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INTERACTIONS OF NATIVE AND MODIFIED CYCLODEXTRINS WITH SOME B-VITAMINS
Calorimetric and ^{1}H NMR study

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Interactions of native and modified α- and β-cyclodextrins with nicotinic acid, pyridoxine and pyridoxal were studied by isothermal titration calorimetry, solution calorimetry, and ^{1}H NMR spectroscopy at 298.15 K and pH 6.8. Weak 1:1 complex formation was found only between α-cyclodextrin and nicotinic acid. The stability constant and corresponding thermodynamic parameters of complex formation ($\Delta_c G$, $\Delta_c H$ and $\Delta_c S$) were calculated using the calorimetric data. The ^{1}H NMR data indicate the shallow insertion of the carboxylic group of the nicotinic acid molecule into α-CD cavity. For all other compounds the weak interactions, not accompanied by complex formation, were characterized by the enthalpic virial coefficients calculated on the basis of McMillan–Mayer approach. The obtained thermodynamic parameters were analyzed in the terms of influence of the solutes' structure on the selectivity of intermolecular host-guest interactions.

Keywords: *calorimetry, complex formation, cyclodextrin, enthalpic interaction coefficients, ^{1}H NMR spectroscopy, nicotinic acid, pyridoxal, pyridoxine*

Introduction

Vitamins are a group of organic compounds that are necessary for human health. Pyridoxine, pyridoxal and nicotinic acid are water-soluble B-vitamins playing essential role as cofactors of various enzymes, and having important functions in metabolism processes. Furthermore, vitamins are the components of different pharmaceutical preparations and they are used as specific drugs. It is well known, that nicotinic acid (vitamin B_5) is often reported as cholesterol-reducing and antipellagra drug, pyridoxine and pyridoxal (vitamin B_6) are recommended for the enhancement of activity of the immune and nervous systems and for the balancing of hormonal changes. Beside the numerous positive effects these vitamins have a number of disadvantages. For instance, flushing or hot flashes are the most common side effects of large doses of the nicotinic acid. Pyridoxine is labile to UV-radiation and oxidation. Bioactivity of vitamins can be also reduced due to undesired chemical reactions during the storage and processing. To counteract these unpleasant effects the encapsulation by cyclodextrins has been proposed and used [1, 2].

Cyclodextrins (CD) are the cyclic oligosaccharides consisting of glucose units and obtained by the decomposition of starch. They have external hydrophilic surface and internal hydrophobic cavity capable to include different guest molecules with appropriate shape and size. In this case the solubility, activity, and stability of guests inserted into CD cavity can be enhanced. The propensity of cyclodextrins to form host-guest complexes (or inclusion complexes) determines their practical application as non-toxic encapsulating agents in pharmaceutical, food, cosmetic and textile industries [2–4]. Moreover, CDs can be used as selectors in analytical methods and techniques [5], for example, in the separation of multivitamin preparations or determination of vitamins in the pharmaceutical formulations. Thus, we focused our attention on investigation of the ability of both native and synthetically modified CDs towards complex formation with selected B-vitamins (Fig. 1).

There are only a few literature data concerning complex formation of CDs with guests of the structure similar to those of nicotinic acid, pyridoxine and pyridoxal [6–8]. It must be emphasized that α-CD binds pyridine, which can be considered as structural unit of vitamins under study. According to Lewis *et al.* [6], the process of complex formation of pyridine with α-CD is characterized by the negative enthalpy and positive entropy changes. As it was

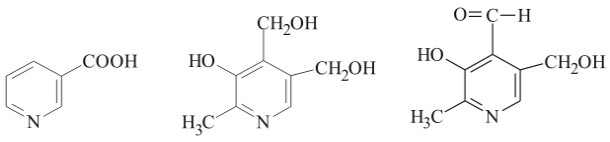

Fig. 1 Structures of B-vitamins under study

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obtained by microcalorimetry [7], methyl nicotinate and ionized nicotinic acid did not display a measurable heat of their reaction with CDs. Zhdanov *et al*. [8] have shown, that binding of β-CD with the hydrophilic derivatives of isonicotinic acid is weak, and inclusion of guest molecule into CD cavity does not occur.

The aims of this study were 1) to investigate the interactions of α-, β-cyclodextrins and their hydroxypropyl derivatives with the nicotinic acid, pyridoxine and pyridoxal in aqueous solution at 298.15 K and pH 6.8; 2) to reveal the systems in which the complex formation takes place; 3) on the basis of the calculated thermodynamic parameters of interaction to analyze the influence of structure of both host and guest molecules and their solvation on the selectivity of complex formation; 4) to determine the active sites of binding and the stoichiometry of the complexes.

Experimental

Materials

All the solutions were prepared by mass using twice-distilled degassed water and analytical grade chemicals. Nicotinic acid, pyridoxine hydrochloride and pyridoxal hydrochloride were supplied by ICN Pharmaceuticals and were not further purified. α-Cyclodextrin (Fluka), β-cyclodextrin (ICN Pharmaceuticals), hydroxypropyl-α- and hydroxypropyl-β-cyclodextrins (Aldrich) were used as received. CDs were stable crystallohydrates, the water content in which determined by thermogravimetry was 9, 14, 7 and 8% for α-CD, β-CD, HP-α-CD and HP-β-CD, respectively. The average degree of substitution was 3.6 and 4.2 for HP-α-CD and HP-β-CD molecules, respectively.

The experiments were carried out at pH 6.8 adjusted by phosphate buffer. Under these experimental conditions nicotinic acid exists as anion [9], while pyridoxine and pyridoxal are neutral [10].

Methods

Calorimetry

Calorimetric measurements were performed using a high-sensitivity MicroCal OMEGA isothermal titration calorimeter, and home-made solution calorimeter at 298.15 K.

The isothermal titration microcalorimeter was equipped with a stainless steel titration vessel of 1.4 mL volume. The vessel was filled with cyclodextrin solution in buffer (0.001 mol kg^{-1}), while 15 μL of buffered vitamins' solution (0.08 mol kg^{-1}) were injected stepwise using a syringe pump equipped with a 250 μL Hamilton syringe. Additionally, titration of α-CD solution at higher concentration (0.002 mol kg^{-1}) by nicotinic acid solution (0.08 mol kg^{-1}), and titration of nicotinic acid solution (0.0006 mol kg^{-1}) by α-CD (0.13 mol kg^{-1}) were carried out to enhance the precision of estimated thermodynamic parameters for α-CD:nicotinic acid complexation.

The titrations were performed at a stirring speed of 400 rpm, and all recorded heat responses ($\Delta_{mix}H$) were corrected for the dilution of both CDs ($\Delta_{dil}H_x$) and vitamins ($\Delta_{dil}H_y$), obtained in the separate dilution experiments, according to the following formula:

$$\Delta H^* = \Delta_{mix}H - \Delta_{dil}H_x - \Delta_{dil}H_y \quad (1)$$

Weakly interacting systems were characterized by the enthalpic virial coefficients calculated on the basis of the McMillan–Mayer theory [11, 12] according to equation:

$$\Delta H^* = 2h_{xy}\, m_x^f\, m_y^f + 3h_{xyy}\, m_x^f\, (m_y^f)^2 + 3h_{xxy}\, (m_x^f)^2\, m_y^f \quad (2)$$

where h_{xy}, h_{xyy}, h_{xxy} – are the enthalpic coefficients of pair (h_{xy}) and triplet (h_{xxy}, h_{xyy}) interactions; m_x^f and m_y^f are the final molalities of CD and vitamin, respectively. Since the final CD concentration was approximately constant, the last term in Eq. (2) was neglected. Therefore, h_{xy} and h_{xyy} coefficients, and their standard deviations were estimated on the basis of Eq. (2) with the aid of least-squares analysis implemented in Gnuplot 4.1 program (www.gnuplot.info).

Systems with complex formation were analyzed according to the 1:1 complexation model, which was additionally confirmed by NMR and implemented in Gnuplot 4.1 program. In order to increase the precision of the determined thermodynamic parameters all the three titration experiments

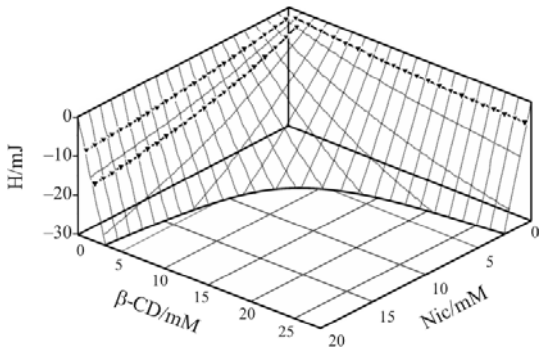

Fig. 2 Surface defining heat effect corresponding to 1:1 complex formation upon mixing given concentration of reagents. The lines follow the three titration experiments performed for nicotinic acid injection to α-CD (two almost parallel lines in the left part of figure), and the opposite experiment with injection of α-CD to nicotinic acid (line almost transverse to the previous two)

Table 1 Experimental data for mixing of aqueous solutions of cyclodextrins and some B vitamins (298.15 K; pH=6.8; m^f is in mmol kg^{-1} and ΔH^* is in kJ mol^{-1})

m_x^f	m_y^f	ΔH^*	m_x^f	m_y^f	ΔH^*	m_x^f	m_y^f	ΔH^*
α-CD+pyridoxal			α-CD+pyridoxine			HP-α-CD+nicotinic acid		
0.8404	0.4915	0.115	0.8404	1.131	0.153	0.7957	1.810	0.243
0.8309	0.9773	0.229	0.8309	2.249	0.311	0.7867	2.699	0.382
0.8215	1.457	0.334	0.8215	3.354	0.480	0.7778	3.578	0.523
0.8122	1.932	0.456	0.8122	4.445	0.641	0.7690	4.446	0.682
0.8030	2.401	0.573	0.8030	5.524	0.801	0.7603	5.304	0.855
0.7939	2.864	0.697	0.7939	6.591	0.965	0.7517	6.152	1.030
0.7849	3.322	0.828	0.7849	7.644	1.127	0.7432	6.989	1.211
0.7760	3.774	0.934	0.7760	8.684	1.288	0.7347	7.816	1.398
0.7672	4.221	1.066	0.7672	9.711	1.454	0.7264	8.632	1.588
0.7585	4.662	1.196	0.7585	10.726	1.616	0.7181	9.438	1.792
0.7499	5.097	1.314	0.7499	11.727	1.778	0.7100	10.234	1.999
0.7414	5.526	1.418	0.7414	12.715	1.935	0.7019	11.019	2.213
0.7330	5.951	1.519	0.7330	13.691	2.034	0.6939	11.793	2.431
0.7246	6.369	1.644	0.7246	14.653	2.249	0.6860	12.558	2.658
0.7164	6.782	1.750	0.7164	15.603	2.340	0.6782	13.312	2.892
0.7082	7.189	1.874	0.7082	16.540	2.541			
HP-α-CD+pyridoxine			β-CD+nicotinic acid			β-CD+pyridoxine		
0.7603	6.591	0.823	1.127	0.933	0.258	1.114	2.257	0.079
0.7517	7.644	0.947	1.114	1.856	0.521	1.102	3.366	0.152
0.7432	8.684	1.068	1.102	2.768	0.788	1.089	4.461	0.229
0.7347	9.711	1.187	1.089	3.669	1.051	1.077	5.544	0.308
0.7264	10.726	1.301	1.077	4.560	1.312	1.065	6.614	0.385
0.7181	11.727	1.409	1.065	5.440	1.571	1.053	7.671	0.464
0.7100	12.715	1.511	1.053	6.309	1.820	1.041	8.715	0.534
0.7019	13.691	1.622	1.041	7.168	2.069	1.029	9.746	0.608
0.6939	14.653	1.728	1.029	8.016	2.312	1.017	10.764	0.681
0.6860	15.603	1.831	1.017	8.853	2.559	1.006	11.769	0.754
0.6782	16.540	1.937	1.006	9.680	2.804	0.994	12.761	0.826
			0.9943	10.496	3.046	0.983	13.740	0.899
			0.9830	11.301	3.286	0.9718	14.706	0.970
			0.9718	12.096	3.527	0.9608	15.659	1.048
			0.9608	12.879	3.768	0.9498	16.599	1.123
			0.9498	13.653	4.005			
HP-β-CD+pyridoxine			β-CD+pyridoxal			HP-β-CD+nicotinic acid		
0.7603	10.726	1.140	1.114	0.9773	0.171	0.8049	4.446	1.616
0.7517	11.727	1.224	1.102	1.458	0.259	0.7958	5.304	1.930
0.7431	12.715	1.306	1.089	1.932	0.344	0.7868	6.152	2.234
0.7347	13.691	1.385	1.077	2.401	0.436	0.7778	6.989	2.541
0.7263	14.653	1.455	1.065	2.864	0.542	0.7690	7.816	2.845
0.7181	15.603	1.521	1.053	3.322	0.627	0.7603	8.632	3.150
0.7099	16.534	1.587	1.041	3.774	0.721	0.7517	9.438	3.448
			1.029	4.221	0.813	0.7431	10.234	3.737
			1.017	4.662	0.917	0.7347	11.019	4.030
			1.006	5.097	1.005	0.7263	11.793	4.314
			0.9943	5.527	1.098	0.7181	12.558	4.600
			0.9830	5.951	1.188	0.7099	13.312	4.875
			0.9718	6.369	1.286			
			0.9608	6.782	1.377			
			0.9498	7.189	1.468			

Table 1 Continued

m_x^f	m_y^f	ΔH^*	m_x^f	m_y^f	ΔH^*	m_x^f	m_y^f	ΔH^*
α-CD+nicotinic acid			α-CD+nicotinic acid			α-CD+nicotinic acid		
2.126	1.008	–1.482	1.497	0.5824	–0.466	0.8764	1.008	–0.690
2.102	2.005	–2.846	2.942	0.5758	–0.890	0.8666	2.005	–1.325
2.078	2.991	–4.085	4.388	0.5693	–1.287	0.8568	2.991	–1.930
2.055	3.966	–5.233	5.817	0.5629	–1.632	0.8472	3.966	–2.487
2.032	4.930	–6.319	7.231	0.5566	–1.951	0.8377	4.930	–3.016
2.009	5.883	–7.315	8.629	0.5504	–2.253	0.8282	5.883	–3.512
1.986	6.825	–8.235	10.011	0.5442	–2.520	0.8189	6.825	–3.979
1.964	7.756	–9.081	11.377	0.5380	–2.747	0.8097	7.756	–4.413
1.942	8.677	–9.857	12.728	0.5320	–2.953	0.8006	8.677	–4.810
1.920	9.588	–10.585	14.064	0.5260	–3.112	0.7916	9.588	–5.189
1.898	10.489	–11.251	15.385	0.5201	–3.319	0.7827	10.489	–5.538
1.877	11.379	–11.871	16.691	0.5142	–3.538	0.7739	11.379	–5.874
1.856	12.260	–12.447	17.982	0.5085	–3.685	0.7652	12.260	–6.194
1.835	13.130	–12.984	19.259	0.5027	–3.852	0.7566	13.130	–6.512
1.815	13.991	–13.480	20.522	0.4971	–3.986	0.7481	13.991	–6.796
1.794	14.842	–13.935	21.770	0.4915	–4.104	0.7397	14.842	–7.061
1.774	15.683	–14.356	23.004	0.4860	–4.208	0.7313	15.683	–7.273
1.754	16.515	–14.736	24.225	0.4805	–4.318	0.7231	16.515	–7.497
1.734	17.338	–15.085	25.431	0.4751	–4.411	0.7150	17.338	–7.703
1.715	18.151	–15.412	26.624	0.4697	–4.483	0.7069	18.151	–7.890
1.695	18.955	–15.702	27.804	0.4645	–4.552	0.6990	18.955	–8.077
1.676	19.750	–15.970				0.6911	19.750	–8.248
α-CD+nicotinic acid (calorimetry of solution)								
0.7308	6.08	–1.627						
0.7366	17.58	–4.111						
0.7165	22.09	–4.922						
0.7182	34.07	–6.745						
0.7335	47.53	–8.361						
0.7234	69.61	–10.352						
0.7123	84.93	–11.406						
0.7351	109.9	–12.743						
0.7286	136.1	–13.803						
0.7386	156.8	–14.468						

concerning the analyzed pair reagents (c.f. isothermal calorimetry methods for the experiments' details) were used simultaneously in the analysis (Fig. 2).

Solution calorimeter was additionally employed for investigation of α-CD+nicotinic acid system in which, as it will be shown below, the complex formation occurs. Detailed description of the solution calorimeter was given in [13]. The calorimeter was calibrated using dissolved KCl in water at 298.15 K. The error of the enthalpy of solution measurements was less than 1%. All calorimetric measurements were performed at 298.15±0.01 K. Solid α-CD samples with constant mass were dissolved in pure solvent (phosphate buffer) and then in the buffered nicotinic acid solutions. The concentration of α-CD was constant, 0.0007 mol kg^{-1}, whereas the concentration of nicotinic acid was changed from 0.03 to 0.16 mol kg^{-1}.

Enthalpies of transfer of α-CD from pure solvent to the nicotinic acid solution ($\Delta_{tr}H(s \rightarrow s+y)$) were calculated as follows

$$\Delta_{tr}H(s \rightarrow s+y) = \Delta_{sol}H(s+y) - \Delta_{sol}H(s) \quad (3)$$

where $\Delta_{sol}H(s+y)$ and $\Delta_{sol}H(s)$ are the enthalpies of solution of α-CD in the nicotinic acid solution (s+*y*) and in the pure solvent (s), respectively. Figure 3 presents the experimental data obtained for α-CD+nicotinic acid system.

The enthalpy of complex formation and the stability constant were calculated simultaneously by use of minimization computer program 'HEAT' [14]. This program allows to remove the contributions from possible processes of dissociation or protonation of both α-CD and nicotinic acid into thermodynamic parameters of complex formation. For this purpose the dissociation/protonation enthalpies of reagents and equilibrium constants of these processes taken from literature [9, 15, 16] were put in the program together with the experimental data (m_x, m_y and $\Delta_{tr}H(s \rightarrow s+y)$).

Primary experimental data obtained by both calorimetric methods are presented in Table 1.

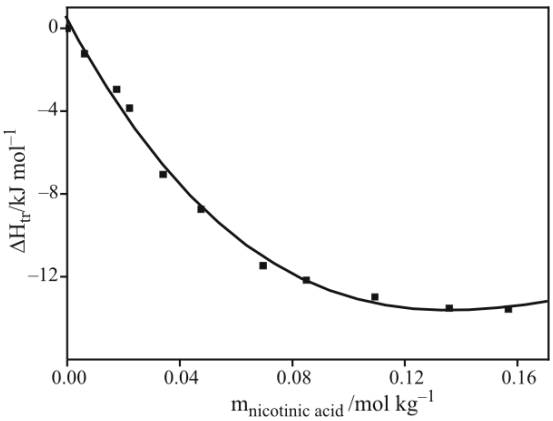

Fig. 3 Enthalpy of α-CD transfer from water to aqueous solution of nicotinic acid *vs*. the nicotinic acid concentration (*T*=298.15 K; pH=6.8; calorimetry of solution)

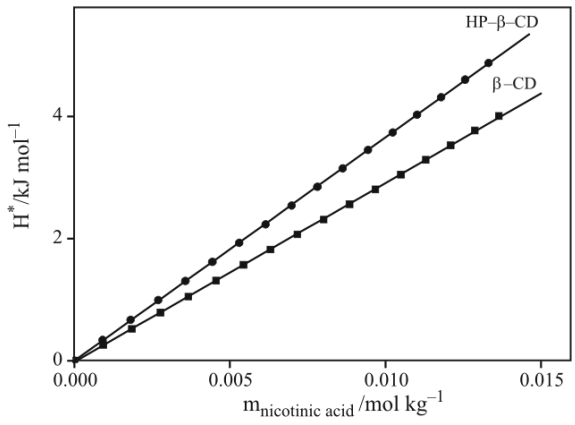

Fig. 4 Experimental titration curves for systems with weak interactions (*T*=298.15 K, pH=6.8)

NMR spectroscopy

^{1}H NMR spectra were recorded using Bruker AC-200 spectrometer (200 MHz). All measurements were carried out at 298.15±0.10 K and pH=6. Cyclohexane was used as external reference. All solutions were prepared gravimetrically using D_2O. The spectra were processed using π/3 shifted squared sine-bell filter and zero-filling up to 64k data point prior to Fourier transformation with the aid of MestRe-C 2.3a software (www.metrec.com). The recorded spectra were interpreted with the aid of literature data [17, 18].

Job method [19] was employed for determination of stoichiometry of the complexes. For this purpose, α-CD and nicotinic acid solutions with equal concentrations (0.11 mol kg^{-1}) were mixed at different proportions to constant volume, and the chemical shift displacements were determined.

Results and discussion

As it was mentioned above, the aim of our work was to study the complex formation of CDs with nicotinic acid, pyridoxine and pyridoxal, which are pyridine derivatives (Fig. 1). It was found, that only interaction between α-CD and nicotinic acid is characterized by the exothermic effect and accompanied by complex formation. Binding isotherms obtained by different calorimetric methods are presented in Figs 2 and 3. Linear dependences with positive slope (Fig. 3) obtained for all other systems confirm the weak interactions between CDs and the majority of B-vitamins. Thus, α-CD possessing the smaller cavity diameter forms complex with nicotinic acid containing only one substitute (ionized carboxylic group) in the *meta*-position of pyridine ring. Probably, in this case the geometric complementarity of guest size to the α-CD cavity dimensions plays an important role, and inclusion of nicotinic acid into α-CD molecule is less inconveniently. Moreover, carboxylic group may be independent binding site with α-CD. The similar situation has been detected in complexation of CDs with terephthalic acid [20], benzoic acid, substituted benzoic acids and benzoate anion [21–24].

Thermodynamic parameters of complex formation of α-CD with nicotinic acid are listed in Table 2. The binding of α-CD with the nicotinic acid is characterized by the negative enthalpy and entropy changes; consequently, the complex is stabilized only by the enthalpy term. Thermodynamic quantities we refer to 1:1 binding model.

^{1}H NMR technique was employed to confirm the stoichiometry of the α-CD/nicotinic acid complex. It is well known from literature [18, 24], that H(3) and H(5) cyclodextrin's protons, located inside the macrocyclic cavity at the wider and narrower rims, respectively, are sensitive to penetration of the guest

Table 2 Thermodynamic parameters of complex formation of α-CD with nicotinic acid, benzoic acid and pyridine at 298.15 K

Complex	lg*K*	$\Delta_c G$/kJ mol^{-1}	$\Delta_c H$/kJ mol^{-1}	$T\Delta_c S$/kJ mol^{-1}
α-CD/nicotinic acid (pH=6.8)	1.2±0.2* 1.4±0.2**	–6.5* –8**	–23.5±0.6* –32±5**	–17.0* –24**
α-CD/benzoate [29]	1.2±0.01	–5.8	–16.3±1.3	–10.5
α-CD/pyridine [6]	2.2±1.4	–12.6	–10.5±3.8	2.1

*obtained by calorimetry of solution;
**obtained by isothermal titration calorimetry from the three independent experiments

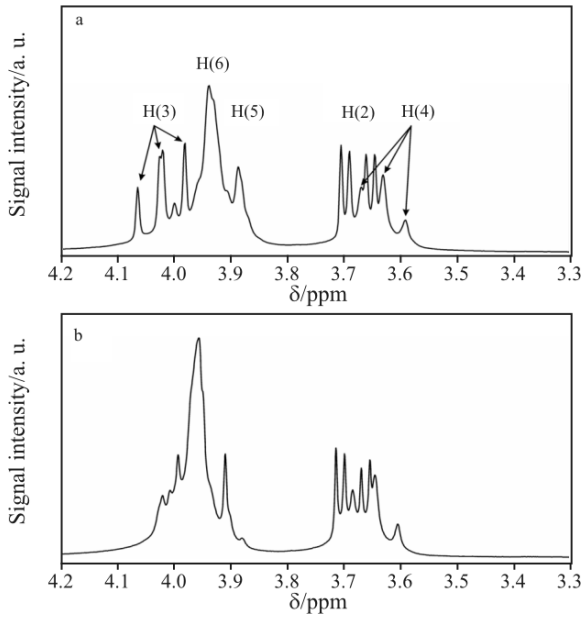

Fig. 5 Part of ^{1}H NMR spectra of α-CD (0.07 mol kg^{-1}): a – in pure D_2O; b – in nicotinic acid (0.04 mol kg^{-1}) solution (*T*=298.15 K, pH=6)

molecule into hydrophobic cavity and, therefore, responsible for the host-guest complexation. Significant upfield shifting of the signal of α-CD proton H(3) was detected after addition of the nicotinic acid (Fig. 5). Therefore, H(3) NMR signal was used to obtain Job plot (Fig 6). The curve presented in Fig. 6 exhibits minimum at 1:1 host/guest concentration ratio that corresponds to 1:1 stoichiometry.

Complexation-induced ^{1}H NMR shifts were also used to obtain information on the binding mode of nicotinic acid with α-CD. Magnitudes of Δδ for H(3) and H(5) protons of the cyclodextrin are usually used as a measure of depth of inclusion of the guest molecule into macrocyclic cavity [18]. Significant chemical shift changes of both H(3) and H(5) protons indicate the deep insertion of the guest molecule into cyclodextrin cavity. In our case Δδ value for H(5) is negligible as compared to Δδ for H(3) proton (Fig. 5). Therefore, on the basis of experimental results we assume only shallow insertion of the nicotinic acid into macrocyclic cavity from the wider rim of CD molecule.

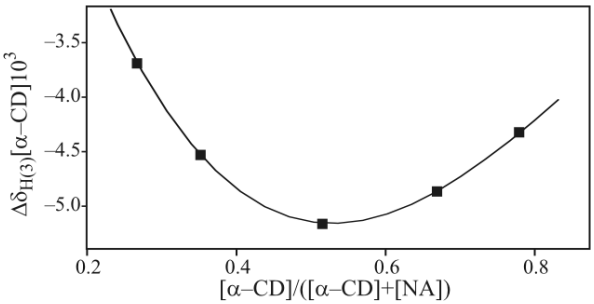

Fig. 6 Job plot for α-CD/nicotinic acid complex

^{1}H NMR spectrum of the nicotinic acid in the presence of different amounts of α- and β-CDs was also recorded. The ^{1}H NMR spectrum of nicotinic acid in pure D_2O consists of four kinds of protons [17], the values of the chemical shifts (δ) are summarized in Table 3. As can be seen from Table 3, addition of β-CD does not induce the change of chemical shifts of nicotinic acid protons (Δδ≈0). Thus, interaction of the nicotinic acid with β-CD is weak and binding does not occur. This result is in a good agreement with the calorimetric data. On the contrary, the NMR signals of the nicotinic acid protons are shifted downfield upon the addition of α-CD (Table 3). The highest Δδ values for H(2) and H(3) protons located close to carboxylate group were obtained. It means that part of the nicotinic acid molecule where the carboxylate group is placed penetrates into macrocyclic cavity.

Participation of the carboxylate group of nicotinic acid in the binding with α-CD can be confirmed by the high negative magnitudes of enthalpy and entropy of complex formation (Table 2). Large negative $\Delta_c H$ value can be explained by the prevalence of exothermic contribution caused by electrostatic and van der Waals interactions as well as by the intermolecular hydrogen bonding. Hydrophobic interactions characterized by positive or small negative enthalpies and positive entropies are minor in this case. It is true that electrostatic interactions can take place in the binding of different guests with the CD's cavity that is polarized [25]. Kitagawa *et al*. [26] performed computer simulations of α-CD interactions with substituted benzoic acids using CNDO/2 method.

Table 3 ^{1}H chemical shift differences ($\Delta\delta=\delta_{\text{in the presence of CD}}-\delta_{\text{free}}$) for nicotinic acid protons induced by addition of α- and β-cyclodextrins (*T*=298.15 K, pH=6)

Proton	$\delta_{\text{pure nicotinic acid}}$/ppm*	Δδ/ppm			
		β-CD (0.005)**	β-CD (0.009)	α-CD (0.04)	α-CD (0.07)
H(2)	8.92	0.00	0.01	0.10	0.16
H(3)	8.22	0.00	0.00	0.10	0.16
H(4)	8.59	0.00	0.00	0.01	0.02
H(5)	7.50	0.00	–0.01	0.02	0.02

*position of signals of the nicotinic acid (0.04 mol kg^{-1}) protons is in the good agreement with the literature data [17]: 8.93 ppm –H(2), 8.24 ppm – H(3), 7.50 ppm – H(5), 8.60 ppm – H(4) (0.15 M; pH=10.45);
**concentration of CDs (mol kg^{-1}) is given in parentheses

Table 4 Enthalpic virial coefficients (h_{xy}/kJ kg mol^{-2} and h_{xyy}/kJ kg^2 mol^{-3}) for interactions of cyclodextrins with some B-vitamins (298.15 K, pH=6.8)

	Pyridoxine		Pyridoxal		Nicotinic acid	
	h_{xy}	h_{xyy}	h_{xy}	h_{xyy}	h_{xy}	h_{xyy}
α-CD	82.3±1.2	1.02±0.06	134.7±1.5	4.6±0.2	–*	–*
β-CD	21.1±0.7	0.59±0.04	74.3±0.5	3.09±0.05	121.9±0.5	1.56±0.03
HP-α-CD	78.9±0.5	0.28±0.02			69.2±0.8	4.50±0.05
HP-β-CD	73.5±0.4	–0.23±0.02			207.8±0.5	2.50±0.03

*were not calculated due to complex formation in this system

The authors noted that electrostatic interactions play a considerable role and determine the orientation of guest inside the host cavity. Connors *et al*. [27] has shown the influence of ionization of –COOH group on the orientation of 4-substituted benzoic acids in the α-CD cavity. Unionized –COOH group is placed at the positive end of the CD dipole, whereas –COO^- group is located near the negative end of the CD dipole. The similar situation can be characteristic for complexation of α-CD with the nicotinic acid. It is necessary to take into account the van der Waals interactions which are responsible for complexation phenomenon and molecular recognition of CDs, as was pointed out by Liu *et al*. [28]. Besides the electrostatic and van der Waals interactions, hydrogen bonding can play an important role in CD complexation. Nicotinic acid has polar groups in their structure (–COO^- group and nitrogen in the pyridine ring) which can form H-bonds with CD's hydroxyls, cavity walls or water molecules included in CD cavity. Thus, all these three kinds of interactions give negative contribution to the enthalpy change.

Comparative analysis of the thermodynamic parameters listed in Table 2 allows to suggest the dominant role of H-bonding and electrostatic interactions. Complex formation of α-CD with nicotinic acid is rather enthalpically favorable and entropically unfavorable as compared to α-CD complexation with pyridine [6] and benzoic acid [29]. Pyridine forms more stable enthalpically-entropically stabilized molecular complex with α-CD. The charged –COO^- group located in the meta-position of the pyridine ring results in considerable decrease of $\Delta_c H$ and $\Delta_c S$ values, mainly due to electrostatic interactions and H-bonding between host and guest molecules. As concerns comparison of thermodynamic parameters of complex formation of α-CD with nicotinic and benzoic acids, the presence of the nitrogen atom in the aromatic ring promotes the decrease of $\Delta_c H$ and $\Delta_c S$ values. This fact can be explained by the possible participation of the nitrogen atom in the formation of additional H-bonds with OH-groups surrounding the macrocyclic cavity.

As it was noted above, in the other systems under study binding does not occur due to the following possible reasons: a) geometric discrepancy of the guest size to the cyclodextrin cavity dimensions; b) presence of side substitutes in the pyridine ring of the guest molecules which serve as steric hindrance for penetration into macrocyclic cavity; c) high hydrophility and strong solvation of guest molecules.

Weak non-bonding interactions were characterized by the enthalpic virial coefficients h_{xy} that represent all enthalpy changes caused by weak solute-solute (van der Waals, electrostatic and hydrophobic interactions, H-bonding, etc.) and solute-solvent interactions. Positive h_{xy} values obtained for all the systems and listed in Table 4 are determined by the prevalence of endothermic effects from dehydration of the solutes. As concerns the interactions of the nicotinic acid with β-CD and HP-β-CD, they are enthalpically unfavorable and are characterized by the highest positive h_{xy} values caused by the dehydration. Obviously, the cavity size of β-CD tends to be too large for a favorable fit of the nicotinic acid molecule. The enthalpic coefficients of pair interactions of β-CD with pyridoxine and pyridoxal are considerably lower than the corresponding ones for systems with α-CD. This fact can be explained by the best size-match of pyridoxine and pyridoxal to the β-CD cavity. Thus, the larger cavity of β-CD is more favorable for B_6 vitamins having numerous substitutes in structure, and attractive interactions characterizing by exothermic effects resulting decrease in h_{xy} play a noticeable role.

The presence of hydroxypropyl groups in the CD molecule does not promote the complex formation. These bulky groups are not able to retain guest molecule by means of possible additional interactions. Probably, they prevent penetration of the guests into hydrophobic cavity.

Conclusions

All the methods used indicated that CDs display selectivity in interactions with pyridoxine, pyridoxal and nicotinic acid in aqueous media. Interactions of

nicotinic acid, pyridoxal and pyridoxine with CDs could be modulated by the cavity dimensions and the structure of guest molecules. Formation of inclusion complex between α-CD and nicotinic acid is mainly enthalpy driven since the deposition of the charged carboxylic group inside the cavity is entropically unfavorable.

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