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Hydrophobically driven hosting – What about the guest?

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ABSTRACT

The hosting of cyclic and linear aliphatic moieties by cucurbit[7]uril and β-cyclodextrin was investigated by means of ITC, 2D ROESY NMR spectroscopy, and by classical MD simulations. The cyclodextrin complexation thermodynamics at 298 K revealed classical hydration of the investigated guests. The results of the comparative calorimetric study clearly pointed out that the dehydration of cucurbituril cavity is accompanied with lower entropy changes compared to the analogous process involving cyclodextrin. A pronounced temperature dependence of $\Delta_r H^\circ$ (hence $\Delta_r S^\circ$) unaccompanied by changes in product structure was observed for all studied systems. The effect was primarily due to temperature-induced disordering of the guest-hydrating water, *i.e.* gradual change from classical- towards non-classical hydration of the aliphatic moieties. The study thus reveals the effect of the guest and the cavity dehydration on the complexation thermodynamics while simultaneously providing rationale bridging the classical and non-classical hydrophobic effect. The obtained results also indicate that closer examination of the temperature influence on the corresponding complexation equilibria could further enhance the utilisation of the thermodynamic potential of hydrophobically driven association and result in a better understanding of water solvation properties.

1. Introduction

The strong and stratified, locally clustered, hydrogen bonding of water molecules [1,2] presents a particular challenge for supramolecular recognition [3]. Over the years two strategies for efficient hosting in aqueous solutions have emerged. The first is to overcome the interactions of receptors and the guests with water by realising stronger interactions, and the second to utilise the hydrogen bonding patterns around reactants as the complexation driving force. The latter approach is primarily used for hosting of non-polar species [4–7]. The first clue regarding the thermodynamics of such reactions can be traced to 1940ties when Frank and Evans proposed that exothermic, entropically unfavourable dissolution of simple gases and hydrocarbons in low-temperature water (298 K and below) can be rationalised by the formation of clathrate-like structures ("icebergs") [8,9]. While some entropy driven processes, such as formation of micelles in ambient-temperature water [10], could be accounted for by the model, the predominantly exothermic inclusion of hydrophobic moieties within natural cyclodextrins [5] and cyclophanes [11] came as a surprise until subsequent investigations revealed that the included water formed weaker hydrogen bonds compared to the bulk [6,12]. The enthalpically favourable inclusion with the mentioned macrocycles was from there on primarily ascribed to the release of energy-rich water (non-classical hydrophobic effect) [4–7,13].

The immense thermodynamic potential of the non-classical hydrophobic effect became recognised once cucurbit[*n*]urils (CBs) entered the stage [14]. Remarkably, the stability constant of the cucurbit[7]uril (**CB7**) complex with size-compatible adamantan-1-ol at 298 K [15] was almost six orders of magnitude higher compared to the analogous product with β-cyclodextrin (**β-CD**) [16]. This was entirely due to much more exothermic inclusion (≈ -60 kJ mol^{-1}), explained by even lower hydrogen-bonding potential of cucurbit[7]uril-confined water (2.96 hydrogen bonds per water molecule in **β-CD** *vs.* 2.52 in **CB7** compared to 3.62 in the bulk) [6]. Further, the number of solvent molecules within the macrocycles was considerably different (7.9 in **CB7** *vs.* 4.4 in **β-CD**) [6], despite the similar cavity volumes (279 Å^3 for **CB7** [17] *vs.* 262 Å^3

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for **β-CD** [18]. Due to the presence of carbonyl groups, cucurbiturils exhibit a particularly high affinity for the inclusion of sterically compatible divalent ions with a hydrophobic backbone (the highest affinity of any so far examined synthetic pair was reported for complexation of permethylated diamantane diammonium guest with **CB7**) [19]. By contrast, the stability constants of cyclodextrin complexes with guests containing different solubilizing groups were much more similar, however the presence of charged functionalities usually resulted in lower stability constants [5,20,21].

The ITC investigations of inclusion reactions involving cyclodextrins [4,5,7] and especially cucurbiturils [6,7,13,15,22] were evidently in favour of the high-energy water interpretation of the product stability. Nevertheless, guest dehydration must strongly influence the binding thermodynamics as well. If one examines the literature data, blueprints of classical hydrophobic effect for inclusion within cyclodextrins can be found. Albeit exothermic, the binding of linear and cyclic aliphatic and aromatic compounds with α- and β-cyclodextrin is accompanied with positive $\Delta_r S^\circ$ values at 298 K [5], and that of adamantane-based guests with γ-cyclodextrin (containing least frustrated water [6]) even endothermic) [5,23]. The dehydration of hydrophobic functionality is by no means the only factor determining the sign and value of reaction entropy. The cavity water and the macrocycle conformation matter since the complete inclusion of adamantyl group within β- and γ-cyclodextrin results in small negative and large positive $\Delta_r S^\circ$, respectively. Of course, when dealing with small hydrophobic compounds (≈ six carbon atoms) the hydration parameters can be experimentally obtained, but this is not the case for larger, less soluble guests. How does the guest dehydration affect the binding thermodynamics in these cases? The answer to this question may lie in temperature-dependent ITC studies. In the early 1990s, Wadsö *et al.* [24] reported that the complexation of linear aliphatic alcohols with α-cyclodextrin is characterized by considerably negative $\Delta_r C_p^\circ$. By contrast, the heat capacity of confined water was comparable to that of the solvent bulk, whereby its expulsion from the receptor resulted in a slight positive contribution to $\Delta_r C_p^\circ$ [25]. Since no substantial changes in reactant conformation were expected upon inclusion, the authors concluded that the decrease of $\Delta_r H^\circ$ with temperature must be related to the guest introduction into the non-polar receptor (*i.e.* dehydration and realized host–guest interactions). The rationale was corroborated by the negative heat capacities for the transfer of aliphatic chains to the hydrocarbon environment ($\Delta_r C_p^\circ \approx$ –(50–60) J K^{-1} mol^{-1} per methylene subunit) [24,26]. Still, the reaction heat capacities for alcohol complexation by α-cyclodextrin were far more negative (≈ –102 J K^{-1} mol^{-1}), which the authors ascribed to more constrained guest conformations within the macrocycle. Subsequently, Ross and Rekharsky[21] reported that the inclusion of a linear guest per CH_2 group within α-cyclodextrin results in considerably different $\Delta_r C_p^\circ$ values (–56 J K^{-1} mol^{-1}), whereas the investigations of the temperature influence of cyclodextrins complexation reactions which followed were predominantly concentrated on the correlation between the dehydrated hydrophobic surface size and the $\Delta_r C_p^\circ$ values [27,28].

In our recent study [16] of the adamantyl-based guests complexation with **β-CD** a strong linear decrease of $\Delta_r H^\circ$ and $T\Delta_r S^\circ$ with temperature ($\Delta_r C_p^\circ$ = –(330–350) J K^{-1} mol^{-1}) was observed. The reversal of $\Delta_r S^\circ$ at $T \approx 305$ K and considerably positive complexation entropy at 278 K indicated that the effect must be primarily due to the removal of the guest-hydrating water. Namely, the rigid adamantyl moiety remained within the receptor throughout the studied temperature range, whereas such strong temperature dependence of dispersive interactions seemed highly unlikely. As a matter of fact, the dispersive interactions share in $\Delta_r C_p^\circ$ of α-cyclodextrin inclusion reactions is rather low and positive [29]. Also, the condensation enthalpies of linear and cyclic alkanes (6–8 carbon atoms) slightly increase, rather than decrease with temperature [30]. Importantly, Priya *et al.* [31] recently reported that the entropy of cyclodextrin cavity water is higher than that of bulk water (298 K). This finding and the positive $\Delta_r S^\circ$ accompanying the inclusion of adamantyl moiety strongly suggest its classical hydration in low-temperature water which seems to gradually shift towards non-classical as temperature increases. According to Chandler [32], Ben-Amotz [33], and Bakker [34] such temperature-induced disordering of hydrating water should be observed for hydrophobic solutes whose dimensions do not exceed 1 nm. If this is indeed so, a strong decrease in complexation enthalpies (and entropies) with temperature is expected irrespective of the host class. On the other hand, the effect could be masked by the pronounced temperature influence on cavity dehydration in other types of receptors. To the best of our knowledge, solely the temperature dependence of an aromatic guest complexation with charged cyclophane receptor was examined so far [11]. The binding was characterized by negative $\Delta_r C_p^\circ$, yet, the charged groups may influence the cavity hydration, and the complex is stabilized by π-π interactions to a certain degree. The cucurbiturils seem like more appropriate receptors with this respect, more so due to their efficacy, related ubiquity, and predominantly non-classical binding thermodynamics [6,7,13,14b,14c,14d,15,22]. Further, the comparative calorimetric studies of inclusion reactions with different receptors enable the evaluation of the entropic effect related to dehydration of their cavities, at least on a relative scale. Interestingly, unlike in the case of cyclodextrins [31], Nguyen and coworkers [35] reported that positive entropy changes accompany the dehydration of the **CB7** cavity.

Considering the still unsettled guest dehydration influence on the thermodynamics of hydrophobically driven inclusion, and the cavity effect on the corresponding $\Delta_r S^\circ$ and $\Delta_r C_p^\circ$ values, we opted for a microcalorimetric study of cyclic and linear aliphatic moieties (**AlkylOH** and **MAlkyl**, Fig. 1) inclusion within **β-CD** and **CB7** over the 278–338 K range. Both **β-CD** and **CB7** are sterically compatible with the chosen hydrophobic subunits which should result in substantial guest and cavity dehydration (pronounced $\Delta_r H^\circ(T)$ dependence). The guests are neutral and contain strongly hydrated polar functionalities to suppress all contributions to hosting apart from those associated with the hydrophobic effect. Still, some effect of the solubilising groups on the inclusion thermodynamics is expected so the study encompasses alcohols and mannosides. To obtain insights into the product structure the temperature-dependent 2D NMR investigations were carried out, as well as solvent-explicit MD simulations of the mannosylated guests, hosts, and the corresponding complexes (300 K).

2. Experimental section

2.1. Materials

n-octanol (**nOctOH**, Fluka, for UV Spectroscopy, ≥ 99.5%), cyclohexanol (**cHexOH**, Carlo Erba, ≥ 98% (GLC)) and *n*-hexanol (**nHexOH**, Aldrich, 98% (GC)) were used as received. Cyclooctanol (**cOctOH**) was prepared by reduction of cyclooctanone [36]. Mannosylated compounds **McOct**, **MnOct**, **McHex**, and **MnHex** (Fig. 1) were synthesised according to the procedure described in the SI. β-cyclodextrin (**β-CD**, Sigma Aldrich, HPLC grade, ≥ 98%) was dried at 150 °C for 3 h prior to use [37]. Cucurbit[7]uril (**CB7**, Sigma Aldrich, hydrate) was standardised with berberine chloride (Sigma Aldrich, ≥ 98 %) according to the procedure described by Nau *et al.* [38] The concentration of berberine chloride was determined spectrophotometrically ($\varepsilon_{342\ nm}$ = 22500 dm^3/mol cm^{-1}, ref. [39]) by means of Agilent Cary 5000 spectrophotometer. All solutions for microcalorimetric experiments were prepared by dissolution of solutes in deionised water (MiliQ).

2.2. Microcalorimetric measurements

Microcalorimetric titrations were performed by means of Microcal VP-ITC (V_{cell} = 1.45 mL) and PEAQ-ITC (V_{cell} = 0.205 mL) calorimeters. The enthalpy changes were obtained upon stepwise, automatic titrant addition and corrected for enthalpy changes of its dilution. The data were processed using the Microcal OriginPro 7.0 and Microcal PEAQ-ITC Analysis Software. The concentrations of titrand and titrant were

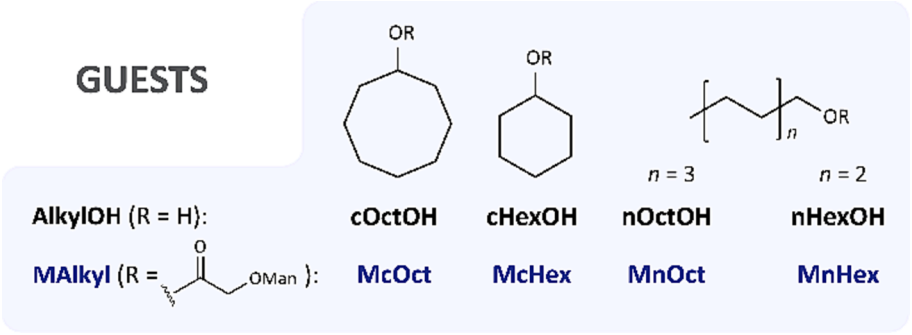

Fig. 1. Structures of investigated guest molecules (Man = mannose).

low in all experiments, and the reactants and the products were neutral species so the values of determined equilibrium constants correspond to K°. All titrations were performed at least in triplicate. All standard complexation thermodynamic parameters for reactions with log $K^\circ \leq$ 7.5 were determined by conducting direct titration experiments. The log K° (hence $\Delta_r G^\circ$) for binding of **cOctOH** with **CB7** was assessed by performing competitive calorimetric titrations (displacement of **β-CD** from **cOctOH** × **β-CD** complex with **CB7**). In the case of **cOctOH** titrations with **CB7**, the volume of injections was varied (decreased around the equivalence point) to determine the complex stability constant (log $K^\circ \geq$ 7.5) and the reaction enthalpy more reliably. Isobaric reaction heat capacities ($\Delta_r C_p^\circ$) were obtained by weighted linear regression analysis of $\Delta_r H^\circ$ *vs.* T dependence.

The instrument reliability was verified by carrying out the microcalorimetric titrations of 18-crown-6 (**18C6**, Sigma Aldrich, 99%) with $BaCl_2$ (Sigma Aldrich, 99.9 %) at 298 K. The thermodynamic complexation parameters obtained using both calorimeters (Table S1) were in excellent agreement with the literature values ($\Delta_r H^\circ = -31.42$ kJ mol^{-1}; $-T\Delta_r S^\circ = -9.90$ kJ mol^{-1}; $\Delta_r G^\circ = -21.52$ kJ mol^{-1}; $K = 5900$ mol^{-1} dm^{-3}) [40].

2.3. Computational investigations

The complexation of **McOct** and **MnOct** with **β-CD** and **CB7** was explored by means of all-atom classical molecular dynamics (MD) simulations utilising the AMBER18 software package [41]. The force field parameters for **β-CD** and **CB7** hosts were taken from Cézard *et al.* [42] and Fenley *et al.* [43], respectively. The General Amber Force Field (GAFF) [44]. was used for the parameterisation of bonded and non-bonded Lennard-Jones potentials while the RESP fitting procedure was carried out using the R.E.D.-III.5 tools [45] for obtaining the partial charges of the guests. All QM geometry optimisations and ESP charges calculations were performed at the HF/6-31G* level of theory using the Gaussian16 program [46]. The TIP3P water model was employed in all simulations [47]. Further details regarding the herein employed computational methods can be found in Section S3.1. of the SI.

2.4. Spectroscopic investigations

The NMR spectra of the guest, the host, and their mixtures in D_2O (Eurisotop, 99.96 % D) were recorded by means of Bruker Avance III HD 400 MHz/54 mm and Bruker Avance Neo 600 MHz/54 mm NMR spectrometers, equipped with inverse broadband room temperature probe (5 mm PA BBI 1H/D–BB) and inverse triple resonance TCI Prodigy cryoprobe (5 mm CPP1.1 TCI 600S3 H&F-CIN-D-05 XT), respectively. The measurements were performed at 278, 298, and 318 K. The 2D ROESY spectra were acquired in the phase sensitive mode and residual water suppression using standard Bruker pulse program roesyphpr. The presaturation ROESY experiments were acquired with 2 K data points in f2 dimension, 256 increments, 32–48 scans, 200 ms mixing time and relaxation delay of 2 s. The ROESY correlation signals were assigned with the aid of COSY and HSQC NMR spectra, recorded utilising standard Bruker pulse programs. The data was processed using TopSpin 3.6 Bruker software.

3. Results and discussion

3.1. Complexation thermodynamics at 298 K

The results of microcalorimetric titrations for all examined host–guest systems are presented in Section S4 in the SI. All titration curves were processed by a 1:1 (host:guest) binding model, resulting in a very good agreement of experimental and fitted data. Furthermore, in some cases, the complex stoichiometry was also evident from a clear break in the titration curve at the equimolar reactant molar ratio. The accordingly determined log K° and corresponding $\Delta_r H^\circ$ and $-T\Delta_r S^\circ$ values at 298 K are shown in Fig. 2 and listed in Table 1 respectively. As seen, the highest affinities were obtained for cyclooctyl-based guests. The stability constants for complexes of *n*-hexyl and *n*-octyl compounds with **CB7** were rather similar and up to two orders of magnitude lower than that with corresponding cyclic analogues.

Expectedly, **β-CD** was a less selective and less efficient receptor than **CB7** [5,48]. From the enthalpic point of view, the hosting of cyclic guests was favoured (particularly of cyclooctyl-based compounds), while the opposite holds for the accompanying entropy changes (especially for **β-CD**). In agreement with literature data [6,7,15,48b,48d], the binding of all compounds with **CB7** at 298 K was in line with the non-classical hydrophobic effect (exothermic, entropically unfavorable ($-T\Delta_r S^\circ > 0$) or virtually isoentropic ($-T\Delta_r S^\circ = -0.4$ kJ mol^{-1} in the case of **nHexOH**).

As in previous investigations, no heat effects were detected upon titration of *n*-hexanol with **β-CD** [49]. The hosting of larger *n*-octanol resulted in measurable enthalpy changes; however, the binding was predominantly entropy-driven. By contrast, the inclusion of their cyclic analogues was much more exothermic and accompanied by small positive $\Delta_r S^\circ$. The herein obtained data were in good agreement with those determined in 0.025 mol kg^{-1} phosphate buffer (pH = 6.9) [20].

The energetically most advantageous complexation of cyclooctyl-based guests with both macrocycles is corroborated by the results of computational (Fig. 3, Figures S94–S96, Table S4) and spectroscopic investigations (Figures S97–S105). The complete inclusion of the bulkiest cyclooctyl group within **CB7** and **β-CD** was observed during MD simulations and by means of ROESY ^{1}H NMR spectroscopy. On the other hand, the spectra revealed less pronounced correlations between *n*-octyl and *n*-hexyl guests and host protons (Figures S99, S101, S103–S105). Apart from that, the mobilities of included chains were larger, leading to broader PMF(ζ) dependencies (Figure S95). Even the protrusion of the octyl chain through the lower rim of β-cyclodextrin was noticed (Fig. 3). Weaker host–guest interactions are hence expected for linear guests, which agrees with their enthalpically less favourable binding.

The flexibility of free **β-CD** was higher than that of **CB7** (structural analysis of the host–guest complexation via radius of gyration (R_g) is

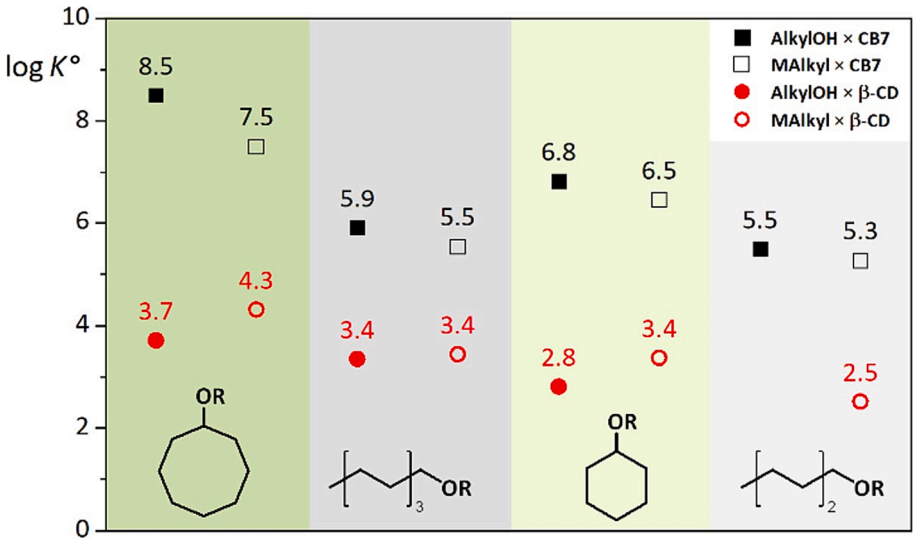

Fig. 2. log K° values for complexation of **AlkylOH** (■ and ●) and **MAlkyl** (□ and ○) with **β-CD** (red circles) and **CB7** (black squares) at 298 K.

Table 1
Thermodynamic parameters for complexation of guests with **β-CD** and **CB7** at 298 K[a].

Guest	**β-CD** $\Delta_r H^{\circ}$ / kJ mol^{-1}	**β-CD** $-T\Delta_r S^{\circ}$ / kJ mol^{-1}	**CB7** $\Delta_r H^{\circ}$ / kJ mol^{-1}	**CB7** $-T\Delta_r S^{\circ}$ / kJ mol^{-1}
cOctOH	−13.75(2)	−7.4(5)	−58.0(3)[b]	7.9(3)[b]
McOct	−17.2(5)	−7.4(6)	−63.5(3)	20.6(1)
nOctOH	−2.69(6)	−16.4(1)	−38.0(2)	4.3(3)
MnOct	−4.88(2)	−14.42(3)	−42.7(6)	11.3(7)
cHexOH	−5.8(4)	−10.5(4)	−39.5(8)	0.8(5)
McHex	−8.47(3)	−10.44(6)	−49.4(5)	12.6(5)
nHexOH	–[c]	–[c]	−31.0(3)	−0.4(4)
MnHex	−3.92(5)	−10.5(2)	−42.5(3)	12.4(4)

[a] Uncertainties of the last digit are given in parentheses as standard errors of the mean ($N = 3$–5).
[b] Determined by a competition titration experiment.
[c] Could not be reliably determined ($\Delta_r H^{\circ} \approx 0$).

provided in Table S4 and Figure S96). The binding of cyclic guests resulted in more open **β-CD** conformation (Fig. 3), while that of **CB7** remained almost the same as in free receptor. This fact, apart from the differences in the organisation of cavity water [6], additionally favoured their inclusion within the rigid cucurbit[7]uril. The conformational changes of **β-CD** upon the accommodation of bulkier cyclic functionalities can also, at least in part, account for the entropically more favourable hosting of linear analogues (Table 1).

The complexation (formation of one species out of two) results in large translational entropy decrease, so the positive $\Delta_r S^{\circ}$(298 K) must be due to the release of hydrating water. Recently Priya *et al.* [31] reported that the expulsion of poorly associated, energy-rich cyclodextrin cavity water is accompanied by negative entropy changes, whereby the entropic penalty per expelled solvent molecule decreases with the ring size (*i.e.* the extent of water association within the cavity). The higher entropy of confined water compared to the solvent bulk arises from its larger rotational and translational mobility. This important finding and the entropically favourable complexation of all guests with **β-CD** indicates the classical hydration of all herein explored hydrophobic subunits at 298 K. The conclusion is strongly supported by negative hydration enthalpies [50] and entropies (calculated from data listen in refs. [50a,51,52]) of *n*-hexane and cyclohexane as well as the endothermic association of linear aliphatic chains (up to 10 carbon atoms) into micelles [10a,10c,53]. Since the complete inclusion of non-polar groups, except those of *n*-octyl-based guests within **β-CD** was

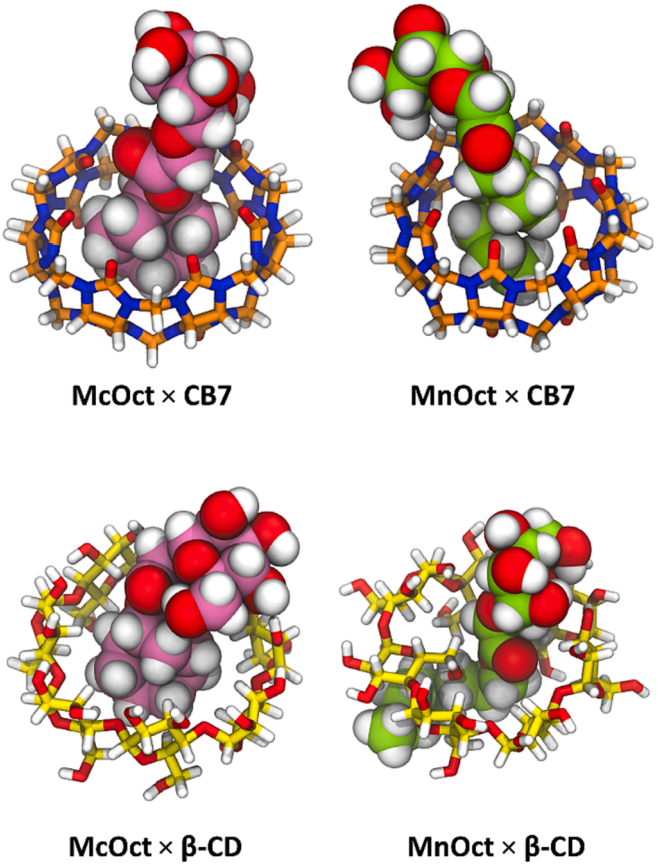

Fig. 3. Representative structures of **McOct** and **MnOct** complexes with **CB7** and **β-CD** at 300 K obtained by means of MD simulations.

observed, the lower $\Delta_r S^{\circ}$ for binding of all other compounds with **CB7** must be primarily due to differences in entropy changes related to the dehydration of receptor cavities. According to MD investigations of Nguyen *et al.* [35], the poorly associated water within **CB7** is both enthalpy- and entropy-deficient. The dehydration of its cavity upon inclusion is therefore expected to be entropically favourable. If this is indeed so, the binding of undeniably classically hydrated guests with this receptor should be particularly entropically favoured at 298 K,

which is in contrast with herein obtained results (Δ_rS° either negative or close to zero). Moreover, the data listed in Table 1 clearly reveal that the dehydration of glycouril-based receptor is accompanied by lower entropy changes than the analogous process for **β-CD**, which, according to Priya *et al.* [31] results in negative entropy changes. The calorimetric results for the complexation of other neutral guests with these two receptors are in agreement with our findings [7,15,16,48b,48d].

Although one cannot determine the sign of ΔS accompanying the receptor dehydration experimentally, there is one strong argument as to why the expulsion of frustrated water out of both receptors is most likely entropically unfavourable (apparently more so for **CB7** than for **β-CD**): the endothermic association of neutral alkyl chains into micelles at 298 K [10a,10c,53]. This experimental finding suggest that the entropically favourable dehydration of chains alone can overcome the enormous decrease in translational entropy upon micelle formation. Consequently, if the dehydration of **CB7** was entropically beneficial, the inclusion reactions of classically hydrated C_6 guests should be strongly entropy favoured which is not the case (Table 1).

By examining the data listed in Table 1 another trend can be observed. The Δ_rS° for complexation of cyclic guests with both receptors were somewhat lower (or similar in the case **MnHex** and **McHex**) compared to those for their linear analogues. This can in part be explained by herein observed higher mobility of included alkyl chains (Figure S95). Namely, if the conformational freedom of included chains was substantially reduced, their complexation would most likely result with considerably lower complexation entropies. On the other hand, the hydration entropies of hexane ($\Delta_{hyd}S^\circ = -225$ J K^{-1} mol^{-1}) [50a,51,52] and cyclohexane ($\Delta_{hyd}S^\circ = -155$ J K^{-1} mol^{-1}) [50a,51,52] suggest stronger organization of hydrating water around linear hydrocarbons. Consequently, the dehydration of alkyl chains accompanying the complexation process is more entropically beneficial compared to cyclic analogues. Our results hence indicate that the highly positive entropic contribution of chain dehydration can adequately compensate for the entropically unfavourable conformational restriction arising from their inclusion within studied macrocycles. As far as their cyclic analogous are concerned, the conformation freedom is lower both in solution and within the macrocycle. This, combined with less entropically beneficial dehydration, eventually leads to entropically favoured hosting of linear moieties. Analogous trends in Δ_rH° and Δ_rS° for complexation of linear and cyclic alkanes by **CB7** were obtained by computational investigations of Gilson, Grimme, and Nau [54]. Further, therein reported stability constants for inclusion of *n*-hexane and cyclohexane ($K \approx 1.5 \times 10^6$ dm^3 mol^{-1} for both guests), obtained by single-point fluorescent dye displacement, are in fair agreement with our results for *n*-hexyl and cyclohexyl guests (Fig. 2, Table 1).

The more pronounced influence of the solubilising functionalities on the reactions involving **CB7** is in accord with the literature data [5,23,48], and can be attributed to the differences in receptor geometry and the polarity of their carbonyl and hydroxyl groups. Namely, the accommodation of hydrophobic moieties within **CB7** leads to more extensive dehydration of its narrow portals (d = 5.4 Å) [48b]. and consequently the guest polar groups compared to reactions involving **β-CD** (d(secondary rim) = 7.8 Å, d(primary rim) = 5.8 Å) [55]. Apart from that, the interactions of **CB7** carbonyls and water molecules are particularly favourable [56], whereby the electron-rich portals of the glycouril-based receptor can potentially engage in dipole–dipole interactions with the hydrophilic parts of the guest. In line, the somewhat more exothermic hosting of mannosides by **CB7** can be explained by the interactions of their C=O group with the electron-rich portals provided that the included part of the guest is tilted with respect to the central cucurbituril axes. The entrapment of hydrating water between the guest carbonyl group and the receptor rims could also lead to additional enthalpic stabilization of the product. Alternatively, the dehydration of the alcohol OH group could be more enthalpically demanding compared to the removal of water molecules surrounding the oxygen atom linking the non-polar moieties and hydrophilic part of the guest.

3.2. The temperature effect on the binding equilibria

As an example of calorimetric results obtained in the 278–338 K range, the Δ_rG°, Δ_rH°, and $-T\Delta_rS^\circ$ for binding of **nOctOH** with **β-CD** and **CB7** are shown in Fig. 4. As seen, a pronounced decrease of Δ_rH° and consequently of Δ_rS° with temperature for complexation of **nOctOH** with both receptors was observed.

The Δ_rH°(338 K)–Δ_rH°(278 K) difference for hosting of this alcohol by **CB7** amounted to a remarkable −33.9 kJ mol^{-1} (more than five orders of magnitude difference in complex stability constant), whereby the sign of Δ_rS° changed from positive to negative around 291 K. The binding of **nOctOH** with **β-CD** was accompanied with positive entropy changes over the entire temperature range, however, the enthalpy sign reversed at 293 K. Of course, the temperature effect on Δ_rH° and $-T\Delta_rS^\circ$ is an opposing one, resulting in weak $\Delta_rG^\circ(T)$ dependence for reactions with both receptors (Fig. 4). The entropically favourable hosting by **CB7** below 291 K is indicative of classical hydration of the guest's hydrophobic subunit, whereas the endothermic to exothermic transition for the binding of *n*-octanol with **β-CD** reveals that the thermodynamic driving force gradually changes from completely entropic to predominantly enthalpic. The analogous Δ_rH° and $-T\Delta_rS^\circ$ temperature dependence was noticed in the case of all other systems (Tables S2 and S3 and Figures S82–S93 in the SI), whereby reversal of Δ_rS° sign with temperature was observed for hosting of **McOct** (327 K), **nOctOH** (337 K), and **MnOct** (330 K) by **β-CD,** and of **nOctOH** (291 K), **cOctOH** (295 K), and **nHexOH** (301 K) by **CB7**.

Generally, temperature may influence not only the organization of the hydrating water and the realized host–guest interactions, but also the inclusion depth of the hydrophobic subunit. By contrast, the hydration of the outer receptor surface remains equal as in free form, whereas the computational and NMR results suggest that the hydration of the mannose subunit does not change upon complexation. Since the correlations between alkyl protons of the guests and the host protons in the ROESY NMR spectra were observed irrespectively of temperature (Figures S98–S105), the $\Delta_rH^\circ(T)$ dependence is not due to notable changes in the complex structure. To rationalize the effect of other contributions to $\Delta_rC_p^\circ$, the process can be divided into the following stages: guest dehydration, cavity dehydration and establishment of host–guest interactions.

According to literature data, the realized dispersion interactions should be weakly temperature dependant and result in less exothermic binding in hot than in cold water. Namely, Olvera *et al.* [29] estimated the dispersive interactions share in $\Delta_rC_p^\circ$ to merely 6 J K^{-1} mol^{-1} per CH_2 group buried within α-cyclodextrin. The finding is also in line with a rather weak increase (approximately 10 %) of hydrocarbon (cyclooctane, *n*-octane, cyclohexane, and *n*-hexane) condensation enthalpies over the 278–338 K interval [30].

Although the solubilising groups affect the values of the heat capacities for reactions with both receptors (Table 2), the realized polar interactions are certainly not the dominant contribution to $\Delta_rC_p^\circ$ in neither of the studied reactions. Namely, the binding is predominantly hydrophobically driven (the standard thermodynamic complexation parameters for both guest classes are comparable, especially for inclusion within **β-CD**) at all examined temperatures (Table 1, Tables S2 and S3). The largest reaction heat capacity difference among alcohols and mannosides was observed for complexation of cyclohexyl-based guests with **CB7** for which the differences in $\Delta_rC_p^\circ$ values amounted to over 100 J K^{-1} mol^{-1}. The discrepancy is in part due to the fact that the reaction heat capacities were obtained by weighted linear regression of $\Delta_rH^\circ(T)$ dependence and are, as such, susceptible to larger errors compared to other reaction thermodynamic parameters. The $\Delta_rC_p^\circ$(**MAlkyl** × HOST)/$\Delta_rC_p^\circ$(**AlkylOH** × HOST) ratio was in all other cases ≥ 0.8. As mentioned in the introduction, small positive heat capacity accompanies the expulsion of **β-CD** cavity water into the bulk [25]. This fact, combined with insights regarding the temperature influence on the guest inclusion depth, and the heat capacity contributions

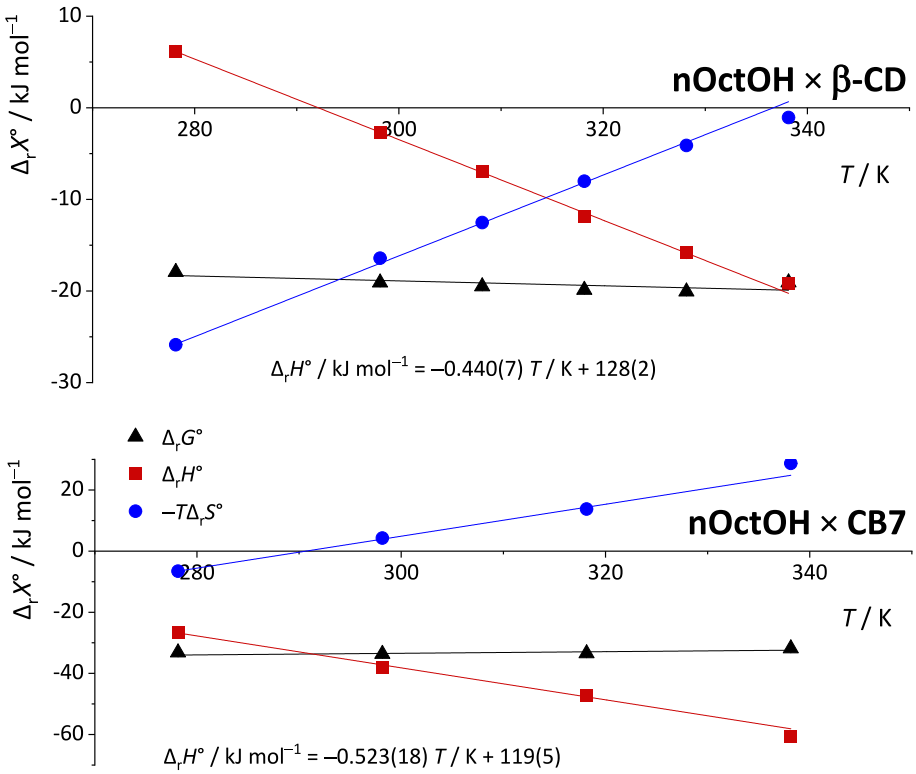

Fig. 4. Temperature dependence of standard thermodynamic parameters for complexation of **nOctOH** with **β-CD** (above) and **CB7** (below).

Table 2
Isobaric reaction heat capacities for complexation of investigated guests with **β-CD** and **CB7**.[a]

Guest	$\Delta_rC_p^\circ$ / J K^{-1} mol^{-1} **β-CD**	**CB7**
cOctOH	−312(10)	−352(19)
McOct	−238(7)	−319(33)
nOctOH	−440(7)	−523(18)
MnOct	−411(13)	−415(5)
cHexOH	−283(29)	−340(15)
McHex	−212(17)	−208(47)
nHexOH		−298(22)
MnHex		−313(65)

[a] Uncertainties of the last digit(s) are given in parentheses as standard deviations obtained by weighted linear regression analysis.

of realized host–guest interactions, suggest that strongly negative $\Delta_rC_p^\circ$ values for the inclusion within **β-CD** must be primarily due to the removal of guest-hydrating water. If this also holds for reactions with glycouril-based receptor the isobaric heat capacities for the complexation of each guest with both receptors should be similar.

The $\Delta_rC_p^\circ$ for complexation of **MnOct** and **McHex** with both hosts are practically within the experimental error, while the largest difference ($\Delta\Delta_rC_p^\circ = \Delta_rC_p^\circ$(GUEST × **CB7**) − $\Delta_rC_p^\circ$(GUEST × **β-CD**) = −0.081 kJ K^{-1} mol^{-1}) was observed for **McOct**. This results in –4.9 kJ mol^{-1} discrepancy in $\Delta(\Delta_rH^\circ(338\ K)–\Delta_rH^\circ(278\ K))$ for reactions of this guest with **CB7** and **β-CD**, respectively. For comparison, the experimentally obtained $\Delta_rH^\circ(338\ K)–\Delta_rH^\circ(278\ K)$ amounts to –20.4 kJ mol^{-1} for cucurbit[7]uril (Table S3) and –14.2 kJ mol^{-1} for β-cyclodextrin (Table S2). Among the examined alcohols, the largest reaction heat capacity difference was obtained in the case of **nOctOH** ($\Delta\Delta_rC_p^\circ = -0.083$ kJ K^{-1} mol^{-1}) which now leads to –5.0 kJ mol^{-1} difference in $\Delta(\Delta_rH^\circ(338\ K)–\Delta_rH^\circ(278\ K))$ for its reaction with **CB7** and **β-CD**. This is again much less than the experimentally determined reaction enthalpy changes over the examined temperature range (–33.9 kJ mol^{-1} for cucurbit[7]uril (Table S3) and –25.3 kJ mol^{-1} for β-cyclodextrin (Table S2)). Consequently, the pronounced $\Delta_rH^\circ(T)$ dependence of all investigated reactions is primarily due to the temperature influence on the removal of hydrating water surrounding the non-polar guest moieties. This also means that the expulsion of **CB7** cavity water must weakly contribute to $\Delta_rC_p^\circ$ values of corresponding inclusion reactions.

The comparable $\Delta_rC_p^\circ$ for reactions involving both receptors are of course expected in the case of complete dehydration of the non-polar moiety and when the involvement of the solubilising group in the hosting process is relatively weak. With this respect, the results with *n*-octyl-based guests, for which the protrusion trough **β-CD** was observed during MD simulations (Fig. 3), should be taken cautiously. The more negative $\Delta_rC_p^\circ$ for binding of **nOctOH** with **CB7** are in accord with computational results. In contrast, the heat capacities for hosting of the corresponding mannoside by both receptors are quite similar. As seen from the data listed in Table 2, the binding of mannosides resulted in larger reaction heat capacities than those of corresponding alcohols, more so for **CB7**. The only exceptions were the reactions involving *n*-hexyl guests and **CB7**, characterized by rather similar $\Delta_rC_p^\circ$ values, however the associated error was substantially larger in the case of reaction with the mannoside (Table 2). Since the ROESY NMR spectra indicate similar inclusion depth of non-polar moieties of both guest classes (Figures S98–S105), the effect is primarily due to realized polar interactions. Given the fact that $\Delta_rC_p^\circ$ for the inclusion within cyclodextrins always decreases with the size of included non-polar surface [21,26,27], it seems that interactions of hosts' (especially **CB7**) portals with mannoside linker atoms result in somewhat higher reaction heat capacities compared to those for hosting of analogous alcohols.

To further corroborate the claim that the herein determined reaction heat capacities are predominantly caused by "melting" of guest-hydrating water, we compared the obtained values with the heat capacities for the transfer from water to gas phase and to the non-polar environment. According to literature data, the isobaric heat capacities for the transfer of alkyl groups from the aqueous solution to the gas phase (estimated using a group contribution method) [57] amount to

–0.52 kJ K^{-1} mol^{-1} (*n*-octyl), –0.41 kJ K^{-1} mol^{-1} (cyclooctyl), –0.39 kJ K^{-1} mol^{-1} (*n*-hexyl), and –0.31 kJ K^{-1} mol^{-1} (cyclohexyl). The values are somewhat lower than the complexation heat capacities, or comparable in the case of **nOctOH** binding with **CB7**. The heat capacities for the transfer of hydrophobic alkyl chains from water to a hydrocarbon environment have been estimated to –0.29 kJ K^{-1} mol^{-1} (6C atoms) and –0.39 kJ K^{-1} mol^{-1} (8C atoms) [50]. Similarly, the $\Delta_r C_p^\circ$ for micellization of neutral amphiphiles amounting to –0.24 kJ K^{-1} mol^{-1} for *n*-hexyl [53], and –0.39 kJ K^{-1} mol^{-1} (refs. [10b,10c,58]) up to –0.46 kJ K^{-1} mol^{-1} (refs. [10c,53]) for *n*-octyl chains were reported. The values are again close to the herein reported reaction heat capacities for the inclusion of corresponding linear guests. The results of our investigations are also consistent with the $\Delta_r C_p^\circ$ values for hosting of linear guests ($\Delta_r C_p^\circ$ = –56 J K^{-1} mol^{-1} per included CH_2 group) by α-cyclodextrin obtained by Ross and Rekharsky [21].

3.3. The guest hydration and its influence on the complexation thermodynamics

The comparative ITC studies revealed that a pronounced, linear decrease of $\Delta_r H^\circ$ with temperature for all herein examined complexation reactions is predominantly due to the gradual disordering of the water involved in the hydration of aliphatic guest moieties. Apart from that, the positive $\Delta_r S^\circ$ accompanying the inclusion within **β-CD** ($T < 318$ K for all studied guests), concomitant with the entropically unfavourable release of its cavity water [31], support the classical (exothermic, entropically unfavourable) hydration of studied hydrophobic groups. In other words, the data are in agreement with the Frank-Evans hydration model (formation of rigid, low-energy hydration spheres which "melt" as temperature increases). Although no evidence for the existence of constrained clathrate-like cages around hydrophobic species has been found, the results of many spectroscopic [33a] and computational [59,61] investigations indicate more pronounced tetrahedral ordering around spherical and linear aliphatic functionalities below 300–320 K. According to Chandler [32] and Ben-Amotz [33], such order–disorder transition should occur for hydrophobic solutes whose dimensions do not exceed 1 nm (the herein explored lipophilic species are below this threshold), whereas the larger non-polar solutes behave as structure breakers, irrespective of temperature. The size limit does not apply to alkyl chains for which the ordering exists regardless of the length, if the segment is not collapsed [62]. However, Hynes *et al.* [63] pointed out that slower relaxation and longer reorientation times of hydrating water [60] do not necessarily imply its iceberg-like organisation around the hydrophobic moieties. The positive entropies associated with the hydration of non-polar molecules could also be a consequence of the loss in H_2O translational and rotational degrees of freedom due to the excluded-volume effect [63,64] enhanced by the small size of the water molecule. Subsequent experimental and computational studies have also challenged the validity of the classical model, with the results ranging from rather weak, albeit favourable solute effect on solvent organisation [65], to completely structure-breaking properties of introduced hydrophobic compounds [66]. Apart from the latter research, the main objection to the iceberg model concerns water immobilisation *vs.* mobility reduction rather than the establishment of somewhat stronger water-water hydrogen bonds. Interestingly, the recent investigations of Havenith *et al.* [67] suggest that the structurisation of hydrating water occurs in the secondary rather than primary hydration spheres of non-polar compounds with the dominant entropic contribution arising from the cavity formation. Although the positive $\Delta_{hyd} S^\circ$ of small non-polar compounds in ambient-temperature water may indeed be primarily due to the excluded volume effect, the accompanying, considerably negative enthalpy changes (e.g. $\Delta_{hyd} H^\circ$(hexane) = –31.6 kJ mol^{-1} and $\Delta_{hyd} H^\circ$(cyclohexane) = –33.2 kJ mol^{-1}) [50a] are an experimental fact difficult to account for without the realisation of more favourable water-water hydrogen bonds. With this respect it is important to realize that only slight differences in the number and strength of hydrogen bonds around the solutes and in the bulk rather than the formation or rigid clathrate-like cages can result in quite strong enthalpic and entropic effect. For instance, if a total of 15 water molecules are involved in the hydration of a non-polar compound and all of them form on average 0.1 hydrogen bond more per molecule compared to bulk, the molar enthalpy per mol of realized hydrogen bonds can be roughly estimated by dividing the condensation enthalpy with the average number of hydrogen bonds per molecule ($-\Delta_{vap} H$(298 K)/3.62). This means that the complete dehydration of a particular non-polar moiety decreases the enthalpic favourability of inclusion for considerable 20 kJ mol^{-1}. The more pronounced structurization arising from additional 0.1 hydrogen bonds per water molecule might not even be observed experimentally or in computational investigations. On the other hand, its effect on the cyclodextrin and cucurbituril complexation thermodynamics will be strong, and since the organisation of H_2O around the hydrophobic moieties' changes with temperature [32–34], considerably temperature dependant. Still, as shown herein, the hosting by **CB**s will be predominantly in accord with the non-classical effect over the wide temperature range, whereas the driving force in the case of **CD**s shifts from completely (or predominantly) classical in low- to non-classical in high-temperature water. This is due to differences in organisation of the cavity-confined water. Specifically, the poor organisation of **CB** cavity water makes it particularly energy- and entropy-rich with respect to the bulk, resulting in strongly exothermic and entropically unfavourable binding despite the temperature-induced "melting" of the guest hydration spheres. By contrast, the release of more bulk-resemblant **CD** water cannot overcompensate for the entropy-driven, endothermic release of guest hydrating water at lower temperatures in such a measure. This in turn results in a strongly temperature-dependant binding force which can reveal the classical hydration of the hydrophobic subunit of the guest *via* positive $\Delta_r S^\circ$. In other words, the thermodynamics governing the inclusion of non-polar functionalities within cyclodextrins can be utilised to obtain insight into corresponding hydration thermodynamics.

4. Conclusions

The complexation of all herein explored guest with both receptors was predominantly driven by the inclusion of the hydrophobic subunits within the non-polar cavities. Further, their entropically favourable binding by **β-CD** at 298 K, concomitant with negative entropy changes accompanying the release of confined water [31], revealed the classical hydration of studied non-polar guest functionalities. The conclusion is strongly supported by exothermic, entropically unfavourable hydration of *n*-hexane and cyclohexane at this temperature [50]. The comparative calorimetric study of **β-CD** and **CB7** binding affinities clearly revealed that the inclusion of non-polar aliphatic moieties within the latter receptor is accompanied by lower $\Delta_r S^\circ$. The release of enthalpy-rich, poorly associated water from the **CB7** cavity hence results in lower entropy changes compared to the analogous process involving **β-CD**.

A pronounced decrease of complexation enthalpy and entropy with temperature was observed for all studied guest-receptor pairs. The carried-out research and literature data concerning cyclodextrins [21,24–27] suggest that negative isobaric reaction heat capacities can be considered as a fingerprint of cyclodextrin and cucurbituril inclusion reactions. Also, in accord with previous investigations involving cyclodextrins [21,27,28], the $\Delta_r C_p^\circ$ decreased with the size of the hydrophobic groups, whereby burial of linear homologues resulted in a steeper reaction enthalpy decrease with temperature. The dissection of all contributions to $\Delta_r C_p^\circ$ and their similarity for inclusion of a particular moiety within both macrocycles indicate that the temperature effect on the binding thermodynamics is predominantly due to changes in the organisation of water around the non-polar guest groups. The agreement between the obtained reaction heat capacities and those for the transfer of analogous hydrocarbons from water to a non-polar environment and to the gas phase further support this claim. The study thus reconciles the

thermodynamics of hydrophobically driven inclusion with thermodynamics governing the hydration of aliphatic functionalities, whereby guest dehydration again emerges as an important factor defining the complex stability as that of the cavity. Concretely, the considerably exothermic, entropically opposed hydration of investigated non-polar moieties in low-temperature water leads to less enthalpy- but more entropy-favoured binding compared to hot medium, in which both the aliphatic groups and the cavities act as chaotropes. The inclusion driving force may hence significantly change with temperature, especially in the case of larger guests (larger number of hydrating water molecules) and less exothermic reactions. In line with this conclusion, the **β-CD** binding thermodynamics shifts from completely (or predominantly) classical in cold- to non-classical in hot water. By contrast, the poorer organisation of **CB7** cavity water results in strongly exothermic, entropically unfavourable binding over the wide temperature range despite the gradual "melting" of guest hydration spheres, thereby masking the entropically favourable release of guest hydrating water at lower temperatures.

The temperature-dependent studies of cucurbituril and especially cyclodextrin binding affinities could hence be used to obtain information with respect to the enthalpy and entropy changes accompanying the dehydration of hydrophobic moieties. This might be important in the context of protein folding [9,32a,32b,32c,68], related π-π stacking [69], and the binding of hydrophobic species to antibiotics and biomacromolecules [28,70] Interestingly, many of these processes are characterised by a baffling negative $\Delta_r C_p$ (a blueprint of classical hydrophobic effect) while simultaneously being enthalpy-driven (non-classical hydrophobic effect) [28]. According to our findings, this indicates that the water involved in the hydration of at least one of the non-polar species experiences gradual disordering with temperature. Moreover, the bivalent influence of such hydrophobe (or such hydrophobes) on the water organisation dominates in the $\Delta_r H^\circ(T)$ dependence (determines the sign of reaction heat capacity). In the end, the importance of ITC studies of supramolecular reactions in a wide temperature range in water cannot be overemphasised. In fact, the herein presented results suggest that the investigations of the temperature effect on the $\Delta_r H^\circ$ and $\Delta_r S^\circ$ may hold a key for the understanding of the underlying reactant hydration influence on the binding affinity.

CRediT authorship contribution statement

Andrea Usenik: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Katarina Leko:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Vesna Petrović Peroković:** Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision. **Željka Car:** Methodology, Investigation, Writing – original draft, Writing – review & editing. **Rosana Ribić:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision. **Katarina Pičuljan:** Methodology, Investigation, Writing – original draft. **Marko Hanževački:** Methodology, Investigation, Writing – original draft, Visualization. **Josip Draženović:** Investigation. **Josip Požar:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Josip Požar reports financial support was provided by Croatian Science Foundation].

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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