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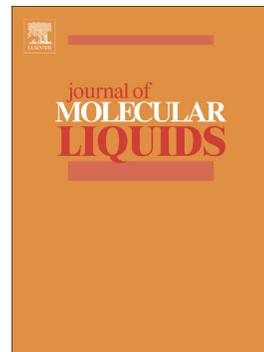
PII: S0167-7322(17)30351-3
DOI: doi: [10.1016/j.molliq.2017.07.015](https://doi.org/10.1016/j.molliq.2017.07.015)
Reference: MOLLIQ 7592

To appear in: *Journal of Molecular Liquids*

Received date: 26 January 2017
Revised date: 29 April 2017
Accepted date: 6 July 2017

Please cite this article as: Evgeniy V. Ivanov, Elena Yu. Lebedeva , Effect of temperature on volumetric behavior of glycine in aqueous mebicar (N-tetramethylglycoluril) at $p \sim 0.1$ MPa, *Journal of Molecular Liquids* (2016), doi: [10.1016/j.molliq.2017.07.015](https://doi.org/10.1016/j.molliq.2017.07.015)

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Effect of temperature on volumetric behavior of glycine in aqueous *mebicar* (*N*-tetramethylglycoluril) at $p \sim 0.1$ MPa

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Abstract

Densities for solutions of glycine in aqueous *mebicar* (*N*-tetramethylated bicyclic *bisurea* or glycoluril) have been determined using a hermetically sealed vibrating-tube densimeter, with an uncertainty of $\sim 1.0 \times 10^{-5} \text{ g}\cdot\text{cm}^{-3}$, at $T = (278.15, 288.15, 298.15, \text{ and } 308.15) \text{ K}$ and $p = (99.6 \pm 0.8) \text{ kPa}$. The solution molality have been ranged from $(0.024 \text{ to } 0.098) \text{ mol}\cdot\text{kg}^{-1}$ for aqueous *mebicar* and from $(0.05 \text{ to } 0.50) \text{ mol}\cdot\text{kg}^{-1}$ for amino acid being studied. These data have been used to calculate both concentration-dependent apparent and standard (partial at infinite dilution) volumes and expansibilities for glycine as a solute. Also, the hydration numbers of the amino acid and glycine – *mebicar* pairwise interaction coefficients have been derived from the standard molar volumes of the glycine transfer from water to aqueous *mebicar* over the whole temperature range chosen. The results have been explained based on the patterns of the glycine hydration and the solute – co-solute interactions.

Keywords: Glycine; *Mebicar*; Aqueous solutions; Transfer volumes.

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1. Introduction

The densimetric study on organic solutes of interest for biochemistry and pharmacology can provide unique insights into the origins of the “intra- and intermolecular events” that are prototypes of biochemical processes in aqueous media [1,2]. Primarily, volumetric experimental methods have been widely used to study the interaction of bioactive molecules both among themselves and with the surrounding solvent. Herewith the packing transformations of a solvent influenced by a solute hydration are of great importance, too [2,3].

In a series of recent works [1,2,4–7], the standard (partial or apparent at infinite dilution) molar volumes of glycine and some other α -amino acids in aqueous non-electrolyte solutions including drugs were interpreted by analyzing the hydration numbers and transfer volumes as well as pair and triple interaction coefficients. Here glycine (hereinafter, Gly) was chosen as a co-solute to aqueous *mebicar* (Meb), as the latter, being a *N*-tetramethyl-derivative of glycoluril or bicyclic *bisurea* of the octane series {Fig. 1(a–b)}, is a clinically efficient tranquilizer [8]. A literature survey reveals that although the studies regarding volumetric properties of Meb in aqueous media have been detailed previously [9,10], no information on packing- and interaction-related thermodynamic characteristics for α -amino acids including Gly in solutions of this heterocyclic compound was found. Meanwhile, these results help in understanding the complex mechanism of molecular interactions occurring in various biochemical processes in the human body [5–7], in particular, between the psychotropically active (mebicar-like) pharmaceuticals and the α -amino acids being a part of the living cell.

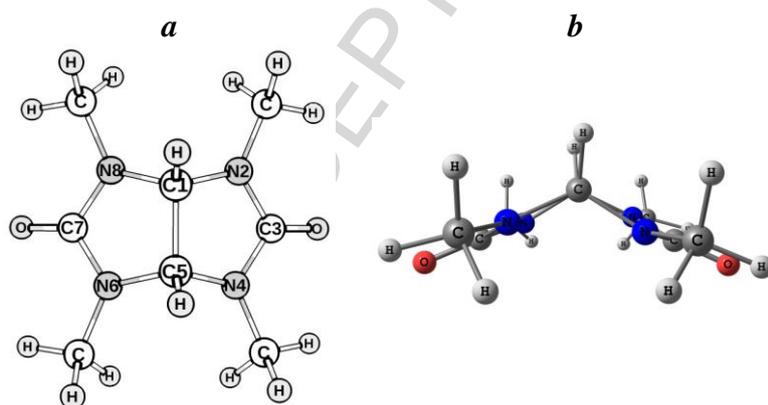


Fig. 1. A simplified structure of the mebicar molecule in two projections: perpendicularly (**a**) and in parallel (**b**) to the bicycle plane. The skeleton has a “half-open book” conformation being characteristic of the most of *N*-alkylated glycoluril-derivatives [9–11,15].

Therefore, the main goal of this study was to evaluate the effect of solution molality and temperature on the volumetric properties and interaction behavior of Gly, a simplest amino acid having no enantiomers, in the presence of mebicar. With that purpose, the density of solutions of Gly in aqueous Meb ρ_s at different molalities, $m_{\text{Meb}} \approx (0.024 \text{ to } 0.098) \text{ mol}\cdot\text{kg}^{-1}$ and $m_{\text{Gly}} \approx (0.05 \text{ to } 0.5) \text{ mol}\cdot\text{kg}^{-1}$, and at different temperatures, $T = (278.15 \text{ to } 308.15) \text{ K}$ with a step of 10

K, have been primarily determined. Being derived from data on $\rho_s(m_{\text{Gly}})$, the concentration-dependent apparent molar volumes $V_{\phi,\text{Gly}}(m_{\text{Gly}})$, standard (at infinite dilution) molar volumes V_{Gly}° and expansibilities $E_{p,\text{Gly}}^{\circ}$ as well as standard molar volumes of transfer $\Delta_{\text{tr}}V_{\text{Gly}}^{\circ}$ (water \rightarrow aqueous Meb) have been analyzed in the Results and discussion section. Within the scope of this study, we have estimated also the number of water molecules N_h hydrated to the amino acid and the volumetric pair-wise interaction coefficients V_{MebGly} at different temperatures.

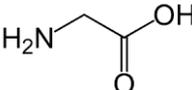
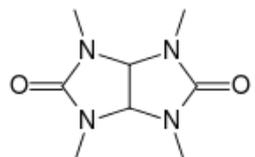
2. Experimental

2.1 Materials

A detail description of the organic compounds employed in densimetric measurements is given in Table 1. Mebicar was synthesized according to the procedure [14,19] based on the cyclocondensation of 1,3-dimethylurea (1,3-DMU: Sigma-Aldrich Co., assay ≥ 99.0 wt.%) with 1,3-dimethyl-4,5-dihydroimidazolidin-2-one. The latter was prepared by reaction of glyoxal (40 wt.% solution in water: Acros Organics, pure grade) with 1,3-DMU.¹ Immediately after purification by crystallizing (see Table 1) and prior to serial experiments, the samples of Gly and Meb were dried *in vacuo* at $T \approx 350$ K for 24 h (to constant mass). The authenticity of the prepared Meb sample was checked additionally using the melting point (Table 1) and ¹H-NMR data being measured on a Bruker AM 300 spectrometer in DMSO-*d*₆ (relative to TMS as the internal standard) at $T = 300$ K. The derived proton-spectrum proved to be in good agreement with those existing in the literature [14,15]. Both organic compounds were stored in a light-proof vacuum dessicator over P₂O₅ before being used.

Table 1

Sample description.

Characteristics	Glycine (Gly)	Mebicar (Meb)
Constitutional formula		
Molecular brutto-formula	C ₂ H ₅ NO ₂	C ₈ H ₁₄ N ₄ O ₂
Molar mass $M_i / (\text{g} \cdot \text{mol}^{-1})$	75.0672	198.2249
IUPAC name	Glycine	1,3,4,6-Tetramethyl- dihydroimidazo[4,5- <i>d</i>]imidazole- 2,5(1 <i>H</i> ,3 <i>H</i>)-dione

¹ The mebicar sample, being used in our experiments, was synthesized and characterized by Prof. A.N. Kravchenko (Laboratory of Nitrogen-containing Compounds of N.D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow).

Trivial (agreed-upon) name	Aminoacetic acid	2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione, or <i>N</i> -tetramethylglycouril
CAS RN	56-40-6	10095-06-4
Source	Sigma-Aldrich Co. (St. Louis, USA)	Original synthesis (see footnote 1 under the text)
Initial Mass Fraction Purity ^a	≥ 0.99	≥ 0.97
Purification Method ^b	Double recrystallization from aqueous EtOH of 1:1 ratio [12]	Double recrystallization from absolute EtOH with the addition of Et ₂ O (at the final stage) [9]
Final Mass Fraction Purity ^a	≥ 0.995	~ 0.995
Mass fraction of residual water ^c	≤ 0.0001	≤ 0.0001
Melting point, $T_{mp,i}$ / (K) ^d	506 ± 1 (decomposes) [13]	501.2 ± 0.2, 499 ± 1 [14], 501 ± 2 [15]
Density, $\rho_{cryst,i}$ / (g·cm ⁻³)	1.5965 ± 0.015 (298.15 K) [13,16], 1.5753 ± 0.013 (323.15 K) [17]	1.23 ± 0.02 (298.15 K) [18] ^e

^a Analyzed using the high performance liquid chromatography (HPLC).

^b EtOH and Et₂O are the ethanol (Fluka: puriss) and diethyl ether (Fluka: ACS reagent), respectively.

^c Titrated using a Karl Fischer method.

^d Italics is our data obtained using a multipurpose differential scanning calorimeter DSC 204 F1 Phoenix (Netzsch-Gerätebau GmbH, Germany).

^e Calculated from volumetric contributions of molecular fragments.

Before preparing a solution, the water (of natural isotope composition) was deionized and twice distilled in a Pyrex glass apparatus, and its electrical conductivity was $\kappa = 1.2 \times 10^{-6} \text{ S}\cdot\text{cm}^{-1}$.

2.2 Density measurements

Each of four “mother” (water + Meb) solutions of a ~500 cm³ was prepared under air-tight conditions on the 1000 g balance with the uncertainty of ± 0.001 g. Given this, the molality of aqueous Meb ranging from $m_{\text{Meb}} \approx (0.024 \text{ to } 0.098) \text{ mol}\cdot\text{kg}^{-1}$ was estimated with the overall uncertainty to be lesser than $\pm 3 \times 10^{-5} \text{ mol}\cdot(\text{kg H}_2\text{O})^{-1}$. All ternary (water + Meb + Gly) solutions as well as an aqueous amino acid of the desired compositions were also prepared by weighing at room temperature using a precise analytical balance LLB200 (Russia) with the error of $\pm 5 \times 10^{-5}$ g. As a result, the Gly content in aqueous solutions m_{Gly} ranging from *ca.* (0.05 to 0.50) mol·kg⁻¹ was determined with the uncertainty being up to $\pm 3 \times 10^{-5}$ mol per 1 kg of water.

Densities of binary (ρ_{aqGly} or ρ_{aqMeb}) and ternary (ρ_s) solutions were measured using a high precision vibrating-U-tube densimeter (Anton Paar DMA 5000 M, Graz, Austria) operated under the static mode and with the automatic viscosity correction [20]. The temperature of the measuring cell was kept constant to ± 0.01 K (with repeatability of 1 mK) at each of four steady-state temperatures: 278.15 K, 288.15 K, 298.15 K, or 308.15 K. All experiments were performed

at the pressure of $p = (99.6 \pm 0.8)$ kPa. The apparatus was calibrated once a day with dry air and freshly prepared water. The densities of the latter ρ_w were assumed to be those of the IAPWS Formulation 1995 [21]. Herewith ρ_w at each temperature was checked by way of comparing with the “Ultra pure water” density standard (Anton Paar, Austria) being in compliance with the NIST requirements. The former was differed from the latter of no more than by $\pm 5 \times 10^{-6}$ g·cm⁻³ at temperatures of interest. To prevent formation of air bubbles (a visually observed effect), all solutions were preheated to 5 K above the measuring temperature before placing them into the densimetric cell of a ~ 1 cm³ volume without contact with the atmospheric moisture. Under such conditions, five-fold density measurements were reproducible to within $\pm 5 \times 10^{-6}$ g·cm⁻³. Given the influence of all possible factors, the error of the measured ρ_s (and ρ_{aqGly} or ρ_{aqMeb} as well) did not exceed statistically $\pm 1 \times 10^{-5}$ g·cm⁻³.

3. Results and discussion

3.1. Densities, apparent and standard molar volumes

The experimental densities of ternary (water + Meb + Gly) solutions are summarized in Tables 1A and 2A (see Appendix A), together with the values of apparent molar volume $V_{\phi, \text{Gly}}$. The latter quantities were computed directly from the molality-dependent ρ_s values using the well-known formula [1–7]

$$V_{\phi, \text{Gly}} = \frac{M_{\text{Gly}}}{\rho_s} - \frac{(\rho_s - \rho_{\text{aqMeb}}) \times 10^3}{\rho_s \rho_{\text{aqMeb}} m_{\text{Gly}}}. \quad (1)$$

In the case of calculating $V_{\phi, \text{Gly}}(m_{\text{Gly}})$ for the aqueous Gly only, ρ_{aqGly} and ρ_w should be instead of ρ_s and ρ_{aqMeb} , respectively, in Eq. (1).

A survey of the existing literature data on trends of changing $\rho_{\text{aqGly}}(m_{\text{Gly}})$ or $V_{\phi, \text{Gly}}(m_{\text{Gly}})$ in aqueous Gly [3,4,6,22–28] showed that they are generally in rather good agreement with ours (Table 1A) over the temperature range under study (Fig. 2). Meanwhile, because the $V_{\phi, \text{Gly}}(m_{\text{Gly}})$ values are dependent on the amino acid concentration effect, i.e. on Gly – Gly interactions, the standard (apparent or partial at infinite dilution) molar volumes $V_{\text{Gly}}^0 (\equiv V_{\phi, \text{Gly}}^0 \equiv \bar{V}_{\text{Gly}}^0)$ are among the most often determined thermodynamic characteristics of aqueous Gly [22–24,29–34] and ternary {water + Gly + co-solvent (co-solute)} solutions [1–7,24–28,35–40].

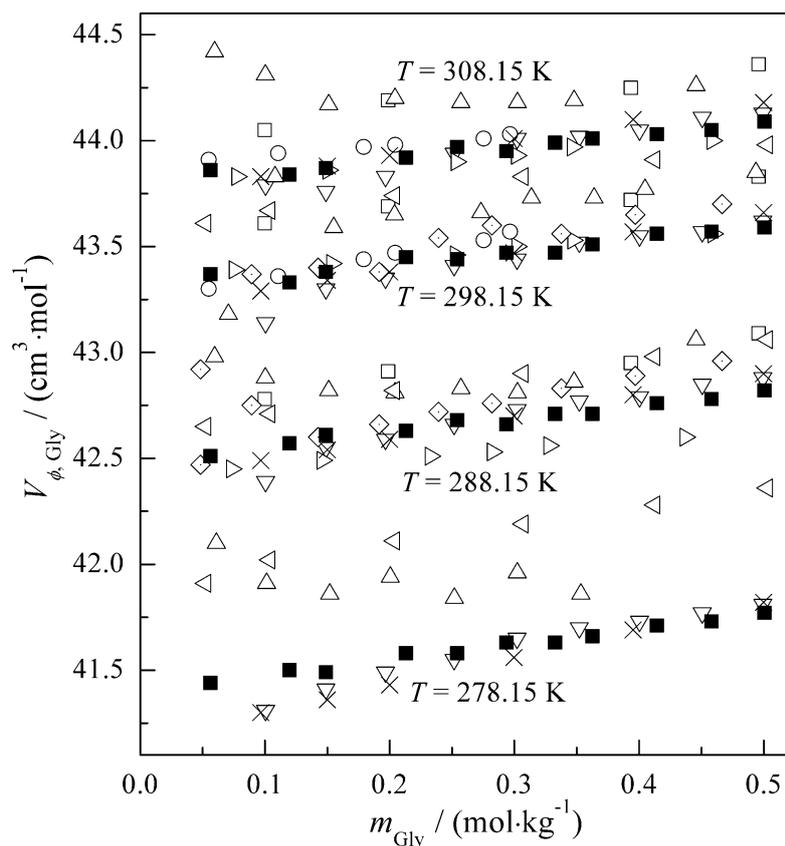


Fig. 2. Apparent molar volumes of glycine in water as a function of solution molality at different temperatures: ■, this work; □, ref. [3]; ○, ref. [4]; ◇, ref. [22]; △, ref. [23]; ▽, ref. [24]; ▷, ref. [25]; ◁, ref. [26]; ×, ref. [27]. For each of the depicted values, the half-width of 95% confidence interval does not exceed $\pm 0.02 \text{ cm}^3 \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$, on the whole.

To obtain the V_{Gly}^0 values for amino acid solutions in both water and aqueous Meb, data on $V_{\phi, \text{Gly}}(m_{\text{Gly}})$ were least squares fitted by applying an F -test (at the 95% confidence level [41]) to the first order (linear) equation

$$V_{\phi, \text{Gly}} = V_{\text{Gly}}^0 + S_V m_{\text{Gly}}, \quad (2)$$

where S_V , being the slope of $V_{\phi, \text{Gly}}$ vs. m_{Gly} , is the adjustable parameter, which is sometimes considered as a volumetric coefficient of the solute – solute pairwise interactions [42].

Table 2

Standard molar volumes V_{Gly}^0 and parameters S_V (*italics*) for glycine in water in comparison with those being taken from the literature sources at different temperatures T and $p \sim 0.1 \text{ MPa}$.^a

Source	$T = 278.15 \text{ K}$	$T = 288.15 \text{ K}$	$T = 298.15 \text{ K}$	$T = 308.15 \text{ K}$
This work	41.40 ± 0.02 <i>0.73 ± 0.07</i>	42.49 ± 0.02 <i>0.64 ± 0.08</i>	43.30 ± 0.03 <i>0.58 ± 0.11</i>	43.80 ± 0.03 <i>0.56 ± 0.09</i>
Z. Yan et al. [23]	41.90 ± 0.10	42.60 ± 0.10	43.50 ± 0.10	44.20 ± 0.10
J.-L. Shen et al. [24]	41.25 ± 0.02 <i>1.16 ± 0.06</i>	42.37 ± 0.02 <i>1.04 ± 0.07</i>	43.12 ± 0.03 <i>1.02 ± 0.07</i>	43.69 ± 0.03 <i>1.88 ± 0.07</i>
M. Martins et al. [27]	41.17 ± 0.02	42.39 ± 0.01	43.20 ± 0.01	43.76 ± 0.02
M. Kikuchi et al. [34]	41.07 ± 0.01 <i>1.18 ± 0.11</i>	42.29 ± 0.02 <i>0.79 ± 0.18</i>	43.19 ± 0.01 <i>0.09 ± 0.13</i>	43.81 ± 0.02 <i>-0.63 ± 0.17</i>
G. Singh et al. [3]	–	42.69 ± 0.05	43.51 ± 0.05	43.99 ± 0.04

	–	0.84 ± 0.08	0.69 ± 0.08	0.73 ± 0.06
T. Banipal et al. [25]	–	42.42 ± 0.01	43.35 ± 0.01	43.79 ± 0.01
H. Kumar et al. [26]	–	41.92 ± 0.01	42.62 ± 0.01	43.56 ± 0.01
	–	0.87 ± 0.02	0.88 ± 0.02	0.89 ± 0.02
A. Pal et al. [28]	–	41.71 ± 0.01	42.11 ± 0.01	42.54 ± 0.01
	–	0.30 ± 0.02	0.34 ± 0.02	0.29 ± 0.02
D. Kharakoz [32]	–	42.40 ± 0.10	43.30 ± 0.10	43.80 ± 0.10
R. Wadi & R. Goyal [35]	–	42.35 ± 0.02	43.26 ± 0.01	44.12 ± 0.01
R. Wadi & P. Ramasami [36]	–	42.54 ± 0.04	43.20 ± 0.03	43.85 ± 0.06
	–	0.82 ± 0.05	0.82 ± 0.04	0.64 ± 0.07
R. Sadeghi & A. Gholamireza [39]	–	42.20 ± 0.01	43.10 ± 0.01	43.71 ± 0.01
	–	1.73 ± 0.02	1.31 ± 0.02	1.07 ± 0.02
A. Pal & N. Chauhan [4]	–	–	43.24 ± 0.01	43.88 ± 0.01
	–	–	1.09 ± 0.03	0.47 ± 0.02
A. Hakin et al. [22]	–	42.48 ± 0.10	43.26 ± 0.10	–
X. Wang et al. [1]	–	–	42.81 ± 0.01	–
F. Millero et al. [29]	–	–	43.19 ± 0.02	–
	–	–	0.86 ± 0.04	–
S. Cabani et al. [30]	–	–	43.33 ± 0.12	–
A. Mishra & J. Ahluwalia [31]	–	–	43.19 ± 0.02	–
	–	–	0.90 ± 0.04	–
L. Xu et al. [37]	–	–	43.11 ± 0.01	–
C. Liu et al. [38]	–	–	43.57 ± 0.02	–
I. Cibulka et al. [40] ^b	–	–	(43.35 ± 0.13)	–

^a Units: V_{Gly}° , $\text{cm}^3 \cdot \text{mol}^{-1}$; S_V , $\text{cm}^3 \cdot \text{kg} \cdot \text{mol}^{-2}$. Uncertainties: $U(T) = \pm 0.01$ K and $U(p) = \pm 0.8$ kPa.

^b $p = 0.35$ MPa.

The values of V_{Gly}° and S_V obtained in such way for binary solutions of Gly in water are collected in Table 2 together with the similar data reported in other sources. In Table 3, the temperature-dependent data on V_{Gly}° being computed for solutions of Gly in aqueous Meb at various concentrations of the latter (m_{Meb}) are listed. The errors of defining our V_{Gly}° values given in both Tables 2 and 3 represent the combined expanded uncertainties which involve the scatter due to approximating procedure with using Eq. (2) as well as systematic errors being from the uncertainties of temperature, pressure and calibration constants [20]. Note also that the number at the fifth decimal place at m_{Meb} in Table 3 as well as in Tables 1A and 2A is indicative due to uncertainty value being pointed in the Experimental section. The same goes for the digit at the sixth decimal place at ρ_s (ρ_{aqGly} or ρ_{aqMeb}) in the Appendix A tables, too.

Table 3

Standard molar volumes of glycine $V_{\text{Gly}}^{\circ}(m_{\text{Meb}})$ in the studied ternary solutions and volumes of transfer $\Delta_{\text{tr}}V_{\text{Gly}}^{\circ}$ (water \rightarrow aqueous mebicar) at different temperatures T and $p = 99.6$ kPa.^a

Volume property	$T = 278.15$ K	$T = 288.15$ K	$T = 298.15$ K	$T = 308.15$ K
$m_{\text{Meb}} = 0.02394$				
$V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	41.48 ± 0.03	42.58 ± 0.02	43.40 ± 0.02	43.91 ± 0.02
$S_V/(\text{cm}^3 \cdot \text{kg} \cdot \text{mol}^{-2})$	0.59 ± 0.08	0.54 ± 0.05	0.47 ± 0.05	0.47 ± 0.06
$\Delta_{\text{tr}} V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	0.08 ± 0.04	0.09 ± 0.03	0.10 ± 0.04	0.11 ± 0.04
$m_{\text{Meb}} = 0.05186$				
$V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	41.57 ± 0.02	42.67 ± 0.02	43.50 ± 0.02	44.02 ± 0.02
$S_V/(\text{cm}^3 \cdot \text{kg} \cdot \text{mol}^{-2})$	0.59 ± 0.05	0.48 ± 0.05	0.42 ± 0.05	0.38 ± 0.05
$\Delta_{\text{tr}} V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	0.17 ± 0.03	0.18 ± 0.03	0.20 ± 0.04	0.22 ± 0.04
$m_{\text{Meb}} = 0.07582$				
$V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	41.64 ± 0.02	42.76 ± 0.02	43.58 ± 0.02	44.12 ± 0.01
$S_V/(\text{cm}^3 \cdot \text{kg} \cdot \text{mol}^{-2})$	0.61 ± 0.06	0.48 ± 0.04	0.42 ± 0.05	0.37 ± 0.02
$\Delta_{\text{tr}} V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	0.24 ± 0.03	0.27 ± 0.03	0.28 ± 0.04	0.32 ± 0.03
$m_{\text{Meb}} = 0.09775$				
$V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	41.71 ± 0.02	42.84 ± 0.02	43.66 ± 0.02	44.22 ± 0.02
$S_V/(\text{cm}^3 \cdot \text{kg} \cdot \text{mol}^{-2})$	0.65 ± 0.06	0.49 ± 0.06	0.37 ± 0.04	0.29 ± 0.05
$\Delta_{\text{tr}} V_{\text{Gly}}^{\circ}/(\text{cm}^3 \cdot \text{mol}^{-1})$	0.31 ± 0.03	0.35 ± 0.03	0.36 ± 0.03	0.42 ± 0.04

^a Uncertainties: $U(T) = \pm 0.01$ K and $U(p) = \pm 0.8$ kPa.

One can see in Fig. 2 that our data on $V_{\phi, \text{Gly}}(m_{\text{Gly}})$ are in very good agreement with those found by Shen et al. [24] and Martins with co-authors [27] at all temperatures being compared. Also, the available results from [4,22,25] for separate temperatures (excepting $T = 278.15$ K) indicate a sufficiently high consistency with the $V_{\phi, \text{Gly}}(m_{\text{Gly}})$ values measured in this work. In other cases [3,23,26] being depicted in Fig. 2, significant differences in the analyzed quantities are observed comparing with ours. This is most probably related to methodological differences in densimetric measurements that are somehow manifested in uncertainties of parameters for the concentration dependence of apparent molar volumes of Gly in the aqueous solution. As we have noted, no information was found in the open literature for the apparent or partial molar volumes of Gly in the presence of Meb being dissolved in water.

As for data on $V_{\phi, \text{Meb}}(m_{\text{Meb}})$ and V_{Meb}° , the analysis of them is hardly expedient since only four $\rho_{\text{aqMeb}}(m_{\text{Meb}})$ values at each of temperatures in a very narrow concentration range were derived here (Tables 1A and 2A). As we mentioned above, the volumetric properties of aqueous Meb in both diluted {down to $m_{\text{Meb}} \approx 0.01 \text{ mol} \cdot (\text{kg H}_2\text{O})^{-1}$ } and concentrated {up to $m_{\text{Meb}} \approx 5 \text{ mol} \cdot (\text{kg H}_2\text{O})^{-1}$ } solutions were comprehensively discussed elsewhere [9,10].

As defined at infinite dilution, the solvent molecules surround each solute molecule (i) and the values of V_i° are free from solute – solute interactions and therefore provide information regarding the solute – solvent interactions [43,44]. Herewith, in the case of ternary system that considered here, the aqueous Meb solution is a “solvent” with respect to a solute Gly.

Being reported in Tables 2 and 3, the V_{Gly}° values increase with rising temperature or content of Meb. Such a situation indicates the presence of both Gly – water and Gly – Meb interactions. For the binary (water + Gly) solutions, a positive “slope” of the $V_{\phi,\text{Gly}}$ vs. m_{Gly} dependences (values of S_V in Table 2) can be interpreted as the “substitutional” solution process (due to filling up the solvent void space) resulting in breakdown of the water structure owing to the solute – solvent interaction [45]. Going to the ternary (water + Meb + Gly) solutions, the value of S_V becomes decreasingly positive with rising glycoluril concentration, except for $T = 278.15$ K (Table 3). It may be due to decrease in solvation of Gly molecules in the aqueous solution of Meb, i.e. release of some water molecules from the hydration shell of the solute in solution, which is greater at higher concentrations of co-solute and temperatures.

Finally, it is also important to indicate that pH measurements were also carried out using a digital pH meter FP 20 (Mettler Toledo, Japan) with the accuracy of ± 0.01 pH at $T = 298.15$ K. At the maximum concentration of the glycoluril solutions ($m_{\text{Meb}} \approx 0.1 \text{ mol}\cdot\text{kg}^{-1}$), a decrease in pH values from 7.57 to 6.63 was observed upon the addition of the amino acid up to $m_{\text{Gly}} \approx 0.5 \text{ mol}\cdot\text{kg}^{-1}$. That is, the pH values for ternary (water + Meb + Gly) mixtures are greater than the value of $\text{p}K_1(\text{COOH}) \approx 2.4$ and less than the value of $\text{p}K_2(\text{NH}_2) \approx 9.8$ for the studied amino acid, and Gly exists mainly in zwitterionic form in both water and aqueous Meb. Herewith the pH values for ternary solutions are increasingly approaching the isoelectric point of Gly being ~ 6.0 . According to the inferences [25,27,40], such a situation results in a change in V_{Gly}° that does not exceed the uncertainty limits of the measurements and calculations (Table 3).

3.2. Standard molar volumes of transfer

The standard molar volumes of transfer of Gly from water to aqueous Meb $\Delta_{\text{tr}}V_{\text{Gly}}^\circ$ at different m_{Meb} have been calculated as following

$$\Delta_{\text{tr}}V_{\text{Gly}}^\circ = V_{\text{Gly}}^\circ(\text{in aqueous Meb}) - V_{\text{Gly}}^\circ(\text{in water}). \quad (3)$$

The data on $\Delta_{\text{tr}}V_{\text{Gly}}^\circ(m_{\text{Meb}})$ together with the uncertainties are listed in Table 3.

From Table 3, it is seen that the positive $\Delta_{\text{tr}}V_{\text{Gly}}^\circ$ values increase monotonically with both the molality of aqueous Meb and the temperature. According to the co-sphere overlap model

[46,47], when two solute particles come close enough, their co-spheres will overlap and this is accompanied by the change in their thermodynamic parameters including volume-related those. When interpreting $\Delta_{tr}V_{Gly}^0$ in our case, there are two main types of interactions between Gly and Meb in water, as is in the amino acid solutions in aqueous amides [38]: (a) hydrophilic (ion) – hydrophilic interactions between the head groups {zwitterionic end groups ($-\text{NH}_3^+$ and $-\text{COO}^-$) or hydrophilic groups [$>\text{C}(\text{H})\text{OH}$ and $>\text{C}(\text{H})\text{NH}_2$]} of Gly and the $-\text{CON}-$ or $>\dot{\text{C}}(\text{H})$ -groups of Meb (Fig. 1), and (b) hydrophilic (ion) – hydrophobic interactions between the above groups of the amino acid and the *N*-sited methyl groups of the glycoluril under study.

Interactions of type (a) would lead to a positive $\Delta_{tr}V_{Gly}^0$ since there is a reduction in the electrostriction effect and the overall water structure is enhanced [38,47]. In other words, some water molecules in the vicinity of a Gly molecule may be released to the bulk water in the presence of the co-solute (Meb). This brings about an increase in volume (or decrease in volume shrinkage) of the solvent, thereby reducing strong interactions between the amino acid and water. Interactions of type (b) would lead to a negative value of $\Delta_{tr}V_{Gly}^0$ because the methyl groups provide an additional tendency for hydrophobic–hydrophilic interactions, resulting in a reduction in the structure of water [38,47]. The observed positive $\Delta_{tr}V_{Gly}^0$ values for Gly (Table 3) suggest that interactions of type (a) predominate over the interactions of type (b). When the temperature or the molality of the co-solute in its aqueous solution increases, the dominant effect should be more notable [5,38]. The increased $\Delta_{tr}V_{Gly}^0$ with increasing m_{Meb} and T strengthens this view.

Indeed, as was concluded previously by Ben-Naim [48], the solvent-induced interactions between two functional groups that can form hydrogen bonds are to be much stronger than the corresponding hydrophobic – hydrophilic (hydrophobic) interactions. As a consequence of that, inter- and intramolecular hydrophilic interactions are probably more significant in biochemical processes than hydrophobic interactions. Given the structure peculiarities of a Meb molecule (Fig. 1) and its behavior in the aqueous medium [9,11], one can assume that the above hydrophilic interactions are directly connected with forming hydrogen bonds between oxygen atoms of the two Meb carbonyls (in both rings) and Gly amino groups. The hydrogen atoms at the “bridging” methine groups {*i.e.*, at the C(1) and C(5) atoms} of a glycoluril molecule (see Fig. 1a) can also form the weaker H-bonds with two proton-acceptors (of Gly acid groups) [11]. However in the latter case, the steric inconsistencies at forming such hydrogen bonds in the studied ternary system can play the more perceptible part.

3.3 Volume-related interaction parameters

Quantitatively, the interaction coefficients were estimated using a formalism based upon the McMillan–Mayer theory of solutions [49,50] which permits the formal separation of effects due to the interaction between the pair of solute molecules and those due to interactions involving three or more solute molecules. This approach was further discussed in [2–4,6,27] and some other works in order to include the solute – co-solute interactions in the hydration spheres where the amino acid is as a solute. So, applied to our study, the $\Delta_{\text{tr}}V_{\text{Gly}}^{\circ}$ value can be expressed by the following equation

$$\Delta_{\text{tr}}V_{\text{Gly}}^{\circ} = 2V_{\text{GlyMeb}}m_{\text{Meb}} + 3V_{\text{GlyMebMeb}}m_{\text{Meb}}^2 + \dots, \quad (4)$$

whose constants were found by fitting the concentration-dependent values of the transfer volume at different temperatures (Table 3).

Considering both the number of available data on $\Delta_{\text{tr}}V_{\text{Gly}}^{\circ}(m_{\text{Meb}})$ at each temperature and the quality of the linear functions obtained (with a minimum r^2 of 0.9993), only the pair-wise interaction parameters $V_{\text{GlyMeb}}(T)$ were estimated rather correctly, which are depicted in Fig. 3. As for triple interaction parameters, the statistical F -test analysis showed that the contribution of term $V_{\text{GlyMebMeb}}$ to $\Delta_{\text{tr}}V_{\text{Gly}}^{\circ}$ is negligible with the high uncertainty when the experimental data are described adequately using Eq. (4). This is in accordance with the conclusions made by Ben-Naim et al. [51] that if one extend the same interaction-related model to study the correlation between pairs and triplets of (identical or different) functional groups of biomolecules, the pair correlations will be substantially more pronounced.

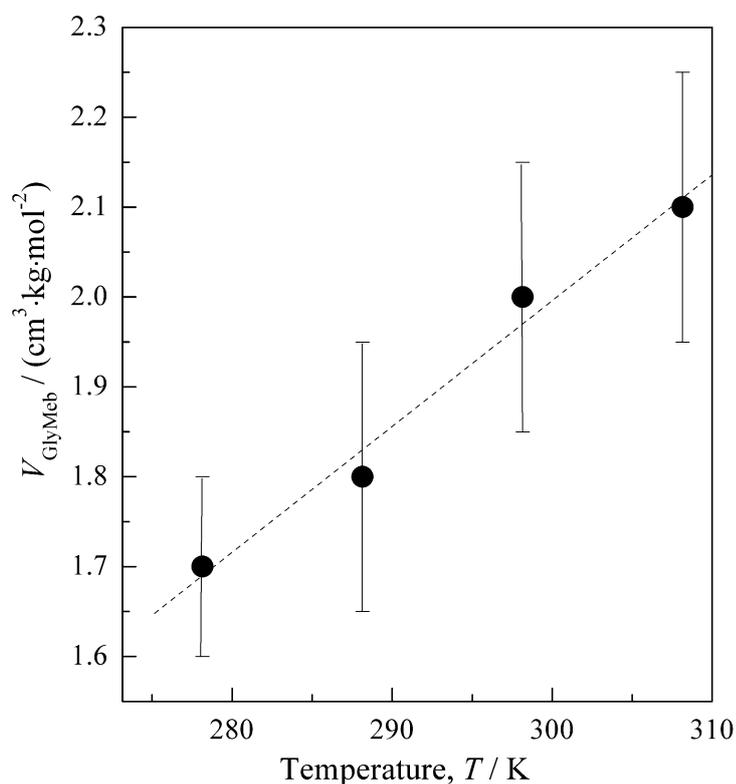


Fig. 3. The volumetric coefficient for glycine – mebicar pair interactions from equation (4) as a function of temperature. The bars limit of a 95% confidence interval for each of values being considered. The dashed line is a linear approximation.

Seen in Fig. 3, the positive contributions from V_{GlyMeb} to $\Delta_{\text{tr}}V_{\text{Gly}}^{\circ}$ show that the interaction between Gly and Meb is mainly pair-wise and the solute – co-solute interaction dominate over the solute – water interaction. Overall positive values of V_{GlyMeb} suggest that interactions occur due to the overlap of hydration spheres of Gly and Meb, which again supports the molecular interpretation drawn from the above co-sphere overlap model. That is, because of the different structural organization of water in these two domains, the volume change will be negative when water is released to the bulk from a co-sphere that is more structured than the bulk and positive when the bulk is more structured. When head groups of Gly interact pair-wise, the overlap of the hydration co-spheres leads to returning of some electrostricted water to the bulk solvent, which is more structured.

The V_{GlyMeb} value increases with temperature (see Fig. 3) although the latter has a rather weak effect on these interaction-related volume changes (but above the error of determining them). Overall, it will point to strengthening dehydration of Gly, which will contribute positively to the transfer volume. Also, if one identifies the prevailing hydrophilic Meb molecules as the water structure breakers, then the structure-breaking effect of them decreases as a result of interactions with Gly molecules. As we mentioned above, such interactions occur most likely through hydrogen-bonding between the Meb carbonyls and amino groups of Gly.

3.4. The hydration number of glycine

The hydration number $N_{h,i}$ (per a solute molecule i) explicitly reveals the degree of hydration of a solute in water. The $N_{h,i}$ quantity reflects the electrostriction effect of the charged ends of an amino acid molecule in the vicinity of water molecules. These values for Gly in aqueous Meb solutions were estimated using the Shahidi et al. [52] method

$$\Delta_{tr} V_{Gly}^{\circ} = 3.0 \times [N_{h,Gly}(\text{in water}) - N_{h,Gly}(\text{in aqueous solution of Meb})] \quad (5)$$

Within the scope of the “continuum model of a solution” by Millero et al. [53], the N_h values for glycine in water at different temperatures can be evaluated by the following equation

$$N_{h,Gly}(\text{in water}) = V_{elect,Gly}^{\circ} / (V_{e,W}^{\circ} - V_{b,W}^{\circ}), \quad (6)$$

where $V_{elect,Gly}^{\circ}$ is the electrostriction partial molar volume (at the standard state) due to the hydration of Gly, $V_{e,W}^{\circ}$ and $V_{b,W}^{\circ}$ are the corresponding molar volumes of electrostricted water (in the hydration shell) and water *in bulk*, respectively. The $(V_{e,W}^{\circ} - V_{b,W}^{\circ})$ quantities at the desired temperatures were calculated by Yan et al. [54] according to the procedure described by Millero with co-authors [53].

To estimate $V_{elect,Gly}^{\circ}$, we used the following equation [38,53,54]

$$V_{elect,Gly}^{\circ} = V_{Gly}^{\circ} - V_{int,Gly}^{\circ} \quad (7)$$

Here, $V_{int,Gly}^{\circ}$ is the intrinsic molar volume of the non-hydrated solute that as is suggested can be made up of two terms, the van der Waals volume and the volume due to packing effects. Following the assumption [53], the $V_{int,Gly}^{\circ}$ values for Gly at different temperatures were estimated from their crystal molar volumes

$$V_{int,Gly}^{\circ} = (0.7/0.634) V_{cryst,Gly}^{\circ}, \quad (8)$$

where 0.7 is the packing density for molecules in organic crystals [55] and 0.634 is the packing density for random packing spheres [53]. The $V_{cryst,Gly}^{\circ} = M_{Gly} / \rho_{cryst,Gly}$ quantities at different temperatures were calculated using data on $\rho_{cryst,Gly}$ in Table 1 and linear equation

$$\rho_{cryst,Gly}(T) / (\text{g} \cdot \text{cm}^{-3}) = \rho_{cryst,Gly}(\theta) + (8.5 \pm 3.8) \times 10^{-4} (T - \theta). \quad (9)$$

In the given equation, T and $\theta = 298.15$ K are the current and reference temperatures. Hence the molar expansibility of Gly $E_{p,cryst,Gly}$ is predicted to be ca. $0.0244 \text{ cm}^3 \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$ at $T = (278.15 \text{ to } 323.15)$ K. The validity of using of Eq. (9) is based on the fact that the density or molar volume of the crystalline Gly undergoes fairly slight changes within the above-mentioned temperature range due to thermal stability of its polymorph structure [56].

Thus, using Eqs (5) and (6), the $N_{h,Gly}$ (in water) and $N_{h,Gly}$ (in aqueous solution of Meb) values were estimated from the experimentally obtained data on V_{Gly}^0 (Tables 2 and 3) as well as from the results of calculation on Eqs. (7) to (9), with the involvement of data [53–55]. The hydration numbers of Gly in water and in aqueous Meb solutions at all the temperatures studied are given in Table 4.

Table 4

Hydration numbers of glycine $N_{h,Gly}$ at different temperatures T and mebicar molalities m_{Meb} .^a

$m_{Meb}/(\text{mol}\cdot\text{kg}^{-1})$	278.15 K	288.15 K	298.15 K	308.15 K
0	3.84	3.16	2.60	2.15
0.02394	3.81	3.13	2.57	2.11
0.05186	3.78	3.10	2.54	2.08
0.07582	3.76	3.07	2.51	2.04
0.09785	3.74	3.04	2.48	2.01

^a See footnote “a” in Table 3.

As follows from Table 4, the hydration numbers of Gly in Meb solutions are less than in water and decrease with increasing concentration of glycoluril at all temperatures, which again indicates that the increase in solute – co-solute interactions reduces the electrostriction effect of the amino acid. This observation supports the above-said view that the bicyclic Meb as a co-solute in aqueous solutions of Gly is similar to the *N*-methyl-substituted amide [38]. It also suggests that, within the investigated range of m_{Meb} , Meb has a visibly weaker dehydrating effect on the Gly than in the case of increasing temperature, especially at low T .

3.5. Effect of temperature on volumetric properties

To compute the values of standard molar expansibility $E_{p,Gly}^0$, the non-linear function of V_{Gly}^0 vs. T was approximated (at $\theta = 298.15$ K) by the quadratic equation [20]

$$V_{Gly}^0(T) = a_0 [\equiv V_{Gly}^0(\theta)] + a_1(T - \theta) + a_2(T - \theta)^2. \quad (10)$$

It follows from Eq. (10) that

$$E_{p,Gly}^0(T) = \left(\partial V_{Gly}^0 / \partial (T - \theta) \right)_p = a_1 + 2a_2(T - \theta). \quad (11)$$

Based on Eqs (10) and (11), the quantities of $E_{p,Gly}^0(\theta)/(\text{cm}^3\cdot\text{mol}^{-1}\cdot\text{K}^{-1})$ were estimated to be (0.0654 ± 0.002) at $m_{Meb} = 0$, (0.0664 ± 0.006) at $m_{Meb} \approx 0.024$, (0.0673 ± 0.007) at $m_{Meb} \approx 0.052$, (0.0681 ± 0.004) at $m_{Meb} \approx 0.076$ and (0.0693 ± 0.008) at $m_{Meb} \approx 0.098$ mol·kg⁻¹. The

detailed results of approximating the $V_{\text{Gly}}^{\circ} - m_{\text{Meb}}$ function for two “border” temperatures are depicted in Fig. 4.

Since the changes in $E_{p,\text{Gly}}^{\circ}$ like those in V_{Gly}° , are influenced the Gly – water and Gly – Meb interactions only, the dependences of this quantity on T and m_{Meb} can be used to extract the additional useful information on the item. As seen in Fig. 4, the $E_{p,\text{Gly}}^{\circ}$ values are positive and increase with rising temperature as well as molality of Meb solution (being beyond the limit of fitting errors). According to the inferences made by Chalikian et al. [33,57], such a situation may be due to that the expansibility of water in the hydration shell of a Gly molecule is much greater than the expansibility of water *in bulk*. This most likely is attributed to the strong H-bonding between the Meb and water molecules, which, in turn, results relatively weaker hydrogen bonding between zwitterionic $-\text{NH}_3^+$ and $-\text{COO}^-$ (or hydrophilic NH_2 and COOH) groups of the amino acid and water molecules [57]. The positive slope of $E_{p,\text{Gly}}^{\circ}$ vs. m_{Meb} in Fig. 4 can serve as support of the given assumption.

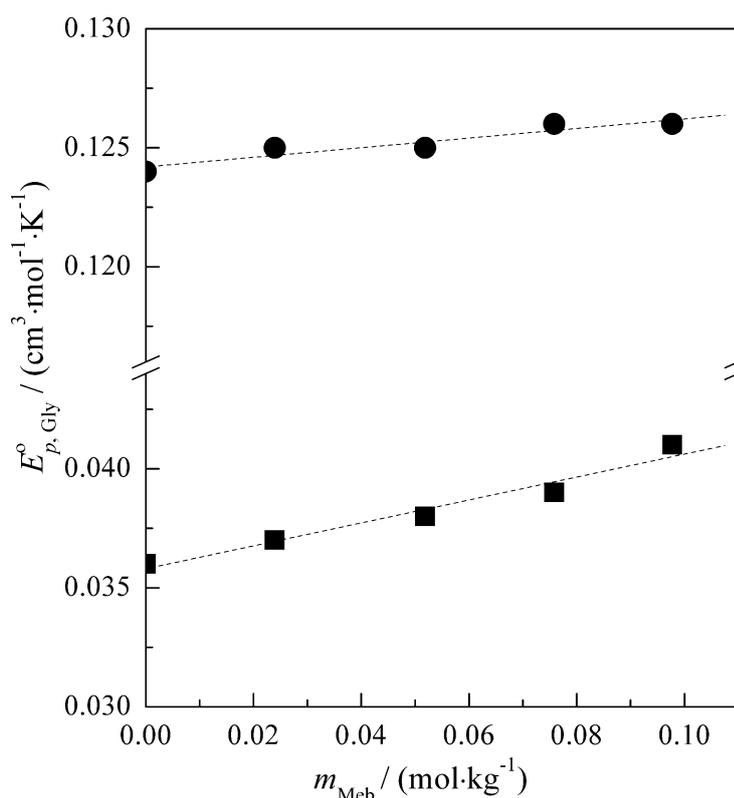


Fig. 4. The standard (partial at infinite dilution) molar expansibilities of the amino acid in ternary solutions (water + glycine + mebicar) as a function of the co-solute (glycoluril) molal concentration at $T = 278.15 \text{ K}$ (■) and $T = 308.15 \text{ K}$ (●). (The value of a 95% confidence interval for each of specified points can be seen above, when the corresponding data at $T = \theta = 298.15 \text{ K}$ are considered.)

The temperature dependences of $E_{p,\text{Gly}}^{\circ}$ were also used to confirm the above-mentioned assumptions on the capability of the solute to promote or destroy the water structure, based on the thermodynamic relation proposed primordially by Hepler [58]

$$\left(\frac{\partial C_{p,\text{Gly}}^{\circ}}{\partial p}\right)_T = -T \left(\frac{\partial^2 V_{\text{Gly}}^{\circ}}{\partial T^2}\right)_p = -T \left(\frac{\partial E_{p,\text{Gly}}^{\circ}}{\partial T}\right)_p, \quad (12)$$

where $C_{p,\text{Gly}}^{\circ}$ is the standard molar isobaric heat capacity of the solute.

On this basis, the structure-breaking and structure-making solutes should have negative and positive derivatives $\left(\frac{\partial E_{p,\text{Gly}}^{\circ}}{\partial T}\right)_p$, respectively. These quantities were evaluated (as the $2a_2$ coefficients) by twofold differentiating the right-hand side of Eq. (10) with respect to $(T - \theta)$. Resulting such approximation, the desired values were found to be negative and comparable in magnitude, being $(-0.003 \pm 0.001) \text{ cm}^3 \cdot \text{mol}^{-1} \cdot \text{K}^{-2}$, at all molalities of aqueous Meb.

In the context of common classification [58], Gly in both water and aqueous Meb solutions should be a predominantly structure-breaking solute, a fact being in a good accordance with the above inferences based on other volume-related interaction characteristics. This means that the electrostriction component of $\left(\frac{\partial E_{p,\text{Gly}}^{\circ}}{\partial T}\right)_p$ has greater influence over the corresponding structural component in the determination of the solute – solvent interactions for the present system. As a result, when the temperature increases, the removal of water molecules from the hydration shell of Gly favours interactions of its molecules with the predominantly hydrophilic molecules of Meb, which also have the predominantly structure-breaking properties [9,59].

4. Concluding remarks

In this work, we have derived the volumetric characteristics of ternary (water + mebicar + glycine) solutions to extend a set of data aimed at a better estimation of the extent of solute – solvent and solute – co-solute interactions. From the results, it is concluded that the hydrophilic – hydrophilic (or ion – hydrophilic) interactions between $>\text{C}(\text{H})\text{OH}$ and $>\text{C}(\text{H})\text{NH}_2$ (or $-\text{NH}_3^+$ and $-\text{COO}^-$) groups of the amino acid and $-\text{CON}-$ or $>\dot{\text{C}}(\text{H})$ -groups of mebicar dominate over the hydrophilic – hydrophobic (or ion – hydrophobic) interactions between the above groups of glycine and *N*-sited methyl groups of the glycoluril studied. Herewith the interactions between glycine and mebicar are mainly pair-wise in this ternary system and they are occurred primarily through the hydrogen bonding among the mebicar $>\text{C}=\text{O}$ -groups and glycine $-\text{NH}_2$ -groups.

The hydration numbers for glycine decrease with rising temperature and concentration of mebicar. However, within the investigated range of molalities of the glycoluril aqueous solution, mebicar has a visibly weaker dehydrating effect on glycine than temperature, especially at low temperatures. Similar to a prevailingly hydrophilic mebicar, glycine in both water and aqueous solutions of co-solute should be considered as a structure breaker solute.

Thus, the trends in transfer and other volumetric properties result from the effects of glycine and mebicar on the water structure which are driven by solute – co-solute interactions.

The analysis presented in this study could help in understanding the behavior of more complex biomolecules in aqueous pharmaceutical solutions, and it may be relevant in areas such as biotechnology and life sciences. Especially as the role of the amino acid – drug interactions in aqueous media remains yet uncertain.

Acknowledgments

All densimetric studies were performed on the setup of the Centre for joint use of scientific equipment of the “Upper-Volga Region Centre of Physicochemical Research”.

Authors are thankful to Prof. A.N. Kravchenko (N.D. Zelinsky Institute of Organic Chemistry of Russian Academy of Sciences) for help in the synthesis procedure and testing of mebicar sample.

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Appendix A

Table 1A

Experimental densities, $\rho_{\text{aqGly}} / (\text{g}\cdot\text{cm}^{-3})$, and smoothed apparent molar volumes, $V_{\phi,\text{Gly}} / (\text{cm}^3\cdot\text{mol}^{-1})$, for aqueous solutions of glycine at different temperatures, T , and molalities, $m_{\text{Gly}} / (\text{mol}\cdot\text{kg}^{-1})$, and at pressure $p = 99.6 \text{ kPa}$ ^a

m_{Gly}	$T = 278.15 \text{ K}$		$T = 288.15 \text{ K}$		$T = 298.15 \text{ K}$		$T = 308.15 \text{ K}$	
	ρ_{aqGly}	$V_{\phi,\text{Gly}}$	ρ_{aqGly}	$V_{\phi,\text{Gly}}$	ρ_{aqGly}	$V_{\phi,\text{Gly}}$	ρ_{aqGly}	$V_{\phi,\text{Gly}}$
0 ^b	0.999964	–	0.999101	–	0.997047	–	0.994035	–
0.05633	1.001854	41.44	1.000931	42.51	0.998830	43.37	0.995793	43.86
0.11971	1.003962	41.50	1.002973	42.57	1.000831	43.33	0.997762	43.84
0.14892	1.004934	41.49	1.003906	42.61	1.001740	43.38	0.998662	43.87
0.21298	1.007033	41.58	1.005949	42.63	1.003727	43.45	1.000623	43.92
0.25420	1.008388	41.58	1.007249	42.68	1.005007	43.44	1.001873	43.97
0.29369	1.009667	41.63	1.008504	42.66	1.006220	43.47	1.003081	43.95
0.33258	1.010934	41.63	1.009715	42.71	1.007418	43.47	1.004248	43.99
0.36255	1.011896	41.66	1.010655	42.71	1.008323	43.51	1.005145	44.01
0.41425	1.013549	41.71	1.012255	42.76	1.009882	43.56	1.006693	44.03
0.45801	1.014946	41.73	1.013607	42.78	1.011208	43.57	1.007994	44.05
0.50061	1.016291	41.77	1.014911	42.82	1.012486	43.59	1.009249	44.09

^a Uncertainties (at the confidence level of 0.95) are: $U(\rho_s) = \pm 1.0 \times 10^{-5} \text{ g}\cdot\text{cm}^{-3}$, $U(V_\phi) = \pm 0.02 \text{ cm}^3 \times \text{mol}^{-1}$, $U(m) = \pm 3 \cdot 10^{-5} \text{ mol}\cdot\text{kg}^{-1}$, $U(T) = \pm 0.01 \text{ K}$, and $U(p) = \pm 0.8 \text{ kPa}$.

^b $\rho_{\text{aqGly}} \equiv \rho_w$.

Table 2A

Experimental densities, $\rho_s/(g\cdot cm^{-3})$, and apparent molar volumes, $V_{\phi,Gly}/(cm^3\cdot mol^{-1})$, for solutions of glycine in aqueous mebicar at different temperatures, T , and molalities, $m_{Gly}/(mol\cdot kg^{-1})$, and at pressure $p = 99.6\text{ kPa}$ ^a

m_{Gly}	$T = 278.15\text{ K}$		$T = 288.15\text{ K}$		$T = 298.15\text{ K}$		$T = 308.15\text{ K}$	
	ρ_s	$V_{\phi,Gly}$	ρ_s	$V_{\phi,Gly}$	ρ_s	$V_{\phi,Gly}$	ρ_s	$V_{\phi,Gly}$
$m_{Meb} = 0.02394$								
0 ^b	1.001131	–	1.000240	–	0.998163	–	0.995130	–
0.04879	1.002764	41.52	1.001820	42.61	0.999704	43.44	0.996649	43.93
0.09598	1.004340	41.49	1.003342	42.61	1.001189	43.43	0.998111	43.94
0.14921	1.006094	41.59	1.005042	42.67	1.002850	43.47	0.999746	43.99
0.19665	1.007659	41.59	1.006555	42.68	1.004326	43.48	1.001199	44.00
0.25238	1.009483	41.62	1.008318	42.71	1.006043	43.52	1.002893	44.03
0.29268	1.010787	41.66	1.009582	42.75	1.007279	43.55	1.004108	44.06
0.34794	1.012582	41.67	1.011316	42.76	1.008973	43.55	1.005776	44.07
0.41101	1.014602	41.72	1.013270	42.80	1.010882	43.59	1.007655	44.11
0.45055	1.015865	41.74	1.014497	42.81	1.012068	43.62	1.008835	44.11
0.48507	1.016963	41.76	1.015558	42.83	1.013108	43.63	1.009856	44.13
0.51160	1.017797	41.78	1.016361	42.86	1.013905	43.64	1.010630	44.15
$m_{Meb} = 0.05186$								
0	1.002522	–	1.001586	–	0.999470	–	0.996413	–
0.05102	1.004225	41.60	1.003234	42.68	1.001077	43.51	0.997995	44.04
0.09520	1.005692	41.61	1.004651	42.72	1.002460	43.53	0.999358	44.05
0.15334	1.007610	41.65	1.006506	42.75	1.004267	43.58	1.001142	44.07
0.19811	1.009076	41.69	1.007928	42.77	1.005655	43.58	1.002503	44.11
0.24895	1.010731	41.73	1.009536	42.78	1.007222	43.60	1.004051	44.10
0.28983	1.012058	41.74	1.010816	42.81	1.008472	43.62	1.005277	44.14
0.34789	1.013936	41.76	1.012624	42.85	1.010238	43.65	1.007019	44.16
0.38379	1.015085	41.79	1.013744	42.85	1.011324	43.67	1.008095	44.16
0.45223	1.017258	41.84	1.015858	42.87	1.013392	43.68	1.010130	44.18
0.51490	1.019247	41.86	1.017771	42.92	1.015263	43.71	1.011970	44.22

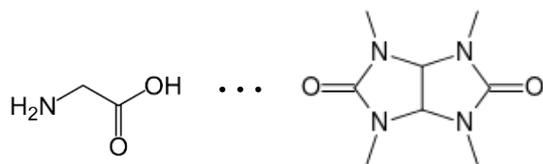
Table 2A. Continued

m_{Gly}	$T = 278.15 \text{ K}$		$T = 288.15 \text{ K}$		$T = 298.15 \text{ K}$		$T = 308.15 \text{ K}$	
	ρ_s	$V_{\phi, \text{Gly}}$						
$m_{\text{Meb}} = 0.07582$								
0	1.003679	–	1.002706	–	1.000553	–	0.997437	–
0.05231	1.005421	41.66	1.004390	42.77	1.002194	43.62	0.999053	44.14
0.10067	1.007021	41.70	1.005935	42.82	1.003704	43.62	1.000539	44.15
0.14629	1.008518	41.75	1.007387	42.84	1.005121	43.64	1.001933	44.17
0.20676	1.010500	41.76	1.009299	42.87	1.006986	43.66	1.003770	44.19
0.25524	1.012079	41.77	1.010826	42.88	1.008469	43.70	1.005233	44.21
0.29322	1.013302	41.81	1.012011	42.90	1.009628	43.71	1.006573	44.23
0.34705	1.015029	41.85	1.013681	42.94	1.011266	43.72	1.007985	44.24
0.40109	1.016757	41.88	1.015356	42.95	1.012892	43.76	1.009589	44.27
0.45147	1.018358	41.90	1.016901	42.98	1.014399	43.79	1.011075	44.29
0.49516	1.019732	41.94	1.018239	43.00	1.015707	43.79	1.012363	44.30
0.50990	1.020189	41.96	1.018692	43.00	1.016150	43.79	1.012797	44.30
$m_{\text{Meb}} = 0.09785$								
0	1.004794	–	1.003752	–	1.001580	–	0.998474	–
0.04977	1.006446	41.76	1.005349	42.87	1.003137	43.70	1.000007	44.22
0.09485	1.007938	41.75	1.006790	42.87	1.004542	43.69	1.001386	44.26
0.14733	1.009657	41.81	1.008450	42.94	1.006166	43.72	1.002983	44.28
0.19290	1.011146	41.83	1.009892	42.93	1.007572	43.72	1.004369	44.27
0.24694	1.012903	41.85	1.011587	42.96	1.009225	43.75	1.005994	44.30
0.29480	1.014438	41.90	1.013074	43.00	1.010683	43.77	1.007436	44.29
0.34002	1.015891	41.92	1.014475	43.02	1.012052	43.79	1.008780	44.32
0.41170	1.018167	41.98	1.016685	43.05	1.014213	43.81	1.010906	44.34
0.45098	1.019410	42.00	1.017891	43.06	1.015380	43.84	1.012068	44.34
0.48025	1.020324	42.03	1.018782	43.08	1.016253	43.85	1.012926	44.36
0.50913	1.021233	42.04	1.019661	43.09	1.017115	43.85	1.013765	44.38

^a See footnote “a” in Table 1A.^b $\rho_s \equiv \rho_{\text{aqMeb}}$.

Graphical Abstract

Volumetric molar properties and solute – co-solute interactions in the (water + mebicar + glycine) solution



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Highlights:

- ▶ Volume properties of ternary (water + mebicar + glycine) solutions were derived.
- ▶ Solution densities were measured at $T = (278.15 \text{ to } 308.15) \text{ K}$ and $p = 99.6 \text{ kPa}$.
- ▶ Volumes of transfer, interaction parameters, and hydration numbers were discussed.
- ▶ Glycine – mebicar interactions are mainly pair-wise and hydrophilic in nature.
- ▶ Glycine dehydration increases with rising temperature and mebicar concentration.

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