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Solute-Solute Interactions in Non-aqueous Solvents. Enthalpic Interaction Coefficients of Substituted Acetamides Dissolved in N,N-Dimethylformamide

M. Bloemendal[1] **and G. Somsen**[1,2]

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Enthalpies of dilution of acetamide, N-methylacetamide, N-ethylacetamide, N-propylacetamide, N-butylacetamide, N,N-dimethylacetamide, N,N-diethylacetamide, N,N-dipropylacetamide and N,N-dibutylacetamide dissolved in N,N-dimethylformamide as solvent have been measured calorimetrically at 25° C. The results are interpreted in terms of the McMillan-Mayer theory. The enthalpic interaction parameters are obtained for pairs, triplets and some quadruplets of solute molecules. All enthalpic pair interaction coefficients but one in this non-aqueous solvent are negative, whereas the triplet coefficients are positive. The concept of 'solvophobic interaction' can be used to explain these results in connection with the assumption of the formation of solute-solvent associates. The enthalpic pair interaction coefficients can be described by the additivity approach of Savage and Wood.

KEY WORDS: Solute-solute interaction; non-aqueous solvents; enthalpies of dilution; substituted acetamides; enthalpic interaction coefficients; group additivity; solvophobic interaction; polarophobic interaction.

1. INTRODUCTION

During the last decade the thermodynamic properties of dilute aqueous solutions of organic compounds have been studied extensively. The results for the most part are interpreted in terms of a peculiar interaction between the solute and the solvent, water, (hydrophobic hydration) and in terms of a mutual interaction between solute molecules, which is mediated by water (hydrophobic interaction,

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[1] Department of Chemistry, Free University, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands.

[2] To whom correspondence should be sent.

hydrophobic bonding). In these approaches the extraordinary 'structure' of liquid water plays a predominant role. Although knowledge of the thermodynamic properties of solutions in other solvents may contribute to a better understanding of the peculiarities of aqueous systems, only little work has been done in that field. In view of this, we started a systematic investigation on the enthalpies of dilution of a number of organic compounds in non-aqueous solvents.

For our purpose experiments in polar solvents are primarily of interest. Liquid amides form an attractive class of solvents, as a small change in the chemical structure of the molecules can result in a considerable change in the solvent properties. For example, formamide and N-methylformamide are strongly associated solvents (due to extensive intermolecular hydrogen bonding), whereas the closely related N,N-dimethylformamide (DMF) is practically non-associated. Since DMF molecules are the smallest amide molecules without intermolecular hydrogen bonding, we have started our study with DMF as the solvent.

As solutes we chose amides, N-alkyl substituted amides and N,N-dialkyl substituted amides, primarily because the alkyl groups in these compounds can be easily varied. Moreover they dissolve well both in water and in polar organic solvents. In addition experimental results about the amide hydrogen bond might give information about the properties of peptide hydrogen bonds in different surroundings.(1)

The results of the dilution experiments are interpreted in terms of the McMillan-Mayer approach.(2) We report in this paper the enthalpic interaction coefficients of acetamide (AA), N-methylacetamide (NMA), N-ethylacetamide (NEA), N-propylacetamide (NPA), N-butylacetamide (NBA), N,N-dimethylacetamide (DMA), N,N-diethylacetamide (DEA), N,N-dipropylacetamide (DPA), and N,N-dibutylacetamide (DBA), all dissolved in DMF, as the solvent.

2. THEORETICAL BACKGROUND

McMillan and Mayer(2) showed that, in a solution at concentrations for which the solvent activity equals the activity of the pure solvent, the osmotic pressure of the solution π can be expressed as

$$\pi = kT \sum_{\mathbf{n}} b_{\mathbf{n}} \prod_{s} a_s^{n_s} \qquad (1)$$

where a_s is the activity of solute molecules s, $\mathbf{n}$ represents a set of numbers of solute molecules of different species s, the summation is taken over all possible sets, $b_{\mathbf{n}}$ is the cluster integral related to set $\mathbf{n}$, n_s

is the number of molecules of species s in the set, and the multiplication is taken over all species. b_n depends on the solute concentration only for electrolytes. Friedman(3,4) showed, starting from (1) and neglecting surface terms, that the excess Helmholtz energy of a solution of non-electrolytes per kg of solvent, A_w^E can be given by a series expansion in the concentration, *i.e.*

$$A_w^E = -VkT \sum_{n\geqslant 2} B_n \prod_s c_s^{ns} \tag{2}$$

In this equation c_s is the concentration in molecules per unit of volume (number density), V is the volume of the solution per kg solvent and B_n is an irreducible cluster integral, which is related to b_n. Excess functions denote excesses over the values of a hypothetical reference solution, in which all activity coefficients are unity at any temperature, pressure and composition.(3) The cluster integrals are related to correction terms describing deviations from the random distribution function. These correction terms are defined in such a way that, for example in the case of a cluster of three molecules, there are, in addition to the term corresponding to the triple, also terms for all possible pairs, which may be formed from the triple cluster.(2) This means that only B_2 can be related directly to the interaction of two clustering molecules. The B_n values for higher **n** contain also terms for all lower clusters.

Equation (2) can be rewritten for the excess Gibbs energy per kg of solvent,(3,4) G_w^E:

$$G_w^E / [\sum_s m_s RT] = -\sum_{n\geqslant 2} [(\prod_s c_s^{ns}) B_n] / \sum_s c_s - \ln[V(\mathbf{m},\pi)/V(0,0)]$$
$$+ [\sum_s m_s RT]^{-1} \int_0^{\pi} [\partial V(\mathbf{m},p)/\partial p] \mathrm{d}p \tag{3}$$

in which m_s is the molality of species s in moles of solute per kg solvent $[m_s = c_s V(\mathbf{m},\pi)/N_A]$, $V(\mathbf{m},p)$ is the volume per kg solvent at molatities m_s of the solutes at pressure p and N_A is Avogadro's number. As shown by Friedman,(3,4) the second and third term of the right side of Eq. (3) can be neglected for many solutes in water. The second term can be estimated from the excess volume of a solution over the pure solvent. De Visser and Somsen(5) measured these excess volumes for solutions of several organic solutes in DMF as the solvent and found them to be extremely small. Hence the second term can be neglected for our systems too. Since the isothermal compressibility of DMF is only slightly larger than that of water,(6,7) it seems justified to neglect the third term likewise. This means that Eq. (3) reduces to

$$G_w^E = -RT \sum_{n\geqslant 2} B_n [N_A/V(\mathbf{m},\pi)]^{n-1} \prod_s m_s^{ns} \tag{4}$$

in which $n = \sum_s n_s$ and where we have written the concentration in terms of the molality.

If $V(\mathbf{m},\pi)$ is considered to be constant in dilute solutions, which is a reasonable assumption for the solvent DMF, a new interaction parameter can be defined:

$$B_n^g = -RB_n[N_A/V(\mathbf{m},\pi)]^{n-1} \tag{5}$$

so that

$$G_w^E = T\sum_{n\geq 2} B_{ns}^g \prod_s m_s^{ns} \tag{6}$$

By standard thermodynamic methods Eq. (6) can be transformed into an expression for the excess enthalpy per kilogram solvent, H_w^E:

$$H_w^E = \sum_{n\geq 2} B_n^h \prod_s m_s^{ns} \tag{7}$$

where

$$B_n^h = -T^2(\partial B_n^g/\partial T)_{p,ms} \tag{8}$$

For a binary system Eq. (7) becomes

$$H_w^E = B_2^h m^2 + B_3^h m^3 + B_4^h m^4 + \ldots \tag{9}$$

The symbol B_2^h chosen for reason of consistency of symbolism, is the same as $\{NN\}_h$ used by Cassel and Wood$^{(8)}$ and h_{xx} used elsewhere in the literature.$^{(9,10)}$ For the excess enthalpy per mole of solute Eq. (9) changes into

$$H^E = B_2^h m + B_3^h m^2 + B_4^h m^3 + \ldots \tag{10}$$

B_2^h, the enthalpic pair interaction coefficient, provides information about the interaction between pairs of solute molecules. This interaction is mediated by the solvent, so that the solvent structure, particularly that around the solute molecules in the so-called cospheres, determines the value of the interaction coefficient to a great extent.$^{(9)}$ Enthalpic interaction coefficients of higher order, B_3^h *etc.*, are less straight-forward to interpret because they contain also contributions from lower order interactions, but B_3^h can be considered as the excess enthalpic coefficient of a triple cluster over all pairs that can be formed from the triple.

Experimental values of the enthalpic interaction coefficients can be obtained by measurements on enthalpies of dilution, solution, or mixing.$^{(11)}$ In this study we use the approach through enthalpies of dilution.

3. EXPERIMENTAL

3.1. Materials

DMF (Baker, Analyzed Reagent), DEA, (Aldrich) and NBA, (Eastman) were dried as described below and used without further purification. DMA (Baker, Analyzed Reagent) was distilled under reduced pressure in the presence of NaOH. The middle fraction was collected and dried.

NEA, NPA, DPA, and DBA were synthesized as described by Giaquinto$^{(12)}$ according to the reaction

$$CH_3COCl + 2RR'NH \rightarrow CH_3CONRR' + RR'NH_2Cl$$

where R(R′) denotes an alkyl group or a hydrogen atom. A solution of one mole acetylchloride in 500 ml benzene was added dropwise to a cooled solution of two moles of the appropriate amine in 500 ml benzene. The final mixture was refluxed for two hours. The reaction mixture was washed three times with a saturated aqueous solution of NaCl containing 5% $NaHCO_3$ and three times with a saturated aqueous solution of NaCl containing 5% HCl. The dialkylacetamides remained in the organic phase. Pure dialkylacetamide was obtained by distillation under reduced pressure. The middle fraction was collected and dried as described below. Contrary to Giaquinto's description,$^{(12)}$ the monoalkylacetamides were extracted into the aqueous phase. They were isolated by means of extraction with n-butanol and purified by distillation. All synthesized amides were identified by their ^1H NMR spectra.

The liquid amides were dried over 4A molecule sieves (Baker) for at least seven days. GLC-analysis indicated a purity better than 99.8%. The water content, determined by a modified Karl-Fisher titration$^{(13)}$ was less than 0.01 mass %.

AA (Baker, Analyzed Reagent) was purified by sublimation. Its water content was less than 0.1 mass %. NMA (Merck, Pure) was fractionally crystallized and stored over 4A molecular sieves at 50 °C for at least four days. GLC-analysis indicated a purity better than 99.5%. The amount of water was less than 0.015 mass%.

All solutions were prepared by weight and kept in a dessicator over P_2O_5. They were never stored longer than two days.

3.2. Procedure

Enthalpies of dilution were measured with a LKB 10700-2 batch microcalorimeter, originally described by Wadsö.(14) The air thermostat of the microcalorimeter was precooled by a Lauda K2R thermostat. The output signal of the calorimeter was amplified by a Keathly 150B microvoltmeter and fed into a Kipp BD12 recorder, where it was integrated electronically with respect to time. The voltage-time-integral is proportional to the heat effect on dilution. The proportional constant is determined by an electric calibration. All experiments were carried out at 25.00±0.05 °C.

The reproducibility of the calorimeter was tested by calibrations at different settings of the amplifier and at different calibration times and currents. It was found to be better than 0.5% at calibration heats over 16 mJ. In view of the errors in the preparation of the solutions and the uncertainty caused by the presence of impurities in the chemicals, we estimate the maximum error in the measurements to be 1.5%, except for very small heat effects.

In some experiments with very small heat effects, instability of the baseline prevented an accurate determination of the integral. In these cases the peak height of the curve was used to determine the heat effect according to the procedure of Tumerman and Zidovezky.(15) The reproducibility of the peak height determinations was better that 2%. Electrical calibrations showed that, for heat effects less than 16 mJ, the integration method and the peak height approach agreed within experimental error.

The dilution of urea in water was used in order to test the accuracy and precision of the calorimeter. From the results we found B_2^h = -348.0±4.2 J-kg-mol^{-2}, which is in good agreement with the value calculated from the results of Hamilton and Stokes(16) (-347), with the value of Cassel and Wood(8) (-352) and with that of Savage and Wood(17) (-351±11). The value of Gucker and Pickard(18) (-359) is slightly larger. Our value for B_3^h (25.9±4.6 J-kg^2-mol^{-3}) compares well with the recent value of Savage and Wood(17) (22.5).

4. RESULTS

The results of the dilution experiments are presented in Table I. In this table m_i and m_f are the initial and final molalities of each dilution experiment, respectively, ΔH_{dil} is the enthalpy of dilution per mole solute and Δ% reflects the relative difference between experimen-

Table I. Enthalpies of Dilution of Several Solutes in DMF at 25 °C[a]

m_i	m_f	ΔH_{dil}	Δ%[b]	m_i	m_f	ΔH_{dil}	Δ%[b]
	Acetamide				N-Methylacetamide		
0.2788	0.1825	28.6	0.5	0.5128	0.1710	40.1	0.5
0.4249	0.2772	39.7	-0.4	0.5216	0.1760	40.0	-0.8
0.4249	0.1388	81.8	0.6	0.7059	0.2308	54.4	0.3
0.6247	0.4107	50.6	-0.4	0.9093	0.5876	34.4	-0.9
0.6247	0.2056	106.8	-1.0	0.9093	0.2956	68.5	0.5
0.8873	0.5803	61.3	-0.6	1.3440	0.8652	48.5	1.2
1.0709	0.6952	67.8	0.7	1.3440	0.4373	95.3	0.3
1.0709	0.3588	146.6	-0.1	1.3857	0.8846	49.6	-0.4
1.5743	0.4985	180.4	1.4	1.8835	1.2006	62.0	0.2
1.7911	1.1632	75.9	-1.2	1.8835	0.5844	125.6	-0.6
1.7911	0.5668	186.4	0.3	2.3582	1.5014	70.6	0.4
				2.3582	0.7315	147.2	-0.8
	N-Ethylacetamide				N-Propylacetamide		
0.3754	0.2473	19.0	-0.6	0.3434	0.2270	23.7	0.3
0.3754	0.1264	38.1	1.3	0.3488	0.1149	48.2	0.4
0.6825	0.4510	33.1	-0.3	0.6861	0.2218	91.6	-0.3
1.1135	0.7120	54.5	0.6	0.6902	0.4492	46.6	-0.4
1.1135	0.3479	106.6	-0.1	0.9706	0.3027	128.0	-0.1
1.5321	0.9831	70.0	0.8	0.9836	0.6288	66.1	0.1
1.5321	0.4803	137.7	-1.3	1.4123	0.9113	87.5	0.2
1.7542	1.1133	78.7	0.5	1.4123	0.4360	177.0	-0.5
1.7542	0.5411	154.6	-1.3	1.9190	1.2041	116.3	0.9
2.0151	1.2717	86.1	-1.1	1.9190	0.5862	228.7	-0.2
2.2265	1.3847	96.7	1.5	2.1105	0.6669	239.5	-0.6
	N-Butylacetamide				N,N-Dimethylacetamide		
0.5546	0.3497	56.2	0.8	0.7633	0.2486	-1.88	-6.3[c]
0.5546	0.1726	106.2	0.2	0.7756	0.2470	-2.18	5.8[c]
0.8351	0.5357	77.4	-0.1	0.8423	0.5453	-1.20	1.0[c]
0.8687	0.2670	157.9	-1.2	0.9254	0.5949	-1.32	-1.0
1.1474	0.7222	104.4	-0.3	1.0726	0.7330	-1.67	-1.6
1.1474	0.3522	203.2	-0.2	1.3275	0.8304	-2.10	0.8
1.7766	0.5274	296.5	-0.3	1.8523	1.1675	-3.03	0.0
1.9956	1.2225	171.9	0.7	1.9671	0.5890	-6.01	1.2
1.9956	0.5730	336.6	1.3	2.7014	0.7830	-8.60	-0.5
2.2488	1.3530	191.9	-0.9				
2.2488	0.6318	369.5	-0.2				

Table I. (Continued)

m_i	m_f	ΔH_{dil}	$\Delta\%^b$	m_i	m_f	ΔH_{dil}	$\Delta\%^b$
N,N-Diethylacetamide				N,N-Dipropylacetamide			
0.7477	0.2400	5.02	0.1	0.4778	0.4051	40.5	1.0
0.8509	0.2691	5.66	-0.8	0.5781	0.3733	24.8	1.3
0.8878	0.2691	6.07	0.3	0.5781	0.1870	46.9	-0.9
0.8942	0.5767	3.09	1.5	0.9164	0.5771	39.4	0.3
1.2968	0.3845	8.62	-0.0	0.9164	0.2864	73.6	-1.0
1.5379	0.4628	9.71	2.4	1.0292	0.3072	83.7	-0.8
1.8173	1.1077	6.26	1.8	1.3494	0.8380	56.7	0.1
1.8173	0.5294	11.67	0.4	1.3494	0.4068	107.0	-0.4
2.0531	0.5780	12.78	-2.1	1.8851	1.1183	79.3	-1.5
2.1334	1.2832	7.01	-1.1	2.0750	1.2344	87.3	1.1
2.2280	0.6420	14.10	2.2	2.0750	0.5739	162.5	0.7
2.3894	1.4238	7.79	-0.3				
N,N-Dibutylacetamide							
0.5055	0.3235	56.0	0.5				
0.5055	0.1552	109.0	-0.7				
0.6865	0.4395	73.3	0.6				
1.0350	0.6335	109.5	-1.0				
1.0350	0.3085	207.5	-0.6				
1.3167	0.7896	138.7	0.5				
1.3167	0.3709	263.2	0.9				
1.8616	1.1190	177.2	-0.1				
1.8616	0.4994	345.5	-1.1				
2.0578	0.5672	375.1	0.7				
2.1134	0.5613	383.6	-0.1				

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[a] Units: m, mol-kg^{-1}; ΔH_{dil}, J-mol^{-1}. [b] $\Delta\% = 100[\Delta H_{dil}(\text{exp}) - \Delta H_{dil}(\text{calc})]/\Delta H_{dil}(\text{exp})$, where $\Delta H_{dil}(\text{calc})$ is calculated from Eq. (12). [c] Because of the high uncertainty, these points are averaged and taken as one in the fit to Eq. (13).

tal and calculated enthalpies of dilution.

ΔH_{dil} can be written as:

$$\Delta H_{dil} = H^E(m_f) - H^E(m_i) \tag{11}$$

where $H^E(m_f)$ and $H^E(m_i)$ are the excess enthalpies per mole solute after and before dilution, respectively. Substitution of Eq. (10) in Eq. (11) gives

$$\Delta H_{dil} = B_2^h(m_f - m_i) + B_3^h(m_f^2 - m_i^2) + B_4^h(m_f^3 - m_i^3) + \ldots \tag{12}$$

or

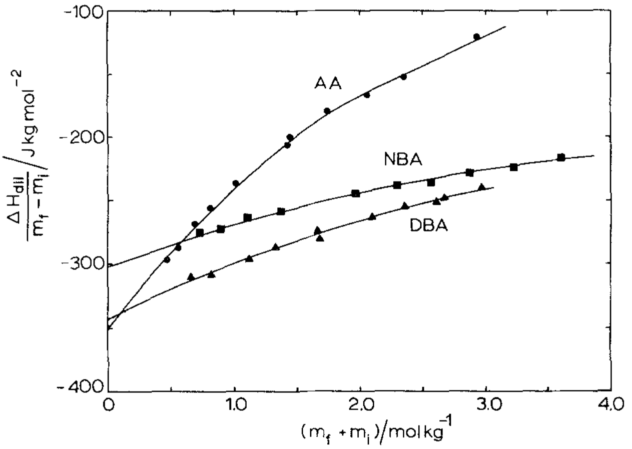

Fig. 1. $\Delta H_{dil}/(m_f\text{-}m_i)$ as a function of m_f+m_i for acetamide, N-butylacetamide and N,N-dibutylacetamide in DMF at 25 °C.

$$\Delta H_{dil}/(m_f\text{-}m_i) = B_2^h + B_3^h(m_f+m_i) + B_4^h(m_f^2+m_i^2+m_im_f) + \ldots \tag{13}$$

For the different solutes Figs. 1 and 2 present $\Delta H_{dil}/(m_f\text{-}m_i)$ as a function of (m_f+m_i). In all cases smooth curves were obtained, so that we could easily extract values of the enthalpic interaction coefficients by fitting the experimental results to Eq. (13). At most three coefficients were used to fit the data. B_4^h was only used, when the Student's *t*-test indicated a probability of more than 95% that B_4^h was not zero. The coefficients and their standard deviations, obtained by a least squares analysis, are collected in Table II. It should be emphasized, that the deviations of the coefficients, as given in parentheses, are the statistical deviations of the fit. The real deviations may be larger due to impurities in the chemicals and to systematic errors in the experiments.

5. DISCUSSION

When the enthalpic pair interaction coefficients, reported here, are compared with those of organic compounds in water (see Savage and Wood[(17)]), it appears that their absolute values are of the same order of magnitude, the latter being on the average two or three times larger than the former. A striking difference, however, is found in the sign of the coefficients. Almost all known enthalpic pair interaction

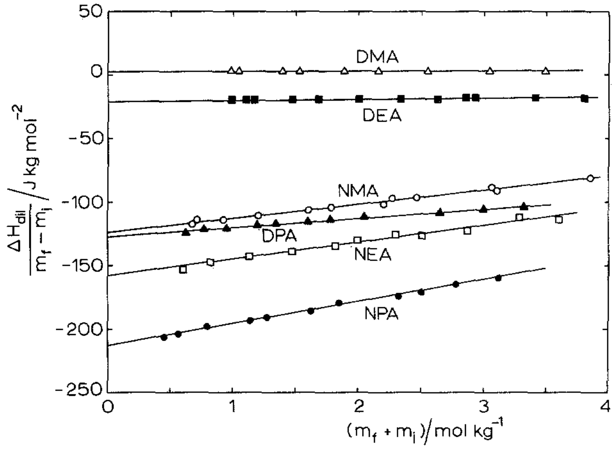

Fig. 2. $\Delta H_{dil}/(m_f - m_i)$ as a function of $m_f + m_i$ for methyl, ethyl and propyl mono-N- and di-N,N-substituted amides in DMF at 25 °C.

coefficients of organic compounds in water are positive, whereas the values in DMF, reported here, are negative with that of DMA as the only exception. As in water the absolute value of the interaction coefficients of related compounds increases strongly with the size of the alkyl groups (see Fig. 3).

The high positive values of B_2^h for molecules with large alkyl groups in water are explained in terms of their hydrophobicity as introduced by Frank and Evans(19) and Kauzmann(20) and the cosphere concept of Gurney.(21) In this view hydrophobic interaction (bonding) is 'the tendency of nonpolar groups to adhere to one another in an aqueous environment.'(22) Overlap of the structured water cospheres around the nonpolar groups results in the elimination of parts of the cospheres, which relax to less structured bulk water. Consequently this thermodynamically favorable process ($\Delta G < 0$) is accompanied by an endothermic enthalpy change ($\Delta H > 0$) and thus by a positive B_2^h. The process is dominated by a strong increase of the entropy.

Although generally the sign of the pair interaction coefficient, B_2^h, in DMF is opposite to that in water, an explanation may be comparable. Yaacobi and Ben-Naim(23) found that methane and ethane molecules, dissolved in a series of alcohols, attract each other. However, the large entropy changes of the aqueous solutions were absent. This kind of 'solvophobic interaction' was also observed by Craft and Wood,(24) who found net attractive forces between hydrocarbon molecules dissolved in NMA. As alkanes are virtually insoluble in DMF,

Table II. Enthalpic Interaction Coefficients for Acetamides in DMF

Solute	B_2^{h} [a]	B_3^{h} [a]	B_4^{h} [a]	σ [b]
AA	-349.6 (2.3)[c]	125.5 (3.4)[c]	-21.6 (1.3)[c]	1.75
NMA	-124.3 (0.5)	10.9 (0.2)	--	0.72
NEA	-157.0 (1.0)	12.1 (0.4)	--	1.37
NPA	-212.7 (0.5)	16.5 (0.3)	--	1.25
NBA	-301.5 (3.8)	35.8 (4.2)	4.4 (1.2)	1.98
DMA	3.60 (0.12)	-0.27 (0.10)	--	0.13
DEA	-10.52 (0.10)	0.64 (0.04)	--	0.14
DPA	-126.6 (0.8)	7.2 (0.4)	--	1.09
DBA	-342.2 (4.5)	46.6 (5.6)	5.2 (1.9)	2.29

[a] Units: B_2^{h}, J-kg-mol^{-2}; B_3^{h}, J-kg^2-mol^{-3}; B_4^{h}, J-kg^3-mol^{-4}; σ, J-kg-mol^{-2}. [b] The standard deviation of the fit to Eq. (13). [c] The numbers in parentheses are the standard deviations of the coefficients.

it is likely that such an interaction occurs in DMF, too. In analogy to the definition of the hydrophobic interaction by Kozak *et al*⁽²²⁾ the attractive interaction in these non-aqueous solvents may be defined as a tendency of nonpolar groups to adhere to one another in a polar medium. It is not likely that structured cospheres are present in the solvent DMF, so that a positive shift in the enthalpy upon adherence of apolar solute molecules can not be expected. On the other hand, an adherence leads to stronger dipole-dipole interactions between the solvent molecules. This would result in an exothermic enthalpy change and hence in negative B_2^{h} values. In this case the driving force of the interaction is an enthalpy change. The attraction of apolar particles to each other in polar solvents has often been called solvophobic interaction, but as hydrophobic interaction and the interaction between n-alkanes in cyclohexane are solvophobic too,⁽²³⁾ we suggest the name 'polarophobic interaction.'

Fig. 3 shows B_2^{h} for acetamides, N-alkylacetamides and N,N-dialkylacetamides dissolved in DMF as a function of the number of C-atoms in the solute molecules. Within each class, increase of the size of the alkylgroups is accompanied by a decrease in B_2^{h}. This can be understood in terms of polarophobic interaction. Enlargement of the apolar part of the molecules results in an increase of the polarophobic interaction and hence in a more negative B_2^{h}. Fig. 3 demonstrates also a decrease in B_2^{h}, when N-protons are present. This shift cannot be due to NH-CO interaction between two solute molecules, since this

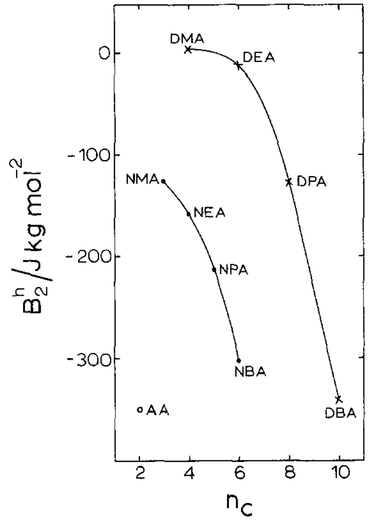

Fig. 3. B_2^h as a function of the number of C-atoms in the solute for several amides dissolved in DMF at 25 °C.

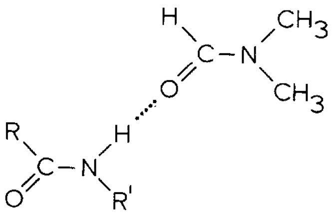

Fig. 4. Possible average conformation of a solute-solvent associate.

interaction occurs with comparable magnitude between solute and solvent molecules. Also it is not likely that it is caused by direct NH-NH interaction, as this would lead to a positive change in the enthalpy. However, we may consider the possibility that the NH-group of the solute forms on the average a hydrogen bond with the carbonyl group of a solvent molecule as indicated in Fig. 4. Self-association of amides, containing NH-groups, by hydrogen bonding has been inferred from different techniques.(25,26) By means of vapor pressure measurements Davies and Thomas(27) studied NMA dissolved in the apolar solvent benzene. They concluded the existence of linear aggregates of dimers, trimers and higher oligomers, where dimers are present even at high dilutions (at 0.1 M). As Kresheck and Klotz(1) conclude, the intrinsic interaction of the NH. . .OC amide hydrogen bond is not sensitive to

Table III. Experimental and Calculated Values of B_2^h in DMF

Solute	n_{CON} [a]	n_{CH_2} [a]	B_2^h(exp) [b]	B_2^h(calc) [c]
AA	3	8½	-350	-327
NMA	2	6½	-124	-151
NEA	2	7½	-157	-168
NPA	2	8½	-213	-191
NBA	2	9½	-302	-221
DMA	1	4½	4	-51
DEA	1	6½	-11	-99
DPA	1	8½	-1226	-181
DBA	1	10½	-342	-297
DMF	1	3½	0	-39

[a] The number of CON and CH_2 groups in the solute (associate) are given by n_{CON} and n_{CH}, respectively. [b] For units, see Table II. [c] Calculated from the enthalpic group interactions in Table IV. For units, see Table II.

the nature of the surrounding solvent. Thus it is to be expected, that this bond will occur in amide-amide mixtures too. Because of the large excess of solvent molecules in our systems, the interaction will occur mainly between a solute and a solvent molecule. If we suppose the solute-solvent associate to interact as one particle, the NH-NH repulsion may be outweighed by the attractive contributions of the extra alkyl and amide groups.

The idea of these associates can be supported by the group additivity concept of Savage and Wood.(17) The basic assumption of this concept is to split up the two interacting molecules in functional groups, where each group of molecule A interacts with each group of molecule B. The total pairwise interaction is the sum of all the group interactions. This gives for the enthalpic interaction coefficient

$$B^{h}_{AB} = \sum_{ij} n_i^{A}\, n_j^{B}\, h_{ij} \qquad (14)$$

where B^h_{AB} is the enthalpic pair interaction coefficient between the molecules A and B, n_i^A is the number of groups of type i on molecule A, n_j^B is the number of groups j on molecule B, and h_{ij} is the contribution to B^h_{AB} of the interaction of one group of type i with one group of type j. Although this approach leads to rough correlations between pair interaction coefficients, it has been proven to be useful for a large number of compounds dissolved in water.(17,28-35) One of the assumptions in the original paper(17) was the equivalence of interactions with CON-, CONH- and $CONH_2$ groups in water. Hence the influence of N-protons was neglected. We have seen already, that introduction of N-protons in the solute molecules in our case has a remarkable influence on B_2^h. This would mean that we should apply Eq. (14) with at least three functional groups, i.e. CH_2, CON, and (N)-H. This would result in an unacceptable number of six interaction parameters h_{ij} to describe nine compounds under consideration. However, the number of interaction parameters can be reduced, if we recall the assumption, that the interacting entity is in fact the solute-solvent associate of Fig. 4. In the associate the N-proton is screened by a DMF molecule, so that the influence of the N-proton is largely reduced and might be neglected. On the other hand the assumption involves the addition of two CH_3 groups, one CH group and one CON group to the original solute molecule. If we adopt the assumption of Savage and Wood(17) to consider a CH_3 group as equivalent to 1.5 CH_2 groups and a CH as 0.5 CH_2, this results in an extra number of 3½ CH_2 groups and one CON group in the interacting entity.

Table IV. Enthalpic Group Interactions in DMF

Interaction	h_{ij}^a	Std.Dev.^{a}
CON/CON	-65	42
CON/CH_2	11	9
CH_2/CH_2	-4.2	1.7

^{a}Units: J-kg-mol^{-2}.

Following the assumption of a solute-solvent associate we have fitted our results to Eq. (14) by means of linear regression analysis. In order to enlarge the number of input data, we have used the value of B_2^h for DMF as a solute in DMF as the solvent, which is bound to be zero. In Table III we present the number of CON and CH_2 groups and the experimental values of B_2^h used in the calculation. The resulting enthalpic group interaction parameters are given in Table IV. The standard deviation of the fit is 60 J-kg-mol^{-2}, which is well within the range of uncertainties reported in other work.(17,28-33) The last column in Table III presents values of B_2^h calculated from the parameters given in Table IV. The agreement with the experimental values is as good as found earlier for aqueous systems.(17,28-33) Hence the assumption of the existence of the above mentioned solute-solvent associate is supported by these results.

As the standard deviations of the enthalpic group interaction coefficients, h_{ij}, are relatively large, we confine ourselves to a discussion of the sign of h_{ij}. The CH_2-CH_2 enthalpic pair interaction coefficient is negative, which is in accordance with the idea of polarophobic interaction described above. Adherence of the apolar alkyl groups results in an exothermic enthalpy change. The endothermic enthalpy change for the CON-CH_2 interaction points to an enthalpically unfavorable interaction between a polar and an apolar group. Finally the CON-CON interaction may be related to dipole-dipole interaction. The dipolar character of amides is mainly due to the electron distribution along the CON axis.

Generally dipole-dipole interaction should result in an exothermic effect and hence in a negative value of h_{ij}. However, it is hard to understand, why a CON-CON interaction between two solute molecules should differ substantially from the same interaction between a solute and a solvent molecule. There might be a relation with the presence of solute-solvent associates. The average dipole moment of a solute-solvent associate is larger than that of a 'free' solute molecule, so that the $h_{\mathrm{CON\text{-}CON}}$ value in Table IV may be regarded as an average of the values for monomeric solute particles and solute particles associated with one or (in the case of AA) two solvent molecules.

The occurrence of solute-solvent associates means that some solvent molecules become part of the solute. Consequently the molalities given in Table I are too low. We have evaluated the experimental results with molalities based on the assumption of solute-solvent association. The resulting values of B_2^h for the mono-N-alkylacetamides were within the experimental error of the results in Table II. For acetamide the corrected enthalpic pair interaction coefficient is 328±4 instead of the original 350±2.3 J-kg-mol^{-2}. It seems reasonable, that in aqueous systems, where several authors(36-38) assume 'clathrate-like cages' of a considerable number of water molecules around the hydrophobic part of the molecules, these corrections are more important. Until now such corrections have been neglected.

In general the enthalpic triplet interaction coefficients, B_3^h, of organic molecules in water have the same sign as B_2^h and their magnitude is often 30-70% of that of B_2^h. This relatively high and positive B_3^h has been related to the cooperative character of hydrophobic interaction,(39) as the positive triplet term may indicate an extra endothermic effect, when more than two molecules interact with each other.

For the enthalpic interaction coefficients collected in Table II, the values of B_2^h and B_3^h appear to have an opposite sign. Hence the interactions in the solvent DMF do not show any cooperativity. On the contrary, a triplet interaction is enthalpically less favorable than the sum of the contributing pair interactions. Steric effects may be responsible.

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