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Enthalpic Interaction Coefficients of Formamides Dissolved in N,N-Dimethylformamide

M. Bloemendal,[1,2] A. H. Sijpkes,[1] and G. Somsen[1,3]

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Enthalpies of dilution of formamide, N-methylformamide, N-ethylformamide, N-propylformamide, N-butylformamide, N-pentylformamide, N,N-diethyl-formamide, N,N-dipropylformamide, N,N-dibutylformamide, and N,N-dipentyl-formamide 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. Enthalpic interaction parameters are obtained for pairs, triplets, and in some cases, quadruplets of solute molecules. In general, the enthalpic pair interaction coefficients are negative, whereas the triplet coefficients are positive. The interaction enthalpies are positive only for N-methylformamide and formamide. The magnitudes of the enthalpic pair and triplet interaction coefficients increase with increasing number of C atoms in the N-alkyl groups. The results for the formamides presented in this paper are compared with those for corresponding acetamides published earlier. Although the trends are comparable, distinct differences are observed. The contribution of the α-CH_3 group at the CO side of the dialkylacetamides to the enthalpic interaction coefficients appears to be negligible. The same is true for α-CH_2 groups at the NH side of a number of amides and related compounds. The enthalpic pair interaction coefficients of the mono-N-alkylsubstituted formamides show a shift of about 100 J-kg-mol^{-2} as compared with isomeric N-alkylacetamides. This is discussed in terms of the difference in proton donating and accepting ability of several types of amide molecules. It is concluded that substitution effects should be incorporated in additivity models for these type of systems.

KEY WORDS: Solute-solute interaction; enthalpies of dilution; substituted formamides; enthalpic interaction coefficients; alpha-CH_2 contributions; substitution effects.

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

[2]Present address: Department of Chemistry, The Hebrew University of Jerusalem 91904, Israel.

[3]To whom correspondence should be sent.

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1. INTRODUCTION

This paper is part of a project in which interactions of solutes in non-aqueous solvents are investigated by means of the determination of enthalpic interaction coefficients based on the McMillan-Mayer theory.[1] In this approach, which has been discussed by several authors,[2-6] the *n*th interaction coefficient refers to the interaction of *n* solute particles mediated by the particular solvent. Especially in water, the 'structure' of the solvent seems to play an important role. Knowledge of the interaction coefficients of solutions in other solvents may contribute to a better understanding of the peculiarities of aqueous systems. Apart from that, the properties of non-aqueous solutions may be interesting from another point of view. In the interior of folded globular proteins interactions occur in an environment which is largely nonaqueous and where amidic and hydrophobic regions exist. Since N,N-dimethylformamide (DMF) contains part of the elements of protein interiors,[7,8] knowledge about the interactions of a number of model solute compounds in this solvent may be of relevance.

Previously, we have reported results for mono- and disubstituted acetamides,[6] unsubstituted amides,[9] and urea and alkyl substituted ureas,[8] in DMF. For the unsubstituted amides, we found that the enthalpic pair coefficients are more or less equal from acetamide to hexanamide, whereas the enthalpic triplet coefficients decrease steadily in this series. This was interpreted in terms of a specific orientation of the interacting solute molecules.[9] We also determined the enthalpic interaction coefficients of formamide in DMF. As these coefficients were completely different from those of the other unsubstituted amides, we have decided to study the effect of the absence of the methyl group on the C atom of the amide group in more detail.

For these reasons, we report in this paper enthalpic interaction coefficients of formamide (FA), N-methylformamide (NMF), N-ethylformamide (NEF), N-propylformamide (NPrF), N-butylformamide (NBF), N-pentylformamide (NPeF), N,N-diethylformamide (DEF), N,N-dipropylformamide (DPrF), N,N,dibutylformamide (DBF), and N,N-dipentylformamide (DPeF), all dissolved in DMF. They were calculated from calorimetric determined enthalpies of dilution. The results for the formamides can be compared with those for the acetamides published before.

2. EXPERIMENTAL

2.1. Materials

DMF (Baker, Analyzed Reagent) was purified and dried as before.[6] DEF (Baker, Analyzed Reagent) was distilled at reduced pressure, NEF (Fluka, Purum) was distilled from benzene, and NMF (Merck z. Synthese) and FA (Baker, Analyzed Reagent) were purified by distillation according to the method of Verhoek.[10]

DPrF and DBF were synthesized according to the reaction

$$HCOOH + HNR_2 \rightarrow HCONR_2 + H_2O$$

1.5 mole of the secondary amine is added dropwise to a stirred solution of 3 moles of formic acid in 200 ml benzene at room temperature. Water and excess acid are removed from the reaction mixtures of DPrF and DBF by 4 and 5 azeotropic distillations from 200 ml benzene, respectively. Finally, the pure compounds were obtained by fractionation at low pressure.

NPrF, NBF, NPeF, and DPeF were synthesized by the reaction

$$HCOOC_2H_5 + HNRR' \rightarrow HCONRR' + C_2H_5OH$$

where R(R′) denotes either an alkyl group or a hydrogen atom. At room temperature one mole of amine is added dropwise to one mole of ethylformate under stirring. Except for DPeF, all reactions are exothermic. The reaction mixture is refluxed during 24 hours. As the reaction proceeds, the reflux temperature approaches the boiling point of ethanol. Finally, ethanol is distilled and the products fractionated at low pressure and stored over 4 A molecular sieves (Baker).

The synthesized amides were identified by their proton NMR spectra in $CDCl_3$. Chemical shifts are given in ppm relative to TMS with $CHCl_3$ as an internal standard. In parentheses, we give the integrated signal intensity and the nature of the signal.[4] In some instances, the coupling constant J is given. The N-alkylformamides appear in two conformations. This leads to integral values less than 1H for the formyl proton. The signal of the formyl proton of the *cis* compound is a doublet due to *trans* coupling with the NH. The *trans* conformation, *i.e.*, the alkyl group *trans* to the formyl proton, occurs

[4]Here, *s* denotes a singlet, *d* a doublet, *t* a triplet, *q* a quartet, *m* a multiplet, and *bs* a broad singlet.

predominantly.

NPrF: δ (90 MHz, $CDCl_3$) = 8.18 (0.81H, *s*); 8.04 (0.19H, *d*, *J*=12 Hz); 5.64 (1H, *bs*); 3.22 (2H, *m*); 1.55 (2H, *m*); 0.93 (3H, *t*, *J*=7 Hz). NBF: δ (90 MHz, $CDCL_3$)=8.18 (0.79H, *s*); 8.07 (0.21H, *d*, *J*=12 Hz); 5.63 (1H, *bs*); 3.29 (2H, *m*); 1.46 (4H, *m*); 0.94 (3H, *t*, *J*=7 Hz). NPeF: δ (90 MHz, $CDCl_3$) = 8.16 (0.73H, *s*); 8.04 (0.27H, *d*, *J*=12 Hz); 5.69 (1H, *bs*); 3.27 (2H, *m*); 1.41 (6H, *m*); 0.98 (3H, *t*, *J*=7 Hz). DPrF: δ (90 MHz, $CDCl_3$) = 8.07 (1H, *s*); 3.18 (4H, *m*); 1.56 (4H, *m*); 0.89 (6H, *t*, *J*=7 Hz). DBF: δ (90 MHz, $CDCl_3$) = 8.07 (1H, *s*); 3.27 (4H, *m*); 1.42 (8H, *m*); 0.93 (6H, *t*, *J*=7 Hz). DPeF: δ (90 MHz, $CDCl_3$) = 8.07 (1H, *s*); 3.23 (4H, *m*); 1.36 (12H, *m*); 0.89 (6H, *t*, *J*=5 Hz).

All compounds were analyzed by means of GLC (column packed with 0.5% Na_3PO_4, 5% Polyglycol 1000 on Chromosorb GAW 80-100 mesh). The indicated GLC purity was better than 99.8%, except for formamide for which it is better than 99.7%. The water content of the amides, determined by a modified Karl-Fischer titration,[11] was less than 0.01 mass% for the synthesized amides and DMF, less than 0.02 mass% for DEF, NMF, and NEF, and less than 0.04 mass% for FA.

All solutions were prepared by weight and kept in a dessicator over granulated P_2O_5 for at most two days.

2.2. Procedure

Enthalpies of dilution were determined with an LKB 10700-2 microcalorimeter. The output of the calorimeter was amplified by a Keithly 150B microvoltmeter and integrated by a Kipp BD12 recorder. Details of the procedure have been described before.[6] To shorten the equilibration time, the method of subsequent dilutions was used.[9,12] In this method, after the first dilution experiment, a maximal and known amount of solution in one of the compartments of the measuring cell is replaced by a known mass of pure solvent. Thus, in the second experiment, a solution is mixed with a highly diluted solution of the same kind. This procedure can be repeated several times.

3. RESULTS

A compilation of the dilution experiments is given Table I. It presents the enthalpic change ΔH when n_A moles of solute at molality $m_{A,i}$ are mixed with n_B moles of solute at molality $m_{B,i}$ (or with pure DMF; n_B = 0 mol, $m_{B,i}$ = 0 mol-kg^{-1}) to give a solution with final

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

$m_{A,i}$	n_A	$m_{B,i}$	n_B	m_f	ΔH	$\Delta\%$[b]
			A: Formamide			
0.5300	0.9446	0	0	0.1701	-40.87	0.7
0.5293	1.9399	0	0	0.3496	-42.33	1.7
0.7749	2.8290	0	0	0.5033	-90.77	-1.0
0.9707	3.5850	0	0	0.6471	-138.2	-0.2
0.9707	1.8275	0	0	0.3278	-138.4	-1.3
1.6224	2.9670	0	0	0.5328	-381.9	-1.1
1.6224	6.0465	0	0	1.0583	-410.4	0.8
1.8599	6.5553	0	0	1.2251	-497.0	0.1
2.8505	4.8653	0	0	0.8858	-1146	0.4
2.9284	10.1258	0	0	1.9239	-1272	-0.9
2.9284	5.4988		0	0.9724	-1224	0.8
			B: N-Methylformamide			
1.1398	2.2381	0	0	0.3893	-6.892	-1.6
1.3751	2.3591	0	0	0.4293	-9.464	0.2
1.9194	3.4173	0	0	0.6066	-20.04	2.0
2.1591	3.7636	0	0	0.6768	-25.22	1.8
2.2253	3.8273	0	0	0.6942	-25.55	-2.2
2.1591	7.1399	0	0	1.3628	-25.60	-1.7
2.4394	8.0080	0	0	1.5446	-33.69	0.6
2.7376	4.7187	0	0	0.8492	-41.76	2.0
2.7376	8.8800	0	0	1.7071	-43.04	-1.3
			C: N-Ethylformamide			
0.6978	1.3253	3.81	14.83	0.2315	9.601	-1.3
0.7373	2.9456	8.42	16.02	0.5021	10.48	0.5
0.7798	1.3901	4.58	16.90	0.2571	11.48	1.7
0.7980	3.1736	9.40	18.85	0.5336	12.05	-3.4
1.0453	4.0733	11.27	22.23	0.6978	19.46	-2.7
1.1481	4.4434	13.05	24.26	0.7798	22.99	2.1
1.3172	5.0330	14.76	27.52	0.8901	27.17	-4.7
1.5938	6.0498	17.91	32.69	1.0822	36.52	-4.6
1.7266	6.3838	18.54	35.11	1.1481	45.69	3.2
2.0608	6.7820	0	0	1.3172	54.19	-4.0
2.6591	4.2182	0	0	0.7980	85.87	-0.9
			D: N-Propylformamide			
0.3071	0.4158	2.27	8.97	0.0801	5.823	4.5
0.4540	0.9249	3.26	13.10	0.1548	15.19	-3.5
0.4584	1.8492	5.66	11.46	0.3071	15.76	2.4
0.7118	0.8620	5.17	20.11	0.1730	25.31	0.1
0.6713	2.8855	7.87	16.49	0.4540	30.89	-5.3
0.7496	2.6203	0	0	0.4796	34.77	-5.0

Table I. Continued

$m_{A,i}$	n_A	$m_{B,i}$	n_B	m_f	ΔH	$\Delta\%^b$
1.0680	1.6700	7.66	29.31	0.3153	63.08	-3.4
0.9895	4.1352	11.75	23.69	0.6713	65.25	2.6
1.1229	3.9017	0	0	0.7118	77.58	0.1
1.5894	5.4026	0	0	0.9895	143.6	-0.7
1.7560	3.2273	0	0	0.5708	168.5	-4.6
1.7560	5.7504	0	0	1.0680	178.6	2.3
2.1433	6.9100	0	0	1.3292	236.3	-3.3
		E: N-Butylformamide				
0.2236	0.4846	0	0	0.0758	8.086	-0.1
0.3954	0.6770	2.88	11.41	0.1212	21.43	4.2
0.4800	1.9592	5.57	11.90	0.3170	35.94	3.8
0.7070	2.7635	0	0	0.4688	70.61	0.0
0.7503	2.8224	0	0	0.4800	80.77	-0.9
0.7503	1.5010	0	0	0.2491	83.78	2.7
0.8917	3.5116	9.13	21.27	0.5638	122.3	1.9
1.2095	2.3020	0	0	0.3954	193.0	-1.3
1.2433	4.7163	12.70	28.72	0.7837	212.9	-2.3
1.8518	2.9428	11.19	46.79	0.5182	386.6	-0.2
2.0652	3.7506	0	0	0.6511	510.7	-0.8
2.0652	6.8117	0	0	1.2433	513.8	-1.5
3.1578	5.0613	0	0	0.8917	1016	0.4
3.1578	9.6137	0	0	1.8518	1022	-0.7
		F: N-Pentylformamide				
0.2434	1.0068	2.74	6.16	0.1588	16.05	-1.3
0.2897	1.1935	3.47	7.29	0.1930	21.94	0.5
0.4438	1.6859	0	0	0.2897	48.26	-0.3
0.4411	1.7931	5.09	10.91	0.2906	50.05	0.8
0.6166	0.5287	4.22	17.27	0.1104	50.27	1.4
0.5754	0.8727	4.00	16.19	0.1597	66.15	-1.4
0.6891	2.4734	8.29	16.60	0.4453	107.7	1.2
0.7046	2.3481	0	0	0.4411	109.4	-0.9
0.7046	1.5373	0	0	0.2635	123.0	-0.2
1.0786	1.9795	0	0	0.3561	246.7	-0.7
1.1430	3.9453	11.77	26.26	0.6990	291.7	1.0
1.3832	4.6009	15.20	31.02	0.8631	378.4	-0.6
1.6470	5.8782	17.67	35.99	1.0551	538.6	0.9
1.8242	5.9459	0	0	1.1430	625.1	1.2
1.8242	3.1718	0	0	0.5754	632.2	-0.2
2.3143	3.7694	0	0	0.6891	930.9	-1.1
2.3143	6.9224	0	0	1.3832	943.5	0.1
2.7834	2.9737	0	0	0.6166	980.7	0.6
1.7834	8.2306	0	0	1.6470	1311	-1.4

Table I. Continued

$m_{A,i}$	n_A	$m_{B,i}$	n_B	m_f	ΔH	$\Delta\%^b$
		G: N,N-Diethylformamide				
0.3758	1.5407	4.86	9.41	0.2567	4.128	4.3
0.5018	0.9673	0	0	0.1664	7.099	-0.1
0.5707	1.2853	4.53	16.21	0.2234	9.494	-0.5
0.6263	2.5406	7.10	15.31	0.4113	11.75	3.6
0.6961	2.9793	7.65	16.91	0.4617	14.64	2.1
0.7503	2.9617	7.90	18.13	0.4973	16.73	1.4
1.1064	2.3403	0	0	0.4049	32.79	-0.7
1.1943	4.4003	0	0	0.7503	37.59	-0.4
1.4689	5.4097	0	0	0.9586	51.45	0.2
1.4689	2.6973	0	0	0.4472	53.94	0.7
1.8177	6.4253	0	0	1.1789	73.30	-0.4
1.8177	3.3697	0	0	0.5707	78.02	-1.1
2.1812	4.0258	0	0	0.6961	110.0	0.8
2.7804	9.2158	0	0	1.7639	159.9	-0.6
2.7804	5.0737	0	0	0.8580	172.4	0.4
		H: N,N-Dipropylformamide				
0.3477	0.5427	2.44	9.98	0.0977	17.05	2.6
0.5351	0.9341	3.95	15.02	0.1712	42.13	3.7
0.6688	1.1898	4.36	18.47	0.2009	67.32	2.9
1.0927	1.9672	0	0	0.3477	161.0	0.2
1.0797	2.0500	0	0	0.3383	167.4	-1.6
1.0927	3.8054	0	0	0.6688	174.4	-1.7
1.2750	4.6519	13.30	28.48	0.8086	223.6	0.2
1.5795	2.8482	0	0	0.4941	329.3	3.0
1.5795	5.5757	0	0	0.9684	340.5	1.7
1.7971	3.0824	0	0	0.5351	386.2	-1.7
2.3012	4.1355	0	0	0.7007	607.4	-1.3
2.3012	6.8294	0	0	1.2750	618.9	2.6
		I: N,N-Dibutylformamide				
0.3116	0.6874	0	0	0.1060	40.51	-1.2
0.4636	0.7046	2.94	12.96	0.1210	68.35	0.3
0.4857	2.0786	5.43	11.73	0.3245	92.68	1.1
0.7544	2.8906	17.02	17.54	0.5982	116.9	2.3
0.7752	1.4838	0	0	0.2543	207.6	-0.4
0.7752	2.5506	0	0	0.4636	210.8	0.9
0.9640	3.5834	9.66	21.76	0.6039	330.7	2.4
1.3022	4.6134	13.81	28.10	0.8322	523.2	2.9
1.5970	5.1757	0	0	0.9640	740.5	-0.3
1.5970	2.8359	0	0	0.4857	750.2	-0.7
2.2696	3.5922	0	0	0.6375	1295	0.2
2.2696	6.6147	0	0	1.3022	1316	0.2
2.7002	4.0605	0	0	0.7544	1662	0.2

Table I. Continued

$m_{A,i}$	n_A	$m_{B,i}$	n_B	m_f	ΔH	$\Delta\%$ [b]
		J: N,N-Dipentylformamide				
0.3021	0.4149	2.03	8.58	0.0754	50.65	-0.2
0.4089	0.5480	2.78	11.40	0.1029	89.76	0.7
0.5512	0.8529	3.92	15.01	0.1615	173.3	1.1
0.6885	0.8184	4.72	18.32	0.1651	214.3	-0.2
0.8977	0.6273	5.35	23.09	0.1298	239.2	0.8
0.6804	2.1640	0	0	0.4089	287.8	-0.9
1.1898	4.1179	0	0	0.8977	509.7	0.2
1.0793	3.8010	10.61	23.38	0.6680	682.5	-0.6
1.1898	1.7271	0	0	0.3021	701.0	-1.3
1.3432	2.2186	10.57	32.27	0.4786	850.8	1.6
1.8574	2.9946	0	0	0.5512	1589	-0.3
1.8574	5.6303	0	0	1.0793	1657	0.6
2.4013	3.6034	0	0	0.6885	2313	0.2
2.4013	6.7509	0	0	1.3432	2433	-0.1

[a] Units: $m_{A,i}$ and m_f, mol-kg^{-1}; $m_{B,i}$, mmol-kg^{-1}; n_A, mmol; n_B μmol; ΔH, mJ. [b] $\Delta\% = 100[\Delta H(\text{exp})-\Delta H(\text{calc})]/\Delta H(\text{exp})$, where $\Delta H(\text{calc})$ is calculated from Eq. (3).

Table II. Enthalpic Interaction Coefficients of Formamides in DMF at 25 °C [a]

Solute	B_2^h	B_3^h	B_4^h
FA	119 (1) [b]	-	-
NMF	3.9 (0.1)	0.20 (0.03) [b]	-
NEF	-17.6 (0.3)	1.9 (0.1)	-
NPrf	-64 (3)	13 (3)	-2.3 (0.7) [b]
NBF	-115 (1)	6.6 (0.2)	-
NPeF	-202 (3)	23 (2)	-2.8 (0.4)
DEF	-23.6 (0.4)	2.8 (0.3)	-0.4 (0.1)
DPrF	-129 (2)	12 (1)	-
DBF	-305 (4)	37 (4)	-3.3 (0.9)
DPeF	-580 (6)	89 (6)	-9 (2)

[a] Units: B_n^h = J-kg^{n-1}-mol^{-n}. [b] The numbers in parentheses are the standard deviation of the coefficients.

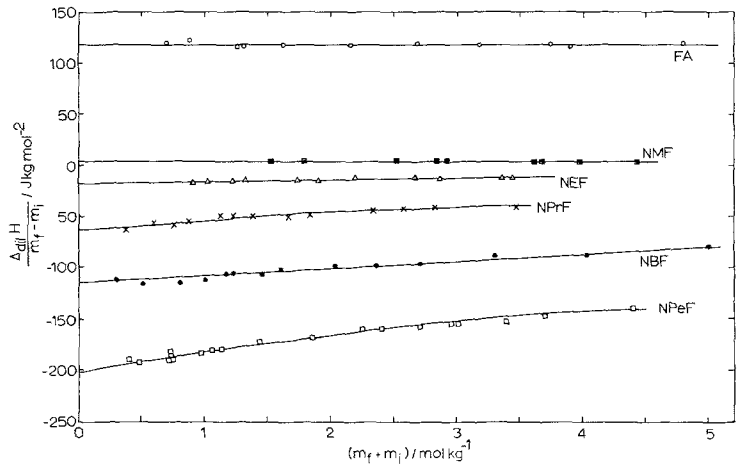

Fig. 1. $\Delta H^{dil}_{(m_i \to m_f)}/(m_f - m_i)$ as function of $(m_f + m_i)$ for formamide and N-alkylformamides in DMF at 25 °C.

molality m_f. ΔH can be written in terms of the excess enthalpies as

$$\Delta H = n_A[H^E(m_f) - H^E(m_{A,i})] + n_B[H^E(m_f) - H^E(m_{B,i})] \quad (1)$$

In this equation $H^E(m)$ denotes the excess enthalpy per mole solute at molality m_i, which can be written as[6,13]

$$H^E = B_2^h m + B_3^h m^2 + B_4^h m^3 + \ldots \quad (2)$$

where B_2^h, B_3^h, B_4^h, ... are the pair, triplet, quadruplet, and higher enthalpic interaction coefficients. Combination of Eqs. (1) and (2) yields

$$\Delta H/n_A = \sum_{n>1} B_n^h[(m_f^{n-1} - m_{A,i}^{n-1}) + n_A^{-1} n_B (m_f^{n-1} - m_{B,i}^{n-1})] \quad (3)$$

We have calculated the enthalpic interaction coefficients by least squares analyses of the results of Table I in terms of Eq. (3). Only coefficients were used for which the Student's t test indicated a probability of more than 95% that their value was not zero. The resulting coefficients and their standard deviations are collected in Table II.

From Eq. (3), it follows that

$$\Delta H^{dil}_{(m_{A,i} \to m_f)} = \Delta H/n_A - n_A^{-1} n_B \sum_{n>1} B_n^h (m_f^{n-1} - m_{B,i}^{n-1}) \quad (4)$$

where $\Delta H^{dil}_{(m_{A,i} \to m_f)}$ is the molar enthalpy change on diluting a solution from initial molality $m_{A,i}$ to final molality m_f. Since

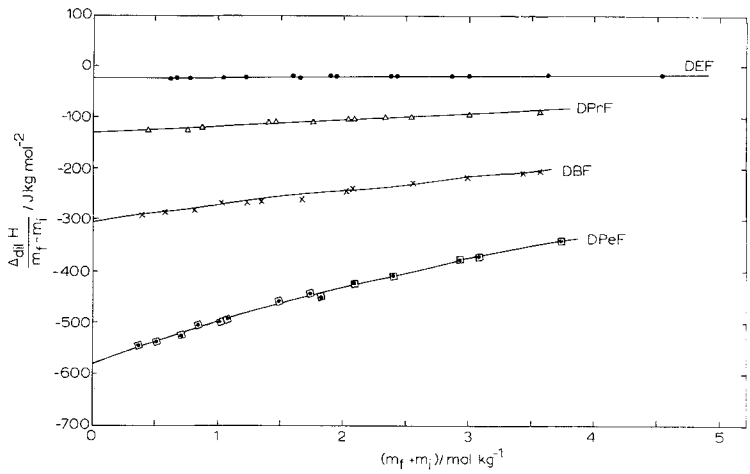

Fig. 2. $\Delta H^{dil}_{(m_i \to m_f)} / (m_f - m_i)$ as function of $(m_f + m_i)$ for N,N-dialkylformamides in DMF at 25 °C.

$$\Delta H^{dil}_{(m_i \to m_f)} / (m_f - m_i) = B_2^h + B_3^h(m_f + m_i) + B_4^h(m_f^2 + m_i^2 + m_f m_i) + \ldots \quad (5)$$

and B_4^h is often small compared to B_3^h, we represent our results in Figs. 1 and 2 in terms of $\Delta H^{dil}_{(m_i \to m_f)} / (m_f - m_i)$ *vs.* $(m_f + m_i)$.

4. DISCUSSION

The enthalpic pair interaction coefficients, B_2^h, of both mono- and dialkyl substituted formamides become more negative with increasing number of C atoms in the alkyl groups. This trend was also found for the alkyl substituted acetamides[6,9] and was attributed to polarophobic interaction. This attractive interaction, found earlier by others,[14,15] would be caused by an increase of the dipole-dipole interaction between the solvent molecules upon adherence of solute molecules, which leads to a negative enthalpic change and hence to negative B_2^h values. When the apolar part of the interacting solute molecules becomes larger, the polarophobic interaction becomes stronger and hence the magnitude of B_2^h increases.[6,9] This is visualized in Fig. 3, where we represent values of B_2^h for FA and substituted formamides in relation to the total number of C atoms in the solute molecules. The figure includes data for corresponding acetamides and unsubstituted amides published before[6,9] and reveals that generally B_2^h decreases from di-N-substituted to isomeric mono-N-substituted amides. This decrease has been interpreted tentatively in terms of the formation of hydrogen bonded

solute-solvent associates leading to a larger amount of apolar and amide groups in the interacting entity which results in a decrease in B_2^h.[6] However, Fig. 3 shows that this decrease in B_2^h is much smaller for formamides than for acetamides. The situation for unsubstituted amides is completely different from that of the substituted amides. B_2^h for FA and acetamide differ considerably (even the sign is opposite), whereas those of the higher unsubstituted amides are almost equal to the value for acetamide. The fact that no strong decrease with increasing chain length is found for the unsubstituted amides has been attributed to specific and preferential interaction of this type of molecules along with the NH_2 group.[9]

Table III. B_2^h for Short Chain Compounds in DMF as Solvent [a]

Methyl Cpds.	B_2^h	Ethyl Cpds.	B_2^h	Ref.
DMA	4	DEA	-11	6
DMF	0	DEF	-24	This Work
BMA	-101	BEF	-117	16
NMA	-124	NEA	-157	6
NMF	4	NEF	-18	This Work
NMU	-2200	NEU	-2108	8

[a] The same abbreviation scheme is used as in the text but adding A = acetamide and U = urea. [b] Units: J-kg-mol^{-2}

As was inferred in a previous paper,[9] the influence on B_2^h of remote CH_2 groups at both sides of the amide groups is generally equal, which should result in one curve for B_2^h of N- and C-alkyl substituted amides in relation to the number of C atoms in the solute molecules. To the contrary, Fig. 3 shows that B_2^h of the dialkyl formamides and dialkyl acetamides do not fit onto one curve. This implies that the α-CH_3 group at the C atom of the CON group is not equivalent in its influence on B_2^h with the other methylene groups in the amide molecule. Fig. 3 shows that in general B_2^h of a dialkylacetamide molecule is close to that of a dialkylformamide molecule with the same N-alkyl groups. In Fig. 4 we have plotted B_2^h and also B_3^h in relation to the number of C atoms in the N-alkyl groups for both dialkylformamides and dialkylacetamides. B_2^h as well B_3^h for both sets of compounds fit onto a single curve within experimental error. This means that for these compounds the α-CH_3 group at the C atom of the amide group influences the interaction coefficients only to

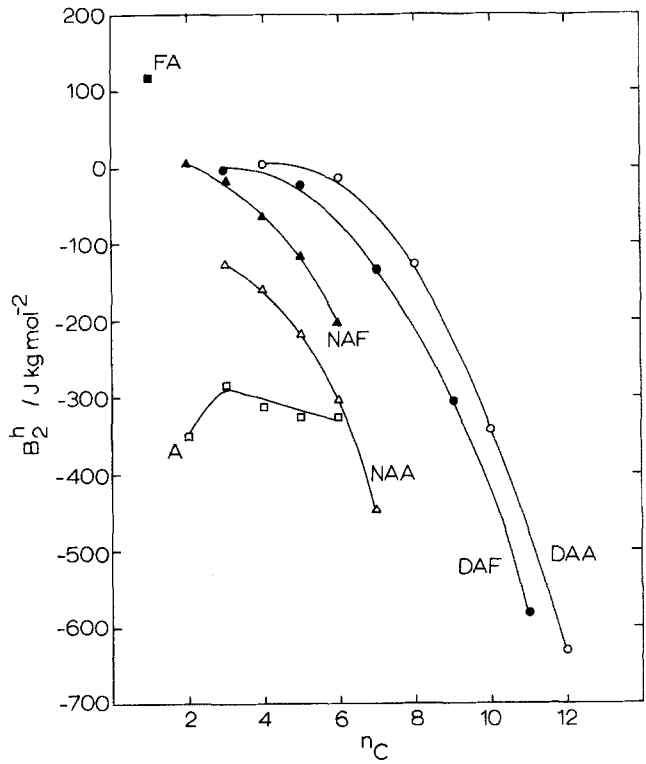

Fig. 3. B_2^h in relation to the number of C atoms in the solute for amides in DMF: DAA = Dialkylacetamides (○); DAF = Dialkylformamides (●); NAF = N-alkylformamides (▲); NAA = N-alkylacetamides (△); A = unsubstituted amides (□); FA = formamide (■).

a small extent. This may be due to the dipole field of the CON group. If so, the influence of an α-CH_2 group at the N atom of the CON group on B_2^h should be relatively small also. In order to check this, we compare in Table III B_2^h of compounds with a N-methyl and a N-ethyl group for several ureas and amides. Since in all cases the difference between of B_2^h for ethyl- and methyl substituted compounds is small, we conclude that the interaction potentials between compounds with either a CON-CH_3 or a CON-C_2H_5 group are almost equal. This should be recognized in considering interactions inside globular proteins.

Also, the mono-N-substituted amides do not fit onto one curve. Fig. 3 reveals a positive shift of about 100 J-kg-mol^{-2} for the B_2^h values of the N-alkyl formamides as compared with isomeric N-alkylacetamides. Unlike the dialkyl substituted amides discussed above, these

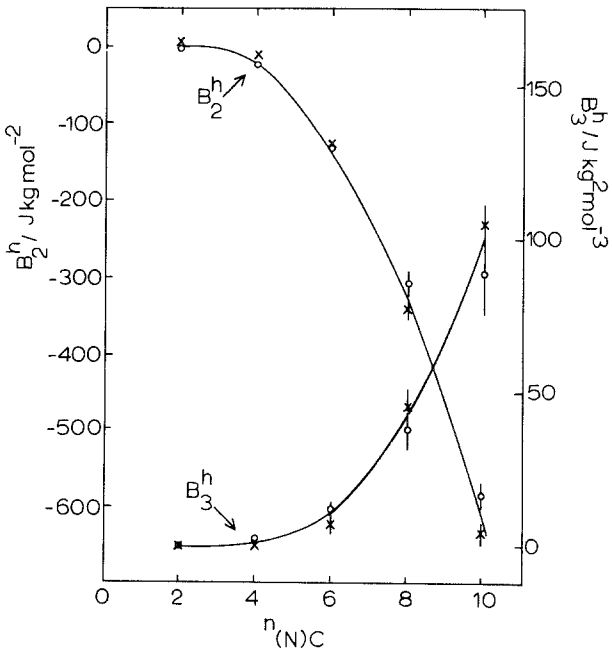

Fig. 4. B_2^h and B_3^h for N,N-disubstituted formamides (○) and acetamides (X) in relation to the number of C atoms in the N-alkyl groups, $n_{(N)C}$.

compounds show no similarity in the values of the enthalpic interaction coefficients, when these are related to the number of C atoms in the N-alkyl groups. Since the value of B_2^h of FA shows an even more positive deflection from the values of unsubstituted amides (see Fig. 3) and no shift is found for the disubstituted amides, we attribute the positive shift of the N-alkylformamides to the presence of a NH group in the solute molecules. The difference in interaction between the formamides and the acetamides may be caused by differences in hydrogen donating character of the NH groups and/or differences in hydrogen acceptor strength of the CO groups. As Pullin and Werner[17] state, hydrogen bonding to amides is highly sensitive to the electronic structure of the carbonyl group, which is influenced by substitution on both the carbonyl carbon and the amide nitrogen[18] through inductive, conjugative, and steric effects.[18-20] Joesten and Schaad[21] have collected enthalpies of hydrogen bonding for a large set of donor-acceptor pairs in different solvents. From this compilation it can be concluded that irrespective of the donor and solvent used, the enthalpy of hydrogen bonding is less negative for N-alkylamides than for N,N-dialkylamides.

Other reports[23-24] confirm this conclusion and also indicate that the enthalpy of hydrogen bonding is less negative for formamides than for the corresponding acetamides. This has been confirmed by MO calculations[25,26] and explained by inductive effects.[20,27] In summary,

$$\Delta H(\text{acetamides}) < \Delta H(\text{formamides}) \tag{6}$$

and

$$\Delta H(\text{dialkylamides}) < \Delta H(\text{monoalkylamides}) \tag{7}$$

According to relation (7), the N-alkylformamide-DMF hydrogen bond is enthalpically more stable than that between two N-alkylformamide molecules. When the stability of a solute-solvent hydrogen bond is compared with that of a solute-solute bond for the N-alkylacetamides the situation is more complicated. Relation (7) favors the former and relation (6) the latter. Due to these counteracting effects, the enthalpy difference between the solute-solvent and solute-solute hydrogen bonds will be smaller than that for other formamides (or are of opposite sign). In accordance with this, Drago *et al.*[27] have found the acceptor strength of NMA and DMF to be more or less equal. Earlier we have indicated that N-alkylamides in DMF as solvent on the average are associated with a DMF molecule and that these solute-solvent entities attract each other.[6,9] This results in a kind of solvent shared solute-solute interaction. However, if some solute molecules adhere to each other closely, the associated solvent molecules will be expelled and a direct solute-solute hydrogen bond may be formed. As pointed out above, this results in an increase in enthalpy for the N-alkylformamides, whereas the enthalpy change for the N-alkylamides will be small or negative. We recall that pair interactions are related to a potential of average force, which is a function (averaged over all possible orientations of solvent molecules) of the set of angles and the scalar distance defining the mutual orientation of the two solute molecules.[28-30] Even for spherically symmetrical particles, when the orientation of the molecules cancels out,[29] B_2^h contains contributions for interactions at every distance. Thus, the positive shift of the N-alkylformamides as compared to the N-alkylacetamides may be caused by the contribution to B_2^h of short distance interaction of two solute molecules by hydrogen bonding.

The enthalpy of hydrogen bonding to the carbonyl group of a FA molecule is less negative than that to the carbonyl group of an N-alkylformamide molecule.[20] Hence, exchange of a FA-DMF hydrogen

bond by a FA-FA bond will lead to an even larger positive enthalpy change than in the case of the N-alkylformamides. Also for FA, two solute-solvent hydrogen bonds may be replaced,[24] which may also contribute to the deviating and positive value of B_2^h for FA.

With regard to the hydrogen donating strength of the NH groups of formamides and acetamides, Spencer *el al.*[24,31,32] conclude that the enthalpy change on the formation of a hydrogen bond between a N-alkylformamide molecule and an amide molecule is less exothermic than that between a N-alkylacetamide and the same amide molecule. They found an even less negative enthalpy change for the hydrogen bond formation between FA and that amide. This means that solute-solvent associates for amides in DMF are enthalpically favored in the order: FA < N-alkylformamide < N-alkylacetamide. As mentioned above, part of the attraction of N-alkylamides is due to the associated solvent molecules. This attraction will give a negative contribution to B_2^h, which is larger for N-alkylacetamides than for N-alkylformamides, corresponding with the observed shift in B_2^h values.

In conclusion, the results of this paper show that the interactions of compounds containing CON (peptide) groups in an amidic medium are influenced by substitution on both sides of the peptide group in agreement with the conclusion of Henson and Swenson.[18] It means that substitution effects should be incorporated in additivity models to obtain reliable results for this type of systems. Moreover, as these systems are used as models for interactions in the interior of proteins,[7,8,24,33] subtle differences in the structure of the side chains of the peptide group may have strong implications for the interactions in proteins and hence for their tertiary structure.

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