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Thermodynamics of the interaction between hydroxypropyl-α-cyclodextrin and alkanols in aqueous solutions

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Abstract

The interactions of hydroxypropyl-α-cyclodextrin (HP-α-CD) with 1-alkanols and with some α,ω-alkanediols have been studied by calorimetric titration at 298.15 K. This technique enables the determination of the enthalpy and association constant for the complex formation, from which Gibbs energy and entropy can be derived. The results are compared to those reported for the complex formation between the native α-cyclodextrin (α-CD) and 1-alkanols or α,ω-alkanediols in the literature. Thermodynamic parameters corresponding to the transfer process of the alkanol from the native to the modified α-CD are also calculated. The results clearly show that the hydrophobic interactions are important in this process, but there are other effects like the size of the alkanol that are also of some importance.

Keywords: Titration calorimetry; Hydroxypropyl-α-cyclodextrin; 1-Alkanols; α,ω-Alkanediols; Inclusion complexes

1. Introduction

Naturally occurring cyclodextrins (CDs) are truncated cone-shaped molecules with a hydrophobic hollow cavity of 7.9 Å depth. They are homochiral cyclic oligosaccharides, the most common of which are composed of 6, 7 or 8 α-1,4-linked D-glucopyranose units [1]. Much of the interest in these molecules arises from their ability to include or encapsulate a hydrophobic part of a guest molecule to form inclusion complexes. Because of their special characteristics, cyclodextrins have a wide variety of applications. They have been suggested, for instance, as candidates to separate some components in chromatography columns [2] or for iodine sorption from nuclear waste gases [3]. Several classes of compounds, that can form inclusion complexes with natural cyclodextrins, have been subjected to systematic thermodynamic studies. These cover almost every class of compounds such as aliphatic alcohols [4–7], diols [5,8], amines and acids [9], amino acids [10] and other compounds [11]. However, only a limited number of systematic thermodynamic studies using modified cyclodextrins have been reported [12–14]. Natural cyclodextrins are themselves of interest as molecular hosts, but much of their utility derives from their modification. The reason for modifications are the change of physical properties of CD such as their solubility in water that increases their applicability in different areas like drug delivery systems

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technology and food industry [15–17]. A calorimetric study, at 298.15 K, is here reported on the interaction between hydroxypropyl-α-cyclodextrin (HP-α-CD) and alcohols. The aim of this study is to analyze the role of the functional groups in the inclusion process, and to compare the results with those in the literature between alcohols and native α-cyclodextrin (α-CD). In this way, the effect of the hydroxypropyl group in the HP-α-CD on complex formation will be evaluated.

2. Experimental

2.1. Materials

All chemicals were purchased from Aldrich. These materials were of the highest purity available and were used without further purification. In order to prepare the solutions we have considered for HP-α-CD an average molecular mass of 1180 g mol^{-1} and a molecular substitution (MS) value of 0.6, both estimated by Aldrich. From a Karl Fischer titration (701 KF Titrino, Metrohm) it was found that the hydration state was HP-α-CD·(5.3)H_2O. Solutions were prepared by weight using distilled and deionized water taking into account the hydration of the cyclodextrin. The concentration of 1-alkanols and HP-α-CD varied between 6.84×10^{-5} and 0.5 mol kg^{-1} of water and 7.77×10^{-4} and 5.8×10^{-2} mol kg^{-1} of water respectively.

2.2. Calorimetry

The differences between the experimental heats in each titration, of two binary solutions containing any of the solutes, and the enthalpies of dilution of the added substance in the appropriate solvent, were determined at 298.15 K. The calorimetric measurements were made by means of a thermal activity monitor (TAM) (Thermometric, Sweden) equipped with a 2201 high performance ampoule calorimeter unit with a 4 ml micro reaction system and a Lund syringe pump with control box. Prior to the start and at the end of each experiment, an electric calibration of the calorimetric unit was carried out in order to adjust the power sensor in the cells. This calorimeter allows the subtraction of the enthalpy of dilution of the injected solution from the total enthalpy of the process by means of a simultaneous titration. This correction was made simultaneously or separately depending of the solubility of the alkanol and concentration used, and in some cases both methods were employed in order to test reproducibility. The concentration of the component present in the cell, typically the CD, was much lower than the one in the syringe and its enthalpy of dilution was proved to be negligible. The injectors as well the collection of titration data were controlled by a microcomputer. Approximately, 30 injections of 6–20 μl were made in each experiment. A Digitam 4.1 software from Thermometric was employed to calculate the equilibrium constants and enthalpies for the complex formation.

3. Calculation of thermodynamic parameters

In this work, we study the interaction of HP-α-CD with several 1-alkanols and α,ω-diols in aqueous solution. Because of the characteristics of both molecules, the expected complex is that formed by the inclusion of the hydrophobic portion of the alkanol into the cyclodextrin. As it is usual [4,6,7,18] we assume 1:1 complexes:

$$M + L \leftrightarrow ML \quad (1)$$

where M denotes the cyclodextrin, L the corresponding alkanol (guest molecule) and ML the complex formed by the inclusion of L into M. The concentrations of these three species are related to the total concentration of M and L in the solution, m_2 and m_3, respectively,

$$[M] = m_2 - [ML] \quad (2)$$

$$[L] = m_3 - [ML] \quad (3)$$

Considering that the activity coefficients, γ, for these compounds are unity, the equilibrium constant of reaction (1) is:

$$K = \frac{[ML]}{[M][L]} \quad (4)$$

Under the symmetric convention for normalization the activity coefficient of the alkanols in the dilute region are really far from the unity [19], the longer the hydrocarbon chain is, the higher the γ-value. However,

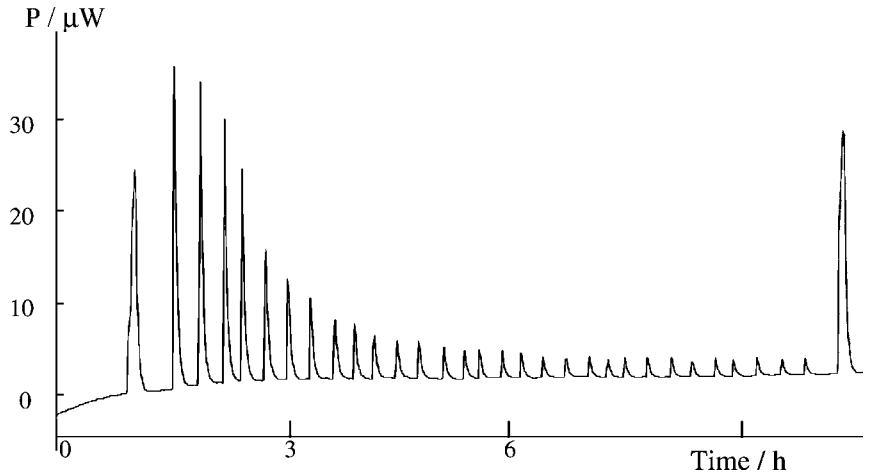

Fig. 1. Experimental power–time plot for the calorimetric titration of HP-α-CD with 1-nonanol. In this experiment, the contribution due to dilution of 1-nonanol has not been still subtracted. The first and the last peaks of the titration experiment correspond to the electric calibrations.

since there is no information about the activity coefficients of the different species under study as a function of the concentration, we will use expression (4) for K. In this way, K is the apparent thermodynamic equilibrium constant.

In a typical experiment with the TAM, a plot like the one shown in Fig. 1 is obtained. In this plot, each peak represents a titration and its area, an energy. Since the signal provided by the calorimeter is the difference between the process taking place in the sample cell (titration of a diluted solution of alkanol over a more diluted solution of cyclodextrin), and the one in the reference cell (titration of the same solution of alkanol, in most of cases, over water), the area of the peaks represents the heat due just to complex formation. If both experiments are made separately, like the one of Fig. 1, the heat due to complex formation can be calculated by subtracting the corresponding signals. To explain the method used to obtain the thermodynamic parameters corresponding to the complex formation process taking into account that the correction due to dilution of alkanol was made experimentally (by titration of alkanol over water in the reference cell). We denote by ΔH_j^* the ratio between the sum of the areas up to the titration j and the mass of the solution in the measuring cell:

$$\Delta H_j^* = \frac{\sum_1^j Q_i}{m_i} \tag{5}$$

The molar enthalpy corresponding to the inclusion of alkanol into the cyclodextrin will be:

$$\Delta H^\circ = \frac{\Delta H_j^*}{[\mathrm{ML}]} \tag{6}$$

Using Eqs. (2), (4) and (6) the following exact [20] expression for complexes 1:1 is obtained:

$$\frac{m_2}{\Delta H_j^*} = \frac{1}{\Delta H^\circ} + \frac{1}{\Delta H^\circ K[\mathrm{L}]} \tag{7}$$

From a least squares fitting of $(m_2/\Delta H_j^*)$ versus 1/[L] it is possible to obtain ΔH° and K. The values of $(m_2/\Delta H_j^*)$ can be computed directly from the areas in the experiment, but the obtaining of [L] values requires an approximation. In Fig. 1, the peaks are smaller and of nearly constant area as the concentration of alkanol into the cell increases. In the experiment showed in this plot, the dilution of the alkanol (1-nonanol) was evaluated separately and so the height of the smaller peaks matches those corresponding to the alkanol dilution. ΔH^*(sat) is defined as the value of ΔH_j^* corresponding to a titration j where all cyclodextrin molecules are already complexed and then [ML] $\approx m_2$. Thus, the complexation enthalpy can be approximated by:

$$\Delta H^\circ \approx \frac{\Delta H^*(\mathrm{sat})}{m_2} \tag{8}$$

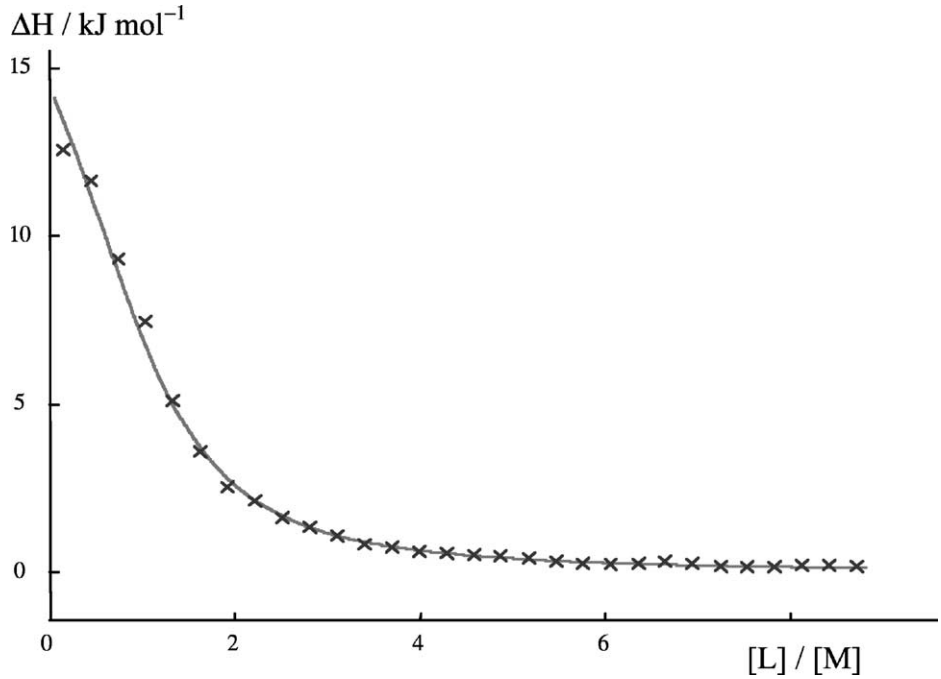

Fig. 2. Result of the fitting to experimental data of Fig. 1, calculated as explained in text.

By equating Eqs. (6) and (8):

$$[\mathrm{ML}] \approx \left[\frac{\Delta H_j^*}{\Delta H^*(\mathrm{sat})}\right] m_2 \tag{9}$$

and from Eqs. (3) and (9) an expression for [L] is obtained:

$$[\mathrm{L}] \approx m_3 - \left[\frac{\Delta H_j^*}{\Delta H^*(\mathrm{sat})}\right] m_2 \tag{10}$$

By fitting the experimental values of $(m_2/\Delta H_j^*)$ versus the values of [L] obtained from Eq. (10), we can obtain a better value to ΔH° that the one computed from Eq. (8). Then we return to calculate new values of [L], which let obtain again ΔH° and K by using the Eq. (7). The final values of the thermodynamic parameters for the complexation process are obtained in this iterative way. In order to verify that the thermodynamic parameters provided by the software Digitam 4.1 from Thermometric are correct, we have developed our own software which calculates ΔH° and K by following the algorithm detailed above. We realized that in order to obtain the same results that the Digitam 4.1, the iterative method must continue until the difference between two successive values of ΔH° is <2%. An example of this fit is showed in Fig. 2. Once we have calculated ΔH° and K, the calculation of the Gibbs energy, ΔG°, and the change of entropy, ΔS°, for the inclusion process are easily obtained by means of:

$$\Delta G^\circ = -RT \ln K \tag{11}$$

$$T\,\Delta S^\circ = \Delta H^\circ - \Delta G^\circ \tag{12}$$

4. Results

In Table 1 the thermodynamic parameters, ΔH°, K, ΔG° and $T\Delta S^\circ$, for the association process involving HP-α-CD and 1-alkanols from 1-propanol to 1-nonanol in aqueous solution, are shown. Association constant and ΔH° for ethanol were not possible to determine in contrast to the same alcohol with the native CD, probably due to the interaction of the alkanol with the external part of the HP-α-CD. This interaction could avoid that the short hydrophobic chain of the ethanol penetrates into the cavity of the CD. The

Table 1
Thermodynamic parameters for the association between HP-α-CD and linear 1-alkanols in aqueous solution at 25 °C

Compound	ΔH° (kJ mol^{-1})	K (kg mol^{-1})	ΔG° (kJ mol^{-1})	$-T\Delta S^\circ$ (kJ mol^{-1})
1-Propanol	−2.3 ± 0.1	30 ± 2	−8.5 ± 0.2	−6.1 ± 0.3
1-Butanol	−5.3 ± 0.1	65 ± 2	−10.4 ± 0.1	−5.1 ± 0.2
1-Pentanol	−7.9 ± 0.2	182 ± 10	−12.9 ± 0.1	−5.0 ± 0.4
1-Hexanol	−11.1 ± 0.2	843 ± 34	−16.7 ± 0.1	−5.6 ± 0.3
1-Heptanol	−10.8 ± 0.2	1124 ± 45	−17.4 ± 0.1	−6.7 ± 0.3
1-Octanol	−11.0 ± 0.3	2061 ± 249	−18.9 ± 0.3	−7.9 ± 0.6
1-Nonanol	−20.1 ± 0.4	3665 ± 234	−20.3 ± 0.2	−0.3 ± 0.5

different energetic contributions are plotted in Fig. 3 as a function of the number of carbon atoms, together with the same thermodynamic information for the native α-CD [7] determined with the same technique. As in the case of the formation of complexes between α-CD and alkanol, ΔH° and K for the formation of complexes between alkanols and HP-α-CD increase (in absolute value) with the chain length because the hydrophobic cavity of the CD is filled more effectively. For the modified CD a sharp change is found in ΔH° and $-T\Delta S^\circ$ when the number of carbon atoms increases from eight to nine while a similar behavior is found for the native CD when going from six to seven carbon atoms. This change in the behavior of the thermodynamic parameters is expected to be related to the arrangement of the alkanol molecule into the CD. The α-CD's are truncated cone-shaped molecules with a hydrophobic hollow cavity of 7.9 Å depth, close to the hydrocarbon chain length of 1-heptanol. So, if the complex is formed by the inclusion of the hydrophobic chain of the alkanol molecule into the CD, as we are assuming, a different arrangement must take place when the hydrophobic chain of the alkanol is longer than the depth of the CD cavity. From our results, we can conclude that the cavity of the modified CD is able to accommodate longer hydrophobic chains than the native one. In the same plot, it is also possible to see that differences in the free energy between α-CD and HP-α-CD for the inclusion process are small for the alkanols under study. This means that the spontaneity of the complex formation and also the equilibrium constant for this process is of the same order for both types of CD's. However, differences in the entropic and enthalpic contributions to the free energy are important. The main contribution to the inclusion process of alkanol into the native α-CD is the enthalpic one regardless of the hydrocarbon chain length finding even very negative values of $-T\Delta S$ for the longer alkanols as it can be seen in Fig. 1. When dealing with the modified CD the differences between ΔH°

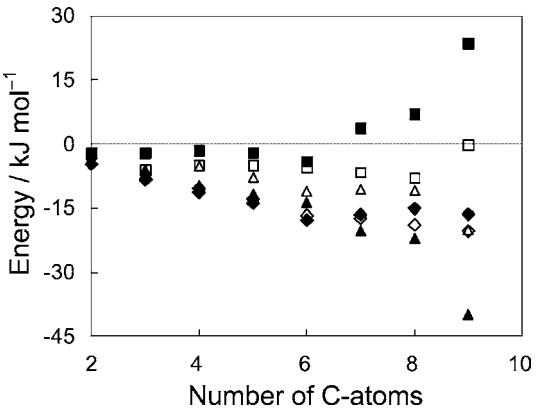

Fig. 3. ΔG° (◆), ΔH° (▲) and $-T\Delta S^\circ$ (■) for the inclusion process of linear alcohols in α-CD taken from [7]. ΔG° (◇), ΔH° (△) and $-T\Delta S^\circ$ (□) for the inclusion process of linear alcohols in HP-α-CD from this work.

Table 2
Thermodynamic parameters for the transfer of linear 1-alkanols from α-CD to HP-α-CD at 25 °C

Compound	$\Delta_{tr}H^\circ$ (kJ mol^{-1})	$\Delta_{tr}G^\circ$ (kJ mol^{-1})	$-T\Delta_{tr}S^\circ$ (kJ mol^{-1})
1-Propanol	3.8	−0.3	−4.1
1-Butanol	4.6	1.1	−3.6
1-Pentanol	3.9	1.0	−2.9
1-Hexanol	2.7	1.1	−1.5
1-Heptanol	9.5	−0.9	−10.4
1-Octanol	11.0	−3.9	−14.9
1-Nonanol	19.9	−3.9	−23.9

Table 3
Thermodynamic parameters for the association between HP-α-CD and linear α,ω-alkanediols in aqueous solution at 25 °C

Compound	ΔH° (kJ mol^{-1})	K (kg mol^{-1})	ΔG° (kJ mol^{-1})	$-T\Delta S^\circ$ (kJ mol^{-1})
1,6-Hexanediol	−10.1 ± 0.7	47 ± 5	−9.5 ± 0.3	1 ± 1
1,8-Octanediol	−14.0 ± 0.3	461 ± 22	−15.2 ± 0.1	−1.2 ± 0.5

and $-T\Delta S^\circ$ are smaller, the entropy dominating the inclusion process for the shorter alkanols and the enthalpy for the longer ones.

It is also possible to calculate the thermodynamic parameters for the transfer of alkanol molecules from the native to the modified CD by subtracting ΔX (HP-α-CD) − ΔX (α-CD), X being the corresponding thermodynamic property: H, G or S. Data for this transfer process are presented in Table 2 and Fig. 4. It is seen that $\Delta_{tr}G^\circ$ is small for the shorter chain alkanols, close to zero, decreasing its value when the hydrocarbon chain length increases. However, the value of $\Delta_{tr}H^\circ$ is clearly positive while $-T\Delta_{tr}S^\circ$ is negative, showing enthalpy–entropy compensation in the transfer process.

Data for the inclusion process of 1,6-hexanediol and 1,8-octanediol in the modified HP-α-CD are reported in Table 3. Association constants and enthalpies for shorter chain alkanediols were not possible to determine (the thermal signal is very small) in contrast to the alkanediols having the same number of carbon atoms when dealing with the native α-CD [7]. In order to justify this finding, we speculate that there are other possibilities for the binding of short diols with the HP-α-CD, apart from the inclusion process, like for instance interaction of the alkanol with the external surface of the modified CD. In the case of even longer chain alkanediols, it was not possible to obtain reliable values of K and ΔH° because of their very low solubility in water. Parameters corresponding to the transfer process from the native to the modified α-CD are listed in Table 4. Although the number of alkanediols analyzed is small, it is clear from the $-T\Delta_{tr}S^\circ$, $\Delta_{tr}H^\circ$, and $\Delta_{tr}G^\circ$ values for this transfer process is not spontaneous from the thermodynamic viewpoint because of the enthalpic contribution.

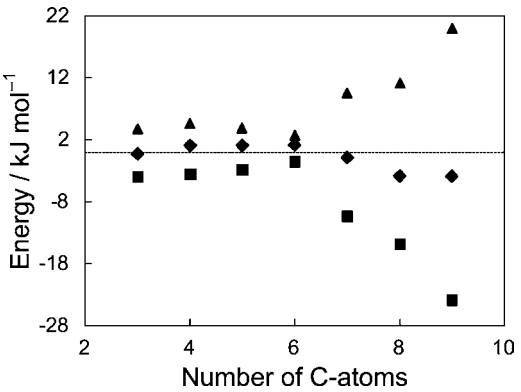

Fig. 4. Thermodynamic parameter for the transfer process of linear alcohols from α-CD to HP-α-CD in aqueous solution: $\Delta_{tr}G^\circ$ (◆), $\Delta_{tr}H^\circ$ (▲) and $-T_{tr}\Delta S^\circ$ (■).

Table 4
Thermodynamic parameters for the transfer of linear α,ω-alkanediols from α-CD to HP-α-CD at 25 °C

Compound	$\Delta_{tr}H^\circ$ (kJ mol^{-1})	$\Delta_{tr}G^\circ$ (kJ mol^{-1})	$-T\Delta_{tr}S^\circ$ (kJ mol^{-1})
1,6-Hexanediol	6.0	1.7	−4.3
1,8-Octanediol	5.1	3.5	−1.6

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