



Enthalpy-related parameters of interaction of simplest α -amino acids with the pharmaceutical *mebicar* (*N*-tetramethylglycoluril) in water at 298.15 K



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ABSTRACT

The enthalpies of dilution of mixed aqueous solutions of glycine (Gly, *x*) or L-alanine (Ala, *x*) with *mebicar* (Meb, *y*), a well-known pharmaceutical, were measured calorimetrically at 298.15 K. The enthalpic heterotactic coefficients for pair, h_{xy} , and triplet, h_{xxy} and h_{xyy} , interactions between hydrated solute molecules were estimated using the McMillan-Mayer formalism. Similar to the homotactic parameters h_{xx} and h_{yy} , the h_{xy} value for the ternary (water + Gly + Meb) system was found to be negative in sign. It points to the predomination of zwitterion (hydrophilic) – hydrophilic interactions in this mixed solution. In the case of the (water + Ala + Meb) system, $h_{xx} > 0$ and $h_{xy} > 0$, a fact testifying to the prevalently hydrophobic character of the Ala – Meb interaction in the aqueous medium.

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1. Introduction

Interactions of drugs with protein constituents in the aqueous medium have attracted a considerable interest in the fields of biochemistry and pharmaceuticals. Such interactions may play a pivotal role in distribution and in acquiring the biocompatibility of pharmaceuticals in the human body [1,2]. The stereochemically achiral glycine (hereinafter, Gly) is found in the protein of all life forms and has the simplest structure being characteristic for typically model bioactive compounds. In turn, L-alanine (in later, Ala) is the levorotary (–)-enantiomer of the simplest chiral α -amino acid with apolar (hydrophobic) side-chain, which is a $-\text{CH}_3$ group.

As a part of research on the thermodynamics of ternary (water + amino acid + glycoluril) solutions [3], the present work reports the enthalpies of dilution, $\Delta_{\text{dil}}H^m$, for Gly and Ala solutions in aqueous *mebicar* (Meb) at 298.15 K. The latter compound (Fig. 1) has found application in the clinical medicine as a high-efficient low-toxicity daytime tranquilizer and a coronary-active drug [4,5].

A phenomenological thermodynamics does not yield directly energy-related aspects of intermolecular interaction. However

one can indirectly derive meaningful inferences from the $\Delta_{\text{dil}}H^m$ values. The point is that they can serve as a basis for calculating the heterotactic and homotactic enthalpic coefficients of pair (h_{xy} , h_{xx} and h_{yy}) and triplet (h_{xxy} , h_{xxy} , h_{xxx} and h_{yyy}) interactions between the amino acid zwitterion and the bicyclic Meb molecule (Fig. 1) under the participation of solvent molecules. For the ternary aqueous solutions being considered here, these interaction-related virial coefficients have been calculated and analysed with using the McMillan-Mayer formalism [1,6–8].

2. Experimental

A detail description of compounds employed in our experiments is given in Table 1.

Mebicar was synthesized according to the procedure [11] based on the regioselective cyclocondensation of 1,3-dimethylurea with 1,3-dimethyl-4,5-dihydroxyimidazolidin-2-one. The product melting point (temperature of fusion, T_{fus}) was measured using a multipurpose differential scanning calorimeter DSC 204 F1 Phoenix (Netzsch-Gerätebau GmbH, Germany) with the heating rate of $10^\circ\text{C}\cdot\text{min}^{-1}$ and gas flow rate (in the argon atmosphere) being $15\text{ cm}^3\cdot\text{min}^{-1}$. The procedure for T_{fus} determination was based on the onset point. The DSC heating curve for Meb and calibration data

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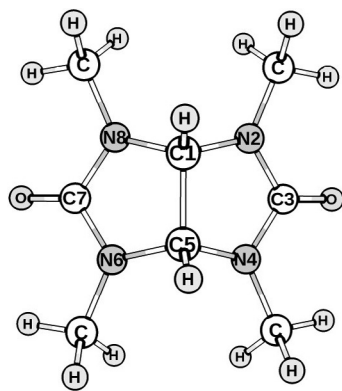


Fig. 1. Mecicar [3].

are contained in the [Supplementary material](#) file (Figs. S1–S3). The $T_{\text{fus}}(\text{Meb})$ value has found to be (501.2 ± 0.2) K, with expanded uncertainty for a 0.95 level of confidence. This result is in very good agreement with the existing literature data, (501 ± 2) K [10,12]. Immediately after purification (Table 1) and prior to serial calorimetry-dilution experiments, the samples of Meb and amino acids were dried to constant mass under vacuum at $T \approx 350$ K for 24 h. The mass fraction of trace water in them (according to a Karl Fischer method) did not exceed 0.0001. All the organic compounds under study were stored in a light-proof vacuum desiccator over P_2O_5 before being used. The water of natural isotope composition was deionized and twice distilled (in a Pyrex glass apparatus) up to a specific conductance of $1.3 \times 10^{-6} \text{ S}\cdot\text{cm}^{-1}$.

The experimental measurements of $\Delta_{\text{dil}}H^m$ were carried out at $T = (298.15 \pm 0.001)$ K and $p = (99.6 \pm 0.8)$ kPa using an automated ampoule-type isoperibol calorimeter (equipped with a 30 cm^3 titanium vessel) whose design and measuring/testing procedure were detailed previously [13,14]. Here we will only note that the minimal enthalpic effect (in the case of aqueous Ala) exceeds the

declared detection limit of a calorimeter by a factor of 30. The standard uncertainty in $\Delta_{\text{dil}}H^m$ measurements is estimated to be no more than 4% at worst.

The experimental data on $\Delta_{\text{dil}}H^m$ (in J per 1 kg of total water in the final state) for all the solutions studied are given in [Tables 2 and 3](#) where m^i and m^f are the initial and final molalities, respectively, determined with an uncertainty of $1 \times 10^{-4} \text{ mol}$ per 1 kg of water. Note that the absence of data on $\Delta_{\text{dil}}H^m$ for mixed (water + Ala + Meb) solutions with the mutual molality being larger than $1.0 \text{ mol}\cdot\text{kg}^{-1}$ (see [Table 3](#)) is due to that the solubility of specified amino acid in the aqueous Meb solutions is limited at the temperature considered.

3. Results and discussion

The enthalpy-heterotactic pair and triplet interaction coefficients, h_{xy} , h_{xyy} and h_{xxx} , were estimated using a so-called *auxiliary* function, $\Delta_{\text{aux}}H_{x,y}^m$, based on the McMillan-Mayer formalism [1,6–8]. According to inferences [1,8], a relationship between $\Delta_{\text{aux}}H_{x,y}^m$ and cross-interaction coefficients h_{xy} , h_{xyy} and h_{xxx} can be expressed as

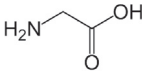
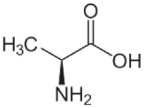
$$\frac{\Delta_{\text{aux}}H_{x,y}^m}{m_y^f(m_x^f - m_x^i)} = 2h_{xy} + 3h_{xyy}(m_x^f + m_x^i) + 3h_{xxx}(m_y^f + m_y^i) + \dots \quad (1)$$

To calculate interaction-related homotactic virial coefficients, h_{xx} , h_{yy} , h_{xxx} and h_{yyy} , Eq. (1) can be transformed into the form [8]

$$\frac{\Delta_{\text{dil}}H_{x(y)}^m(m_{x(y)}^i \rightarrow m_{x(y)}^f)}{m_{x(y)}^f(m_{x(y)}^f - m_{x(y)}^i)} = h_{xx(yy)} + h_{xxx(yy)}(m_{x(y)}^f - m_{x(y)}^i) + \dots \quad (2)$$

In fitting Eqs. (1) and (2), a least-squares method was employed. The theoretical zero-values of $\Delta_{\text{dil}}H^m$ representing the dissolution of a pure solvent in oneself were also included in the fit. For all

Table 1
Sample description.

Solute Sample	Molecule formula; Molar mass, M_i ($\text{g}\cdot\text{mol}^{-1}$)	IUPAC name; CAS RN ^a	Source ^b	Initial mass fraction purity	Purification method ^c	Final mass fraction ^d
Glycine (Gly) Glycine (Gly)	<chem>C2H5NO2</chem> ; 75.0672	Aminoethanoic acid; 56-40-6	Sigma- Aldrich Co. (USA)	≥ 0.99	Double recrystallization from aqueous ethanol of 1:1 ratio	≥ 0.998
 L-Alanine (Ala) L-Alanine (Ala)	<chem>C3H7NO2</chem> ; 89.0941	2S)-2-Amino-propionic acid; 56-41-7	Sigma- Aldrich Co. (USA)	≥ 0.99	Double recrystallization from aqueous ethanol of 1:1 ratio	≥ 0.998
 Mebicar (Meb) Mebicar (Meb)	<chem>C8H14N4O2</chem> ; 198.2249	1,3,4,6-Tetramethyl-dihydro- imidazo[4,5-d]imidazole-2,5 (1H,3H)-dione; 10095-06-4	Original synthesis	≥ 0.98	Double recrystallization from absolute ethanol (with addition of diethylether at the final stage)	≥ 0.995

^a Another agreed-upon (trivial) names for Mecicar: 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione or 2,4,6,8-(N-)tetramethylglycoluril.

^b The Mecicar specimen was synthesized and tested under the guidance of Prof. A.N. Kravchenko (Laboratory of Nitrogen-containing Compounds, N.D. Zelinsky Institute of Organic Chemistry of the RAS, Moscow).

^c Ref [9] (for amino acids) and ref 10 (for Mecicar).

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

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