

Influence of the Solvation Upon the Reaction of α -Cyclodextrin with Carboxylic Acids, Their Methyl Esters, and Their Sodium Salts in Aqueous Solution Studied by Calorimetric Measurements

Hans-Jürgen Buschmann^{1,*} and Eckhard Schollmeyer¹

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The complex formation of α -cyclodextrin with carboxylic acids, their methyl esters, and their sodium salts has been studied using calorimetric titrations. The stronger solvation of the carboxylic sodium salts compared with the free acid or their methyl esters lowers the values of the reaction enthalpy and entropy. Complex formation is influenced in the positive direction by the release of "high-energy water" from the cavity of α -cyclodextrin. The values of the reaction enthalpy and entropy increase for the complex formation of α -cyclodextrin with increasing chain length of the carboxylic acids and their derivatives, and reach an approximately constant upper limit in the case of five methylene groups.

KEY WORDS: α -Cyclodextrin; carboxylic acids; complex formation; solvation.

1. INTRODUCTION

Cyclodextrins (CDs) are polysaccharides built from six to eight ($\alpha = 6$, $\beta = 7$, $\gamma = 8$) D-glucose units.⁽¹⁾ They are formed during the enzymatic degradation of starch. The shape of the cyclodextrin molecules is torus-like, see Fig. 1. All polar groups are located on the outside of the molecule. As a result, the interior of the cavities is rather hydrophobic. The inside of the β -cyclodextrin cavity has an effective permittivity of 48.⁽²⁾ A large number of nonpolar organic molecules form complexes with cyclodextrins in aqueous solution, and in many cases their stability constants have been reported.^(3,4) The physical and chemical properties of the complexed molecules change as a result of this complexation. The thermal

¹Deutsches Textilforschungszentrum Nord-West e.V., Adlerstrasse 1, D-47798 Krefeld, Germany; e-mail: buschmann@dtnw.de.

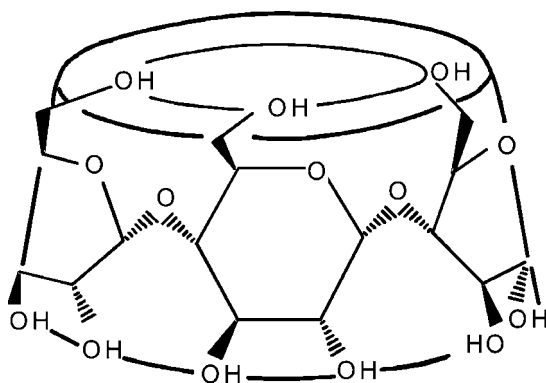


Fig. 1. Chemical structure of α -cyclodextrin.

stability of the guest molecules and also their stability against oxidation increase in the solid state. The solubilities of cyclodextrin complexes with slightly soluble substances are higher compared with the pure uncomplexed substances. These factors are mainly responsible for the practical applications of cyclodextrins, e.g., in pharmacy.⁽⁵⁾

The stability of complexes formed in solution with α -cyclodextrin is influenced by the size of the guest molecules. Steric factors may hinder the formation of complexes. Mainly hydrophobic interactions are responsible for the complex formation between the uncharged host and guest molecules. From crystal structure information it is known that α -cyclodextrin forms a hydrate with six water molecules.⁽⁶⁾ Four water molecules are located outside and two inside the cavity. The water molecules inside the cavity of α -cyclodextrin are energetically not comparable with water molecules in the bulk phase. These water molecules inside the cavity are not able to form hydrogen bonds as in the bulk phase. Thus, they were called "high-energy water" by Saenger.⁽⁷⁾ The release of these water molecules from the cavity should result in favorable enthalpic and entropic contributions to the Gibbs free energy. Cyclodextrin complexes are also formed with organic molecules having polar groups. These groups are located outside and the nonpolar part of the molecule inside the cavity. However, the polar groups may also influence the stability of the complexes formed. The strength of the solvation should be responsible for the observed differences in complex formation for ammonium and carboxylic groups compared to hydroxyl groups.⁽⁸⁾ These groups have different sizes and therefore additional factors may be responsible for the observed differences.

To further understand the host-guest interactions, we decided to study the complex formation between carboxylic acids, their methyl esters, and their sodium salts with α -cyclodextrin.

2. EXPERIMENTAL

All carboxylic acids and their methyl esters were commercial samples of the highest available purity. The sodium salts of the carboxylic acids were prepared by neutralization of aqueous solutions with sodium hydroxide. The α -cyclodextrin (α -CD) used is of the highest purity (pharmaceutical grade, Wacker). Bidistilled water was used as solvent. The titrations were performed in non-buffered solutions as described in the literature.⁽⁹⁾

The calorimetric titrations were performed using a Tronac Model 450 calorimeter (TRONAC Inc.). During the calorimetric titration, a solution of the ligand α -CD (between 0.06 and 0.08 mol L⁻¹) is added continuously to the solution containing the carboxylic acid (4×10^{-3} to 5×10^{-3} mol L⁻¹). The use of carboxylic acids and their derivatives is limited by their solubility in aqueous solution.

The procedures for calibration of the calorimeter and evaluating the data have already been described in detail.⁽¹⁰⁻¹²⁾ The accuracy of our calorimeter was checked using as standard reactions the reaction between the crown ether 18C6 and barium perchlorate ($\log K = 3.65 \pm 0.02$ and $\Delta H = -(32.8 \pm 0.4)$ kJ mol⁻¹), and the reaction between β -CD and cyclohexanol ($\log K = 2.87 \pm 0.02$ and $\Delta H = -(17.5 \pm 0.7)$ kJ mol⁻¹) in aqueous solution. Both values are in excellent agreement with the results reported in the literature.^(13,14)

3. RESULTS AND DISCUSSION

In Table I the stability constants and the reaction enthalpies and entropies are summarized for the complexation of carboxylic acids, their methyl esters, and their sodium salts with α -CD. Results reported in the literature are also listed for comparison. The agreement between most of the measured data and those taken from the literature is very good. Some differences are observed in the case of the sodium salts of the carboxylic acids with a high number of methylene group. The concentration dependent formation of aggregates of these acids may be responsible.

As shown in Fig. 2, the stability constants increase with increasing number of methylene groups. However, the differences between the values of the free acids, of the corresponding sodium salts, and the methyl esters are rather small. Thus no serious discussion of these differences is possible. A more detailed discussion of the reaction enthalpies and entropies should give some insight into the influence of solvation upon the complexation reactions.

For all guest molecules, the values of the reaction enthalpies becomes more exothermic with an increasing number of methylene groups and the values of the reaction entropy become more negative, see Table I. The complex formation is favored by enthalpic and disfavored by entropic contributions. A mutual partial compensation of enthalpic and entropic contributions takes place, and as a result,

Table I. Values of Log K (K in $L \cdot mol^{-1}$) and Thermodynamic Data (ΔH in $KJ \cdot mol^{-1}$ and $T\Delta S$ in $KJ \cdot mol^{-1}$) for the Complex Formation of Carboxylic Acids, Their Methyl Esters, and Their Sodium Salts with α -Cyclodextrin in Aqueous Solution at 25 °C

Acid	Free acid			Methyl ester			Sodium salt		
	log K	$-\Delta H$	$T\Delta S$	log K	$-\Delta H$	$T\Delta S$	log K	$-\Delta H$	$T\Delta S$
Acetic acid	2.14 ± 0.04	2.8 ± 0.5	9.4 ± 0.7	2.50 ± 0.05	4.9 ± 0.7	9.3 ± 1.0	—	—	—
Propionic acid	2.01 ± 0.06	8.1 ± 0.4	3.3 ± 0.8	2.39 ± 0.04	8.7 ± 0.5	4.9 ± 0.7	2.42 ± 0.03	1.1 ± 0.2	12.7 ± 0.3
Butyric acid	2.10 ± 0.06	22.0 ± 0.5	-10.1 ± 0.9	2.38 ± 0.01	12.7 ± 0.3	1.1 ± 0.6	2.43 ± 0.05	0.9 ± 0.4	12.9 ± 0.7
	2.13 ^a	23.2 ^a	-11.1 ^a				1.19 ^a	5.8 ^a	1.0 ^a
							1.10 ^b	10.6 ^b	-4.4 ^b
<i>n</i> -Pentanoic acid	2.54 ± 0.03	32.5 ± 0.6	-18.1 ± 0.8	2.53 ± 0.03	22.4 ± 0.2	-8.0 ± 0.3	2.44 ± 0.03	6.5 ± 0.5	7.4 ± 0.6
	2.73 ^a	29.8 ^a	-14.2 ^a				1.88 ^a	10.1 ^a	0.6 ^a
<i>n</i> -Hexanoic acid	2.76 ± 0.05	34.3 ± 0.9	-18.6 ± 0.8	— ^d	— ^d	— ^d	2.53 ± 0.04	12.8 ± 0.5	1.6 ± 0.7
	2.91 ^a	32.2 ^a	-15.1 ^a				2.32 ^a	14.2 ^a	-1.0 ^a
							2.48 ^b	14.2 ^b	-0.1 ^b
							2.71 ^c	6.1 ^c	
<i>n</i> -Heptanoic acid	2.74 ± 0.07	40.2 ± 1.1	-24.6 ± 1.5	— ^d	— ^d	— ^d	2.50 ± 0.06	21.6 ± 0.7	-7.4 ± 1.0
							2.93 ^b	17.5 ^b	-0.9 ^b
							3.01 ^c	12.2 ^c	
<i>n</i> -Octanoic acid	3.26 ^a	46.9 ^a	-28.3 ^a	— ^d	— ^d	— ^d	2.86 ± 0.03	26.4 ± 0.6	-10.2 ± 0.8
							2.96 ^a	46.9 ^a	-30.0 ^a
							3.39 ^b	20.5 ^b	-1.2 ^b
							3.13 ^c	18.6 ^c	
<i>n</i> -Nonanoic acid				— ^d	— ^d	— ^d	3.00 ± 0.02	26.8 ± 0.5	-9.8 ± 0.7
							2.40 ^c	38.4 ^c	
<i>n</i> -Decanoic acid	3.22 ^a	28.3 ^a	-10.0 ^a	— ^d	— ^d	— ^d	3.19 ± 0.07	23.2 ± 0.4	-5.1 ± 0.8
							2.98 ^a	26.5 ^a	-9.6 ^a
							2.40 ^c	50.7 ^c	
<i>n</i> -Undecanoic acid	— ^d	— ^d	— ^d	— ^d	— ^d	— ^d	4.00 ± 0.03	25.7 ± 0.6	-3.0 ± 0.8
<i>n</i> -Dodecanoic acid	— ^d	— ^d	— ^d	— ^d	— ^d	— ^d	4.26 ± 0.04	26.4 ± 0.7	-2.2 ± 0.9

^a From reference.⁽¹⁶⁾

^b From reference.⁽¹⁷⁾

^c From reference.⁽¹⁸⁾

^d The solubility is too low for calorimetric titrations.

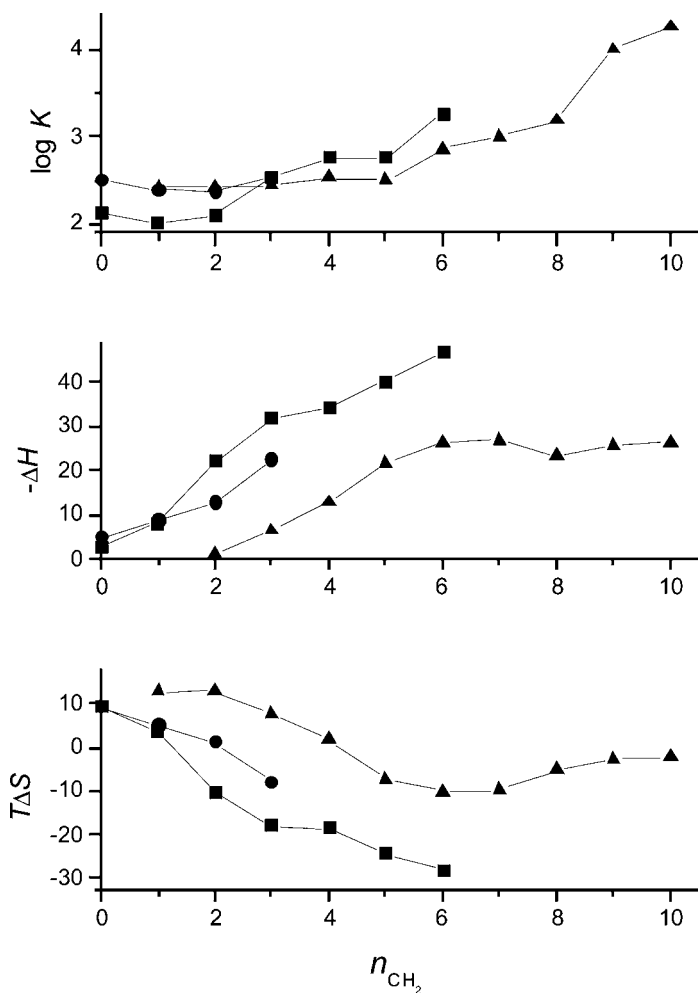


Fig. 2. Values of $\log K$ (K in $L\ mol^{-1}$) and thermodynamic results (ΔH in $kJ\ mol^{-1}$ and $T\Delta S$ in $K\ kJ\ mol^{-1}$) for the complex formation of carboxylic acids (■), their methyl esters (●), and their sodium salts (Δ) with α -CD in aqueous solution at $25^\circ C$ as a function of the number of methylene groups n_{CH_2} .

the stabilities of the complex increase only slightly with the chain length of the guest molecule. In Fig. 1 the reaction enthalpies and entropies are also shown as a function of the number of methylene groups. In both plots the free carboxylic acid and their methyl ester behave very similar. These values are nearly identical. For the sodium salts the values of the reaction enthalpies become nearly constant value

for $n \geq 7$. Due to their limited solubility, no data for the corresponding carboxylic acids and their methyl esters can be measured.

For $n \geq 3$ a nearly constant difference is observed between the reaction enthalpies for the complexation of carboxylic acids and their sodium salts. The stronger solvation of the sodium salt is responsible. During complex formation, a partial desolvation of the carboxylic group takes place. Due to electrostatic interactions between the negative charged carboxylic group and the water molecules, these molecules are more strongly bound than in the case of the undissociated COOH group or the methyl ester. A very rough estimation of the number of additional replaced water molecules, Δn_w , from the sodium salts of the carboxylic acids compared with the free acids, can be made by using the heat of fusion of water ($\Delta H_{\text{fusion}} = 6.0 \text{ H kJ mol}^{-1}$)⁽¹⁵⁾ and the reaction enthalpies reported in Table I. For example, the difference in the number of replaced water molecules for the complex formation of octanoic acid and their sodium salt with α -CD yields:

$$\Delta n_w = \frac{\Delta H_{\text{salt}} - \Delta H_{\text{acid}}}{\Delta H_{\text{fusion}}} = 3.4 \quad (1)$$

This result is also valid for the other acids examined. During the complex formation with α -CD, about 3 mol of water are liberated from the sodium salts compared with the free acids.

This interpretation is also supported by the reaction entropies. The number of solvent molecules, Δn_w , released during the complex formation also influences the values of the reaction entropy. From the difference between the reaction entropies for the complexation of the sodium salts and the free acids one can estimate the difference of the number of released solvent molecules using the entropy of fusion ($\Delta S_{\text{fusion}} = 22.01 \text{ H kJ mol}^{-1}$)⁽¹⁵⁾. For octanoic acid and its sodium salt one has, for example,

$$\Delta n_w = \frac{T \Delta S_{\text{salt}} - T \Delta S_{\text{acid}}}{T \Delta S_{\text{fusion}}} = 2.7 \quad (2)$$

Comparable results are obtained for the other acids. Taking into account that all other effects influencing the reaction enthalpies and entropies have been neglected, the agreement between these two estimated values of Δn_w is very good.

Without a knowledge of all contributions to the reaction enthalpies and entropies, no fundamental discussion of the solvation changes for α -CD and the guest molecules is possible. However, for the free acids, their methyl esters, and their sodium salts, a nearly constant increase with the number of CH₂-groups is observed for the thermodynamic values. This effect can be attributed to the liberation of the so called "high-energy water" from the cavity of the α -CD molecules.

These results clearly demonstrate the influence of solvation changes during the complex formation of uncharged molecules with α -CD. Both the solvation changes of the guest molecules as well as the host molecules have an important

influence upon the experimentally obtained values. However the complex formation is mainly favored by the release of water molecules from the cavity of α -CD while the partially desolvation of the guest molecules disfavors this reaction.

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