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COMPLEXATION OF ALIPHATIC ALCOHOLS BY α- AND β-CYCLODEXTRINS AND THEIR PARTIAL METHYLATED DERIVATIVES IN AQUEOUS SOLUTION

H.-J. Buschmann, H. Dong and E. Schollmeyer

Deutsches Textilforschungszentrum Nord-West e. V., Adlerstrasse 1, D-47798 Krefeld, Germany

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Abstract

The complexation of aliphatic alcohols by α- and β-cyclodextrins and their partially methylated derivatives has been studied by means of calorimetric titrations in aqueous solution. The methyl substituents have no pronounced influence upon the complex formation. α-Cyclodextrin and the partially methylated derivative form with only few exceptions more stable than β-cyclodextrin. With increasing chain length of the alcohols the values of the stability constants and reaction enthalpies increase in case of the complex formation with α-cyclodextrin and partially methylated α-cyclodextrin. In contrast the complex formation becomes disfavoured by the reaction entropy with an increasing number of methylene groups. The values of the reaction enthalpies with the β-cyclodextrins are close to zero. Thus the complexation is only favoured by entropic contributions.

Keywords: alcohols, calorimetry, complex formation, cyclodextrins

Introduction

Cyclodextrins (CDs) are polysaccharides made up of six to eight (α=6, β=7, γ=8) *D*-glucose monomers linked covalently at the 1 and 4 carbon atoms. The internal rigid cavities are relatively hydrophobic and have diameters ranging from 0.50 to 0.85 nm (Fig. 1). Inside the hydrophobic cavities guest molecules can be included [1–6]. Due to the complex formation the solubility of unpolar organic substances in aqueous solution increases. This effect is mainly used in pharmaceutical applications [3, 7–11]. The complex formation of a large number of guest molecules with cyclodextrins has already been studied [3, 12]. However, in most cases no thermodynamic data are known.

Different experimental techniques have been used to measure the stability of the complexes formed. Most commonly the stability constants are determined by spectroscopic methods, e.g. UV, fluorescence, NMR, by solubility and by competitive reactions. The reliability of the different methods has recently been compared for the complexation of surfactants with cyclodextrins [13]. Obviously direct calorimetric ti-

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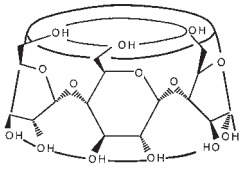

Fig. 1 Schematical structure of α-CD

trations simultaneously lead to very accurate values of the stability constants and reaction enthalpies and entropies. Stability constants and reaction enthalpies for the complexation of aliphatic alcohols taken from the literature also show few discrepancies [14–22]. On the other hand no results have been reported for the complexation of aliphatic alcohols with partially methylated cyclodextrins.

Thus, we studied the complexation of aliphatic alcohols by α- and β-CD and their partially methylated derivatives using calorimetric methods. The knowledge of the thermodynamic parameter is important for a better understanding of the different factors influencing the complex formation.

Experimental

The aliphatic alcohols 1-butanol (Fluka), 1-pentanol (Fluka), 1-hexanol (Merck), 1-heptanol (Fluka) and 1-octanol (Merck) are of the highest purity commercially available. α-Cyclodextrin (α-CD), β-cyclodextrin (β-CD), and the partially methylated cyclodextrin derivatives (average degree of substitution 1.8) 1.8-methyl-α-cyclodextrin (1.8M-α-CD) and 1.8-methyl-β-CD (1.8M-β-CD) (all Wacker) are used without further purification.

The calorimetric titrations a performed using a Tronac Model 458 calorimeter. A ligand solution (0.06–0.08 mol l^{-1}) is added continuously (buret rate: 0.3232 ml s^{-1}) to a solution of the guest molecules ($4\cdot10^{-3}$–$5\cdot10^{-3}$ mol l^{-1}). The heat Q produced during titration is related to the reaction enthalpy ΔH by the following equation after correction of all non-chemical heat effects:

$$Q=\Delta n\Delta H$$

with Δn as the number of moles of the complex formed. The mathematical treatment of the experimental data is already described in detail in the literature [23–25].

Results and discussion

The results obtained for the complexation of aliphatic alcohols and different cyclodextrins are summarized in Table 1 together with some data from the literature. Large deviations with results from the literature are only found in few cases. The cyclodextrins and their partially methylated derivatives behave comparable.

Table 1 Stability constants ($\log K_1$, K_1 in $dm^3\ mol^{-1}$) and thermodynamic values ΔH and $T\Delta S$ (in $kJ\ mol^{-1}$) for the formation of cyclodextrin complexes with aliphatic alcohols in aqueous solution at 25°C

Alcohol	Value	α-CD	1.8M-α-CD	β-CD	1.8M-β-CD
1-Butanol	log*K*	2.46±0.07 1.95[a] 3.96[b] 2.00[c] 1.92[d] 2.00[e]	2.05±0.04	1.26±0.06 1.44[h] 1.23[i] 4.08[b]	2.47±0.05
	$-\Delta H$	5.7±0.9 10.7[d] 7.9[b] 9.9[e]	9.9±0.6	0.9±0.5 3.0[b]	5.3±0.7
	$T\Delta S$	8.3±1.3 0.2[d] –14.b[f] 1.5[e]	1.8±0.8	6.3±0.8 –21.0[b]	8.7±1.0
1-Pentanol	log*K*	2.56±0.02 2.51[a] 4.27[f] 2.44[c] 2.39[d] 2.44[e]	2.46±0.03	1.86±0.07 3.96[f] 1.88[h] 1.79[i]	–k
	$-\Delta H$	13.1±0.8 13.9[f] 14.9[d] 11.8[e]	10.9±0.7	–1.5±0.6 2.2[f]	1.2±0.4
	$T\Delta S$	1.5±0.9 –10.4[f] –1.3[d] 2.1[e]	3.1±0.9	12.1±3.2 –24.8[f]	
1-Hexanol	log*K*	2.48±0.02 2.95[a] 2.85[d] 3.89[g] 2.58[c] 3.12[e]	2.27±0.04	2.34±0.08 2.45[h] 2.28[i] 3.77[g]	2.59±0.07
	$-\Delta H$	22.7±0.7 18.2[d] 29.1[g] 13.8[e]	21.1±0.6	–1.0±0.6 0.6[g]	–1.7±0.5
	$T\Delta S$	–8.6±0.8 –2.0[d] 6.9[g] 4.0[e]	–8.2±0.8	14.3±1.1 –22.1[g]	16.4±0.9

Table 1 Continued

Alcohol	Value	α-CD	1.8M-α-CD	β-CD	1.8M-β-CD
1-Heptanol	log*K*	2.90±0.03 3.36[a] 2.27[c] 3.07[d] 2.89[e]	2.49±0.05	2.64±0.07 2.82[h] 2.79[i]	3.13±0.05
	–Δ*H*	26.4±0.7 22.8[d] 20.2[e]	24.0±0.6	0.3±0.5	–3.1±0.7
	*T*Δ*S*	–9.9±0.8 –5.4[d] –3.7[e]	–9.9±0.9	14.7±0.9	20.9±1.0
1-Octanol	log*K*	3.27±0.02 3.80[a] 2.64[e]	3.01±0.4	2.83±0.05 3.25[h] 3.20[i]	–k
	–Δ*H*	31.8±0.8 22[e]	25.7±0.6	6.4±0.6	–3.4±0.5
	*T*Δ*S*	–13.2±0.9 –7[e]	–8.6±0.8	9.7±0.9	

[a][14]; [b][15]; [c][16]; [d][17]; [e][18]; [f][19]; [g][20]; [h][21]; [i][22];
[k]Not calculable from the thermal curve

The stability constants increase with ascending number of methylene groups of the aliphatic alcohols (Fig. 2). However, the reasons for this observation are quite different for the α- and β-CD´s. The values of the reaction enthalpies increase linear with the number of CH_2-groups for the reactions with α-CD (Fig. 4). The CH_2-increment is 6.5 kJ mol^{-1}. This value is slightly higher as the value reported earlier (3.9 kJ mol^{-1} [17]). In contrast the values of the reaction enthalpies are close to zero for the reactions with β-CD.

Only in case of butanol the complex formation with α-CD is favoured by entropic contributions. With increasing number of the methylene groups the reaction entropies become more and more negative (Fig. 2). All reaction entropies for the complex formation with β-CD are positive. Thus, these reactions are only favoured by entropic contributions.

The following reaction steps are expected to take place during the complex formation:

- partial or complete desolvation of the guest molecule,
- partial or complete elimination of water molecules from the cyclodextrin cavity,
- reduction of the conformational freedom of the host and guest molecules,
- change of the number of particles due to complex formation (one guest molecule and one host molecule form one complex) and
- interactions between the host and guest molecules.

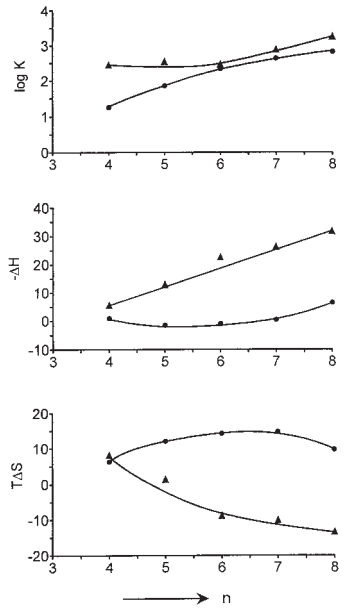

Fig. 2 Stability constants (log*K*) and thermodynamic parameters Δ*H* and *T*Δ*S* for the complexation of aliphatic alcohols by α- (▲) and β-cyclodextrin (←) in aqueous solution at 25°C as a function of the number of carbon atoms *n* of the aliphatic alcohols

Attemps to calculate all these individual contributions to the measurable overall thermodynamic parameters have been reported [26, 27]. These reaction steps influence both the reaction enthalpy and entropy. The water molecules inside the cavity of the cyclodextrins are not energetically comparable with water molecules in the bulk phase. Inside the cavity of the cyclodextrins these water molecules are not able to form hydrogen bonds as in the bulk phase. Thus, the water molecules inside the cavity are named as 'high-energy water' by Saenger [28]. The release of these water molecules from the cavity should result in favourable enthalpic contributions to the reaction enthalpy. This effect is only observed in case of the complex formation with the α-CD ligands. The decrease of the reaction entropies is caused by the reduction of the conformation freedom of the included guest molecules.

Obviously no 'high-energy water' is included in the cavity of the β-CD´s. As a result the values of the reaction enthalpies are close to zero. The positive values of the reaction entropies are caused by the release from water molecules from the cavity of the β-CD´s. However, the conformational freedom of the complexed molecules is reduced and therefore the values of the reaction enthalpies are nearly independent of the chain length of the aliphatic alcohols.

These explanations are supported by the number of water molecules included inside the cavities of α- and β-CD. Inside the cavity of α-CD only two [28] and inside

the cavity of β-CD nine water molecules [28] are included. Obviously these water molecules are responsible for the different behaviour of α- and β-CD and their partially methylated derivatives. The presence of some methylene groups at the core of the cyclodextrins has no influence upon the complex formation.

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References

1 M. L. Bender and M. Komiyama, Cyclodextrin Chemistry, Springer-Verlag, Berlin 1978.
2 W. Saenger, Angew. Chem., Int. Ed. Engl., 19 (1980) 344.
3 J. Szejtli, Cyclodextrin Technology, Kluwer, Dordrecht 1988.
4 R. J. Clarke, J. H. Coates and S. F. Lincoln, Adv. Carbohydr. Chem. Biochem., 46 (1988) 205.
5 D. Duchene and D. Wouessidjewe, J. Coord. Chem., 27 (1992) 223.
6 G. Wenz, Angew. Chem. Int. Ed., 33 (1994) 803.
7 K.-H. Frömming and J. Szejtli, Cyclodextrins in Pharmacy, Kluwer, Dordrecht 1994.
8 J. Szejtli, Med. Res. Rev., 14 (1994) 353.
9 D. Duchene and D. Wouessidjewe in S. Dumitriu (Ed.), Polysaccharides in Medical Applications, Marcel Dekker, New York (1996) 575.
10 T. Loftsson and M. E. Brewster, J. Pharm. Sci., 85 (1996) 1017.
11 T. Loftsson, Pharmazie, 53 (1998) 733.
12 M. V. Rekharsky and Y. Inoue, Chem. Rev., 98 (1998) 1875.
13 H. Mwakibete, R. Christantino, D.M. Bloor, E. Wyn-Jones and J. F. Holzwarth, Langmuir, 11 (1995) 57.
14 Y. Matsui and K. Mochida, Bull. Chem. Soc. Jpn., 52 (1979) 2808.
15 M. Fujisawa, T. Kimura and S. Takagi, Netsu Sokutei, 18 (1991) 71.
16 S. Andini, G. Castronuovo, V. Elia and E. Gallotta, Carbohydr. Res., 217 (1991) 87.
17 D. Hallén, A. Schön, I. Shehatta and I. Wadsö, J. Chem. Soc., Faraday Trans., 88 (1992) 2859.
18 G. Castronuovo, V. Elia, M. Niccoli, F. Velleca and G. Viscardi, Carbohydr. Res., 306 (1998) 147.
19 S. Takagi and M. Maeda, J. Inclusion Phenom., 2 (1984) 775.
20 S. Takagi, M. Fujisawa and T. Kimura, Chem. Express, 6 (1991) 93.
21 A. Buvári, J. Szejtli and L. Barcza, J. Inclusion Phenom., 1 (1983) 151.
22 K. J. Sasaki, S. D. Christian and E. E. Tucker, Fluid Phase Equilibria, 49 (1989) 281.
23 J. J. Christensen, J. Ruckman, D. J. Eatough and R. M. Izatt, Thermochim. Acta, 3 (1972) 203.
24 D. J. Eatough, R. M. Izatt and J. J. Christensen, Thermochim. Acta, 3 (1972) 219.
25 D. J. Eatough, R. M. Izatt and J. J. Christensen, Thermochim. Acta, 3 (1972) 233.
26 I. Tabushi, Y.-i. Kiyosuke, T. Sugimoto and K. Yamamura, J. Am. Chem. Soc., 100 (1978) 916.
27 Y. Matsui, T. Nishioka and T. Fujita, Topics Curr. Chem., 128 (1985) 61.
28 W. Saenger. M. Noltemeyer, P. C. Manor, B. Hingerty and B. Klar, Bioorg. Chem., 5 (1976) 187.
29 T. Steiner, G. Koellner, S. Ali, D. Zakim and W. Saenger, Biochem. Biophys. Res. Commun., 188 (1992) 1060.