Interactions of xanthine and its derivatives with cyclodextrins in aqueous solutions

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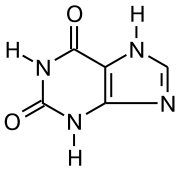
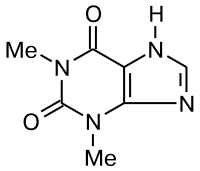
Using calorimetry, ^{1}H NMR, UV spectroscopy, and solubility methods, the interactions of natural and hydroxypropylated α-, β-, and γ-cyclodextrins with xanthine and its methylated derivatives (theophylline, theobromine, and caffeine) were studied in aqueous solutions at 298.15 K. Cyclodextrins revealed low complexation ability toward xanthine and its methylated derivatives. Hydroxypropyl-γ-cyclodextrin with the largest internal cavity is the most effective solubilizing agent for this type of compounds. The calculated thermodynamic parameters are discussed in terms of structural effects of cyclodextrins and purine alkaloids on the character of their intermolecular interactions in aqueous medium.

Key words: thermodynamics, cyclodextrin, purine alkaloids, inclusion complex.

The present work is a continuation of the earlier studies[1—6] on the natural and substituted α- and β-cyclodextrin (CD), which are promising solubilizing and encapsulating materials for purine alkaloids (caffeine, theophylline, and theobromine). Cyclodextrins are cyclic oligosaccharides of natural origin the molecules of which have hydrophilic surface and hydrophobic internal cavity.[7] Placed inside the CD molecular cavity, various organic compounds can significantly change their physicochemical properties (for example, solubility, stability, *etc.*). Inclusion complexes based on CD are water-soluble and safe for human beings, therefore their use in pharmaceutical, food, and cosmetic industries increases every year.[8—10]


Xanthine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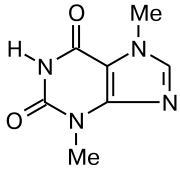
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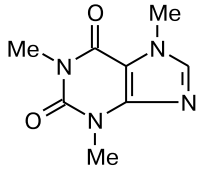
Caffeine

The xanthine derivatives under consideration are the most important representatives of the purine alkaloids; they possess biological and pharmacological activity. Poor water solubility and possible undesirable side effects reduce the value of the purine alkaloids as pharmaceuticals. The solubility and bioavailability of the purine alkaloids can possibly be improved if used as the inclusion complexes with CD.

A number of studies has been devoted to the increase in solubility and the prolonged therapeutic action of purine alkaloids by complexing with β-CD.[11—18] Nevertheless, the data obtained by different authors are quite contradictory (Table 1). For example, the enhancement of the solubility of theophylline in the presence of β-CD due to the formation of the 1 : 1 inclusion complex has been documented.[11] The stability constant of the complex (K = 1.62 L mol^{-1}), which was determined using the solubility method, differed substantially from the same parameter inferred from fluorimetric measurements (K = 130 L mol^{-1}).[12] Similar disagreement was observed for the inclusion complexes of caffeine with hydroxypropyl-β-CD (HP-β-CD): in one study, the increase in the solubility of caffeine due to complexation with HP-β-CD was observed,[13] while the opposite effect was documented in the other one.[14] It should be emphasized that information on the interaction of purine alkaloids with α- and γ-CD is missing, no studies on the complexation of xanthine with CD have been carried out.

Thus, the aim of the present work was to continue the study on complexation of α-CD and HP-γ-CD with xanthine, theophylline, theobromine, and caffeine in aqueous solutions, as well as to compare the complexing ability of various CD towards the purine alkaloids based on the thermodynamic parameters of interaction.

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Table 1. Published data on the complexation of CDs with purine alkaloids

Complex*	log*K*	Experimental conditions		Method
		T/K	Buffer	
β-CD—theophylline	0.21	293	—	Solubility[11]
	2.11	293	Britton—Robinson	Fluorimetric measurements[12]
HP-β-CD—theophylline	2.37	293	Britton—Robinson	Fluorimetric measurements[12]
β-CD—theobromine	2.86	293	Britton—Robinson	Fluorimetric measurements[12]
HP-β-CD—theobromine	2.88	293	Britton—Robinson	Fluorimetric measurements[12]
β-CD—caffeine	2.23	293	Britton—Robinson	Fluorimetric measurements[12]
HP-β-CD—caffeine	2.60	293	Britton—Robinson	Fluorimetric measurements[12]
	2.85	303	Phosphate (pH 7.4)	Solubility[13]
	2.46	298	—	Fluorescence measurements[15]

* HP is hydroxypropyl.

Experimental

Xanthine (Fluka), theophylline (1,3-dimethylxantine, MP Biomedicals), theobromine (3,7-dimethylxantine, MP Biomedicals), caffeine (1,3,7-trimethylxantine, MP Biomedicals), α-CD (Fluka), and HP-γ-CD (Aldrich) are commercially available. Randomly substituted HP-γ-CD has the average substitution degree of 0.6 per glucopyranose unit. All used CD are stable crystal hydrates, the amount of water in crystal lattices was taken into account in the calculations of concentrations. All solutions were prepared by weight using freshly bidistilled water.

Solubility method. The solubility of xanthine and its methylated derivatives was determined in water and in aqueous CD solutions of variable concentrations. The saturated solutions placed in glass tubes were continuously stirred at 298.15±0.05 K for 48 h. After achieving the equilibrium (determined by periodic measurements of concentration), the solutions were centrifuged at 298.15 K, then the resulting solutions were filtered using Acrodisc CR Syringe Filter (PTFE, 0.2 μm pore size), diluted with water or aqueous solutions of CD, and UV spectra were recorded. The average value of solubility was calculated using the data from three measurements.

UV spectroscopy. The UV spectra were recorded on an SPh-46 spectrophotometer (Russia) in quartz cells (1 cm) at room temperature. The concentration of purine alkaloids was constant value; the concentration of CD was the variable parameter. The CD solution of the corresponding concentration was used as a reference.

Calorimetry. The solution enthalpies of CD in water and aqueous solutions of purine alkaloids were measured with an ampoule isothermal calorimeter at 298.15±0.01 K. Calorimetric instrument have been described in details elsewhere.[19] The experimental errors of the heat effects of dissolution did not exceed 0.6%.

The enthalpies of transfer of CD from water to aqueous solutions of purine alkaloids $\Delta_{tr}H(w \rightarrow w + y)$ were calculated on the base of the experimental data by the following equation:

$$\Delta_{tr}H(w \rightarrow w + y) = \Delta_{s}H(w + y) - \Delta_{s}H(w), \qquad (1)$$

where $\Delta_{s}H(w)$ and $\Delta_{s}H(w + y)$ are the solution enthalpies of CD in water (w) and aqueous solution of purine alkaloids (w + *y*), respectively. In the calorimetric measurements, the concentration of CD was a constant value, and for various CD was in the range of $5 \cdot 10^{-4}$—$1.7 \cdot 10^{-3}$ mol kg^{-1}, while the concentration of purine alkaloids varied from 0 to the maximum possible value limited by solubility.

The enthalpies of transfer of CD from water to aqueous solutions of purine alkaloids $\Delta_{tr}H(w \rightarrow w + y)$ were plotted against the concentrations of purine alkaloids (see, for example, Fig. 1).

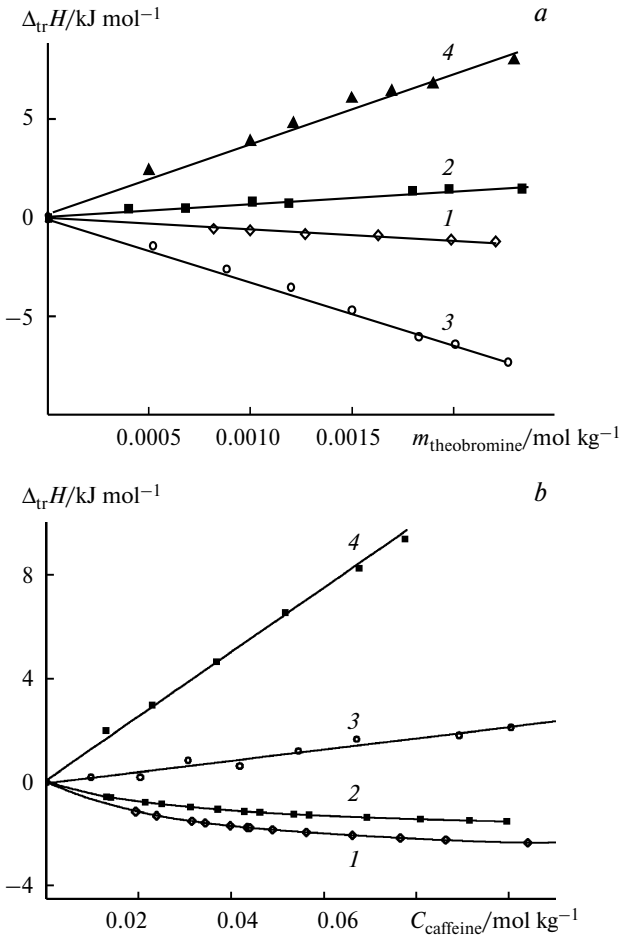

Fig. 1. Enthalpy of transfer of CD from water to aqueous solutions of purine alkaloids *vs.* alkaloid concentration (298.15 K): α-CD (*1*), β-CD (*2*), HP-β-CD (*3*), and HP-γ-CD (*4*).

In the majority of cases, the concentration dependences have linear character. Therefore, the interactions in such systems were characterized by the enthalpic virial coefficients, which were calculated by the equation based on the McMillan—Mayer theory:[20,21]

$$\Delta_{tr}H(w \rightarrow w + y)/m_y = 2h_{xy} + 3h_{xyy}m_y, \quad (2)$$

where h_{xy} and h_{xyy} are the enthalpic coefficients of pairwise and triple interactions, respectively, m_x and m_y are the molalities of CD and purine alkaloid, respectively.

Caffeine is better soluble in water than xanthine, theophylline, and theobromine. Consequently, the possibility to obtain more concentrated solutions of caffeine led to the increase in the yield of the inclusion complex. This feature was reflected by appearance of the inflection points on the curves that described interactions of caffeine with α- and β-CD (see Fig. 1, *b*). For these two systems, the stability constants (*K*) and enthalpy changes ($\Delta_c H^\circ$), standard free-energy changes ($\Delta_c G^\circ$), and entropy changes ($\Delta_c S^\circ$)[1,2] for the complex formation were calculated using the HEAT program package.[21]

^{1}H NMR spectroscopy. The ^{1}H NMR spectra were recorded on a Bruker AC-200 instrument operating at 200 MHz in D_2O at 298.15±0.10 K. The chemical shifts are given in the δ scale relative to cyclohexane (external standard).

Results and Discussion

Interactions of xanthine with CD were studied by UV spectroscopy and the solubility method, since the ^{1}H NMR spectroscopy and calorimetry cannot be used due to very poor solubility of xanthine in water. The UV spectra of xanthine were recorded in the presence of different concentrations of CD. Addition of 100-fold molar excess of CD did not affect the position of the absorption maximum and its intensity indicating weak interactions of xanthine with CD.

The calculations of geometry of xanthine molecule performed using the HyperChem 7.01 program package revealed that the internal cavities of β-CD and HP-γ-CD are the most structurally suitable for the formation of the inclusion complexes. Therefore, the detailed study of the interactions of xanthine with β-CD, HP-β-CD, and HP-γ-CD were performed by the solubility method. The solubility of xanthine was determined in aqueous solutions of β-CD,[6] HP-β-CD,[6] and HP-γ-CD of variable concentrations. The increase in the solubility of xanthine was observed in the presence of all mentioned CD (Fig. 2, *a*). The linear character of the solubility plot of xanthine *vs.* CD concentrations was observed. According to Higuchi and Connors,[23] this dependence corresponded to the A_L type and indicated 1 : 1 stoichiometry of the complexes formed. The stability constants of such complexes were calculated by the following equation:

$$K = b/[S_0(1 - b)], \quad (3)$$

where S_0 is the solubility of the alkaloid in water, *b* is the slope of the solubility plot. It is of note that the S_0 values obtained in the present study are in good agreement with those documented.[24—26] The *K* values calculated using Eq. (3) are given in Table 2. Alkaloids are prone to self-association in solutions,[26,27—29] but this was neglected in the calculations. However, as it has recently been shown,[29] β-CD prevented the self-association of caffeine due to the formation of the 1 : 1 inclusion complex. Therefore, in the present work, as in many others devoted to the studies of the complexation of purine alkaloids with CD,[12,13,15] it was assumed that it is the monomeric forms of xanthine and its methylated derivatives that interact with CD.

It can be seen from the data given in Table 2 that the *K* values are in the range of 4.5—20.8 kg mol^{-1}, which suggested low stability of complexes of xanthine with CD in aqueous solutions. The increase in the size of the internal CD cavity and introduction of hydroxypropyl substituents favor the complexation resulting in the increase in the *K* values. In the case of HP-γ-CD, the formation of the most stable complex was observed.

The solubility diagrams of theophylline and theobromine are shown in Figs 2, *b*, *c*. Analysis of the *K* values (see Table 2) shows an increase in the stability of the complexes on going from α-CD to the bulkier HP-γ-CD. For example, theobromine gave more stable complexes with all studied CD, while the influence of the position of the methyl groups on the *K* values is insignificant.

It is known[20,21,30] that enthalpic virial coefficients are the contributions in the corresponding free-energy coefficients (g_{xy}) and reflect the enthalpy changes in the system caused by the solute—solute and solute—solvent interactions. Typically, the interaction of CD with guest molecules is noncovalent and includes the hydrogen bonding, hydrophobic, van der Waals, and electrostatic interactions.[31] Each of these type of interactions along with desolvation process contribute to of the h_{xy} values (Table 3).

It followed from these data that the interactions of theophylline and theobromine with α-CD and HP-β-CD were favorable as regards enthalpy ($h_{xy} < 0$), while their interactions with β-CD and HP-γ-CD were endothermic ($h_{xy} > 0$).

Table 2. Stability constants (*K*) of complexes of cyclodextrins with purine alkaloids calculated by the Higuchi—Connors method ($T = 298.15$ K)

Alkaloid	*K*/kg mol^{-1}			
	α-CD	β-CD	HP-β-CD	HP-γ-CD
Xanthine	—[a]	4.5±0.1[b]	10.7±0.1[b]	20.8±0.1
Theobromine	3.0±0.1	2.1±0.1[b]	<1[b,c]	4.1±0.1
Theophylline	1.2±0.1	2.0±0.1[b]	<1[b,c]	3.1±0.1
Caffeine	—[a]	4.1±0.2	<1[b,c]	5.5±0.2

[a] Was not studied.
[b] See Ref. 6.
[c] The complexes are weak ($K < 1$) or are not formed.

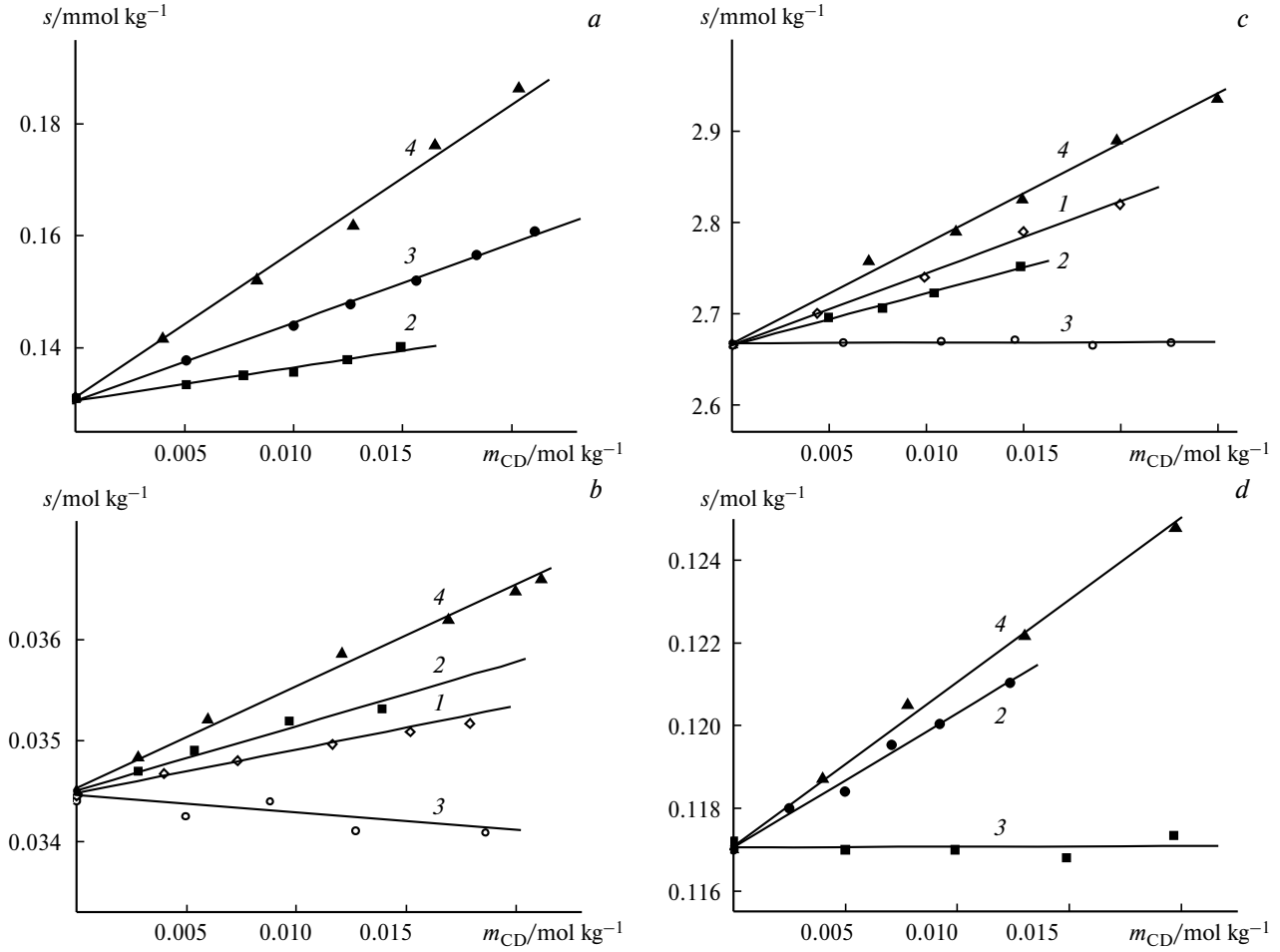

Fig. 2. Solubility of purine alkaloids: xanthine (*a*), theophylline (*b*), theobromine (*c*), and caffeine (*d*) in the presence of cyclodextrins (298.15 K): α-CD (*1*), β-CD (*2*), HP-β-CD (*3*), and HP-γ-CD (*4*).

The sizes of the theophylline and theobromine molecules calculated by the HyperChem 7.01 program package are 7.6×6.0 and 6.8×6.7 Å^2, respectively. The α-CD internal cavity has a diameter of 4.7—5.2 Å and a depth of 7.9 Å (see Ref. 7). It is obvious that the α-CD internal cavity is too small for inclusion of theophylline or theobromine. Indeed, the ^{1}H NMR spectra of theophylline in water and aqueous α-CD solutions[5] exhibited no changes in the chemical shifts for the theophylline protons, which might be caused by the weak interaction with CD. Probably, the exothermic effects and negative values of the enthalpic coefficients (h_{xy}) of the interactions of theophylline and theobromine with CDs are due to the predominance of the van der Waals interactions and hydrogen bonding between the polar groups of purine alkaloids and the external hydroxy groups of CD. However, one cannot exclude some penetration of the lateral methyl groups of the alkaloids into the macrocyclic cavity, which could explain certain enhancement in the solubility of theophylline and theobromine in the presence of α-CD.

Table 3. Enthalpy parameters of interaction of CD with purine alkaloids in water at 298.15 K

Alkaloid	h_{xy}/kJ kg mol^{-2}			
	α-CD	β-CD	HP-β-CD	HP-γ-CD
Theobromine	−355±17	489±59[a]	−1230±71[a]	2378±92
Theophylline	−11±2[b]	12±1[b]	−145±7[b]	126±9
Caffeine	—	—	8±2[c]	64±4[c]

[a] See Ref. 6.
[b] See Ref. 5.
[c] See Ref. 4.

Interactions of theophylline and theobromine with β-CD exhibited endothermic effect, $h_{xy} > 0$ (see Table 3). The β-CD cavity diameter (6.0—6.5 Å)[7] better suits to the size of the theophylline and theobromine molecules. In this case, the penetration of theophylline or theobromine in the macrocyclic cavity is more probable, which was demonstrated by the change in the chemical shifts for the theophylline protons in the presence of β-CD.[5]

Thus, the hydrophobic groups of alkaloids occupy the β-CD cavity, which leads to the increase in their solubility (see Fig. 2, *b*, *c*). The interaction of theophylline or theobromine with β-CD results in partial destruction of the solvent shells of the reagent, which gave the positive (endothermic) contribution into the enthalpy of interaction. In addition, hydrophobic interactions of the methyl groups of alkaloids with the macrocyclic cavity, which also exhibit the positive enthalpy changes, cannot be ruled out as well.

Partial substitution of the OH groups of β-CD by the 2-hydroxypropyl groups increased the diameter of the internal cavity, however, these bulky substituents can exert the steric hindrance for the inclusion of the guest molecule into the macrocyclic cavity. We found that the interactions of HP-β-CD with theophylline and theobromine are the most exothermic (see Table 3), *i.e.*, the most favorable as regards enthalpy. Despite, no increase in the solubility of the alkaloids was found in the presence of HP-β-CD (see Fig. 2, *b*, *c*). These data suggest the surface interactions due to the hydrogen bonding between the polar groups of the alkaloids and HP-β-CD.

The influence of CD on the solubility of theophylline and theobromine was observed again on going to HP-γ-CD (see Fig. 2, *b*, *c*). Probably, the increase in the cavity diameter of HP-γ-CD favors structurally the formation of the inclusion complexes, which were found to be the most stable (see Table 2). The relatively high positive h_{xy} values, which were found for the interaction of theophylline and theobromine with HP-γ-CD, are due to greater release of the solvent molecules from the solvent shells of the reagents to the bulk. Thus, the endothermic character of binding could be explained by more intense dehydration of the guest and the host and possible hydrophobic interactions. The ^{1}H NMR spectra exhibited no significant changes in the chemical shifts for the theophylline protons, the Δδ values being in the range of 0.00—0.02 ppm. Therefore, it could be assumed that no firm contact between theophylline and the macrocyclic cavity occurred due to the large size of the latter, and the complexation is rather due to significant changes in the solvent structure.

Caffeine is more hydrophobic than theobromine and theophylline.[32] Therefore, it manifested higher affinity to the CD hydrophobic cavity and forms complexes with unsubstituted α- and β-CD (see Fig. 1, *b* and Table 4).[1—3] It clearly followed from these data that the complexation exhibited small negative $\Delta_c H^\circ$ values and positive $\Delta_c S^\circ$ values with prevailing entropic contribution to the free energy. Due to the higher solubility of caffeine, the ^{1}H NMR spectra of α- and β-CD in the presence of caffeine were recorded.[3] The ^{1}H NMR spectra of CD revealed the signals for all protons. It is of note, that only the H(3) and H(5) protons located inside the cavity are sensitive to the formation of the inclusion complexes. No changes in the chemical shifts were found upon addition of caffeine to the α-CD solution (Δδ = 0.00 ppm),[3] which suggests that the caffeine molecule did not penetrate into the α-CD cavity. In this case, the interaction has surface character and involves the van der Waals forces and hydrogen bonding. In contrast, the complexation of caffeine with β-CD resulted in significant changes in the chemical shifts for the H(3) (Δδ = –0.03 ppm) and H(5) (Δδ = –0.05 ppm), which indicated the formation of the inclusion complexes.[3] Consequently, the inclusion complexation enhanced the solubility of caffeine in the presence of β-CD (see Fig. 2, *d*).

The interaction of caffeine with HP-β-CD exhibited positive endothermic effect ($h_{xy} > 0$) and no inclusion complex was detected (see Fig. 1, *b*). As it was suggested above, theophylline and theobromine interact with the outer surface of the HP-β-CD molecule exhibiting negative changes in enthalpy (see Table 3). The difference observed could be due to the additional methyl group in the caffeine molecule, which prevents the interaction of the nitrogen atom with the polar groups of HP-β-CD. For the complexation of the purine alkaloids with calcium and magnesium cations, similar decrease in the coordination ability was observed on going from theophylline to caffeine.[33] It is of note that the surface interactions of HP-β-CD with caffeine do not increase the solubility of the latter (see Fig. 2, *d*). In the ^{1}H NMR spectra, no changes in the chemical shifts were found in the presence of the excess of HP-β-CD,[4] confirming that the complexation did not occur.

Interaction of HP-γ-CD with caffeine exhibited the high positive h_{xy} values (see Table 3). It could be assumed that the penetration of the bulky caffeine molecule in the cavity of the largest HP-CD results in strong dehydration of the components and hydrophobic interactions. In all these processes, the endothermic effect (h_{xy}) predominated.

It is of note that the thermodynamic parameters of the interaction of α-CD and HP-γ-CD with the purine alkaloids studied were obtained and analyzed for the first time (see Tables 2 and 3). It was of interest to compare the data obtained by us with the published data (see Table 1). It clearly follows from the data given in Tables 1 and 4 that the stability constants of the inclusion complexes of caffeine and theophylline with β-CD and HP-β-CD determined in the present study are in good agreement with those found previously[11] by the solubility method for solutions in pure distilled water and significantly differ from

Table 4. Thermocynamical parameters of formation of the 1 : 1 complex of CDs with caffeine in water at 298.15 (see Refs 1 and 2)

Complex	K/kg mol^{-1}	$-\Delta_c G^\circ$	$-\Delta_c H^\circ$	$T\Delta_c S^\circ$
		kJ mol^{-1}		
α-CD—caffeine	31±3	8.5	3.4±0.2	5.1
β-CD—caffeine	30±2	8.4	2.2±0.2	6.2

the K values obtained by fluorimetry and fluorescence in buffer solutions.[12,13,15] This discrepancy could be explained by different experimental conditions and approaches used for the data processing. On the one hand, the constants listed in Tables 2 and 4 are standard as they correspond to the ideal 1 M solution with the properties of infinitely dilute solution under standard conditions (P = 1 atm, T = 298.15 K). The constants determined in buffer solutions are the apparent values as the ionic strength of the solutions is not equal to zero. On the other hand, the composition of the buffer may affect the state of the component in the solution (hydratation, self-association tendency, *etc*.) and, hence, their ability to complexation, which is reflected in the K values. Similar solvent effects have been observed earlier.[25,26,34] For instance, the presence of inorganic and organic compounds in aqueous solutions led to the changes in physicochemical properties of methylxanthines.[25] Addition of lithium and sodium chlorides increased the stability constants of the 1 : 1 complex of theophylline with methyl cinnamate, while addition of the organic solvent (for example, MeCN, MeOH, or ethyl acetate) significantly decreased the K values.[34]

It should be noted in conclusion, that the size of the macrocyclic cavity has a significant influence on the interaction of CD with the purine alkaloids. HP-γ-CD with the largest internal cavity formed the most stable complexes with the alkaloids, and this CD is the most effective solubilizing agent for this type of compounds.

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