (Table 2) testify that hydrophobic interactions are not the driving force of β-CD binding with ABA. Comparison of thermodynamic parameters of β-CD complex formation with isomeric ABA allows one to note that inclusion of mABA is accompanied by more intense dehydration and, as consequence, binding in this system is generally entropically driven. Thus, the obtained results point out that solvent reorganization plays an important role in β-CD complex formation.

Analysis of thermodynamic parameters listed in Table 2 allows one to emphasize the following points. Firstly, complex formation of CDs with ABA is determined by the position of the NH_2 group. In particular, binding of pABA with both CDs results in formation of more stable inclusion complexes. Secondly, the CD cavity dimensions influence only the enthalpy of complex formation and have no influence on the complex stability. Binding of ABA with α-CD was found as more enthalpically favourable.

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