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Dedicated to Prof. Menachem Steinberg on the occasion of his 65th birthday

THERMODYNAMICS OF WATER/β-CYCLODEXTRIN SYSTEM

An interaction model

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Abstract

The thermodynamics of β-cyclodextrin dehydration is investigated, by parallel DSC/TG experiments, on both fully and partially hydrated samples. The apparent dehydration enthalpies per mole of water are impossibly high and this fact suggests that another phenomenon, in addition to the rupture of the β-cyclodextrin/H_2O hydrogen bonds, contributes to the peak area. All the experimental evidence agrees with an 'interaction model' which assumes that deydration is accompanied by a slow and reversible rearrangement of the β-cyclodextrin structure.

Keywords: β-cyclodextrins, dehydration enthalpies, water interactions

Introduction

Cyclodextrins are cyclic oligosaccharides which form complexes with water and many organic molecules [1, 2]. Among the three natural forms of cyclodextrin (α, β, γ) the β one has drawn particular attention mostly for commercial and availability reasons. β-cyclodextrin (β-CD) is a hepta-amylose widely used in drug delivery systems. A great deal of information is presently available on its crystal structure [3], both above and below an ordering transition involving the hydrogen bonds [4, 5]. Most of the work has been performed with the fully hydrated form of β-CD, and few papers have paid some attention to the complex hydration-rehydration processes of β-CD [6, 7]. We have previously shown that

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a structural transformation takes place during dehydration [8]. More recently [9] we have discussed in detail the role of such a transformation and shown that it is strictly linked to dehydration. In that paper we also showed that dehydration is assisted by a 'compensation mechanism' for which β-CD contributes a constant amount of energy for each H_2O mole. Although such a conclusion was mainly based on the results by thermal analysis, no detailed discussion was presented on the thermal measurements by which it was deduced that the enthalpy associated with the structural transformation contributes substantially to the DSC peak usually assigned to dehydration of β-CD. The aim of this work is to shed light upon the thermodynamics of hydration/dehydration in β-CD.

Experimental

Apparatus and procedures

Commercial β-CD (Roquette, France) was first dissolved in water and recrystallized by slow evaporation at room temperature (*rt.*). The composition of the recrystallized sample, which we will call the precursor, has been determined by thermogravimetric analysis to be β-CD·$12H_2O$. The crystals were crushed in an agate mortar and two sieve fractions were collected: 180–250 μm and 38–54 μm.

The precursor samples underwent two types of treatments:

a. '*Ex situ* samples'. A fully dehydrated sample was first obtained by annealing the precursor at 160°C for times ranging from 12 h to two days, and then slowly cooling it to *rt.* under vacuum (13 Pa). Controlled rehydration was then achieved by exposing the sample to 100% relative humidity at *rt.* in a sealed glass vessel for different times (up to 1 day); the amount of rehydration is determined by the time of exposure to moisture. The DSC/TG recordings with these samples were taken in air from *rt.* to 160°C.

b. '*In situ* samples'. The recrystallized sample was annealed at a temperature T_{iso} ranging from 50 to 60°C directly in the TG/DSC apparatus under a flow of N_2 bubbled through water at *rt.* Temperature and duration of this isothermal stage determine the amount of water left in the sample. Subsequently, the temperature was scanned to 160°C in a wet nitrogen atmosphere.

The dehydration process of both in situ and ex situ samples has been followed with a TA 2000 Thermal Analysis System interfaced with a DSC unit (DuPont 910) and a TG unit (DuPont 951). For each sample, parallel DSC and TG experiments were performed: we applied the same heating rate (1 or 2°C min^{-1}) and scan range (to 160°C) to paired experiments, and consistently used samples weighting about 10 mg. The data quoted in the following do not show any significant dependence upon the duration of annealing at 160°C, the crystal grain size, and the heating rate.

Results and discussion

Qualitative considerations

From the parallel TG-DSC experiments we obtain the amount of water released during the heating runs to 160°C and what we may call the apparent deydration enthalpy. The data are reported both for '*ex situ*' and '*in situ*' samples in Tables 1 and 2, respectively. We quote the weight losses as a percentage of the initial mass ($\Delta M\%$). Also reported in the Tables are the parameters [$1/n_{\mathrm{dyn,ex}}$, Table 1] and [$n_{\mathrm{iso}}/n_{\mathrm{dyn,in}}$, Table 2] where n represents the number of water molecules released per mole of β-CD during the isothermal annealing (n_{iso}) and during the heating run in ex situ ($n_{\mathrm{dyn\text{-}ex}}$) and in situ samples ($n_{\mathrm{dyn\text{-}in}}$). The apparent dehydration enthalpy is given in J g^{-1} (ΔH_{DSC}) and in J mol(H_2O)$^{-1}$ (ΔH_{s}).

Table 1 '*Ex situ*' samples. $\Delta M\%$ is the percentage mass loss due to the dehydration. ΔH_{DSC} represents the heat associated to the DSC peak (J g^{-1} of sample). ΔH_{s} is the apparent specific dehydration enthalpy (J mol(H_2O)$^{-1}$). cr. I and cr. II denote the results obtained by integrating the DSC peaks by integration criterion I and II respectively (Fig. 1)

$\Delta M\%$	$1/n_{\mathrm{dyn,ex}}$	ΔH_{DSC} (cr. I)	ΔH_{DSC} (cr. II)	ΔH_{S} (cr. I)	ΔH_{S} (cr. II)
16.00	0.083	380.8	380.8	42840	42840
15.47	0.087	394.5	394.5	45902	45902
14.80	0.091	426.8	361.3	51908	43942
13.81	0.099	418.7	367.0	54573	47835
13.55	0.101	364.3	346.0	48394	45963
12.79	0.108	435.5	364.5	61290	51298
11.90	0.117	399.2	331.0	60383	50067
11.40	0.123	404.2	336.7	63821	53163
10.51	0.135	385.6	321.0	66040	54976
9.97	0.143	420.8	326.8	75972	59000
9.43	0.152	387.7	327.7	74004	62551
7.88	0.185	382.0	296.0	87259	67614
7.20	0.204	418.5	297.2	104625	74300
5.08	0.296	386.7	276.3	137020	97902
4.35	0.349	365.6	253.3	151282	104894
4.05	0.376	373.4	260.9	165956	115957
3.80	0.401	394.5	257.0	186868	121737
3.34	0.459	406.3	250.7	218968	135083

Table 2 '*In situ*' samples. $\Delta M\%_{iso}$ and $\Delta M\%_{dyn,in}$ are the percentage mass losses due to dehydration over the isothermal and dynamic stage respectively. ΔH_{DSC} represents the heat associated to the DSC peak (J g^{-1} of sample). ΔH_S is the apparent specific dehydration enthalpy (J mol$(H_2O)^{-1}$)

$\Delta M\%_{iso}$	$\Delta M\%_{dyn,in}$	$n_{iso}/n_{dyn,in}$	ΔH_{DSC}	ΔH_S
3.22	11.48	0.281	312.0	48920
3.65	10.93	0.334	301.7	49685
3.65	10.80	0.338	279.8	46663
5.09	11.06	0.460	315.9	51412
7.44	7.21	1.032	242.4	60516
8.70	5.90	1.474	234.0	71390
10.50	4.26	2.465	211.1	89200
11.50	3.10	3.710	196.4	114039
12.00	2.19	5.479	180.0	147945

Table 1 reports two sets of ΔH_S values because of an ambiguity in determining the DSC peak area in the ex situ samples. As Fig. 1 shows, the baseline level is quite different before and after the peak. The figure indicates two possible integration criteria (I and II) that lead to the two ΔH_S series reported in Table 1.

We may note in Table 1 that ex situ samples which were almost fully rehydrated yield ΔH_S values of about 45000 J mol$(H_2O)^{-1}$, i.e., in the upper range of the values expected if water was hydrogen-bonded to β-CD. With decreasing the

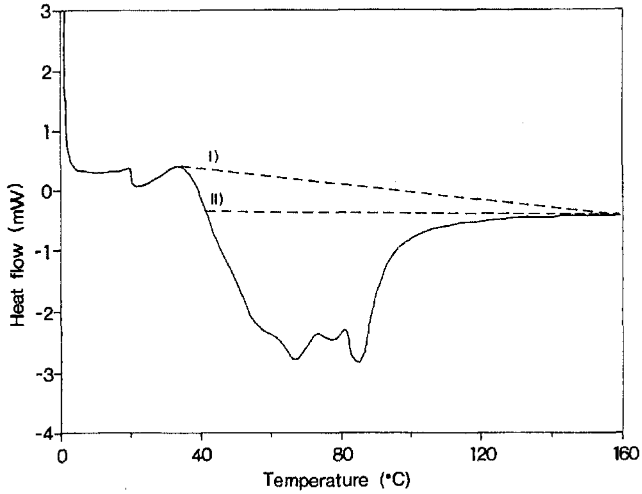

Fig. 1 DSC curve of a partially hydrated sample. The dashed lines [I) and II)] represent the two different criteria adopted for peak area determination

water content, the intensity of the DSC peak is not correspondingly reduced, and ΔH_s increases much above the range of reasonable hydrogen bond energies. It may be argued that a substantial portion of this energy is needed to demolish the β-CD/β-CD bonds which are formed during partial dehydration.

Quantitative considerations: the interaction model

The simplest model we may conceive which accounts for the above findings is based upon the following assumptions:

a. The energy required for the release of one water mole from β-CD during a heating run does not depend upon hydration and has a constant value;

b. following partial dehydration, β-CD/β-CD bonds are established through a slow rearrangement process; for each mole of water released a constant energy equal to $\Delta H_{\beta\text{-CD}}$ is acquired by these bonds;

c. during a heating run to the fully dehydrated form we should supply both the energy required for the release of water and the breaking of the β-CD/β-CD bonds.

'*In situ*' samples

The apparent dehydration heat per mole of β-CD comprises two contributions.

1. During the isothermal stage n_{iso} moles of water have been released; after relaxation, the energy associated with the β-CD lattice has decreased by

$$\Delta H_1 = \Delta H_{\beta\text{-CD}} n_{\text{iso}} \tag{1}$$

which equals the extra energy to be supplied during the heating run.

2. For assumption a), the energy needed for the release of $n_{\text{dyn,in}}$ moles of water is simply

$$\Delta H_2 = \Delta H_{H_2O} n_{\text{dyn,in}} \tag{2}$$

The apparent dehydration enthalpy per mole of water can be rewritten as

$$\Delta H_s = \frac{\Delta H_1 + \Delta H_2}{n_{\text{dyn,in}}} = \Delta H_{\beta\text{-CD}} \frac{n_{\text{iso}}}{n_{\text{dyn,in}}} + \Delta H_{H_2O} \tag{3}$$

Equation (3) says that ΔH_s *vs.* $n_{\text{iso}}/n_{\text{dyn,in}}$ should yield a straight line. This point is accurately verified (Fig. 2) and from a linear best fit with our data we have

$$\Delta H_{\beta\text{-CD}} = 19.30 \text{ kJ mol}(H_2O)^{-1}$$

$$\Delta H_{H_2O} = 42.13 \text{ kJ mol}(H_2O)^{-1}$$

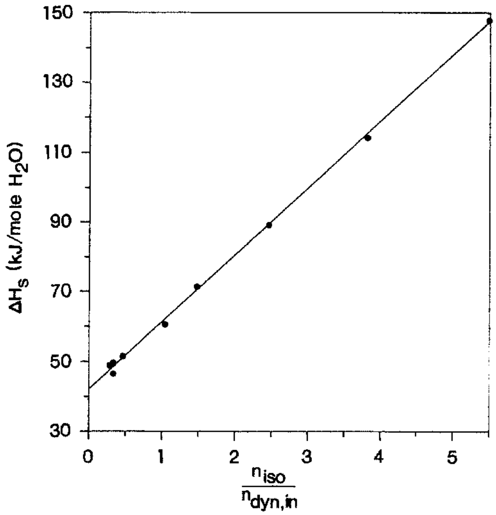

Fig. 2 Apparent dehydration enthalpies ΔH_s (kJ $(\mathrm{mol(H_2O)})^{-1}$) *vs.* $[n_{\mathrm{iso}}/n_{\mathrm{dyn,in}}]$ for '*in situ*' samples [see text for symbols meaning]

In other words, about half the bond energy needed for water removal is initially supplied through formation of intermolecular β-CD-β-CD bonds.

'*Ex situ*' samples

In this case, the relative water deficit is not given directly, sample by sample, by the mass loss during the isothermal stage, and should be estimated assuming that all dehydrated samples have a saturation water content n_{sat}. Equation (1) is now rewritten as

$$\Delta H_1 = \Delta H_{\beta\text{-CD}}\ (n_{\mathrm{sat}} - n_{\mathrm{dyn,ex}}) \tag{1'}$$

while Eq. (2) becomes

$$\Delta H_2 = \Delta H_{\mathrm{H_2O}} n_{\mathrm{dyn,ex}} \tag{2'}$$

The apparent deydration enthalpy now is

$$\Delta H_s = \frac{\Delta H_1 + \Delta H_2}{n_{\mathrm{dyn,ex}}} = \Delta H_{\beta\text{-CD}} \frac{n_{\mathrm{sat}} - n_{\mathrm{dyn,ex}}}{n_{\mathrm{dyn,ex}}} + \Delta H_{\mathrm{H_2O}} =$$

$$= \Delta H_{\beta\text{-CD}} \frac{n_{\mathrm{sat}}}{n_{\mathrm{dyn,ex}}} + (\Delta H_{\mathrm{H_2O}} - \Delta H_{\beta\text{-CD}}) \tag{3'}$$

and a linear best fit of the data of Table 1 yields with criterion I:

$$n_{sat}\Delta H_{\beta\text{-CD}} = 436.1 \text{ kJ mol}(\beta\text{-CD})^{-1}$$

$$\Delta H_{H_2O} - \Delta H_{\beta\text{-CD}} = 9.28 \text{ kJ mol}(H_2O)^{-1}$$

while with criterion II the result is (Fig. 3)

$$n_{sat}\Delta H_{\beta\text{-CD}} = 244.5 \text{ kJ mol}(\beta\text{-CD})^{-1}$$

$$\Delta H_{H_2O} - \Delta H_{\beta\text{-CD}} = 23.17 \text{ kJ mol}(H_2O)^{-1}$$

It is obvious that the equations for in situ and ex situ samples are the same if we identify n_{iso} with n_{sat}–$n_{dyn,ex}$. Also, if criterion II is used, the ex situ data yield a ΔH_{H_2O}–$\Delta H_{\beta\text{-CD}}$ value in nice agreement with the one predicted from the in situ data; by combining the slope values from Figs 2 and 3 (criterion II) we also obtain a very reasonable n_{sat}=12.6, very close to the expected value of 12.

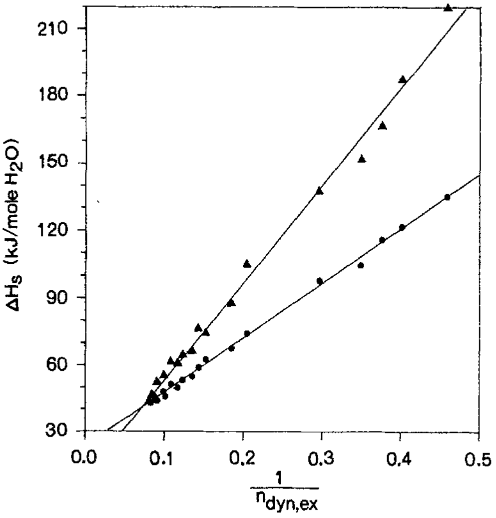

Fig. 3 Apparent dehydration enthalpies ΔH_s (kJ mol$(H_2O)^{-1}$) *vs.* [$1/n_{dyn,ex}$] for *'ex situ'* samples [see text for symbols meaning']. Triangles: integration criterion I; Circles: integration criterion II

Conclusions

From an interpretation of the in situ and ex situ data in terms of our simple model we obtain strong evidence that criterion II for integration of the DSC peaks is the correct one. This is quite reasonable because it may be expected that partially dehydrated samples absorb water when exposed to the air moisture in the DSC cell. This causes an exothermic shift of the baseline which is believed to be the main source of problems with the closure of the DSC peak. As expected, the phenomenon is more relevant in samples where dehydration is nearly complete.

The apparent specific dehydration enthalpies do not depend on the different sample thermal history. Indeed the behaviour of both '*in situ*' and '*ex situ*' samples may be represented by a unique equation. This fact strongly implies that the structural rearrangement following dehydration is an essentially reversible process. As shown in our recent paper on the subject [9] this is fully confirmed by X-ray powder diffraction data.

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References

1 M. L. Bender and M. Komiyana, Cyclodextrin Chemistry, Springer, Berlin 1978.
2 W. Saenger, Angew. Chem. Int. Ed. Engl., 19 (1989) 344.
3 K. Lindner and W. Saenger, Angew. Chem. Int. Ed. Engl., 17 (1978) 694.
4 H. Hanabata, T. Matsuo and H. Suga, J. Incl. Phen., 5 (1987) 325.
5 V. Zabel, W. Saenger and S. A. Mason, J. Am. Chem. Soc., 108 (1986) 3664.
6 Y. Nakai, K. Yamamoto, K. Terada, A. Kajiyama and I. Sasaki, Chem. Pharm. Bull., 34 (1986) 2178.
7 P. Claudy, P. Germain, J. M. Letoffe, A. Bayol and B. Gonzales, Thermochim. Acta, 161 (1990) 75.
8 A. Marini, V. Berbenni, V. Massarotti, P. Mustarelli, R. Riccardi, A. Gazzaniga, F. Giordano, G. Bruni and M. Villa, Solid State Ionics, 63–65 (1993) 358.
9 A. Marini, V. Berbenni, G. Bruni, V. Massarotti, P. Mustarelli and M. Villa, J. Chem. Phys., 103 (1995) 7532.