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Enthalpies of solution of *DL*-α-Alanyl-*DL*-α-Valine in aqueous solution of amides at 298.15 K

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ABSTRACT

The enthalpies of solution of *DL*-α-Alanyl-*DL*-α-Valine in aqueous solution of formamide, *N*-methylformamide, *N*,*N*-dimethylformamide, *N*,*N*-diethylformamide and *N*,*N*-dimethylacetamide were determined by calorimetry at 298.15 K over the concentration range x_2 = 0–0.4 mole fractions. Standard enthalpies of solution $\Delta_{sol}H_m^\circ$ and transfer $\Delta_{tr}H_m^\circ$ from water to mixed solvents were computed. The enthalpy coefficients of pairwise *DL*-α-Alanyl-*DL*-α-Valine–amide interactions were calculated. The interrelation between the enthalpy characteristics of solution (transfer) of *DL*-α-Alanyl-*DL*-α-Valine and the structure and physicochemical characteristics of solvents, as well as the composition of mixtures were revealed.

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1. Introduction

This work continues our studies of the thermodynamic characteristics of dissolution and solvation of amino acids [1–4] and peptides [5–9] in mixed aqueous–organic solvents. Interest in *DL*-α-Alanyl-*DL*-α-Valine (hereinafter, Ala-Valine) stems from peculiarities of its hydration as well as solvation in the aqueous alcohols [8]. Previously [8], it was ascertained that hydrophobic effects associated with the specifics of molecular structure of the Ala-Valine play the important role in intermolecular interactions with components of aqueous–organic mixtures. As regards of the medium for studying the processes of Ala-Valine dissolution, we used the concentrated aqueous solutions of some amides. With point of view of the solution thermodynamics, the aqueous amide is an important solvent due to the hydrophobic-hydrophilic character of intermolecular interactions. Besides the amide molecule can be served as a model to study the peptide–peptide interactions [11]. The peptide–urea interactions are of great interest for biophysical chemistry, too, since they concern the denaturation processes of proteins. Therefore, in a number of works, the results on studying the interactions in aqueous amino acids were extended to some (water + amide) solutions. The important place in disclosing the mechanism of denaturation of proteins and biopolymers occupy the works devoted to interactions between the amino acid and urea [12–18], amino acid and amide [13–15], amino acid and alcohol [16–18] molecules. However, the high-concentrated mixtures have been used in a few works only. Up to now, as far as we know, virtually no data on the thermodynamic characteristics of dissolution (solvation) of Ala-Valine in water solutions of formamide (FA), *N*-methylformamide (NMF), *N*,*N*-dimethylformamide (DMF), *N*,*N*-diethylformamide (DEF) and *N*,*N*-dimethylacetamide (DMA) at 298.15 K are available. In the present paper, we report the standard enthalpies of dissolution of Ala-Valine in aqueous solution of amides (FA), NMF, DMF and DMA at 298.15 K.

2. Experimental

Chromatographically, homogeneous Ala-Valine (Reanal Co., Hungary) were recrystallized twice from water–ethanol mixture, dried in a vacuum chamber at 333 K for 48 h, and kept over P_2O_5 under vacuum in desiccator. The molal concentration (m) of the peptide solutions was varied in the range of $0.005 < m < 0.015$ mol/kg in mixed solvent. FA, NMF, DMF and DEF were distilled twice under reduced pressure from NaOH according to [19]. DMA was dried over molecular sieves 4A (which had been dried in vacuum above 473 K for more than 15 h) for 2 days and fractionally distilled at reduced pressure. Water content determined by Karl Fisher titration [20] did not exceed 0.03 wt% for all amides. Water was purified by deionization and double distillation until a specific conductivity of *ca.* 1.0×10^{-5} S m^{-1}. Mixtures were prepared by weight.

The enthalpies of solution $\Delta_{sol}H^m$ for Ala-Valine were measured at 298.15 ± 0.005 K with an isoperibol (ampoule-type) calorimeter fitted with a 60 cm^3 reaction vessels and electrical calibration.

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Table 1
Standard enthalpies (kJ/mol) of dissolution ($\Delta_{sol}H^{\circ}$) of *DL*-α-Alanyl-*DL*-α-Valine 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	m_2[a]	DMA
1.242	−5.05 ± 0.02	0.814	−4.94 ± 0.02	0.717	−4.71 ± 0.02	0.805	−4.25 ± 0.02	0.507	−3.97 ± 0.02
2.345	−4.79 ± 0.02	1.646	−4.16 ± 0.02	1.193	−4.55 ± 0.02	1.396	−2.73 ± 0.02	0.978	−3.52 ± 0.01
3.748	−4.09 ± 0.02	2.411	−3.26 ± 0.02	2.102	−3.56 ± 0.02	1.772	−1.16 ± 0.02	1.085	−2.12 ± 0.01
5.079	−3.42 ± 0.01	3.869	−2.45 ± 0.01	2.598	−2.42 ± 0.01	2.468	−0.56 ± 0.01	1.763	−0.78 ± 0.01
7.521	−2.83 ± 0.02	4.701	−1.53 ± 0.02	3.528	−2.07 ± 0.02	2.952	0.58 ± 0.02	2.181	0.90 ± 0.01
8.477	−2.21 ± 0.01	5.829	−0.68 ± 0.01	4.372	−1.08 ± 0.01	3.724	0.99 ± 0.01	3.619	2.99 ± 0.01
10.867	−1.96 ± 0.01	8.681	0.53 ± 0.01	5.586	−0.32 ± 0.01	4.464	1.94 ± 0.01	4.685	5.07 ± 0.02
12.756	−1.66 ± 0.01	9.909	1.34 ± 0.01	6.503	0.84 ± 0.01	5.513	2.96 ± 0.01	6.654	7.96 ± 0.02
17.652	−1.03 ± 0.01	12.404	1.73 ± 0.01	9.282	2.11 ± 0.01	6.710	3.87 ± 0.01	7.739	9.78 ± 0.02
25.445	−0.61 ± 0.01	17.463	3.27 ± 0.01	12.996	4.03 ± 0.02	8.889	5.53 ± 0.02	10.811	11.60 ± 0.03
35.557	−0.56 ± 0.01	24.523	3.51 ± 0.01	18.183	6.38 ± 0.02	12.412	6.11 ± 0.02	15.173	11.30 ± 0.03
50.858	−0.11 ± 0.01	34.557	3.91 ± 0.02	25.926	9.41 ± 0.02	17.797	7.98 ± 0.03	21.625	11.03 ± 0.03

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

The calorimeter setup and experimental procedure were described in detail previously [10,21]. The relative random error of measurements was less than 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 [22,23]. Our values of ($\Delta_{sol}H^{m}$ ($m = 0.111$ mol kg^{-1}) = 17.60 ± 0.04 kJ mol^{-1} and $\Delta_{sol}H^{\circ}$ = 17.23 ± 0.07 kJ mol^{-1}) agree with of recommended literature values 17.58 ± 0.02 kJ mol^{-1} [22] and 17.22 ± 0.04 kJ mol^{-1} [23], respectively).

3. Results

The standard enthalpies of solution $\Delta_{sol}H^{\circ}(\equiv\Delta_{sol}H^{\infty})$ were calculated by averaging the results of five measurements of $\Delta_{sol}H^{m}$ for each composition of the aqueous amide; on dependence of $\Delta_{sol}H^{m}$ on m was observed in the mixed solvents studied. The experimental data on $\Delta_{sol}H^{\circ}$ (together with the average deviations) obtained for Ala-Valine in aqueous solution amides under study are summarized in Table 1. The enthalpies of transfer of Ala-Valine from water to aqueous amide, ($\Delta_{tr}H^{\circ}$), graphically presented in Fig. 1 were calculated from the experimental enthalpies for Ala-Valine dissolution in the pure water, ($\Delta_{sol}H^{\circ}(w)$), and in the amide-containing aqueous solution, ($\Delta_{sol}H^{\circ}(w+y)$):

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

Enthalpy of dissolution of Ala-Valine in water ($\Delta_{sol}H^{\circ}(w) = -5.68 \pm 0.04$) was taken from [9].

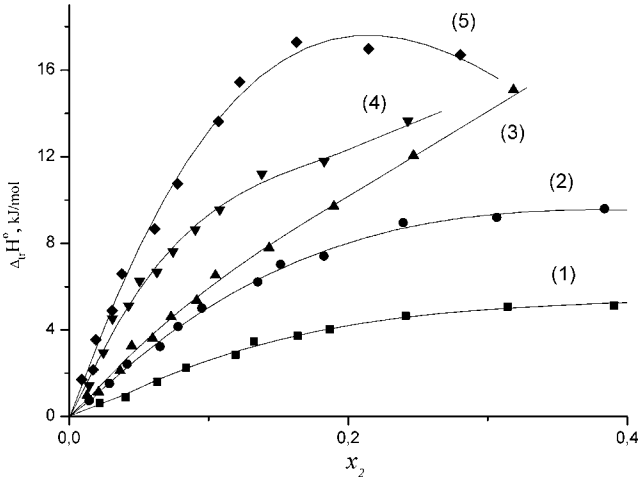

Fig. 1. Enthalpies of transfer $\Delta_{tr}H^{\circ}$ of *DL*-α-Alanyl-*DL*-α-Valine from water into the H_2O + FA (1), H_2O + MFA (2), H_2O + DMF (3), H_2O + DEF (4), H_2O + DMA (5) mixed solvent as functions of amide mole fraction x_2 at 298.15 K.

4. Discussion

From Fig. 1 follows that the features of change of $\Delta_{tr}H^{\circ}$ vs. x_2 function depend on both amide concentration and nature of *N*-alkyl-substitution in the co solvent molecule. In the concentration region $0 < x_2 < 0.15$, the endothermicity of Ala-Valine dissolution increases monotonically. Here water undergoes destructuring under the action of both Ala-Valine and amide molecules. Simultaneously, Ala-Valine solvation shells are formed, largely of water molecules. In this concentration range, interparticle interactions in the ternary aqueous systems can be characterized in terms of the McMillan–Mayer theory [24] adapted by Kauzmann [25], Friedman [26], and Desnoyers [27] for calculating the enthalpy coefficients of pairwise interactions, h_{xv}.

For this purpose, the $\Delta_{sol}H^{\circ}$ (m_2) functions were approximated by a third-degree polynomial of the form

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

where m_2 is the molal concentration of the amide, and a_i are coefficients calculated by a method of least squares. The correlation coefficient R and the Student criterion (S.D.) value varied from 0.992 to 0.997 and from 0.151 to 0.495, respectively. The h_{xy} value was calculated from the a_1 coefficient related to the coefficient of pairwise interactions as $h_{xy} = a_1/2$ [28]. The h_{xy} values for all systems in question are listed in Table 2. The positive sign at h_{xy} values for aqueous solution of FA and alkylated amides show that the solutes are strongly hydrated by H_2O molecules, where as the interaction between hydrated Ala-Valine and amide molecules is weak. The replacement of an *N*-sited hydrogen atom in FA by an alkyl radical increases the enthalpy coefficients of pairwise interactions. This is evidence that Ala-Valine–alkyl-substituted amide interactions are weaken, increasing the endothermic effect of solution.

All components of the ternary systems studied are capable of forming H-bonds with each other. Here with, H_2O, FA, MFA form networks of H-bonds [29,30]. The $\Delta_{sol}H^{\circ}$ value for Ala-Valine in such systems is determined by the ratio between the energy consumed for the dissociation of H-bonds in self-associates, energy of dehydration of the Ala-Valine (amide) and the energy released in the formation of heterocomponent H-bonds.

The curves in Fig. 1 show that the $\Delta_{tr}H^{\circ}$ (x_2) dependence for Ala-Valine in (H_2O + FA) is substantially different from similar dependences for Ala-Valine in water-*N*- and water-*N*,*N*-substituted amide systems. In our opinion, the least positive

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

Substance	FA	MFA	DMF	DEF	DMA
Ala-Valine	245 ± 24	514 ± 48	607 ± 88	1230 ± 216	1598 ± 194

(by sign) h_{xy} value for (H_2O + FA) mixture points to following. The energies of H_2O–H_2O, H_2O–FA, and FA–FA H-bonds are comparable [31] that results in low positive enthalpies of (H_2O + FA) mixing over the whole range of compositions [32]. Therefore, the endothermic contribution from dehydration of FA molecules will be the least among the chosen amides. Note that the enthalpic coefficients of pairwise interaction between a zwitterion of glycine and a molecule of formamide ($h_{xy} = -224\,J\,kg\,mol^{-2}$) or urea ($h_{xy} = -390\,J\,kg\,mol^{-2}$) are negative in sign [13]. It is result of a predominant high-exothermic effect of the direct interaction between a zwitterion of glycine (urea) and a molecule of amide, as compared to the endothermic effect of dehydration of glycine (urea) and amide in aqueous medium. The H-by-CH_3 substitution in a glycine molecule results in an increase of positive (in sign) value of $h_{xy} = 10\,J\,kg\,mol^{-2}$ [4] which is caused by the decrease in exothermic contributions from electrostatic interactions between a zwitterion of alanine and a polar molecule of FA under the influence of the hydrophobic hydration of an amino-acid alkyl group. The similar tendency to increasing the positive h_{xy} (in magnitude) for alkyl-substituted amino acids and peptides in the same mixed solvents (in particular, in aqueous amides) was observed by authors of some other works [12–14]. Processing from changes in $\Delta_{tr}H^{\circ}$, an increase in the concentration of FA above 0.15 mole fractions in the aqueous solution weakly strengthens Ala-Valine solvation because the endothermic processes of continued decomposition of H_2O balance the energy of newly formed heterocomponent H-bonds and FA self-associates. The replacement of *N*-sites hydrogen atom in a molecule of FA to form MFA induces an increase of the endothermic effect of solution with increasing the concentration of the specified formamide derivative. The similar effect is induced by strengthening of hydrophobic properties of MFA. In addition, the energy of H bonds in NMF is slightly lower than that in FA because of the greater flexibility of the *N*-site-methylated chain structure of the former [33,34]. Therefore the contribution in $\Delta_{tr}H^{\circ}$ from the destruction of MFA self-associates will be visible less, and itself MFA hydrated is stronger. Unlike FA and MFA, *N*,*N*-alkylated amides do not form intermolecular H-bonds and are typical aprotic polyfunctional solvents. An increase in the endothermic effect of solution (transfer) in the series of (H_2O + DMF) < (H_2O + DEF) < (H_2O + DMA) mixtures is likely caused by the strengthening of their hydrophobic properties [35]. According to findings [14,18], the hydrogen-bonding between water molecules around the peptide alkyl groups is stronger than those in bulk water. This effect transferred to water molecules in the hydration shells of both zwitterion and peptide group strengthens their hydration. That is, the endothermic effect of partial dehydration of the reinforced hydration layers of both peptide zwitterion and peptide group becomes the more pronounced. Besides, an increase in the size of hydrocarbon groups in the *N*(*C*)-substituted amides results in the greater degrees of destruction of a tetrahedral grid of H-bonds between water molecules. Thus, the total effect of interactions studied becomes more endothermic. We will mark, that an appreciable decrease in $\Delta_{tr}H^{\circ}$ at transfer of Ala-Valine from (H_2O + DMF) to (H_2O + DEF) is most likely due to the presence of the steric hindrances for the solute–solvent interactions (through van der Waals contacts) and the energy expenditure at creating of the hydration cavities. Intensifying endothermic effects on going from DMF to DMA is due to weakening of the interaction between the peptide zwitterion and the alkyl-derivative amide. Thereby, it adds to the prevalence of endothermic processes of dehydration of molecules in aqueous solutions. It is probably bound by that "formyl" CH_3, interfacing with a carbonyl group, has strong inductive influence on electronic frame of a carbonyl group [36].

From data of Table 1 follows that the endothermicity of dissolution of Ala-Valine increases in the (H_2O + FA) < (H_2O + MFA) < (H_2O + DMF) < (H_2O + DEF) < (H_2O + DMA) series. The specified sequence of intensifying the endothermic process of dissolution of Ala-Valine in the aqueous amides studied is caused by the following.

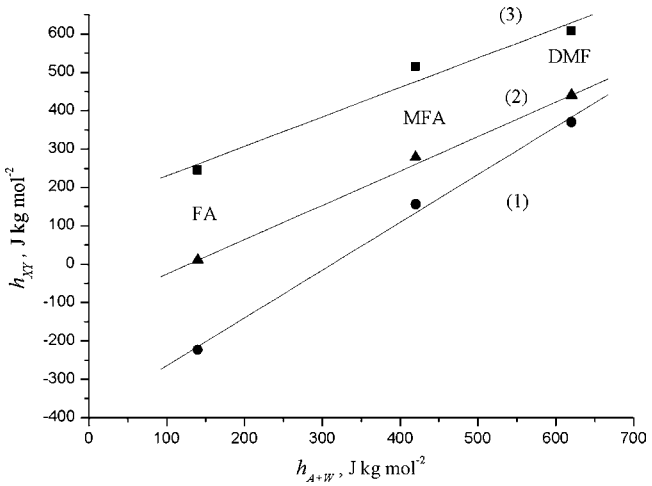

Fig. 2. Dependence enthalpic coefficients of pairwise interactions (h_{xy}) *DL*-α-Alanyl-*DL*-α-Valine and formamides (Table 2) from enthalpic coefficients of pairwise interactions (h_{A+W}) of the formamides and water [36]. (1) Glycine [3], (2) *DL*-α-Alanine [4,38], and (3) *DL*-α-Alanyl-*DL*-α-Valine.

(a) It can be connected with the energy of intermolecular interactions which are strengthened in the above sequence. This is confirmed by the enthalpies of mixing of water with amide [36,37]. The similar change in the energy of intermolecular interactions in the specified mixtures is characteristic for glycine [3,13] and alanine [4], too. It should be also noted that the dependence of $\Delta_{sol}H^{\circ}$ against x_2 for glycine in aqueous alcohols ($0 < x_2 < 0.3$ mole fraction of alcohol) repeats a trend of $\Delta_{mix}H^{\circ}$ against x_2 for aqueous amide in the same of concentration interval with an inversion in sign and with a maximum (minimum) at $x_2 \approx 0.2$ [3]. In other words, in the case of dissolution of Ala-Valine, the energy expenditures for destroying the structure of mixed solvent grow in the same row.

(b) It can be connected also with the energy of pairwise intermolecular Ala-Valine–amide interaction that is related linearly with energy of pairwise water–amide interactions (see Fig. 2). The increase of a number of CH_3-groups in an amide molecule causes the weakening of pairwise Ala-Valine–amide as well as glycine–amide and alanine–amide interactions. One can see in Fig. 2 that the substitution of hydrogen atom by an alkyl radical in a glycine molecule loosens the pairwise interactions between amino acid and amide, too. A presence in the Ala-Valine molecule of three alkyl groups results in weakening its pairwise intermolecular interactions with molecules of amides to a larger extent. It is induced by the effect of hydrophobic alkyl groups, causing the charge redistribution in a peptide (amide) molecule [7] and intensifying the hydration of zwitterions. Herewith the electrostatic peptide–amide interactions are weakened. Besides they can preclude the formation of H-bonds between the peptide and amide molecules, creating additional steric hindrances. An increase of amide concentration ($x_2 > 0.25$) result in rise of a number of amide molecules in the solvent shell that induces the strengthening the enthalpy contributions from the van der Waals forces, bipolar–bipolar, induction, and dispersive interactions and hydrogen bonding. It is accompanied by increasing the exothermic enthalpy effect of dissolution of Ala-Valine as a concentration of amides rises.

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References

[1] V.I. Smirnov, V.G. Badelin, Russ. J. Phys. Chem. 77 (5) (2003) 713.
[2] V.I. Smirnov, V.G. Badelin, Russ. Biophys. 49 (3) (2004) 375.
[3] V.I. Smirnov, V.G. Badelin, Russ. J. Phys. Chem. 80 (3) (2006) 357.
[4] V.I. Smirnov, I.N. Mezhevoi, V.G. Badelin, Russ. J. Phys. Chem. 80 (5) (2006) 672.
[5] V.I. Smirnov, I.N. Mezhevoi, V.G. Badelin, Russ. J. Phys. Chem. 81 (5) (2007) 727.
[6] V.I. Smirnov, I.N. Mezhevoi, V.G. Badelin, Russ. J. Phys. Chem. 81 (8) (2007) 1245.
[7] V.I. Smirnov, V.G. Badelin, Russ. J. Phys. Chem. 82 (7) (2008) 1206.
[8] V.I. Smirnov, V.G. Badelin, Russ. J. Phys. Chem. 82 (9) (2008) 1555.
[9] V.I. Smirnov, V.G. Badelin, Russ. J. Phys. Chem. 82 (12) (2008) 2069.
[10] V.I. Smirnov, V.G. Badelin, Thermochim. Acta 471 (2008) 97.
[11] G.M. Blackburn, T.H. Lilley, P.J. Milburn, J. Solut. Chem. 15 (2) (1986) 99–108.
[12] C. Jolicoeur, B. Riedl, D. Desrochers, L.L. Lemelin, R. Zamojska, O. Enea, J. Solut. Chem. 15 (2) (1986) 109.
[13] B. Palecz, J. Solut. Chem. 24 (6) (1995) 537.
[14] B. Palecz, J. Thermal Anal. 54 (1998) 265.
[15] B. Palecz, J. Thermal Anal. 45 (1995) 805.
[16] T.H. Lilley, R.H. Wood, J. Chem. Soc., Faraday Trans. I 76 (1980) 901.
[17] G. Castronuovo, V. Elia, F. Velleca, Can. J. Chem. 77 (7) (1999) 1218.
[18] G. Castronuovo, V.E.C. Postiglione, F. Velleca, Thermochim. Acta 339 (1999) 11.
[19] H. Sijpkes, A.A.C.M. Oudhuis, G. Somsen, T.H. Lilley, J. Chem. Thermodyn. 21 (1989) 343.
[20] V.A. Klimova, Main Methods for Analysis of Organic Compounds, Khimiya, Moscow, 1967 (in Russian).
[21] E.V. Ivanov, V.K. Abrosimov, V.I. Smirnov, J. Chem. Thermodyn. 39 (2007) 1614.
[22] I. Wadsö, R.N. Goldberg, Pure Appl. Chem. 73 (2001) 1625.
[23] D.G. Archer, J. Phys. Chem. Ref. Data 28 (1999) 1.
[24] W.G. McMillan Jr., J.E. Mayer, J. Chem. Phys. 13 (1945) 276.
[25] J.J. Kozak, W.S. Knight, W. Kauzmann, J. Chem. Phys. 48 (1968) 675.
[26] C.V. Krishnan, H.L. Friedman, J. Solut. Chem. 2 (1973) 119.
[27] J.E. Desnoyers, G. Perron, L. Avedikian, J.P. Morel, J. Solut. Chem. 5 (9) (1976) 631.
[28] H. Piekarski, M. Tkaczyk, J. Chem. Soc., Faraday Trans. 87 (22) (1991) 3661.
[29] J.N. Spencer, S.K. Berger, C.R. Powell, B.D. Henning, G.S. Furman, W.M. Loffredo, E.M. Rydberg, R.A. Neubert, C.E. Shoop, D.N. Blauch, J. Phys. Chem. 85 (1981) 1236.
[30] M. Jelinska-Kazimierczuk, J. Szydlowsky, J. Solut. Chem. 30 (2001) 623.
[31] A.M. Zaichikov, Russ. J. Gen. Chem. 71 (2001) 162.
[32] A.M. Zaichikov, O.E. Golubinskii, Russ. J. Phys. Chem. 70 (1996) 1971.
[33] H. Ohtaki, S.I. Ishiguro, in: G. Mamantov, A.I. Popov (Eds.), Chemistry of Non-aqueous Solutions. Current Progress, VCH Publ., New York, 1994, p. 180.
[34] Yu.G. Bushuev, V.P. Korolev, in: A.M. Kutepov (Ed.), Concentrated and Saturated Solutions, Nauka, Moscow, p. 264.
[35] Ym.M. Kessler, A.M. Zaitsev, Solvophobic Effekts, Ellis Horwood, Chichester, 1994.
[36] M. Bloemendal, A.C. Rouwf, G. Somsen, J. Chem. Soc., Faraday Trans. 1 82 (1986) 53.
[37] V.P. Belousov, A.G. Morachevskii, M.Yu. Panov, Thermal Properties of Solutions of Nonelectrolytes, Khimiya, Leningrad, 1981 (in Russian).
[38] J. Fernandez, T.H. Lilley, J Chem. Soc., Faraday Trans. 88 (17) (1992) 2503.