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Thermodynamics of Solvation of Urea and Some Monosubstituted *N*-Alkylureas in Water at 298.15 K

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The enthalpies of solution, $\Delta_{sol}H_m$, in water of urea, *N*-methylurea, *N*-ethylurea, *N*-propylurea, *N*-butylurea, *N*-isobutylurea, and *N*-*tert*-butylurea were measured by isothermal calorimetry at $T = (296.84, 306.89, 316.95)$ K. The molar enthalpies of solution at infinite dilution, $\Delta_{sol}H_m^\infty$, at $T = 298.15$ K were derived and added to the molar enthalpies of sublimation, $\Delta_{sub}H^\circ{}_m$, at the same temperature to obtain the molar enthalpies of solvation at infinite dilution, $\Delta_{solv}H_m^\infty$. The partial molar heat capacities at infinite dilution at $T = 298.15$ K, $C_{p,2}^\infty$, were also calculated by the summation of $\Delta_{sol}C_{p,m}^\infty$, derived from our experimental data, and molar heat capacities, $C_{p,m}$(cr), of urea and *N*-alkylureas from the literature. The contribution of the CH_2 group to solvation enthalpy and partial molar heat capacity was -3.3 kJ·mol^{-1} and 90.8 J·K^{-1}·mol^{-1}, respectively, in very good agreement with data in the literature. Simple additive schemes were used to estimate the average molar enthalpy of solvation and partial molar heat capacity at infinite dilution of the HN−CO−NH functional group. Results are discussed in terms of current models for hydration and hydrogen bond formation for urea and its N-alkyl derivatives in water.

Introduction

Interactions between solutes and their aqueous environment play a fundamental role in many biological processes.[1−4] Understanding the thermodynamics of solvation in water of low molecular mass hydrophobic or hydrophobic−hydrophilic organic compounds is of great interest in many fields of chemistry and biology.[5] Urea and its alkylderivatives, which contain both hydrophilic and hydrophobic moieties, display peculiar hydration properties.[6−8] Moreover, urea modulates the conformational stability of biopolymers because it is an effective protein denaturant. By contrast, *N*-alkylureas are effective in the refolding of denaturated proteins as a function of the length and number of their alkyl substituents.[9] Protein denaturation is a complex process and other factors besides hydrophobic/hydrophilic interactions are involved. If the native structure and stability of globular proteins in aqueous solution can be thought of as mainly due to the hydrophobic interactions, *N*-alkylurea derivatives should strengthen these interactions and drive protein folding. Moreover, the solution behavior of urea and its derivatives has been extensively studied to explain associations in the aqueous environment, such as protein folding, formation of micelles, and molecular recognition. Many thermodynamic,[6−8,10−13] spectroscopic,[9] dielectric,[14] and ultrasonic[15] investigations have been made of the properties of urea−water and alkylurea−water systems. Recent computer simulation studies of water[16−18] have proposed a molecular dynamics model in which the local concentration of hydrogen-bonding groups/molecules plays a dominant role. In this view, the solution behavior of *N*-alkylureas in water should be appreciably affected by the hydrophobic groups attached to urea.[15]

In this paper, we report thermodynamic data on the behavior in water solution at infinite dilution of urea and a series of six *N*-alkylureas to better understand the effect of urea alkyl substituents. The effects of lengthening and branching of the alkyl chain were considered. The enthalpies of solvation, $\Delta_{solv}H_m^\infty$, and partial molar heat capacities, $C_{p,2}^\infty$, at infinite dilution at $T = 298.15$ K were obtained through the measurement at three temperatures of the enthalpies of solution, $\Delta_{sol}H_m^\infty$, by isothermal calorimetry.

The solvation process can be divided into cavity formation and solute−solvent interaction accompanied by local structural changes in the solvent, such as changes in the extent of hydrogen-bonding network. Enthalpy of solvation at infinite dilution contains information about the solute−solvent interaction. In particular, a large positive heat capacity change is characteristic of the hydrophobic effect and has been associated with the enhancement of the local order of water.

The contribution of the CH_2 group to the solvation enthalpy and partial molar heat capacity were derived and compared with literature data. We also calculate the contribution of the HN−CO−NH functional group to both parameters through simple additive schemes.

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Table 1. Experimental Molar Enthalpies of Solution in Water, $\Delta_{sol}H_m$, for Urea and *N*-Alkylureas at T = (296.84, 306.89, and 316.95) K for Different Molality, m, Values

compound	m / 10^{-2} mol·kg^{-1}	$\Delta_{sol}H_m$ / kJ·mol^{-1}	m / 10^{-2} mol·kg^{-1}	$\Delta_{sol}H_m$ / kJ·mol^{-1}	m / 10^{-2} mol·kg^{-1}	$\Delta_{sol}H_m$ / kJ·mol^{-1}
U	T = 296.84 K		T = 306.89 K		T = 316.95 K	
	0.601	15.38	0.695	15.10	0.628	14.96
	1.590	15.02	1.162	15.28	0.738	14.65
	2.171	15.44	1.367	15.14	0.822	15.15
	2.858	15.30	1.461	15.10	1.068	15.40
	5.032	15.29	2.233	15.18	1.289	15.30
					1.664	15.21
					1.782	14.88
					2.540	14.86
MEU	T = 296.84 K		T = 306.89 K		T = 316.95 K	
	1.080	10.30	0.350	10.84	1.136	11.64
	1.393	10.40	0.650	11.15	1.151	11.77
	1.614	10.67	0.677	11.14	1.220	11.77
	1.851	10.01	0.796	11.59	1.341	11.58
	2.373	10.55	1.127	11.21	1.500	11.90
	2.673	10.50			1.622	12.01
					1.707	11.35
MMU	T = 296.84 K		T = 306.89 K		T = 316.95 K	
	0.917	11.57	0.311	11.81	0.867	11.98
	1.141	11.47	0.355	11.90	1.079	11.87
	1.831	11.65	0.705	11.34	1.334	11.61
	1.883	11.43	1.035	11.82	1.495	11.55
	2.734	11.40	1.095	11.54	1.665	11.49
			1.795	11.40	2.073	11.61
MPU	T = 296.84 K		T = 306.89 K		T = 316.95 K	
	0.919	9.33	0.694	11.37	0.683	12.43
	1.112	9.38	1.008	10.78	0.700	12.46
	1.211	9.55	1.086	10.93	0.757	12.44
	1.289	9.61	1.259	10.79	0.837	12.60
	1.484	9.18	1.259	10.77	1.099	12.69
	1.668	9.39	1.328	10.82		
MBU	T = 296.84 K		T = 306.89 K		T = 316.95 K	
	0.571	16.96	0.532	19.21	0.723	21.68
	0.708	16.92	0,784	19.43	0.875	21.59
	0.921	16.76	0.825	19.45	0.888	21.46
	1.009	16.75	0.898	19.25	0.955	21.76
	1.093	16.70	0.944	19.21	1.188	21.67
			0.983	19.31		
M*t*BU	T = 296.84 K		T = 306.89 K		T = 316.95 K	
	0.464	9.16	0.371	10.91	0.396	12.44
	0.772	9.11	0.422	11.03	0.457	12.71
	1.505	9.08	0.500	11.04	0.568	12.72
	1.843	9.33	1.178	11.37	0.590	12.72
M*i*BU	T = 296.84 K		T = 306.89 K		T = 316.95 K	
	0.590	9.31	1.067	11.11	0.727	12.20
	0.774	9.16	1.277	10.95	0.800	12.21
	0.783	9.08	1.582	10.53	0.972	12.27
	0.810	9.30	1.590	11.02	1.123	12.09
	0.865	9.15				
	1.089	9.36				
	1.407	9.03				

Experimental Section

Materials. Methylurea (MMU), ethylurea (MEU), and butylurea (MBU) were from EGA-Chemie (commercial purity 99 %, 97 %, and 99 %, respectively); propylurea (MPU) was from Kodak (purity not indicated by the supplier); isobutylurea (M*i*BU) and *tert*-butylurea (M*t*BU) were from Fluka (commercial purity 97 %); and urea was from Aldrich (commercial purity 99 %). All compounds were purified by up to five successive crystallizations from absolute ethanol (Fluka puriss, purity > 99.8 %) solutions for urea and ethylacetate (Fluka puriss, > 99.5 %) solutions for the six N-alkyl derivatives of urea, as described earlier.[19] All products were then dried to constant mass under reduced pressure at room temperature. Purity was always better than 0.995 mass fraction, as determined by the DSC peak profile method.[20]

Hexane and cyclohexane from Aldrich (commercial purity > 99 %) were employed in the calibration tests of the calorimeter without any further purification. Deionized bidistilled water HPLC grade from Aldrich was used for solution preparation.

Enthalpy of Solution at Infinite Dilution Measurement. Enthalpies of solution, $\Delta_{sol}H_m$, in water were measured at T = (296.84, 306.89, and 316.95) K using a CRMT-SETARAM rotating calorimeter (Tian-Calvet type) with a 100 mL cell in which a glass ampule containing the sample was broken as already described.[21] The calibration tests were made by the Joule effect, using the calibration cell with a 1000 Ω constantan resistance supplied by SETARAM, and by determining the standard enthalpy of mixing of hexane−cyclohexane mixtures.[22] The temperature was kept constant to ± 0.05 K as from the calibration made by means of certified thermocouples kindly supplied by IMGC-CNR of Torino. Four to eight independent measurements of enthalpy of solution at different concentration values were performed for each sample. The final concentration

Table 2. Molar Enthalpies of Solution at Infinite Dilution in Water, $\Delta_{sol}H_m^\infty$, for Urea and *N*-Alkylureas at T = (296.84, 306.89, and 316.95) K and Their Values at 298.15 K

	$\Delta_{sol}H_m^{\infty\,a}$/kJ·mol^{-1}							
compound	N^b	T = 296.84 K	N^b	T = 306.89 K	N^b	T = 316.95 K	T = 298.15 K	literature
U	5	15.28 ± 0.16	5	15.13 ± 0.12	8	15.03 ± 0.22	15.26 ± 0.05	15.27[c], 15.28[d], 15.29[e]; 15.30[f], 15.31[g]; 15.32[h]
MMU	5	11.62 ± 0.13	6	11.74 ± 0.18	6	12.18 ± 0.21	11.60 ± 0.13	11.19[i]
MEU	6	10.23 ± 0. 36	5	10.79 ± 0.43	9	11.75 ± 0.25	10.26 ± 0.16	10.69[i]
MPU	6	9.50 ± 0.36	6	10.91 ± 0.35	5	12.00 ± 0.28	9.71 ± 0.12	
MBU	5	17.31 ± 0.08	6	19.22 ± 0.29	5	21.53 ± 0.36	17.51 ± 0.17	
M*i*BU	7	9.36 ± 0.18	4	11.76 ± 0.28	4	12.40 ± 0.22	9.85 ± 0.12	
M*t*BU	4	9.07 ± 0.14	4	10.76 ± 0.08	4	12.03 ± 0.51	9.33 ± 0.17	

[a] Linearly extrapolated values at $m = 0$. Uncertainties at 95 % confidence limits. [b] Number of experimental determinations. [c] Ref 23. [d] Ref 24. [e] Ref 25. [f] Ref 26. [g] Ref 27. [h] Ref 28. [i] Ref 29.

Table 3. Molar Heat Capacities of Urea and *N*-alkylureas as a Function of Temperature from Equation 4

	T range	solid		T range	gaseous[c]	
compound	K	A	B	K	A	B
U	250−330	93.12 ± 0.01[a]	0.27 ± 0.01[a]	300−600	50.73 ± 1.51	0.17 ± 0.01
MMU	250−320	115.50 ± 0.36[a]	0.37 ± 0.01[a]	300−600	75.91 ± 1.70	0.21 ± 0.01
MEU	220−280	151.50 ± 0.21[a]	0.52 ± 0.01[a]	300−600	98.34 ± 2.35	0.27 ± 0.01
MPU	300−330	196.26 ± 0.32[b]	0.48 ± 0.02[b]	300−600	121.63 ± 2.78	0.32 ± 0.01
M*i*PU	250−310	169.07 ± 0.95[a]	0.59 ± 0.04[a]	300−600	122.31 ± 3.15	0.33 ± 0.02
MBU	250−320	205.41 ± 1.42[a]	0.82 ± 0.05[a]	300−600	144.91 ± 3.22	0.38 ± 0.02
M*t*BU	250−320	185.59 ± 0.06[a]	0.47 ± 0.01[a]	300−600	147.42 ± 3.86	0.39 ± 0.02

[a] Ref 32. [b] Ref 33. [c] Refs 30 and 31.

Table 4. Molar Enthalpies of Sublimation for Urea and *N*-Alkylureas at 298.15 K Derived from Data in Table 3 by Using Equation 3

			$H_m(T_{exp}) - H_m^o$(298.15 K)		
	T_{exp}	$\Delta_{sub}H_m^o(T_{exp})$	kJ·mol^{-1}		$\Delta_{sub}H_m^o$(298.15 K)
compound	K	kJ·mol^{-1}	(g)	(cr)	kJ·mol^{-1}
U	354	94.6 ± 0.5[a]	3.16	5.62	97.06 ± 0.5
MMU	337	94.9 ± 0.4[a]	3.09	4.77	96.58 ± 0.4
MEU	337	97.0 ± 1.1[a]	4.03	6.25	99.22 ± 1.1
MPU	351	98.3 ± 0.6[b]	10.51	14.42	102.46 ± 0.6
M*i*PU	354	97.1 ± 0.6[a]	7.43	10.23	99.90 ± 0.6
MBU	354	100.3 ± 0.4[a]	8.74	12.76	112.22 ± 0.4[c]
M*i*BU	377	101.1 ± 1.1[b]			103.60 ± 1.1[d]
M*t*BU	354	94.2 ± 0.9[a]	8.77	11.10	96.53 ± 0.9

[a] Ref 44. [b] Ref 41. [c] Including enthalpies of two solid-to-solid-phase transitions (7.02 and 0.88) kJ·mol^{-1} at (313.1 and 344.9) K, respectively.[19] [d] Value re-adjusted to 298.15 K by Kabo et al.[45]

of the solutes was in the range of ($3.1\cdot10^{-3}$ to $5.0\cdot10^{-2}$) mol·kg^{-1}. The measured enthalpies of solution in water for urea and its six mono-N-alkyl derivatives at the three experimental temperatures are reported in Table 1. Enthalpies of solution at infinite dilution at the experimental temperature were obtained by linear extrapolation to $m = 0$ of each set of data (Table 2). The extrapolated molar enthalpies of solution were then fitted as a linear function of temperature:

$$\Delta_{sol}H_m^\infty = a + b(T - 298.15) \tag{1}$$

where $a = \Delta_{sol}H_m^\infty$ at T = 298.15 K (Table 2). The value of $\Delta_{sol}H_m^\infty$ (298.15 K) = 15.26 kJ·mol^{-1} obtained for urea is in excellent agreement with literature data[23−28] as shown in Table 2. The values obtained for MMU and MEU are also in good agreement with those reported by Rouw and Somsen.[29] Moreover, a check was made by determining the molar enthalpy of solution at infinite dilution of urea at T = 298.15 K with an appropriately calibrated "batch" microcalorimeter LKB 2107. An average value of (15.28 ± 0.04 kJ·mol^{-1}) was obtained, which is identical to that measured in this work.

Results and Discussion

Enthalpy of Solvation. The molar enthalpy of solvation of urea and its N-alkyl derivatives in water at infinite dilution at 298.15 K represents the enthalpy change resulting from the transfer of one mole of solute from the ideal gaseous phase to aqueous solution at infinite dilution. Thus, its standard value can be calculated from the combination of molar enthalpy of solution at infinite dilution $\Delta_{sol}H_m^\infty$ and standard molar enthalpy of sublimation $\Delta_{sub}H^\circ{}_m$ both at T = 298.15 K:

$$\Delta_{solv}H_m^\infty = \Delta_{sol}H_m^\infty - \Delta_{sub}H_m^o \tag{2}$$

Sublimation enthalpies at 298.15 K were derived from the experimental values measured at the temperature T_{exp} and the corresponding enthalpy change from T_{exp} to 298.15 K of both gaseous and solid phases from the equation:

$$\Delta_{sub}H_m^o(298.15\text{K}) = \Delta_{sub}H_m^o(T_{exp}) - \int_{T=298.15K}^{T_{exp}} [C_{p,m}(g) - C_{p,m}(cr)]dT \tag{3}$$

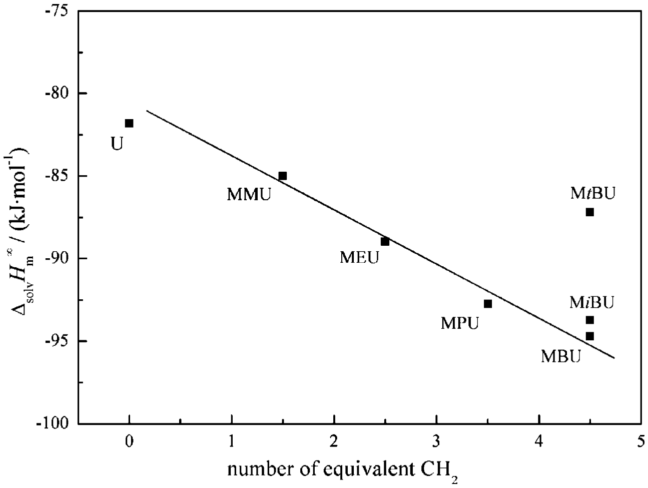

Figure 1. Molar enthalpies of solvation at infinite dilution as a function of the number of equivalent CH$_2$ groups at T = 298.15 K for urea and N-alkyl derivatives. The plot refers to the four linear *N*-alkylureas only.

Table 5. Molar Enthalpies of Solvation at Infinite Dilution in Water at T = 298.15 K of Urea and *N*-Alkylureas Derived from Equation 2

	$\Delta_{\rm sol}H_{\rm m}^{\infty}$	$\Delta_{\rm sub}H_{\rm m}^{\rm o}$	$\Delta_{\rm solv}H_{\rm m}^{\infty}$
compound	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}
U	15.26 ± 0.05	97.06 ± 0.5	−81.80 ± 0.55
MMU	11.60 ± 0.13	96.58 ± 0.4	−84.98 ± 0.53
MEU	10.26 ± 0.16	99.22 ± 1.1	−88.96 ± 1.26
MPU	9.71 ± 0.12	102.46 ± 0.6	−92.75 ± 0.72
MBU	17.51 ± 0.17	112.22 ± 0.4	−94.71 ± 0.57
M*i*BU	9.85 ± 0.22	103.60 ± 1.1	−93.75 ± 1.32
M*t*BU	9.33 ± 0.17	96.53 ± 0.9	−87.20 ± 1.07

Heat capacities of gaseous *N*-alkylureas were estimated through the Benson additivity group scheme,[30,31] and those for their solid state were obtained by linear interpolation/extrapolation of literature data in the experimental temperature range.[32,33] Two sets of parameters A and B for the solid and gaseous states were then calculated from the equation:

$$C_{p,\rm m}/(\rm J{\cdot}K^{-1}{\cdot}mol^{-1}) = A + B(T/\rm K - 298.15) \qquad (4)$$

where $A = C_{p,\rm m}$ (298.15 K) (Table 3).

Several literature data are available for the experimental enthalpies of sublimation of urea and *N*-alkylureas.[34−44] However, these results, including some of our earlier tensimetric values,[37,41] are rather scattered. A consistent set of experimental values measured in the same laboratory by calorimetry only was thus selected.[44] When calorimetric data were not available, as for MPU and M*i*BU, we considered our values in ref 41. $\Delta_{\rm sub}H^{\circ}_{\rm m}$(298.15K) for MPU was obtained through eq 3, whereas for M*i*BU our value re-adjusted to 298.15 K by Kabo et al.[45] was employed. The set of selected sublimation enthalpies and their corresponding values at 298.15 K are listed in Table 4.

Table 6. Molar Enthalpies of Solvation at Infinite Dilution for HN−CO−NH Functional Group in Water at T = 298.15 K for *N*-Alkylureas Calculated from Equation 5

	$\Delta_{\rm solv}H_{\rm m}^{\infty}$	$\Sigma\Delta_{\rm solv}H_{\rm m}^{\infty\,a} + \Delta_{\rm solv}H_{\rm m}^{\infty}$ [H]^b	$\Delta_{\rm solv}H_{\rm m}^{\infty}$ (FG)
compound	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}
MMU	−84.98 ± 0.53	−13.88	−71.1 ± 0.5
MEU	−88.96 ± 1.26	−17.27	−71.7 ± 1.3
MPU	−92.75 ± 1.22	−20.66	−72.1 ± 1.2
MBU	−94.71 ± 0.57	−24.05	−70.7 ± 0.6
M*i*BU	−93.75 ± 1.32	−22.72	−71.0 ± 1.3
M*t*BU	−87.20 ± 1.07	−21.99	−65.2 ± 1.1

[a] Ref 54. [b] $\Delta_{\rm solv}H_{\rm m}^{\infty}$ [H] estimated by an additivity scheme from data in ref 54 (see eq 6).

Table 7. Partial Molar Heat Capacities at Infinite Dilution, $C_{p,2}^{\infty}$, in Water at T = 298.15 K for Urea and *N*-Alkylureas Derived from Equation 8

	$\Delta_{\rm sol}C_{p,\rm m}^{\infty}$	$C_{p,\rm m}^{*}$(cr)	$C_{p,2}^{\infty}$
compound	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}
U	−18.95 ± 1.15	93.12 ± 0.01^a	74.2 ± 1.2
MMU	27.85 ± 0.92	115.50 ± 0.40^a	143.9 ± 1.3
MEU	75.59 ± 1.15	151.50 ± 0.21^a	227.1 ± 1.4
MPU	124.31 ± 8.65	196.26 ± 0.32^a	320.6 ± 9.0
MBU	209.85 ± 1.20	205.41 ± 1.42^a	415.3 ± 2.6
M*i*BU	151.15 ± 5.06	200.52 ± 0.95^b	351.7 ± 6.0
M*t*BU	147.19 ± 1.21	185.59 ± 0.06^a	332.8 ± 1.3

[a] Values from Table 3, column 3. [b] Estimated value (see text).

The values of enthalpies of solvation at 298.15 K for urea and the six *N*-alkylureas are presented in Table 5 together with the corresponding enthalpies of solution and sublimation used for their derivation. In Figure 1, the enthalpies of solvation of *N*-alkylureas are plotted as a function of the number of equivalent CH$_2$ groups in their alkyl chains, and it is worth specifying that a CH$_3$ group is assumed equivalent to 1.5 CH$_2$ groups.[46] A very good linearity was found for the four linear *N*-alkylureas (MMU, MEU, MPU, and MBU). The slope representing the contribution of the methylene group to the overall enthalpy of solvation was $\Delta_{\rm solv}H_{\rm m}^{\infty}$[CH$_2$] = (−3.30 ± 0.34) kJ·mol^{-1}, in good agreement with values reported in the literature[1,4,21,47−53] for some homologous series of alkyl compounds. Urea and the two branched *N*-alkylureas were not considered for linearization. However, urea and M*i*BU showed a slight departure from the linear plot, and only M*t*BU strongly deviated from it. The less exothermic value of enthalpy of solvation for M*t*BU can be ascribed to the effect of the branched alkyl chains, which generates a reduction of water-accessible surface area (ASA) by respect to linear and isobutyl substituent, thus affecting both functional group and alkyl chain interactions with the solvent.

A simple additivity scheme was used to evaluate the contribution of the HN−CO−NH functional group (FG) to the solvation enthalpy of the *N*-alkylureas at T = 298.15 K. Calculation was made by subtracting from the experimental $\Delta_{\rm solv}H_{\rm m}^{\infty}$ of each compound the sum of the solvation enthalpies of the alkyl groups in the molecule, obtained from data of Makhatadze and Privalov,[54] plus that of atomic hydrogen:

$$\Delta_{\rm solv}H_{\rm m}^{\infty}[\rm FG] = \Delta_{\rm solv}H_{\rm m}^{\infty}(\textit{N}\text{-alkylurea}) - \{\textstyle\sum[\Delta_{\rm solv}H_{\rm m}^{\infty}(\text{alkyl group})] + \Delta_{\rm solv}H_{\rm m}^{\infty}[\rm H]\} \qquad (5)$$

The value $\Delta_{\rm solv}H_{\rm m}^{\infty}$[H] = −5.6 kJ·mol^{-1} was obtained from data in ref 54 by the following scheme:

$$\Delta_{\rm solv}H_{\rm m}^{\infty}[\rm H] = 1/3\{(\Delta_{\rm solv}H_{\rm m}^{\infty}[-CH_3] - \Delta_{\rm solv}H_{\rm m}^{\infty}[-CH_2-]) + (\Delta_{\rm solv}H_{\rm m}^{\infty}[-CH_2-] - \Delta_{\rm solv}H_{\rm m}^{\infty}[-CH<]) + (\Delta_{\rm solv}H_{\rm m}^{\infty}[-CH<] - \Delta_{\rm solv}H_{\rm m}^{\infty}[>C<])\} \qquad (6)$$

The $\Delta_{\rm solv}H_{\rm m}^{\infty}$ [HN−CO−NH] values are remarkably constant for MMU, MEU, MPU, MBU, and M*i*BU giving an average value of (−71.3 ± 0.6) kJ·mol^{-1} (Table 6). The rather different value of $\Delta_{\rm solv}H_{\rm m}^{\infty}$[FG] for M*t*BU (−65.2 kJ·mol^{-1}) is a consequence of the less exothermic enthalpy of solvation of M*t*BU by comparison with the MBU and M*i*BU values (Table 6, column 2). If $\Delta_{\rm solv}H_{\rm m}^{\infty}$[HN−CO−NH] is calculated by the summation of the enthalpies of solvation of single CO and NH

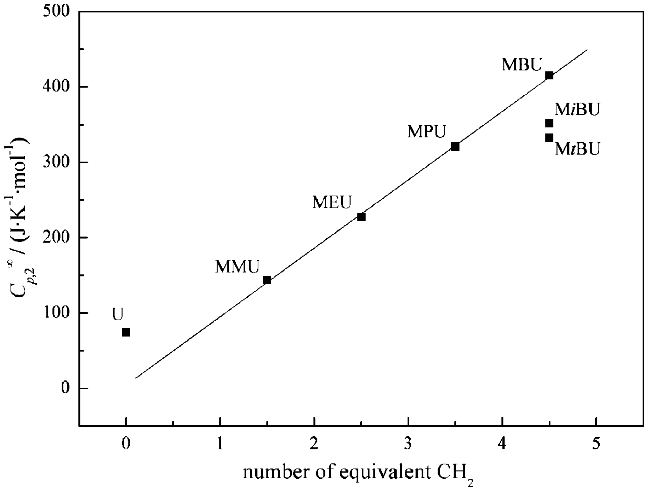

Figure 2. Partial molar heat capacities at infinite dilution as a function of the number of equivalent CH_2 groups at $T = 298.15$ K for urea and N-alkyl derivatives. The plot refers to the four linear *N*-alkylureas only.

groups[54,55] or CONH[56] and NH groups, the average value is overestimated by about 25 % (-96.3 kJ·mol^{-1}).

Partial Molar Heat Capacity. The molar heat capacity change for the solution process, $\Delta_{sol}C^{\infty}_{p,m}$, for urea and *N*-alkylureas was obtained from the slope of eq 1:

$$b = (\partial \Delta_{sol}H^{\infty}_{m}/\partial T)_p = \Delta_{sol}C^{\infty}_{p,m} \tag{7}$$

Partial molar heat capacities at infinite dilution at $T = 298.15$ K, $C^{\infty}_{p,2}$, were then calculated by summing the $\Delta_{sol}C^{\infty}_{p,m}$ values and molar heat capacities of pure compounds, $C_{p,m}$(cr), at the same temperature (Table 3, column 3):

$$C^{\infty}_{p,2} = \Delta_{sol}C^{\infty}_{p,m} + C_{p,m}(\text{cr}) \tag{8}$$

Since no experimental $C_{p,m}$(cr) value is reported in the literature for M*i*BU, it was estimated by the following additivity scheme:

$$C_{p,m}(\text{cr})[\text{M}i\text{BU}] = C_{p,m}(\text{cr})[\text{M}i\text{PU}] + C_{p,m}(\text{cr})[\text{CH}_2] \tag{9}$$

where $C_{p,m}$(cr)[M*i*PU] = (169.07 ± 0.95) J·K^{-1}·mol^{-1} (Table 3) and $C_{p,m}$(cr)[CH_2] = (31.45 ± 2.64) J·K^{-1}·mol^{-1} obtained as the slope of the linear function $C_{p,m}(\text{cr}) = f(n)$, with n = number of equivalent CH_2 groups in the *N*-alkylureas.

$C^{\infty}_{p,2}$ values given in Table 7 are positive and increase linearly with the number of equivalent CH_2 groups in the alkyl chains. M*i*BU and M*t*BU values are lower than that of MBU. Plotting $C^{\infty}_{p,2}$ of MMU, MEU, MPU, and MBU as a function of the number of their equivalent methylene groups gave a slope of (90.77 ± 1.93) J·K^{-1}·mol^{-1} (Figure 2) in excellent agreement with literature data for linear alkanes and alkyl compounds.[1,47,48,50,52,53,57,58] An average value of (89.5 ± 0.7) J·K^{-1}·mol^{-1} was calculated by Nichols et al.[58] for seven classes of organic compounds, and a value of 87.9 J·K^{-1}·mol^{-1} was obtained by Lilley et al.[59] for several *N*-amino acid amides and peptides. In an earlier paper we obtained $C^{\infty}_{p,2}[CH_2]$ = (89.3 ± 0.6) J·K^{-1}·mol^{-1} for a series of *N*-acetylamino acid amides.[55]

The contributions of the functional group HN−CO−HH to the overall $C^{\infty}_{p,2}$ values were estimated through an additivity scheme similar to that used for $\Delta_{solv}H^{\infty}_{m}$[FG] (see eq 5):

$$C^{\infty}_{p,2}[\text{HN}{-}\text{CO}{-}\text{NH}] = C^{\infty}_{p,2}(N\text{-alkylurea}) - \left\{\sum C^{\infty}_{p,2}(\text{alkyl group}) + C^{\infty}_{p,2}[\text{H}]\right\} \tag{10}$$

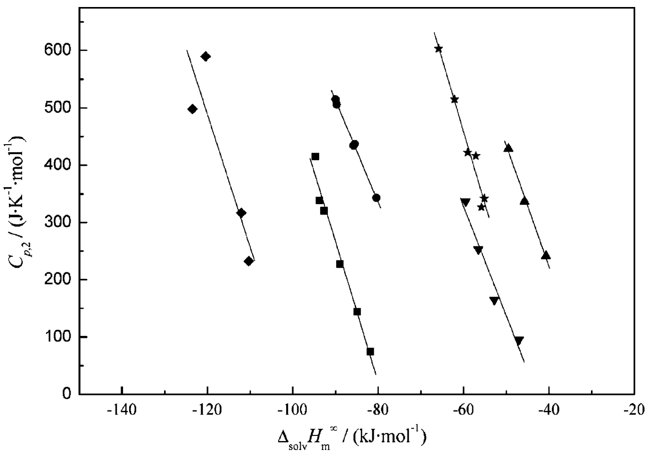

Figure 3. Interplay between partial molar heat capacity and molar enthalpy of solvation at infinite dilution at $T = 298.15$ K for *N*-alkylureas compared with other series of compounds bearing single or combined carbonyl and amine groups: ■, *N*-alkylureas; ◆, *N*-acetylamino acid amides; ●, *N*-alkylamides; ▼, carboxylic acids; ★, primary alkylamines; ▲, alkyl ketones.

Table 8. Partial Molar Heat Capacity for HN−CO−NH Functional Group in Water at T = 298.15 K Calculated for the Four Linear *N*-Alkylureas by Equation 10

	$C^{\infty}_{p,2}$	$\sum C^{\infty}_{p,2}{}^{a} + C^{\infty}_{p,2}[\text{H}]^{a}$	$C^{\infty}_{p,2}$ [FG]
compound	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}
MMU	143.9 ± 1.3	224	−80.1 ± 1.3
MEU	227.1 ± 1.4	314	−86.9 ± 1.4
MPU	320.6 ± 9.0	404	−83.4 ± 9.0
MBU	415.3 ± 2.6	494	−78.7 ± 2.6
		average value = −82.3 ± 3.6	

[a] Ref 58.

where the values of $C^{\infty}_{p,2}$ for CH_2 and CH_3 alkyl groups and atomic hydrogen were taken from Nichols et al.[58] An average value $C^{\infty}_{p,2}$[HN−CO−NH] = (−82.3 ± 3.6) J·K^{-1}·mol^{-1} was thus obtained for the four linear *N*-alkylureas (Table 8). This value is less negative than the same quantity obtained by summation of single CO and NH group contributions (−130 J·K^{-1}·mol^{-1}).[58]

In Figure 3 a plot of $C^{\infty}_{p,2}$ versus $\Delta_{solv}H^{\infty}_{m}$ for the *N*-alkylureas is presented and compared with those of other homologous series of linear alkyl compounds bearing carbonyl, amine or single and coupled peptide groups. The sequence of lines correlates well to the increasing hydration effect of the functional groups, alkylketones,[21,61,62] primary alkylamines,[1,57,58,60] carboxylic acids,[57,58] *N*-alkylamides,[49,57,58] *N*-alkylureas, and *N*-acetylamino acid amides.[55] The fairly parallel plots in Figure 3 lead us to infer a similar hydration process for all these compounds. The steep slopes are due to a relative low increase of the enthalpy of solvation as a function of C atoms in the alkyl chains with respect to a substantial increment of the corresponding partial molar heat capacity. An increase in the C atom number, in fact, leads to a more extended hydrophobic hydration and promotes a relatively small increase of $\Delta_{solv}H^{\infty}_{m}$ by comparison with that of $C^{\infty}_{p,2}$, a quantity that, in our case, is very sensitive to the changes of the first solvation shell of methylene groups. An opposite behavior was reported earlier by some of us for the hydration of polyhydric alcohols.[63] In that case, the strong increase of the $\Delta_{solv}H^{\infty}_{m}$ of polyols generated by the extensive formation of solute−water H-bonds and the relatively lower increment of $C^{\infty}_{p,2}$ due to the substitution of H by OH resulted in a strong flattening of the interplay slope.

Conclusions

(i) Enthalpy of solvation and partial molar heat capacity of *N*-alkylureas displayed a linear dependence on the number of equivalent $\mathrm{CH_2}$ groups in the alkyl chains and gave slopes of $\Delta_{\mathrm{solv}}H_{\mathrm{m}}^{\infty}[\mathrm{CH_2}] = (-3.30\ 0.34)\ \mathrm{kJ \cdot mol^{-1}}$ and $C_{p,2}^{\infty}[\mathrm{CH_2}] = (89.3 \pm 0.6)\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$, respectively, in very good agreement with literature data.

(ii) Branching from the *n*- to the isobutyl substituent produced a slightly less negative $\Delta_{\mathrm{solv}}H_{\mathrm{m}}^{\infty}$ value, as already observed for other mono-functional alkyl compounds, such as primary amines, *N*-alkylamides, and carboxylic acids, whereas branching from the *n*- to the *tert*-butyl substituent gave rise to a higher change.[1] Moreover, branching from the *n*- to both iso- and *tert*-butyl substituents produced a substantial decrease of $C_{p,2}^{\infty}$ values. Both variations are attributable to the reduction of water-accessible surface area due to the branching of the alkyl chains. More precisely, the decrease of $\Delta_{\mathrm{solv}}H_{\mathrm{m}}^{\infty}$ is due to the reduction of hydrophilic hydration of the functional group and the decrease of $C_{p,2}^{\infty}$ to the reduction of hydrophobic hydration of alkyl chains.

(iii) The derived average contribution of HN−CO−NH to the enthalpy of hydration of *N*-alkylureas ($-71.3\ \mathrm{kJ \cdot mol^{-1}}$) is definitely less negative than the value estimated by summation of the contributions of single groups ($-96.3\ \mathrm{kJ \cdot mol^{-1}}$). On the other hand, the average contribution of the functional group to the overall partial molar heat capacity of *N*-alkylureas ($-82.3\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$) is also less negative than the sum of the contributions of single groups ($-130\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$). Both departures are attributable to the hydrophilic-hydrophobic effects mentioned.

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