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Dehydration of β-cyclodextrin: facts and opinions

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Abstract

The thermodynamics of dehydration of β-cyclodextrins, β-CD$\cdot n$H$_2$O, is discussed. Despite the presence of different types of water, the enthalpies of dehydration per mole of β-CD, (with $n > 2$) depend linearly upon n, yielding a slope of 23.5 kJ (mol H_2O)$^{-1}$. This value is substantially smaller than the isosteric heat of dehydration, as determined through DSC data, and estimated from dehydration isotherms at two different temperatures. This implies that the β-CD substrate contributes to dehydration by relaxing to an energetically favoured state; this relaxation ends with an endothermic transformation to a different crystalline structure, which is primarily driven by the loss of water, and occurs near $n = 2$. The enthalpies of dissolution, measured in a recent paper by Bilal et al., also have a linear dependence upon n. However, this linear law apparently covers also the range of the structural transformation and its slope of 10.50 kJ (mol H_2O)$^{-1}$ is not consistent with our data. The possible reasons for the discrepancy are discussed.

Keywords: β-Cyclodextrins; Compensation mechanism; Dehydration enthalpies; Structural transformation

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1. Introduction

While water has always been a fashionable theme of research, hydration of biological systems was not a glamorous subject until two recent publications in Science [1, 2] rekindled interest in the thermodynamics of the process. β-CD is probably a good

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example of a model biological system [3]; it contains water molecules in a variety of configurations (both "hydrophobic" and "hydrophilic"), it has a well known structure, is a sturdy substrate, and its hydration is essentially a reversible phenomenon. However, the system is sufficiently complex that attention should be paid to the existence of different phases and very long equilibration times. Furthermore, not everything is known about the thermodynamics of β-CD and the primary purpose of this work is to critically examine what is known, and what is not, about the subject.

In a paper of a few years ago, Claudy et al. [4] presented TGA and DSC data on the dehydration of β-cyclodextrin [$\beta\text{-CD}\cdot n\text{H}_2\text{O}$ with $n \leq 12.6$, $\beta\text{-CD} = (\text{C}_6\text{H}_{10}\text{O}_5)_7$] in sharp disagreement with our observations, and those of the literature. Claudy claimed that thermal dehydration takes place in two distinct steps, involving respectively seven and four molecules of water per β-CD molecule, while according to our data [5] and a kinetic analysis by Szafranek [6] dehydration is apparently a single-stage process. Claudy found that in argon most water is released at around 100°C [4] while our β-CD samples were fully dehydrated in dry nitrogen at room temperature and our thermal dehydration in wet N_2 was complete below 90°C [5]. An article by Bilal and Claudy [7] has just appeared in this journal; in it they acknowledge that dehydration of β-CD occurs in a single stage; data are also presented for the molar heat of dissolution in water, $\Delta_{\text{diss}}H$, of β-CD with different water content (n). Over the full range of n, the heat of dissolution measured by Bilal apparently follows very accurately a linear dependence upon the water content

$$\Delta_{\text{diss}}H(n) = (-91.22 + 10.50\,n)\ \text{kJ (mol } \beta\text{-CD})^{-1} \qquad (1)$$

Of course, there are no reasons to assume that heats of dissolution and of dehydration should be comparable; however, it may be useful to investigate if and why they are related. This paper will show that the picture of dehydration of β-CD presented by Bilal and Claudy [7] is partly inconsistent with the results of recent work in our laboratory [8].

2. The enthalpies of dehydration

A DSC experiment usually determines an *isobaric heat of dehydration*, which is also called the *enthalpy of dehydration*, ΔH, although Bilal et al. apparently give a different meaning to these words. We have carefully measured [8] the enthalpy of dehydration per mole of β-CD, for different water contents, and found it to be approximately a linear function of n

$$\Delta H(n) = (A' + Bn)\,\text{kJ (mol } \beta\text{-CD})^{-1} \quad \text{for} \quad 2 \leq n \leq n_{\text{sat}} \qquad (2)$$

where n_{sat} is the hydration level obtained in a water-saturated atmosphere at room temperature. The reason why this equation does not apply at low hydration is related to a slow structural transformation, driven by dehydration and taking place at a critical water content $n_c \approx 2$ [5].

There is a systematic difference between n_{sat} of water-recrystallized samples (average value: $\langle n_{\text{sat}} \rangle = 10.75 \pm 0.15$) and of samples which underwent a cycle of full dehydration and rehydration in air ($\langle n_{sat} \rangle$) = 12.6 ± 0.2). Furthermore, separate plots of ΔH for recrystallized and rehydrated samples yield values of A' which are proportional to the experimental average values, $\langle n_{sat} \rangle$, for rehydrated and recrystallized samples. We find empirically that all our data for $n > 2$ are fitted very well (correlation coefficient $r = 0.998$) by the expression

$$\Delta H(n) = (19.0 n_{sat} + 23.5\, n)\ \text{kJ (mol } \beta\text{-CD)}^{-1} \tag{3}$$

Fig. 1 represents the average behaviour of recrystallized (solid line) and rehydrated samples (dotted line) along with the DSC data of Bilal (triangles).

There are two ways of interpreting Eq. (3), and both lend themselves to an experimental verification.

(1) We may say that the enthalpy of dehydration per mole of water is equal to

$$\frac{\mathrm{d}\Delta H}{\mathrm{d}n} = 23.5\ \text{kJ} (\text{mol H}_2\text{O})^{-1} \tag{4}$$

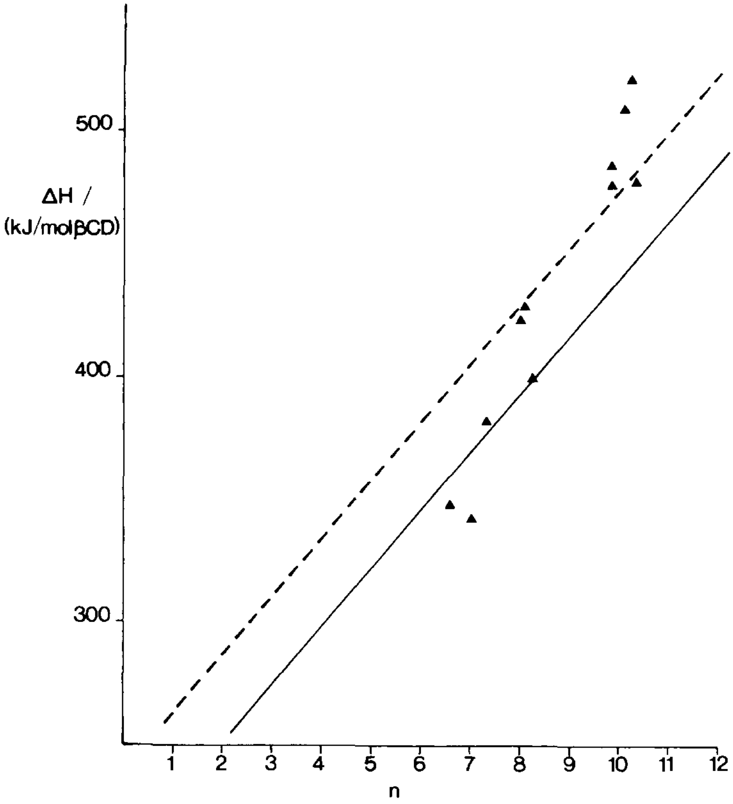

Fig. 1. Molar dehydration enthalpy $\Delta H(n)$ as a function of n for water-recrystallized (full line) and water-rehydrated (dashed line) β-CD samples. The triangles are the data reported by Bilal [7].

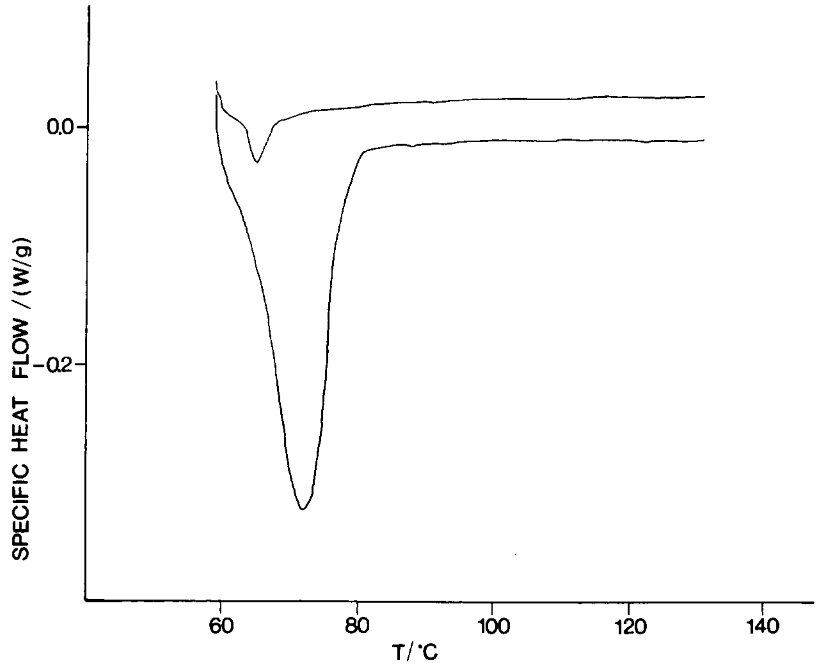

Fig. 2. DSC runs of a sample dehydrated for 3.3 h at 59°C in wet N_2 ($n = 1.6$, bottom trace) and of a sample dehydrated 24 h under the same conditions ($n = 1.2$, top trace).

and that $A' \approx 210$ kJ (mol β-CD)$^{-1}$ represents the enthalpy of the structural transformation when $n_{\text{sat}} = 11$. While the thermal effects of transformation and dehydration are usually intertwined in a DSC run, determinations of ΔH for n just above and just below the critical hydration level, n_c, should lead to a direct determination of the transition enthalpy A'.

With a set of parallel TGA, DSC and X-ray experiments we have roughly identified n_c as 59°C. In fact, Fig. 2 compares DSC runs at $n = 1.6$, just above n_c, and $n = 1.2$, just below it. The large difference between the areas of the two peaks corresponds to ≈ 200 kJ (mol β-CD)$^{-1}$, as predicted by Eq. (3).

(2) We may rewrite Eq. (3) as

$$\Delta H = [19.0(n_{\text{sat}} - n) + (23.5 + 19.0)n] \text{ kJ (mol } \beta\text{-CD)}^{-1} \tag{5}$$

We have split the enthalpy change required to reach full dehydration into a first contribution, which we assume to depend upon the β-CD substrate, and a second one due to the water molecules alone. It may appear that we have artificially separated the change of enthalpy into parts due to the substrate and due to water. However, this interpretation is suggested by the experimental fact that the property of the substrate embodied in A' apparently scales with the equilibrium water content n_{sat}. Eq. (5) assumes that this dependence holds for the full range of water content: when a mole of water is released, the substrate relaxes and supplies 19.0 kJ (mol H_2O)$^{-1}$. In the absence of this substrate relaxation, $d\Delta H/dn$ would be equal to 42.5 kJ (mol $H_2O)^{-1}$. This latter quantity may be identified with the *isosteric heat of dehydration* per mole of water, $\Delta_s H$. i.e., the enthalpy we would measure at n = constant, i.e., in the absence of a modification of the substrate.

The isosteric heat enters the Clausius–Clapeyron equation for the vapour pressure p which, in the ideal gas approximation, reads

$$\left[\frac{\partial \ln p}{\partial T}\right]_{n=\mathrm{const}} = \frac{\Delta_s H}{R T^2} \tag{6}$$

It is well known [9] that the isosteric heat may be substantially different from the isobaric enthalpy $d\Delta H/dn$ determined by calorimetry, and we may attempt to estimate it directly from the two dehydration isotherms reported in the literature [10, 11].

If we assume that the relationship between n and p is described by a Langmuir expression

$$n = n_{\mathrm{sat}} \frac{p}{p + p_0} \tag{7}$$

we can obtain the temperature-dependent parameter p_0 from the data of Steiner at 18°C [10] ($p_0 = 112$ Pa) and those of Nakai at 40°C [11] ($p_0 = 457$ Pa). This change of p_0 with T would give $\Delta_s H \approx 50$ kJ (mol $H_2O)^{-1}$. We feel that this estimate supports our main conclusion that the isosteric heat is substantially larger than the isobaric heat of dehydration. However, this estimate is quite uncertain, owing to the assumptions used to derive it, and we cannot assign an error to it. The value $\Delta_s H \approx 42.5$ kJ (mol $H_2O)^{-1}$ obtained above is more reliable, being based upon more than a hundred measurements.

3. Dehydration and dissolution

Bilal and Claudy [7] argue that the relationship between heat of dissolution and enthalpy of dehydration may be explained as follows:

(1) The average ($\langle\rangle$) enthalpy of dehydration per mole of water in β-CD has been defined by these authors as

$$\left\langle \frac{\Delta H(n)}{n} \right\rangle \approx 50.2\,\mathrm{kJ}\,(\mathrm{mol}\ H_2O)^{-1} \tag{8}$$

where the average has been performed over the set of data of Fig. 1, with $6.6 \leq n \leq 10.4$.

(2) Within experimental error, this dehydration enthalpy equals the sum of the differential dissolution enthalpy per mole of water $d\Delta_{\mathrm{diss}}H(n)/dn \approx 10.5$ kJ (mol $H_2O)^{-1}$ and the heat of vaporisation of water at 100°C $\Delta_{\mathrm{vap}}H \approx 40.6$ kJ (mol $H_2O)^{-1}$.

A major pitfall of this argument is that the average enthalpy of dehydration per mole of water, Eq. (10), not to be confused with either the isobaric or isosteric enthalpy, is not an unequivocally defined quantity. We may rewrite Eq. (3) as

$$\frac{\Delta H(n)}{n} = \left(23.5 + 19.0\frac{n_{\text{sat}}}{n}\right)\text{kJ}\,(\text{mol H}_2\text{O})^{-1} \tag{9}$$

If we put into this expression $n_{\text{sat}} = 12.6$ and $n = 9.07$ (i.e. the average water content of the DSC samples of Bilal) we obtain the "magic" value of 50 kJ (mol H_2O)$^{-1}$. However, according to Eq. (9), the average dehydration enthalpy per mole of water has an unexpectedly high value of 42.5 kJ (mol H_2O)$^{-1}$ for fully hydrated samples, and a definitely "impossible" value of 143 kJ (mol H_2O)$^{-1}$ when $n = 2$. Not even the smaller value appears consistent with the fact that β-CD loses water well below 100°C, and its cavity is filled with easily replaceable, high energy water molecules. Even more disturbing, this average enthalpy of dehydration changes with the hydration level, whereas the argument of Bilal requires it to be constant.

We may apply the reasoning of Bilal to two different processes, A and B, which both start with a mole of solid and partially hydrated cyclodextrin, $\beta\text{-CD}\cdot n\text{H}_2\text{O(s)}$, and some liquid water, $n_{\text{sol}}\text{H}_2\text{O(l)}$, and end with n moles of water in air ($\uparrow$) and a mole of β-CD in solution, $\beta\text{-CD}\cdot n_{\text{sol}}\text{H}_2\text{O(sln)}$:

$$\begin{array}{l}\left\{\begin{array}{ll}\text{A1:} & \beta\text{-CD}\cdot n\text{H}_2\text{O(s)} \xrightarrow{\Delta H(n)} \beta\text{-CD(s)} + n\text{H}_2\text{O}\uparrow \\ \text{A2:} & \beta\text{-CD(s)} + n_{\text{sol}}\cdot\text{H}_2\text{O(l)} \xrightarrow{\Delta_{\text{diss}}H(0)} \beta\text{-CD}\cdot n_{\text{sol}}\text{H}_2\text{O(s ln)}\end{array}\right. \\ \left\{\begin{array}{ll}\text{B1:} & \beta\text{-CD}\cdot n\text{H}_2\text{O(s)} + (n_{\text{sol}} - n)\cdot\text{H}_2\text{O(l)} \xrightarrow{\Delta_{\text{diss}}H(n)} \beta\text{-CD}\cdot n_{\text{sol}}\text{H}_2\text{O(s ln)} \\ \text{B2:} & n\text{H}_2\text{O(l)} \xrightarrow{n\Delta_{\text{vap}}H} n\text{H}_2\text{O}\uparrow\end{array}\right.\end{array} \tag{10}$$

If the Hess law can be applied, we should have

$$\Delta H(n) - n\Delta_{\text{vap}}H = \Delta_{\text{diss}}H(n) - \Delta_{\text{diss}}H(0)$$

or, by dividing by n and using Eq. (9)

$$\frac{\Delta_{\text{diss}}H(n) - \Delta_{\text{diss}}H(0)}{n} = \left[19.0\frac{n_{\text{sat}}}{n} - 17.1\right]\text{kJ}\,(\text{mol H}_2\text{O})^{-1} \tag{11}$$

According to Bilal, the left side term is constant and equal to 10.5 kJ (mol H_2O)$^{-1}$, while according to Eq. (11) it reaches this value only near $n \approx 8.4$, while it is about 2 kJ (mol H_2O)$^{-1}$ for a water-saturated sample.

The discrepancy may be because the partially dehydrated samples used in the DSC and solvation experiments are different, and are not in equilibrium with the atmosphere. However, since dehydration is essentially a fast and reversible phenomenon [8], the thermodynamic state of β-CD is reasonably well defined by its temperature and water content, as long as we are not too close to the region where the slow structural transformation begins.

To explain the above inconsistency, we should consider the possibility of differences between the nominally similar samples used in the DSC and in the dissolution experiments. The water content in our DSC runs was determined with parallel TGA experiments which both began with samples in equilibrium with the atmosphere. In the experiments of Bilal, the substance was stored under argon and its water content thermogravimetrically determined before and after the experiment. We believe that this procedure may lead to large uncertainties in the water content because both manipulation and storage may substantially modify the water content of partially dehydrated β-CD. If the argon is dry, we expect the sample to fully dehydrate, even at room temperature while even traces of water will be rapidly soaked up by the dehydrated form of β-CD. Maybe Bilal had little appreciation of this point, and the large difference, for small, n, between his differential heat of dissolution and that given by Eq. (11) may be because his dehydrated samples rehydrated differently within different chambers.

4. Conclusions

We have characterised several features of the dehydration process of β-CD, which appear to be largely determined by a "compensation mechanism"; the β-CD substrate supplies nearly half of the isosteric dehydration enthalpy per mole of water, and fully restores its losses through an endothermic phase transformation. If the lack of agreement between our DSC data and the solvation enthalpies of Bilal turns out not to be an artefact, a more complex picture should be put forward.

Acknowledgments

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