Thermodynamics of β-cyclodextrine/water Interactions

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From a purely enthalpic standpoint, the β-CD hydration, as studied by semiempirical calculations, appears improbable, in contrast to experiment. For the spontaneous hydration process, a compensation mechanism, connected with substrate stabilization and/or entropy increase, is suggested on the basis of simple thermodynamic considerations. The analysis is done on the basis of a single parameter $E_w (> 0)$, which represents the energy needed to transfer a mole of water from the liquid to the β-CD absorbed phase.

The model, although simple, allows predictions largely consistent with the experimental results, while suggesting possible interpretations.

Key words: β-cyclodextrine, Water interactions, Thermodynamics.

Introduction

β-cyclodextrine (β-CD) is a cyclic oligosaccharide composed of seven α,D-glucose units with a toroidal symmetry that makes it similar to a truncated cone. Because of its marked tendency to form inclusion complexes, the molecule is very important in the pharmaceutical and supramolecular fields. The inclusion compounds are normally formed in aqueous medium, and thus the role of water in the complexation reaction seems very important.

In a previous paper [1] semiempirical calculations (AM1 and PM3) were carried out on the experimental [2] and conformationally optimized β-cyclodextrine (β-CD) undecahydrate $\beta\text{-CD} \cdot 11\,H_2O$. The calculated β-CD-water interaction energies are generally very small and indicative for each water molecule under an unfavorable condition compared to that of pure liquid water.

In particular, the interaction energies of the different dimers (β-CD + single water molecule) in the experimental conformation calculated as

$$\Delta H_{\text{int}}(AB) = \Delta_f H(AB) - \Delta_f H(A) - \Delta_f H(B)$$

according to AM1 have an average value of $-6\,\text{kJ mol}^{-1}$, while that of the water dimer is $-22\,\text{kJ mol}^{-1}$, in agreement with experiment.

No significant difference was observed between internal and external waters, although most of the internal waters show very small absolute values of $\Delta_f H$ indicative of conformational instability. Also the water-water interaction energies of the hydrate are so small that they rule out the hypothesis that the hydration process is stabilized by strong water-water interactions.

Very similar results were found for the conformationally optimized hydrate: in this case the internal waters appear to be more stable, but their interaction energies with β-CD are even smaller.

Thus, from a purely enthalpic standpoint, the β-CD tendency to hydration appears negligible; this is in apparent contrast with the experimental evidence of 6–7 waters within the molecular cavity (i.e. a number very close to the maximum allowed by the cavity volume) of the hydrate which is formed by recrystallization of β-CD from water, and moreover with the rapid (less than an hour) rehydration of anhydrous β-CD at room temperature in wet atmosphere [3].

The present paper suggests a possible compensation mechanism to this unfavorable enthalpic situation in the spontaneous hydration process.

1. Model

When the hydrate is formed by recrystallization from water according to the process

$$\beta\text{-CD}_{(s)} + n\,H_2O_{(l)} \rightarrow \beta\text{-CD} \cdot n\,H_2O_{(s)}\,, \tag{1}$$

there is an energy cost ($E_w > 0$/mole of water) given by the enthalpy needed to break the original water-water bonds of the n absorbed water molecules (i.e. ≈ 22 kJ/mole of water) minus that gained by the β-CD/water

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interaction (i.e. ≈ 6 kJ/water mole), in other words an enthalpy increase for water.

In order to be spontaneous, process (1) must be accompanied by a compensation mechanism (i.e. a substrate enthalpy decrease and/or an internal entropy increase) that can be generally indicated by a positive $T\Delta S^{\mathrm{abs}}$ term such that

$$T\Delta S^{\mathrm{abs}} \geq n\, E_{\mathrm{w}}\,. \tag{2}$$

Since equilibrium is reached with $n = n_{\max}$,

$$T\Delta S^{\mathrm{abs}} = n_{\max}\, E_{\mathrm{w}}\,. \tag{3}$$

The hydration-dehydration process of β-CD has been deeply analyzed in [3] both by thermal measurements (TGA, DSC) and by X-ray and NMR techniques.

In particular, this work pointed out that the hydration process involves a phase transformation, that is a substrate modification confirmed by X-ray analysis.

The formal entropic gain associated with the hydration process could then be ascribed to the substrate modification. The enthalpic nature degree of $T\Delta S^{\mathrm{abs}}$ will depend on the process reversibility, for a globally reversible process being

$$-\,T\Delta S^{\mathrm{abs}} = \Delta_{\mathrm{trans}} H^{\mathrm{abs}} = -\,n_{\max}\, E_{\mathrm{w}}\,. \tag{4}$$

Moreover, if only partial hydration occurs, the quantity

$$-\,\mathrm{E}_{\mathrm{w}}\,(n_{\max} - n) \tag{5}$$

is the stabilization energy, or residual energy, i.e. the amount not used in the absorption of the n water molecules. In other words, this term represents the driving force of hydration.

Process (1) can then be generalized as ($0 \leq n \leq n_{\max}$)

$$\begin{aligned}&\beta\text{-CD}\cdot n\,\mathrm{H_2O_{(s)}} + (n_{\max} - n)\,\mathrm{H_2O_{(l)}}\\ &\qquad \rightarrow \beta\text{-CD}\cdot n_{\max}\,\mathrm{H_2O_{(s)}}\end{aligned} \tag{6}$$

with thermal effect

$$\Delta H^{\mathrm{abs}} = -\,E_{\mathrm{w}}\,(n_{\max} - n) + T\Delta S^{\mathrm{i}}\,, \tag{7}$$

ΔS^{i} being the measure of the irreversibility of process (6).

On the contrary, in the dehydration process, energy must be supplied to the system to compensate the negative $T\Delta S^{\mathrm{des}}$ term ($= -\,T\Delta S^{\mathrm{abs}}$), i.e. for the reversible dehydration process an energy $\Delta_{\mathrm{trans}} H^{\mathrm{des}}$ given by

$$\Delta_{\mathrm{trans}} H^{\mathrm{des}} = -\,T\Delta S^{\mathrm{des}} = n_{\max}\, E_{\mathrm{w}}\,. \tag{8}$$

2. Discussion

Bilal et al. [4] have recently measured the heat of dissolution in water, ΔH_{sol}, of β-CD crystals containing various amounts of water ($0 \leq n \leq 11$):

$$\begin{aligned}&\beta\text{-CD}\cdot n\,\mathrm{H_2O_{(s)}} + \text{water solvent}\\ &\qquad \rightarrow \beta\text{-CD}_{\text{(water solution)}}\,.\end{aligned} \tag{9}$$

They found the following linear dependence of ΔH_{sol} on n:

$$\Delta H_{\mathrm{sol}} = -\,91.22 + 10.5\,n \text{ kJ per mole of } \beta\text{-CD}\,. \tag{10}$$

This equation can be readily obtained on the basis of the assumed model.

If the dissolution process is subdivided into the two following steps:

a) hydration of solid β-CD is reversibly completed to $n = n_{\max}$ with the thermal effect ΔH^{abs},
b) β-CD · $n_{\max}\,\mathrm{H_2O_{(s)}}$ is dissolved in water with the thermal effect $\Delta H^{*}_{\mathrm{sol}}$,

then according to (7), one obtains

$$\Delta H_{\mathrm{sol}} = -\,E_{\mathrm{w}}\,(n_{\max} - n) + \Delta H^{*}_{\mathrm{sol}}\,.$$

Claudy et al. [5] measured $\Delta H^{*}_{\mathrm{sol}} = 23.2$ kJ per mole of β-CD, consequently

$$\begin{aligned}\Delta H_{\mathrm{sol}} &= -\,E_{\mathrm{w}}\,(n_{\max} - n) + 23.2\\ &= (-\,E_{\mathrm{w}}\,n_{\max} + 23.2) + E_{\mathrm{w}}\,n\,.\end{aligned}$$

With $n_{\max} = 11$ and $E_{\mathrm{w}} = 10.5$, one obtains

$$\Delta H_{\mathrm{sol}} = -\,92 + 10.5\,n\,. \tag{11}$$

Thus the model reproduces fairly well the experimental trend of ΔH_{sol}, only the calculated and experimental E_{w} value differing, which could be due to the irreversibility of the hydration process. In any case, if the real behavior is that described by the model, the quantity 10.5 kJ/water mole is not the energy released during the hydration process by water, but instead by the substrate.

It is also interesting to observe that the experimental [3] value of $n_{\max}$ depends on the type of hydration process: $n_{\max} = 10.75 \pm 0.15$ for the water recrystallized samples, while for those obtained from fully dehydrated β-CD rehydrated in wet atmosphere $n_{\max} = 12.6 \pm 0.2$. According to (4), if E_{w} can be considered constant, different $n_{\max}$ values will be obtained at different temperatures.

Moreover, the model reproduces also the experimental relations found in [3] for the dehydration enthalpies ΔH^{des}.

If the dehydration process is carried out reversibly in two steps:

a) $\beta\text{-CD} \cdot n\,\mathrm{H_2O_{(s)}} \rightarrow \beta\text{-CD}_{(s)} + n\,\mathrm{H_2O_{(1)}}$, (12)

b) $n\,\mathrm{H_2O_{(1)}} \rightarrow n\,\mathrm{H_2O_{(g)}}$ with thermal effect $\Delta_{\mathrm{vap}} H$ per mole of water,

according to the model one obtains

$$\Delta H^{\mathrm{des}} = E_{\mathrm{w}}(n_{\max} - n) + n\,\Delta_{\mathrm{vap}} H\,. \quad (13)$$

It should also be noted that $\Delta_{\mathrm{vap}} H$ must be equal to the sum of two terms, namely E_{w} plus the enthalpy, W, needed to transfer a mole of water from β-CD to the vapor phase:

$$\Delta_{\mathrm{vap}} H = E_{\mathrm{w}} + W. \quad (14)$$

Since $\Delta_{\mathrm{vap}} H$ should be in the range 40–45 kJ mol^{-1}, the W term of the model is in the range 24–29 kJ mol^{-1}.

The results of [3] on many samples with different water content showed that the dehydration process is characterized by a positive ΔH^{des} which depends linearly on n as

$$\Delta H^{\mathrm{des}} = A\,(n_{\max} - n) + (A + B)\,n \quad (15)$$

with $A = 19.0$ and $B = 23.5$ kJ mol^{-1}.

Thus, the experimental dehydration enthalpy is that described by the model if $E_{\mathrm{w}} = A$ and $W = B$.

In this case the experimental E_{w} value is larger than the calculated one: it should be underlined that dehydration measurements were carried out at temperatures varying from 20 to 120 °C.

Moreover, (13) can also be written (see (8)) as

$$\Delta H^{\mathrm{des}} = n_{\max} E_{\mathrm{w}} + W n\,, \quad (16)$$

which reproduces the other experimental relation found in [3]

$$\Delta H^{\mathrm{des}} = A\,n_{\max} + B\,n\,. \quad (17)$$

Finally, it should be observed that no agreement was found (see (13)) with the following relation proposed in [4] for the "enthalpy, ΔH_{mes}, of the endothermic effect measured during dehydration of β-CD":

$$\Delta H_{\mathrm{mes}} = \Delta_{\mathrm{dehydr}} H + \Delta_{\mathrm{vap}} H = 9.6 + 40.6\ \text{kJ per mole of water}\,,$$

where the two terms are referred to the steps (12) into which the dehydration process was decomposed.

3. Conclusions

Although based on simple thermodynamic considerations, the model proposed to describe β-CD hydration/dehydration phenomena appears able on one hand to interpret the mechanism through the compensation criterion and on the other hand to describe the experimental relations found in literature.

This model brings into evidence the enthalpic level of the absorbed water molecules: in respect to that of liquid water it is higher by the quantity E_{w}.

The E_{w} values that can be deduced from the experimental data are ≈ 11 (see (11)) and ≈ 19 (see (15)) kJ per water mole in the case of hydration and dehydration, respectively. The value indicated by semiempirical calculations is ≈ 16 kJ per water mole.

If one takes into account: a) the non-isothermality of the dehydration measurements; b) the partial irreversibility of the processes; c) the experimental uncertainties; d) the approximate nature of the semiempirical calculations, one must conclude that E_{w} is decisively a positive quantity. Thus the β-CD absorbed water is largely "free": this appears consistent with other experimental observations, particularly with the hydrate NMR studies [6] and with structural ones [7]: "β-CD hydrate is an impressive example of a solid in which fast diffusion of water molecules is possible without the presence of permanent diffusion channels".

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