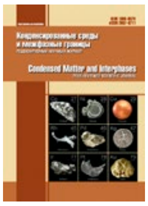

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Physicochemical study of the processes of β-cyclodextrin hydrates dehydration

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Abstract

The research involved synthesizing β-cyclodextrin hydrates of the β-CD·nH$_2$O (n = 11.9–0.9) composition.

The obtained compounds were studied by powder X-ray diffraction (XRD), which revealed the transition from a monoclinic unit cell to an orthorhombic one with a decrease in the water content in the samples. The pressure of saturated vapor of the water in the β-CD·nH$_2$O (n = 10.6–7.0) hydrates was measured by static tensimetry with membrane null-manometer over a wide temperature range (293–384 K) under conditions of a quasi-constant hydrate composition. The measured vapor pressure increases in proportion to the increase in the water content of the hydrate samples.

The experimental data reduced to a single composition of β-CD·1H$_2$O were approximated by the ln$p$(1/T) equation, from which the thermodynamic parameters ($\Delta_{\mathrm{pr}}H^{\circ}_{T}$ and $\Delta_{\mathrm{pr}}S^{\circ}_{T}$) of the process of β-cyclodextrin hydrate dehydration were calculated. This information was used to estimate the binding energies of the water molecules to the β-CD framework.

Keywords: β-cyclodextrin hydrates, PXRD, Static tensimetry, Saturated vapor pressure, Dehydration enthalpy and entropy

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1. Introduction

The macromolecules of cyclodextrins (CDs) consist of glucopyranose units interconnected by α-1,4-glycosidic bonds. Among the most studied and widely used cyclodextrins are α-, β-, and γ-cyclodextrins consisting of 6, 7, and 8 glucopyranose units. The shape of the resulting macromolecule is described as a truncated cone with a hydrophobic interior cavity and a hydrophilic outer surface. Due to their structure, cyclodextrins form inclusion compounds (complexes) with numerous guest molecules that can be fully or partially incorporated into the cyclodextrin cavity. Due to the ability of cyclodextrins to change the physicochemical properties of the incorporated guest molecules, i.e. thermal stability, volatility, solubility, resistance to oxidation, visible and UV radiation, and, most importantly, due to their non-toxicity, these compounds are widely used in pharmaceutics [1–3], food [4, 5] and cosmetic [6, 7] industries, analytical chemistry [8], catalysis [9–12], separation of mixtures [13-15], agrochemistry [16], etc. The history, structures, properties, and various application areas of cyclodextrins and their inclusion complexes are described in several recent reviews [17–19].

Since cyclodextrins in the solid state always contain water molecules (inside their cavity and in the intermolecular space), the process of forming cyclodextrin complexes consists in the partial or complete substitution of water molecules with other guest molecules. Therefore, it is important to know the thermodynamic characteristics of the processes of cyclodextrin dehydration. β-cyclodextrin is one of the most popular cyclodextrins. Its overall production exceeds all other cyclodextrins, and, judging by the number of published articles, this cyclodextrin is the most studied. Despite a huge number of studies, there is hardly any information on thermodynamic characteristics that allow estimating the binding energy of water in β-cyclodextrin hydrates. It is known that in the structures of cyclodextrin hydrates, one part of the water molecules fills the cavity of the macromolecule, and the other part connects the macromolecules to each other with hydrogen bonds. First X-ray diffraction studies determined the structures of two β-cyclodextrin hydrates crystallizing from aqueous solutions: β-CD (β-CD·12H_2O) dodecahydrate [20] and β-CD (β-CD·11H_2O) undecahydrate [21]. Both are cell type structures, the differences are mainly in the distribution of water molecules between the cavity and the intermolecular space: in the β-CD·12H_2O, there are 6.5 H_2O molecules in the cavity and 5.5 H_2O in the intermolecular space, while in β-CD·11H_2O, this distribution is 6.13 H_2O and 4.88 H_2O, respectively. Later, another isomorphic structure of the β-CD·7.5H_2O hydrate was found [22], in which one H_2O molecule is incorporated in the cavity, and the remaining 6.5 are distributed in the intermolecular space. The β-CD hydrate in contact with the mother solution has a composition of ~ β-CD·12H_2O, however, at room temperature and ~ 50% humidity, its composition changes to β-CD·10.5H_2O and the process is reversible [23]. The study of the structures of β-CD hydrates [24] at different humidity levels showed that with a decrease in humidity from 100 to 15%, the process of the hydrate dehydration from the composition of β-CD 12.3H_2O to β-CD·9.4H_2O is fast (it takes minutes), continuous, reversible, and proceeds mainly due to the loss of water from the inner cavity of the β-CD macromolecule. The structure is preserved up to a moisture content of 15%, however, there is a slight decrease in the volume of the unit cell. NMR spectroscopy data [25] also indicated the non-stoichiometric nature of β-CD hydrates in the β-CD 10.5H_2O – β-CD·12H_2O interval. The study of dehydration by powder diffraction (PXRD), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) showed [26] that the hydrated phase of β-CD remains thermodynamically stable up to about β-CD·2H_2O at room temperature and higher. Dehydration of β-CD·11H_2O hydrates is described as a single-stage process in the temperature range of 50–110 °C [27] and 64–100 °C [28]. It takes one stage for β-CD hydrates with β-CD·11.3H_2O, β-CD·10.5H_2O, β-CD·10H_2O (commercial sample) compositions to lose water in the range of 40–80 °C [29]. The thermal behavior of the β-CD·11H_2O commercial sample studied by the TGA and DSC methods (from –150 to 300 °C) indicates a two-stage dehydration process: 7 moles of H_2O are lost during the first stage and 4 moles during the second stage [30]. In the same study, the enthalpy of the β-CD·11H_2O hydration was determined by the method of dissolution calorimetry at 25 °C, which was −102.8 ± 1.1 kJ/mol for the process of β-CD(s) + $11H_2O(l)$ = β-CD·$11H_2O(s)$. The specific enthalpy of the dehydration of the β-CD·$11H_2O$ calculated from the experimental curves obtained by the method of simultaneous thermogravimetric and differential analysis in [31] for the β-CD·$11H_2O(s)$ = β-CD(s) + $11H_2O(l)$ process was 40±2 kJ/ mol at T = 100 °C. As can be seen from the above review, the data obtained in previous studies can be contradictory and the available thermodynamic characteristics are not enough for quantitative estimation of the dehydration processes of β-cyclodextrin hydrates.

In this paper, the dehydration processes of β-CD hydrates were studied by powder X-ray diffraction (PXRD) and by static tensimetry with membrane null-manometer over a wide temperature range (293–384 K). As shown in our previous work on the study of α-cyclodextrin hydrates [32], measuring vapor pressure during dehydration by static tensimetry allows characterizing this process and obtaining its quantitative thermodynamic characteristics.

2. Experimental

2.1. Materials

The experiments were conducted on β-cyclodextrin (Wacker Fine Chemicals, β-CD Cavamax WG7 Pharma, mass fraction of the dry main substance ⩾ 0.98). The hydrate with the highest water content (β-CD $11.9H_2O$) was obtained by recrystallization from distilled water (⩾ 0.9999). Samples with a lower water content were obtained by drying the resulting hydrate in a desiccator over P_2O_5. The composition of the sample was controlled by weight. After the samples reached the required composition, they were kept for several days in a hermetically sealed container to achieve equilibrium.

2.2. Diffraction experiments

Diffraction experiments were performed on a Bruker D8 Advance diffractometer (Cu$K\alpha$ radiation, λ = 1.5418 Å). Samples were mixed with ~ 10 vol. % of finely ground silicon powder, which was used as the internal standard. Powder diffraction patterns were recorded at 20 °C. The parameters of the unit cell of the hydrate were refined for all clearly visible reflexes in the range of angles 3–28°. The CHEKCELL software was used for the refinement of cell parameters [33]. Powder patterns were indexed using the WinPLOTR package [34].

2.3. Static tensimetry

The temperature dependence of the pressure of the water vapor of the β-CD·nH_2O (n = 10.9; 9.6; 7.0) hydrates was measured by static tensimetry using a Novikov-Suvorov glass (pyrex) null manometers [35]. The experimental unit was described in detail in our previous works [36–38]. The pressure was measured to a precision of 0.4 Torr with due account of the error compensation, the cathetometer measurement error, and the inaccuracies associated with the irreversible temperature drift of the null position. The temperature accuracy estimated from the results of the thermocouple (Pt-Pt10Rh) calibration by mercury and naphthalene was 0.3 °C. The error of maintaining a constant temperature in the 3-zone furnace of the unit was 0.1 °C, the radial and linear temperature gradients in the working cell of the manometer did not exceed 0.5 °C. The volume of the working cell of the manometer was determined with an accuracy of 10^{-1} cm^3 by weighing an empty manometer and a manometer filled with water. A weighed hydrate sample (±10^{-4} g) was put into the chamber of the null-manometer and pumped out for 1–2 min at room temperature under dynamic vacuum (10^{-2} Torr); the gauge was then disconnected from the vacuum system by a gas burner and placed into the furnace of the unit. The pressure values were recorded after the coincidence of two or three measurements with an interval of 15 to 20 minutes at a fixed temperature. Experimental pressures measured at the same temperature during both heating and cooling of the manometer were consistent within the reduced measurement errors, which is the criterion for obtaining equilibrium data.

The conditions of the experiments are given in Table 1. The ratio of the mass of the sample to the volume of the working cell (m_{water}/V) was chosen so that the composition of the condensed phase could be considered as quasi-constant: the loss of water in the β-CD·nH_2O samples at the maximum temperature of the experiment varied from 0.97 to 3.64% of the total amount of water (Table 1).

Table 1. Conditions for tensimetric experiments with β-CD·nH_2O: n is the number of moles of water per mole of β-CD, m is the mass of the weighed portion of the sample, m_{water} is the mass of the water in the sample, V is the volume of the manometer

Experiment number	n	m, г	m_{water}, g	m_{water}/V, g/l	Water loss at T_{max}, %
1	10.9	1.0156	0.1498	16.53	2.28
2	9.6	1.3995	0.1846	13.54	3.64
3	7.0	2.7021	0.2700	44.26	0.97

Table 2. Parameters of unit cells and volumes of unit cells for the main samples of β-CD hydrate with different compositions

Samples	sp. gr.	a, Å	b, Å	c, Å	b, deg.	V, Å^3
β-CD·11.9H_2O (1)	$P2_1$	20.874(16)	10.176(4)	15.147(17)	111.04(7)	3003(4)
β-CD·11.9H_2O (2)	$P2_1$	21.286(60)	10.256(16)	15.048(46)	112.33(28)	3039(15)
β-CD·10.0H_2O (1)	$P2_1$	20.845(25)	10.201(5)	15.141(17)	110.75(12)	3011(7)
β-CD·10.0H_2O (2)	$P2_1$	21.185(63)	10.200(12)	15.158(45)	112.19(29)	3033(15)
β-CD·0.9H_2O	орт.*	26.422(5)	16.082(5)	12.521(3)	–	5318

* orthorhombic unit

3. Results and discussion

3.1. XRD experiments

Powder diffraction patterns of seven β-CD·nH_2O hydrate samples with different water content (n = 11.9-0.9) were recorded. The obtained powder diffraction patterns are shown in Fig. 1.

Powder diffraction patterns of β-CD·11.9H_2O and β-CD·10.0H_2O samples were indexed in a monoclinic unit cell (variant (1) in Table 2).

The obtained parameters of the cells were close to those described in [24] for compositions synthesized at a humidity of ⩾ 50%. Nevertheless, the unit cell parameter a and the monoclinic angle obtained during indexing were respectively 2% and 1° less than those reported in the cited work. Using the values given in [24] as the starting parameters resulted in slightly large errors in the refined parameters of the cell (variant (2) in Table 2). Overall, the coincidence between the obtained powder diffraction patterns and those obtained during previous research [24] can be considered satisfactory. For the β-CD·7.9H_2O and β-CD·6.1H_2O samples, the general view of the powder patterns differed little from those discussed above. The main difference was the appearance of several weak additional reflexes, most likely related to the dehydrated phase. Overall, it can be stated that for β-CD·nH_2O in the

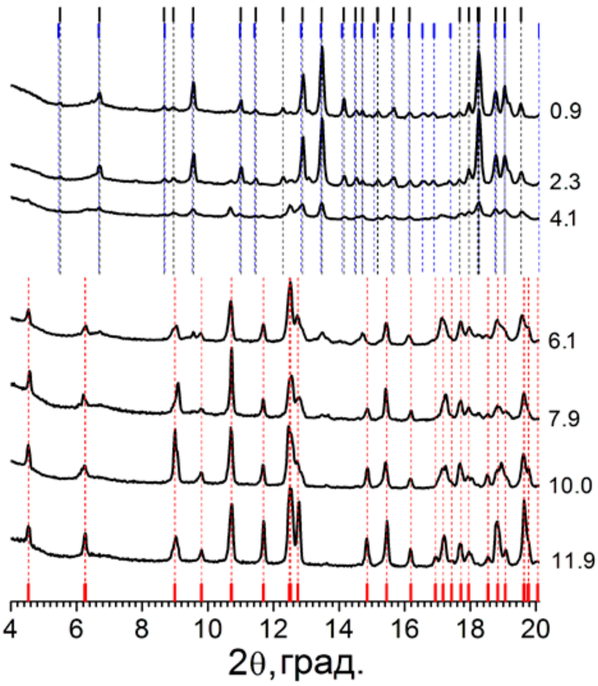


Fig. 1. Powder diffraction patterns of β-CD·nH_2O hydrate samples. The values of n for the corresponding samples are given to the right of the curves. The red strokes and lines correspond to the expected positions of the reflexes calculated for the β-CD·11.9H_2O sample (variant (1) in Table 2). The blue strokes and lines correspond to the positions of the dehydrated β-CD, according to data in [39]. Black strokes and lines correspond to the positions of the reflexes calculated for the β-CD·0.9H_2O sample

range of compositions of $n = 11.9$-6.1, the hydrate structure changed insignificantly. It was slightly wider than the homogeneity range $n = 10.5–12.0$ previously reported in [25].

It is known [20, 24] that inside the cavity of β-CD·12H_2O there are about 6.5 water molecules. It can be assumed that the change in compositions in the range of $n = 11.9–6.1$ occurred due to the removal of intracavitary water, which did not lead to a change in the packing of cyclodextrin molecules. With the further removal of water, the intensity of the peaks on the powder patterns dropped sharply and the peaks expanded. The quality of the powder patterns deteriorated sharply (powder pattern of the β-CD·4.1H_2O sample in Fig. 1). The changes can be attributed to hydrate amorphization. Two samples with a minimum water content, β-CD·2.3H_2O and β-CD·0.9H_2O, had almost identical powder patterns (Fig. 1), which were indexed in the orthorhombic crystal system (Table 2). We failed to find detailed crystallographic data for anhydrous β-CD in previous publications. However, [39] provides an unprocessed powder pattern for an anhydrous sample. We found that the position of the main peaks in this powder pattern was well matched to our data (Fig. 1). Thus, the study of powder diffraction patterns of samples of β-CD·nH_2O hydrates showed that the loss of water from the inner cavity of the cyclodextrin molecule to a composition with $n = 6.1$ did not lead to a change in the appearance of the powder diffraction pattern, i.e. there were no significant changes in the structure of the hydrate. Further loss of water led first to partial amorphization of the hydrate, and then to the formation of a new crystalline phase, with a structure which, apparently, corresponded to the anhydrous β-CD. Indexing of the powder pattern of this phase showed that it most likely belonged to the orthorhombic crystal system.

3.2. Measuring the vapor pressure of water

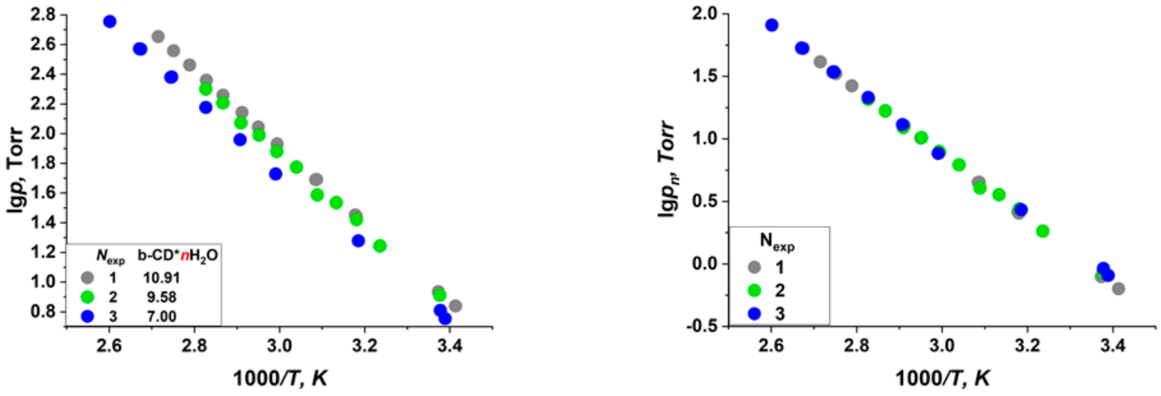
Three experiments were conducted to measure the temperature dependence of the saturated vapor pressure of water in the studied hydrates by static tensimetry with membrane null-manometers. The obtained data are shown in Fig. 2a in the $\lg p–1000/T$ coordinates.

It can be seen from the figure that the experimental data for different compositions of β-CD·nH_2O lie parallel to each other. When reduced to a single composition of β-CD·1H_2O ($p_n = p/n$), the experimental data coincided (Fig. 2b), as was observed in our study of α-CD hydrates [32]. Such a coincidence is possible only if the water-β-CD bond is the same in terms of energy for different compositions.

The data reduced to the β-CD·1H_2O composition (38 experimental points) were processed by the method of least squares using the criterion function described in detail in our papers [40–41]:

$$\begin{gathered}\psi = \sum_{i=1}^{N}\sum_{j=1}^{ni}\left[p_{\mathrm{e}}^{(ij)} - p_{\mathrm{p}}^{(ij)}\right]^2 / W_{ij},\\ W_{ij} = \Delta p_{ij}^2 + \left(\frac{dp}{dT}\right)_{ij}^2 \Delta T_{ij}^2,\end{gathered} \tag{1}$$

where N is the number of experiments; n_i is the number of experimental points in the jth expe-



a b

Fig. 2. (a) Experimental data in the $\lg p – 1000/T$ coordinates for β-CD·nH_2O, where $n = 7.0; 9.6; 10.9$. (b) Temperature dependence of saturated vapor pressure for β-CD·1H_2O, where $p_n = p/n$

riment; $p_e^{(ij)}$ is the experimentally measured pressure; $p_p^{(ij)}$ is the pressure calculated using the isotherm equation; and W_{ij} is the weight function taking into account the pressure and temperature errors. The criterion function ψ uses the principle of maximum likelihood in the method of least squares to estimate the thermodynamic parameters of the process.

The parameters sought were the enthalpy and entropy of the dehydration process at an average temperature since there were no data on the β-CD·1H$_2$O heat capacity. The minimization of the criterion function (1) in the sought parameters space was carried out using a program that applied the algorithm of the modified Newton-Gauss method allowing for the choice of the step size and the direction.

The results of processed data are shown in Table 3. The uncertainties in the obtained values of $\Delta_{pr}H^{\circ}_{Tav}$ and $\Delta_{pr}S^{\circ}_{Tav}$ corresponded to a 95% confidence interval. The temperature dependence of the calculated pressure dispersion was described by the equation $\sigma^2 = a/T^2 - b/T + c$.

Deviations of experimental pressure values (p_n(exp.)) from those calculated by the equation from Table 3 (p_n(calc.)) did not exceed the errors of pressure and temperature measurements. The points were randomly scattered (Fig. 3), which indicated the absence of systematic errors in our study.

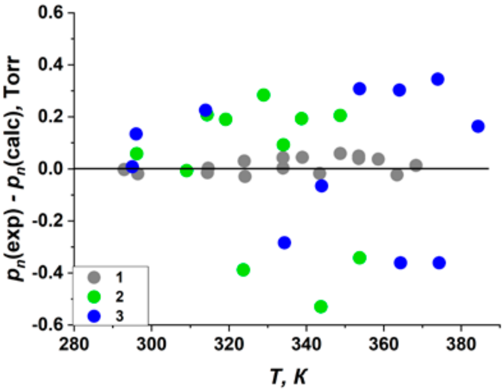


Fig. 3. The difference between the values of the experimental pressure (p_n(exp)) and the pressure calculated from the equation from Table 3 (p_n(calc)) for the process of β-CDH$_2$O dehydration

The obtained equation of temperature dependence of pressure (ln($p/p°$), Table 3) allowed calculating the vapor pressure of water over β-CD nH$_2$O at a given temperature T for any n from 7.0 to 10.9 by multiplying the vapor pressure value ($p/p°$) for $n = 1$ by the number of n moles of water in the β-CD·nH$_2$O hydrate:

$$p/p^{\circ} = n\exp(A - B/T) \qquad (2)$$

Fig. 4 shows the data obtained in this work and the data obtained earlier for α-CD·H$_2$O [32] in comparison with the process of water evaporation [42]. The saturated vapor pressure of pure water during the evaporation process was much higher

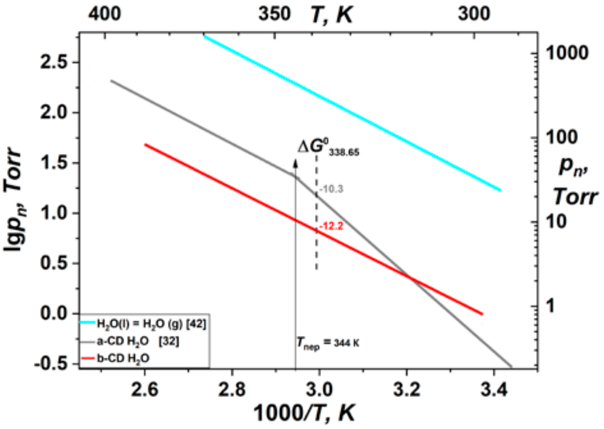


Fig. 4. Temperature dependences of the saturated vapor pressure of water in the processes of β-CD·H$_2$O, α-CD·H$_2$O dehydration [32], and the evaporation of pure water [42]. The values of the changes in the Gibbs energy ($\Delta G^{\circ}_{348.85}$/kJ·mol^{-1}) during the binding of 1 mole of gaseous water to 1 mole of solid α- or β-cyclodextrin are presented at the average temperature of the interval (T_{av} = 338.65 K) investigated in this work. The black arrow marks the temperature of solid-phase transition in α-CD hydrates

Table 3. Thermodynamic characteristics of the process of β-CD 1H$_2$O dehydration: temperature dependence of the saturated vapor pressure ln ($p/p°$) ± 2σ = A – B/T, where $p°$ is the standard pressure of 1 atm; $\sigma^2 = f(T)$ is the dispersion of the calculated pressure; the enthalpy ($\Delta_{pr}H^{\circ}_{Tav}$) and entropy ($\Delta_{pr}S^{\circ}_{Tav}$) of the process at the average temperature of the studied interval (T_{av} = 338.65 K)

ΔT, K	ln ($p/p°$) = A – B/T; $\sigma^2 = a/T^2 - b/T + c$	$\Delta_{pr}H^{\circ}_{Tav}$ kJ/mol	$\Delta_{pr}S^{\circ}_{Tav}$ J K^{-1}·mol^{-1}
292.95–384.35	ln($p/p°$) ± 2σ =13.31 -5976/T; σ^2 = 396.3/T^2 - 2.200/T+0.0031	49.7±0.3	110.7±0.9

than the water pressure over the β-CD and α-CD hydrates. On the α-CD·H_2O dehydration line, there was a break that corresponded to a solid-phase transition in α-CD·H_2O hydrates [43]. In the β-CD·nH_2O hydrates, such a transition was not detected in the studied ΔT and Δn intervals.

The binding energy of water-β-cyclodextrin can be characterized by a change of Gibbs energy during the process of binding of 1 mole of gaseous water and 1 mole of solid β-CD:

$$\beta\text{-CD(s)} + H_2O(g) = \beta\text{-CD}\cdot H_2O(s),$$
$$\Delta G^{\circ}_{T} = -RT\ln(p/p^{\circ}). \quad (3)$$

The obtained thermodynamic data (Table 3) was used to estimate quantitatively the binding energy of the molecules of water and β-CD: $\Delta G^{\circ}_{338.65} = -12.2\pm0.3$ kJ/mol. In the case of α-CD H_2O [32], $\Delta G^{\circ}_{338.65} = -10.3\pm0.5$ kJ/mol (Fig. 4).

4. Conclusions

The method of X-ray diffraction was used to show that the monoclinic structure characteristic of β-CD·11.9H_2O hydrate is maintained over the range n = 6–11.9. When n < ~2, the powder diffraction patterns of the samples were indexed in the orthorhombic crystal system. For intermediate n, the samples were mixtures of the hydrates discussed above. The static tensimetry with membrane null-manometers was used to measure temperature dependences of the vapor pressure of water over β-CD·nH_2O (n = 10.9; 9.6; 7.0) under conditions of a quasi-constant hydrate composition. An analysis of the obtained dependences showed that the vapor pressure increases proportionally with increasing water content in the initial hydrate samples. The experimental data were used to calculate the thermodynamic parameters of the dehydration process. The equation for the $\ln p - 1/T$ dependence found in this work allows calculating the vapor pressure over β-CD-nH_2O hydrates in the studied temperature range for any value of n from 7.0 to 10.9. In addition, the results of the study can be used to quantitatively estimate the binding energy of water to β-CD molecules. Thermodynamic characteristics of dehydration processes were obtained for the first time and are valuable data not only for fundamental science, but also for the practical application of β-cyclodextrin hydrates.

Contribution of the authors

The authors contributed equally to this article.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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