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Complexes of Short-Chain Alcohols with β-Cyclodextrin

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Abstract. The complex formation of β-cyclodextrin with short chain aliphatic alcohols has been studied. The stability constants of 1 : 1 complexes, determined spectrophotometrically, increase monotonically in the series of normal alcohols, while branching in the chain results in a further increase in stability. With smaller monoalcohols, complexes containing more than one guest molecule are formed as well, but the relative stability of these complexes decreases with increasing chain length and branching. The stabilities of 1 : 1 complexes decrease with an increasing number of OH-groups, probably due to a stronger hydration. This reflects both the roles of space filling and hydrogen bridging

Key words: Cyclodextrin, inclusion, alcohols.

0. Introduction

The stabilities of cyclodextrin inclusion complexes are influenced by several factors, such as space filling, hydrophobic interactions, hydrogen bonding and solvation effects [1], but the relative importance of these may be quite different for different types of guest molecules. To get a better insight into the nature of the interactions, an adequate series of accurate stability constants are needed. There are a lot of data available in the literature but the inconsistencies are often large and relatively few really systematic investigations have been published [2].

In the present work, we have studied the interactions between β-cyclodextrin and the following alcohols: linear chain aliphatic alcohols from methanol up to 1-octanol, some branched chain alcohols such as *i*-propanol, *i*- and *t*-butanol and cyclohexanol, and ethylene glycol, 1,2-propylene glycol and glycerol.

1. Experimental

The stability constants were determined by a spectrophotometric method, based on the competing reactions between two guests (phenolphthalein and the alcohol studied) and the cyclodextrin [3,4]. Upon adding β-cyclodextrin to a purple-colored slightly alkaline

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phenolphthalein solution, the optical density decreases on account of the formation of a colorless phenolphthalein–cyclodextrin complex. In the presence of another potential guest molecule (e.g., alcohols) only a fraction of the cyclodextrin cavities can interact with the phenolphthalein, resulting in a weaker discoloration effect.

The β-cyclodextrin (a CHINOIN product) was recrystallized from hot water and the reagent-grade phenolphthalein was recrystallized from an ethanol-water mixture. The alcohols (analytical purity grade) were stored over anhydrous sodium carbonate for some days in order to remove acidic impurities and moisture, and then distilled at normal pressure or *in vacuo*.

Concentration of the solutions:

phenolphthalein: 3×10^{-5} mol dm^{-3}

β-cyclodextrin: varied from 1×10^{-5} up to 2.5×10^{-4} mol dm^{-3}

alcohols: see Tables I–III (but their concentration was kept constant during a series).

The pH of the solutions was adjusted with 2×10^{-2} mol dm^{-3} sodium carbonate, and the absorbances were measured at 25 ± 2 °C with a Spectromom 361 spectrophotometer, in 10 mm cells at 550 nm wavelength.

The molar absorption coefficient of phenolphthalein has been measured in moderate alkaline solution, where

$$\varepsilon = \frac{A}{[\mathrm{I}]} = \frac{A}{c_\mathrm{I}} \,. \tag{1}$$

At pH = 10.5, as used in the experiments, an apparent molar absorption coefficient can and has been measured in every series:

$$''\varepsilon'' = \frac{A}{c_\mathrm{I}} = \frac{\varepsilon}{1 + K_{\mathrm{IH}^+}[\mathrm{H}^+]} \tag{2}$$

As the alcohols are known to interact with phenolphthalein, their presence alters this apparent molar absorption coefficient:

$$\varepsilon^* = \frac{A}{c_\mathrm{I}} = \frac{\varepsilon}{1 + K_{\mathrm{IH}^+}[\mathrm{H}^+] + K_{\mathrm{AI}}[\mathrm{A}] + K_{\mathrm{AIH}^+}[\mathrm{H}^+][\mathrm{A}] + \cdots} \,, \tag{3}$$

but this effect at constant temperature, pH and ionic strength (as given), and with a relatively great excess of alcohol, is constant.

ε^* can and has been measured in every alcohol–water mixture and, since the alcohol concentration was kept constant in the series with an increasing concentration of cyclodextrin, the concentrations of phenolphthalein ([I] and reduced c_I^*) could be calculated directly. Every alcohol with different concentrations has been studied in such series at least 10 times and, several others 25 times.

2. Results

The experimental data were transformed into apparent stability constants for the β-cyclodextrin–phenolphthalein complexes:

$$\beta^*_{\mathrm{CDI}} = \frac{c_\mathrm{I}^* - [\mathrm{I}]}{(c_{\mathrm{CD}} - c_\mathrm{I}^* + [\mathrm{I}])\,[\mathrm{I}]} \tag{4}$$

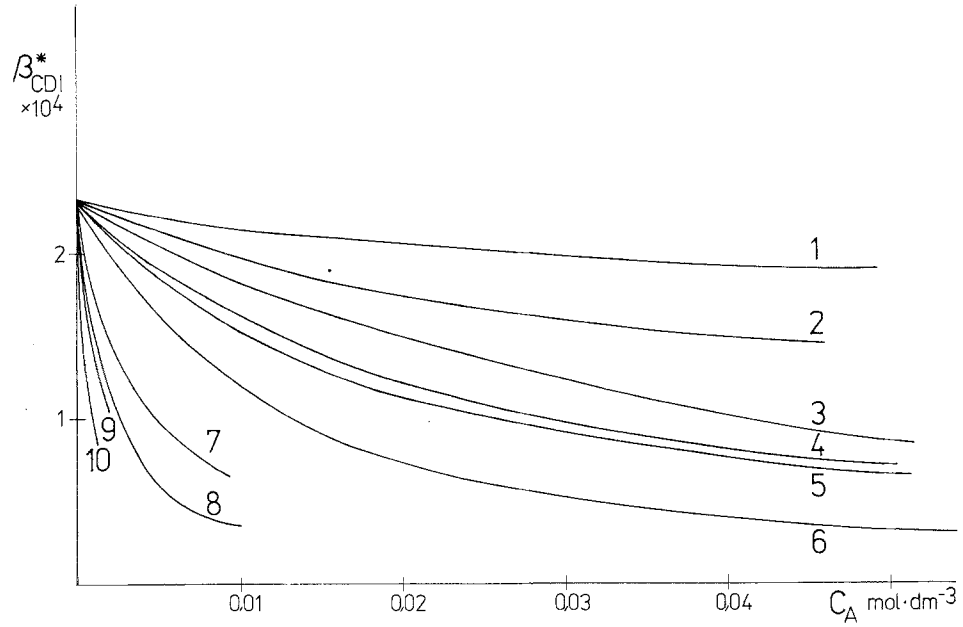

Fig. 1. Correlation between the apparent stability constant of a β-cyclodextrin–phenolphthalein complex and the concentration of monoalcohols. c_A is the total concentration of the alcohol: 1: *n*-propanol, 2: *i*-propanol, 3: *n*-butanol, 4: *i*-butanol, 5: *t*-butanol, 6: 1-pentanol, 7: 1-hexanol, 8: cyclohexanol, 9: 1-heptanol, 10: 1-octanol.

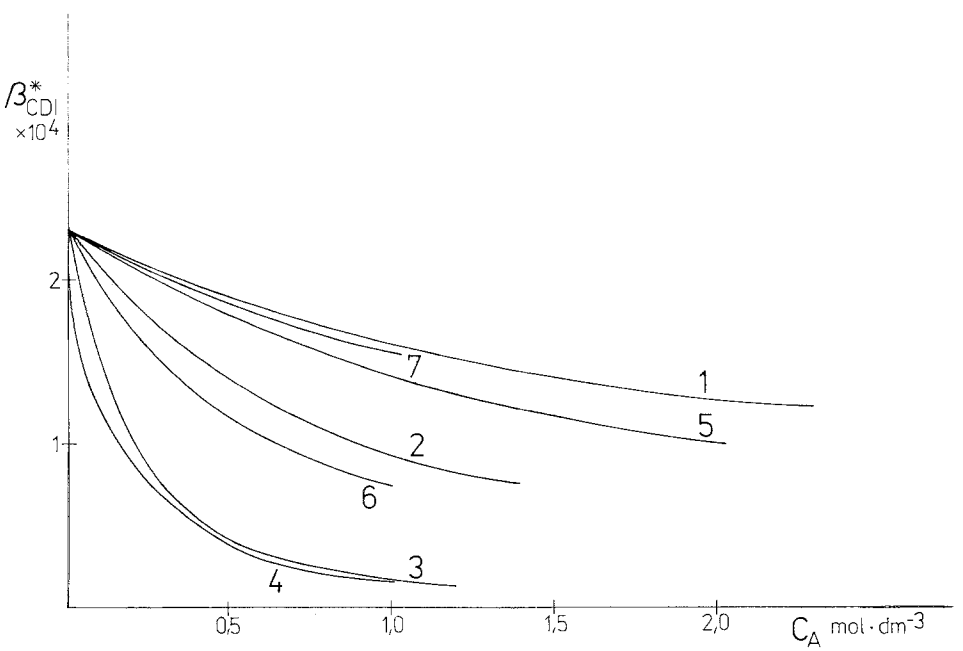

Fig. 2. Correlation between the apparent stability constant of a β-cyclodextrin–phenolphthalein complex and the concentration of various alcohols (c_A): 1: methanol, 2: ethanol, 3: *n*-propanol, 4: *i*-propanol, 5: ethylene glycol, 6: propylene glycol, 7: glycerol.

where c_I^* and c_{CD}, the (reduced) total concentrations of phenolphthalein and β-cyclodextrin, respectively, are known and [I], the equilibrium concentration of the free phenolphthalein, can be directly measured. The results are shown on Figures 1 and 2.

The most remarkable fact is that the competing effect of the branched-chain molecules is always greater than that of the corresponding normal alcohols. In addition, slight differences can be observed in the shapes of the curves (see propanols in both Figures 1 and 2), suggesting that the stoichiometry of the complexes are not necessarily identical. Moreover, Figure 2 illustrates that with an increasing number of OH-groups, the effect of the alcohols is decreased.

3. Discussion

Stability constants have been calculated for the different β-cyclodextrin – alcohol complexes from the experimental data. To a first approximation, we tried to fit the data to the pattern of simple binary complexes:

$$CD + I \rightleftharpoons CDI \qquad \beta_{CDI} = \frac{[CDI]}{[CD]\,[I]} = 2.3 \times 10^4 \tag{5}$$

$$CD + A \rightleftharpoons CDA \qquad \beta_{CDA} = \frac{[CDA]}{[CD]\,[A]} \tag{6}$$

where CD, I and A stand for the free β-cyclodextrin, phenolphthalein and alcohol, resp.; CDI and CDA are the complexes, β_{CDI} and β_{CDA} being the corresponding stability constants and [ ] always denoting the equilibrium concentrations.

Using equations (4)–(6), the connection between the apparent stability constant (β^*_{CDI}) and the real one can be expressed, as

$$\beta^*_{CDI} = \frac{\beta_{CDI}}{1 + \beta_{CDA}\,[A]}\,. \tag{7}$$

When this simple pattern proved to be insufficient, Equation (7) was completed by terms taking into consideration the formation of such complexes as e.g.,

$$CD + 2\,A \rightleftharpoons CDA_2 \qquad \beta_{CDA_2} = \frac{[CDA_2]}{[CD]\,[A]^2}$$

$$\left[K_2 = \frac{[CDA_2]}{[CDA]\,[A]} = \frac{\beta_{CDA_2}}{\beta_{CDA}}\right] \tag{8}$$

or

$$CD + I + A \rightleftharpoons CDIA \qquad \beta_{CDIA} = \frac{[CDIA]}{[CD]\,[I]\,[A]}\,; \tag{9}$$

thus

$$\beta^*_{CDI} = \frac{\beta_{CDI} + \beta_{CDIA}\,[A]}{1 + \beta_{CDA}\,[A] + \beta_{CDA_2}\,[A]^2 + \beta_{CDA_3}\,[A]^3 + \cdots} \tag{10}$$

The primary β^*_{CDI} values have been evaluated by a computer program using Equation 10 in a trial-and-error procedure, searching the set of equilibrium constants to find the best fit and also calculating the 3σ values given in the tables.

3.1. LINEAR-CHAIN MONOALCOHOLS

The stability constants obtained for the non-branched monoalcohols are summarized in Table I.

Table I. Stability constants of linear chain monoalcohol–β-cyclodextrin complexes

Alcohol	Conc. range mol dm^{-3}	β_{CDA}	β_{CDA_2}	K_2	β_{CDA_3}	K_3	β_{CDA_4}	K_4
methanol	0–2.0	0.4 ± 0.1	(–)	(–)	(–)	(–)	(–)	(–)
ethanol	0–2.0	1.2 ± 0.1	0.28	0.23	0.072	0.25	(0.017)	(0.24)
n-propanol	0–1.2	5.0 ± 0.5	7.3	1.5	(–)	(–)	–	–
n-butanol	0–0.33	27.6 ± 1.2	62	2.2	–	–	–	–
1-pentanol	0–0.07	76 ± 11	–	–	–	–	–	–
1-hexanol	0–0.01	280 ± 13	–	–	–	–	–	–
1-heptanol	0–0.002	660 ± 54	–	–	–	–	–	–
1-octanol	0–0.001	1770 ± 130	–	–	–	–	–	–

$$K_2 = \frac{\beta_{CDA_2}}{\beta_{CDA}}, \qquad K_3 = \frac{\beta_{CDA_3}}{\beta_{CDA_2}}, \text{ etc.}$$

It is remarkable that the stability constants of the 1 : 1 complexes increase monotonically with increasing chain length, without any breakdown or extremely sharp increase that could distinguish between the so-called outer-sphere type (only hydrogen bonded) and real inclusion complexes. Plotting the (log β_{CDA}) values against the carbon atom number of alcohol molecules, an almost straight line is obtained. It is noteworthy that a previous work [7] with amylose and short chain alcohols reported a similar correlation between K_{diss} and the chain length.

The experimental data obtained with lower alcohols, however, do not fit the values calculated for the assumed 1 : 1 stoichiometry, for complexes containing two or more guest molecules must also be taken into account.

In the case of β-cyclodextrin–ethanol, formation of complexes with molar ratios of 1 : 2, 1 : 3, and even 1 : 4 (though with large uncertainties because of the cumulation of errors), could be deduced. However, the 1 : 1 complex has the greatest stability and there are no significant differences between the equilibrium constants of further complex formation steps (K_2, K_3, K_4).

The situation must be similar with methanol but the low stabilities do not allow us to calculate further constants over β_{CDA}.

With an increasing number of carbon atoms in the guest molecule, the tendency towards formation of ternary, quanternary, etc. complexes is strongly reduced. The experimental data obtained for propanol and butanol can be satisfactorily interpreted by assuming the simultaneous existence of 1 : 1 and 1 : 2 complexes, while from 1-pentanol upwards, 1 : 2 complexes are no longer formed. Even for propanol and butanol, the equilibrium constants related to the interaction of the second alcohol molecule (K_2) are relatively decreased (compared with the K_2/β_{CDA} ratios).

3.2. BRANCHED-CHAIN ALCOHOLS

Branching in the chain causes a significant increase in the stability of 1 : 1 complexes (see Table II and Figure 1). The difference is striking between 1-hexanol and cyclohexanol. (On the plot of log β_{CDA} against the number of carbon atoms, the values of the branched isomers and cyclohexanol all fall above the straight line obtained for normal alcohols.) At the same time, the stability constants of the 1 : 2 complexes are smaller than those for the corresponding normal alcohols; for *t*-butanol no 1 : 2 complex could be detected at all.

Table II. Stability constants of the non-linear alcohol–β-cyclodextrin complexes

Alcohol	Conc. range mol dm^{-3}	β_{CDA}	β_{CDA_2}	K_2
n-propanol	0–1.2	5.0 ± 0.5	7.3	1.5
i-propanol	0–1.0	7.9 ± 1	7.0	0.9
n-butanol	0–0.33	27.6 ± 1.2	62	2.2
i-butanol	0–0.4	47 ± 1	70	1.5
t-butanol	0–0.5	54 ± 1.5	–	–
1-hexanol	0–0.01	280 ± 13	–	–
cyclohexanol	0–0.01	620 ± 50	–	–

The above results obtained for monoalcohols reflect the role of space filling (and hydrophobic) interactions. However, the fact that guest molecules of similar space filling characteristics are characterized by rather different β_1 values (e.g., dioxane = 24; benzene = 150 [5]; cyclohexanol = 620 or benzoic acid = 800 [6]) proves that hydrogen bonding must also play a significant role.

3.3. DI- AND TRIHYDROXY COMPOUNDS

Table III illustrates that the stability constants of 1 : 1 complexes show a decreasing tendency within a series of alcohols with identical numbers of carbon atoms with an increase in the number of OH-groups. This is probably due to the increasing hydration.

Table III. Effect of the number of OH-groups on the stability constants of alcohol–β-cyclodextrin complexes

Alcohol	Conc. range mol dm^{-3}	β_{CDA}	β_{CDA_2}
ethanol	0–2.0	1.2 ± 0.1	0.28
ethylene glycol	0–2.0	0.7 ± 0.1	–
n-propanol	0–1.2	5.0 ± 0.5	7.3
1,2-propylene glycol	0–1.0	1.9 ± 0.1	–
glycerol	0–1.0	0.5 ± 0.1	–

The conclusion that strongly-hydrated polyhydroxy compounds (as, e.g., glucose) do not form inclusion complexes with cyclodextrins, seems to be of general validity [8].

In the experiments the concentration of β-cyclodextrin was much smaller than that of the alcohols. It is obvious, therefore, that nowhere could complexes containing a 2 : 1

cyclodextrin : guest ratio be detected. For more concentrated cyclodextrin solutions, the existence of 2 : 1 complexes cannot be excluded (first of all with glycerol). Of course, the low solubility of the β-cyclodextrin sets a limit to such experiments.

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