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.

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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

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_2O and D_2O 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 $t_{mp} = 110 \pm 1$ °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 $C_{12}H_{22}N_4O_2$ 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_2O 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_2O and D_2O (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_2O or D_2O) 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_2O and D_2O 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].