Thermochimica Acta 520 (2011) 153–155

Contents lists available at ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Short communication

Enthalpies of solution of glycylglycylglycine in aqueous solution of amides at 298.15 K

Valeriy I. Smirnov*, Valentin G. Badelin

Laboratory of Thermodynamics of Non-electrolytes Solutions and Biologically Active Substances, Institute of Solution Chemistry, Russian Academy of Sciences, 1 Akademicheskaya Street, 153045 Ivanovo, Russia

ARTICLE INFO

Article history:
Received 13 December 2010
Received in revised form 19 February 2011
Accepted 24 February 2011
Available online 6 April 2011

Keywords:
Peptides
Enthalpies of solution and transfer
Mixtures of water with organic solvents

ABSTRACT

Calorimetric measurements have been carried out at 298.15 K in aqueous solutions of glycylglycylglycine containing formamide, *N*-methylformamide, *N*,*N*-dimethylformamide and *N*,*N*-diethylformamide at concentrations of amides as co-solvents up to 0.4 mole fractions. The results obtained have been used to calculate the standard enthalpies of solution ($\Delta_{sol}H^\circ$) and transfer ($\Delta_{tr}H^\circ$) of the glycylglycylglycine from water into the mixtures as well as enthalpy coefficients of pair-wise interaction (h_{xy}) of the solute with amide in aqueous media. The h_{xy} values were correlated with the properties of organic solvents using Kamlet–Taft equation. The results of the calorimetric measurements have been discussed with regard to the intermolecular interactions occurring in these systems.

1. Introduction

The present paper is a continuation of our studies of amino acids and peptides in water–organic solutions [1–6]. Organic solvents are known to be very important organic synthesis substances, used in the fields of medicine, pharmacology and biopolymer chemistry. They can affect strongly the solubility and denaturation of proteins, and enzyme activities. These processes depend to a large extent on the interactions between the solution components, and particularly on the solvation of peptide molecules. By this time, many studies have been done with aqueous amino acid and peptide systems, but much less have been done with binary mixtures of organic solvent and water [7–12]. Besides, the range of organic solvent concentration in water was narrow enough (did not exceed 8 mol/kg). The major object of this work is to study the influence of various physico-chemical properties of organic solvents on their interaction with glycylglycylglycine (GlyGlyGly) in water–organic mixtures. Therefore, here we report the enthalpies of GlyGlyGly dissolution, $\Delta_{so}H^\circ$ in aqueous solution of formamide (FA), *N*-methylformamide (MFA), *N*,*N*-dimethylformamide, (DMF) and *N*,*N*-diethylformamide (DEF) with content of amide in the studied mixtures up to 0.4 mole fractions. Chosen amides differ from each other in the molecular structure and size as well as donor–acceptor ability, polarity, polarizability and the exerted effect on the water structure.

2. Experimental

GlyGlyGly (Aldrich Chemical Co., Ltd., mass fraction: 0.99) was dried under given pressure at room temperature, and it was then kept over P_2O_5 in a desiccator. The molal concentration (m) of GlyGlyGly varied in the range (5×10^{-3} to 1.5×10^{-2} mol kg^{-1}) of the mixed solvent. FA and DMF (Fluka) were distilled twice under reduced pressure over NaOH according to [13]. MFA and DEF (Sigma–Aldrich, purum, assay: 99%) were used without further purification. Water content determined by Karl Fisher titration [14] did not exceed 0.03 wt.% for all amides. The water was purified by deionization and double distillation up to a specific conductivity of *ca.* 1.0×10^{-5} S m^{-1}. All measurements were made at (298.15 ± 0.01) K. The solutions before measurement were prepared by weight. The values of $\Delta_{sol}H^m$ for GlyGlyGly were measured using an "isoperibol" hermetic calorimeter. The calorimeter setup, testing and experimental procedure were described in detail previously [4,5,15]. The relative random error of measurements did not exceed 0.5%.

3. Results

The measured molal enthalpies of solution of GlyGlyGly were found to be independent of its content within the investigated range of the GlyGlyGly concentration, hence, the standard enthalpies of solution, $\Delta_{sol}H^\circ(\equiv \Delta_{sol}H^\infty)$at 298.15 K were calculated as the mean from $\Delta_{sol}H^m$ values of all independent calorimetric experiments with the given mixed solvent composition. The obtained values of $\Delta_{sol}H^\circ$ for GlyGlyGly in the investigated

---

* Corresponding author. Tel.: +7 0932 351859; fax: +7 0932 336237.
E-mail addresses: vis@isc-ras.ru, svi5015@ivnet.ru (V.I. Smirnov).

0040-6031/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.tca.2011.02.039

Table 1
Standard enthalpies (kJ/mol) of dissolution ($\Delta_{sol}H^\circ$) of glycylglycylglycine in aqueous solution of amides at 298.15 K.

m_2[a]	FA	m_2[a]	MFA	m_2[a]	DMF	m_2[a]	DEF
1.242	16.98 ± 0.01	0.814	17.79 ± 0.02	0.717	17.84 ± 0.02	0.805	18.56 ± 0.01
2.345	14.89 ± 0.01	1.646	17.85 ± 0.02	1.193	18.18 ± 0.02	1.396	19.48 ± 0.02
3.748	13.81 ± 0.02	2.411	17.93 ± 0.02	2.102	18.51 ± 0.02	1.772	19.98 ± 0.01
5.079	12.85 ± 0.01	3.869	17.99 ± 0.01	2.598	18.89 ± 0.01	2.468	20.31 ± 0.01
7.521	11.72 ± 0.02	4.701	18.23 ± 0.02	3.528	19.11 ± 0.02	2.952	20.81 ± 0.02
8.477	11.28 ± 0.01	5.829	18.39 ± 0.01	4.372	19.48 ± 0.01	3.724	21.12 ± 0.01
10.867	10.27 ± 0.01	8.681	18.45 ± 0.01	5.586	19.94 ± 0.01	4.464	21.19 ± 0.01
12.756	9.55 ± 0.01	9.909	18.69 ± 0.01	6.503	20.22 ± 0.01	5.513	21.22 ± 0.01
17.652	8.87 ± 0.01	12.404	18.78 ± 0.02	9.282	21.23 ± 0.02	6.710	21.06 ± 0.01
25.445	8.31 ± 0.02	17.463	18.82 ± 0.01	12.996	21.79 ± 0.02	8.889	20.36 ± 0.02
35.557	7.22 ± 0.02	24.523	18.69 ± 0.02	18.183	20.42 ± 0.02	12.412	18.87 ± 0.02
–	–	34.557	16.78 ± 0.02	25.926	11.23 ± 0.02	17.797	17.26 ± 0.03

[a] -The molal concentration of amides, mol/kg.

systems and their standard deviations are given in Table 1. The transfer enthalpy $\Delta_{tr}H^\circ$ is derived from Eq. (1).

$$\Delta_{tr}H^\circ = \Delta_{sol}H^\circ(w+y) - \Delta_{sol}H^\circ(w), \qquad (1)$$

where $\Delta_{sol}H^\circ$ $(w+y)$ is the enthalpy of solution in each of aqueous solution of organic solvent and $\Delta_{sol}H^\circ$ (w) is the enthalpy of GlyGlyGly solution in pure water ($\Delta_{sol}H^\circ(w) = 17.62 \pm 0.05$ kJ/mol was taken from paper [16]). The changes in $\Delta_{tr}H^\circ$ for GlyGlyGly against the amide mole-fraction content are shown in Fig. 1.

4. Discussion

From Fig. 1 it is possible to notice that values of transfer enthalpies for GlyGlyGly are exothermic in all studied concentration range of FA for H_2O + FA mixture. In the case of H_2O + MFA, H_2O + DMF and H_2O + DEF mixtures the transfer enthalpies for GlyGlyGly are endothermic for concentration of substituted amide $x < 0.25$ and exothermic with an increase of concentration $x > 0.25$. Herewith endothermic $\Delta_{tr}H^\circ$ values of GlyGlyGly are increasing monotonically with the increase of *N*-substituted amide content up to $x_2 \approx 0.1$–0.15. The slopes of the $\Delta_{tr}H^\circ = f(x_2)$ dependences in this range increase in the series: MFA < DMF < DEF. Here the substances are well hydrated and the endothermic enthalpy contributions from the dehydration of GlyGlyGly and amide molecules probably prevail over exothermic ones from the peptide–amide interactions. In the case of (H_2O + FA) mixture the $\Delta_{tr}H^\circ$ value for GlyGlyGly is negative by sign and smoothly decreases (in magnitude) as the content of FA increases. The exothermicity of a transfer process testifies the preferential role of a direct intermolecular interaction between FA and GlyGlyGly to the processes of associated molecule dissociation of FA and the processes of dehydration of peptide and FA molecules. The process of $\Delta_{tr}H^\circ$ change with the increase in concentration of FA above 0.15 mole fractions in the aqueous solution weakly strengthens GlyGlyGly solvation because the endothermic processes of continued decomposition of self-associates H_2O and FA balance the energy of newly formed heterocomponent H-bonds. In the case of (H_2O + MFA H_2O + DMF and H_2O + DEF) mixtures in the range of $0.15 < x_2 < 0.2$, the endothermic effects caused by the solvent, structural reorganization and dehydrating GlyGlyGly and co-solvent molecules are compensated by the exothermic effects of direct interactions between polar groups of the interacting components. Here, the endothermic maxima on the curves of $\Delta_{tr}H^\circ$ against x_2 are observed for many peptides in the similar mixtures [5,17,18]. The maximum height depends on the structure and the physico-chemical properties of co-solvent. The increase in a molecular size of peptide as well as in the co-solvent hydrophobicity shifts this extremum in the water-rich region. At $x_2 > 0.2$, the exothermic contribution of GlyGlyGly–co-solvent interactions to the total enthalpy interaction effect becomes predominant and consequently, the $\Delta_{tr}H^\circ$ vs. x_2 curve becomes opposite in the direction.

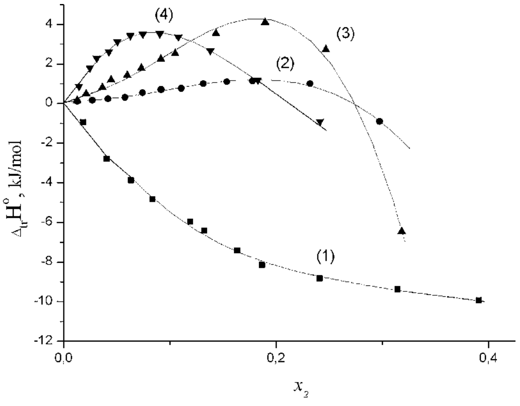

Fig. 1. Enthalpies of transfer $\Delta_{tr}H^\circ$ of GlyGlyGly from water into the H_2O + FA (1), H_2O + MFA (2), H_2O + DMF (3) and H_2O + DEF (4) mixed solvent as functions of the amide mole fraction (x_2) at 298.15 K.

The interparticle interactions in the ternary aqueous system with small concentration of co-solvent can be characterized in terms of McMillan–Mayer theory [19] adapted by Kauzmann, Friedman and Desnoyers [20–22] for calculating the enthalpy coefficients of pair-wise interactions h_{xy}. For this purpose, the $\Delta_{sol}H^\circ$ versus m_2 function was approximated by the third-order polynomial equation (2).

$$\Delta_{sol}H^\circ = a_0 + a_1 m_2 + a_2 m_2^2 + a_3 m_2^3 \qquad (2)$$

where m_2 is the molal concentration of amide, and a_1, a_2, a_3 are coefficients calculated by a least-squares method. The correlation coefficient, *R*, and the Student criterion value, t_α, ranged from 0.991 to 0.998 and from 0.047 to 0.336, respectively. The calculated values of h_{xy} for all systems in question are presented in Table 2. The earlier obtained data concerning the interactions of GlyGlyGly with EtOH,

Table 2
Enthalpic coefficients of pair-wise interactions, (hxy), between glycylglycylglycine and organic solvents in aqueous solutions at 298.15 K and parameters of organic solvents [23,24].

Solvent	h_{xy} (J kg/mol^2)	$(\delta^2/1000)_1(V_2/100)$ (J/mol)	π^*	α	β
FA	−561 ± 16	0.912	0.97	0.71	0.55
AN	−212 [2]	1.203	0.75	0.19	0.31
DMSO	220 [1]	1.627	1.00	0.00	0.76
MFA	47 ± 6	1.340	0.90	0.62	0.80
DMF	183 ± 34	1.775	0.88	0.00	0.69
EtOH	260 [4]	1.339	0.54	0.83	0.77
n-PrOH	503 [4]	1.714	0.52	0.78	0.82
i-PrOH	760 [4]	1.756	0.48	0.76	0.95
H_2O	–	–	1.09	1.17	0.18

PrOH, i-PrOH [4], DMSO [1] and AN [2] are presented in the same place. The values of h_{xy} are a measure of interactions proceeding between the hydrated molecules of GlyGlyGly and hydrated amide molecules. The total effect is a sum of superimposing endothermic processes of partial dehydration of the hydration shields of reacting substances and exothermic interactions between GlyGlyGly and amide molecules. The positive sign of h_{xy} values for the aqueous solutions of (MFA, DMF and DEF) shows that the solutes are strongly hydrated by H_2O molecules, while the interaction between hydrated GlyGlyGly and co-solvent molecules is weak. On the contrary, a negative value of h_{xy} for (H_2O + FA, H_2O + AN) suggests that the interactions between the co-solvent and the GlyGlyGly molecules prevail over the effects of their dehydration. We have shown before [3,17,18] that the enthalpy coefficients of pair-wise intermolecular interaction of amino acids or peptides with organic co-solvents depend on the properties of these solvents and can be quantitatively expressed in the form of a multi-parameter equation (a modified Kamlet–Taft equation [23,24]). Therefore, to analyse the data of enthalpy coefficients of pair-wise interactions of GlyGlyGly with molecules of different organic solvents in water–organic mixtures, we used the same Eq. (3) which was previously applied to the analysis of analogous data in the similar mixtures for the glycine and glycylglycine [3,6].

$$h_{xy} = A_0 + A_1\left(\frac{\delta^2}{1000}\right)_1\left(\frac{V_2}{100}\right) + A_2(\pi_1^*\pi_2^*) + A_3(\alpha_1\beta_2) + A_4(\beta_1\alpha_2) \qquad (3)$$

where $\pi_1{}^*$ and $\pi_2{}^*$ are indexes of solvents dipolarity/polarizability of H_2O and organic co-solvent, respectively (it is the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect); α_1, α_2 are parameters which reflect the solvents hydrogen-bond donor acidity (HBD); and β_1, β_2 are parameters which scale the solvents hydrogen-bond acceptor basicity (HBA), providing a measure of the solvent ability to solubilize the solute by accepting a proton through a hydrogen bond; $\delta^2/1000$ and $V_2/100$ are the structural contributions both of water and the co-solvent to the formation of cavities (these parameters are decreased respectively by factors of 1000 and 100 to simplify the estimation of the relative contributions of various parameters to h_{xy}); δ^2 is the solubility parameter according to Hildebrandt conception (δ^2 is proportional to the cohesion energy density) and V_2 is the molar volume of the organic solvent being the ratio between its molecular weight and density (it reflects possible effect of structural factors). The solvent parameters were taken from [23–27], and the calculations were performed according to the IUPAC recommendations in the field of correlation analysis in chemistry. As a result of the calculation, we obtained the Eq. (4).

$$\begin{aligned} h_{xy} = {} & 246.87 + 129.98\left(\frac{\delta^2}{1000}\right)_1\left(\frac{V_2}{100}\right) - 1195.29(\pi_1^*\pi_2^*) \\ & -2943.27(\alpha_1\beta_2) + 1155.56(\beta_1\alpha_2), \end{aligned} \qquad (4)$$

$R = 0.985$, $n = 8$, $t_\alpha = 75.87$

It can be seen that the increase in polarity, polarizability and HBD of the co-solvent enhances their interaction with the GlyGlyGly molecules. On the other hand, an increase in the molar volume and HBA of the organic co-solvent weakens the pair-wise interactions. Comparing parameters of Eq. (4) with similar parameters in the equations received for glycine [3] and glycylglycine [6], it is possible to note the following: All the variables in these equations coincide by sign. It means that the interparticle interactions of glycine and its oligomers with the same co-solvents have a similar nature. Thus, the basic contribution to the strengthening of the interparticle interaction of glycine and its oligomers with molecules of organic solvents, contributes a polarity/polarizability and HBD ability of co-solvent. However, the values of coefficients of the variables in Eq. (2) are increased in magnitude in the series Gly < GlyGly < GlyGlyGly. It is connected with rising specific solvation of a peptide group and with increasing the molar volume of a peptide molecule as well as with strengthening its donor–acceptor properties.

The received Eq. (3), fairly correlates the enthalpy coefficients of pair-wise interactions of GlyGlyGly with physico-chemical properties of solvents and allows one to forecast the value of h_{xy} for the GlyGlyGly with solvents for which experimental data are lacking.

References

[1] V.I. Smirnov, V.G. Badelin, Thermochemistry of dissolution of glycine, glycylglycine and diglycylglycine in a mixed solvent water-dimethyl sulfoxide at 298.15 K, Russ. Biophys. 49 (2004) 375–380.

[2] V.I. Smirnov, V.G. Badelin, Solvation of glycine and its oligomers in a water-acetonitrile binary solvent at 298.15 K, Russ. J. Phys. Chem. 79 (2005) 583–586.

[3] V.I. Smirnov, V.G. Badelin, The enthalpies of solution of DL-α-alanine in water–organic solvent mixtures at 298.15 K, Russ. J. Phys. Chem. 80 (2006) 672–677.

[4] V.I. Smirnov, V.G. Badelin, The enthalpies of solution of glycylglycine and diglycylglycine in aqueous alcohols at 298.15 K, Thermochim. Acta 471 (2008) 97–99.

[5] V.I. Smirnov, V.G. Badelin, Enthalpies of solution of DL-α-alanyl-DL-α-valine in aqueous solution of amides at 298.15 K, Thermochim. Acta 485 (2009) 72–75.

[6] V.I. Smirnov, V.G. Badelin, Enthalpies of solution of glycylglycine in water–organic solvent media at 298.15 K, Thermochim. Acta 501 (2010) 55–58.

[7] B. Palecz, Enthalpies of interaction of glycine with some amides in aqeous solutions at 298.15 K, J. Therm. Anal. 45 (1995) 805–809.

[8] H. Piekarski, B. Nowicka, Calorimetric studies of interactions of some peptides with electrolytes, urea and ethanol in water at 298.15 K, J. Therm. Anal. 102 (2010) 31–36.

[9] T.S. Banipal, G. Singh, Densities and partial molar volumes of some amino acids and diglycine in aqueous n-propanol solutions at 25 °C, J. Solution Chem. 32 (2003) 997–1015.

[10] J.F. Reading, G.R. Hedvig, Thermodynamic properties of peptide solutions 4. Partial molar volumes and heat capacities of aqueous solutions of some glycyldipeptides, J. Solution Chem. 18 (1989) 159–172.

[11] T.S. Banipal, D. Kaur, P. Lai, P.K. Banipul, Densities and viscosities of glycine, DL-a-Alanine, DL-a-Amino-n-butyric acid, and L-leucine in aqueous 1,2-propanediol solutions at 298.15 K, J. Chem. Eng. Data 47 (2002) 1391–1395.

[12] Y. Li, L. Rui-Sen, H. Xin-Gen, X. Gui-Ying, Enthalpic interaction of amino acids with ethanol in aqueous solutions at 25 °C, J. Solution Chem. 32 (2003) 273–281.

[13] A.J. Gordon, R.A. Ford, The Chemist's Companion: A Handbook of Practical Data, Techniques and References, Wiley, New York, 1972.

[14] V.A. Klimova, Main methods for analysis of organic compounds, Khimiya, Moscow (1967) (in Russian).

[15] E.V. Ivanov, V.K. Abrosimov, V.I. Smirnov, Enthalpies of solution of 1,1,3,3-tetramethylurea in normal and branched alkanols (C_2–C_4) at 298. 15 K, J. Chem. Thermodyn. 39 (2007) 1614–1619.

[16] V.G. Badelin, V.I. Smirnov, I.N. Mezhevoi, Dependence of enthalpies of hydration of amino acids and oligopeptides from their molecular structure, Russ. J. Phys. Chem. 76 (2002) 1305–1308.

[17] V.I. Smirnov, V.G. Badelin, The enthalpies of solution of L-a-alanyl-L-a-alanine in water–organic solvent mixtures at 298.15 K, Russ. J. Phys. Chem. 82 (2008) 1555–1559.

[18] V.I. Smirnov, I.N. Mezhevoi, V.G. Badelin, The thermochemical characteristics of solution of DL-α-alanylglycine and DL-α-alanyl- DL-α- alanine in water–organic solvent mixtures at 298.15 K, Russ. J. Phys. Chem. 81 (2007) 1245–1249.

[19] W.G. McMillan, J.E. Mayer, The statistical thermodynamics of multicomponent systems, J. Chem. Phys. 13 (1945) 276–305.

[20] J.J. Kozak, W.S. Knight, W. Kauzmann, Solute–solute interactions in aqueous solutions, J. Chem. Phys. 48 (1968) 675–690.

[21] C.V. Krishnan, H.L. Friedman, Studies of hydrogen bonding in aqueous alcohols: enthalpy measurements and model calculations, J. Solution Chem. 2 (1973) 119–138.

[22] J.E. Desnoyers, G. Perron, L. Avedikian, J.P. Morel, Enthalpies of the urea-tet/f-butanol-water system at 25 °C, J. Solution Chem. 5 (1976) 631–644.

[23] M.J. Kamlet, J.L.M. Abbout, M.H. Abraham, R.W. Taft, Linear solvation energy relationships. 23. A comprehensive collection of the solvalochromic paramenters, pi.alfa, and bets, and some methods for simplifying the generalized solvalochromic equation, J. Org. Chem. 48 (1983) 2877–2887.

[24] M.J. Kamlet, R.M. Doherty, M.H. Abraham, et al., Linear solvation energy relationships. 41. Important differences between aqueous solubility relationships for aliphatic and aromatic solutes, J. Phys. Chem. 91 (1987) 1996–2004.

[25] M.J. Kamlet, R.W. Taft, The solvatochromic comparison method. I. The,. beta. -scale of solvent hydrogen-bond acceptor (HBA) basicities, J. Am. Chem. Soc. 98 (1976) 377–383.

[26] M.J. Kamlet, J.L.M. Abboud, R.W. Taft, The solvatochromic comparison method. 6. The. pi.* scale of solvent polarities, J. Am. Chem. Soc. 99 (1977) 6027–6038.

[27] R.W. Taft, J.L.M. Abboud, M.J. Kamlet, M.H. Abraham, Linear solvation energy relations, J. Solution Chem. 14 (1985) 153–156.