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The interactions between some *N*-acetyl-*N*′-methyl-L-α-amino acid amides and urea in water at 298.15 K

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Abstract

The enthalpies of solution of *N*-acetyl-*N*′-methylglycinamide, *N*-acetyl-*N*′-methyl-L-α-alaninamide, *N*-acetyl-*N*′-methyl-L-α-leucinamide and *N*-acetyl-*N*′-methyl-L-α-serinamide have been measured in water and in aqueous urea solutions with molalities from 0.25 to 3.0 mol kg^{-1} at 298.15 K. From these data the standard dissolution enthalpies of amides in aqueous urea solutions have been determined. The results have been treated according to McMillan–Mayer's theory in order to obtain the enthalpic coefficients of the interactions between amino acid derivatives and urea molecules. The obtained parameters were compared with the hydrophobic scale for the amino acid side chains.

Keywords: *N*-Acetyl-*N*′-methyl-L-α-amino acid amide; Urea; Enthalpies of solution; Enthalpic interaction coefficient

1. Introduction

The diversity of interactions between proteins and the medium components resulting from the complex structure of these macromolecules makes it difficult to assess the influence of particular types of interactions in which they take part. In the interpretation of the properties of biological systems an important role is played by information obtained from examinations of aqueous solutions of simple organic substances whose molecular structure mimics the structural elements of polypeptide chains.

The present study is a continuation of thermodynamic research, carried out by our group, of the interactions between natural L-α-amino acids [1–5] and small peptides [6,7] with electrolytes or non-electrolytes in water. The present paper discusses the results of calorimetric measurements of aqueous solutions containing *N*-acetyl-*N*′-methyl-L-α-amino acid amides and urea. Characteristic structural elements of the selected amides (CH_3–CONH–C$^{\alpha}$HR–CONH–CH_3) include amino acid side substituents, R, adjacent to two polar groups being analogous to peptide bonds in proteins. As distinct from other model compounds of proteins, the molecules of the compounds under investigation have no zwitterionic of amino acids groups, which allows one to eliminates the contribution of Coulombic forces in the complex mechanism of interactions. The selected urea molecule is used as a differentiating model molecule. Moreover, urea exists in living organisms as one of the components of the urea metabolic cycle and its molecule contains also the same functional groups as those in polypeptide protein chains.

Thermodynamic parameters that well describe the interactions between two molecules of the examined substances in aqueous solutions are the enthalpic coefficients of heterogeneous pair interaction. These coefficients, derived from McMillan–Mayer's theory [8], modified by Friedman and Krishnan [9], Franks et al. [10] and Desnoyers et al. [11], illustrate the summary energetic effects of the interactions between amide and urea molecules that take place with a competitive participation of water molecules. In order to determine the enthalpic pair interaction coefficients, the dissolution enthalpies of several *N*-acetyl-*N*′-methyl-L-α-amino acids (Am) in water and aqueous urea solutions were measured by calorimetry at 298.15 K.

2. Experimental

Samples of *N*-acetyl-*N*′-methylglycinamide, *N*-acetyl-*N*′-methyl-L-α-alaninamide, *N*-acetyl-*N*′-methyl-α-L-leucinamide (all Bachem, Feinchemikalien AG) and *N*-acetyl-*N*′-methyl-L-α-serinamide (prepared at the Department of Organic Chem-

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istry, University of Łódź) were dried under reduced pressure at room temperature. Urea (Aldrich Chemical Co. Ltd., mass fraction: 0.99) was crystallized from water–methanol mixtures and also dried at 333 K under reduced pressure. All aqueous solutions of urea were prepared by mass using twice-distilled water. The enthalpies of solution were measured in water and in aqueous solutions of urea using an isoperibol calorimeter [6] at 298.15 K. The accuracy was ±0.5%. Water–urea solvent 0.25–3.00 mol(U) $\text{kg}^{-1}(H_2O)$ were prepared by weight. The standard enthalpies of solution of amino acids derivatives were determined by the linear extrapolation to zero amides (Am) concentration of the six to eight independent measurements. The molalities of the solutes of amides (Am) were $(2–7) \times 10^{-3}$ mol(Am) kg^{-1}(solvent). The errors are the standard deviations of the molar dissolution enthalpies.

3. Results and discussion

The determined standard enthalpies of solution of *N*-acetyl-*N*′-methyl-L-α-amino acid amides in water, together with the appropriate literature values [12–14] are listed in Table 1. The corresponding data for aqueous solutions of urea are given in Table 2. The values of $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ depend on the kind of amide molecule and on the urea content in the system. The standard enthalpies of *N*-acetyl-*N*′-methylglycinamide and *N*-acetyl-*N*′-methyl-L-α-serinamide are positive whereas the values of the same function for the subsequent two amides are negative. It is interesting to notice that the dissolution enthalpy of *N*-acetyl-*N*′-methyl-L-α-leucinamide increases within the whole investigation range of urea content, in contrast to others amide derivatives.

Table 3
Heterogenous interaction parameters of *N*-acetyl-*N*′-methylamino acid amides with urea h_{AmU} and the hydrophobicity parameter of the amino acid side chain Δf_{t}

N-Acetyl-*N*′-methyl-amino acid amide	h_{AmU} (J kg mol^{-2})	Amino acid	Δf_{t} [18] (kJ mol^{-1})
AcGlyNHCH_3	−255 ± 29 (−269)[a]	Glycine	0
AcAlaNHCH_3	−70 ± 8 (−66)[a]	Alanine	2.09
AcLeuNHCH_3	270 ± 27	Leucine	7.53
AcSerNHCH_3	−273 ± 51	Serine	−1.26

[a] Barone et al. [17].

On the basis of the enthalpic pair interaction parameters model the interactions occurring in the investigated solutions were analysed. To that end the determined standard enthalpy of solution was expressed as a function of the solution molality [11]:

$$\Delta_{\text{sol}}H_{\text{m}}^{\infty}(\text{W}+\text{U}) = \Delta_{\text{sol}}H_{\text{m}}^{\infty}(\text{W}) + 2h_{\text{AmU}}m_{\text{U}} + 3h_{\text{AmUU}}m_{\text{U}}^{2} + \cdots \qquad (1)$$

where $\Delta_{\text{sol}}H_{\text{m}}^{\infty}(\text{W}+\text{U})$ is the standard molar enthalpy of solution of amide (Am) in aqueous solution of urea, $\Delta_{\text{sol}}H_{\text{m}}^{\infty}(\text{W})$ the corresponding enthalpy of solution in pure water, m_{U} the molal concentration of urea in water with the unit of mol(U) kg^{-1}(water), h_{AmU} the enthalpic pair interaction coefficient and h_{AmUU} is the enthalpic triplet interaction coefficient. As the h_{AmUU} coefficients contain some contributions from the pairwise interaction terms [15] they are not discussed in this paper.

According to the usual interpretation, the enthalpic coefficient h_{AmU} (Table 3) describes the total energetic effect of the interaction of heterogeneous amide–urea pair including the contribution of the solvent molecules surrounding the interacting solute molecules. For the systems investigated here, the

Table 1
Standard enthalpies of solution $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ of *N*-acetyl-*N*′-methyl-L-α-amino acid amides in water at 298.15 K

Solute	Symbol	$\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ (kJ mol^{-1})	
		Present results[a]	Literature values
N-Acetyl-*N*′-methylglycinamide	AcGlyNHCH_3	1.72 ± 0.01	1.66 [12], 1.67 [13], 1.76 [14]
N-Acetyl-*N*′-methyl-L-α-alaninamide	AcAlaNHCH_3	−3.50 ± 0.01	−3.51 [12], −2.75 [14]
N-Acetyl-*N*′-methyl-L-α-leucinamide	AcLeuNHCH_3	−9.77 ± 0.09	−10.38 [12], −9.79 [14]
N-Acetyl-*N*′-methyl-L-α-serinamide	AcSerNHCH_3	1.89 ± 0.09	

[a] $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ with the standard deviation of the measured values.

Table 2
Standard enthalpies of solution $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ of *N*-acetyl-*N*′-methyl-L-α-amino acid amides in aqueous solutions of urea at 298.15 K

m_{U} (mol kg^{-1})	$\Delta_{\text{sol}}H_{\text{m}}^{\infty\,\text{a}}$ (kJ mol^{-1})			
	AcGlyNHCH_3	AcAlaNHCH_3	AcLeuNHCH_3	AcSerNHCH_3
0.25	1.64 ± 0.02			1.75 ± 0.02
0.50	1.48 ± 0.01	−3.56 ± 0.02	−9.55 ± 0.05	1.62 ± 0.02
1.00	1.27 ± 0.02	−3.61 ± 0.03	−9.31 ± 0.02	1.34 ± 0.02
1.50	1.04 ± 0.04	−3.66 ± 0.01	−9.08 ± 0.02	1.22 ± 0.01
2.00	0.90 ± 0.05	−3.67 ± 0.02	−8.87 ± 0.02	1.06 ± 0.02
2.50		−3.68 ± 0.01	−8.71 ± 0.03	0.82 ± 0.01
3.00	0.59 ± 0.02	−3.68 ± 0.02	−8.59 ± 0.02	0.76 ± 0.02

[a] $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$ with the standard deviation of the measured values.

mentioned effect is a sum: (a) an exothermic effects of the process connected with the direct interactions between the polar groups of skeleton of *N*-acetyl-*N′*-methyl-L-α-amino acid amide (–CONH–C$^{\alpha}$H–CONH–) and the polar urea molecule; (b) an exothermic effect of the interaction between urea and the side polar substituent of amide; (c) an endothermic effect accompanying the removal of some water molecules from the hydration layers of polar groups of amide and urea molecules. The latter effect is influenced by an additional energetic contribution of dehydration connected with the presence of the hydrophobically hydrated methyl groups in the peptide chain as well as in the amino acid radicals of the examined amide molecules. (According to Savage and Wood's [16] glycine side chain –H is treated as 0.5CH_2 group.)

The h_{AmU} values obtained, together with those derived from enthalpies of dilution by Barone et al. [17] are presented in Table 3. The negative values of h_{AmU} for the systems containing $AcGlyNHCH_3$, $AcAlaNHCH_3$, $AcSerNHCH_3$ suggest that the interactions between urea and peptide molecules dominate the effects of dehydration of the substances present in the solution. As can be seen, the introduction of methyl groups to the hydrocarbon chain of the $AcGlyNHCH_3$ molecule causes a considerable increase in the value of the enthalpic pair interaction coefficient for the pairs of amide with urea. A positive shift in the h_{AmU} values can result from the enhanced hydrophobicity of the amide molecule in the following sequence: $AcGlyNHCH_3 < AcAlaNHCH_3 < AcLeuNHCH_3$. Consequently, the h_{AmU} value for $AcLeuNHCH_3$–urea pair becomes positive and it indicates that the endothermic contribution connected with the dehydration plays a dominating role in the behaviour of this system. From the comparison of the enthalpic interaction coefficients for $AcAlaNHCH_3$–urea and $AcSerNHCH_3$–urea it results that the replacement of the hydrogen atom in the alkyl side chain of $AcAlaNHCH_3$ with –OH group increases the exothermic effect associated with the interaction between amide and urea molecules in water (Table 3).

It is evident from the h_{AmU} values that the amide side groups have a significant effect on the pairwise interactions. The changes in the interaction parameter values for the systems investigated here are similar to those observed for the aqueous solutions containing urea and analogous L-α-amino acids (glycine, alanine, leucine and serine) [2,4]. Recently, we have found that the enthalpic coefficients of interaction between the amino acid zwitterions and the urea in water can be interpreted in terms of the hydrophobic or hydrophilic effects of the side chains of the solutes on their interactions with a polar urea molecule [3]. Thus, it seems to be interesting to compare the enthalpic coefficients obtained in this work with the parameter characterizing the properties of amino acid side chains including in *N*-acetyl-*N′*-methyl-L-α-amino acid amide molecules. It can be seen (Table 3) that the changes of the h_{AmU} values show a similar trend as the free energies of transfer of hydrophobic side chain from organic solvent to water Δf_t which, in Nazaki and Tanford's opinion [18], describe the hydrophobic–hydrophilic character of this chain. It was additionally observed (Fig. 1) that the urea–amide pair interaction coefficients in aqueous solution well correlate with the hydrophobicity parameter of amino acid side chains based on the values of enthalpic homogeneous pair interaction coefficients of natural amino acids, h_{AA} [1,3]. The linear relationship suggests that the contributions of amino acid radicals (–R) to the overall interactions between *N*-acetyl-*N′*-methyl-L-α-amino acid amides (examined in this study) and urea are similar to those of these radicals made to the interactions of homogeneous amino acid–amino acid pairs in water.

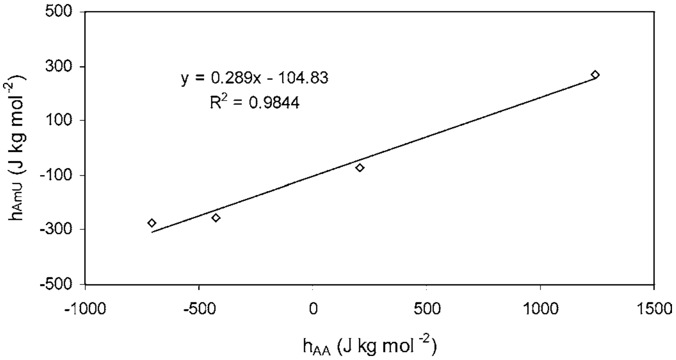

Fig. 1. Relationship between the ethalpic interaction coefficients for the urea–amino acids derivatives pairs h_{AmU} and the homogenous interaction parameters of L-α-amino acids in water h_{AA} [1].

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