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D₂O−H₂O solvent isotope effects on the enthalpies of bicaret hydration and dilution of its aqueous solutions at different temperatures

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ABSTRACT

The molar enthalpies of solution of bicaret or 2,4,6,8-tetraethyl-2,4,6,8-tatraazabicyclo[3.3.0]octane-3,7-dione in ordinary (H_2O) and heavy (D_2O) water at (278.15, 288.15, 298.15, 308.15, and 318.15) K as well as the enthalpies for dilution of its H/D isotopically distinguishable aqueous solutions at 298.15 K were measured calorimetrically. The standard (at infinite dilution) molar enthalpies and heat capacities of solution, and the enthalpic coefficients for pair (h_{22}) and triplet (h_{222}) interactions between hydrated solute molecules, along with D_2O–H_2O solvent isotope effects (IEs) on the studied quantities were computed. The enthalpic effects of bicaret dissolution and corresponding IEs were found to be negative and decreasing in magnitude with increasing temperature. On the contrary, the h_{22} and h_{222} values as well as IEs on them were found to be positive. These facts indicate that the bicaret hydration being predominantly hydrophobic is enhanced in the D_2O medium. The hydration behavior of the solute considered was discussed in comparison with that for mebicar or 2,4,6,8-tetramethyl-2,4,6,8-tatraazabicyclo[3.3.0]octane-3,7-dione using the previously obtained data.

1. Introduction

It is known that the changes in local molecular structure on going from one solvent to another are usually so substantial that the enthalpic effects in solutions have to be considered virtually on an individual basis for each of solvating media. Some of the difficulties are avoided if the desired thermochemical characteristics of a solute are examined in ordinary (H_2O) and heavy (D_2O) water. The point is that the corresponding D_2O–H_2O solvent isotope effects (hereinafter, IEs) then give the useful information on both structure-energy differences between H/D isotopically distinguishable solvents and interactions of a solute molecule with each of them [1–12]. The H_2O-by-D_2O replacement in aqueous solutions

is dictated by the fact that deuteration is a quantum effect inducing the changes in donor-accepting ability of water molecules. It brings about the formation of deuterium (D-) bonds that are stronger but more susceptible to destruction under the influence of solute molecules and temperature compared to the similar protium (H-) bonds [3,13–16].

From this viewpoint, the experimental approach including a combination of solution/dilution isothermal calorimetry and $H_2O \rightarrow D_2O$ solvent isotope substitution methods allows one to establish at the molecular level the role of hydrogen-bonding and hydrophobic effects in the structure-forming process, which are manifested in the enthalpy-related characteristics of dissolution (hydration) and/or solute–solute interaction [3,16–23].

Previously [17–19,23], we have studied the temperature-dependent standard (at infinite dilution) molar enthalpies of solution, $\Delta_{sol}H_2^{\infty}$, of mebicar or 2,4,6,8-tetramethyl-2,4,6,8-tatraazabicyclo[3.3.0]octane-3,7-dione (see Fig. 1) in H_2O and D_2O
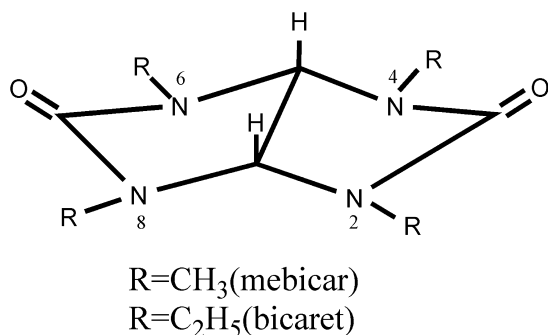
R=CH$_3$(mebicar)
R=C$_2$H$_5$(bicaret)

Fig. 1. Schematically simplified molecular structure of 2,4,6,8-tetralkyl-substituted derivative of glycoluril (bicyclic bisurea).

as well as the integral enthalpies for dilution, $\Delta_{dil}H_2^m$, of its H/D isotopically distinguishable aqueous solutions at 298.15 K.[1] Being a low-toxicity drug (tranquillizer), the mebicar exhibits some interesting features of hydration behavior and solute–solute interactions. So, we have found that the hydrophilic component of mebicar hydration (by $>$C=O groups and N/C-sited hydrogens) is dominating despite the presence of four methyl groups in two conjugate five-membered rings of its molecule. Taking this into account, it appears fairly interesting to assess the influence of further lengthening the N-sited "peripheral" hydrocarbon chains, to form the bicaret, on the above enthalpy-related interaction parameters in isotopically distinguishable aqueous media.

Similar to mebicar, the structurally achiral bicaret (Fig. 1) exhibits a broad spectrum of biological activity [24,25]. Such an activity of 2,4,6,8-tetraalkylated derivatives of glycoluril (or bicyclic bisurea) might be correlated with certain geometric features of their molecules. In particular, this could be due to the dihedral angle (being *ca.* 119°) formed by the mean planes of both conjugate five-membered rings. Owing to rigidity of the heterocyclic core and *cis*-fusion of the rings, the molecule adopts a conformation of half-open book or gullwing shape (see in Fig. 1) [24,26].[2] But, when bicaret is subjected to hydration, together with a markedly increasing contribution of hydrophobic component (due to substitution of methyl groups by ethyl those), a configurational factor becomes more significant, too. It is a result of the more branched structure of bicaret compared to that of mebicar. One would expect that it will be reflected in the enthalpy-related effects caused by bicaret solvation (hydration) in the H/D isotopically distinguishable aqueous media.

Thus, the principal objective of the given work was to obtain new information on the $\Delta_{sol}H_2^\infty$ values for bicaret or 2,4,6,8-tetraethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione in H$_2$O and D$_2$O at T = 278.15, 288.15, 298.15, 308.15, and 318.15 K as well as the enthalpic interaction coefficients, h_{22} and h_{222}, using data on $\Delta_{dil}H_2^m$ at 298.15 K and $p \sim 0.1$ MPa. In this paper we have discussed also the corresponding IEs, comparing them with similar results obtained previously for mebicar.

2. Experimental

Bicaret was synthesized according to the procedure [25]. The product yield was 72%. The product melting point determined using a Sanyo Gallenkamp instrument was t_{mp} = 110 ± 1 °C,

which is in good agreement with the values reported previously: t_{mp} = 107–109 °C [25,27]. The molecular structure of a sample synthesized was confirmed by the results of elemental analysis on an MS-30 mass spectrometer as well as NMR spectroscopic data. Being given as a percentage ratio of the found amount to the calculated one, the relative elemental composition of a C$_{12}$H$_{22}$N$_4$O$_2$ sample was 1.002 (C), 0.987 (H) and 0.985 (N). The ^{13}C NMR spectrum was measured on a Bruker AM 300 (75.5 MHz) spectrometer in DMSO-d_6. The chemical shifts, δ/ppm, were (relative to TMS as the internal standard): 13.11 (CH$_3$), 37.28 (NCH$_2$), 67.15 (CH), and 158.10 (C=O) at T = 298 K. The synthesized sample of bicaret was additionally recrystallized from absolute ethanol (Fluka, puriss) and then dried *in vacuo* at $T \approx 320$ K to constant mass.

Water of natural isotope composition was twice distilled in an apparatus made of Pyrex glass up to a specific conductivity (κ) of 1.6×10^{-6} S cm^{-1}. Heavy water ("AstraKhim", St. Petersburg; 99.92 at% D; $\kappa = 1.2 \times 10^{-6}$ S cm^{-1}) was used as such. In accordance with the results of an additional densimetric analysis, with due account of the "reference" data on D$_2$O density [28], the deuterium content in the studied heavy water was confirmed up to ±0.01 at% D.

The molar enthalpies of solution, $\Delta_{sol}H_2^m$, for bicaret in water H/D isotopologues were measured at the above-enumerated temperatures and ambient pressure using an automated isoperibol ampoule-type calorimeter fitted with an electrical calibration after each experiment. A glass ampoule containing the sample was broken in a 30 cm^3 titanium vessel. The detection limit of the apparatus is 10^{-5} K, and the temperature instability in the bath is 10^{-3} K in the temperature range considered. Procedure of experimental measurements of $\Delta_{sol}H_2^m$ and testing of the instrument were detailed previously [29,30].

The measurements of $\Delta_{dil}H_2^m$ were carried out at 298.15 K using the same calorimeter. The experimental procedure was described in general outline in our recent report [31]. Here, the several solutions of bicaret in H$_2$O and D$_2$O (where m ranged from ~0.5 up to ~1.5) were prepared. These solutions in quantity of 0.3–0.6 g were transferred with a syringe into glass ampoules that had a narrow neck which could be sealed with the aid of a microburner. The filled ampoules were attached to an ampoule-holder. An ampoule crushing against a sprocket ampoule-destroyer (being fastened to the stirrer shaft) initiated a dilution process in the pure aqueous (H$_2$O or D$_2$O) medium. The heat of dilution was from 0.2 to 2.0 J which caused the change in temperature by 0.001–0.01 K. That is, the minimal enthalpic effect exceeds the declared detection limit of a calorimeter (see above) by a factor of 100. The uncertainty in $\Delta_{dil}H_2^m$ measurements is estimated to be no more than 5% at worst.

3. Results

The calorimetric measurements showed that the $\Delta_{sol}H_2^m$ values in the concentration region considered do not depend on m within the experimental error at all the temperatures chosen. As a result, the $\Delta_{sol}H_2^\infty$ values have been calculated as average-weighted $\left|\Delta_{sol}H_2^m\right|_{av}$ using the half-width confidence interval (U) that determined by the Peters formula [32]:

$$U = \pm \frac{t_{0.95}n/(n-1)\sum_{i=1}^{n}\left|x_i - \tilde{x}_i\right|}{n(n-1)^{1/2}}$$

where $t_{0.95}$ is a Student criterion at a 95% confidence level, n is the number of runs, $x_i = \Delta_{sol}H_2^m$, and $\tilde{x}_i = \left|\Delta_{sol}H_2^m\right|_{av}$.

The experimental data on $\Delta_{sol}H_2^\infty$ for bicaret in H$_2$O and D$_2$O are listed in Table 1. In tern, the $\Delta_{dil}H_2^m$ values for its H/D isotopically distinguishable aqueous solutions are given in Table 2 where m_i and m_f are the initial and final molalities, respectively.

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[1] Hereinafter, the subscripts 1 and 2 denote a water isotopologue and a glycoluril derivative, respectively. A superscript m (molality) is defined as the number of moles of a bicaret per 1 kg of a solvent.

[2] Herewith methyl groups of the bicaret alkyl radicals are under the "wings" of the folded molecular frames in *gauche* orientations toward C–N bonds connected with a C–C bridge of the bicyclic compound considered [24].

Table 1

Standard (at infinite dilution) molar enthalpies of solution, $\Delta_{sol}H_2^\infty$ /(kJ mol^{-1}), of bicaret in ordinary and heavy water with the corresponding solvent isotope effects, $\delta\Delta_{sol}H_2^\infty(H_2O \rightarrow D_2O)$, at different temperatures.

T/K	Bicaret in H$_2$O		Bicaret in D$_2$O		$\delta\Delta_{sol}H_2^\infty(H_2O \rightarrow D_2O)$
	m^a	$\Delta_{sol}H_2^\infty$	m^a	$\Delta_{sol}H_2^\infty$	
278.15	0.0037–0.0057	−15.66 ± 0.06	0.0041–0.0070	−16.67 ± 0.08	−1.01 ± 0.10
288.15	0.0039–0.0065	−11.20 ± 0.10	0.0049–0.0072	−12.13 ± 0.05	−0.93 ± 0.11
298.15	0.0036–0.0070	−6.83 ± 0.08	0.0026–0.0061	−7.68 ± 0.07	−0.85 ± 0.11
308.15	0.0043–0.0075	−2.33 ± 0.04	0.0029–0.0069	−3.08 ± 0.10	−0.75 ± 0.11
318.15	0.0040–0.0069	1.97 ± 0.09	0.0034–0.0064	1.33 ± 0.08	−0.64 ± 0.12

[a] The molality range in which the $\Delta_{sol}H_2^m$ values were averaged (at number of experimental determinations being N_m = 4 in all cases).

Table 2

The integral enthalpies for dilution, $\Delta_{dil}H_2^m$, of solutions of bicaret in ordinary and heavy water at 298.15 K.[a]

Bicaret solutions in H$_2$O			Bicaret solutions in D$_2$O		
m_1	m_f	$\Delta_{dil}H_2^m$	m_i	m_f	$\Delta_{dil}H_2^m$
0.6510	0.0100	−9.3	0.4980	0.0077	−7.9
0.6510	0.0077	−7.3	0.4980	0.0075	−6.3
0.9961	0.0158	−27.1	1.0088	0.0162	−41.4
0.9961	0.0101	−17.3	1.0088	0.0087	−21.1
1.4134	0.0130	−32.8	1.4525	0.0160	−63.5
1.4134	0.0110	−28.1	1.4525	0.0159	−64.4

[a] The $\Delta_{dil}H_2^m$ values are given in J per kg of water in the final solutions [33].

Table 3

Enthalpy-related homotactic interaction coefficients, h_{22} and h_{222}, for bicaret solutions in ordinary and heavy water with the corresponding solvent isotope effects, $\delta h_{22(222)}$ ($H_2O \rightarrow D_2O$), at 298.15 K. (For comparison, the previously published results of studying the H/D isotopically distinguishable solutions of mebicar included in the table, too[a]).

Solute	$h_{22}(H_2O)$	$h_{22}(D_2O)$	$\delta h_{22}(H_2O \rightarrow D_2O)$	$h_{222}(H_2O)$	$h_{222}(D_2O)$	$\delta h_{222}(H_2O \rightarrow D_2O)$
Bicaret	1389 ± 102	1804 ± 164	415 ± 193	303 ± 81	673 ± 120	370 ± 145
Mebicar	−2042 ± 68[b]	−2663 ± 122[b]	−621 ± 140[b]	903 ± 62[b]	1287 ± 123[b]	384 ± 138 [b]

[a] Units: h_{22} or δh_{22}, J kg mol^{-2} and h_{222} or δh_{222}, J kg^2 mol^{-3} (the reported uncertainties correspond to U at the 95% confidence limits).
[b] Reference [23]. Other our data [18]: $h_{22}(H_2O)$ = −1870 ± 270, $h_{22}(D_2O)$ = −2660 ± 300 and δh_{22} ($H_2O \rightarrow D_2O$) = −730 ± 400.

The enthalpy-homotactic pairwise and triplewise interaction coefficients, h_{22} and h_{222}, were estimated by fitting the $\Delta_{dil}H_2^m$ values (Table 2) with the known polynomial expansion based on the McMillan–Mayer formalism [23,33,34].

$$\Delta_{dil}H_2^m(m_i \rightarrow m_f)/(J\ kg^{-1})$$

$$= h_{22}m_f(m_f - m_i) + h_{222}m_f(m_f^2 - m_i^2) + \cdots \quad (1)$$

In fitting of this equation, a least-squares method was employed. The fitting was tried with the polynomial of increasing degree, choosing that of highest degree, for which all the coefficients are significant with respect to their own 95% confidence limit. Being computed by Eq. (1), the h_{22} and h_{222} values for the H/D isotopically distinguishable aqueous solutions of bicaret, together with the similar results for mebicar, are summarized in Table 3.

The results given in Table 1 made it possible to calculate a change in the standard molar heat capacity at dissolving bicaret, $\Delta_{sol}C_{p,2}^\infty = (\partial\Delta_{sol}H_2^\infty/\partial T)_p$ in H$_2$O and D$_2$O. For this purpose, the temperature dependences of $\Delta_{sol}H_2^\infty$ were approximated by the linear equation

$$\Delta_{sol}H_2^\infty(T) = \Delta_{sol}H_2^\infty(\theta) + \Delta_{sol}C_{p,2}^\infty(T - \theta) \quad (2)$$

where $\Delta_{sol}H_2^\infty$ (θ) is the solution enthalpy at a reference temperature θ = 298.15 K. The form of Eq. (2) assumes that the $\Delta_{sol}C_{p,2}^\infty$ values, being equal to 441.3 ± 5.2 J mol^{-1} K^{-1} in H$_2$O and 450.5 ± 4.7 J mol^{-1} K^{-1} in D$_2$O, do not depend on T in the chosen temperature range.

4. Discussion

Based on the results presented in Table 1 and derived from Eq. (1), one may conclude that the process of bicaret dissolution in both ordinary and heavy water is accompanied by a heat evolution, at least, in the temperature range up to $T \approx 313.6$ K for protiated system and $T \approx 315.2$ K for deuterated one. When the temperature goes above the specified inversion points (where $\Delta_{sol}H_2^\infty = 0$), the bicaret dissolves with an increasing endothermic effect. The H$_2$O-by-D$_2$O isotope substitution has a rather pronounced influence on $\Delta_{sol}H_2^\infty$, varying this quantity by 1.0 kJ mol^{-1} (or ∼6.5% of the total) at T = 278.15 K and by 0.6 kJ mol^{-1} (or ∼33% of the total) at T = 318.15 K. Since the uncertainty in the $\delta\Delta_{sol}H_2^\infty(H_2O \rightarrow D_2O)$ determination does not exceed ±0.12 kJ mol^{-1} (see in Table 1), it will be a good plan to carry out the subsequent discussion of the IEs in question.

According to [35–37], the large and positive value of $\Delta_{sol}C_{p,2}^\infty$ (in water) especially when accompanied by a negative sign at the temperature-dependent $\Delta_{sol}H_2^\infty$ is indicative of a prevailingly hydrophobic hydration of the solute. The point is that increasing $\Delta_{sol}C_{p,2}^\infty$ reflects primarily the structure and energy changes caused by increasing the number of shorter water–water hydrogen bonds in the nearest vicinity of nonpolar groups [37]. That is, although the interaction of carbonyl groups with a water isotopologue seems to be significant [38,39], the hydrophobic constituent (around N-sited C$_2$H$_5$ groups) of the bicaret hydration is dominating.

In this context, of special interest is the fact that the $\Delta_{sol}C_{p,2}^\infty$ quantity for mebicar is positive too (see in Fig. 2a), being almost one-third of the bicaret value. So by using Eq. (1) and data on $\Delta_{sol}H_2^\infty$ (T) taken from [19,35], we obtain $\Delta_{sol}C_{p,2}^\infty$ to be equal to 168 ± 12 and 155 ± 15 J mol^{-1} K^{-1} for mebicar in H$_2$O and D$_2$O, respectively. However, as seen in Fig. 2b, the introduction of each of glycoluril derivatives simultaneously into the ordinary and heavy water leads to radically different enthalpy-isotopic effects
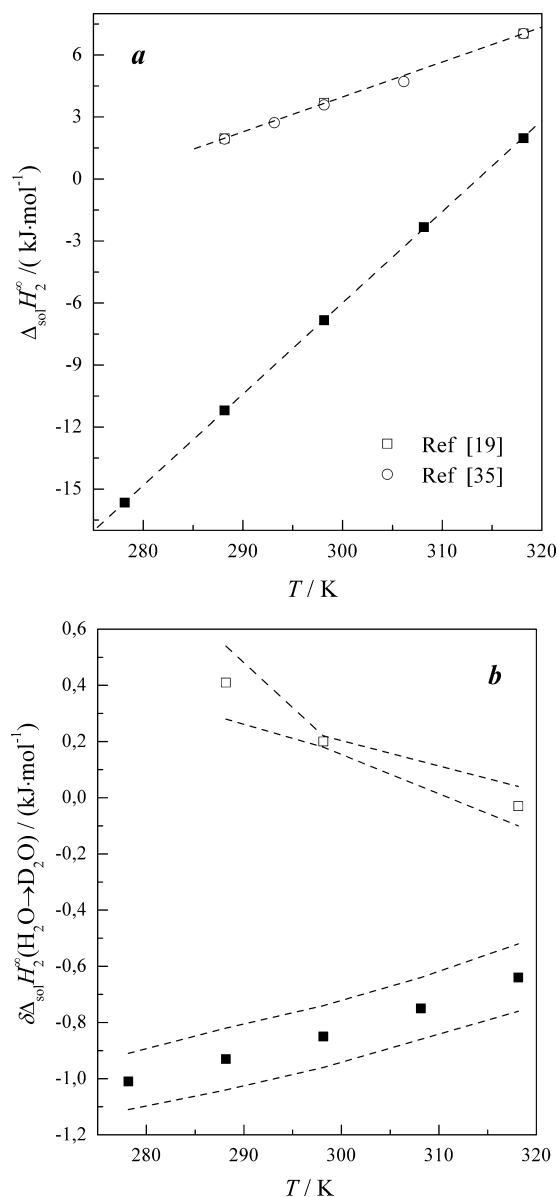
Fig. 2. (a) The standard molar enthalpies of solution of bicaret (closed symbols) and mebicar (open symbols) in H_2O as a function of temperature. The confidence interval half-width (U) does not exceed $\pm 0.12\,kJ\,mol^{-1}$ for bicaret (Table 1) and $\pm 0.13\,kJ\,mol^{-1}$ for mebicar (Refs [19,35]). (b) The temperature dependences of D_2O–H_2O solvent isotope effects on the standard molar enthalpy of solution/hydration of bicaret (closed symbols) and mebicar (open symbols) in the aqueous media. The dotted lines limit the half-width of a 95% confidence interval for each of the quantities considered.

when the temperature is rising. In the case of mebicar, the IE on $\Delta_{sol}H_2^\infty$ becomes decreasingly positive down to zero at $T \approx 318\,K$ (i.e., $\delta\Delta_{sol}C_{p,2}^\infty < 0$), taking the negative values at higher temperatures. Quite the opposite situation is observed for bicaret whose $\delta\Delta_{sol}H_2^\infty(H_2O \to D_2O)$ value somewhat decreases in magnitude (i.e., $\delta\Delta_{sol}C_{p,2}^\infty > 0$), remaining negative over the whole temperature range studied. Such a distribution of $\Delta_{sol}H_2^\infty$ is in agreement with the agreed-upon conclusion [4–7,40] that in binary aqueous systems with D_2O, positive thermodynamic quantities are more positive while the negative quantities are more negative than those for H_2O-containing systems. This "generality" and the above fact that the hydrogen-bonding in heavy water is stronger explain largely why the $\delta\Delta_{sol}C_{p,2}^\infty(H_2O \to D_2O)$ values for bicaret and mebicar are opposite in sign.

Since standard enthalpy characteristics do not contain the contribution from interaction between molecules of a solute [41], the $\delta\Delta_{sol}H_2^\infty$ value is numerically equal to a change in the standard molar enthalpy of bicaret hydration, $\delta\Delta_{hydr}H_2^\infty$, upon the $H_2O \to D_2O$ substitution. In view of this, both negative $\delta\Delta_{sol}H_2^\infty$ and positive $\delta\Delta_{sol}C_{p,2}^\infty$ (Fig. 2b) can be considered as evidence that, like the previous situation with aqueous tetramethylurea (TMU) and its cyclic derivatives [20–23], the hydrophobic constituent of bicaret hydration is enhanced in D_2O.

In accordance with data depicted in Fig. 2a and b, the process of mebicar hydration proceeds in another way. The presence of only N-sited terminal methyl groups in the molecule (Fig. 1) is responsible for weakening its hydrophobicity. Herewith the hydrophilic constituent in both $\Delta_{hydr}H_2^\infty$ and $\delta\Delta_{hydr}H_2^\infty(H_2O \to D_2O)$ should increase, as was shown previously [1,2,42] by studying the interaction-related properties of aqueous urea and its alkyl-derivatives. It has been found [1] that IE on the partial molar heat capacity at infinite dilution for hydrophilic urea in water, $\delta C_{p,2}^\infty \approx -10.4\,J\,mol^{-1}\,K^{-1}$, is analogical by sign and magnitude as in the above case of mebicar. By using the millimeter absorption and ^{13}C NMR spectroscopic studies of aqueous mebicar [38,39], it has been concluded that two carbonyl oxygens form H(D) bonds with four water molecules according to a mechanism of positive hydration [43]. The HC—CH bridging group can form H bonds with two other water molecules, too, whereas the hydrogen-bonding ability of nitrogen atoms is sterically hindered. Herewith at least two water molecules incorporated in the hydration shell retain their rotation mobility, as has been observed for urea negative hydration [43].

The total energy released during the formation of these bonds and from hydrophobic hydration probably does not replace all of the energy spent to destroy the mebicar crystal lattice and to form the cavity in the solvent, a process that is accompanied by the disturbance of the H- or D-bond network of water. This explains why the $\Delta_{sol}H_2^\infty$ values positive and the degree of mebicar hydration in D_2O is somewhat smaller than in H_2O, at least at $T < 318\,K$. Concerning the bicaret hydration, one can assume that its molecules are stronger proton acceptors, compared to mebicar ones, in the aqueous medium. A possible explanation is that the C=O H(D)—O-interactions are the most energetically pronounced when the molecule polarity (dipole moment) is the greatest [1]. Taking into account the fact of more complex conformational structure of bicaret, such an explanation seems to be quite reasonable.

Thus, one may expect that the exothermic contribution to both $\Delta_{sol}H_2^\infty$ and $\delta\Delta_{sol}H_2^\infty$ ($H_2O \to D_2O$) is higher for bicaret than that for mebicar due to higher molecule hydrophobicity and hydrogen-bonding ability. However the authentic nature of these unusual enthalpy and enthalpy-isotopic effects observed at dissolving the glycolurils compared still remains unclear and needs further investigation. In terms of thermodynamic properties only, solute–solvent interactions on the molecular level are impossible to define explicitly. Obviously, quantum–chemical and spectroscopic results would be very helpful to confirm the above suggestions.

To understand this situation more clearly, the computed (using Eq. (1)) values of h_{22} as well as h_{222} for both bicaret and mebicar solutions in H_2O and D_2O must be considered too. The analysis of data presented in Table 3 convinces us that the existing differences in the mechanisms of hydration of bicaret and mebicar are clearly manifested in the numerical values of the interaction coefficient in question. Suffice it to say that, similar to the above situation with $\Delta_{sol}H_2^\infty$ and $\delta\Delta_{sol}H_2^\infty(H_2O \to D_2O)$ as a whole, the h_{22} values for the solutes compared are opposite in sign.

The positive sign at the h_{22} coefficient shows that the homotactic interactions between bicaret molecules, like the case of TMU molecules that can serve only as the hydrogen bond acceptor $\sim 2060\,J\,kg\,mol^{-1}$ in H_2O and $\sim 2460\,J\,kg\,mol^{-1}$ in D_2O [23]),

are to be prevailingly hydrophobic in nature. It means that the solute molecules in H/D isotopically distinguishable aqueous media should experience some repulsion although the overlapping of co-spheres with the same hydration type should promote association. However, according to [44], such an overlapping of co-spheres in the case of hydrophobically hydrated solute leads to considerable enhancement of clathrate-formation in the nearest vicinity of its nonpolar groups,[3] a factor that facilitates the separation of hydrated solute molecules. It is likely that for bicaret, as it is for TMU, the latter effect prevails over the former. This is supported by the increase in h_{22} at deuteration of solvent molecules (Table 3).

The character of 2–2 intermolecular interactions for {H_2O (or D_2O) + mebicar} sharply differs from that in aqueous bicaret. By analogy with a typically hydrophilic urea ($h_{22} \sim -330\,J\,kg\,mol^{-1}$ in H_2O and $\sim -430\,J\,kg\,mol^{-1}$ in D_2O [18]), mebicar molecules interact rather strongly with each other to form the solvent-separated pairs [45] despite the presence of four N-sited alkyl substituents, as in bicaret or TMU molecules. The H_2O-by-D_2O substitution leads to enhancement of self-association of the hydrated mebicar molecules ($\delta h_{22} < 0$ in Table 3). This is in agreement with the above suggestion that the interaction of a mebicar molecule is predominantly hydrophilic in nature. According to data of ^{13}C NMR spectroscopic studies [39], it may be realized by the formation of intermolecular H- or D-bonds through not only carbonyl oxygens, but also "glyoxalic" C—H groups (see in Fig. 1).

Thus, the existing differences in the hydration behavior of mebicar and bicaret are eloquently illustrated by differences in the trend of changing the above enthalpy-isotopic effects induced by the replacement of protium with deuterium in a solvent molecule. In the case of the former solute, $\delta h_{22} < 0$ and $\delta \Delta_{sol} C_{p,2}^{\infty} < 0$ at $\delta \Delta_{sol} H_2^{\infty}$ (or $\delta \Delta_{hydr} H_2^0$) > 0, at least at $T < 318\,K$, while for the latter solute, the reverse pattern is observed, $\delta h_{22} > 0$ and $\delta \Delta_{sol} C_{p,2}^{\infty} > 0$ at $\delta \Delta_{sol} H_2^{\infty}$ (or $\delta \Delta_{hydr} H_2^0$) < 0. Seen in this light, most interesting is the fact that the cross-coefficients h_{222} as well as corresponding IEs, $\delta h_{222}(H_2O \rightarrow D_2O)$, have a positive sign for both glycoluril derivatives under comparison (Table 3). Herewith if in (D_2O + bicaret) the h_{222} value is almost twice as many as in (D_2O + bicaret), in ordinary aqueous solutions this ratio becomes already threefold. Note that in the case of "hydrophobic" TMU, these quantities were found to be smaller in magnitude but negative by sign [23]. Such a situation may be responsible for decreasing of the "molecular hydrophobicity" on going from TMU to bicaret and further to mebicar. However the unusual fact that the values of $\delta h_{222}(H_2O \rightarrow D_2O)$ for bicaret and mebicar are equal between themselves (see in Table 3), unfortunately, is not yet subject to a reasonable explanation.

5. Short summary

Based on the results presented in Tables 1 and 3 as well as in Fig. 2a and b, we may conclude that, despite the formation of rather strong heterocomponent hydrogen bonds in the aqueous (H_2O or D_2O) solutions of bicaret, a hydrophobic constituent is the predominant one in the total enthalpy effect of solute hydration and this is enhanced in heavy water. Both the $\Delta_{hydr} H_2^0$ ($\Delta_{sol} H_2^{\infty}$) values and corresponding IEs for the solute in question decrease markedly when temperature is rising. The given facts seem to be in accordance with the tendency to weakening of hydrophobic hydration of a solute with increasing temperature due to breaking of hydrogen bonds and the subsequent destruction of the spatially coordinated local structure of a surrounding solvent. Herewith, due to the higher rate of thermal predestruction of the initial

structure of heavy water, a negative-to-positive sign inversion of the enthalpy-isotopic effect of bicaret hydration could occur hypothetically in the range of $T = 389\,(\pm 11)\,K$.

We have established that the molecules of bicaret are hydrated stronger than those of its tetra-N-methylated analog, or mebicar. The hydration of mebicar should be also treated as a superposition of two mechanisms, hydrophobic and hydrophilic. However in the given case, the latter is predominating. The existing differences in the hydration behavior of mebicar and bicaret are eloquently illustrated by differences in the trend of changing the enthalpy-isotopic effects induced by the replacement of protium with deuterium in a solvent molecule. In the case of mebicar, $\delta h_{22} < 0$ and $\delta \Delta_{sol} C_{p,2}^{\infty} < 0$ at $\delta \Delta_{sol} H_2^{\infty}$ (or $\delta \Delta_{hydr} H_2^0$) > 0, at least at $T < 318\,K$, while for bicaret, the reverse pattern is observed, $\delta h_{22} > 0$ and $\delta \Delta_{sol} C_{p,2}^{\infty} > 0$ at $\delta \Delta_{sol} H_2^{\infty}$ (or $\delta \Delta_{hydr} H_2^0$) < 0.

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