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Enthalpy Characteristics of L-Asparagine Interaction with Glycerol, Ethylene Glycol, and 1,2-Propylene Glycol in Aqueous Solutions

I. I. Mezhevoi and V. G. Badelin

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

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Abstract—Integral dissolution enthalpies $\Delta_{sol}H^m$ of L-asparagine in the mixtures of water with glycerol, ethylene glycol, and 1,2-propylene glycol at the concentration of organic solvents up to 0.24 mole fraction were measured by the calorimetry method. The standard enthalpies of dissolution ($\Delta_{sol}H^0$) and transport ($\Delta_{tr}H^0$) of amino acids from water to the mixed solvents were derived. The calculated enthalpy coefficients of the molecule pair interactions of L-asparagine–cosolvent are positive, except for the amino acid–glycerol–water system. The data obtained are interpreted in terms of prevalence of different types of interactions in solution and effect of the cosolvent nature on the thermochemical characteristics of the L-asparagine dissolution.

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It is known that polyols are involved in the stabilization of the natural conformation of globular proteins [1]. Therefore, the study of interactions between proteins and polyalcohols is necessary for understanding the mechanisms of the conformational stability of biopolymers in solution. However, a rather complex structure of the protein compounds complicates the thermodynamic study of these interactions. Therefore quite often the interaction is studied of small biomolecules (amino acids, peptides, etc.) with the components of the solution, reflecting in some way the behavior of proteins in mixed solvents. This model approach has been proposed earlier and now is successfully applied [2–4].

Table 1 lists the experimental data on the $\Delta_{sol}H^0$ of L-asparagine (Asn) in mixed solutions of water with glycerol (G-ol), ethylene glycol (1,2-EtD), and 1,2-propylene glycol (1,2-PrD). The dependence of the transfer enthalpies $\Delta_{tr}H^0$ of Asn from water in water-organic mixtures on the mole fraction of cosolvent (x_2) are shown in Fig. 1.

Figure 1 shows that the nature of variation of the thermochemical characteristics vs the concentration of various cosolvents in three-component solutions differs considerably. So at the change of $\Delta_{tr}H^0$ the inversion of the sign for Asn occurs only in solutions of 1,2-PrD at a concentration of $x_2 \sim 0.17$. In the glycerol solution the transfer enthalpy is negative in the whole concentration range, and in the 1,2-propylene glycol solutions it is positive. This means that the transfer enthalpy is determined by various contributions with opposite signs of the interactions of different nature competing in solution and on the solvation processes. To interpret the observed behavior we used a model approach based on the interactions of solute and cosolvent [5]. In the three-component systems of amino acid–organic cosolvent–water the molecules of hydrated solutes are close enough for overlapping their hydration shells. The resulting $\Delta_{tr}H^0$ for L-asparagine is determined by the sum of contributions with different signs:

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

where ΔH_1 corresponds to the ion-bipolar interactions between the centers of zwitterionic amino acids and the OH groups of polyols, ΔH_2 is hydrophilic–hydrophilic group interactions between the O=C–NH$_2$ group of amino acid and OH group of a polyol through the formation of a hydrogen bond, ΔH_3 comprises hydrophobic–hydrophilic interactions between the nonpolar parts of amino acid or organic cosolvent and the OH group of co-solvent or zwitterionic center of L-asparagine, ΔH_4 is hydrophobic–hydrophobic interac-

Table 1. Standard dissolution enthalpies $\Delta_{sol}H^0$ (kJ mol^{-1}) of L-asparagine in the mixed water–polyol solvents at 298.15 K

H_2O–glycerol		H_2O–ethylene glycol		H_2O–1,2-propylene glycol	
m_y[a]	$\Delta_{sol}H^0$	m_y[a]	$\Delta_{sol}H^0$	m_y[a]	$\Delta_{sol}H^0$
0	22.57±0.10	0	22.57±0.10	0	22.57±0.10
0.7564	22.50±0.11	0.8526	22.86±0.10	0.7235	22.93±0.09
1.4260	22.35±0.11	1.9798	23.07±0.11	1.3507	23.21±0.10
2.1023	21.93±0.11	2.8769	23.34±0.10	2.3223	23.59±0.11
3.1908	21.26±0.10	4.4083	23.62±0.11	3.2363	23.77±0.11
4.1289	20.73±0.10	5.2381	23.76±0.11	4.2534	23.94±0.11
5.6073	19.46±0.08	7.4501	23.97±0.11	5.6024	24.03±0.12
6.8757	18.35±0.09	9.2387	24.05±0.12	7.4432	23.80±0.11
8.2628	16.91±0.08	11.5595	23.98±0.11	8.6258	23.31±0.11
10.2002	15.30±0.08	14.8321	23.51±0.11	10.7654	22.58±0.10
11.9733	13.90±0.07	17.5234	22.75±0.10	12.9876	21.89±0.09

[a] Organic co-solvent molality (mol kg^{-1}).

tions between nonpolar part of amino acid and polyol. According to this model, the first and second types of interactions make a negative contribution to $\Delta_{tr}H^0$ of amino acid transfer from water to aqueous-organic solvents, while the third and fourth types of interactions are positive. Positive values of $\Delta_{tr}H^0$ for Asn in all solutions of 1,2-propylene glycol and ethylene glycol up to the concentrations shown in Fig. 1 indicate the dominance of the third (ΔH_3) and fourth (ΔH_4) types of interactions. After passing the peak, the $\Delta_{tr}H^0$ of both ethylene and 1,2-propylene glycols begins to decrease and becomes negative in the case of ethylene glycol, which means an increase in the exothermicity of the dissolution and the dominance of ion-bipolar and hydrophilic–hydrophilic group interactions between the hydrated amino acid and a polyhydric alcohol. Apparently, with increasing concentration of cosolvent, the interaction between the polar groups of a polyol and zwitterionic centers of L-asparagine become stronger, which leads to an increase in the proportion of exo-effects in the ternary solution. Interestingly, the dependence of the system L-asparagine–glycerol–water has no extremum, and the enthalpy of transfer begins to decrease gradually straight from the origin. Apparently, this is due to the presence of an additional OH group in the glycerol molecule compared with ethylene and 1,2-propylene glycols, which significantly increases the proportion of bipolar and ion–hydrophilic–hydrophilic group interactions in solution. The occurrence of the peaks at different mole fractions of the studied cosolvents suggests that the contributions from the hydrophobic–hydrophilic and hydrophobic–hydrophobic group interactions are maximal at the respective concentrations of the polyols.

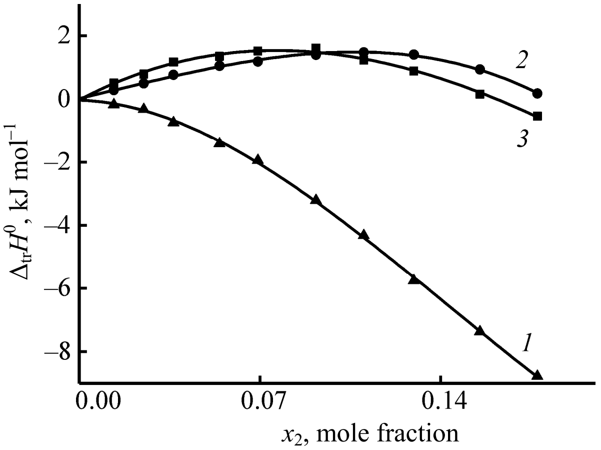

Fig. 1. The enthalpy of L-asparagine transfer ($\Delta_{tr}H^0$) from water to the mixtures: water– glycerol (*1*), water–ethylene glycol (*2*) and water–1,2-propylene glycol (*3*), vs. mole fraction (x_2) of the organic cosolvent at 298.15 K.

The interspecies interactions in ternary aqueous systems are described in the framework of the McMillan–Mayer theory [6] by calculating the enthalpy coefficients of pair interactions (h_{xy}) of the amino acids with a molecule of organic solvent. For the calculation, the concentration dependence of $\Delta_{sol}H^0 = f(m_y)$ for the amino acid in aqueous-organic solutions was approximated by a third degree polynomial [Eq. (2)].

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

where m_y is molal concentration of organic cosolvent, a_0, a_1, and a_2 are the approximation coefficients calculated by the least-squares method.

As a result, we obtained the following equation for asparagin in aqueous solutions of glycerol [Eq. (3)], ethylene glycol [Eq. (4)], and 1,2-propylene glycol [Eq. (5)]:

$$\Delta_{\mathrm{sol}}H^0 = (22.56\pm0.09) - (0.12\pm0.07)m_y\text{-}\ldots \quad (3)$$
$$r\ 0.999,\ SD\ 0.070,\ n\ 10,$$

$$\Delta_{\mathrm{sol}}H^0 = (22.60\pm0.03) + (0.28\pm0.02)m_y\text{-}\ldots \quad (4)$$
$$r\ 0.997,\ SD\ 0.026,\ n\ 10,$$

$$\Delta_{\mathrm{sol}}H^0 = (22.57\pm0.07) + (0.71\pm0.05)m_y\text{-}\ldots \quad (5)$$
$$r\ 0.993,\ SD\ 0.055,\ n\ 10.$$

The values of constant terms in Eqs. (3)–(5) correspond to the standard enthalpies of dissolution of L-asparagine in pure water and are in a good agreement with our data $\Delta_{\mathrm{sol}}H^0(\mathrm{Asn}) = 22.57 \pm 0.10$ kJ mol^{-1} (Table 2). Published values of $\Delta_{\mathrm{sol}}H^0$ in water for L-asparagine vary considerably: $\Delta_{\mathrm{sol}}H^0(\mathrm{Asn}) = 20.95 \pm 0.14$ [7], 21.64 ± 0.05 [8], 6.24 [9], 31.51 [10] kJ mol^{-1}.

To calculate the enthalpy coefficients of pair interactions h_{xy} the coefficient a_1 is used associated with h_{xy} through the relation: $h_{xy} = a_1/2$ [11]. As a result, we obtained the values for asparagine in solutions of polyols listed in Table 2.

All the coefficients h_{xy} are positive in the case of aqueous-organic solvents, except for the L-asparagine–glycerol–water system. This means that the endothermal processes associated with the restructuring of three-component solution and the release of water molecules from hydration shells of L-asparagine and organic solvents prevail over the direct interactions of the solvated polar groups of the interacting molecules. The enthalpy pair interaction coefficients are increasing in the series: glycerol < ethylene glycol < 1,2-propylene glycol. Higher h_{xy} value for 1,2-propylene glycol compared with ethylene glycol is due to the presence in the molecule of the former of an additional methyl group, which contributes to hydrophobic hydration resulting in the strengthening of hydrogen bonding of water around the CH_3 groups [15]. This contributes to the solution restructuring at the interaction of solvated molecules, increases the endo-effects and h_{xy}. Less positive h_{xy} values for the glycerol compared to 1,2-propylene glycol are associated with the substitution of hydrogen atom in the methyl group of the 1,2-propylene glycol molecule by the polar OH group capable of forming donor-acceptor bonds. As a result, exothermal dissolution of asparagine increases and the enthalpy interaction parameter h_{xy} for the system of L-asparagine–glycerol decreases and becomes negative.

Table 2. Enthalpy pair interaction coefficients h_{xy} (J kg mol^{-2}) of amino acids with polyhydric alcohols in aqueous solutions at 298.15 K

Amino acid	Glycerol	Ethylene glycol	1,2-Propylene glycol
L-Asparagine	–62±34	141±8	357±16
L-Serine [12]	135±7	264±77	471±16
L-Cysteine [13]	200±7	310±7	536±13
L-Alanine [14]	355±7	444±13	694±19

As can be seen from Table 2, all coefficients h_{xy} for amino acids decrease in the series Ala > Cys > Ser > Asn. The coefficient for the alanine bearing a non-polar CH_3 group is larger compared with the amino acids that have polar side substituents, due to the effects of hydrophobic hydration. Replacing the SH group by the OH results in an increase in exothermic interactions between the molecules of a polyol and amino acid zwitterion due to the greater capability of serine OH group in comparison with the SH group of cysteine to form donor–acceptor bonds [16]. More negative coefficient for asparagine is determined by the presence in its molecule of an additional site of specific solvation, O=C–NH_2, causing an increase in exothermic dissolution.

It is interesting to note the correlation dependence of the enthalpy pair interaction coefficients of L-asparagine zwitter-ions on the number of OH groups in propanol (PrOH), isopropanol (*i*-PrOH) and the studied cosolvent molecules. The enthalpy interaction coefficients of L-asparagine with alcohols were we

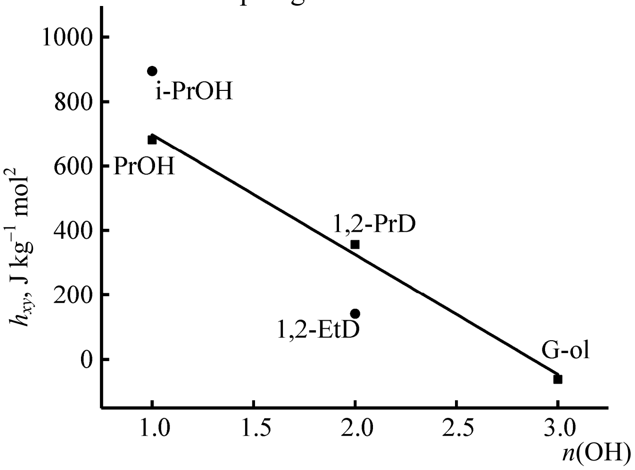

Fig. 2. Dependence of enthalpy pair interaction coefficients (h_{xy}) of L-asparagine with organic solvents in water on the number of OH groups (n) in the molecule of alcohol.

obtained earlier, their values were: h_{xy}(PrOH) = 682±61, h_{xy}(i-PrOH) = 895±61J kg mol^{-2} [17]. The obtained linear dependences of h_{xy} on the number of OH groups in the molecules of alcohols are shown in Fig. 2. As seen from Fig. 2, the h_{xy} values for PrOH, 1,2-propylene glycol and glycerol fit to a straight line: h_{xy} = 1070–372n_{OH}, (r = 0.989). The absence of a methyl group in the ethylene glycol molecule compared with 1,2-propylene glycol lowers the value of h_{xy}. On the contrary, the CH_3 group in the side chain of isopropanol makes h_{xy} more positive compared with that of linear propanol (Fig. 2). This may be due to the steric and hydrophobic effects affecting the hydrogen bonding of water around the methyl groups. As a result, the proportion of endo-effects in the ternary system increases, and h_{xy} becomes more positive.

Thus, the thermochemical parameters $\Delta_{\mathrm{tr}}H^0$ and h_{xy} of the interaction of L-asparagine with the studied organic solvents depend largely on the nature of intermolecular interactions (ion-bipolar interactions and hydrogen bonding), the structural features of co-solvents and hydration (dehydration) of the substances, and hydrophobic effects in the ternary system.

EXPERIMENTAL

The integral enthalpies of dissolution were measured on a hermetically sealed four-ampule variable temperature calorimeter with an isothermal shell designed by us, allowing to carry out a series of successive measurements of the thermal effects at the dissolution of several samples of the substance in the same volume of solvent without reloading the calorimeter cell [18]. The reaction part of the calorimeter and all internal parts contacting with solution are made of titanium alloy VT-1. The calorimetric cell capacity is ~110 ml. Temperature control system stability during the calorimetric measurements was maintained with an accuracy 10^{-3} K. Thermometric and energy sensitivity of the calorimeter was 2×10^{-4} K mm^{-1} and 1×10^{-3} J mm^{-1} of the recorder scale. The thermal effect was compensated by means of electrical current. To assess the accuracy and reliability of the calorimeter units, we measured heat effects of dissolution of KCl in water at 298.15 K. From the results of ten independent measurements of the enthalpies of KCl dissolution in H_2O, and the data on the enthalpies of dilution [19] we obtained the value of the standard enthalpy $\Delta_{\mathrm{sol}}H^0$ = 17.23±0.06 kJ mol^{-1}, which agrees well with the recommended value in the literature (17.22±0.04 kJ mol^{-1}) [20, 21].

The L-asparagine concentration was varied in the range of 0.004 to 0.007 mol kg^{-1}. Enthalpies of solution $\Delta_{\mathrm{sol}}H^{\mathrm{m}}$ of amino acid in the studied concentration range (up to 0.007 mol kg^{-1}) does not depend on the concentration of the biomolecule, therefore as the standard values of $\Delta_{\mathrm{sol}}H^0$ we adopted arithmetic means of the thermal effects of dissolution $\Delta_{\mathrm{sol}}H^{\mathrm{m}}$ obtained in 3–4 measurements. L-asparagine (Aldrich, 98%) before the experiment was recrystallized from water–ethanol mixture and dried in a vacuum at 343 K for 48 h. Water after deionization was distilled twice (specific conductivity 10^{-5} Ω^{-1} cm^{-1}). Organic solvents (from Aldrich): glycerol (99.5%), ethylene glycol (99%), and 1,2-propylene glycol (99%) were used without further purification. Mixed water solvents were prepared gravimetrically.

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