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Comparative thermodynamic study on complex formation of native and hydroxypropylated cyclodextrins with benzoic acid

Irina V. Terekhova*

Institute of Solution Chemistry of RAS, Ivanovo, Russian Federation

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ABSTRACT

Complex formation of native and hydroxypropylated α-, β- and γ-cyclodextrins with benzoic acid in water was studied by means of calorimetry of solution at 298.15 K. The 1:1 complexes are formed with α- and β-cyclodextrins, while 1:2 binding stoichiometry was observed for γ-cyclodextrins. Thermodynamic parameters of complex formation of hydroxypropylated cyclodextrins were determined for the first time and analyzed. Comparison of binding affinity of native and modified cyclodextrins was carried out.

1. Introduction

Cyclodextrins (CDs) have been widely used in drug delivery systems, bioencapsulation processes as well as in separation technologies [1–3]. All these practical applications of CDs are based on their ability to form inclusion complexes with different organic compounds. To this end, complex formation of CDs is comprehensively studied, and a great number of articles devoted to this subject has been published. Moreover, various modified CDs synthesized in recent years are frequently used as host molecules because they are more soluble in water and in some cases display higher binding affinity to guest molecules in comparison with native CDs.

Complex formation of parent α-, β- and γ-cyclodextrins with the simplest aromatic carboxylic acid–benzoic acid (BA) has been investigated in detail by different experimental methods [4–17]. It has been shown that BA is inserted in CD cavity, and 1:1 binding takes place in all cases except γ-CD, which is able to form 1:2 complexes in the presence of excess amount of BA [10]. Thermodynamic parameters of complex formation available in literature are summarized in Table 1. As can be seen from these data, smaller cavity of α-CD is more suitable for incorporation and retention of BA molecule. In this case, binding is more exothermic and accompanied by formation of more stable complexes.

To the best of our knowledge, interactions of modified CDs with BA were not studied. Therefore, the aim of this work was to examine the binding affinity of hydroxypropylated CDs to BA. Binding of BA with native α-CD and β-CD was also studied in order to reveal the influence of hydroxypropyl groups on complexation process.

2. Experimental

2.1. Materials

Benzoic acid, hydroxypropyl-α-cyclodextrin (HP-α-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and hydroxypropyl-γ-cyclodextrin (HP-γ-CD) were obtained from Aldrich. Substitution degree of HP-CDs was 0.6 per glucose unit. α-CD and β-CD were from Fluka. All chemicals have a purity >99% and were used as received. CDs contain water, the content of which was determined thermogravimetrically and was equal to 8.2, 6.4 and 9.0% for HP-α-CD, HP-β-CD and HP-γ-CD, respectively. This was taken into account in concentration calculations. Solutions were prepared by weight in fresh bidistilled water. All of the mass measurements were performed on an electronic balance Sartorius Genius ME (Germany) with repeatability of ±0.025 mg.

2.2. Solution calorimetry

Solution calorimeter was used for determination of the heat of CD dissolution at 298.15 K. For this purpose, crystalline samples of CDs were placed in glass ampoules and dissolved in pure water and then in aqueous solutions of BA. In calorimetric experiments, the concentration of CDs was constant, whereas the BA concentration was varied from 0 to 0.03 mol kg^{-1}. More detailed description of

* Fax: +7 4932 336237.
E-mail address: ivt@isc-ras.ru

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Table 1
Literature data on complex formation of native cyclodextrins with benzoic acid in water.

K (M^{-1})	$\Delta_c G$	$\Delta_c H$	$T\Delta_c S$	Method and experimental conditions	Ref.
	(kJ mol^{-1})				
α-CD/BA (1:1)					
720	−16.3	–	–	^{1}H NMR	[4]
800 ± 83	−16.6	–	–	^{1}H NMR; pD = 3.00, J = 0.5; 298 K	[6]
751 ± 1	−16.4	−42.5 ± 0.6	−26.1	Potentiometry; 298 K	[7]
339	−14.4	−41.80 ± 0 .96	−27.4	Circular dichroism; 298 K	[9]
909 ± 83	−16.9	−33.9 ± 2.0	−17.0	Calorimetry; 303 K	[10]
750 ± 60	−16.4	–	–	Potentiometry; 298 K, J = 0.1 (KCl)	[11]
1000 ± 33	−17.1	−40.2 ± 0.4	−23.1	Calorimetry; 298 K	[12]
β-CD/BA (1:1)					
372 ± 45	−14.7	–	–	UV + circular dichroism; pH 6.2	[13]
339	−14.4	−22.3 ± 0.3	−7.9	Circular dichroism; 298 K	[9]
370 ± 27	−14.9	−15.0 ± 1.0	−0.1	Calorimetry; 303 K	[10]
546 ± 2	−15.6	−17 ± 1	−1.4	Potentiometry; 298 K	[8]
126 ± 24	−12.0	−32 ± 11	−20	Calorimetry; 298 K	[12]
120 ± 6	−12	−23 ± 1	−11	UV-spectroscopy	[14]
γ-CD/BA					
125 ± 6 (1:1)	−12.1	−4.5 ± 0.2	−7.6	Calorimetry; 303 K	[10]
91 ± 4 (1:2)	−11.4	−31.5 ± 2.0	−20.3	Calorimetry; 303 K	[10]

the solution calorimeter has been done previously [18]. The error of the enthalpy of solution measurements was less than 1%.

Enthalpies of transfer of CDs from water to BA solutions ($\Delta_{tr}H$) were calculated as follows:

$$\Delta_{tr}H = \Delta_{dis}H(\mathrm{BA} + \mathrm{H_2O}) - \Delta_{dis}H(\mathrm{H_2O}) \quad (1)$$

where $\Delta_{dis}H(\mathrm{BA} + \mathrm{H_2O})$ and $\Delta_{dis}H(\mathrm{H_2O})$ are enthalpies of CD dissolution in BA solution and water, respectively. Enthalpies of transfer as well as the initial concentrations of the reagents are listed in Table 2. Dependences of the enthalpies of transfer from BA concentration are presented in Fig. 1(a–c).

Enthalpies of transfer were analyzed by nonlinear regression method using computer program HEAT, which allows to obtain binding constants and enthalpy changes simultaneously [19]. Search of unknown parameters (lg$K$ and $\Delta_c H$) is reduced to the numerical minimization of functional F:

$$F = \sum_{1}^{N} w_i(\Delta H_{i\ \mathrm{exp}} - \Delta H_{i\ calc})^2 \quad (2)$$

where ΔH_i is the thermal effect of i-th reaction, N is the number of experiments, w_i is the weight factor calculated as $w_i = A/(\delta\Delta H_i)^2$ (where A is the coefficient chosen from the condition $\Sigma\, w_i = N$ and $\delta\Delta H_i$ is the absolute error of the measurement of ΔH_i).

For α-CD and β-CD complex formation, calculations were performed in terms of 1:1 binding mode that has been well established and reported in literature [4–17]. For HP-CDs, different binding modes such as 1:1, 1:2 and 2:1 were tested in data processing. Fitting results illustrated in Fig. 1(a–c) show that the best agreement between experimental and calculated points is observed for 1:1 complex formation of HP-α-CD (Fig. 1a) and HP-β-CD (Fig. 1b), and for 1:2 complexation of HP-γ-CD (Fig. 1c). Thus, complex formation follows the equilibrium:

$$\mathrm{CD} + n\mathrm{BA} = \mathrm{CD}^{\bullet}\mathrm{BA}_n \quad (3)$$

in which n = 2 for HP-γ-CD complexation and n = 1 for all other CDs under consideration.

Free energy and entropy changes of complex formation were estimated from well-known thermodynamic equations:

$$\Delta_c G^0 = -RT\ln K \quad (4)$$

$$\Delta_c G^0 = \Delta_c H^0 - T\Delta_c S^0 \quad (5)$$

Table 2
Experimental data on complex formation of benzoic acid with cyclodextrins in water at 298.15 K.

$m_{BA} \times 10^2$	$m_{CD} \times 10^4$	$-\Delta_{tr}H$ (kJ mol^{-1})
(mol kg^{-1})		
α-CD + BA		
0.043	8.797	**7.15**
0.154	8.839	18.68
0.331	9.153	26.50
0.504	8.549	29.93
0.731	8.957	32.11
1.067	9.059	33.76
1.525	8.501	34.89
1.979	9.055	35.49
3.021	8.703	36.20
β-CD + BA		
0.140	10.496	3.67
0.337	10.307	6.51
0.508	10.650	7.88
0.782	10.443	9.18
1.004	10.082	9.82
1.538	10.276	10.69
1.979	10.389	11.09
HP-α-CD + BA		
0.114	5.223	11.36
0.308	4.707	18.83
0.542	5.064	22.15
0.814	4.804	23.96
1.116	5.075	25.02
1.640	4.708	25.99
2.181	4.913	26.53
2.959	4.791	26.97
HP-β-CD + BA		
0.282	4.231	8.16
0.533	5.153	10.16
0.799	5.148	11.19
1.098	4.973	11.82
1.481	5.062	12.29
1.741	4.850	12.50
2.164	5.460	12.74
2.463	4.056	12.87
2.653	4.912	12.93
HP-γ-CD + BA		
0.267	5.647	1.06
0.603	5.144	4.44
0.834	5.038	7.14
1.033	5.480	9.31
1.320	5.344	12.05
1.625	5.191	14.34
1.979	5.015	16.29
2.455	5.224	18.05
2.992	5.435	19.31