

Temperature-dependent thermochemical properties of the *Mebicaret* (2,4-dimethyl-6,8-diethylglycoluril) solutions in H₂O and D₂O at the ambient pressure



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ABSTRACT

The enthalpies of solution of *Mebicaret* or 2,4-dimethyl-6,8-diethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione in ordinary (H₂O) and heavy (D₂O) water at (278.15, 279.15, 288.15, 298.15, 308.15, and 313.15) K as well as the enthalpies of 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 D₂O–H₂O solvent isotope effects (IEs) on the studied quantities were computed. The enthalpic effects of *Mebicaret* dissolution in H₂O and D₂O experience a negative-to-positive sign inversion nearby 303 K and 304 K, respectively, whereas the corresponding IEs were found to be wholly negative (by sign) and decreasing in magnitude with increasing temperature. The h_{22} values as well as IEs on them were found to be negative, too. On the contrary, the values of h_{222} are positive and comparable in magnitude with h_{22} ones. These facts indicate that the *Mebicaret* hydration, being enhanced in the D₂O medium, is dualistic by the nature with the prevailing hydrophilic mechanism.

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1. Introduction

As a part of our continuous efforts to obtain information on the enthalpic effects caused by a dissolution/dilution of achiral *N*-tetraalkylated glycoluril-derivatives in the H/D isotopically distinguishable aqueous media [1–3], we report here results of a calorimetric study of 2,4-dimethyl-6,8-diethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (titled a *Mebicaret*, see Fig. 1a) solutions in ordinary (H₂O) and heavy (D₂O) water.

It is known that some representatives of this class of heterocyclic compounds possess the pronounced physiological or biological activity, serving as a basis to design the promising drugs [4]. Among the *N*-alkyl glycoluril derivatives, tetra-substituted compounds are considered to be the most active [5,6]. Herewith it is assumed that

their activity decreasing markedly with the decrease in the number and bulk of *N*-alkyl substituents [5,7]. The psychotropic pharmaceuticals *Mebicar* (2,4,6,8-tetramethylglycoluril, Fig. 1b) and *Albicar* (2,6-dimethyl-4,8-diethylglycoluril) are well-known tranquilizers and antidepressants [1–5,8–11]. Other representatives of the specified fully *N*-alkylated bioactive compounds, *Mebicaret* (see Fig. 1a) and *Bicaret* (2,4,6,8-tetraethylglycoluril, Fig. 1c), possessing anxiolytic and sedative activity, are much less studied [3,5,7,12]. At the same time the lack of reliable data on their thermodynamic properties in both crystalline and dissolved states does not allow identifying the peculiarities of hydration of pharmacophore (hydrophobic and proton-donor/acceptor) centers of the molecules in question.

Earlier we (with some other co-authors) have carried out a number of such studies for the aqueous *Mebicar* [1,2,13–15] and *Bicaret* [3,7]. As seen in Fig. 1a–c, a *Mebicaret* molecule can be considered as the “intermediate” for the molecules of these two heterocyclic compounds simultaneously. Seen in this light, we consider it would

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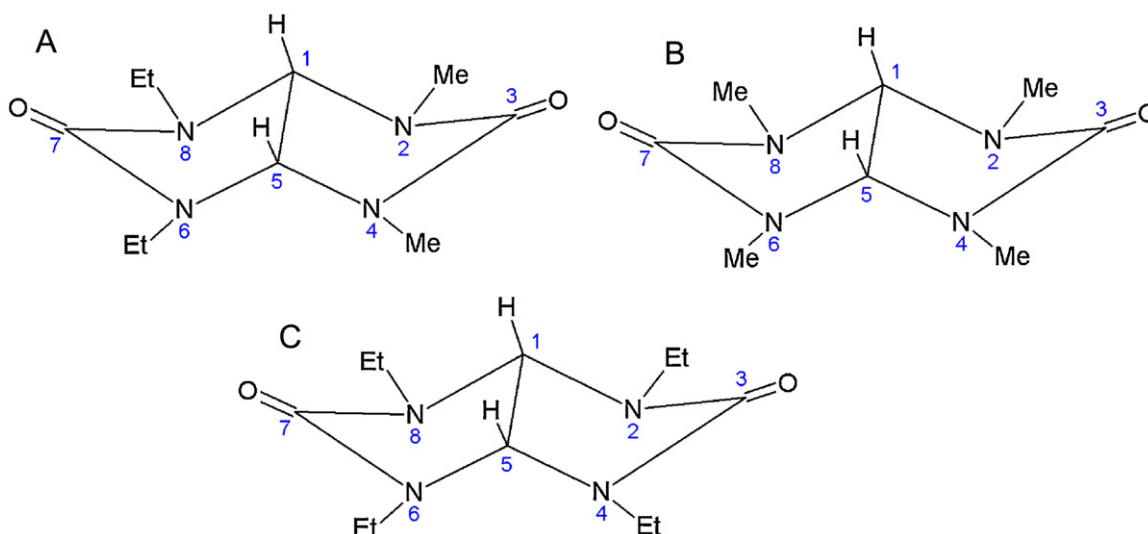


Fig. 1. The schematically simplified structure of Mebicaret (a), Mebicar (b) or Bicaret (c) molecule with the labeling of atoms (owing to rigidity of the heterocyclic core and *cis*-fusion of the five-membered rings, a glycoluril's molecule adopts the conformation of “half-open book” or “gull-wing” shape [5,8]). Here, Me = methyl group, Et = ethyl group.

be interesting to assess the influence of structure- and energy-related changes caused by increasing in volume of nonpolar groups in one of the five-membered rings of a *N*-tetraalkylated glycoluril-derivative on the features of its interaction in aqueous medium (including the hydration effect).

Based on what is stated above, within the scope of this study, we discussed the D_2O – H_2O solvent isotope effects (hereinafter, IEs or δ) on the standard molar enthalpy, $\Delta_{sol}H_2^0$, and heat capacity, $\Delta_{sol}C_{p,2}^0$, of Mebicaret dissolution, as well as on enthalpy-related (virial) coefficients of pairwise and triple interactions, h_{22} and h_{222} , between its molecules in water H/D-isotopologues. By virtue of the quantum nature of H_2O -by- D_2O replacement [16–18], such approach 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 molar enthalpy-related characteristics of dissolution and interaction. The calorimetric experiments were performed at $T=(278.15, 279.15, 288.15, 298.15, 308.15, \text{ and } 313.15)$ K and $p \sim 0.1$ MPa, the conditions under which the $\Delta_{sol}H_2^0$ values for Bicaret in H_2O and D_2O were derived [3] (for Mebicar in D_2O such measurements were performed at three temperatures only [1]). The enthalpies of dilution of H/D isotopically distinguishable aqueous solutions of Mebicaret, $\Delta_{dil}H_2^0$, were carried out at $T=298.15$ K.

Immediately prior to considering the obtained results, note also that at present there is some ambiguity in naming of the title compound. So, its IUPAC name is 1,3-dimethyl-4,6-diethyl-tetrahydroimidazo[4,5-d]imidazole-2,5(1*H*,3*H*)-dione (Table 1). At the same time this naming does not reflect the fact of the existence of asymmetric contiguous C(1) and C(5) atoms being termed as a “glyoxalic bridge” that form the heterocyclic structure of a glycoluril molecule [5,8]. To eliminate this ambiguity, a more agreed-upon name for such glycolurils is used now in the literature [8,19,20]: bicyclic bisureas of the octane series or 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones. Given this, further for simplicity, we will stick with a trivial name of the compound in question.

2. Materials and methods

A detail description of chemical compounds employed in this work is given in Table 1.

Mebicaret was synthesized in accordance with the procedure [20]: by way of cyclocondensation of 4,5-dihydroxy-1,3-dimethylimidazolidin-2-on with 1,3-dimethylurea under the influence of heating and stirring. The product yield was 59%. The synthesized sample was recrystallized from acetone with further drying for 24 h *in vacuo* at $T=320$ K (to constant mass); its melting point and standard molar enthalpy of fusion determined with a differential scanning calorimeter DSC 204 F1 Phoenix were 367.7 (± 0.5) K and 25.4 (± 0.5) $\text{kJ}\cdot\text{mol}^{-1}$, respectively. In the parentheses, the expanded uncertainty with a 95% level of confidence is given. The purity of the prepared sample was checked using a high performance liquid chromatography (HPLC in Table 1). Additionally, the ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AM 300 spectrometer in $\text{DMSO}-d_6$. Being derived by such way, the chemical shifts, δ/ppm , and coupling constants, J/Hz , were: 1.07 (t, 6H, Me, $^3J=7.2$), 2.81 (s, 6H, Me), 3.16 (dq, 2H, CH_2N , $^2J=14.2$, $^3J=7.1$), 3.34 (dq, 2H, CH_2N , $^2J=14.2$, $^3J=7.1$), 5.17 (s, 2H, CH) and 30.20 (C–Me), 30.03 (N–Me), 37.19 (CH_2), 69.55 (CH), 157.83, 158.78 (C=O), respectively, at $T=300$ K. We have found it necessary to present the ^1H NMR and ^{13}C NMR spectra for the Mebicaret sample in Figs. S1 and S2, which are given as a Supplementary material. Noteworthy is the fact that the proton NMR-spectrum (Fig. S1) corresponding to the structure depicted in Fig. 1a contains two sextets, being placed in the (3.0 to 3.5) ppm region. These sextets are the multiplet-type AMX_3 systems. Moreover, there are extra peaks at 2.50 ppm and 3.35 ppm being related to DMSO and H_2O , respectively (Fig. S1). Prior to calorimetric measurements, the sample of Mebicaret was additionally dried in a vacuum chamber for 48 h at $T=320$ K and the residual water content in it, determined with a Karl-Fischer titration (using a Mettler Toledo C30 titrator), was about 0.007 wt.%. Before and after serial experiments, the Mebicaret sample was stored in a light-proof vacuum dessicator over P_2O_5 .

Water of natural isotope composition was twice distilled in a Pyrex-glass apparatus up to a specific conductivity (κ) of $1.6\cdot 10^{-6}$ $\text{S}\cdot\text{cm}^{-1}$. Heavy water (“AstraKhim”, St. Petersburg, Russia; 99.9 at.% D; $\kappa=1.2\cdot 10^{-6}$ $\text{S}\cdot\text{cm}^{-1}$) was used as such.

The concentration-dependent molar enthalpies of the Mebicaret dissolution in water H/D isotopologues, $\Delta_{sol}H_2^m$ (m is a solution molality), were measured at the chosen temperatures and $p=(99.6\pm 0.8)$ kPa using an automated isoperibol ampoule-type calorimeter fitted with an electrical calibration before and

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