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INFLUENCE OF THE NATURE OF N-ALKYLATION OF GLYCOLURILS ON THEIR SOLVATION STRUCTURAL EFFECTS IN H/D-ISOTOPOLOGUES OF WATER BASED ON THE RESULTS OF THERMODYNAMIC STUDY OF SOLUTIONS

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This review is based on the analysis of data on the structural and thermodynamic properties of tetra-N-alkyl-substituted bicyclic bis-urea of the octane series (glycolurils), singly and dissolved in H_2O and D_2O, obtained by other authors. The paper discusses issues of the influence of the stereochemical nature of these bioactive compounds on their hydration processes. The researched substances are the low-toxic glycolurils with pharmacologically pronounced psychotropic effects, known under the commercial names Mebicar (tetra-N-methylanalog), Bicaret (tetra-N-ethylanalog), and the cis- and trans-N-diethyl-dimethyl-analogs, Mebicaret and Albicar. The last listed glycoluril, which is chiral in stereochemical nature, was investigated as racemate. The study also included the analysis of the available results of calorimetric, densitometric, and spectroscopic (for Mebicar) studies of glycolurils solutions in H/D isotopologues of water as well as quantum-chemical calculations of molecular parameters of these heterocyclic compounds in the ideal gas phase. It has been shown that the hydration of each of the studied tetra-N-alkyl-substituted glycolurils can be generally regarded as a superposition of two mechanisms – hydrophobic and hydrophilic. In the case of Bicaret, the former is dominant, while for Mebicar the latter obviously predominates. Regarding to the structural state and solvation in aqueous medium of glycolurils with mixed N-alkyl-substitution such as Albicar and Mebicaret, the stereochemical nature of their molecules predetermines a kind of "thermodynamic balance (dualism)" between the mentioned mechanisms. The paper outlines the distinctive features of the hydration process of racemic Albicar against the effects of intermolecular interaction in aqueous solution of achiral Mebicaret.

Introduction

Alkylsubstituted urea derivatives are mostly bio- and physiologically active compounds, among which bicyclic *bis*-ureas of the octane series, trivially called *glycolurils*, are of special interest [1-6]. The structure of the "molecular framework" of glycoluril is illustrated in Fig. 1.

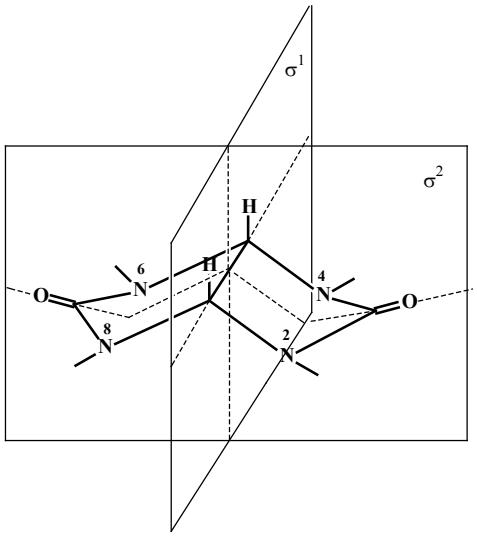


Fig. 1. Structure of glycoluril molecule with symmetry planes (σ^1 and σ^2) [2, 4]

Many representatives of this class of heterocyclic compounds possess rather wide spectrum of pharmacological effects and either are already effectively applied in medical practice, or serve as a basis for promising medicines. For example, over the past decades, the low-toxicity psychotropic drug *mebicar* (other names are *adaptole* and *mebix*), where the active substance is 2,4,6,8-tetramethylglycoluril, has been successfully used in medicine as a daytime tranquilizer, adaptogen, and antidepressant [3, 7-12]. A drug of chiral origin, *albicar* (2,6-diethyl-4,8-dimethylglycoluril, see Fig. 1), is being put into clinical trials. It has a broader spectrum of pharmacological effects in terms of treatment of neuropsychiatric disorders [13-17]. Additionally, the achiral equimolecular analogues of *albicar* with potential medical (antidepressant/anxiolytic) application – *N,N-mebicaret* and *N,N′-mebicaret* (2,4-diethyl-6,8-dimethyl- and 2,8-diethyl-4,6-dimethylglycoluril, respectively) were synthesized recently [1, 4-6, 18, 19]. *Bicaret* (2,4,6,8-tetraethylglycoluril), which possesses evident sedative activity, should be singled out among other tranquilizer drugs of this family of azaheterocycles [3-6, 20, 21].

The uniqueness of the nitrogen-containing compounds under consideration is because their relatively simple in structure bicyclic molecules possess extremely low toxicity and high speed of passage through lipid membranes *in vivo*. In particular, *mebicar* is ~150 times less toxic than known similar pharmacological agents – *diazepam* (*seduxen*) or *phenazepam* [3, 7, 11]. It is assumed [22] that the ability of these compounds to exhibit both hydrophilic and lipophilic properties is responsible for the bio- and physical availability of the considered alkylsubstituted glycolurils: they can easily penetrate cell membranes in the living organism and cross the *blood-brain* barrier, establishing a "relationship" between brain tissue cells (neural networks) and the capillaries of the circulatory system. Moreover, a high degree of bioavailability of this group of drugs is combined with the ease of their excretion from the living body [7, 14, 20]. However, the molecular mechanism of the pharmacological action of these compounds remains poorly understood.

To establish the nature of the physiological effect of the glycolurils considered, it is important to have information not only about the membrane permeability and the structure features of their molecules, but also about the structural and thermodynamic properties of these

compounds both in the crystalline and in the dissolved (solvated) state [4, 8-10, 12]. This information is necessary, first of all, to reveal *pharmacophoric activity* of functional (hydrophobic and proton-donor/acceptor) groups during the formation of "hydrate (solvate) complexes" involving the biomolecules in question. To describe pharmacophore in more detail [23, 24], the concepts of "excluded volume" as well as the allowed intervals of spatial orientation of hydrogen bonds are often introduced. Gathering information about these properties is also important in terms of creating models reflecting the state of a physiologically active compound in a living organism. This can be developed further by creating the physicochemical basis for QSPR (*Quantitative Structure-Property Relationships*) models that predict functional activity and allow screening of newly synthesized drugs with potential medical applications [4].

The results of studies conducted in this field of solution physicochemistry show that, along with conclusions from spectroscopic analysis [1, 6, 25], data on the standard thermodynamic characteristics of glycolurils dissolution in water and mixed solvents provide indispensable information on both intermolecular interactions in the formed binary (triple) system and on its structural features. These features are known to carry information only about *supramolecular* (i.e., structural-average) properties of the liquid-phase system [26-29], so the necessary information about the intermolecular interaction can be obtained indirectly using various approaches and approximations [27-30]. A number of problems were avoided when studying the thermodynamic properties of tetra-*N*-alkyl-substituted glycolurils in isotopic analogues of water (H_2O and D_2O). The $D_2O \rightarrow H_2O$-isotope effects (IEs) of the solvent, due to the quantum nature of their origin [30-36], carry valuable information on the nature of intermolecular specific interactions and hydrophobic effects, as well as on the structural transformations in the newly formed hydrate complex [4].

We wanted to summarize the results of our works and works of other authors during the last two decades. To do that, in this review, we have systematized the data from calorimetric, densitometric, spectroscopic, and some other studies on the solutions of tetra-*N*-alkyl-substituted glycoluril derivatives (*mebicar*, *albicar*, N,N-*mebicaret,* and *bicaret*) in plain and deuterated water. The approach based on the reasonable combination of precision experimental methods with the $H_2O \rightarrow D_2O$-isotopic substitution procedure allowed us to analyze in detail the manifestations and specific features of hydrophilic and hydrophobic hydration of the pharmacophore molecules of the considered group of substances and to draw conclusions about the state of the latter in the aqueous medium under insignificant solvent structure perturbation.

For the comprehensive analysis of the obtained standard volumetric and enthalpy characteristics of dissolution and solvation of the mentioned glycoluriles in H_2O and D_2O, we deemed necessary to involve available data on their physico-chemical and thermodynamic properties in individual (crystalline and gaseous) state. We would like to remind that according to IUPAC recommendations [26, 36], its state in a hypothetical ideal solution of unit concentration, in which molecules are in the same energy and structural state as in an infinitely diluted by component 2 solution, is taken as the *standard state* of the dissolved substance (2) in solution. The standard solvent state (1) in solution is the pure solvent state at pressure 0.1 MPa and "current" temperature. In other words, the standard state postulates the complete absence of concentration-dependent 2-2-interactions of the dissolved compound, which greatly facilitates

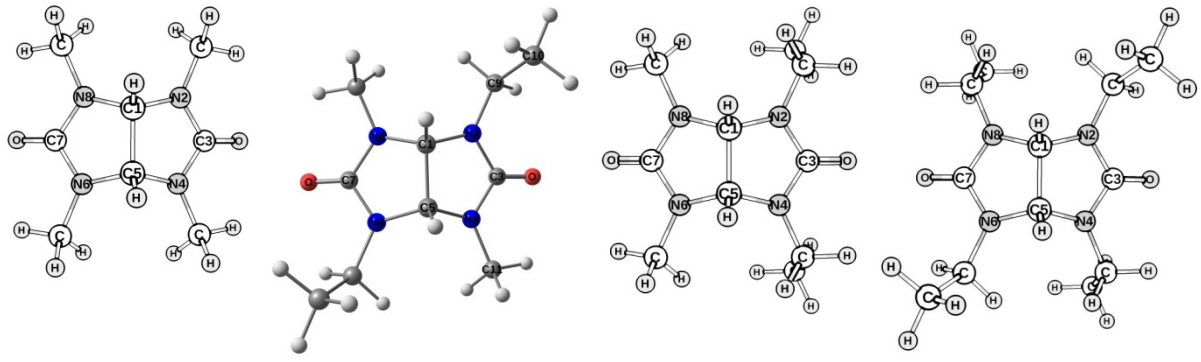
the interpretation of thermodynamic effects induced by 1-2-interactions in the resulting binary liquid-phase system.

COMPARATIVE CHARACTERIZATION OF TETRA-*N*-ALKYLSUBSTITUTED GLYCOLURIL DERIVATIVES AND H/D-ISOTOPE WATER ANALOGUES

Properties of tetraalkylated glycolurils in the individual state

As we noted above, the bicyclic alkyl derivatives of urea under consideration are mostly effective low-toxicity drugs for psychotropic (neurotropic) purposes. Thanks to the purposeful efforts of the staff of the Laboratory of Nitrogen-Containing Compounds at the N.D. Zelensky Institute of Organic Chemistry, RAS, the process of stereocontrolled synthesis of these glycolurils, based on cyclocondensation reaction involving glyoxal or 4,5-dihydroxy-2-imidazolidinone [37], is constantly being improved [2, 5, 17].

Stereochemical aspects of the tetra-*N*-alkylated glycoluril structure are that due to the rigidity of the heterocyclic framework and *cis*-membering of annelinated imidazolidine (five-membered) rings, their molecular structures in general have the shape of a *half-opened book* or "seagull wings" [1-6, 17, 38, 39] (see Fig. 1). Due to the presence of asymmetric "glyoxal" carbon atoms C(1) and C(5), many of these compounds are *chiral* and are in racemic form. Among the glycolurils considered here, only the *trans*-coordinated *albicar* has both properties (Fig. 2). However, due to the existing problems of isolation of *R*/*S*-enantiomerically pure crystals of this compound [2, 5, 13, 15], hereinafter we will discuss only the results of studies of structural and thermodynamic properties of racemic form of *albicar* in individual and dissolved (in H_2O and D_2O) states. In turn, glycoluriles are *achiral* if they have the symmetry plane σ^1 or σ^2, i.e. corresponding to *N*(2,4)-, *N*(2,8)- or *N*(2,4,6,8)-positions of the same alkyl substituents. This group of compounds includes *mebicar*, *bicaret*, and *N,N*(*N'*)-*cis*-isomers of *mebicaret* (see Fig. 1 and 2). Unfortunately, we have not yet been able to obtain reliable experimental data on the physicochemical and thermodynamic characteristics of *N,N'-mebicaret* (2,8-diethyl-4,6-dimethylglycoluril) both in the individual state and as a dissolved substance in aqueous media H_2O and D_2O. Therefore, hereinafter we will discuss only achiral *N,N*- or 2,4-diethyl-6,8-dimethyl-substituted glycoluril (for convenience we will call it *mebicaret* — see Fig. 2, *c*), the relevant properties of which are well studied.



a *b* *c* *d*

Fig. 2. Equilibrium structures of the investigated glycolurils according to quantum-chemical (DFT) calculations: *a – mebicar*, *b – albicar*, *c – mebicaret*, *d – bicaret*

Table. 1 contains compiled information on the properties of the compared glycolurils in the crystalline state. Note that there are different interpretations of the names of these compounds in the scientific literature. Thus, according to the IUPAC nomenclature classification, they form a family of tetra-*N*-alkyl-substituted tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dions [37]. At the same time, currently another (trivial) nomenclature is more widely used for naming the representatives of this class of organic compounds [1-5, 40]: alkylsubstituted in corresponding *N*-positions of 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dions (or glycolurils).

Table 1. Some physico-chemical and thermodynamic characteristics of the studied tetra-*N*-alkyl-substituted glycolurils [4]

Glycoluril	CAS [a]	M_2 [b]	$T_{melt.}$ [c]	$\Delta_{melt.}H_2^*$ [d]
Mebicar $C_8H_{14}N_4O_2$	10095-06-4	198.223	507.3	36.4
Albicar $C_{10}H_{18}N_4O_2$	71540-88-0	226.279	392.3	20.2
Mebicaret $C_{10}H_{18}N_4O_2$	71540-89-1	226.279	367.7	25.4
Bicaret $C_{12}H_{22}N_4O_2$	42563-65-5	254.332	388.2	27.4

[a] Chemical Abstracts Service registration number.

[b] Molar mass, g·mol^{-1}.

[c] Melting point, K.

[d] Standard enthalpy of melting, kJ·mol^{-1}.

Comparison of the values $T_{melt.}$ and $\Delta_{melt.}H_2^*$ measured by differential scanning calorimetry (using DSC 204 F1 Phoenix) (see Table 1) suggests that the significant increase in temperature and enthalpy of melting of *mebicar* is associated with a significant strengthening of the molecular crystal lattice of tetra-*N*-methylated glycoluril. Although there is a relative comparability of $T_{melt.}$ for *mebicaret*, *bicaret*, and chiral *albicar*, the latter has the lowest the melting heat, apparently, due to the stereochemical features of the structure of the racemic form of this compound. According to [13], due to the formation of H-bonds via methine groups of glyoxal bridge, *albicar* molecules are grouped into layers with hydrophobic "coating" from ethyl radicals that in many respects explains the fact of metastability of the formed racemic crystals.

The enthalpy of sublimation, which is more sensitive to the energy state of the crystal structure, $\Delta_{subl.}H_2^*$, has so far been obtained only for *mebicar* (108.6 ± 3) kJ·mol^{-1} at T = 298.15 K) by mass spectroscopic method with a Knudsen effusion cell [39]. The crystal structures of other compounds of the studied series showed quite low thermal stability, decomposing under heating or temperature hysteresis (metastability) in heating-cooling processes indicating the absence of thermodynamic equilibrium in the effusion cell due to the phase transformations in the system. In turn, crystallographic data were obtained only for *bicaret* and *albicar* [1, 13]. There are no similar results for *mebicar* in the literature due to the problems associated with the *biniality* (dichotomy) of its crystal in diffraction studies, but the common conclusions of the authors [1, 13, 38] indicate that the molecular structures of the glycolurils compared are conformationally similar. Each of the pentanuclear cycles of the molecule individually has an almost planar structure with a maximum deviation of atoms from the average cycle plane not exceeding 5·10^{-10} cm. This can also be seen in the small values of the corresponding dihedral angles of no more than 9.5°. However, due to the significant steric tension that exists between

adjacent cycles, the structure of the glycoluril molecule as a whole is far from planar [1, 4, 13, 38, 39, 42].

We have carried out (jointly with assoc. prof. Yu. A. Zhabanov from ISUCT, Ivanovo) the quantum-chemical calculations of the geometric parameters of molecules and electron spectra of the glycolurils of the considered series. They allowed us to detail the conformational features of their structure (see Fig. 1 and 2) due to the rigidity of the heterocyclic framework and the annelated *cis*-joining between adjacent nitrogen atoms. To do that, we have applied the high-level density functional theory (DFT) method with the basis sets B3LYP/cc-pVTZ and B3LYP/cc-pVQZ [39, 41, 42]. It was found that the difference in inter-nuclear distances of the compared molecules does not exceed $1 \cdot 10^{-10}$ cm, and the values of the valence angles diverge by no more than 2°. In other words, the introduction of C_2H_5 groups into the *N*-methyl-substituted positions of the heterocyclic backbone has no significant influence on the geometrical structure of the studied molecules (see Fig. 1 and 2). This is indicated by the similarity of electronic absorption spectra for tetra-*N*-alkyl-substituted glycolurils with maximum wavelength in the UV region around 180 nm (Fig. 3).

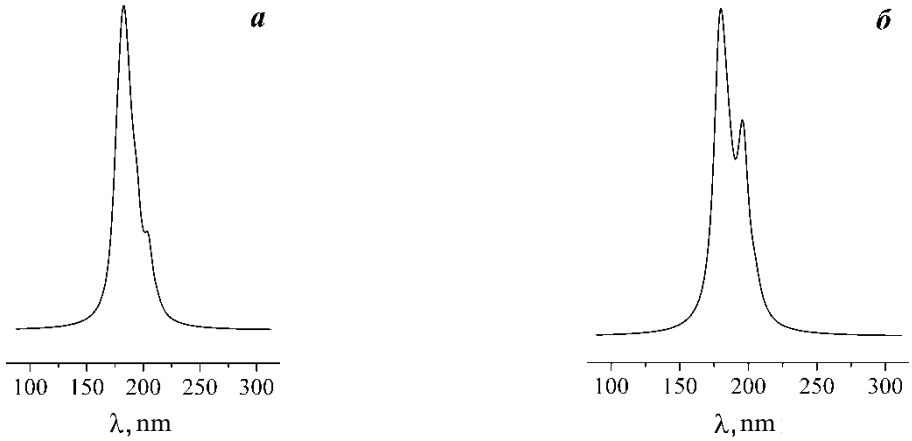


Fig. 3. Calculated (within DFT) electronic spectra of *mebicaret* (*a*) and *bicaret* (*b*)

At the same time, the branching of the peripheral hydrocarbon *N*-substituents in the transition from *mebicar* to *bicaret* complicates the stereochemical nature of the molecule because of several additional conformational states which differ in the position of ethyl radicals relative to the plane of the heterocyclic structure. Conformers of this kind differ not only in the energy state, but also in the type of structural symmetry. For example, the *mebicar* molecule in equilibrium has the C_2 symmetry structure, and the structure of *N,N-mebicaret* conformer with minimal energy in the equilibrium state belongs to the C_s symmetry point group. In turn, the basic *N,N′-mebicaret* conformers possess a C_1 symmetry structure. From the calculated six energy states of *bicaret* molecule, the minimal energy level appeared to be possessed by a conformer with such an arrangement of ethyl groups, which provides the greatest distance from each other of the corresponding CH_3-groups. The structure of the indicated conformer (with non-planar cycles) belongs to the point group of symmetry C_1.

As mentioned above, the conformation of the bicyclic backbone in all studied cases has a structure resembling the shape of seagull wings or a half-opened book (see Fig. 1), with an average labile "opening angle" between the planes of two cyclic fragments ~119° [1, 38]. In *bicaret*, *albicar*, or *mebicaret* crystals, the terminal CH_3-groups of ethyl radicals are located under the

wings of the "folded" structure of the molecule in the *gosh*-position with respect to the C-N-bonds that connect both cycles with the C-C-junction (glyoxal bridge, see Fig. 1). It should be noted that C-H···O contacts play an important role in the redistribution of electron density in glycoluril molecule at its full *N*-alkylation, associated with the increase of "peripheral" hydrocarbon chain [13]. Thus, the transition from *mebicar* to *bicaret* can lead not only to a change in the donor/acceptor capacity of carbonyl oxygen and methine ("bridging") protons but also to the *elimination* of "activity" of said protons due to the screening of pharmacophore centers because of increasing steric obstacles to the formation of hydrogen bonds. Consideration of such factors is a necessary condition for justification of thermodynamic effects of dissolution and solvation of the considered glycoluril derivatives in H/D-isotopologues of water [4].

Structural and isotopic differences between ordinary and heavy (deuterated) water

According to IUPAC terminology [43], isomeric compounds whose molecules differ only in isotopic composition should be referred to as *isotopologues*. The latter include the H/D-isotopologues of water, H_2O and D_2O, which allows us to use these names further when discussing the thermodynamic and structural effects of dissolution and hydration of glycolurils.

Based on numerous previous studies (compiled, for example, in [4, 30-36, 44-46]), we can state that the liquid phase of heavy water (D_2O) is inherently more structured than the H_2O medium. The greater structuredness of D_2O is combined with a higher rate of change of its structural state under the influence of changing temperature and concentration of the dissolved substance. This can be explained by the fact that the local structural formations of H/D-isotopologues of water are highly mobile near-ordered systems with slightly different intermolecular hydrogen bonding energies. If the value of the latter in an environment of ordinary water: is on average ~15.5 kJ·mol^{-1} [34, 44, 47], then in absolutely deuterosubstituted water the D-bonding energy increases by ~1 kJ·mol^{-1} [4, 30, 31, 34-36]. Therefore, the same effects on the H/D isotopologues of water cause approximately the same effect, but since the relative number of hydrogen bonds and their strength are greater in the case of D_2O, the overall structural change is greater in the heavy water environment.

One of the main reasons for the H/D-isotopic difference in the hydrogen bonding energy of water is the quantum effect, which is the difference in the amplitudes of the anharmonic zero oscillations of H_2O and D_2O molecules [31-34, 45, 46]. This circumstance also causes a change in the inter-nuclear distances in the water molecule and, as a consequence, its van der Waals volume $v_{\mathrm{vdv},2}$. Thus, O–H → O–D substitution induces a ~3% bond reduction [35], while the values $v_{\mathrm{vdv},2}$ reduce for 0.07 nm^3 [34, 36]. In turn, this leads to a change in the donor-acceptor properties of the water molecule, i.e., its ability to form hydrogen bonds with neighboring molecules. According to the conclusions [34, 48], the consequence of the electron density redistribution in the molecular quantum-chemical complexes of water at the substitution of H_2O for D_2O is the strengthening of the electron-accepting ability of aqueous medium during a general weakening of its electron-donating properties. This circumstance, along with a decrease in the frequencies of hindered libration (torsion vibrations) by ~2.4 kJ·mol^{-1} [49] and the valence deformation vibrations of the intramolecular O–H bond at the proton replacement by a deuteron, predetermines an increase in the dissociation energy of hydrogen bonds in heavy water [4, 31-34].

Note that the approaches available in the literature for the analysis of differences in the structural properties of H/D-isotopologues of water contain many conditions. However, in the study of the inherently relative thermodynamic characteristics of dissolution with the corresponding IEs, the change in the supramolecular (or macro-) structure of the liquid, which does not require any particular model, is paramount.

RESULTS OF EXPERIMENTAL STUDY OF PROPERTIES OF GLYCOLURILS AS DISSOLVED SUBSTANCES IN WATER ISOTOPOLOGUES

Analysis of spectroscopic data on mebicarsolutions

The results of ^{13}C-NMR spectroscopic study of *mebicar* solutions in water isotopologues [4] are important for the investigation of hydration specifics of tetra-*N*-alkyl-substituted glycolurils.

Analysis of the evolutions temperature dependences of the chemical shifts δ of the carbon atoms (^{13}C) of *mebicar* in H_2O and D_2O presented in Fig. 4 show that the main contribution to the formation of heterocomponent hydrogen bonds in solution is made by carbonyl (>C=O) groups. At the same time, the way the dependences change in Fig. 4 suggests that H(D)-bonds can form with the aqueous environment by bridging C–H-groups of the *mebicar* molecule. The latter is especially important for such a different (from the more "branched" tetra-*N*-alkylated glycolurils) nature of *mebicar* hydration. Moreover, the temperature dependences illustrated in Fig. 4 of the relative IEs in $\delta(^{13}C)$ induced by different molecular fragments of *mebicar* lead to a number of other important conclusions.

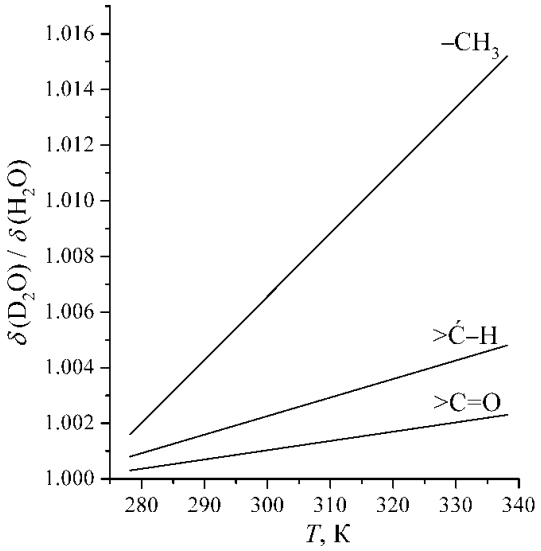


Fig. 4. Temperature dependences of relative IEs in chemosweeps $\delta(^{13}C)$ for a *mebicar* molecule in an aqueous solution with a molar concentration $m \approx 4$ mol·(kg water)$^{-1}$

Firstly, the most significant transformations of the solvent structure (H_2O or D_2O) with increasing temperature happen in the area of hydration of the methyl group of the *mebicar* molecule. This indicates the dominant role of the hydrophobic component in the hydration process of this group. On the other hand, this fact confirms the conclusions [50] that in D_2O medium, the effects of hydrophobic hydration of non-polar molecules (fragments) are more pronounced than in ordinary water. Secondly, the contribution from specific >Ċ-H···O interactions to the structural effects of the solvent around the glyoxal bridge of the *mebicar* molecule appears to be more significant compared to the contribution from the hydrophobic hydration of this grouping. Thirdly, the effects of the formation of heterocomponent hydrogen bonds (hydrophilic hydration) apparently make the main contribution to the changes in enthalpy and volume characteristics of the *mebicar* dissolution process in H_2O and D_2O with the formation of the corresponding hydrate complexes.

Based on the results of millimeter absorption (MMA-) spectroscopy [25], the carbonyl group of the *mebicar* molecule is capable of forming up to four bonds with H_2O (D_2O) molecules in accordance with the "polar positive hydration" mechanism. At the same time, as we have already noted above, the character of changes in the data presented in Fig. 4 dependence suggests that H(D)-bonds can form with the aqueous environment by bridging C–H-groups of the *mebicar* molecule. However, according to the authors [25], this structuring effect is due to "hydrophobic immobilization" of two to three water molecules in the space around two methyl and four methyl groups (see Fig. 2, *a*). Moreover, at least two more water molecules in the hydrate shell are retained with rotational mobility, similar to the case of the so-called "negative hydration" of urea [51].

As the volume (branching) of alkyl *N*-substituents increases, the hydrophobic properties of the glycoluril molecule increase with the transition from *mebicar* to *mebicaret* (*albicar*) and further to *bicaret*. At the same time, steric hindrances for its specific (through hydrogen bonds) interactions with the surrounding aqueous medium also increase. Together, this leads both to the elimination of the ability of methyl groups of *bicaret* molecule to form heterocomponent hydrogen bonds with water isotope molecules and to the disappearance of the structural basis for the effect of negative hydration of tetra-*N*-alkylated glycoluril.

Enthalpy and heat capacity characteristics of dissolution and hydration

Table 2 combines data on standard (which is infinite dilution) molar enthalpy characteristics of the dissolution process ($\Delta_p H_2^\circ$) of the considered tetra-*N*-alkyl-substituted glycoluril derivatives in H_2O and D_2O media [4, 18, 52-55]. The values $\Delta_d H_2^\circ$ were obtained by averaging the integral enthalpic dissolution effects $\Delta_d H_2^m$, measured in the range T = (278–318 K) using a high-precision isoperibolic (variable temperature with isothermal shell) calorimeter [56].

Table 2. Standard enthalpic dissolution characteristics, $\Delta_d H_2^\circ$ /(kJ·mol^{-1}), of tetra-*N*-alkyl-substituted glycolurils in plain and heavy water at different temperatures and p = 0.1 MPa

T, K	*Mebicar*[a]		*Albicar*		*Mebicaret*		*Bicaret*	
	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O
278.15	–	–	−7.80 ± 0.05	−8.37 ± 0.07	−6.95 ± 0.07	−7.35 ± 0.05	−15.66 ± 0.06	−16.67 ± 0.08
279.15	–	–	−7.49 ± 0.06	−8.06 ± 0.05	−6.67 ± 0.05	−7.03 ± 0.07	–	–
288.15	1.96 ± 0.13	2.37 ± 0.03	−4.98 ± 0.05	−5.46 ± 0.06	−4.17 ± 0.04	−4.52 ± 0.07	−11.20 ± 0.10	−12.13 ± 0.05
298.15	3.67 ± 0.01	3.87 ± 0.01	−2.15 ± 0.04	−2.53 ± 0.04	−1.47 ± 0.06	−1.76 ± 0.04	−6.83 ± 0.10	−7.68 ± 0.07
308.15	–	–	0.63 ± 0.07	0.38 ± 0.08	1.41 ± 0.06	1.17 ± 0.06	−2.33 ± 0.04	−3.08 ± 0.10
313.15	–	–	2.15 ± 0.06	1.92 ± 0.06	2.80 ± 0.07	2.64 ± 0.04	–	–
318.15	7.03 ± 0.03	7.00 ± 0.06	–	–	–	–	1.97 ± 0.09	1.33 ± 0.08

[a] Data for the protonated system from [53] (in kJ·mol^{-1}): 1.96 ± 0,07 (288.15 K); 3.58 ± 0.04 (298.15 K) and 7.03 ± 0.07 (318.15 K).

Table 2 shows that the currently available information on the values $\Delta_d H_2^\circ(T)$ for H/D-isotope-differentiated aqueous glycoluril-containing systems can be directly compared only at two temperatures (288.15 and 298.15 K). With this in mind, Fig. 5 illustrates the temperature-dependent trends of solvent IE in $\Delta_d H_2^\circ(T)$. Moreover, the size of the geometrical symbols in the figure generally corresponds to the measurement error of $\delta\Delta_d H_2^\circ(H_2O \rightarrow D_2O)$.

As can be seen from the data in Table 2, the dissolution of *mebicar* in H/D-isotopologies of water is accompanied by a heat absorption that increases with increasing temperature. Extrapolation of $\Delta_d H_2^\circ$ to $T = 278.15$ K shows that the enthalpic effect of *mebicar* dissolution in H_2O comes close to zero. In this case, the positive IE in $\Delta_d H_2^\circ$ increases to ~ 0.6 kJ·mol^{-1} (see Fig. 5). However, when T = 318.15 K is reached, the value $\delta\Delta_d H_2^\circ$ ($H_2O \rightarrow D_2O$) for tetra-*N*-methylated glycoluril becomes zero. The transition to *N*-dimethyl-diethyl analogues (*albicar*, *mebicaret*) and from the latter to *bicaret* is accompanied by a sequential increase in the exothermicity of the dissolution process in H_2O and D_2O, essentially by the same value: ~ 8 kJ·mol^{-1} at T = 278.15 K and ~ 5.5 kJ·mol^{-1} at T = 298.15 K (see Table 2).

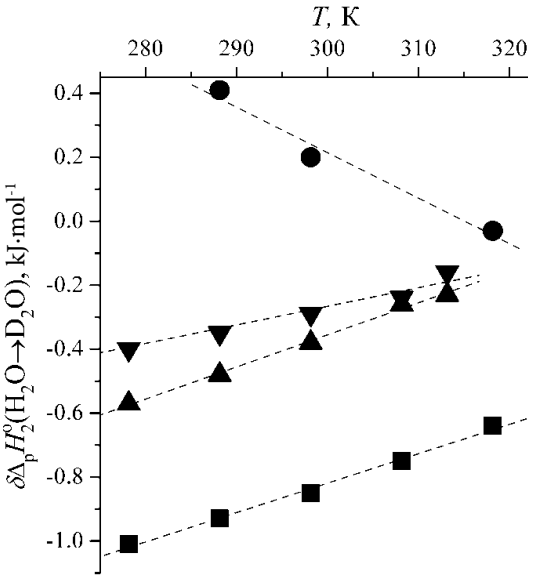


Fig. 5. Temperature dependences of H/D-isotope effects of solvent in the standard molar enthalpy of dissolution of *mebicar* (●), *mebicaret* (▼), *albicar* (▲) and *bicaret* (▪) in aqueous medium

At the same time, the most interesting fact is the inversion of the sign $\Delta_d H_2^\circ$ from negative to positive for ethyl-containing glycolurils in each of the water isotopologues (see Table 2). The temperature $T_{inv.,2}$ at which this inversion is observed is close, on average, to 304 K for *mebicaret*, to 307 K for *albicaret*, and to 315 K for *bicaret*. If we represent $\Delta_d H_2^\circ$ as the difference between the enthalpy of solvation of the dissolved substance $\Delta_s H_2^\circ$ and its condensation in its own (crystalline) medium, $\Delta_{cond.} H_2^* = -\Delta_{subl.} H_2^*$ [4, 27], we can conclude that at temperatures higher than $T_{inv.,2}$, the dehydration process of glycoluril molecules becomes dominant due to the shift in the balance of intermolecular interactions. Obviously, as in the case of *mebicar*, the total energy expenditure for the destruction of the crystal lattice of the dissolved glycoluril and the formation of a solvate cavity in the solvent are no longer fully offset by the effects of stabilization of the structure of the latter due to the formation of heterocomponent hydrogen bonds and hydrophobic hydration. The deuterosubstitution in water molecules has very little effect on the indicated redistribution of contributions in $\Delta_d H_2^\circ(T)$ (see Table 2). However, given the independence of the enthalpy-isotope effect as a transfer function from 2–2-interactions, analysis of $\delta\Delta_d H_2^\circ$ ($H_2O \rightarrow D_2O$) in Fig. 5 is a more reasonable step in terms of obtaining additional information on the hydration features of the heterocyclic compounds discussed here.

Fig. 5 shows that temperature has a differentiating effect on the direction of changes of $\delta\Delta_d H_2^\circ$ when comparing *mebicar* with its ethyl-containing analogues. On the one hand, the demonstrated distribution of enthalpy-isotopic effects is in agreement with the generally accepted conclusion [4, 54, 57, 58] that both positive and negative values of thermodynamic

quantities should increase in absolute terms during transfer from H_2O from D_2O. On the other hand, the difference in the signs of the derivative of $(\partial(\delta\Delta_d H_2^\circ)/\partial T)_d$ or IE in the dissolution heat capacity, $\delta\Delta_p C_{p,2}^\circ$($H_2O$→$D_2O$), indicates an obvious difference in the hydration mechanisms of *mebicar* and *bicaret*. In the case of *mebicaret* and *albicar*, a conclusion can be drawn about the presence of a certain "structural dualism" in the influence of their molecules on the hydrate environment.

Table 3. Thermal capacity characteristics of the dissolution process, $\Delta_d C_{d,2}^\circ$/ (J·mol^{-1}·K^{-1}) of the studied glycolurils in normal and heavy water with the corresponding solvent isotope effects at T = 298.15 K and p = 0.1 MPa [4, 18, 52, 54, 55]

Compound	$\Delta_d C_{d,2}^\circ$		$\delta\Delta_d C_{d,2}^\circ$
	H_2O	D_2O	H_2O→D_2O
Mebicar	169 ± 9 [a]	155±11	–14 ± 14
Albicar	282.7±3.4	292.9±2.6	10.2 ± 4.3
Mebicaret	278.3±3.5	284.1±4.6	10.2 ± 5.8
Bicaret	441.3±5.2	450.5±4.7	9.2 ± 7.0

[a] Data from [53]: (167 ± 18) J·mol^{-1}·K^{-1}

As can be seen from data from Table 3, the heat capacity component of the dissolution process $\Delta_d C_{d,2}^\circ = (\partial(\Delta_d H_2^\circ)/\partial T)_d$ increases by almost 100% when transitioning from *mebicar* to *albicar* and *mebicaret* and almost 200% when replacing *mebicar* with *bicaret*, which indicates the molecules hydrophobic properties strengthening in the indicated directions. At the same time, the value $\delta\Delta_{d(c)} C_{d,2}^\circ$ (H_2O→D_2O) for *mebicar* is, within the margin of error, the same as that for typically hydrophilic urea ($\Delta_d C_{d,2}^\circ$ ≈ -10.4 J·mol^{-1}·K^{-1} [59]), which is a strong argument for the above assumption that the tetra-*N*-methylated glycoluril is predominantly hydrophilic. On the contrary, the IE in the heat capacity of hydration of other (ethyl-containing) heterocycles is positive, but numerically indistinguishable due to a sufficiently high error of their calculation (see Table 3). Let us also note that larger positive values of $\Delta_d C_{d,2}^\circ$ in absolute value (see Table 3) indicate the presence of not only hydrophobicity, but also a general strong interaction of dissolved glycoluril molecules with water isotopologue, including the effects of H(D)-bond formation. An example of this is the heat capacity effects of dissolution of saccharides in water [60].

At the same time, while large (in absolute value) $\delta\Delta_d H_2^\circ$ (H_2O→ D_2O) and $\Delta_d C_{d,2}^\circ$ for *bicaret* (see Fig. 5 and Table 3) are associated with the predominantly hydrophobic nature of its molecules, there is a much more structurally complex situation in the case of hydration of *mebicaret* and its chiral in nature *trans*-analog *albicar* (see Fig. 2, *b, c*). The molecules of the mentioned glycolurils can be represented as a kind of "intermediates" of *mebicar* and *bicaret* molecules. However, unlike the latter, they have a more balanced "set" of pharmacophores (hydrophilic and hydrophobic) centers.

The thermodynamic dissolution characteristics of these mixed-alkylated heterocyclic compounds have generally comparable values. Small (up to (0.2 ± 0.1) kJ-mol^{-1}) differences are found only in $\delta\Delta_d H_2^\circ$ (H_2O→D_2O) at low temperatures (see Fig. 5). This leads us to note the absence of a noticeable influence of the stereochemical nature (i.e., mutual arrangement of *N*-substituted positions) of dimethyldiethylglycoluril molecule on the character of interaction of this compound with water isotopologue. It is possible that in thesterical transition from

mebicar to *albicar* or *mebicaret*, there is still an opportunity for specific interaction of the solute molecule with H_2O or D_2O molecules through bridging (methine) hydrogen atoms. And this possibility, judging by the available insignificant differences of IE in $\delta\Delta_{p(c)}H_2^{\circ}$, is connected with specifics of coordination of *N*-substituted positions in the glycoluril molecule.

Table 4. Enthalpy homotactic factors of 2-2-interactions, h_{22}/ (J·kg·mol^{-2}), between tetra-*N*-alkylated glycoluril molecules in H/D isotopologues of water and corresponding solvent isotopic effects, δh_{22} ($H_2O \rightarrow D_2O$), at T = 298.15 K [18, 54, 63, 64]

Compound	h_{22} (H_2O)	h_{22} (D_2O)	δh_{22}($H_2O \rightarrow D_2O$)
Mebicar[a]	–2042 ± 68	2663 ± 122	–621 ± 140
Albicar	–627 ± 15	–804 ± 34	–177 ± 37
Mebicaret	–358 ± 23	–436 ± 39	–78 ± 45
Bicaret	1389 ± 102	1804 ± 164	415 ± 193

[a] Data from [61,62] (J·kg·mol^{-2}): (-1870 ± 270) in H_2O and (-2660 ± 300) in D_2O.

Given the fact that there is a thermodynamically valid relationship between the enthalpic characteristics of 1-2- and 2-2-interactions [18, 28, 60, 63], additional information on the state of *albicar* and *mebicaret* molecules in H/D-isotope-different aqueous media was extracted from the analysis of the Table 4 parameters of pairwise interactions h_{22}. The latter were obtained by measuring the enthalpies of dilution solutions of tetra-*N*-alkylated glycoluriles, $\Delta_{dil.}H_2^m$, in normal and heavy water at 298.15 K followed by processing (decomposition) of $\Delta_{dil.}H_2^m$ within known approximations [9, 28, 63-66].

Table 4 shows that the values of h_{22} with the corresponding IE of the solvent quite clearly reflect the stereospecificity of the hydration of the compared glycolurils. Aqueous solutions of *mebicaret* and *albicar* correspond to negative values of h_{22}. In the transition from the first of these compounds to the second, there is an almost 100% increase in the numerical values of h_{22} and δh_{22} ($H_2O \rightarrow D_2O$). The negative sign of h_{22} formally indicates that displacement of H_2O or D_2O molecules from more densely packed hydrate *co*-sphere into the environment (*in bulk*) leads in general to the growth of H(D)-bonding degree of these molecules [4,60]. If we postulate the invariability of the hydrophobic component of h_{22}, then the fact of the increase in the negative value of this parameter should most likely be attributed to the greater availability of proton-donor/acceptor centers of *albicar* to specific 2–2-interactions with the formation of solvate-divided pairs. Proton substitution by deuterons in water molecules causes a more prominent association between *albicar* molecules compared to *mebicaret*, indicating an increasing role of H(D)-bonding in the hydration of the chiral (*trans*-)isomer.

Considering a noticeable increase of negative values of h_{22} for *mebicar* in H_2O and D_2O (see Table 4), as well as patterns of changes in thermodynamic characteristics for these systems in Table 3 and Fig. 5, it can be argued that in this case the predominance of the hydrophilic "mechanism" of glycoluril hydration is obvious. On the other hand, the positive h_{22} for *bicaret* in H/D water isotopologues are in agreement with the conclusion we made above about the predominantly hydrophobic nature of the molecules of this compound. This means that the overlapping of molecular hydrate *co*-spheres leads to a marked enhancement of clathrate formation (strengthening of the aqueous environment structure with an increase in its openwork) near alkyl groups, which contributes to the separation of molecules [60-63]. This assumption is

confirmed by the growth of h_{22} during the formation of bicaret solution in heavy water (see Table 4).

As for the structural state in aqueous medium of heterocycles with mixed N-alkyl substitution – albicar and mebicaret, the stereochemical nature of their molecules predetermines a kind of balance between the above mechanisms or structural-thermodynamic dualism in the hydration process. Fig. 6 correlations prove the existence of thermodynamically reasonable relationship between the values $\Delta_d H_2^\circ$ (see Table 2) and h_{22} (see Table 4). Moreover, the analysis of functions $\Delta_d H_2^\circ - h_{22}$ suggests that the "realization" of such a relationship in the case of glycolurils dissolved in H_2O and D_2O depends largely on the presence or absence of optical isomerism in their bicyclic molecules. Obviously, the characteristics of racemic *albicar* do not correspond to those illustrated in Fig. 6 correlation dependences for its achiral analogues.

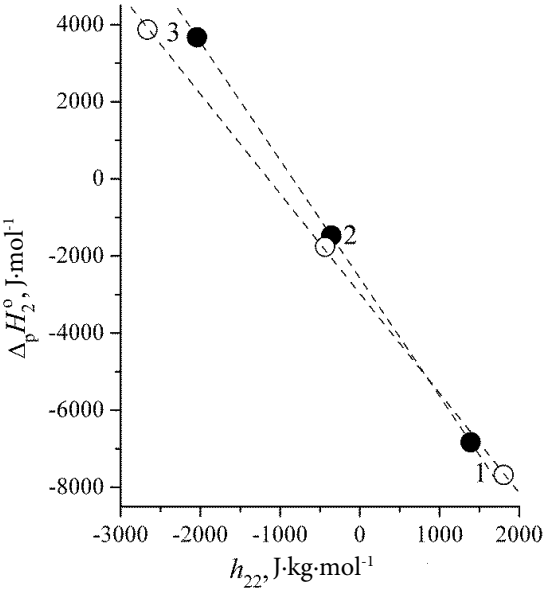


Fig. 6. Correlation relationships between standard molar enthalpies of dissolution and homotactic enthalpy coefficients of paired 2–2-interactions for compared achiral glycolurils in plain water (●) and heavy water (○) at 298.15 K [18]: *bicaret* (1), *mebicaret* (2), and *mebicar* (3)

As can be seen from Fig. 6, each of the correlation relationships between the parameters $\Delta_d H_2^\circ$ and h_{22} at T = 298.15 K is an almost linear function that can be expressed analytically by the results of its approximation (using the least squares method) by a first order equation:

$$\Delta_d H_2^\circ (H_2O) = -(2.58 \pm 0.09)\cdot 10^3 - (3.06 \pm 0.06) h_{22},\ R \approx 1.0;\ \sigma_{0,95} = 11{,}1\ \text{J·mol}^{-1}, \quad (1)$$

$$\Delta_d H_2^\circ (D_2O) = -(2.97 \pm 0.80)\cdot 10^3 - (2.59 \pm 0.43) h_{22},\ R \approx 0.9998;\ \sigma_{0,95} = 105\ \text{J·mol}^{-1}. \quad (2)$$

The data described by relations (1) and (2) in Fig. 6 prove that the effects of hydrophobic hydration and formation of hydrogen bonds are more pronounced in deuterated aqueous medium. At the same time, the solvation behavior of *bicaret* confirms the conclusion about the predominantly hydrophobic nature of its molecules. At the same time, the inclusion of *mebicar* molecules in the structural matrix of normal or heavy (D_2O) water leads to a radically different effect peculiar to the process of hydration of predominantly hydrophilic molecules. Fig. 6 clearly shows the mentioned "duality" of the solvation nature of the *mebicaret*, expressed through the correlated thermodynamic characteristics.

Standard volumetric ("packing") characteristics of the studied glycolurils in H/D isotopologues of water

Table 5 contains the results of calculations of the standard partial molar volumes, V_2°, glycolurils of the studied series (see Fig. 2, *a-d*) in H_2O and D_2O environments [19, 67-69]. The values V_2° were obtained by extrapolating the concentration dependences of the apparent molar volume, $V_{f,2}$, of dissolved glycoluril to the state of its infinitely diluted solution. In turn, the

calculation procedure V_2° and $V_{f,2}$ [67-71] were based on solution density data, which were obtained with an error 0.01-0.03 kg-m^{-3} by measurements on an Anton Paar DMA 5000 M precision densimeter (with a vibrating U-tube) [71, 72].

Table 5. Standard (partial at infinite dilution) molar volumes, V_2°/(m^3·mol^{-1}), tetra-*N*-alkyl-substituted glycolurils in normal and heavy water at different temperatures and p = 0.1 MPa

T, K	*Mebicar*		*Albicar*		*Mebicaret*		*Bicaret*	
	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O
278.15	–	–	188.34 ± 0.02	186.93 ± 0.03	188.43 ± 0.02	186.83 ± 0.02	220.58 ± 0.01	219.78 ± 0.01
288.15	157.02 ± 0.10	156.28 ± 0.06	189.85 ± 0.02	189.00 ± 0.02	190.11 ± 0.02	189.00 ± 0.02	222.54 ± 0.01	222.06 ± 0.01
298.15	158.87 ± 0.13	158.40 ± 0.07	191.29 ± 0.03	190.89 ± 0.04	191.72 ± 0.02	190.96 ± 0.02	224.47 ± 0.01	224.14 ± 0.01
308.15	160.29 ± 0.10	160.09 ± 0.08	192.81 ± 0.03	192.78 ± 0.04	193.25 ± 0.02	192.85 ± 0.01	226.34 ± 0.01	226.14 ± 0.01
318.15	161.34 ± 0.04	161.31 ± 0.08	194.34 ± 0.01	194.56 ± 0.03	194.80 ± 0.01	194.68 ± 0.01	228.17 ± 0.01	228.10 ± 0.01

Analysis of the data in Table 5 and Fig. 7 shows that in all cases considered here, the deuterosubstitution in the solvent molecules (water) leads to a decrease in V_2°, especially noticeable at low temperatures. That is, as the temperature decreases around the molecules of each of the tetra-*N*-alkyl-substituted glycolurils in heavy water, an increasingly denser hydrate shell is formed than in "normal" water. This is not unusual given the fact that the negative volume contributions to V_2° hydrophobic and heterocomponent hydrogen bond formation effects in solution increase (in absolute value) at $H_2O \rightarrow D_2O$ substitution [19, 59, 67-69]. Obviously, the differences in the intermolecular interaction that determine the sign and magnitude of the IE in V_2° (Fig. 7) become most noticeable in the region of temperatures corresponding to the highest structurization of H/D-isotopes of water, i.e., between the temperatures at which the molar volumes of H_2O and D_2O take minimum values ($V_{min.,1}$): ~ 277 K and ~ 284 K, respectively [31, 34, 44].

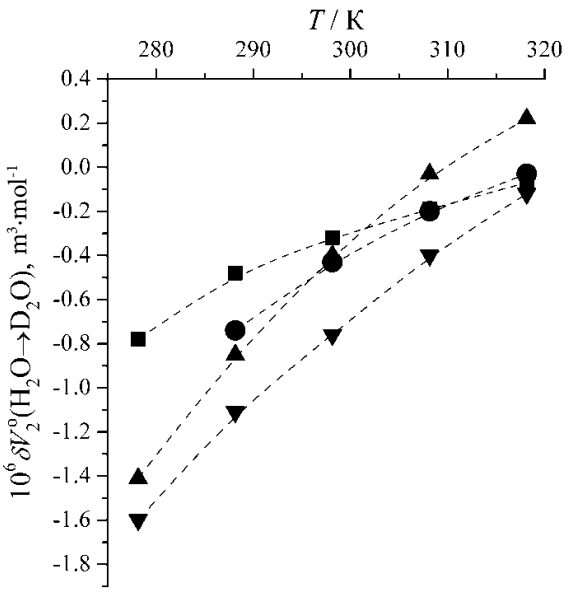


Fig. 7. Temperature dependences of H/D-isotopic solvent effects in standard molar volume for tetra-*N*-alkylated glycoluriles in aqueous medium: *mebicar* (●), *mebicaret* (▼), *albicar* (▲), and *bicaret* (▪)

The values of all studied glycolurils increase with increasing temperature V_2°, which is associated with the weakening of hydration and loosening of hydrate shells due to thermal expansion of the standard solution. Since the medium of heavy water is more structured compared to that of normal water [4, 31-34, 44, 48], there is a regular thermoactivated decrease in the solvent IE in V_2° (see Fig. 7). At T = 318.15 K the IE in V_2° becomes nearly zero regardless of the stereochemical nature of the achiral tetra-*N*-alkylated glycoluril, and in the case of the chiral *albicar* at the same temperature, the structure of the deuterated hydrate complex becomes even

more loose, as compared to the protonated analogue. Meanwhile, the results shown in Fig. 7 do not give a complete picture of the nature of the packing of the aqueous environment of the solvated glycoluril molecule.

In part, this kind of information can be extracted from the analysis of the relative *packing density* of the formed hydrate complex [34,73]: $d = V_2^\circ / V_{\text{vdv},2}$ where $V_{\text{vdv},2} = v_{\text{vdv},2} N_\text{A}$ is the volume which formally occupies one mole of van der Waals molecules with volume $v_{\text{vdv},2}$ (N_A – Avogadro number). d basically represents the fraction V_2°, occupied by the internal volume of the dissolved substance [73], which here is $V_{\text{vdv},2}$. The values $V_{\text{vdv},2}$ were calculated based on the approach [74] (using *Cambridge Structural Database*) as the sum of the volumes of atomic increments depending on the structural features of the environment of each C, O, N, and H atom in an alicyclic organic molecule. The values $V_{\text{vdv},2}$ thus estimated for *mebicar*, *mebicaret* /*albicar*, and *bicaret* were 101.3·10^{-6}, 120.2·10^{-6}, and 139.1·10^{-6} m^3·mol^{-1}, respectively.

Fig. 8 shows data on the d parameter in isotope-differentiated glycoluril-containing aqueous systems, from which it is seen that the transition from *mebicar* to *mebicaret* or *albicar* and further to *bicaret* is accompanied by a significant loosening of the hydrate shell of the molecule. This confirms the conclusions about the increasing effect of hydrophobic hydration in the indicated direction drawn from the analysis of the calorimetric results of the standard solutions discussed here in H/D-isotopes of water. The share of free (or so-called *excluded* [73]) space in the structural packing of the formed hydrate complex when replacing H_2O with D_2O in the solvent molecules is markedly reduced only in the region of temperatures below T = 298 K. There are clear "packing" differences in stereochemical nature of glycolurils with mixed type of alkyl substitution in the same area. Another fact to note is the formation of significantly more densely packed local structures involving *mebicar* molecules in the environment of H(D)-isotopologue of water, emphasizing the predominantly hydrophilic nature of the hydration of this glycoluril.

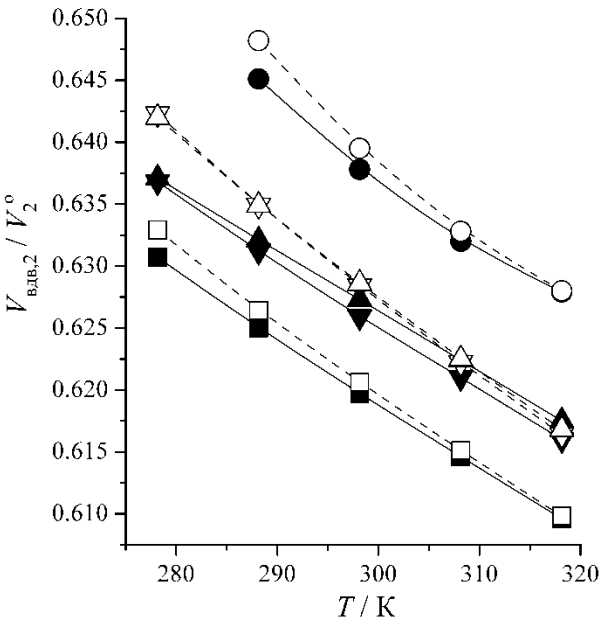


Fig. 8. Temperature dependences of the relative packing density of solvated tetra-*N*-alkylglycoluril molecules in H_2O (solid symbols) and D_2O (hollow symbols): *mebicar* (○,●), *mebicaret* (∇,▼), *albicar* (Δ,▲) and *bicaret* (□,▪). (Values $V_{\text{vdv},2}$ are postulated to be constant over the selected temperature range)

Similar conclusions follow from the analysis of standard molar (isobaric) expansibilities of tetra-*N*-alkyl-substituted glycolurils, $E_{\text{d},2}^\circ = (\partial V_2^\circ / \partial T)_\text{d}$, in normal and heavy water (Fig. 9). The values $E_{p,2}^\circ$ were obtained by approximating the temperature dependences V_2° in H_2O and D_2O by a second-degree equation using the least squares method (LSM) followed by differentiation by $(T - \theta)$, where θ = 298.15 K is the comparison temperature [67-69, 71].

Fig. 9 shows that increasing the temperature in general has a rather weak effect on the structural packing of each of the hydrate complexes with ethyl-containing glycolurils. The fact

of a sharp weakening of the "thermal sensitivity" of the latter, as compared with local structural formations in aqueous solutions of *mebicar*, is most likely associated with the greater hydrophobicity of the *mebicaret*/*albicar* and *bicaret* molecules and the lower availability of their donor and acceptor pharmacophore centers for specific (through the formation of H or D bonds) interaction with water isotopologue molecules. When analyzing the data presented in Fig. 9, one can note the differentiating influence of temperature on the direction of changes in $E^{\circ}_{p,2}$ in *albicar* solution in H_2O and D_2O, which proves that there are distinctive features of hydration of this isomer of *mebicaret*, which is chiral in stereochemical nature.

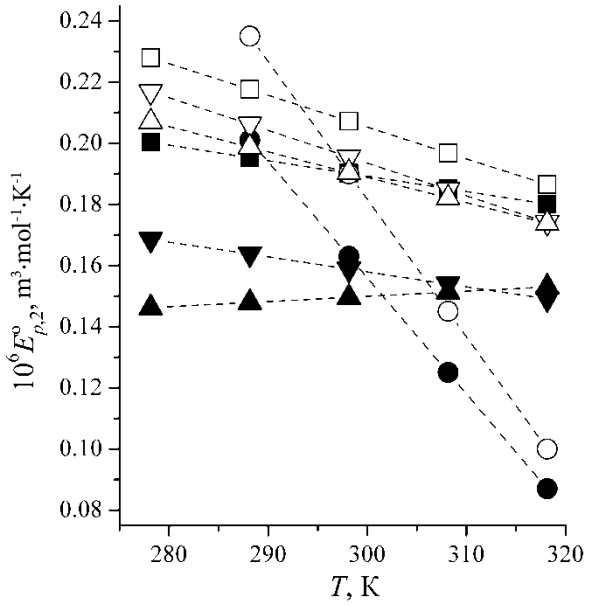


Fig. 9. Temperature dependences of standard molar expansibilities of tetra-*N*-alkylated glycolurils in H_2O (solid symbols) and D_2O (hollow symbols): *mebicar* (○,●), *mebicaret* (∇,▼), *albicar* (Δ,▲) and *bicarat* (□,▪)

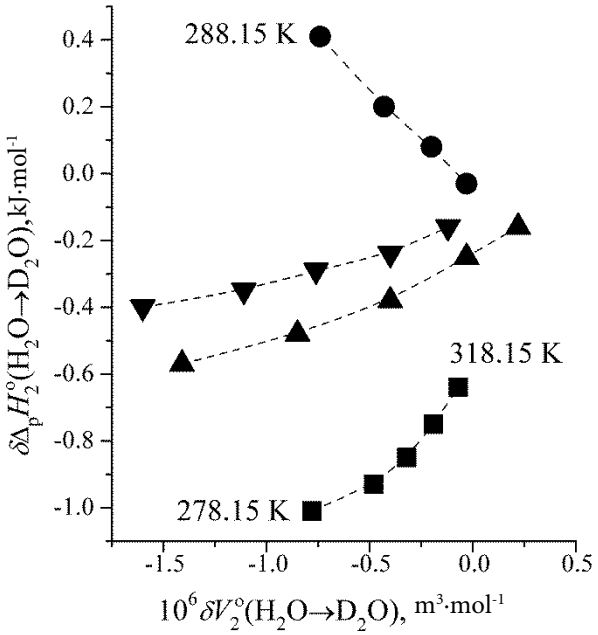


Fig. 10. Correlation relationships between H/D-isotope effects of solvent in standard molar enthalpy of dissolution and standard molar volume of *mebicar* (●), *mebicaret* (▼), *albicar* (▲), and *bicaret* (▪) in water in the studied temperature range

Finally, Fig. 10 demonstrates the possibility of a thermodynamically reasonable relationship not only between the thermochemical characteristics of 2-1 2-2 interactions in aqueous (H_2O or D_2O) solutions of tetra-*N*-alkyl-substituted glycolurils (see Fig. 6), but also between the solvent IEs in the enthalpy and volumetric characteristics of the hydration process of these compounds. Fig. 10 also presents the correlation data for *bicaret* and *mebicaret*, which are upward and downward curves in opposite sign IE temperature regions. In turn, the corresponding functions for *mebicaret* and *albicar* together form a kind of "arrow rod" with a "tip" corresponding to the positive value of $\delta\Delta_d H^{\circ}_2$ ($H_2O \rightarrow D_2O$) in chiral glycoluril. The IEs in V°_2 for hydrated achiral glycolurils take on a zero value near T = 318.15 K during an additional enthalpic-isotopic contribution due to differences in both specific interactions and the effects of hydrophobic nature (see Fig. 10).

Conclusions

We can state that the hydration of each of the studied tetra-*N*-alkyl-substituted glycolurils can be generally regarded as a superposition of two mechanisms – hydrophobic and

hydrophilic. In the case of *bicaret* (tetraethylglycoluril), the first one dominates, while for *mebicar*, (tetramethylglycoluril), the second one dominates. Regarding to the structural state and solvation in aqueous medium of heterocycles with mixed substitution such as *albicar* and *mebicaret* (*N*-diethyldimethylglycolurils), the stereochemical nature of their molecules predetermines a kind of "thermodynamic balance" between the mentioned mechanisms. The presence of racemic form of *albicar* (*trans*-substituted isomer) due to equilibrium existence of two optical *R*/*S*-enantiomers is revealed in a number of distinctive features of hydration process of this chiral tetra-*N*-alkylated glycoluril. In particular, this is reflected in a decrease in the melting heat and an increase in the enthalpy effects of dissolution in H_2O and D_2O, including the corresponding solvent IEs, as compared to those of the achiral *cis*-substituted isomer (*mebicaret*).

Obviously, the results discussed in this review may be useful for understanding both the stereochemical features of hydration and the contribution of solvent (water) effects to the mechanism of pharmacological activity of *mebicar*, *albicar*, and other glycoluril derivatives – from among those reviewed here and newly synthesized. This is due to the fact that $H_2O \rightarrow D_2O$-substitution, being a quantum effect, is a very subtle tool to analyze changes in the solvent structure and intermolecular interactions induced both by temperature effects and the presence of dissolved glycoluril molecules. The specified circumstances assume the conditions of thermodynamic and other studies at which a set of objects of studying and methodology of experiments and calculations should be kept unchanged. These requirements formed the basis of the concept that defined the content of this review.

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