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Enthalpies of L-threonine dissolution in some aqueous amides at 298.15 K

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ABSTRACT

The enthalpies of L-threonine dissolution in aqueous formamide, *N*-methylformamide, *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide were determined by calorimetry at 298.15 K and amide mole fractions up to $x_2 \sim 0.3$. The standard enthalpies of solution $\Delta_{sol}H^\circ$ and transfer $\Delta_{tr}H^\circ$ from water to the mixed solvent as well as the enthalpy coefficients of L-threonine–amide pairwise interactions were calculated. The interrelation of the enthalpies of dissolution and transfer for L-threonine with structural features of each of aqueous amides was determined.

1. Introduction

The mixtures of aliphatic amides with water are the object of many investigations [1–3]. They are frequently used for studying the interrelation between the solubility of medicines and the dielectric constant of mixed solvents, and the influence of the solvent structure on the solvation of the third component as well [4–6]. Furthermore, amides can serve as the model substances in the studies of the properties of peptide in aqueous solutions, because their molecules contain the functional group (–CONH), which is a fragment of protein systems [7–9]. The general purpose of our studies consists in the thermodynamic analysis of dissolution and solvation processes for amino acids [10–12] and peptides [13–15] in the multicomponent systems. In the present work, we have investigated the processes of L-threonine interaction with amides of different natures of *N*-methylation (namely, formamide, *N*-methylformamide, *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide) in aqueous solutions at 298.15 K by using an isoperibol calorimetry method. The results of calorimetric measurements are discussed with regard to the intermolecular interactions that occur in the systems considered.

2. Experimental

The chromatographically homogeneous L-threonine (Aldrich, Assay: ≥98%) was recrystallized twice from water + ethanol mixture. It was dried in a vacuum chamber at 333 K for 48 h and kept over P_2O_5 under vacuum in the desiccator. The molal concentration (m) of the L-threonine solutions was varied in the range of $0.005 < m < 0.015\ \mathrm{mol\,kg^{-1}}$ in the mixed solvent. FA, NMF and DMF were distilled twice under reduced pressure from NaOH according to [16]. DMA was dried over molecular sieves 0.4-nm (which had been dried in a vacuum above 473 K for more than 15 h) for two days and fractionally distilled at the reduced pressure. Water content determined by Karl Fisher titration [17] did not exceed 0.03 wt% for all the amides. Water was purified by deionization and double distillation until a specific conductivity of *ca.* $1.0 \times 10^{-4}\ \mathrm{S\,m^{-1}}$. All measurements were made at 298.15 ± 0.01 K. Mixtures were prepared by weight. The solution enthalpies, $\Delta_{sol}H^m$, for L-threonine were measured in the isoperibol calorimeter. The calorimeter setup and experimental procedure were detailed previously [15,18]. The relative random error of measurements was <0.5%. The calorimeter was tested by measuring (10 experiments) the enthalpy of solution of potassium chloride (KCl) in water at 298.15 K according to [19,20]. Our values $\Delta_{sol}H^m$ ($m = 0.111\ \mathrm{mol\,kg^{-1}}$) = $17.60 \pm 0.04\ \mathrm{kJ\,mol^{-1}}$ and $\Delta_{sol}H^\circ = 17.23 \pm 0.07\ \mathrm{kJ\,mol^{-1}}$ agree with that of recommended literature values $17.58 \pm 0.02\ \mathrm{kJ\,mol^{-1}}$ [19] and $17.22 \pm 0.04\ \mathrm{kJ\,mol^{-1}}$ [20], respectively.

3. Results

The standard enthalpies of solution ($\Delta_{sol}H^\circ$) were calculated by averaging the results of five measurements of $\Delta_{sol}H^m$ for each composition of the aqueous amide, because in the investigated range of L-threonine concentrations a dependence of $\Delta_{sol}H^m$ on m was not observed. The experimental data on $\Delta_{sol}H^\circ$, together with the

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

m_2[a]	FA	m_2[a]	MFA	m_2[a]	DMF	m_2[a]	DMA
1.242	10.21 ± 0.02	0.814	10.65 ± 0.02	0.717	11.12 ± 0.02	0.476	11.29 ± 0.02
2.345	10.08 ± 0.02	1.646	11.21 ± 0.02	1.193	11.81 ± 0.02	0.978	12.15 ± 0.02
3.748	9.94 ± 0.02	2.411	11.77 ± 0.02	2.102	12.58 ± 0.02	1.553	12.76 ± 0.01
5.079	9.87 ± 0.01	3.869	12.58 ± 0.01	2.598	13.11 ± 0.01	2.136	13.46 ± 0.01
7.521	9.63 ± 0.02	4.701	12.99 ± 0.02	3.528	13.87 ± 0.02	2.852	14.38 ± 0.01
8.477	9.60 ± 0.01	5.829	13.28 ± 0.01	4.372	14.61 ± 0.01	3.565	15.17 ± 0.01
10.867	9.56 ± 0.01	8.681	13.84 ± 0.01	5.586	15.48 ± 0.01	4.439	16.18 ± 0.02
12.756	9.37 ± 0.01	9.909	14.19 ± 0.01	6.503	16.24 ± 0.01	5.368	17.12 ± 0.02
17.652	9.15 ± 0.01	12.404	14.81 ± 0.01	9.282	17.29 ± 0.01	6.472	17.78 ± 0.02
25.445	9.11 ± 0.02	17.463	15.52 ± 0.01	12.996	18.24 ± 0.01	7.714	18.24 ± 0.02
35.557	8.92 ± 0.02	24.523	16.11 ± 0.01	18.183	18.98 ± 0.02	10.759	18.32 ± 0.02
–	–	34.557	15.57 ± 0.02	25.926	19.21 ± 0.02	15.079	17.73 ± 0.03

[a] The molal concentration of amides (mol kg^{-1}).

average deviations, obtained for L-threonine in aqueous solution of amides are presented in Table 1. The transfer enthalpies of L-threonine from water to an aqueous amide, $\Delta_{tr}H^{\circ}$, are presented graphically in Fig. 1. The values of $\Delta_{tr}H^{\circ}$ were calculated from the experimental enthalpies of L-threonine dissolution in the pure water, $\Delta_{sol}H^{\circ}(w)$, and in the amide-containing aqueous solution, $\Delta_{sol}H^{\circ}(w+y)$:

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

The enthalpy of L-threonine dissolution in water ($\Delta_{sol}H^{\circ}(w) = 10.33 \pm 0.06$ kJ mol^{-1}) was taken from [21].

4. Discussion

From the inspection of Fig. 1 one can see that $\Delta_{tr}H^{\circ}$ vs. x_2 for L-threonine depends considerably on the structure of amide as well as from its content in the mixed aqueous solution. The curves depicted in the figure are similar in shape to those obtained previously [10–12] for solutions of glycine, alanine and valine in aqueous amides. The endothermicity {or exothermicity for the (H_2O + FA) mixture} of L-threonine dissolution within the concentration region $0 < x_2 < 0.15$ increases monotonically. Here, the aqueous component is subjected to destructuring under the action of both L-threonine and amide molecules. At the same time the L-threonine solvation shells predominantly consist of water molecules. In the ternary aqueous system with small concentration of co-solvent, the interparticle interactions can be characterized in terms of McMillan–Mayers theory [22] adapted by Kauzmann, Friedman, and Desnoyers [23–25] using enthalpy coefficients of pairwise interactions, h_{xy}. For calculating h_{xy}, the $\Delta_{sol}H^{\circ}$ vs. m_2 functions were approximated by a third-power polynomial of the following form:

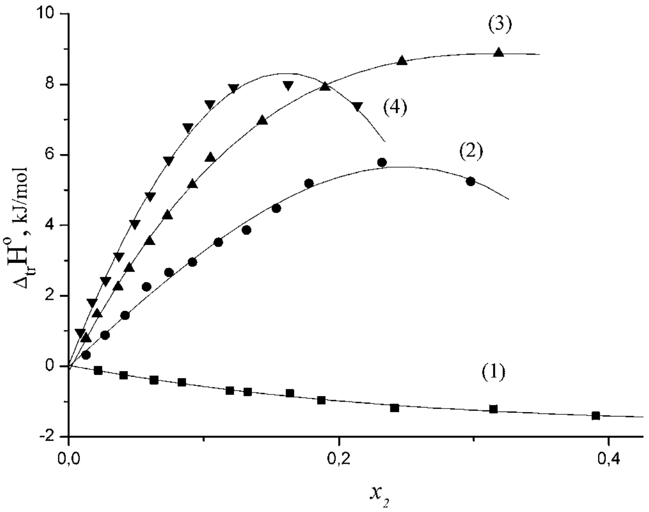

Fig. 1. Enthalpies of transfer, $\Delta_{tr}H^{\circ}$, of L-threonine from water into H_2O + FA (1), H_2O + MFA (2), H_2O + DMF (3) and H_2O + DMA (4) as a function of amide mole fraction, x_2, at 298.15 K.

$$\Delta_{sol}H^{\circ} = a_0 + a_1m_2 + a_2m_2^2 + a_3m_2^3 \quad (2)$$

where m_2 is the molal concentration of the amide, and a_i is the coefficient calculated by a method of least squares. The correlation coefficient R and the Student criterion t_{α} were ranged from 0.991 to 0.998 and from 0.048 to 0.199, respectively. The h_{xy} value was calculated from the a_1 coefficient related to the coefficient of pairwise interaction as $h_{xy} = a_1/2$. The results were h_{xy} (J kg mol^{-2}) = (−57.5 ± 8), (318 ± 35), (607 ± 15) and (895 ± 60) for FA, MFA, DMF and DMA, respectively. The positive sign at h_{xy} values for the aqueous solution of alkylated amides shows that the solutes are strongly hydrated by H_2O molecules, while the interaction between hydrated L-threonine and amide molecules seems to be rather weak. On the contrary, a negative value h_{xy} for (H_2O + FA) suggests that the interactions between the co-solvent and L-threonine molecules dominate over the effects of their dehydration. The components of the ternary systems studied are capable of forming H-bonds with each other. In addition, such components as H_2O, FA and MFA form strong intramolecular hydrogen bonding. The enthalpy effect of L-threonine dissolution in each of the specified systems is determined by the ratio between the energy consumed for H-bond dissociation in self-associates, the energy of L-threonine (or amide) dehydration and the energy released in forming the heterocomponent hydrogen bonding. The curves in Fig. 1 show that the $\Delta_{tr}H^{\circ}$ vs. x_2 dependence for L-threonine in the (H_2O + FA) mixtures are different from the similar dependences for L-threonine in both (H_2O + *N*-substituted amide) and (H_2O + *N*,*N*-substituted amide) systems. The h_{xy} value for the (H_2O + FA) mixture is negative (by sign) and small in magnitude. It can be connected with the following. The H bond energies for H_2O–H_2O, H_2O–FA, and FA–FA are comparable [26]. As a result, the enthalpy of mixing of FA with H_2O is weak–positive in the entire range of the mixture compositions [27]. Besides, such a change in h_{xy} for L-threonine can be connected simultaneously with the destruction of FA self-associates and their hydration. Herewith the further dehydration of FA molecules will take place when they interact with the L-threonine molecules. Therefore, the endothermic contribution from dehydration of FA molecules will be the least among the studied amides. The replacement of the *N*-sited hydrogen atom in FA by a CH_3-group is accompanied not only by the increase in the absolute value of the enthalpy coefficient of pairwise interaction but also by a change of its sign. This effect is induced by both strengthening of hydrophobic properties of MFA and the generally lower energy of intramolecular H-bonds in NMF than that in FA [28]. Hence the contribution in $\Delta_{tr}H^{\circ}$ from the destruction of MFA self-associates

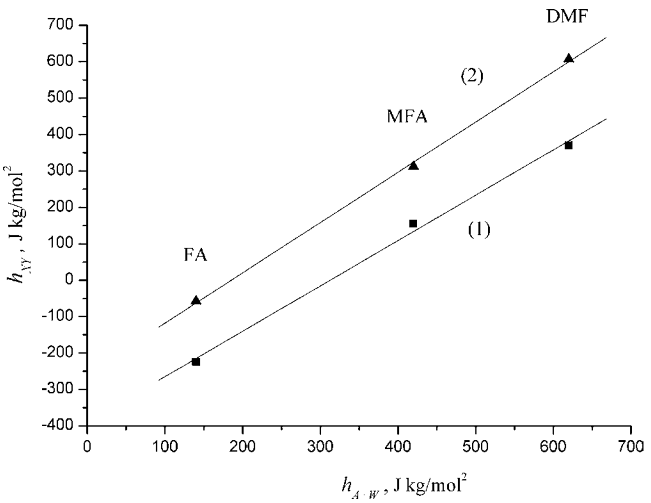

Fig. 2. Correlation between the enthalpic coefficients of pairwise interactions (h_{xy}) of L-threonine with formamides (Table 2) and the enthalpic coefficients of pairwise interactions (h_{A+W}) of formamides with water [1]: (1) glycine [3] and (2) L-threonine.

Table 2
Enthalpic coefficients of pairwise interactions (h_{xy}, J kg mol^{-2}) between L-threonine and amides in aqueous solutions at 298.15 K.

Substance	FA	MFA	DMF	DMA
L-Threonine	−57.5 ± 8	318 ± 35	607 ± 15	895 ± 60

will be less pronounced and MFA is hydrated the stronger than FA. DMF and DMA are typical aprotic polyfunctional solvents, which not form intermolecular H-bonds (in the pure state) and have in the molecules two and three hydrophobic CH_3-groups, respectively. Increasing endothermicity of the dissolution process on going from MFA to DMF and DMA is caused by weakening the interaction between the L-threonine zwitterion and alkyl-substituted amide due to hydrophobic effects of a second CH_3-group. It makes the endothermic processes of dehydration of molecules in aqueous solutions predominant ones. The fact of increasing the endothermic effect of the L-threonine interaction with DMA compared to DMF are probably explained by that a "formyl" CH_3 group attached directly to a $>C{=}O$ one has a strong inductive influence on the electronic "frame" of a carbonyl group [1]. From data of Table 1 follows that the endothermicity of L-threonine dissolution increases in the (H_2O + FA) < (H_2O + MFA) < (H_2O + DMF) < (H_2O + DMA) series. The specified sequence of intensifying the endothermic process of L-threonine dissolution in the aqueous amides studied can be connected with the increasing energy of intermolecular interactions. This is confirmed by the enthalpies of mixing of water with an amide [1,29]. In addition, it can be connected also with the energy of pairwise intermolecular L-threonine–amide interaction that is related linearly with the energy of pairwise H_2O–amide interactions (see Fig. 2). For the sake of comparison, we have show also in Fig. 2 the curves for the enthalpy coefficients of pairwise interactions of glycine from water into the (H_2O + FA), (H_2O + NMF) and (H_2O + DMF) that were found in the previous studies [10]. The increase of a number of CH_3-groups in an amide molecule causes the weakening of pairwise L-threonine–amide as well as glycine–amide interactions. Going from glycine to L-threonine, the endothermic coefficients of pairwise interactions between L-threonine and amide become the more positive. This is due to hydrophobic hydration around L-threonine alkyl groups that result in increase of hydration of both a zwitterion and hydroxyl group of the amino acid considered. That is, the effect of partial dehydration of the "reinforced" hydration layers of an L-threonine zwitterion and OH-group becomes the more pronounced, and the total interaction effect in question becomes the more endothermic. In the concentration region $0.15 < x_2 < 0.2$ for DMA ($0.2 < x_2 < 0.3$ for MFA or $x_2 > 0.25$ for DMF), the endothermic effects caused by both the structural rearrangement of the solvent and the dehydration of L-threonine and amide molecules are gradually compensated by the exothermic effects of direct interactions between these solutes. With increasing the concentration of MFA or DMA (at $x_2 > 0.2$), the exothermic contribution from L-threonine–amide interactions begins to be prevailing in the total interaction enthalpic effect. Herewith the trend of $\Delta_{tr}H^\circ$ vs. x_2 dependence changes to the opposite one. In the case of the (H_2O + FA) mixture, the exothermic contribution of the direct L-threonine–FA interaction is still prevailing over the endothermic contributions of the continued destruction of FA shelf-associates and the dehydration of FA and L-threonine molecules.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tca.2010.03.014.

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