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Enthalpies and heat capacities of solution of racemic N-methyl-substituted glycolurils in water at T = (278.15 to 313.15) K



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1. Introduction

It is known that some representatives of the cyclic N-alkylsubstituted derivatives of urea have the pronounced physiological or biological activity. The bicyclic bisureas of an octane series, being 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones or glycolurils (see in Fig. 1), take up a special place among them. These compounds serve as a basis to design the promising drugs [1]. However 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. In many ways these peculiarities are due to the ability of chiral glycoluril (as a racemate) is divided into two $\{R-(+) \text{ and } S-(-)\}$ enantiomers, whose thermodynamic and physic-chemical characteristics are somewhat different from each other. Herewith one of enantiomers is usually the more bioactive compared to the racemic form.

It should be noted in this connection that none of the three methyl-substituted compounds studied is a diastereomeric mix-

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ABSTRACT

The molar enthalpies of solution of racemic (with enantiomer ratio of 1:1) 2-monomethyl-, 2,6-dimethyl-, and 2,4,6-trimethylglycolurils (2-MMGU, 2,6-DMGU and 2,4,6-TMGU, respectively) in water were measured calorimetrically in the temperature range between (278.15 and 313.15)K and at p = 99.6 kPa. Derived from experimental data, the standard (at infinite dilution) molar enthalpic characteristics of the dissolution process are positive by sign and increase with rising temperature as well as in a sequence of 2,4,6-TMGU < 2,6-DMGU < 2-MMGU. In the same way, the standard heat capacity of solution decreases distinctly, leading to the conclusion that the effect of hydrophobic hydration is more pronounced for the more *N*-methylated solute. It was suggested that, despite the presence of hydrophobic moieties (*N*-sited methyl groups) in the molecules considered, a hydrophilic constituent (via H-bonding) seems to be the predominant one in the total enthalpy effect of a solute hydration.

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ture. It is caused by the structure features of these molecules. Due to rigidity of the heterocyclic core and *cis*-fusion of the fivemembered rings, these glycoluril-derivatives adopt a conformation of a "half-open book" or "gull-wings" [2,3]. Because of this, they contain the asymmetric conjugate C–C atoms. Beginning only with the *N*-ethyl-substituted chiral glycolurils, the diastereotropic methylene protons are defining a stereochemical nature of their molecules [1]. Given this, 2-monomethylglycoluril (2-MMGU) or 2,4,6-trimethylglycoluril (2,4,6-TMGU) is crystallized as a racemate with the equimolecular ratio of R-(+)- and S-(–)-enantiomers [4,5]. At the same time 2,6-dimethylglycoluril (2,6-DMGU) forms the conglomerate (or mixture of homochiral crystals) which is capable of spontaneous separation into enantiomers with the ratio of 1:1 [1,6].

As we mentioned above, the racemic and enantiomeric forms possess somewhat differing characteristics in a crystalline state (although, according to the ¹H NMR spectra, the geometries of a glycoluril-derivative in homo- and heterochiral crystals are similar [6]). Surely, it would be interesting to compare the thermodynamic hydration effects for the specified molecular forms. Meanwhile, taking into account the fact that the segregation of each racemate into enantiomers (in the sufficient quantity for experiments) is often a laborious and/or high-priced route for now, we have analyzed here the some thermodynamic characteristics of dissolution





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Fig. 1. The schematically simplified molecular structures of the studied chiral glycolurils with the atom's numeration: (a) 2-mohomethylglycoluril, (b) 2,6-dimethylglycoluril, and (c) 2,4,6-trimethylglycoluril.

(hydration) for the titled compounds being in the racemic form only. A consideration of similar properties of their enantiomers as solutes will be our separate task in the future.

Seen in this light, the thermochemical study of aqueous solutions of *N*-alkyl-substituted glycolurils seems to be very informative. Previously [7–9], the enthalpy-related characteristics of solution and hydration of achiral unsubstituted glycoluril (GU), 2,4-dimethylglycoluril (2,4-DMGU) and 2,4,6,8-tetramethylglycoluril (2,4,6,8-TMGU, or the pharmaceutical *mebicar*) in water have been discussed. In this work, we report data on the molar enthalpies of solution, $\Delta_{sol}H_2^m$, of chiral (racemic with enantiomer's ratio of 1:1) 2-MMGU, 2,6-DMGU and 2,4,6-TMGU in water (Fig. 1). The calorimetric experiments were performed at T = (278.15, 279.15, 288.15, 298.15, 308.15, and 313.15) K and $p = (99.6 \pm 0.08)$ kPa. The experimental $\Delta_{sol}H_2^m$ values were used to compute the standard (at infinite dilution) molar enthalpies, $\Delta_{sol}H_2^o$, and heat capacities, $\Delta_{sol}C_{p,2}^o = (\partial \Delta_{sol}H_2^0/\partial T)_p$, for the process of dissolution/hydration of these three heterocyclic compounds.

2. Experimental

A detail description of compounds employed in the calorimetric measurements is given in Table 1. All *N*-methyl-substituted glycolurils were laboratory-synthesized in accordance with the

procedure [1,4,5,11,12] based on the regioselective cyclocondensation of *N*-methyl-substituted urea derivative (puriss grade, Aldrich) with the 4,5-dihydroxyimidazolidin-2-one or its mono-N-methylderivative (during the 2,4,6-TMGU synthesis [4]). The last two monocyclic compounds were prepared by the reaction of glyoxal, being taken as a 40% aqueous solution (Acros, pure grade), with urea or mono-N-methylurea [4,5]. Herewith the racemic nature of 2-MMGU and 2,4,6-TMGU was confirmed by the results of studying of a solution optical activity (rotation) using a Polamat A polarimeter. According to the polarimetry data, the synthesized sample of (\pm) -2,6-DMGU was optically inactive (i.e., it had a enantiomer ratio of 1:1), too. The preparations were additionally recrystallized from absolute ethanol (EtOH: Fluka, puriss) followed by slow precipitation through the addition of diethyl ether (Et₂O: Fluka, ACS reagent) to give purer products. The compounds purified were then repeatedly dried in vacuo at $T \approx 320$ K for 2,4,6-TMGU and $T \approx 370$ K for 2-MMGU or 2,6-DMGU to constant mass. The final mass-fraction purity of each of the glycolurils compared was from 0.992 to 0.995 (see Table 1), as determined using a high performance liquid chromatography (HPLC) based on the ECOM setup.

The "authenticity" of the racemic samples after synthesis was established also using their ¹H NMR data. The measurements were carried out on a Bruker AM 300 spectrometer in DMSO- d_6 (relative to TMS as the internal standard) at T = 300 K. Being derived by such way, the chemical shifts, δ /ppm, and coupling constants, J/Hz, were

Table 1

Sample description.					
Characteristics	2-Monomethylglycoluril	2,6-Dimethylglycoluril	2,4,6-Trimethyglycoluril		
Abbreviated name	2-MMGU	2,6-DMGU	2,4,6-TMGU		
IUPAC (CAS) name	1-Methyl-	1,3-Dimethyl-	1,3,4-Trimethyl-		
	tetrahydroimidazo[4,5-	tetrahydroimidazo[4,5-	tetrahydroimidazo[4,5-		
	d]imidazole-2,5(1H,3H)-dione	d]imidazole-2,5(1H,3H)-dione	d]imidazole-2,5(1H,3H)-dione		
Other agreed-upon name	2-Methyl-2,4,6,8-	2,6-Dimethyl-2,4,6,8-	2,4,6-Trimethyl-2,4,6,8-		
(being used in the organic	tetraazabicyclo[3.3.0]-octane-	tetraazabicyclo[3.3.0]-octane-	tetraazabicyclo[3.3.0]-octane-		
synthesis)	3,7-dione	3,7-dione	3,7-dione		
CAS RN	28889-54-5	17754-76-6	263403-90-3		
Molecular formula	$C_5H_8N_4O_2$	$C_6H_{10}N_4O_2$	$C_7H_{12}N_4O_2$		
Molar mass/(g mol ⁻¹), according to [10]	156.1443	170.1712	184.1980		
Melting point, T_{mp}/K	534.8 ± 0.2^a	550.2 ± 0.2^a	365.7 ± 0.2^{a}		
-	(533.2±2[5,12])	(542.2±1[1])	$(400.2 \pm 1 \ [4])$		
Standard enthalpy of fusion, $\Delta_{fus}H_2^o/(kJ mol^{-1})$	$34.1\pm0.5^{\rm a}$	24.4 ± 0.5^{a}	$20.1\pm0.5^{\rm a}$		
Source	Zelinsky Institute of Organic Chemistry				
	of the RAS, Moscow, Russia)				
Initial mass fraction purity	>0.95	≥0.95	≥0.95		
Purification method	The recrystallization from absolute EtOH with the addition of ${ m Et_2O}$				
Final mass fraction purity	~0.995	~0.993	~0.992		
Analysis method	HPLC	HPLC	HPLC		

^a The reported uncertainty corresponds to expanded uncertainty, $U_{T(H)}$ (at the 0.95 level of confidence).

found to be the following: 2.61 (s, 3H, Me), 5.14 (d, 1H, CH, J=8.2), 5.20 (d, 1H, CH, J=8.2), 7.25 (s, 1H, NH), 7.27 (s, 1H, NH), 7.44 (s, 1H, NH) for 2-MMGU and 2.61 (s, 6H, 2Me), 5.10 (s, 2H, 2CH), 7.52 (s, 2H, 2NH) for 2,6-DMGU. These results, being presented graphically (in the form of spectrograms) as a Supplementary material (Figs. S1 and S2), are in good agreement with those existing in the literature [1,5,12]. As for 2,4,6-TMGU, we have presented here the relevant ¹H NMR and ¹³C NMR data for this glycoluril-derivative in DMSO- d_6 at T = 300 K for the first time (earlier [4], the data on δ in CDCl₃ at the same temperature were published only). The results also were provided as a Supplementary material, in the form of detailed NMR-spectrograms (see Figs. 3S and 4S).

In Table 1, data on melting point, T_{mp} , and standard molar enthalpy of the fusion (melting), $\Delta_{fus}H_2^o$, for the investigated glycoluril-derivatives are shown together with values, being found in other sources. The results of thermal analysis of the samples were derived from heating curves in the melting region using a multipurpose differential scanning calorimeter DSC 204 F1 Phoenix (Netzsch-Gerätebau GmbH, Germany). As follows from data of Table 1, our values of T_{mp} are in fairly good agreement with the results reported by other authors, perhaps, with the exception of the quantity for 2,4,6-TMGU. We believe that it may be mainly due to differences in details of the experimental procedure. Unfortunately, there is no information on ways of the preparing and thermal testing the 2,4,6-TMGU sample in the work [4], whereas in our case, the most accurate method of measuring t_{mp} was employed. It is worthy of noticing also the fact that the $\Delta_{fus}H_2^0$ value decreases with sequential increasing the number of methyl groups on the N(2)-, N(4)-, and N(6)-sited positions in a glycoluril's molecule. Going from 2-MMGU to 2,6-DMGU and further to 2,4,6-TMGU, this tendency becomes decreasingly pronounced (see Table 1).

After and before experiments, each glycoluril's sample was stored in a light-proof vacuum dessicator over P_2O_5 . The water (of natural isotope composition) was deionized and then twice distilled in a Pyrex-glass apparatus up to electrical conductivity of 1.5×10^{-6} S cm⁻¹.

The molality-dependent molar enthalpies of solution, $\Delta_{sol}H_2^m$, of the glycolurils compared were measured using an ampoule-type sealed microcalorimeter with isothermal shell. The setup was fitted with a 60 cm³ titanium vessel. The procedure for experimental measurements and testing the microcalorimeter were detailed previously [13,14]. Four to five measurements of $\Delta_{sol}H_2^m$ at different *m* were performed at each temperature.

3. Results and discussion

The results of calorimetric measurements indicated that the $\Delta_{sol}H_2^m$ values within the measurement error do not depend on m at all the temperatures chosen. As a consequence, the values of $\Delta_{sol}H_2^o$ were calculated as average-weighted $|\Delta_{sol}H_2^m|_{av}$ in the studied range of m. The procedure for calculating $|\Delta_{sol}H_2^m|_{av}$ is described previously [14,15]. The temperature-dependent data on $\Delta_{sol}H_2^\infty$ are tabulated in Table 2.

Data of Table 2 point out the fact that the process of dissolution of all three glycoluril-derivatives in water is endothermic over the whole temperature range of interest. A positive sign at $\Delta_{sol}H_2^o$ suggests that the total energy released during the formation of heterocomponent H bonds and from hydrophobic hydration of a solute (the exothermic contribution) does not replace all of the energy spent to destroy a glycoluril's crystal lattice and to form the cavity in the solvent (the endothermic contribution). The latter process is accompanied by the disturbance of the hydrogenbonded network of water in the nearest environment of the solute glycoluril-derivative. In other words, the glycoluril-water

Table 2

Standard molar enthalpies of dissolution, $\Delta_{sol}H_2^o$, of the studied glycolurilderivatives in water at different temperatures, *T*, and *p* = 99.6 kPa.^a

T/K	$m / \{ mol (kg H_2 O)^{-1} \}^{b}$	N ^c	$\Delta_{\rm sol}H_2^o \pm \delta_H/({\rm kJ}~{\rm mol}^{-1})^{\rm d}$	
2-Monomethylglycoluril				
278.15	0.0057-0.0091	4	23.00 ± 0.04	
279.15	0.0075-0.0109	5	23.05 ± 0.03	
288.15	0.0136-0.0154	4	23.44 ± 0.06	
298.15	0.0117-0.0141	4	24.00 ± 0.08	
308.15	0.0125-0.0145	4	24.76 ± 0.08	
313.15	0.0103-0.0153	5	25.19 ± 0.08	
2,6-Dimethylglycoluril				
278.15	0.0062-0.0075	4	11.92 ± 0.04	
279.15	0.0052-0.0055	4	12.02 ± 0.04	
288.15	0.0050-0.0059	4	12.94 ± 0.12	
298.15	0.0101-0.0109	4	13.88 ± 0.06	
308.15	0.0043-0.0068	4	14.93 ± 0.03	
313.15	0.0048-0.0050	4	15.40 ± 0.09	
2,4,6-Trimethylglycoluril				
278.15	0.0077-0.0095	5	3.28 ± 0.06	
279.15	0.0066-0.0073	4	3.40 ± 0.06	
288.15	0.0048-0.0071	5	4.63 ± 0.09	
298.15	0.0058-0.0086	4	5.91 ± 0.13	
308.15	0.0051-0.0078	5	7.32 ± 0.08	
313.15	0.0049-0.0075	4	7.98 ± 0.06	

^a The expanded uncertainties, *U*, do not exceed: $U(m) = \pm 0.0001 \text{ mol kg}^{-1}$, $U(T) = \pm 0.001 \text{ K}$ and $U(p) = \pm 0.8 \text{ kPa}$ (level of confidence = 0.95).

^b The molality range in which the $\Delta_{sol}H_2^m$ values were averaged.

^c The number of independent measurements of $\Delta_{sol}H_2^m$.

^d δ_H is the half-width of a 95% confidential interval for $\Delta_{sol}H_2^o$.

interaction is to be weaker than the interaction between solute molecules in their own crystal substance. Indeed, since the standard state is understood as the state of a hypothetically ideal solution or gas phase [16,17], the hydration of a solute can be identified with the condensation of 1 mol of its gaseous (monomeric) molecules in an infinitely large amount of a solvent [18].¹

As the temperature rises, the $\Delta_{sol}H_2^0$ values become increasingly positive (see in Table 2). Interestingly, $\Delta_{sol}H_2^0$ decreases in the same manner as it is observed in the case of changing $\Delta_{fus}H_2^0$ (Table 1) on going from 2-MMGU to 2,6-DMGU and further to 2,4,6-TMGU. It would be more "thermodynamically justified", if a similar correlation existed between $\Delta_{sol}H_2^0$ and the molar enthalpy of sublimation, $\Delta_{sub}H_2^0$ (or hydration, $\Delta_{hydr}H_2^0$). But, due to the problem of decomposition of glycoluril's samples during their heating, we were unable to derive the reliable information on $\Delta_{sub}H_2^0$ (using the Knudsen's effusion mass-spectrometric method [19]).

Such a distribution in the dissolution enthalpies (Table 2) is not surprising. Here, the point is that the hydrophobicity of a solute becomes increasingly pronounced in a sequence of 2-MMGU < 2,6-DMGU < 2,4,6,8-TMGU (i.e., with the increase in the number of methyl groups in a glycoluril's molecule). When the specified glycoluril-derivatives are subjected to dissolution in water, the given circumstance should be manifested in the relative strengthening of hydrophobic constituent of a solute hydration.

To understand a situation with enthalpy effects of dissolution more clearly, heat capacity changes in the specified process, $\Delta_{sol}C_{p,2}^o$, for all aqueous glycoluril-derivatives under study, must be considered, too. We have attempted to do it below.

¹ Here, the point is that the evaporation or sublimation process at standard state can be identified with the opposite process of condensation where the solute is postulated to be solvated in its own environment. Hence the sign and quantity of the standard enthalpy of dissolution are being determined by the difference between solute-solvent and solute-solute interactions [18].

The analysis of data in Table 2 has shown that the dependence of $\Delta_{sol}H_2^o$ vs. *T* for 2,6-DMGU and 2,4,6-TMGU can be approximated by a simple linear equation [9,15]

$$\Delta_{\text{sol}} H_2^o(T) - \Delta_{\text{sol}} H_2^o(\theta) = \Delta_{\text{sol}} C_{p,2}^o(T - \theta), \tag{1}$$

where θ = 298.15 K is the "reference temperature". In fitting of this equation, a least-squares method was employed with choosing the degree, for which all the coefficients are significant with respect to their own 95% confidence limit.

The form of Eq. (1) assumes that the $\Delta_{sol}C_{p,2}^{o}$ values, being equal to $(99.5 \pm 1.9) \text{J} \text{mol}^{-1} \text{K}^{-1}$ for 2,6-DMGU and $(134.4 \pm 2.3) \text{J} \text{mol}^{-1} \text{K}^{-1}$ for 2,4,6-TMGU in H₂O, do not depend on the current value of *T* within the temperature range chosen. In the case of (H₂O+2-MMGU), the $\Delta_{sol}H_2^o - T$ function is nonlinear and the corresponding data of Table 2 can be adequately described by a least square method applied to model (1) with the additional quadratic term: $(\partial \Delta_{sol}C_{p,2}^o/\partial T)_p(T - \theta)^2$. The following temperature-dependent $\Delta_{sol}C_{p,2}^o$ values for 2-MMGU in water have been derived in such way ($\delta_{C_p} = \pm 1.3 \text{J} \text{mol}^{-1} \text{K}^{-1}$): 33.9 (278.15 K), 35.5 (279.15 K), 50.1 (288.15 K), 66.4 (298.15 K), 82.6 (308.15 K), and 90.7 (313.15 K). Assuming the $\Delta_{sub}H_2^o$ value does not change in the temperature range studied, the $\Delta_{sol}C_{p,2}^o$ value is numerically equal to a change in the standard molar heat capacity of glycoluril hydration, $\Delta_{hydr}C_{p,2}^o$.

According to [20], a large and positive $\Delta_{sol}C_{p,2}^o (\cong \Delta_{hydr}C_{p,2}^o)$ reflects structural changes in the solvent induced by increasing energy fluctuations (due to increasing the number of shorter water–water H bonds) in the nearest vicinity of nonpolar groups. Given this, one can confirm that the effect of hydrophobic hydration of a solute is to be more pronounced in the aqueous medium containing 2,4,6-TMGU. Herewith, using the data [7,21], we have obtained $\Delta_{sol}C_{p,2}^o$ for achiral 2,4,6,8-TMGU (mebicar) to be equal to (168.7 ± 8.4) J mol⁻¹ K⁻¹ that is almost 2.5 times greater than the corresponding value for 2-MMGU at 298.15 K. In the given context, of special interest is the fact that the $\Delta_{sol}C_{p,2}^o(\theta)$ quantity varies virtually in proportion to the number of methyl-substituents, N_c , within a series of 2-MMGU < 2,6-DMGU < 2,4,6-TMGU < 2,4,6,8-TMGU (see Fig. 2).

Being depicted in Fig. 2, the $\Delta_{sol}C_{p,2}^o - N_C$ function have allowed us to estimate the value of $\Delta_{sol}C_{p,2}^o(\theta)$ for the unexplored GU (due to its very low solubility), i.e., for the case when $N_C = 0$. For this purpose, we have expressed the given relation in an analytical form

$$\Delta_{\text{sol}} C_{p,20}^{0}(\theta) / (\text{J mol}^{-1} \text{K}^{-1}) = 31.8(\pm 2.9) + 34.2(\pm 0.9) \cdot N_{\text{C}}.$$
 (2)

The first term in the right-hand side of Eq. (2) is the predicted value of $\Delta_{sol}C_{p,2}^{o}$ for GU at θ = 298.15 K, although this assumption should be experimentally tested. The coefficient at $N_{\rm C}$ represents the average-weighted value of the heat capacity increment $\delta_{Cp}(\rm CH_2)$ in the above-mentioned glycoluril's series.

In the first place, it is worth noting that, unlike the family of acyclic *N*-methyl-substituted ureas [22,23], the δ_{C_p} (CH₂) contribution for each of the considered heterocyclic derivatives in an aqueous medium was estimated to be the same (within the limit of error), regardless of the stereochemical nature of a molecule methylation. The second point of interest is a decrease in $\Delta_{sol}C_{p,2}^o$ by (9 ± 3) J mol⁻¹ K⁻¹ at replacement of 2,6-DMGU by the equimolecular 2,4-DMGU [9].² The situation is more complicated here, because each of glycoluril-derivatives compared contains two CH₃ groups attached to nitrogen atoms in different ways (Fig. 1). The hydration sphere of these compounds most probably consists of eight water



Fig. 2. The correlation between the standard molar heat capacities of the glycolurilderivatives studied in water and the number of *N*-sited methyl groups in the solute molecules at 298.15 K.

molecules, two bound to each of carbonyls, one to each of nitrogen protons. The HC–CH bridging group can form H bonds with two other water molecules [8,24,25]. Unlike the *trans*-configured 2,6-DMGU, both methyls of 2,4-DMGU are located in the same five-membered ring, predetermining the stereochemically achiral nature of this molecule. Hence two unsubstituted NH groups are in the adjacent ring, a situation being characteristic for the concurrent hydration of urea and its 1,3-dimethyl-derivative [26]. Seen in this light, the less pronounced changes in $\Delta_{sol}H_2^o$ of 2,4-DMGU depending on *T* may be caused by the decreasing steric hindrances for the solute–solvent interactions through C=O…H– and N…H–Obonding.

Previously [24,25], by using the millimeter-wave absorption and ¹³C NMR spectroscopic studies of aqueous mebicar, it has been concluded that two carbonyl oxygens form H bonds with four water molecules according to a mechanism of "positive hydration", whereas the hydrogen-bonding ability of nitrogen atoms is sterically hindered. Herewith, at least two water molecules incorporated in the hydration shell of a 2,4,6,8-TMGU molecule (probably about CH groups) retain their rotation mobility, as has been observed for urea "negative hydration" [27]. Given this and the fact that each of the glycoluril-derivatives considered here contains (1–3) NH groups, the hydrophilic (via hydrogen-bonding) interactions are to be predominating in hydration of their molecules, although the hydrophobic constituent (around *N*-sited CH₃ groups) in the case of 2,4,6-TMGU seems to be significant.

This inference is confirmed by the enthalpy coefficients for pairwise 2–2 interactions, h_{22} , which for the aqueous mebicar were found to be ca. $-2042 \text{ J kg mol}^{-1}$ [28]. In other words, by analogy with hydrophilic urea ($h_{22} \approx -330 \text{ J kg mol}^{-1}$ [29]), the 2,4,6,8-TMGU molecules in an aqueous medium interact rather strongly with each other to form solvent-separated pairs despite the presence of the four (as in 1,1,3,3-tetramethylurea) methyl groups. Allowing for increase of the proton-donor ability in a sequence of 2,4,6,8-TMGU < 2,4,6-TMGU < 2,6-DMGU < 2-MMGU, this fact indicates that the hydrophilic component of hydration of the studied glycoluril-derivatives generally dominates over the hydrophobic

² In the case of aqueous 2,4-DMGU, $\Delta_{sol}C_{p,2}^{o}(\theta) = (90.4 \pm 2.2) \text{ J mol}^{-1} \text{ K}^{-1}$ [9].

constituent and the given tendency is to be strengthened when the $N_{\rm C}$ in a molecule decreases.

4. Concluding remarks and future work

Based on the experimental results obtained in this work, we may suggest that the effect of hydrophobic hydration is more pronounced for the more *N*-methylated glycoluril-derivative. At the same time, despite the presence of hydrophobic moieties, from one to three methyls, in the molecules considered, a hydrophilic constituent (via H-bonding) seems to be the predominant one in the total enthalpy effect of a solute hydration. This trend is enhanced within a series of 2,4,6-TMGU < 2,6-DMGU < 2-MMGU, due to the formation of rather strong heterocomponent H bonds in the aqueous solutions of glycoluril-derivatives in question.

Of special interest is the fact that the standard molar heat capacity of dissolution, $\Delta_{sol}C_{p,2}^o/(J \text{ mol}^{-1} \text{ K}^{-1})$, varies virtually in proportion to the number of methyls (N_C) within a series of 2-MMGU (66) < 2,6-DMGU (100) < 2,4,6-TMGU (134) < 2,4,6,8-TMGU (169), at T=298.15 K. From here, the heat capacity increment $\delta_{C_p}(\text{CH}_2)$ is estimated to be ca. 34 J mol⁻¹ K⁻¹. The given fact is not yet subject to a reasonable explanation. However, this made it possible to estimate the $\Delta_{sol}C_{p,2}^o$ (298.15 K) value for the unsubstituted achiral GU whose solubility in water is very small. So for the case of N_C = 0, $\Delta_{sol}C_{p,2}^o \approx 32(\pm 3)$ J mol⁻¹ K⁻¹ although this assumption should be experimentally tested.

Meanwhile, the "authentic nature" of temperature-dependent enthalpy effects observed at dissolving the glycoluril-derivatives studied still remains unclear and needs further investigation. Also, the future work on this problem should focus on studying the enthalpy coefficients for pairwise solute–solute interactions, being derived from data on the enthalpies of dilution of the above glycoluril-containing aqueous system. A subsequent our goal would be the investigation of thermochemical properties of aqueous solutions of enantiomerically pure title compounds, in order to clarify and develop the above inferences.

In conclusion, we want to note that, in terms of thermodynamic properties only, solute–solvent interactions on the molecular level are impossible to define explicitly. The conclusions from a single property (such as a change in heat capacity during the solute dissolution) will essentially depend on the extent to which the property is sensitive to "long-range" effects [30]. Obviously, the spectroscopic and quantum–chemical results would be very helpful to confirm the above suggestions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tca.2015.09.023.

References

- [1] R.G. Kostyanovsky, K.A. Lyssenko, A.N. Kravchenko, O.V. Lebedev, G.K. Kadorkina, V.R. Kostyanovsky, Crystal properties of N-alkylsubstituted glycolurils as the precursors of chiral drugs, Mendeleev Commun. 11 (2001) 134–136, http://dx.doi.org/10.1070/MC2001v011n04ABEH001469.
- [2] E.G. Atavin, A.V. Golubinskii, A.N. Kravchenko, O.V. Lebedev, L.V. Vilkov, Electron diffraction study of molecular structure of mebicar, J. Struct. Chem. 46 (2005) 417–421, http://dx.doi.org/10.1007/s10947-006-0119-9.
- [3] A.N. Kravchenko, E.Yu. Maksareva, P.A. Belyakov, A.S. Sigachev, K.Yu. Chegaev, K.A. Lyssenko, O.V. Lebedev, N.N. Makhova, Synthesis of 2-monofunctionalized 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones, Russ. Chem. Bull. Int. Ed 52 (2003) 192–197, http://dx.doi.org/10.1023/ A: 1022473004714.
- [4] A.N. Kravchenko, O.V. Lebedev, E.Yu. Maksareva, New condensation methods in the synthesis of bicyclic bisureas, Mendeleev Commun. 10 (2000) 27–28, http://dx.doi.org/10.1070/MC2000v010n01ABEH001186.
- [5] E. Grillon, R. Gallo, M. Pierrot, J. Boileau, E. Wimmer, Isolatiaon and X-ray structure of intermediate dihydroxyimidazolidine (DHI) in the synthesis of glycoluril from glyoxal and urea, Tetrahedron Lett. 29 (1988) 1015–1016, http://dx.doi.org/10.1016/0040-4039(88)85322-X.
- [6] R.C. Kostyanovsky, G.K. Kadorkina, K.A. Lyssenko, V.Yu. Torbeev, A.N. Kravchenko, O.V. Lebedev, G.V. Grintselev-Knyazev, V.R. Kostyanovsky, Chiral drugs via the spontaneous resolution, Mendeleev Commun. 12 (2002) 6–8, http://dx.doi.org/10.1070/MC2002v012n01ABEH001521.
- [7] E.V. Ivanov, V.K. Abrosimov, D.V. Batov, Effect of temperature on the H/D-isotope effects in the enthalpy of hydration of tetramethyl-bis-carbamide, Russ. Chem. Bull. Int. Ed 55 (2006) 741–743, http://dx.doi.org/10.1007/s11172-006-0323-y.
- [8] E.V. Ivanov, V.I. Smirnov, V.K. Abrosimov, Influence of N-methylation effect on the dissolution enthalpy of glycoluril in water, Russ. J. Gen. Chem. 77 (2007) 482–483, http://dx.doi.org/10.1134/S1070363207030231.
- [9] E.V. Ivanov, D.V. Batov, V.V. Baranov, A.N. Kravchenko, V.K. Abrosimov, Standard enthalpies and heat capacities of solution of 2,4-dimethyl- and 2,4-diethylglycolurils in water at temperatures from (278.15 to 313.15) K, Thermochim. Acta 586 (2014) 72–74, http://dx.doi.org/10.1016/j.tca.2014.04. 012.
- [10] M.E. Wieser, N. Holden, T.B. Coplen, J.K. Böhlke, M. Berglund, W.A. Brand, P. De Bièvre, M. Gröning, R.D. Loss, J. Meija, T. Hirata, T. Prohaska, R. Schoenberg, G. O'Connor, T. Walczyk, S. Yoneda, X.-K. Zhu, Atomic weights of the elements 2011 (IUPAC Technical Report), Pure Appl. Chem. 85 (2013) 1047–1078, http://dx.doi.org/10.1351/PAC-REP-13-03-02.
- [11] J. Nematollahi, R. Ketcham, Imidazoimidazoles. I. The reaction of ureas with glyoxal. Tetrahydroimidazo[4,5-d]imidazole-2,5-diones, J. Org. Chem. 28 (1963) 2378–2380, http://dx.doi.org/10.1021/jo01044a055.
- [12] D. Kühling, Über die Acylierung von Glykolurilen, Liebigs Ann. Chem. (1973) 263–277, http://dx.doi.org/10.1002/jlac.197319730215 (in German).
- [13] A.V. Kustov, A.A. Emel'yanov, A.F. Syschenko, M.A. Krest'yaninov, N.I. Zheleznyak, V.P. Korolev, A calorimetric setup for measuring heat effects of processes in solutions, Russ. J. Phys. Chem 80 (2006) 1532–1536, http://dx. doi.org/10.1134/S0036024406090317.
- [14] E.V. Ivanov, V.K. Abrosimov, V.I. Smirnov, Enthalpies of solution of tetramethyl-bis-urea (Mebicarum) in amides and acetone at 298.15 K, Thermochim. Acta 463 (2007) 27–31, http://dx.doi.org/10.1016/j.tca.2007.07. 008.
- [15] E.V. Ivanov, D.V. Batov, G.A. Gazieva, A.N. Kravchenko, V.K. Abrosimov, D₂O-H₂O solvent isotope effects on the enthalpies of bicaret hydration and dilution of its aqueous solutions at different temperatures, Thermochim. Acta 590 (2014) 145–150, http://dx.doi.org/10.1016/j.tca.2014.05.011.
- [16] I. Mills, T. Ćvitač, K. Homann, N. Kallay, K. Kuchitsu, Quantities, Units and Symbols in Physical Chemistry (IUPAC, Phys. Chem. Div.), 2nd ed., Blackwell Science, Oxford, 1993.
- [17] M.B. Ewing, T.H. Lilley, G.M. Olofsson, M.T. Ratzsch, G. Somsen, Standard quantities in chemical thermodynamics: fugacities, activities and equilibrium constants for pure and mixed phases (IUPAC Recommendations), Pure Appl. Chem. 66 (1994) 533–552, http://dx.doi.org/10.1351/pac199466030533.
- [18] E.V. Ivanov, Thermodynamic interrelation between excess limiting partial molar characteristics of a liquid nonelectrolyte, J. Chem. Thermodyn. 47 (2012) 437–440, http://dx.doi.org/10.1016/j.jct.2011.11.018.
- [19] V.V. Tyunina, A.V. Krasnov, E. Yu. Tyunina, V.G. Badelin, G.V. Girichev, Enthalpy of sublimation of natural aromatic amino acids determined by Knudsen's effusion mass spectrometric method, J. Chem. Thermodyn. 74 (2014) 221–226, http://dx.doi.org/10.1016/j.jct.2014.02.003.
- [20] K.R. Gallagher, K.A. Sharp, A new angle on heat capacity changes in hydrophobic solvation, J. Am. Chem. Soc. 125 (2003) 9853–9860, http://dx. doi.org/10.1021/ja029796n.
- [21] V.P. Korolev, A.V. Kustov, D.V. Batov, N.L. Smirnova, Yu.A. Lebedev, Group-related hydrophilic and hydrophobic effects of hydration of tetramethylbisurea and N,N'-dimethylpropyleneurea in solutions, Biophysics 53 (2008) 544–549 (in Russian).
- [22] G. Della Gatta, E. Badea, M. Jóźwiak, P. Del Vecchio, Thermodynamics of solvation of urea and some monosubstituted *N*-alkylureas in water at 298.15 K, J. Chem. Eng. Data 52 (2007) 419–425, http://dx.doi.org/10.1021/ je060360n.
- [23] G. Della Gatta, E. Badea, M. Jóźwiak, G. Barone, Hydrophobic-hydrophilic solvation of variously substituted N-alkylureas in aqueous solution: a

calorimetric study at a temperature of 298.15 K, J. Chem. Eng. Data 54 (2009) 2739–2744, http://dx.doi.org/10.1021/je9003405.

- [24] Yu.I. Khurgin, O.V. Lebedev, E.Yu. Maksareva, V.A. Zavizion, V.A. Kudryashova, M.M. Vorob'ev, G.A. Orekhova, A.N. Danilenko, Intermolecular interactions in aqueous solutions of mebicar, Russ. Chem. Bull. 44 (1995) 1138–1139, http:// dx.doi.org/10.1007/BF00707074.
- [25] V.V. Alexandriiskii, E.V. Ivanov, V.K. Abrosimov, NMR-¹³C studies of aqueous solutions of tetramethyl-*bis*-urea, in: Proc. 2nd Int. Meet. "NMR in Life Sciences", St. Petersburg, Russia, July 11–15, 2005, p. 60.
- [26] J.N. Spencer, J.W. Hovick, Solvation of urea and methyl-substituted ureas by water and DMF, Can. J. Chem. 66 (1988) 562–565, http://dx.doi.org/10.1139/ v88-096.
- [27] Yu.I. Khurgin, V.A. Kudryashova, V.A. Zavizion, Investigation of intermolecular interactions in solutions by means of millimeter-wave spectroscopy. 4. Negative and positive hydration in aqueous solutions of urea, Bull. Acad. Sci.

U.S.S.R. Div. Chem. Sci. 39 (1990) 259–265, http://dx.doi.org/10.1007/ BF00960649.

- [28] E.V. Ivanov, D.V. Batov, Enthalpy-related interaction parameters in H/D isotopically distinguishable aqueous solutions of tetramethylurea cyclic derivatives at 298.15 K, Thermochim. Acta 523 (2011) 253–257, http://dx.doi. org/10.1016/j.tca.2011.05.019.
- [29] J.J. Savage, R.H. Wood, Enthalpy of dilution of aqueous mixtures of amides, sugars, urea, ethylene glycol, and pentaerythritol at 25 °C: enthalpy of interaction of the hydrocarbon, amide, and hydroxyl functional groups in dilute aqueous solutions, J. Solution Chem. 5 (1976) 733–750, http://dx.doi. org/10.1007/BF00643457.
- [30] J.G. Mathieson, B.E. Conway, H₂O–D₂O solvent isotope effect in the apparent molal volume and compressibility of urea, J. Solution Chem. 3 (1974) 781–788, http://dx.doi.org/10.1007/BF00955710.