

УДК 547.458.68+547.56 : 536.6

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## MOLECULAR COMPLEXES OF $\beta$ -CYCLODEXTRIN WITH BENZENE DERIVATIVES

### Introduction

Cyclodextrins (CDs) are cyclic compounds composed of  $\alpha$ -(1,4)-linkages of a number of D(+)-glucopyranose units.  $\beta$ -Cyclodextrin ( $\beta$ -CD) consists of seven glucose units. All the glucosyl-O-bridges point into the centre of the molecule, producing a torus shape. The primary hydroxyl groups project from one outer edge, and the secondary hydroxyl groups from the other. The result is a molecule with a hydrophobic centre and a relatively hydrophilic outer surface. The cavity dimensions for  $\beta$ -CD are: the internal diameter about 75 nm (7.5 Å) and the depth 75 nm [1, 2].

One of the most important characteristics of CDs is the formation of inclusion complexes with various compounds (guests) in which guest molecules are included in the cavity of CDs (host).  $\beta$ -CD forms inclusion complexes with organic compounds mainly at a molar ratio of 1:1, the molecular mass of the guest molecule is usually 80–250.

The complexation between CD and the substrate (S) may be expressed by Eq. (1):



The dissociation constant of the complex,  $K_d$ , is given by

$$K_d = \frac{[\text{C}][\text{S}]}{[\text{CD} \cdot \text{S}]} \quad (\text{M}). \quad (2)$$

The reciprocal of  $K_d$  is the equilibrium (formation) constant  $K$  ( $\text{M}^{-1}$ ).

Different methods are used to study complex formation in water solution, to determine the values of  $K_d$  and thermodynamic parameters, as well as to investigate the structure of complexes. Spectrophotometry [3] and the solubility method [4] are widely used to determine the  $K_d$  values and other parameters which describe equilibria in solutions. For the same purposes, gel chromatography can be used as well [5]. To study the geometry and structure of CD complexes, their  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra may be used [6].

In many cases, direct microcalorimetric measurements can be recommended to determine simultaneously the dissociation constant values and enthalpy of complexation which, consequently, permit calculation of changes in free energy and entropy in the process of complexation. In our studies, we used the flow-mix system of an LKB microcalorimeter and a batch instrument, elaborated the models and methods for this purpose, and calculated the values of  $K_d$  and thermodynamic parameters for complexes of  $\alpha$ -,  $\beta$ - and  $\gamma$ -CD with different guest molecules [7–10].

In this paper, some new data are presented for the complexes of  $\beta$ -CD with phenols, aromatic alcohols, and aniline derivatives. The results are discussed together with those obtained by us earlier.

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## Experimental

The dried "Chinoin"  $\beta$ -CD and chemically pure substrates were used in distilled water solutions.

Microcalorimetric measurements were carried out on a DAK-1-1A differential microcalorimeter having a reaction vessel of special construction described previously [11]. In each experiment 3 ml of the  $\beta$ -CD solution and 2 ml of the substrate solution were mixed.

Calculations of the  $K_d$  and heat effect (enthalpy change) values were performed using IBM personal computer according to the methods published earlier [10].

## Results and discussion

A thermochemical study of  $\beta$ -CD complexes has been carried out with different phenols (m-cresol, 4-nitrophenol, resorcinol, and its 5-methyl- and 2,5-dimethyl derivatives), aniline, benzyl alcohol, and their derivatives. From the experimental data, values of the dissociation constant,  $K_d$ , and change of enthalpy,  $\Delta H$  were calculated and then changes in the free energy  $\Delta G$  and entropy  $\Delta S$  in the process of complexation were found. The results are summarized in the Table.

As seen in the Table, phenols form relatively strong inclusion complexes with  $\beta$ -CD having a change in the free energy of about  $-10$  kJ per mol. For 4-nitrophenol it is known that this compound penetrates into the cavity of CD, the nitro group first, i. e. the host molecule prefers the nitro group in comparison with the hydroxyl one. The results for the complex of  $\beta$ -CD with 2-methylphenol indicate that the phenolic hydroxyl group is also quite acceptable for the CD cavity. Evidently, resorcinol and its derivatives locate in the CD cavity with both the hydroxyl groups in the cavity, which are placed there probably symmetrically. This conclusion can be drawn from the comparison of similar thermodynamic parameters of complex formation of resorcinol and orcinol.

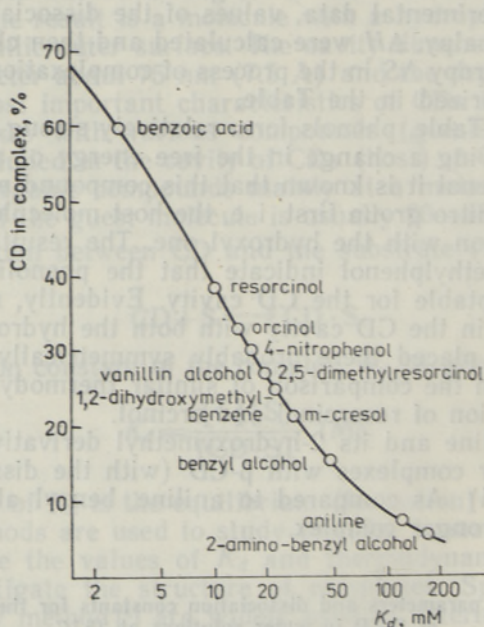
As guests, aniline and its 2-hydroxymethyl derivative form relatively unstable molecular complexes with  $\beta$ -CD (with the dissociation constant higher than 0.1 M). As compared to aniline, benzyl alcohol enables the formation of a stronger complex.

Thermodynamic parameters and dissociation constants for the 1:1 complexes of  $\beta$ -CD in water solutions at 25 °C

Guest molecule	$K_d$ , M	$\Delta G$ , kJ/mol	$\Delta H$ , kJ/mol	$\Delta S$ , J/mol·K
1,3-dihydroxybenzene (resorcinol)	0.010	-11.6	-18.2	-21.6
1,3-dihydroxy-5-methylbenzene (5-methylresorcinol, orcinol)	0.014	-10.8	-19.3	-28.2
1,3-dihydroxy-2,5-dimethylbenzene (2,5-dimethylresorcinol)	0.0203	-9.8	-13.2	-11.2
1-hydroxy-4-nitrobenzene (4-nitrophenol)	0.0165	-10.4	-26.1	-52.1
1-hydroxy-3-methylbenzene (3-methylphenol, m-cresol)	0.0291	-8.9	-21.4	-41.1
aminobenzene (aniline)	0.120	-5.4	-15.2	-34.7
1-amino-2-hydroxymethylbenzene (2-amino-benzyl alcohol)	0.168	-4.5	-16.9	-40.9
hydroxymethylbenzene (benzyl alcohol)	0.048	-7.7	-13.8	-20.3
1,2-dihydroxymethylbenzene	0.0228	-9.5	-6.1	11.2
1-hydroxy-2-methoxy-4-hydroxymethylbenzene (vanillin alcohol)	0.020	-9.9	-6.2	11.9

It is very interesting that the molecular complexes of  $\beta$ -CD with 1,2-dihydroxymethylbenzene and vanillin alcohol are very similar, with practically equal thermodynamic parameters, and a positive change of entropy (see the Table). This may be occasional. But there is a possibility that the structure of these complexes is also similar. In this case it may be assumed that only one of the  $\text{CH}_2\text{OH}$ -groups of 1,2-dihydroxymethylbenzene penetrates deeper into the cavity (not so far as the same group of benzyl alcohol), the other group (and hydroxyl and methoxy groups of vanillin alcohol) remain outside.

Illustratively the dissociation constants of different molecular complexes are presented in the Figure. For comparison, benzoic acid is also shown as the substrate with the lowest  $K_d$  value found in our experiments [10]. The overall molar concentration of both  $\beta$ -CD and the substrate were taken to be equal in the solution, 0.1 M, and the percentage of  $\beta$ -CD and substrate bound in complexes is calculated and given on the ordinate.



Values of the dissociation constant  $K_d$  and the content of 1:1 molecular complex (percentage of  $\beta$ -CD and substrate in the complex) of  $\beta$ -cyclodextrin with different aromatic compounds in water solution at 25°C. Overall concentration of  $\beta$ -CD and substrate is 0.01 M.

Unfortunately, microcalorimetry does not permit elucidation of the structure of molecular complexes. Some progress in this field has been achieved using TMR spectroscopy. Interesting disputable host-guest models for the alkylbenzene complexes with  $\alpha$ -,  $\beta$ - and  $\gamma$ -CD have been published by Sanemasa and Akamine [12], in which the direction of inclusion and the extent of guest penetration have been given for different, relatively weak inclusion complexes. In any case, using different methods and collecting new data on CD complexes with many organic compounds, the structure problems will be solved step by step.

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Presented by Ü. Lille

Received  
Feb. 7, 1991

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### $\beta$ -TSÜKLODEKSTRIINI MOLEKULAARKOMPLEKSID BENSEENI DERIVAATIDEGA

Mikrokalorimeetrilisel meetodil on uuritud  $\beta$ -tsüklodekstriini 1:1 inklusioonühendite teket fenoolidega, aniliini ja bensüülalkoholi derivaatidega vesilahustes 25 °C juures. On määratud komplekside dissotsiatsioonikonstantide ning nende tekkimise termodünaamiliste parameetrite väärtused. Komplekside stabiilsuse võrdlemise põhjal on tehtud oletusi nende struktuuri kohta.

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### МОЛЕКУЛЯРНЫЕ КОМПЛЕКСЫ $\beta$ -ЦИКЛОДЕКСТРИНА ПРОИЗВОДНЫМИ БЕНЗОЛА

Микрокалориметрическим методом исследовано образование в соотношении 1:1 инклюзионных соединений  $\beta$ -циклодекстрина с фенолами, производными анилина и бензилового спирта в водных растворах при 25 °C. Определены значения констант диссоциации комплексов и термодинамические параметры их образования. На базе сравнения стабильности комплексов предложена их вероятная структура.