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Thermochemical Study of Solvation of Aliphatic Carboxamides in Aqueous Formamide Solutions

A. M. Zaichikov and N. G. Manin

Ivanovo University of Chemical Engineering, Ivanovo, Russia
Institute of Solution Chemistry, Russian Academy of Sciences, Ivanovo, Russia

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Abstract—The entahlpies of solution of formamide, acetamide, and propionamide in aqueous formamide solutions (formamide concentration ≤ 8 mol kg^{-1}) at 298.15 K were measured. The entahlpies of transfer of amides from water to the mixed aqueous-organic solvent were calculated and compared with published data on the enthalpies of transfer of amides into aqueous urea solutions. The opposite trend in variation of the enthalpies of transfer of amides in these systems with increasing concentration of the nonaqueous component is due to different proton-donor power of formamide and urea relative to water. The enthalpy coefficients of pair interaction of amides with formamide in ternary aqueous solutions were calculated. Their positive values are due to endothermic interaction with formamide of the alkyl groups of amide molecules. The relative hydrophobicity of amides with different degrees of substitution of the amide group was estimated.

The thermodynamic properties of binary and ternary aqueous solutions containing aliphatic carboxamides are being studied for several decades [1, 2]. This interest is largely due to the fact that amide molecules contain protein fragments and therefore can be used as model systems in studies of biomolecules. This paper is a part of the thermochemical study of interparticle interactions and state of these organic substances in water–formamide mixtures. Previously we studied in the entire composition range the ternary system water–formamide–dimethylacetamide [3]. Dilute solutions of formamide in water are convenient objects for studying solute–solute interactions, since formamide is a typical hydrophilic substance [1] and its amide groups form hydrogen bonds similar in energy to water–water bonds [3, 4]. At the same time, features of thermochemical behavior of heterofunctional organic compounds in aqueous solutions of formamide are poorly studied [5]. The main goal of this work was to study by the thermochemical experiment the features of interaction of polar and nonpolar groups of carboxamides, differing in the degree of substitution of the amide group, with formamide in its aqueous solutions. The results were compared with published data for ternary aqueous systems containing amides and urea, i.e., hydrophilic substances with the same polar groups as in formamide.

The enthalpies of solution at infinite dilution of amides in aqueous formamide solutions (see Experimental), determined in this work, are listed in Tables 1 and 2. The enthalpies of solution of amides in water are listed in Table 3. Our results nicely agree with data of [6–11] but significantly differ from the enthalpies of solution measured in [12].

Table 1. Enthalpies of solution at infinite dilution of primary and secondary amides in aqueous formamide solutions at 298.15 K (ΔH_s^0, kJ mol^{-1})

m_y, mol kg^{-1}	Formamide	Acetamide	*N*-Methylformamide	*N*-Ethylformamide	*N*-Methylacetamide
0.5	1.84 ± 0.03	9.70 ± 0.01	–6.83 ± 0.08	–8.45 ± 0.05	–12.95 ± 0.07
1.0	1.75 ± 0.01	9.73 ± 0.03	–6.77 ± 0.05	–8.25 ± 0.01	–12.62 ± 0.01
1.5	1.67 ± 0.05	9.74 ± 0.06	–6.68 ± 0.01	–8.08 ± 0.09	–12.30 ± 0.02
2.0	1.52 ± 0.01	9.77 ± 0.02	–6.62 ± 0.01	–7.85 ± 0.06	–12.08 ± 0.03
2.5	1.48 ± 0.01	9.82 ± 0.03	–6.44 ± 0.03	–7.70 ± 0.02	–11.67 ± 0.01
3.0	1.39 ± 0.01	9.89 ± 0.04	–6.42 ± 0.01	–7.52 ± 0.06	–11.56 ± 0.05
4.0	1.27 ± 0.01	9.92 ± 0.04	–6.36 ± 0.02	–7.22 ± 0.09	–11.28 ± 0.01
8.0	0.91 ± 0.01	–	–	–	–

Table 2. Enthalpies of solution at infinite dilution of tertiary amides in aqueous formamide solutions at 298.15 K (ΔH_s^0, kJ mol^{-1})

m_y, mol kg^{-1}	Dimethylformamide	Dimethylacetamide	Diethylformamide	Diethylacetamide	Dimethylpropionamide
0.5	–14.93 ± 0.02	–20.88 ± 0.07	–17.40 ± 0.07	–23.34 ± 0.06	–21.80 ± 0.01
1.0	–14.68 ± 0.05	–20.48 ± 0.07	–16.87 ± 0.06	–22.74 ± 0.01	–21.28 ± 0.11
1.5	–14.45 ± 0.04	–20.02 ± 0.04	–16.44 ± 0.02	–22.19 ± 0.08	–20.85 ± 0.06
2.0	–14.25 ± 0.02	–19.79 ± 0.03	–16.14 ± 0.05	–21.61 ± 0.02	–20.30 ± 0.04
2.5	–14.13 ± 0.03	–19.40 ± 0.02	–15.73 ± 0.03	–21.29 ± 0.03	–20.02 ± 0.04
3.0	–13.91 ± 0.05	–19.17 ± 0.02	–15.59 ± 0.02	–20.91 ± 0.06	–19.52 ± 0.03
4.0	–13.54 ± 0.04	–18.86 ± 0.06	–15.08 ± 0.02	–20.25 ± 0.02	–18.90 ± 0.04
8.0	–13.04 ± 0.04	–17.94 ± 0.01	–13.93 ± 0.07	–18.65 ± 0.07	–

Table 3. Enthalpies of solution at infinite dilution of amides in water at 298.15 K (ΔH_s^0, kJ mol^{-1})

Amide	ΔH_s^0	References	Amide	ΔH_s^0	References
Formamide	1.97 ± 0.05	[a]	Dimethylformamide	–15.22 ± 0.06	[a]
	2.03 ± 0.01	[6]		–15.21 ± 0.02	[6]
	1.97 ± 0.01	[7]		–15.27 ± 0.01	[7]
	2.03 ± 0.01	[8]		–15.22 ± 0.13	[11]
Acetamide[b]	9.63 ± 0.07	[a]	Diethylformamide	–17.97 ± 0.04	[a]
	9.64 ± 0.01	[6]		–19.60 ± 0.90	[12]
	9.73 ± 0.02	[7]	Dimethylacetamide	–21.42 ± 0.04	[a]
	9.74 ± 0.01	[8]		–21.46 ± 0.04	[7]
N-Methylformamide	–6.98 ± 0.07	[a]		–21.41 ± 0.01	[11]
	–7.14 ± 0.01	[6]		–21.42 ± 0.01	[12]
	–7.11 ± 0.01	[7]	Diethylacetamide	–24.08 ± 0.11	[a]
	–6.99 ± 0.16	[9]		–24.00 ± 0.10	[11]
N-Methylacetamide	–13.36 ± 0.04	[a]		–25.00 ± 0.70	[12]
	–13.56 ± 0.04	[9]	Dimethylpropionamide	–22.34 ± 0.05	[a]
	–13.30 ± 0.01	[10]		–22.40 ± 0.50	[12]
N-Ethylformamide	–8.70 ± 0.06	[a]			
	–9.70 ± 0.40	[11]			

[a] This work. [b] Solid substance (the other substances are liquids).

Figure 1 shows the concentration dependences of the enthalpies of transfer of amides from water to aqueous formamide solutions, approximated by quadratic dependences (1) [13]:

$$\Delta H_{tr}^0 = \Delta H_s^0(\mathrm{A,\ water–formamide}) - \Delta H_s^0(\mathrm{A,\ water}) = am + bm^2. \quad (1)$$

Here ΔH_s^0(A, water–formamide) and ΔH_s^0(A, water) are the standard enthalpies of solution of amides A in aqueous formamide and water, respectively; *m* is the molal concentration of formamide; and *a* and *b* are approximation coefficients calculated by the least-squares method. The lower part of Fig. 1 schematically shows the enthalpies of transfer of some amides from water to aqueous urea solutions as functions of the molar concentration of urea (data of [10]). Also given are the enthalpies of transfer of hexamethylphosphoramide from water to these mixed solvents [14] (the interest in hexamethylphosphoramide is due to its particularly strong, as compared to other nonelectrolytes, effect on water).

Figure 1 shows that solvation of all the amides studied in this work is weakened with increasing concentration of formamide. An exception is unsubstituted formamide whose solvation is enhanced. Let us start discussion with data on *N*,*N*-disubstituted amides. The enthalpies of transfer, equal to the difference between the enthalpies of solvation of amides in water and the mixed solvent, become more positive with increase in the size of alkyl substituents and in the electron-donor power. With increasing concentration of formamide the enthalpies of transfer of diethylacetamide and hexamethylphosphoramide increase to the greatest extent. The enthalpy of solvation is the sum of the enthalpies of cavity formation and of nonspecific and specific interaction between the solute and solvent. We have shown previously that the major contribution to the enthalpy of hydration of tertiary amides is made by interaction with water of their polar groups which form with water stronger hydrogen bonds than the water–water bonds [15, 16]. This is the major cause of appreciable exothermic effects in mixing of water with *N*,*N*-dialkylamides over the entire composition range [17]. Formamide, like water, has two hydrogen atoms capable of hydrogen bonding, but its proton-donor power is lower than that of water [18]. Therefore, the heteromolecular hydrogen bonds involving formamide protons are less strong than the hydrogen bonds formed by water protons [9, 19]. An increase in the concentration of formamide in water results in gradual decrease of the proton-donor power of the mixed solvent relative to pure water [20]. The greatest loss in the hydrophilic constituent of amide solvation in the water–formamide system will be observed for substances that are strong electron donors and form the strongest hydrogen bonds with water. Most probably, this factor is largely responsible for the most pronounced weakening of solvation of diethylacetamide and hexamethylphosphoramide (Fig. 1).

The important constituent of nonspecific interaction of nonelectrolytes with water is hydrophobic hydration [1]. Repeated attempts were made to estimate experimentally the contribution of the hydrophobic effect to the thermodynamic functions of hydration. Examples are studies [7, 9] in which the enthalpy of the structure-making effect on water of the methyl groups of secondary amides was estimated at –7 kJ mol^{-1}. However, the difference between the enthalpies of this effect on water of dimethylacetamide and dimethylformamide (DMF) is –6.8 kJ mol^{-1} in [9] and –3.2 kJ mol^{-1} in [7], which is due to different calculation procedures. With increasing size of hydrocarbon substituents in amide molecules, the contribution of the hydrophobic effect to the enthalpy of hydration increases [7]. In terms of the model of structure formation in solutions of hydrophilic nonelectrolytes, the new water–nonelectrolyte network of hydrogen bonds in formamide solutions is built on the basis of the initial water structure [21]. Analysis of the dielectric permittivity data showed that this leads to the structure-breaking effect of formamide molecules on water [22]. As the formamide concentration is increased, the water structure gradually transforms into the formamide structure [19, 23]. All these factors favor decrease in the absolute values of the effect of amide solvophobic solvation in mixed solvents relative to the enthalpy of the hydrophobic effect in water. Presumably, the decrease in the hydrophobic hydration effect will influence to the greatest extent the solvation of diethylacetamide and hexamethylphosphoramide in which the total volume of alkyl groups is the largest.

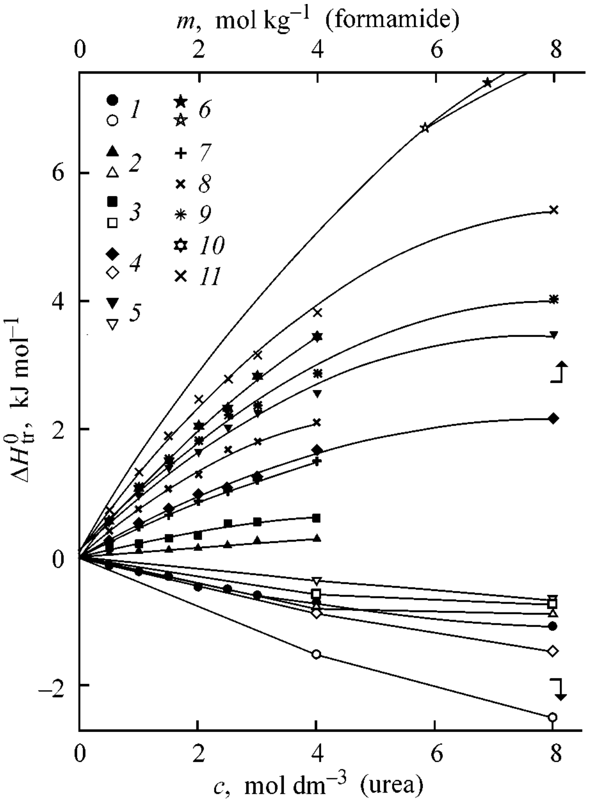

Fig. 1. Enthalpy of transfer of amides from water to (*1–11*, *dark symbols*) aqueous formamide and (*1–6*, *light symbols*) aqueous urea solutions at 298.15 K: (*1*) formamide, (*2*) acetamide, (*3*) *N*-methylformamide, (*4*) dimethylformamide, (*5*) dimethylacetamide, (*6*) hexamethylformamide, (*7*) *N*-ethylformamide, (*9*) diethylformamide, (*10*) dimethylpropionamide, and (*11*) diethylacetamide.

Also, the breaking effect of formamide molecules on the open-work structure of water increases the energy consumption for cavity formation in the mixed solvent owing to decreased role of the cavity mechanism of solvation [2]. The action of all these factors in the same direction results in the higher location of the $\Delta H^{0}_{\mathrm{tr}}(m)$ curves in Fig. 1 for dialkylacetamides which, as compared to the corresponding formamides, have the higher electron-donor power [18], the higher molar volume, and an additional hydrophobic group (CH_3). The $\Delta H^{0}_{\mathrm{tr}}(m)$ curve for dimethylpropionamide, which exhibits the electron-donor power similar to that of dimethylacetamide [24] and contains an additional methylene group, lies between the curves for diethylacetamide and diethylformamide. In hexamethylphosphoramide exhibiting very high hydrophobic and hydrophilic properties [1, 18], the contributions of the hydrophobic and hydrophilic constituents to the enthalpy of hydration are high and comparable [15, 25]. Since the molecular volume of hexamethylphosphoramide is also the largest, its solvation in aqueous formamide is weakened to the greatest extent. The absence of one alkyl group at the nitrogen atom in secondary amides, as compared to the corresponding tertiary amides, results in smaller molar volume and lower hydrophobic properties [1] and basicity [24]. Therefore, transfer of *N*-monosubstituted amides is less endothermic than that of the corresponding *N*,*N*-dialkylamides. The small negative values of ΔH^0_{tr} of formamide may be due to a slight increase in the electron-donor power of the mixed solvent as compared to water [20]. Replacement of the formyl proton by the methyl group in the acetamide molecule results in the change of the sign of ΔH^0_{tr} for primary amides.

The urea molecule differs from the formamide molecule by the presence of the second NH_2 group. The physicochemical properties of aqueous solutions of urea suggest weak interaction in this system; however, their analysis and conclusions about the character of urea hydration are rather contradictory. For example, Devyatkov *et al.* [26] suggested that the water environment is destabilized in the vicinity of the NH_2 groups (negative hydration), whereas in the vicinity of the C=O group the structurization is observed (positive hydration). At the same time, recent computer simulation in [27] gave the opposite result. Low values of excess thermodynamic functions of mixing in mixtures of water with additions of urea or formamide allow these systems to be considered as almost ideal systems. The low absolute values of the excess enthalpies are primarily due to almost total compensation of heat consumption for cleavage of hydrogen bonds in the pure components by the heat release in formation of heteroassociates. However, a minor growth of the positive values of the excess enthalpies of mixing [2, 28] indirectly supports the viewpoint that urea, similar to formamide, exerts the overall structure-breaking effect on water [22, 26, 29]. The different proton-donor power of these substances should be noted. Comparison of data in [9, 30, 31] shows that the strength of hydrogen bonds formed by protons of these substances with the carbonyl group of amides decreases in the order NH_2 (urea) > water > NH_2 (formamide).

This fact, and also practically coinciding concentration dependences of the enthalpies of transfer of hexamethylphosphoramide to both binary systems (Fig. 1) suggest that the decrease in the structure-making effect and increase in the enthalpy of cavity formation will be more pronounced on adding urea to water, as compared to the water–formamide mixture. Qualitative consideration of the enthalpies of transfer of aliphatic amides from water to aqueous urea solutions (Fig. 1), similar to that made above, suggests that the reasonable cause of decrease in the negative values of ΔH^0_{tr} of amides with increasing concentration of urea is the stronger electron-withdrawing power of urea compared to water. This fact is most probably responsible for the different concentration dependence of the enthalpies of transfer of amides from water to aqueous solutions of formamide and urea. In this connection, the fact that the largest positive values of ΔH^0_{tr} in the system water–urea are observed for hexamethylphosphoramide seems unexpected. One of the causes of this fact is probably a strong effect of hydrophilic urea on hexamethylphosphoramide via water structure in solution. The presence of six methyl groups in hexamethylphosphoramide is responsible for fairly large effect of its hydrophobic hydration in water [15, 25]. Study of the ternary system water–urea–hexamethylphosphoramide by high-frequency dielectrometry showed that urea eliminates the hydrophobic hydration effects characteristic of the binary system water–hexamethylphosphoramide [32]. The effect of urea on solvation of aliphatic amides should be similar; according to [32], urea should exert a stronger effect on more hydrophobic nonelectrolytes. Thus, the fact that the mutual arrangement of the $\Delta H^0_{\text{tr}}(c)$ curves for amides differing in the degree of *N*-substitution in aqueous urea solutions differs from that in aqueous formamide solutions is apparently due to competition of several contributions of different sign to the enthalpy of transfer of nonelectrolytes from water to aqueous urea solutions.

For ternary aqueous systems in the region of small additions of nonelectrolytes the concentration dependence of ΔH^0_{tr} is mainly determined by the coefficients of pair interaction of nonaqueous components [1]. These coefficients bear important quantitative information about the energy of interaction of dissolved nonelectrolytes, reflecting the total effect of interaction of solvated molecules. The enthalpy coefficients of interaction of nonaqueous components in ternary solutions were calculated in terms of the McMillan–Mayer theory [33] using Eq. (2) [34]:

$$\Delta H^0_{\text{tr}}/m_y = 2h_{xy} + 3h_{xyy}m_y + 3h_{xxy}m_x. \tag{2}$$

Here ΔH^0_{tr} are the enthalpies of transfer of amides from water to aqueous formamide solutions; m_y and

Table 4. Enthalpy coefficients of pair interactions of amides with formamide, urea, and amides in aqueous solutions at 298.15 K (J kg mol^{-2})

Amide	Cosolute			n_{CH_2}
	formamide, h_{xy}	urea, h_{xy}	amide, h_{xx}	
Formamide	–126(8)	–161(6) [35]	–115(1) [5]	0.5
Acetamide	59(10)	–142(4) [35]	1(14) [35]	1.5
N-Methylformamide	134(16)	–132(2) [35]	272(2) [36]	2.0
N-Ethylformamide	261(13)	–2(1) [37]	350(16) [38]	3.0
N-Methylacetamide	418(14)	15(6) [35]	286(8) [39]	3.0
Dimethylformamide	289(10)	–155(9) [35]	737(6) [5]	3.5
Dimethylacetamide	551(18)	–70(8) [35]	1081(28) [40]	4.5
Diethylformamide	602(13)	36(11) [35]	1767(19) [35]	5.5
Diethylacetamide	753(17)	135(10) [35]	2355(30) [35]	6.5
Dimethylpropionamide	556(12)	–	1797(9) [40]	5.5
Hexamethylphosphoramide	–	–	5160(260) [41]	9.0

m_x are the molal concentrations of formamide and amides; h_{xy}, h_{xyy}, and h_{xxy} are the enthalpy coefficients of pair and ternary interactions of amides (x) with formamide (y). The coefficients h_{xy} and h_{xyy} were determined by the least-squares method neglecting the last term of Eq. (2) in view of small concentrations m_x. The results of calculations of the coefficients h_{xy} are listed in Table 4. In parentheses are given the rms errors of approximations (2). The enthalpy coefficient of pair interaction formamide–formamide in water, calculated by us from the dependence $\Delta H^0_{tr}(m)$, almost coincides with the h_{xx} values obtained from data on the enthalpies of dilution [5] (Table 4) and enthalpies of mixing (H^E) [41]. Our values of h_{xx} of tertiary amides [42], calculated from the data on H^E [17], reasonably agree with published data on h_{xx} (Table 4). Also given in Table 4 is the coefficient h_{xx} for hexamethylphosphoramide, calculated in [41] from the enthalpies of mixing determined in [43].

All the coefficients of heterotactic pair interactions, calculated in this work, are positive and increase with increasing total size of alkyl groups. The coefficients h_{xy} of interaction of acetamides with formamide are always more positive than those of interaction of formamides with formamide. In Table 4 our results are compared with published data on the enthalpy coefficients of pair interactions of amides with urea in water. In Fig. 2 the coefficients h_{xy} are plotted vs. the number of equivalent CH_2 groups in alkyl substituents of amides (Table 4). According to [36], the CH groups were considered equivalent to 0.5 methylene group, and CH_3 groups, to 1.5 methylene groups. The straight lines approximating our data have a slope close to that obtained in [35], where it was assumed that the coefficients h_{xy} can be subdivided in two groups corresponding to the tertiary and other (primary and secondary) amides. The overall slope of the straight lines characterizes the contribution to the enthalpy coefficients h_{xy} from interaction of the formamide or urea molecule with the methylene group of amides in aqueous solutions. The portions intercepted on the ordinate are averaged contributions from interaction of the amide groups in amide molecules with formamide and urea.

Table 4 and Fig. 2 show that the positive values of the heterotactic coefficients h_{xy} in aqueous-formamide solutions are due to endothermic interaction of solvated hydrocarbon groups of the molecules with the solvated formamide molecule. This agrees with previous calculations of the increments of contributions

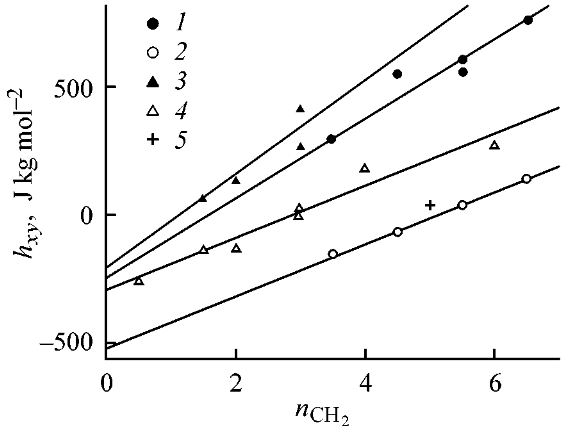

Fig. 2. Enthalpy coefficients of pair interactions vs. the number of equivalent methylene groups: (*1*) tertiary amide–formamide, (*2*) tertiary amide–urea, (*3*) secondary (primary) amide–formamide, (*4*) secondary (primary) amide–urea, and (*5*) *N*-*tert*-butylformamide–urea.

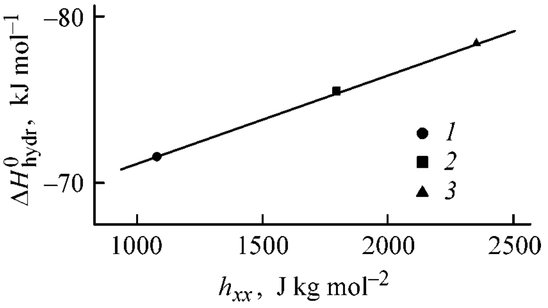

Fig. 3. Correlation between the enthalpies of hydration of tertiary amides and the enthalpy coefficients of pair interactions amide–amide in water: (*1*) dimethylacetamide, (*2*) dimethylpropionamide, and (*3*) diethylacetamide.

to the enthalpy pair coefficients, which showed that interaction of the CH_2 group in water with any polar group is accompanied by an endoeffect [5, 44]. The endothermicity of this process is probably due to desolvation of the alkyl radicals at mutual approach of the dissimilar solvation shells of the interacting species in aqueous solution. The exothermicity of interaction of amide groups in the amide molecules with formamide in its aqueous solution is due to formation of heteromolecular hydrogen bonds. However, in water–formamide mixtures this contribution to h_{xy} is not prevailing. Polar groups of amides interact with formamide less exothermally than with urea, which is due to the high proton-donor power of urea. In aqueous solutions of urea, the signs of h_{xy} are determined by competition of the exo and endo contributions. The less exothermic interaction with urea of the polar groups of primary and tertiary amides, as compared to tertiary amides, is most probably due to their different basicity, which regularly increases in going from primary to secondary amides [24, 45]. Our data show that this difference is not manifested in aqueous solutions of formamide. According to analysis made in [46], urea and formamide can be classed with hydrophilic substances, with formamide being more hydrophobic than urea. Rouw and Somsen [7] found that the enthalpy of hydration of formamide has a minor hydrophobic constituent. This fact is apparently responsible for the stronger slope of the dependences $h_{xy}(n_{CH_2})$ in aqueous solutions of formamide as compared to urea solutions. Furthermore, as suggested by computer simulation [47], in the vicinity of the formamide CH group there are four hydrophobically hydrating water molecules which cooperate with hydrophilic water and ensure additional stabilization of the hydration sphere of formamide. Partial dehydration will make an additional endothermic contribution to h_{xy} and also favor stronger slope of the function $h_{xy}(n_{CH_2})$.

The above-considered version of the method of group additivity of contributions to the coefficients h_{xy} satisfactorily describes aqueous solutions of urea containing fairly compact aliphatic amides. For more complex molecules in the case of steric hindrance or preferred orientations in interactions, there can be significant deviations from the additive scheme, as illustrated in Fig. 2 for *N*-monosubstituted *tert*-butylformamide. Calculation by the additive scheme of the enthalpy coefficient of interaction of *N*-acetyl-*L*-phenylalaninamide with formamide in water also led to inadequate results [48]. The factors disturbing the correlation $h_{xy}(n_{CH_2})$ in formamide solutions are not only different basicities of carbonyl groups in amide molecules but also the possibility of preferred orientation of amide molecules in their interaction with formamide.

In Table 4 the obtained values of h_{xy} are compared with the enthalpy coefficients of pair interactions amide–amide in water. According to a phenomenological approach in [2], for mainly hydrophobic interaction of solutes in water the typical relations are $g_{xx} < 0$, $Ts_{xx} > h_{xx} > 0$. In homological series of substances interacting in aqueous solutions mainly via hydrocarbon substituents, with increasing length of the alkyl chain the coefficients g_{xx} become more negative, and the coefficients h_{xx}, more positive. The same conclusion follows from data in Table 4 and data of [40] for DMF (g_{xx} = –129 J kg mol^{-2}), dimethylacetamide (g_{xx} = –177 J kg mol^{-2}), and dimethylpropionamide (g_{xx} –500 J kg mol^{-2}) having a branched structure. Previously we noted [41] that the coefficients h_{xx} of amides correlate with the number of carbon atoms (N_C) in hydrocarbon fragments of their molecules; such correlations are typical of thermodynamic properties of binary aqueous solutions [1]. Hydrophobic interactions arise from hydrophobic hydration whose thermodynamic parameters reflect the response of the three-dimensional network of hydrogen bonds in water on introduction of hydrophobic groups. The correlation of the enthalpies of hydration of amides with N_C was revealed in [12]; as follows from [7], the contribution of the hydrophobic constituent to the enthalpy of hydration increases with increasing volume of nonpolar substituents. Taking into account close correlation between the effects of hydrophobic hydration and hydrophobic interaction, and also data in [12, 41], we should expect parallel variation of their enthalpy characteristics such as the enthalpy of hydration and the coefficients h_{xx} suggested even as criteria of hydrophobicity [1]. Figure 3 illustrates this hypothesis for tertiary amines with a similar basicity of the carbonyl groups. Secondary amines, owing to the presence of the NH group, are capable of self-association in water through homomolecular hydrogen bonds. The positive values of h_{xx} of *N*-alkylamides (Table 4) and data in [36, 40] suggest that the secondary amides, similar to tertiary amides, interact in water primarily via their hydrocarbon substituents.

It was noted in [35, 38] that, as hydration of amides in ternary aqueous systems becomes more exothermic, the values of h_{xy} become more positive. Therefore, Lilley [49] suggested that the enthalpy coefficients h_{xy} become more positive as the enthalpies of hydration of amides become more negative. Figure 4 illustrates the validity of this hypothesis for aqueous solutions of formamide. The enthalpies of hydration were calculated from the enthalpies of solution (Table 3) and of vaporization of amides [50] occurring in the liquid state at 298.15 K. Figures 3 and 4 show that the coefficients of interactions amide–amide and amide–formamide in aqueous solutions include significant contributions from desolvation, increasing as the hydration of aliphatic amides is enhanced (i.e., with increasing total length of their alkyl chains). The correlation of the enthalpy coefficients of pair interactions amide–amide and amide–nonelectrolyte with the enthalpies of hydration of amides suggests correlation between h_{xx} and h_{xy}; this correlation does exist, as illustrated by Fig. 5. At the same time, the parallel variation of these coefficients makes it necessary to consider h_{xy} as the parameter of relative hydrophobicity of the compounds under consideration.

The problem of a criterion for the hydrophobicity of heterofunctional compounds such as, e.g., amides under consideration is still urgent. The best parameter for this purpose is the second derivative with respect to pressure of the second virial coefficient $(dB_{22}/dp)_T$ [1, 51]. However, its calculation is often complicated because of the lack of numerous required experimental data or their insufficient accuracy. Therefore, attempts are made to use as hydrophobicity criteria more readily accessible parameters calculated from thermodynamic characteristics [41, 51]. In [1, 13] it was suggested to construct the relative hydrophobicity scale using the enthalpy coefficients h_{xy} determined in ternary aqueous systems. Each of the substances of the set under consideration can enter into a similar specific interaction with a cosolvent, which is the case for the systems studied in this work. Data in Table 4 and the results of [38, 52] allow construction of five series of the relative hydrophobicity of amides. It should be noted that Fernandez and Lilley [38] and Palecz [52] calculated the coefficients of pair interactions of the same set of amides with glycine in water from the enthalpies of dilution and solution. Whereas the values of h_{xy} for primary and tertiary amides are reasonably consistent, the values for *N*-methylacetamide and *N*-ethylformamide obtained in [38, 52] differ by nearly 100%. Therefore, the values of h_{xy} for these secondary amides were excluded from further consideration. On the basis of the remaining data, we can rank aliphatic carboxamides in the following order with respect to relative hydrophobicity: formamide < acetamide < *N*-methylformamide < dimethylformamide < dimethylacetamide < diethylformamide < diethylacetamide.

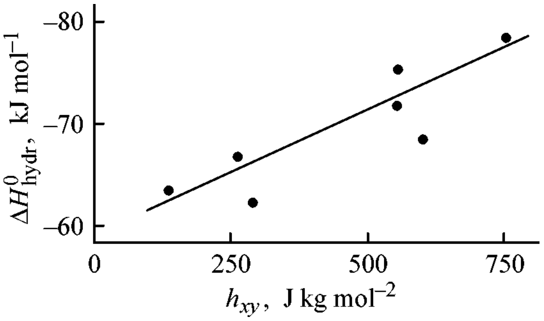

Fig. 4. Correlation between the enthalpies of hydration of amides and the enthalpy coefficients of their pair interactions with formamide in aqueous solutions at 298.15 K.

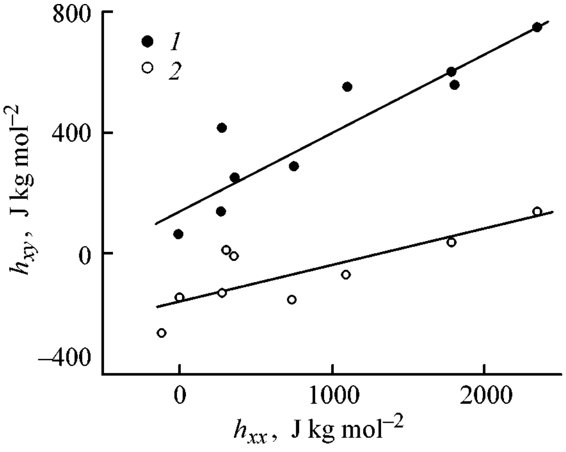

Fig. 5. Correlation between the enthalpy coefficients of pair interactions amide–amide and coefficients of interactions (*1*) amide–formamide and (*2*) amide–urea in water.

This order coincides with that based on the values of the pair coefficients h_{xx} (Table 4), also suggested as criteria of relative hydrophobicity. It is significant that the values of h_{xy} and h_{xx} for diethylformamide and dimethylpropionamide (Table 4), not studied in [35, 38, 52], are fairly close. The coefficient h_{xx} of hexamethylphosphoramide considerably exceeds those of the other amides; furthermore, hexamethylphosphoramide exhibits the highest value of $(dB_{22}/dp)_T$ [1]. Presumably, its relative hydrophobicity as judged from h_{xy} will also be stronger than that of diethylacetamide (the most hydrophobic among the examined carboxamides). Table 4 shows that the coefficients h_{xx} and h_{xy} regularly increase with increasing number of equivalent methylene groups. In [41] it was shown that the parameter $(dB_{22}/dp)_T$ and the coefficient h_{xx} correlate with the number of carbon atoms in alkyl groups of alkyl molecules and with each other; it was also suggested that, when there is a correlation with N_C, the coefficients of pair interactions can be used as a measure of relative hydrophobicity of substances. The parallel variation of the coefficients h_{xy} and h_{xx} (Fig. 5) with respect to each other and to the published values of $(dB_{22}/dp)_T$ of amides suggests that, if it is impossible to calculate more reliable hydrophobicity parameters, the coefficient h_{xy} can be used as a criterion of relative hydrophobicity of substances.

Concluding the discussion of experimental data, we note once again that the enthalpies of transfer of hexamethylphosphoramide from water to aqueous solutions of formamide and urea are fairly close (Fig. 1). This fact suggests that the endothermic contributions from cavity formation and elimination of hydrophobic hydration in the water–formamide mixture are lower than in the water–urea mixture. For compact aliphatic amides (Fig. 1) the opposite trend of the concentration dependences of ΔH^0_{tr} and the opposite signs of the coefficients h_{xy} in these binary aqueous mixtures are primarily due to different proton-donor powers of formamide and urea relative to water. The positive values of h_{xy} for diethylamides suggest *a priori* that their transfer from water to aqueous urea solutions will be endothermic. The positive values of the heterotactic coefficients h_{xy} in aqueous formamide solutions are due to interaction with formamide of nonpolar alkyl radicals of amide molecules. We believe that the larger slope of the dependences $h_{xy}(n_{\mathrm{CH_2}})$ in these mixtures as compared to the water–urea system is due to the higher hydrophobicity of formamide as compared to urea, owing to the presence of the formyl proton. The polar groups of amides interact with formamide in aqueous solutions less exothermally than with urea, which is due to weaker electron-withdrawing power of formamide. The correlations between the enthalpies of hydration, coefficients h_{xx}, and coefficients of pair interactions amide–formamide suggest that interaction of amides with formamide includes significant contributions from their desolvation. The order of the relative hydrophobicity based on the h_{xy} criterion shows that the hydrophobicity of aliphatic carboxamides of different degree of *N*-substitution increases with increasing total size of their alkyl groups.

In the subsequent paper we will consider the state of tertiary amides and hexamethylphosphoramide in the water–formamide mixed solvent over the entire composition range.

EXPERIMENTAL

Pure grade formamide was purified by freezing, vacuum-distilled, dried over 3 Å molecular sieves (Aldrich), and distilled again. Dimethylformamide (ultrapure grade), diethylformamide (Fluka), dimethylpropionamide (Aldrich), dimethylacetamide (Fluka), diethylacetamide (pure grade), *N*-methylformamide (Aldrich), and *N*-ethylformamide (Fluka) were purified similarly to [42]. *N*-Methylacetamide (pure grade) was purified by double vacuum distillation with drying of the intermediate product over 4 Å molecular sieves (Aldrich) at 323 K and used in the experiment as supercooled liquid. Analytically pure grade acetamide was recrystallized twice from anhydrous methanol and dried in a vacuum for 72 h at room temperature. The moisture content of organic solvents, determined by Fischer titration, did not exceed 0.03%; the physicochemical characteristics of the amides (melting points, densities) agreed with the reference data [53]. Water–formamide mixtures were prepared gravimetrically using freshly double-distilled water.

The enthalpies of solution were measured at 298.15 K in a variable-temperature ampule calorimeter with isothermal jacket; the volume of the reaction vessel was 50 $\mathrm{cm^3}$ [54]. The temperature was maintained to within 0.002 K. The thermal and temperature sensitivities of the calorimeter were, respectively, 5×10^{-4} J $\mathrm{mm^{-1}}$ and 5×10^{-5} deg $\mathrm{mm^{-1}}$ of the recorder scale. The enthalpies of solution were measured at solute concentrations less than 0.08 mol $\mathrm{kg^{-1}}$ of solvent. The standard molar enthalpies of solution were calculated as average values of two to four runs at a given solvent composition. As experimental error is given the standard deviation.

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