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Thermodynamics of inclusion complex formation of hydroxypropylated α- and β-cyclodextrins with aminobenzoic acids in water

W. Zielenkiewicz · I. V. Terekhova · M. Wszelaka-Rylik · R. S. Kumeev

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Abstract Calorimetry, densimetry, ^{1}H NMR and UV–vis spectroscopy were used to characterize inclusion complex formation of hydroxypropylated α- and β-cyclodextrins with *meta*- and *para*-aminobenzoic acids in aqueous solutions at 298.15 K. Formation of more stable inclusion complexes between *para*-aminobenzoic acid and cyclodextrins was observed. The binding of aminobenzoic acids with hydroxypropyl-α-cyclodextrin was found to be enthalpy-governed owing to the prevalence of van der Waals interactions and possible H-binding. Complex formation of hydroxypropyl-β-cyclodextrin with both acids is mainly entropy driven. The increased entropy contribution observed in this case is determined by dehydration of solutes occurring during the revealed deeper insertion of aminobenzoic acids into the cavity of hydroxypropyl-β-cyclodextrin. By comparing complex formation of aminobenzoic acids with native and substituted cyclodextrins it was found that the availability of hydroxypropyl groups slightly influenced the thermodynamic parameters and did not change the binding mode or driving forces of interaction.

Keywords Aminobenzoic acid · Cyclodextrins · Inclusion complex formation · Thermodynamics

W. Zielenkiewicz · M. Wszelaka-Rylik
Institute of Physical Chemistry of Polish Academy of Sciences, 44/52 Kasprzaka, 01-224 Warsaw, Poland

I. V. Terekhova (✉) · R. S. Kumeev
Institute of Solution Chemistry of Russian Academy of Sciences, 1 Akademicheskaya str., Ivanovo 153045, Russian Federation
e-mail: ivt@isc-ras.ru

Introduction

Investigation and application of cyclodextrins (CDs) and their inclusion complexes in food, cosmetic and pharmaceutical industries as well as in separation technologies has greatly increased in the last decades [1–3]. CDs are cyclic oligosaccharides obtained by the degradation of starch and consisting of six (α-CD), seven (β-CD) and eight (γ-CD) glucose units. They are nontoxic and safe to use as encapsulating materials for drugs and biologically active compounds. Availability of a relatively non-polar internal cavity in the toroidal structure of CD brings about the inclusion complex formation of CDs with various organic molecules. The properties (solubility, stability, test, activity) of guest molecules placed inside the CD cavity can be significantly changed. Thus, the practical importance of CDs inclusion complexes is evident.

The possibility to use CDs for encapsulation of aminobenzoic acids (ABA) was discussed in our previous publications [4–6]. Aminobenzoic acids were chosen as guest molecules because of their properties; *p*-aminobenzoic acid (*p*ABA) is an essential nutrient that is required for folic acid synthesis by many organisms. Moreover, *p*ABA is often used in sunscreen formulations as a UV filter protecting the skin against ultra-violet radiation. *m*-Aminobenzoic acid (*m*ABA) being the biologically inactive structural isomer of *p*ABA is involved in the synthesis of dyes. Both acids are slightly soluble in water. Thus, inclusion complex formation with CDs can improve the physicochemical properties of ABAs.

Our previous investigations were concerned with complex formation of ABAs with native α- and β-cyclodextrins in solution [4–6]. These complexes were also intensively studied in literature [7–15]. The obtained results showed that the thermodynamic characteristics of complex formation in

aqueous solution are more affected by the ABA structure than the CD cavity dimensions. In the solid state, the formation of the 1:1 inclusion complex between β-CD and *p*ABA was confirmed by X-ray analysis [16]. *p*ABA was found to penetrate deeply into β-CD cavity, with the amino group located on the wider side of cavity and the carboxyl at the narrow side. The binding mode of *p*ABA with β-CD in the solid state is in agreement with those observed for the aqueous solution by Stalin et al. [14] and by us [4].

The complexation of ABAs with native CDs was studied in detail, whereas the binding with substituted CDs received relatively little consideration. To the best of our knowledge, only complex formation of hydroxypropyl-β-cyclodextrin with *p*ABA was investigated and reported by Shuang et al. [7]. It should be noted that modified CDs have received much attention in recent years due to their higher solubility and improved physicochemical properties.

Thus, the aim of our work was to study complex formation of hydroxypropylated α- and β-CDs with *p*ABA and *m*ABA in water at 298.15 K using calorimetry, densimetry, ^{1}H NMR and UV–vis spectroscopy. Specifically, it was planned to obtain the thermodynamic characteristics of complexation; to propose the binding mode and driving forces of interaction; to analyze the influence of reagent structure on the complex formation process; and to compare the binding affinity of native and hydroxypropylated CDs to ABAs.

Experimental

Materials

Hydroxypropyl-α-cyclodextrin (HP-α-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) were purchased from Sigma–Aldrich. The average substitution degree was 0.6 per glucose unit. Water content in CDs was determined thermogravimetrically. *p*ABA and *m*ABA (from MP Biomedicals) were not further purified. All solutions were prepared by weight on the basis of double-distilled, degassed water. Deuterated water of 99.9% isotopic purity was used in ^{1}H NMR measurements.

Methods

Calorimetry

Calorimetric measurements were performed using a high-sensitivity MicroCal OMEGA isothermal titration microcalorimeter at 298.15 K. The calorimeter was equipped with a stainless steel titration vessel (1.3611 mL) filled with CD solution (0.001 mol kg^{-1}). The 8 μL of ABA solution (0.01 mol kg^{-1}) were injected stepwise using a syringe pump equipped with a 250 μL Hamilton syringe. The measured thermal effects were corrected for the dilution of CD and ABA solutions. The values of stability constants and enthalpy of complex formation were calculated using standard Microcal program.

UV–vis spectroscopy

Absorption spectra were recorded in the range of 200–400 nm on a UV-2401 PC UV–VIS Recording Spectrometer (Shimadzu, Japan) equipped with TCC-240 A temperature controlled cell holder.

The quantitative determination of the stability constants is based on the absorbance variation of ABA in the presence of different amounts of CD. In this case, the ABA concentration was constant (6.7×10^{-4} mol kg^{-1}) and the CD concentration was changed from 0 to 4×10^{-2} mol kg^{-1}. The CD solutions of corresponding concentration were used in the reference cuvette. The experiments were carried out using 1 cm quartz cuvettes at different temperatures (293.15, 298.15, 308.15 and 318.15 K).

^{1}H NMR

^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer operating at 200 MHz. Cyclohexane was used as reference substance. The chemical shift changes ($\Delta\delta$) of ABA protons were determined at 298.15 ± 0.10 K. The concentration of ABA remained rigorously constant (0.005 mol kg^{-1}), while CD concentrations were varied from 0 to 0.025 mol kg^{-1}.

Densimetry

The densities of solutions were measured at 298.15 ± 0.01 K using a vibrating-tube digital densimeter (model DMA 4500, Anton Paar, Austria) with a precision of 1×10^{-5} g cm^{-3}. The densimeter was daily calibrated with dry air and freshly prepared bidistilled 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 [17] was found.

The apparent molar volumes of CDs (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 CD molar mass; m is the molality; d_0 and d are the densities of solvent and solution, respectively. For binary systems (CD + 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 ABA. The V_Φ were determined at constant CD concentration (0.005 mol kg^{-1}) and varying ABA concentration (0–0.04 mol kg^{-1}).

Results and discussion

In this work, thermodynamic study on complex formation of HP-α-CD and HP-β-CD with ABAs was carried out. The obtained thermodynamic parameters of complex formation reported in Tables 1, 2, 3, 4 were related to the process:

$$\mathrm{CD} + \mathrm{ABA} = \mathrm{CD} \times \mathrm{ABA}. \quad (2)$$

It was assumed that introduction of hydroxypropyl groups in CD molecule does not change the 1:1 stoichiometric ratio established early for complex formation of native α-CD and β-CD with ABAs [4–15]. In aqueous solution, ABAs can exist in three different states ranging from the fully protonated, through neutral, to anionic form. The pK values of the ionization are well known in the literature: $pK_1 = 3.1$ and $pK_2 = 4.8$ for *m*ABA and $pK_1 = 2.4$ and $pK_2 = 4.9$ for *p*ABA [18]. CDs dissociate in the alkaline medium (p$K \sim 12.2$) [19]. The predominance of each of the forms depends on pH. Measured pH of solutions of *m*ABA and *p*ABA was 3.9 and 3.7, respectively. These values are close to the isoelectric point of ABA at which the electrically neutral forms of all reagents are predominating. Thus, complex formation between CDs and the neutral species of ABAs takes place.

Table 1 reports the thermodynamic parameters of complex formation of hydroxypropylated α- and β-CDs with *m*ABA and *p*ABA evaluated from the calorimetric and UV–vis spectroscopic experiments. Thermodynamic parameters of complex formation of α-CD and β-CD with ABAs obtained in our previous work [6] are also included in Table 1. Calorimetric data are given in Fig. 1. Complexation of HP-β-CD with *m*ABA was accompanied by thermal effects that were too small to calculate K and $\Delta_c H^0$. Therefore, the UV–vis spectroscopy was used. The UV–vis spectra of *m*ABA were recorded in the presence of HP-β-CD and HP-α-CD at various temperatures. Spectroscopic study on complexation of HP-α-CD with *m*ABA was also performed in order to compare the results obtained by calorimetry and UV–vis spectroscopy. It supported the validity of spectroscopic data.

Table 2 Stability constants of *m*ABA/CD complexes at different temperatures

T/K	K/kg mol^{-1}	
	HP-α-CD	HP-β-CD
293.15	98 ± 3	94 ± 3
298.15	91 ± 3	96 ± 3
308.15	72 ± 3	96 ± 3
318.15	60 ± 3	98 ± 3

Figure 2 shows the absorbance spectra of *m*ABA in the presence of HP-α-CD and HP-β-CD. The addition of HP-α-CD and HP-β-CD increases the intensity and induces the red shift of absorption maxima at 306 nm in pure state of *m*ABA. The absorbance spectra reflect the isosbestic points, suggesting the complex formation. Figure 3 illustrates the concentration dependences of the absorbance obtained for several temperatures. Stability constants of the complexes were estimated using the nonlinear fitting procedure described previously [5]. The values of K at different temperatures are given in Table 2. Subsequently, the enthalpy and entropy of complex formation were evaluated from the temperature dependence of the stability constant (Fig. 4) according to equation:

$$\ln K = -\Delta_c H^0/RT + \Delta_c S^0/R. \quad (3)$$

As it is seen from Table 2, stability constants depend on temperature only in the case of *m*ABA/HP-α-CD complexation. The enthalpies of complex formation obtained from calorimetry and UV–vis spectroscopy data are in a

Table 1 Thermodynamic parameters of complex formation of CDs with aminobenzoic acids in water at 298.15 K

Complex	lg K	$\Delta_c G^0$/kJ mol^{-1}	$\Delta_c H^0$/kJ mol^{-1}	$T\Delta_c S^0$/kJ mol^{-1}
HP-α-CD/*m*ABA	2.0 ± 0.2	−11.4	−16.7 ± 0.3	−5.3
	2.0 ± 0.1[a]	−11.4[a]	−15.9 ± 0.7[a]	−4.5[a]
HP-β-CD/*m*ABA	2.0 ± 0.1[a]	−11.4[a]	≈0[a]	≈11.4[a]
HP-α-CD/*p*ABA	3.2 ± 0.2	−18.3	−36.5 ± 0.5	−18.2
HP-β-CD/*p*ABA	2.9 ± 0.2	−16.6	−11.7 ± 0.3	4.9
α-CD/*m*ABA [7]	1.8 ± 0.2	−10.3	−21.9 ± 0.6	−11.6
β-CD/*m*ABA [7]	1.8 ± 0.1	−10.2	−2.2 ± 0.1	8.0
α-CD/*p*ABA [7]	3.2 ± 0.2	−18.3	−41.0 ± 0.4	−22.7
β-CD/*p*ABA [7]	2.9 ± 0.1	−16.6	−14.2 ± 0.2	2.4

[a] Derived from UV–vis spectroscopy data

Table 3 Complexation-induced chemical shifts and stability constants of complexes of aminobenzoic acids with hydroxypropyl-cyclodextrins (298.15 K)

Complex	lg K	$\Delta_c\delta$/ppm				
		H(2)	H(3)	H(4)	H(5)	H(6)
HP-α-CD/*m*ABA	1.8 ± 0.1	0.04 ± 0.01	–	−0.16 ± 0.01	−0.06 ± 0.01	0.04 ± 0.01
HP-*β*-CD/*m*ABA	1.9 ± 0.2	−0.31 ± 0.01	–	−0.19 ± 0.01	−0.11 ± 0.01	−0.33 ± 0.01
HP-α-CD/*p*ABA	3.1 ± 0.3	0.29 ± 0.01	0.01 ± 0.01	–	0.01 ± 0.01	0.26 ± 0.01
HP-*β*-CD/*p*ABA	2.8 ± 0.4	−0.08 ± 0.01	−0.13 ± 0.01	–	−0.13 ± 0.01	−0.08 ± 0.01

Table 4 Thermodynamic characteristics of complex formation of hydroxypropyl-cyclodextrins with aminobenzoic acids in water at 298.15 K

Complex	lg K	$V_\Phi(\mathrm{CD})_f$/cm^3 mol^{-1}	$V_\Phi(\mathrm{CD})_c$/cm^3 mol^{-1}	$\Delta_{tr}V$/cm^3 mol^{-1}
HP-α-CD/*m*ABA	–[a]	791	789 ± 0.5	−2
HP-*β*-CD/*m*ABA	1.9 ± 0.1	861	885 ± 0.6	24
HP-α-CD/*p*ABA	2.9 ± 0.3	791	778 ± 0.5	−13
HP-*β*-CD/*p*ABA	2.6 ± 0.3	861	879 ± 0.8	18

[a] Calculation of K gives a considerable error due to very low ΔV

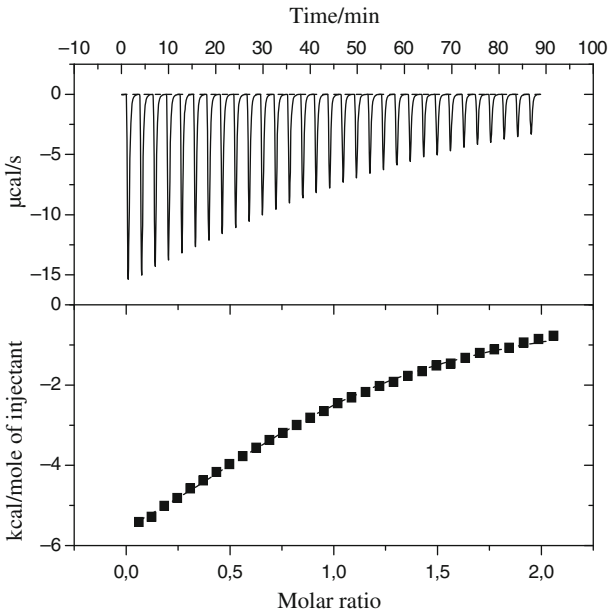

Fig. 1 ITC data for binding of *p*ABA (0.001 mol kg^{-1}) to HP-α-CD (0.01 mol kg^{-1}) at 298.15 K

good agreement (Table 1). The invariance of K with the temperature increase for binding of *m*ABA with HP-*β*-CD denotes the approximately zero enthalpy change, which is consistent with the calorimetric results.

Table 1 shows that the complex formation of HP-α-CD with *p*ABA and *m*ABA is enthalpy driven. By contrast, the complexes of HP-*β*-CD with both acids are enthalpy–entropy stabilized. This indicates that the difference in the cavity dimensions is reflected in different driving forces of complex formation and binding modes, which will be proposed below. Here, we consider the Δ_cH^0 and Δ_cS^0 values (Table 1). The enthalpy and entropy of CD complex formation contain the contributions from the following processes: (1) dehydration of reagents upon binding; (2) release of "high-energy" water from the CD cavity [20]; (3) formation of the complex due to non-covalent interactions [20]; (4) hydration of the complex. The first three processes are particularly important and mainly determine the magnitudes of Δ_cH^0 and Δ_cS^0.

Complexation of *p*ABA and *m*ABA with HP-α-CD having a smaller cavity diameter is more exothermic than that with HP-*β*-CD. It is known from previous work [4] that ABAs are included into α-CD cavity. Thus, the tight fitting of both ABAs into HP-α-CD cavity takes place. Such binding should be accompanied by stronger van der Waals interactions between ABA and HP-α-CD, which results in the high exothermicity of complexation. This in turn leads to a substantial loss in the degrees of freedom of the reagents and, as a consequence, the entropy loss is observed ($\Delta_cS^0 < 0$) (Table 1).

The larger cavity of HP-*β*-CD can promote a deeper insertion of ABAs, with more water molecules substituted by the ABA molecule upon complex formation and released in the bulk aqueous solution. This results in the enthalpy gain [20]. However, this is not the case for HP-*β*-CD complexation. Data from Table 1 show that the enthalpy of HP-*β*-CD complex formation with both *m*ABA and *p*ABA is less exothermic in comparison with Δ_cH^0 for HP-α-CD complexes. Probably, exothermic effects from van der Waals interactions and possible H-bonding as well as from the expulsion of cavity-bound water are overlapped by the endothermic effects from dehydration and hydrophobic interactions. Upon binding, the hydration shells of solutes are partially broken up and release of water

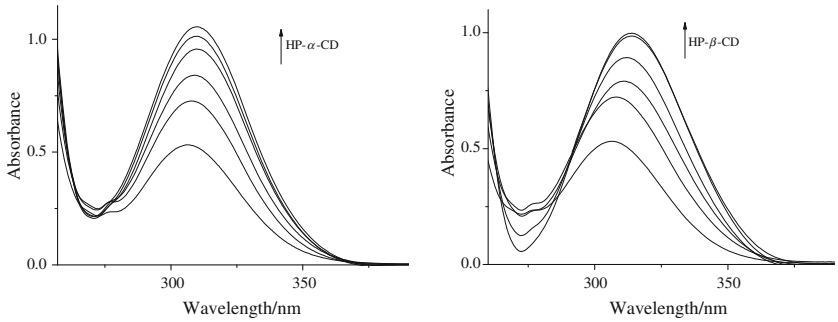

Fig. 2 The effect of HP-α-CD and HP-β-CD on UV–vis spectrum of *m*ABA (298.15 K)

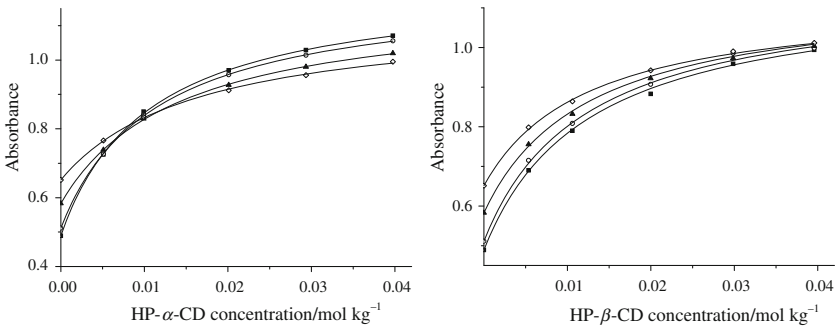

Fig. 3 Dependences of the *m*ABA absorbance from CD concentration (*filled square* 293.15 K, *open circle* 298.15 K, *filled triangle* 308.15 K, *open diamond* 318.15 K)

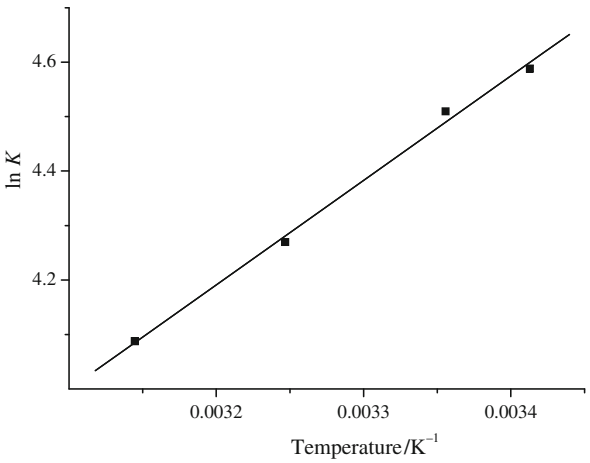

Fig. 4 van't Hoff plot for complex formation of *m*ABA with HP-α-CD

molecules to the disordered bulk solvent takes place, producing the positive contribution to $\Delta_c H^0$ and $\Delta_c S^0$. Moreover, hydrophobic interactions of the ABA aromatic ring with relatively apolar cavity of CD, which are also accompanied by the positive enthalpy and entropy values, possibly result in the increase of $\Delta_c H^0$ and $\Delta_c S^0$.

As compared with *m*ABA, the binding of *p*ABA with HP-α-CD and HP-β-CD is more exothermic and results in formation of more stable complexes (Table 1). There are two possible explanations for this. First, the amino group in *para*-position of the aromatic ring can be structurally favorable for complex formation with CDs. Perhaps, insertion of *p*ABA can be realized more easily due to the better shape-matching with the cavity. Second, the distinction in the solvation state of *m*ABA and *p*ABA molecules in aqueous solution can cause the different binding affinity. Evidence of predominant occurrence of *m*ABA as zwitterions in water and in the solid state was published in [21]. In contrast to *m*ABA, *p*ABA exists in neutral molecular form [22], less hydrated and, consequently, exhibiting higher complexing ability. According to this, interaction of *p*ABA with HP-α-CD and HP-β-CD is high-exothermic and results in formation of more stable complexes.

Hydroxypropylated CDs have some of the OH-groups substituted by hydroxypropyl groups. Hydroxypropyl groups in the CD exterior can result in a variety of complex formation processes owing to the changes in the cavity dimensions and hydrophobicity. Complexing properties of native and hydroxypropylated CDs can be compared from Table 1. It can be seen that hydroxypropyl groups practically do not affect the stability constants. Only a slight decrease of K is observed for complex formation of hydroxypropylated CDs with *m*ABA (Table 1). However, the influence of hydroxypropyl-groups on $\Delta_c H^0$ and $\Delta_c S^0$ was more noticeable. The increase in the enthalpy and entropy changes can be caused by the positive contribution from dehydration of bulky substituents upon complex formation.

^{1}H NMR technique can provide evidence for the inclusion complex formation of ABAs with hydroxypropylated CDs. Some concentration dependences of the chemical shift changes ($\Delta\delta$) are shown in Fig. 5. ^{1}H NMR spectra of CD protons were not examined because of the overlapping of some peaks. Stability constants and complexation-induced chemical shifts ($\Delta_c\delta$) listed in Table 3 were

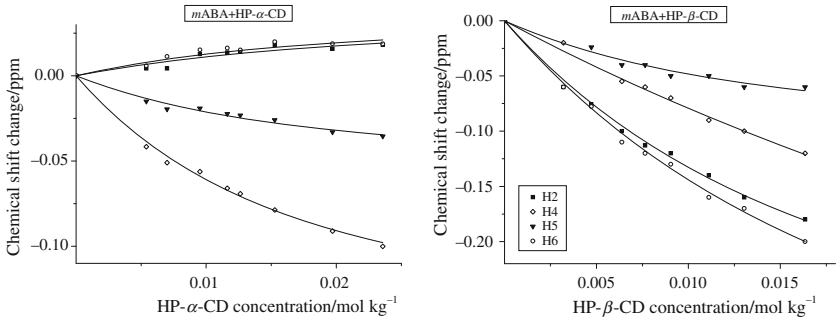

Fig. 5 Dependences of the chemical shift changes of *m*ABA protons from CD concentration (298.15 K)

calculated by non-linear regression analysis [4]. Comparison of K reported in Tables 1 and 3 shows a convergence of these values within the limits of experimental error.

The difference between $\Delta_c\delta$ observed for the investigated systems (see Table 2) shows that there are different binding modes involved. For complex formation of *m*ABA with HP-α-CD, the measurable $\Delta_c\delta$ for H(4) and H(5) protons of the aromatic ring were observed. This means that there is a shallow penetration of only a part of the aromatic ring of *m*ABA into the cavity of HP-α-CD. Probably, the NH_2-group in the *meta*-position serves as a steric hindrance during inclusion complex formation. Binding mode is different for complex formation of *m*ABA with HP-β-CD possessing a larger cavity diameter, when considerable $\Delta_c\delta$ values were detected for all protons of the aromatic ring. The $\Delta_c\delta$ is maximal for H(2) and H(6) protons which are close to the carboxylic group, indicating a deeper insertion of *m*ABA and location of the carboxylic group inside the HP-β-CD cavity.

Complex formation of *p*ABA with HP-α-CD induces a downfield shift of the signals of H(2) and H(6) protons. Probably, the amino group in *para*-position is favorable for the inclusion of aromatic ring with carboxylic group into the HP-α-CD cavity. Upon binding with HP-β-CD, the upfield shifts obtained for the signals of all *p*ABA protons show again the deeper penetration of guest into the macrocyclic cavity.

Our results are in agreement with the previous data [13–15, 22] and show that the hydroxypropyl substituents do not dramatically change the binding mode of ABAs with CDs. It should also be noted that the revealed deeper insertion of both *m*ABA and *p*ABA in the cavity of HP-β-CD accompanied by the stronger dehydration and hydrophobic interactions is consistent with the less negative enthalpy and entropy changes observed for these processes (Table 1).

Dehydration plays important role during complex formation of HP-β-CD. To clarify the role of the solvent, we performed the volumetric measurements. The experimental dependence of the apparent molar volume of HP-β-CD from *m*ABA concentration is shown in Fig. 6. From this dependence the stability constant and the apparent molar

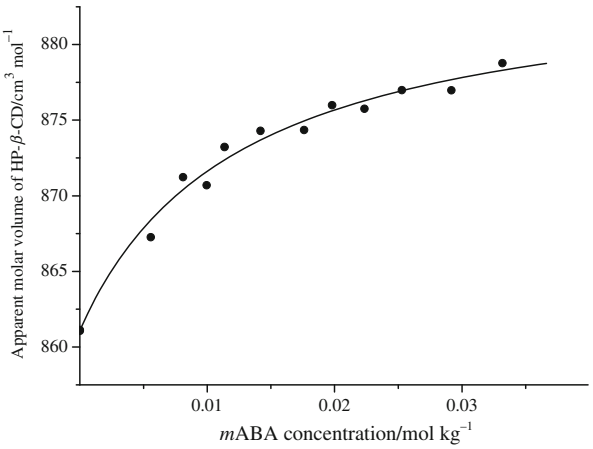

Fig. 6 Dependence of the apparent molar volume of HP-β-CD from *m*ABA concentration (298.15 K)

volume of fully complexed CD ($V_{\Phi,c}$) can be obtained as previously described [23]. Calculated K and $V_{\Phi,c}$ together with the experimental apparent molar volumes of free CD ($V_{\Phi,f}$) are summarized in Table 4. The $V_{\Phi,f}$ values are consistent with data obtained by Milioto et al. [24]. Trend of K variation remains in agreement with that revealed by calorimetry and ^{1}H NMR.

Generally, the volume changes accompanying the complex formation are explained on the basis of the volumes of transfer ($\Delta_{tr}V$):

$$\Delta_{tr}V = V_{\Phi,c} - V_{\Phi,f}. \quad (4)$$

The values of $\Delta_{tr}V$ are presented in Table 4. The magnitude and sign of $\Delta_{tr}V$ are determined by the ratio of two contributions from dehydration of CDs with ABAs occurring upon complex formation. One of them is the positive contribution caused by the volume increase due to the expulsion of cavity-bound water to the bulk solvent [25, 26]. The other is the contribution originating from destruction of solvation shells of the solutes and it is interpreted in terms of the cosphere overlap model [26, 27]. The magnitude of the second contribution depends on the nature of solute–solute interactions. According to this model, the overlap of cospheres of two hydrophilic solutes produces a volume increase, whereas the overlap of

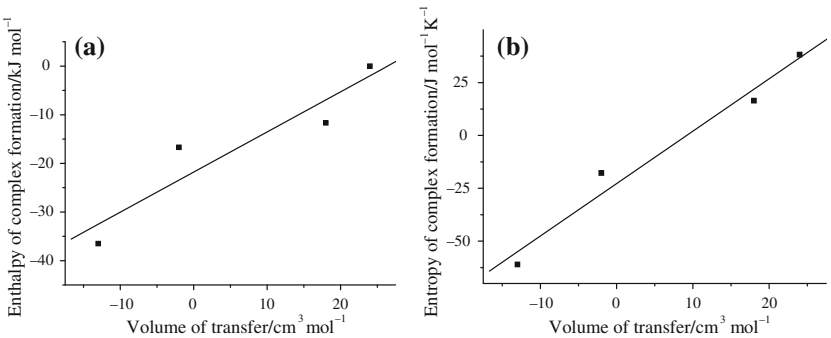

Fig. 7 Correlation between volumes of transfer and enthalpy (**a**) and entropy (**b**) of complex formation

hydrophilic–hydrophobic and hydrophobic–hydrophobic groups results in volume decrease.

The $\Delta_{tr}V$ are negative for complex formation of HP-α-CD with *p*ABA and *m*ABA, and positive for the binding of HP-β-CD with both acids. The same tendency was found earlier for complexation of ABA with native α-CD and β-CD [6].

When ABAs are included into the CD cavity, water molecules are expulsed in the bulk solvent. Empty cavity of α-CD contains two water molecules [28] whereas the β-CD cavity contains from five to seven water molecules [25, 29]. Binding modes proposed on the basis of ^{1}H NMR data argue in favor of the shallow penetration of ABAs into HP-α-CD cavity, with a partial release of cavity-bound water and, consequently, with reduced positive contribution from this process. Thus, the decrease in volume of HP-α-CD upon complex formation with ABAs is due to the prevalence of negative contribution from interaction of hydrophilic–hydrophobic and hydrophobic–hydrophobic groups. According to ^{1}H NMR, HP-α-CD binds only a part of the aromatic moiety of *m*ABA molecule (Table 3), decreasing the interaction in this system and the change of volume. On the other hand, the location of the carboxylic group of *p*ABA inside the HP-α-CD cavity, which is not excluded according to ^{1}H NMR, induces the hydrophilic–hydrophobic interactions and a considerable decrease of $\Delta_{tr}V$.

The deeper inclusion of ABAs into HP-β-CD cavity, which was revealed by ^{1}H NMR, is due to the release of more molecules of cavity-bound water, increasing the positive contribution to $\Delta_{tr}V$. The volume change upon substitution of cavity-bound water by guest molecule is

$$\Delta_{tr}V = nV(H_2O) - V(g) \quad (5)$$

where n is the number of ejected molecules of cavity-bound water; $V(H_2O)$ and $V(g)$ are the molar volumes of water and included guest molecule ($V(H_2O) = 18.07$ cm^3 mol^{-1} [25]) [30]. The partial molar volumes of *m*ABA (93.8 cm^3 mol^{-1}) and *p*ABA (102.8 cm^3 mol^{-1}) [6] were taken for $V(g)$ because the whole ABA molecule is placed inside, resulting in 6.5 and 6.7 water molecules expelled when *m*ABA and *p*ABA enter the HP-β-CD cavity. This result is in agreement with literature data [29–32]. In particular, González-Gaitano et al. [31] obtained $n = 6.5$ for complex formation of β-CD with decyltrimethylammonium bromide. The number of water molecules released from β-CD cavity upon binding with adenosine 5′-monophosphate and acetylsalicylic acid was found as $n = 6$ [32] and $n = 5.5$ [30], respectively.

The obtained results show that complexation of ABAs mainly with HP-β-CD involves the considerable solvent reorganization. This statement is supported by the less negative enthalpy and entropy values observed for HP-β-CD binding (Table 1). The following concordant orders of variation of thermodynamic properties of complex formation were found:

$\Delta_{tr}V$ HP-β-CD + *m*ABA > HP-β-CD + *p*ABA > HP-α-CD + *m*ABA > HP-α-CD + *p*ABA

Δ_cH HP-β-CD + *m*ABA > HP-β-CD + *p*ABA > HP-α-CD + *m*ABA > HP-α-CD + *p*ABA

Δ_cS HP-β-CD + *m*ABA > HP-β-CD + *p*ABA > HP-α-CD + *m*ABA > HP-α-CD + *p*ABA.

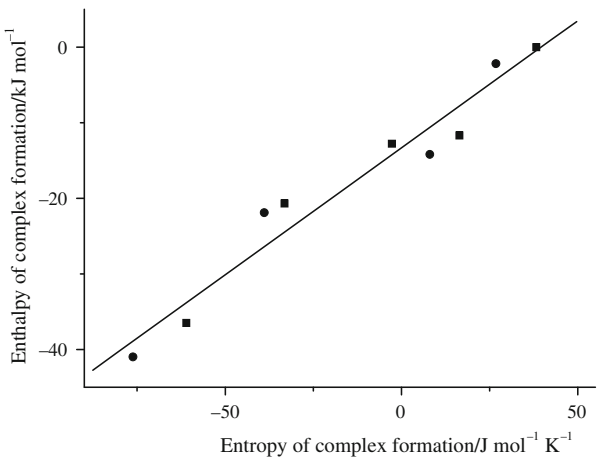

Fig. 8 Enthalpy–entropy compensation effect for complex formation of aminobenzoic acids with native (*filled circle*) and hydroxypropylated (*filled square*) α- and β-cyclodextrins in water at 298.15 K

The fact that more water molecules are released to the bulk solvent upon complexation, and also that lower exothermicity of binding and a higher degree of disorder in the system are observed is confirmed by the linear dependences $\Delta_c H = f(\Delta_{tr} V)$ and $\Delta_c S = f(\Delta_{tr} V)$ as well as by the enthalpy–entropy compensation effect, illustrated in Figs 7 and 8, respectively. The linear relationship between $\Delta_c H$ and $\Delta_c S$ (Fig. 8) means that enthalpy gain due to complex formation is compensated by the entropy loss.

Conclusions

Inclusion complex formation of HP-α-CD and HP-β-CD with isomeric aminobenzoic acids was studied by various experimental methods. Thermodynamic parameters of the 1:1 complex formation were calculated and analyzed in terms of the influence of reagents structure and solvent role. It was shown that CDs exhibit higher binding affinity to *p*ABA than to *m*ABA. Inclusion of ABAs into the cavity of HP-α-CD is enthalpy favorable owing to prevalence of van der Waals interactions and H-bonding as the main driving forces of binding. The observed deeper insertion of ABAs into the larger cavity of HP-β-CD is accompanied by considerable reorganization of solvent. Introduction of hydroxypropyl groups in CD molecules has no considerable influence on the complexation process.

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