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Thermochemical Study of Glycylglycine Interaction with Polyhydric Alcohols in Aqueous Solution

I. N. Mezhevoi and V. G. Badelin

Krestov Institute of Solutions Chemistry, Russian Academy of Sciences,
ul. Akademicheskaya 1, Ivanovo, 153045 Russia
e-mail: inm@isc-ras.ru

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Abstract—Integral enthalpies of glycylglycine dissolution ($\Delta_{sol}H^m$) in aqueous solutions of glycerol, ethylene glycol, and propylene glycol have been determined at the organic co-solvent concentration up to 32 mol %. The standard dissolution enthalpy ($\Delta_{sol}H^0$) and standard enthalpy of transfer of the peptide from water into the binary solvent ($\Delta_{tr}H^0$) have been calculated. The influence of various types of interactions and the structural features of the interacting molecules on the enthalpy of glycylglycine dissolution has been analyzed.

Keywords: molecular interaction, aqueous solution, calorimetry, dissolution enthalpy, glycylglycine, polyhydric alcohol, peptide

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Structural stability and functional activity of protein compounds is known to depend on the solvent composition, environmental temperature gradient, the presence of surfactants, pressure changes, and other physicochemical stimuli [1–5]. In particular, the polyhydric alcohols studied in this work participate in stabilization of native conformation of globular proteins [6]. Study of interactions involving oligopeptides (models of proteins) in aqueous-organic mixed solvents allows for deeper understanding of mechanisms of structural stability of complex biopolymers and of their chemical and biological activity.

Table 1 lists the experimentally determined enthalpies of dissolution $\Delta_{sol}H^0$ of glycylglycine (Gly-Gly) in the binary mixtures of water with glycerol, ethylene glycol, or propylene glycol. The enthalpies of transfer $\Delta_{tr}H^0$ of the dipeptide from water into the binary solvents are plotted in the Figure as a function of the alcohol molar fraction (x_2).

From the plots it is seen that the transfer enthalpy reaches a maximum at a certain molar fraction of the organic co-solvent. In general, the transfer enthalpy is determined by a number of various competing interactions including solvation processes. The obtained data were analyzed in terms of the solute–co-solvent interaction applying the approach developed earlier [7–9].

In the dipeptide–alcohol–water three-component mixtures the hydrates solute molecules exist in a fairly densely packed solution. Therefore, the solvate shells of the molecules are overlapped, resulting in the change of the intermolecular interactions. The calculated enthalpies of transfer of Gly-Gly were combined of several terms, see Eq. (1).

$$\Delta_{tr}H^0 = -\Delta H_1 - \Delta H_2 + \Delta H_3 + \Delta H_4. \quad (1)$$

In Eq. (1), ΔH_1 reflects the ion-bipolar interactions between the polar fragments of the dipeptide (carboxylic, carbonyl, and amino groups) and the polyhydric alcohol hydroxy groups; ΔH_2 stands for the enthalpy of donor-acceptor interactions involving peptide bonds of the dipeptide and the alcohol hydroxy groups; ΔH_3 is assigned to the hydrophobic-hydrophilic interactions between the non-polar dipeptide fragments and hydroxy groups of the co-solvent or zwitter-ion sites of Gly-Gly; and ΔH_4 reflects the hydrophobic-hydrophobic interactions between non-polar moieties of the dipeptide and the alcohols.

The first two types of interactions brought the negative contribution into the $\Delta_{tr}H^0$ value, whereas the contribution of the other two interaction types was positive. The overall transfer enthalpy was positive for the most of the studied systems (cf. figure), pointing at the predominant contributions of the ΔH_3 and ΔH_4

Table 1. Standard enthalpy of dissolution ($\Delta_{sol}H^0$, kJ/mol) in the binary water–alcohol solvents at 298.15 K

Glycerol		Ethylene glycol		Propylene glycol	
m_y[a]	$\Delta_{sol}H^0$	m_y[a]	$\Delta_{sol}H^0$	m_y[a]	$\Delta_{sol}H^0$
0.8754	12.00±0.06	0.9323	12.16±0.06	0.0945	12.36±0.05
1.4274	12.27±0.06	1.8412	12.80±0.05	1.7034	13.31±0.07
2.2143	12.57±0.07	2.9623	13.49±0.06	2.4434	13.79±0.05
3.1153	12.86±0.06	4.2743	14.04±0.07	3.1835	14.22±0.06
4.1674	13.05±0.06	5.7245	14.72±0.07	4.1366	14.78±0.07
5.2611	13.20±0.07	7.4567	15.13±0.08	5.4621	15.13±0.08
7.2923	13.23±0.07	9.4453	15.62±0.08	6.3729	15.37±0.08
9.4701	13.05±0.06	11.3867	15.97±0.08	8.0123	15.36±0.08
11.1176	12.76±0.06	14.3289	16.00±0.07	10.6028	14.71±0.07
12.5764	12.45±0.05	17.6245	15.68±0.06	13.0943	13.54±0.06
15.0644	11.96±0.04	21.3387	15.27±0.06	16.1357	12.23±0.06
18.5698	11.57±0.04	25.7799	14.42±0.05	19.6510	10.46±0.05

[a] Molality of the polyhydric alcohol solution (mol/kg).

terms. The maximum in the transfer enthalpy plots was due to the increased contribution from the exothermal processes (hydrogen bonding and ion-bipolar interactions) at higher concentration of the organic cosolvent. The contribution from the hydrophobic-hydrophilic and the hydrophobic-hydrophobic interactions was the most prominent at the solvent composition corresponding to the $\Delta_{tr}H^0$ maximum.

Quantitative analysis of the interparticle interactions in the studied systems was performed via regression analysis in the frame of the McMillan–Mayer theory [10] involving calculation of enthalpy coefficients of pair interactions (h_{xy}) of glycylglycine and the polyhydric alcohols. The $\Delta_{sol}H^0$ values were fitted with the third-order polynomial of the alcohol molality m_y [Eq. (2)], the a_i being coefficients determined via the least squares method.

$$\Delta_{sol}H^0 = a_0 + a_1m_y + a_2m_y^2 + a_3m_y^3. \quad (2)$$

The regression analysis gave the following equations corresponding to dissolution of glycylglycine in aqueous solutions of glycerol [Eq. (3)], ethylene glycol [Eq. (4)], and propylene glycol [Eq. (5)].

$$\Delta_{sol}H^0 = (11.52\pm0.02) + (0.61\pm0.01)m_y - \ldots, \quad (3)$$

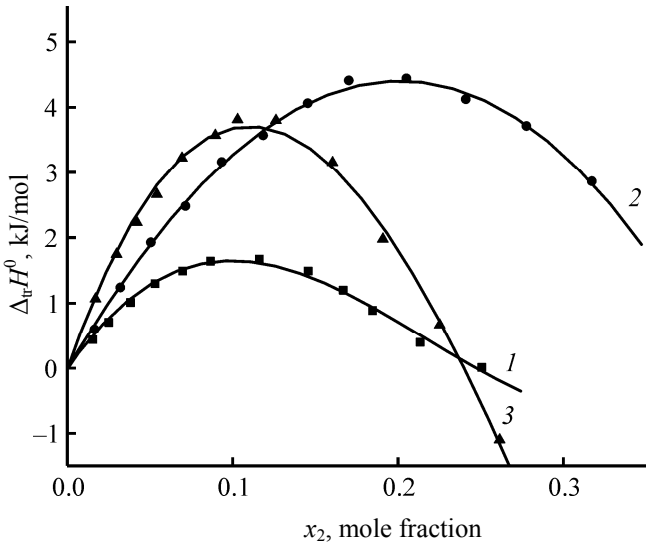
R 0.999, SD 0.018, n 12,

$$\Delta_{sol}H^0 = (11.53\pm0.06) + (0.75\pm0.02)m_y - \ldots, \quad (4)$$

R 0.998, SD 0.062, n 12,

$$\Delta_{sol}H^0 = (11.55\pm0.09) + (1.19\pm0.04)m_y - \ldots, \quad (5)$$

R 0.998, SD 0.078, n 12.



Enthalpy of transfer of glycylglycine from water into its mixture with glycerol (*1*), ethylene glycol (*2*), and propylene glycol (*3*) as a function of the polyhydric alcohol concentration (x_2) at 298.15 K.

Table 2. Enthalpy coefficient of pair interactions (h_{xy}, J kg mol^{-2}) of glycine and glycylglycine with polyhydric alcohols in aqueous solution at 298.15 K

Co-solvent	Glycine	Glycylglycine
Glycerol	251.5 [15]	303±5
Ethylene glycol	356.3 [15]	375±11
Propylene glycol	550.3 [15]	593±39

The free term of Eqs. (3)–(5) corresponded to the standard enthalpy of Gly-Gly dissolution in pure water, its values coinciding well with the earlier determined reference values: $\Delta_{sol}H^0$(Gly-Gly) 11.56±0.07 [11], 11.67 [12], and 11.81±0.0.03 [13]. The enthalpy pair interaction parameters h_{xy} were calculated as $h_{xy} = a_1/2$ [14]. In order to compare the thermochemical properties of Gly-Gly and the monomeric unit (glycine), the enthalpy parameters of pair interaction of the latter with polyhydric alcohols were extracted from the reference literature [15]. The mentioned parameters are given in Table 2.

The enthalpy parameters of pair interactions of Gly-Gly were positive. Hence, the endothermic processes related to structural changes of the three-component solutions and the release of water molecule from the hydrate shells of the dipeptide and the alcohols dominated over the direct interactions of the solvated polar groups. The pair interaction parameters increased in the series glycerol < ethylene glycol < propylene glycol. The higher h_{xy} parameter in the case of propylene glycol than that in the case of ethylene glycol was due to the presence of methyl group enhancing the hydrophobic hydration (improvement of hydrogen bonding between water molecules located around the CH_3 groups) [16]. The decrease in h_{xy} in the case of glycerol was due to the hydrogen atom substitution with polar hydroxy group capable of hydrogen bonds formation and enhancing the exothermal effect of Gly-Gly dissolution.

The pair interaction parameters were marginally higher in the case of glycylglycine as compared to glycine. That was due to the additional exothermal effect of dissolution introduced by the CONH capable of donor-acceptor interactions. The dipole moment of glycylglycine molecule is higher than that of glycine {μ(Gly) 1.50 D and μ(Gly-Gly) 2.35 D [17]}, resulting in the additional contribution of ion-dipole exothermal interactions. On the other hand, the dipeptide molecule is larger as compared with the amino acid, and the entropy contribution to the dissolution thermodynamics was more prominent in the case of the dipeptide, giving rise to certain endothermic effects. Hydrophobic interactions reflected association of the non-polar fragments of the molecules in aqueous solutions. Various electrostatic interactions and hydrogen bonding are known to favor the hydrophobic interactions thus increasing the endothermic dissolution effect [18–20]. The presence of additional methyllene group in the dipeptide molecule enhanced the solvophobic effects and interactions increasing the entropy.

To conclude, a certain balance of various types of interactions exists in the three-component dipeptide–polyhydric alcohol–water system. The findings of this work have added to the information discussed in our earlier contributions [21–23].

EXPERIMENTAL

Integral enthalpy of dissolution was measured using a sealed four-ampoule varied-temperature calorimeter equipped with an isothermal shell. Such a construction allowed for sequential measurements of a series of thermal effects upon dissolution of several portions of the tested substance in the same volume of the solvent without need to recharge the calorimeter cell [24]. The reaction chamber of the calorimeter and all the internal pieces in contact with the solution were made of titanium alloy VT-1. The calorimeter cell volume was 110 mL. The temperature was maintained constant at $\pm 10^{-3}$ K during the calorimetry measurements. The temperature and energy sensitivity of the calorimeter was 2×10^{-4} K/mm and 1×10^{-3} J/mm of the detector scale, respectively. The heat effect was compensated with electricity. The accuracy of the calorimeter was checked by measuring the heat effect of KCl dissolution in water at 298.15 K. The value obtained accounting for the dilution enthalpy [25] was $\Delta_{sol}H^0$ 17.23±0.06 kJ/mol (n = 10), coinciding well with the reference value (17.22±0.04 kJ/mol) [26, 27].

The dipeptide concentration was 0.004–0.006 mol/kg. The dissolution enthalpy of Gly-Gly $\Delta_{sol}H^m$ was independent of the dipeptide concentration in the studied concentration range; hence, the standard $\Delta_{sol}H^0$ valued were determined as mean of the 2–3 independent $\Delta_{sol}H^m$ measurements.

Glycylglycine (Acros, 99%) was recrystallized from aqueous ethanol and dried in a vacuum at 343 K during 48 h prior to the experiments. Water was twice

distilled (specific conductance 10^{-5} Ω^{-1} cm^{-1}). Organic solvents (glycerol 99.5%, ethylene glycol 99%, and propylene glycol 99%; all from Aldrich) were used as received. The binary solvents were prepared by weighing the appropriate components.

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