Hydrophobic−Hydrophilic Solvation of Variously Substituted *N*-Alkylureas in Aqueous Solution: A Calorimetric Study at a Temperature of 298.15 K[†]

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Enthalpies of solution, $\Delta_{sol}H_m$, in water, of some di-, tri-, and tetra-substituted *N*-alkylureas were measured by isothermal calorimetry at $T = (296.84, 306.89, \text{and } 316.95)$ K. The molar enthalpies of solution at infinite dilution (i.d.), $\Delta_{sol}H_m^\infty$, and molar heat capacity changes for the solution process at i.d., $\Delta_{sol}C_{p,m}^\infty$, were obtained at $T = 298.15$ K. Molar enthalpies of solvation, $\Delta_{solv}H_m^\infty$, and partial molar heat capacities, $C_{p,2}^\infty$, at i.d. were then calculated from the molar enthalpies of sublimation or vaporization and molar heat capacities, $C_{p,m}$, of pure compounds in solid or liquid states, respectively. The methylene group contributions to the enthalpy of solvation was -3.7 kJ·mol^{-1} for di- and tri-*N*-alkylureas and -3.2 kJ·mol^{-1} for tetra-*N*-alkyureas, whereas the contribution to partial molar heat capacity was 91 J·K^{-1}·mol^{-1} and 93 J·K^{-1}·mol^{-1}, respectively, in very good agreement with our earlier data for monosubstituted *N*-alkylureas and the literature data for various homologous series of alkyl-substituted compounds. Contributions of the functional groups of *N*-alkylureas were derived and compared with our earlier data for mono-*N*-alkylureas.

Introduction

The thermodynamics of hydrophobic and hydrophilic solvation in aqueous solutions has become of great biochemical interest; for example, knowledge of the quality and strength of solute−solvent interactions in water is important for the understanding of protein folding, protein−protein binding, protein/nucleic acid binding, and biomembrane formation. Moreover, improvements in the sensitivity and accuracy of calorimeters have resulted in the collection of a wealth of new data for these processes.[1−7] Thermodynamic parameter variations associated with protein folding and binding stem almost entirely from the desolvation of polar and nonpolar groups.[3,8,9] Burial of nonpolar groups constitutes the dominant stabilizing interaction in protein folding and binding of ligands, namely, the hydrophobic interaction.[10,11] At room temperature, the hydrophobic interaction is driven by the low solubility of nonpolar compounds in water and is due to the unfavorable decrease in their entropy (or increase in structure). This effect has been described in many ways: "icelike structure", icebergs, flickering clusters, clathrates, and pentagonal clusters.[12−14] Many experimental and theoretical studies of the thermodynamics of the hydrophobic effect[15−18] have added to the seminal publications on the subject.[10,14,19] Heat capacity change associated with the solvation process is the prominent features of this effect,[2,11,15,18,19] and its determination is essential for understanding the hydration of both polar and nonpolar compounds.

The present paper follows our thermodynamic investigations on the solute−solvent interaction of model compounds in aqueous solution.[20−24] Urea and its alkylderivatives are low-molecular-mass compounds that contain both hydrophilic and hydrophobic moieties and display peculiar hydration properties.[14,19,25] We have recently described the thermodynamic properties of urea and some of its monosubstituted *N*-alkylderivatives in diluted aqueous solution at 298.15 K, as determined by isothermal calorimetry.[24] This work is an extension of our earlier study and provides data on the molar enthalpy of solvation, $\Delta_{solv}H_m^\infty$, and partial molar heat capacity, $C_{p,2}^\infty$, for some di-, tri-, and tetra-*N*-alkylureas in aqueous solution at infinite dilution (i.d.). The enthalpies of solution, $\Delta_{sol}H_m^\infty$, were measured by isothermal calorimetry, and both $\Delta_{solv}H_m^\infty$ and $C_{p,2}^\infty$ were obtained. The contributions to the molar enthalpy of solvation and partial molar heat capacity of both methylene and polar functional groups in di-, tri-, and tetra-*N*-alkylureas were derived and compared with the values estimated through additivity schemes.

Experimental Section

Materials. Dimethyl-1,1-urea, D(1,1)MU, and diethyl-1,1-urea, D(1,1)EU, were from Aldrich (stated mass fraction purity of 0.99) dimethyl-1,3-urea, D(1,3)MU, diethyl-1,3-urea, D(1,3)EU, and tetramethyl-1,1,3,3-urea, T(1,1,3,3)MU, from EGA-Chemie (with stated mass fraction purity of 0.98); trimethyl-1,1,3-urea,

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

compound	$\frac{m}{10^{-2}\ \mathrm{mol \cdot kg^{-1}}}$	$\frac{\Delta_{\mathrm{sol}}H_m}{\mathrm{kJ \cdot mol^{-1}}}$	compound	$\frac{m}{10^{-2}\ \mathrm{mol \cdot kg^{-1}}}$	$\frac{\Delta_{\mathrm{sol}}H_m}{\mathrm{kJ \cdot mol^{-1}}}$
D(1,1)MU	T = 296.84 K		D(1,1)EU	T = 296.84 K	
	1.269	12.00		0.474	2.95
	1.396	11.77		0.791	2.51
	1.946	11.46		0.920	2.82
	2.315	11.71		0.939	2.44
	2.811	11.80		0.989	2.83
	2.847	11.88		1.321	2.84
	3.077	11.80		T = 306.89 K	
	T = 306.89 K			0.217	4.68
	0.327	12.96		0.325	4.62
	0.791	12.82		0.619	4.49
	0.865	12.67		0.771	4.42
	1.033	12.82		T = 316.95 K	
	T = 316.95 K			0.694	7.33
	0.414	13.76		0.706	7.27
	0.716	13.72		0.758	7.32
	0.893	13.65		0.961	7.30
	1.043	13.71		1.058	7.17
D(1,3)MU	T = 296.84 K		D(1,3)EU	T = 296.84 K	
	1.000	0.75		0.610	0.19
	1.240	0.63		0.738	0.14
	1.246	0.69		0.987	0.18
	1.559	0.79		1.134	0.12
	1.746	0.61		T = 306.89 K	
	T = 306.89 K			0.529	2.68
	1.099	2.29		0.584	2.70
	1.142	2.25		0.940	2.83
	1.389	2.26		1.372	2.19
	1.579	2.19		T = 316.95 K	
	1.773	2.17		0.519	5.12
	T = 316.95 K			0.717	4.97
	0.771	3.39		0.768	5.18
	1.085	3.40		1.078	5.23
	1.299	3.30			
	1.513	3.29			
Tr(1,1,3)MU	T = 296.84 K		T(1,1,3,3)EU	T = 296.84 K	
	1.018	–1.76		0.723	–27.59
	1.152	–1.77		0.776	–27.48
	1.174	–1.77		1.029	–27.74
	1.714	–1.79		1.035	–27.74
	1.730	–1.83		T = 306.89 K	
	T = 306.89 K			0.406	–22.38
	1.219	0.083		0.657	–22.07
	1.457	0.082		0.826	–22.19
	1.599	0.086		0.841	–21.64
	1.632	0.079		T = 316.95 K	
	T = 316.95 K			0.473	–18.32
	0.210	1.53		0.501	–18.25
	0.275	1.58		0.922	–18.29
	1.414	1.51		0.931	–18.09
	1.466	1.46		0.951	–18.00
	1.700	1.57			
T(1,1,3,3)MU	T = 296.84 K				
	0.650	–24.24			
	0.787	–24.30			
	0.858	–23.79			
	0.999	–23.94			
	1.512	–23.84			
	T = 306.89 K				
	1.121	–23.21			
	1.567	–22.20			
	1.732	–23.27			
	1.834	–23.23			
	T = 316.95 K				
	0.699	–21.19			
	1.006	–21.29			
	1.010	–20.69			
	1.442	–21.63			
	1.657	–20.96			

Tr(1,1,3)MU, was from Alfa Products (mass fraction purity of 0.97), and tetraethyl-1,1,3,3-urea, T(1,1,3,3)EU, was from Fluka (with purity not indicated by the supplier). All compounds were purified by up to five successive crystallizations from ethylacetate (Fluka puriss., mass fraction purity > 0.995) solutions over molecular sieves as described earlier.[26] All products were then dried to constant mass under reduced pressure at room temperature. Final purity was always better than 0.995 mass fraction, as determined by the differential scanning calorimetry (DSC) peak profile method.[27]

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

	$\Delta_{\mathrm{sol}}H_{\mathrm{m}}^{\infty a}$							
	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
D(1,1)MU	7	11.79 ± 0.24	4	13.03 ± 0.16	4	13.80 ± 0.07	12.00 ± 0.16	12.01(0.05)^c
D(1,3)MU	5	0.79 ± 0.19	5	2.45 ± 0.06	4	3.53 ± 0.08	1.07 ± 0.02	1.05(0.03)^c, 1.00(0.03)^d, 0.78(0.02)^e
D(1,1)EU	6	2.86 ± 0.17	4	4.78 ± 0.01	5	7.52 ± 0.13	3.02 ± 0.28	
D(1,3)EU	4	0.23 ± 0.07	4	3.06 ± 0.31	4	4.93 ± 0.23	0.70 ± 0.03	
Tr(1,1,3)MU	5	−1.68 ± 0.03	4	0.09 ± 0.01	5	1.53 ± 0.04	−1.42 ± 0.11	
T(1,1,3,3)MU	5	−24.45 ± 0.27	4	−23.18 ± 0.17	5	−21.01 ± 0.64	−24.38 ± 0.31	−24.53(0.01)^c −23.70(0.18)^d −23.96(0.08)^e
T(1,1,3,3)EU	4	−27.03 ± 0.23	4	−22.83 ± 0.54	5	−18.47 ± 0.19	−26.50 ± 0.05	

[a] Linearly extrapolated values at $m = 0$. Uncertainties at 95 % confidence limits. [b] Number of experimental determinations. [c] Ref 31. [d] Ref 32. [e] Ref 33.

Hexane and cyclohexane from Aldrich (stated mass fraction purity > 0.99) and urea (standard reference material) from NBS (National Bureau of Standards) were employed with no further purification to calibrate the calorimeter. Deionized bidistilled water HPLC grade from Aldrich was used for solution preparation.

Calorimetric Measurements. Enthalpies of solution, $\Delta_{\mathrm{sol}}H_m$, in water were measured at T = (296.84, 306.89, and 316.95) K with a CRMT-SETARAM rotating calorimeter (Tian-Calvet type). A glass ampule containing the sample was broken in its 100 mL cell, as already described.[28] The calibration tests were made by the Joule effect using the calibration cell fitted with a 1000 Ω constantan resistance supplied by SETARAM, as well as by determining the standard enthalpy of mixing of (hexane + cyclohexane)[29] and the enthalpy of dilution of aqueous solutions of urea.[30] Conversion factors of $(7.36 \pm 0.03) \cdot 10^{-5}$ J·mm^{-1}·s^{-1} were obtained at both (296.84 and 306.89) K and $(7.25 \pm 0.02) \cdot 10^{-5}$ J·mm^{-1}·s^{-1} at 316.95 K. Two out of three calibration methods were made using the same procedure as for sample measurements. As a consequence, the intrinsic uncertainty associated with each measurement of solution enthalpy corresponds in principle to that of the conversion factors at various temperatures. The temperature was kept constant to ± 0.05 K as from the calibration made with certified thermocouples kindly supplied by the National Institute for Metrologic Research (INRiM) in Turin. Four to seven measurements of enthalpy of solution at different concentration values were performed for each sample. The final concentration of the solutes was in the range of $(2.1 \cdot 10^{-3}$ to $3.1 \cdot 10^{-2})$ mol·kg^{-1}.

Results and Discussion

Enthalpy of Solution at Infinite Dilution. Enthalpies of solution at i.d. at the three experimental temperatures were obtained by linear extrapolation to $m = 0$ of each set of data (Table 1). The extrapolated molar enthalpies of solution were then fitted as a linear function of temperature:

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

where $a = \Delta_{\mathrm{sol}}H_m^{\infty}$ at T = 298.15 K (Table 2). The values obtained for D(1,1)MU, D(1,3)MU, and T(1,1,3,3)MU are in excellent agreement with the literature data at T = 298.15 K,[31−33] as shown in Table 2. There are no previous data for the other *N*-alkylureas. The standard molar enthalpies of solution are positive (endothermic) for the four di-*N*-alkylureas, slightly negative for Tr(1,1,3)MU, and strongly negative (exothermic) for the two tetra-*N*-alkylureas.

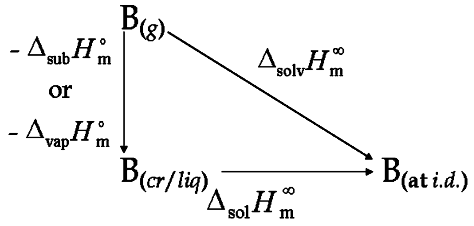

Figure 1. Combination of solution enthalpy and sublimation/vaporization enthalpy gives solvation enthalpy relevant to the transfer of one mole of solute from its ideal gaseous phase to solution at infinite dilution (eq 2).

Table 3. Molar Enthalpies of Solvation in Water at Infinite Dilution at T = 298.15 K of Di-, Tri-, and Tetra-substituted *N*-Alkylureas from Equation *2*

	$\Delta_{\mathrm{sol}}H_m^{\infty}$	$\Delta_{\mathrm{sub}}H_m^{\circ}$	$\Delta_{\mathrm{solv}}H_m^{\infty}$
compound	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}
D(1,1)MU	12.00 ± 0.16	96.1 ± 1.4^a	−84.1 ± 1.4
D(1,3)MU	1.07 ± 0.02	88.8 ± 0.4^a	−87.7 ± 0.4
D(1,1)EU	3.02 ± 0.28	95.8 ± 0.5^a	−92.8 ± 0.6
D(1,3)EU	0.70 ± 0.03	95.4 ± 0.3^a	−94.7 ± 0.3
Tr(1,1,3)MU	−1.42 ± 0.11	88.6^b	−90.0
		$\Delta_{\mathrm{vap}}H_m^{\circ}$	
		kJ·mol^{-1}	
T(1,1,3,3)MU	−24.38 ± 0.31	66.2^b	−90.6
T(1,1,3,3)EU	−26.50 ± 0.05	76.9^b	−103.4

[a] Ref 34. [b] Values obtained from the calculated enthalpies of formation in solid/liquid and gaseous states at 298.15 K.[35]

Enthalpy of Solvation. The combination of solution and sublimation or vaporization enthalpies gives the enthalpy of solvation corresponding to the transfer of one mole of solute from the ideal gaseous phase to aqueous solution at i.d. (Figure 1):

$$\Delta_{\mathrm{solv}}H_m^{\infty} = \Delta_{\mathrm{sol}}H_m^{\infty} - \Delta_{\mathrm{sub}}H_m^{\circ} \qquad (2)$$

For di-*N*-alkylureas, sublimation enthalpies at 298.15 K were taken from the literature,[34] while the enthalpy of sublimation of Tr(1,1,3)MU and enthalpies of vaporization of T(1,1,3,3)MU and T(1,1,3,3)EU at 298.15 K were derived from their enthalpies of formation in solid/liquid and gaseous states calculated by Domalski and Hearing.[35] Standard enthalpies of solvation obtained from eq 2 and listed in Table 3 enabled us to differentiate among mono-, di-, tri-, and tetra-substituted *N*-alkylureas. In fact, $\Delta_{\mathrm{solv}}H_m^{\infty}$ of symmetrical disubstituted *N*-alkylureas, D(1,3)MU (−87.8 kJ·mol^{-1}) and D(1,3)EU (−94.7 kJ·mol^{-1}), practically correspond to those of linear monosubstituted *N*-alkylureas with the same number of C atoms, namely,

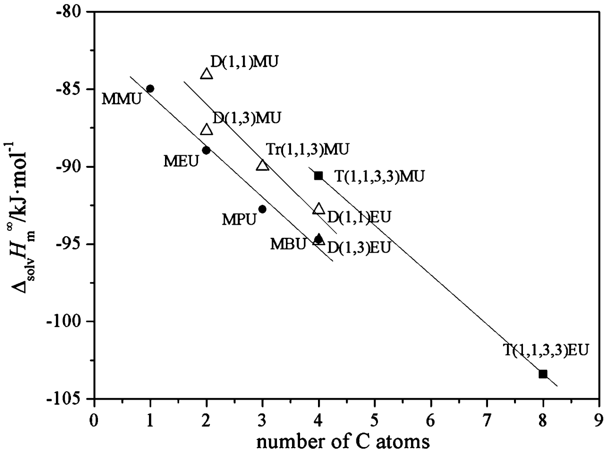

Figure 2. Molar enthalpies of solvation at infinite dilution as a function of the number of C atoms at $T = 298.15$ K for mono-, di-, tri-, and tetra-*N*-alkylureas. MMU = *N*-methyl-urea, MEU = *N*-ethyl-urea, MPU = *N*-propyl-urea, MBU = *N*-butyl-urea, M*i*BU = *N*-isobutyl-urea, and M*t*BU = *N*-tertbutyl-urea.

N-ethylurea (−88.9 kJ·mol^{-1}) and *N*-butylurea (−94.7 kJ·mol^{-1}).[24] The asymmetrical ones, D(1,1)MU and D(1,1)EU, however, display less negative values of the enthalpy of solvation as observed for the branched monosubstituted *N*-alkylureas (*N*-isobutylurea and *N*-tertbutylurea).[24] This behavior should be attributed to the reduction of water accessible surface area (ASA) and corresponding lower hydrophobic effect in asymmetrical/branched compounds by respect to symmetrical/linear ones. Moreover, less negative $\Delta_{solv}H_m^\infty$ values of Tr(1,1,3)MU and T(1,1,3,3)MU with respect to those reported for *N*-propylurea (−92.8 kJ·mol^{-1})[24] and *N*-butylurea,[24] respectively, can be attributed to the same effects.

The linear dependence of solvation enthalpy on the number of C atoms in alkyl chains for mono- di-, tri-, and tetra-*N*-alkylureas is presented in Figure 2. The slope representing the solvation enthalpy of the methylene group was (−3.9 ± 0.6) kJ·mol^{-1} for di- and trisubstituted *N*-alkylureas and −3.2 kJ·mol^{-1} for tetra-*N*-alkylureas, in good agreement with that of linear mono-*N*-alkylureas, (−3.3 ± 0.3) kJ·mol^{-1},[24] as well as several other homologous series of alkyl compounds, for example, alkanes, alkanols, ketones, esters, amines, and amides, in the literature.[20,22,36−41]

Furthermore, the contribution of the functional groups, FG, to the solvation enthalpy of *N*-alkylureas, was calculated by subtracting the contribution of the H atom or atoms from the values obtained by extrapolation to $N_C = 0$ of each set of data, that is, linear mono-*N*-alkylureas, 1,3-di-*N*-alkylureas, 1,1-di-*N*-alkylureas, and tetra-*N*-alkylureas:

$$\Delta_{solv}H_m^\infty[\mathrm{FG}] = \Delta_{solv}H_m^\infty[N_C = 0] - n\Delta_{solv}H_m^\infty[\mathrm{H}] \quad (3)$$

where n is 1 for mono-*N*-alkylureas, 2 for di-*N*-alkylureas, 3 for trimethylurea, and 4 for tetra-*N*-alkylureas and $\Delta_{solv}H_m^\infty[\mathrm{H}] = -5.6$ kJ·mol^{-1}.[24] A common regression together with di-*N*-alkylureas was used for Tr(1,1,3)MU. The $\Delta_{solv}H_m^\infty$[FG] values are very close to those calculated from the following additivity scheme (Table 4):

$$\Delta_{solv}H_m^\infty[\mathrm{FG}] = \Delta_{solv}H_m^\infty[N\text{-alkylurea}] - \sum\Delta_{solv}H_m^\infty[\text{alkyl group}] \quad (4)$$

where the enthalpies of solvation of alkyl groups are from Makhatadze and Privalov.[3] It is worth noting that the $\Delta_{solv}H_m^\infty$[FG] values progressively decrease: mono-*N*-alkylureas > 1,3-di-*N*-alkylureas > 1,1-di-*N*-alkylureas > Tr(1,1,3)MU > tetra-*N*-alkylureas. The same sequence was found by Spencer and Hovick[42] for the enthalpies of N−H hydrogen bond formation per mole of compound: MMU (−18.0 kJ·mol^{-1}), D(1,3)MU (−16.3 kJ·mol^{-1}), D(1,1)MU (−9.6 kJ·mol^{-1}), and Tr(1,1,3)MU (−11.3). An average value of −56.3 kJ·mol^{-1} was obtained by subtracting the enthalpies of N−H hydrogen bond formation from $\Delta_{solv}H_m^\infty$[FG] of the same compounds, very close to $\Delta_{solv}H_m^\infty$[N−CO−N] calculated in this work for T(1,1,3,3)MU, −57.5 kJ·mol^{-1}. This substantial contribution of the N−CO−N group to the solvation of the FGs of *N*-alkylureas can be ascribed to the nonplanar geometry and unique properties of electronic structure of urea and its derivatives in aqueous solution, which favor a high density of hydrogen bonds between the compound and the surrounding water.[43]

Table 4. Enthalpies of Solvation at Infinite Dilution in Water of Functional Groups, $\Delta_{solv}H_m^\infty$ [FG], in Monoalkyl, 1,3-Dialkyl, 1,1-Dialkyl, and Tetraalkyl Derivatives of Urea

			$\Delta_{solv}H_m^\infty$[FG]	
			kJ·mol^{-1}	
N-alkylureas	N[a]	FG	extrapolated[b]	calculated[c]
monoalkyl[d]	4	NH−CO−NH$_2$	−76.5	−77.0
1,3-dialkyl	2	NH−CO−NH	−69.5	−71.3
1,1-dialkyl	2	N−CO−NH$_2$	−64.2	−68.5
trialkyl	1	N−CO−NH	−61.3	−65.2
tetraalkyl	2	N−CO−N	−55.4	−57.5

[a] N = number of *N*-alkylureas. [b] Extrapolated from the experimental $\Delta_{solv}H_m^\infty$ values (see text). [c] Calculated by eq 5. [d] From experimental data in ref 24.

Table 5. Partial Molar Heat Capacities at Infinite Dilution, $C_{p,2}^\infty$, in Water at 298.15 K for Di-, Tri-, and Tetra-*N*-Alkylureas from Equation 6

			$C_{p,2}^\infty$	
	$\Delta_{sol}C_{p,m}^\infty$	$C_{p,m}$(cr)	J·K^{-1}·mol^{-1}	
compound	J·K^{-1}·mol^{-1}	J·K^{-1}·mol^{-1}	this work	literature[c]
D(1,1)MU	100.0 ± 7	134.29 ± 0.05[a]	234.3 ± 7	248
D(1,3)MU	136.3 ± 8	133.25 ± 0.03[a]	269.6 ± 8	274
D(1,1)EU	232.2 ± 12	183.31 ± 0.01[a]	415.5 ± 12	
D(1,3)EU	233.7 ± 14	219.04 ± 0.10[a]	452.7 ± 14	
Tr(1,1,3)MU	159.6 ± 10	183.85[b]	343.5 ± 10	
		$C_{p,m}$(liq)		
		J·K^{-1}·mol^{-1}		
T(1,1,3,3)MU	171.1 ± 13	229.60 ± 0.02[a]	400.7 ± 13	434
T(1,1,3,3)EU	425.7 ± 5	345.70 ± 0.01[a]	771.4 ± 5	

[a] Values from experimental data in ref 44. [b] Estimated value (see text). [c] Ref 45.

Partial Molar Heat Capacity. The molar heat capacity change for the solution process, $\Delta_{sol}C_{p,m}^\infty$, for di-, tri-, and tetrasubtituted *N*-alkylureas at $T = 298.15$ K was calculated by differentiating eq 1 (Table 5):

$$\Delta_{sol}C_{p,m}^\infty = (\partial\Delta_{sol}H_m^\infty/\partial T)_p = b \quad (5)$$

Their large positive values are due to the hydrophobic hydration of the aliphatic chains.

Partial molar heat capacities at i.d. and $T = 298.15$ K, $C_{p,2}^\infty$, were then obtained by summing the $\Delta_{sol}C_{p,m}^\infty$ values and molar heat capacities of pure compounds, $C_{p,m}$(cr/liq), at the same temperature:

$$C_{p,2}^\infty = \Delta_{sol}C_{p,m}^\infty + C_{p,m}(\mathrm{cr/liq}) \quad (6)$$

All $C_{p,m}$ values were derived from the experimental data of Kabo et al.,[44] except that for Tr(1,1,3)MU which was estimated

Table 6. Variation of Molar Heat Capacity Change for the Solution Process, $\Delta_{\mathrm{sol}}C^{\infty}_{p,m}$, and Partial Molar Heat Capacity, $C^{\infty}_{p,2}$, at Infinite Dilution of Di-, Tri-, and Tetra-alkylureas Due to One H-Atom Substitution by a $-CH_3$ Group

	$\delta\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$		$\delta C^{\infty}_{p,2}$	
	$J\cdot K^{-1}\cdot mol^{-1}$		$J\cdot K^{-1}\cdot mol^{-1}$	
N-alkylurea	this work	literature[a]	this work	literature[a]
1/2[D(1,1)MU − U[b]]	60	56	80	80
1/2[D(1,3)MU − U[b]]	78	69	98	93
1/3[Tr(1,1,3)MU − U[b]]	60		89	
1/4[T(1,1,3,3,)MU − U[b]]	48	46	82	86

[a] Ref 45. [b] $\Delta_{\mathrm{sol}}C^{\infty}_{p,m}[U] = -18.95\ J\cdot K^{-1}\cdot mol^{-1}$ and $C^{\infty}_{p,2}[U] = 74.2\ J\cdot K^{-1}\cdot mol^{-1}$ from ref 24.

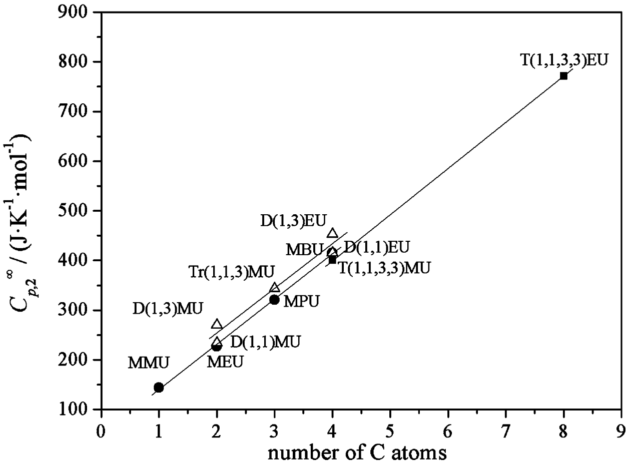

Figure 3. Partial molar heat capacities at infinite dilution as a function of the number of C atoms at $T = 298.15$ K for mono-, di-, tri-, and tetra-*N*-alkylureas. MMU = *N*-methyl-urea, MEU = *N*-ethyl-urea MPU = *N*-propyl-urea MBU = *N*-butyl-urea M*i*BU = *N*-isobutyl-urea, M*t*BU = *N*-tertbutyl-urea.

from the group contributions calculated by Domalski and Hearing.[35] The $C^{\infty}_{p,2}$ values of *N*-alkylureas (Table 5, column 4) increase with the number of carbon atoms in the alkyl chains. In particular, the partial molar heat capacities of symmetrical di-*N*-alkylureas are higher than those of the corresponding asymmetrical di-*N*-alkylureas since their hydrophobic hydration cospheres are less perturbed by the functional group in symmetrical compounds, as suggested by Spencer and Hovick.[42] For a further examination of the alkyl-substitutent steric effect on hydrophobic hydration, we calculated the variation of both molar heat capacity change and partial molar heat capacity due to a H atom substitution by a $-CH_3$ group for all of the methyl derivatives of urea (Table 6). Addition of a methylene group to urea to form D(1,3)MU was found to increase both $\Delta_{\mathrm{sol}}C^{\infty}_{p,m}$ and $C^{\infty}_{p,2}$ more than those for D(1,1)MU, Tr(1,1,3)MU, and T(1,1,3,3)MU. Our findings are in agreement with the literature data.[46]

The plot of $C^{\infty}_{p,2}$ values as a function of the number of C atoms in the alkyl chains drawn for both di- and tri-*N*-alkylureas, as well as for tetra-*N*-alkylureas, are parallel to both each other and that of mono-*N*-alkylureas (Figure 3). The slope was (91.1 ± 8) $J\cdot K^{-1}\cdot mol^{-1}$ for di- and tri-*N*-alkylureas and (92.7 ± 3.3) $J\cdot K^{-1}\cdot mol^{-1}$ for tetra-*N*-alkylureas, very close to our previous value for mono-*N*-alkylureas, (90.8 ± 1.9) $J\cdot K^{-1}\cdot mol^{-1}$, and in good agreement with the literature data for linear alkanes and several series of linear monofunctional alkyl compounds (89.6 ± 0.7) $J\cdot K^{-1}\cdot mol^{-1}$,[38,46] *N*-acetyl-amino acid amides and peptides 87.9 $J\cdot K^{-1}\cdot mol^{-1}$,[47] *N*-substituted alkylamides, carboxylic acids, and sodium salts of carboxylic acids (90.85 ± 0.16) $J\cdot K^{-1}\cdot mol^{-1}$.[48] In an earlier paper we obtained $C^{\infty}_{p,2}[CH_2] = (89.3 \pm 0.6)\ J\cdot K^{-1}\cdot mol^{-1}$ for a series of *N*-acetyl amino acid amides.[23] These results substantiate the view that group additivity is a suitable method to calculate the methylene contribution to $C^{\infty}_{p,2}$ for organic molecules in a diluted aqueous solution. In addition, this value can be usefully employed to complicated systems, such as proteins, DNA, biomembranes, and so forth.[47−49]

Table 7. Partial Molar Heat Capacity of the Functional Groups, $C^{\infty}_{p,2}$[FG], in Monoalkyl, 1,3-Dialkyl, 1,1-Dialkyl, and Tetraalkyl Derivatives of Urea

			$C^{\infty}_{p,2}$[FG]	
			$kJ\cdot mol^{-1}$	
N-alkylureas	*N*[a]	FG	extrapolated[b]	calculated[c]
monoalkyl[d]	4	$NH-CO-NH_2$	−17	−15
1,3-dialkyl	2	$NH-CO-NH$	−48	−43
1,1-dialkyl	2	$N-CO-NH_2$	−81	−79
trialkyl	1	$N-CO-NH$	−131	−128
tetraalkyl	2	$N-CO-N$	−238	−222

[a] *N* = number of *N*-alkylureas. [b] Extrapolated from the experimental $C^{\infty}_{p,2}$ values (see text). [c] Estimated by eq 8. [d] From the experimental data in ref 24.

The partial molar heat capacities of the functional groups (Table 7) were obtained by means of the method used for the solvation enthalpies:

$$C^{\infty}_{p,2}[\mathrm{FG}] = C^{\infty}_{p,2}[N_{\mathrm{C}} = 0] - nC^{\infty}_{p,2}[\mathrm{H}] \qquad (7)$$

and compared with the values calculated from the equation:

$$C^{\infty}_{p,2}[\mathrm{FG}] = C^{\infty}_{p,2}[N\text{-alkylurea}] - \sum C^{\infty}_{p,2}[\text{alkyl group}] \qquad (8)$$

using the partial molar heat capacities of $-CH_3$ and $-CH_2-$ groups.[46] The $C^{\infty}_{p,2}$[FG] value derived from symmetrical disubstituted ureas was less negative than that derived from the unsymmetrical *N*-alkylureas, as expected.

Conclusions

(i) Enthalpy of solvation and partial molar heat capacity at i.d. of mono-, di-, tri-, and tetra-*N*-alkylureas displayed a linear dependence on the number of C atoms in the alkyl chains and gave common slopes of $\Delta_{\mathrm{solv}}H^{\infty}_{m}[CH_2] = (-3.0 \pm 0.4)\ kJ\cdot mol^{-1}$ and $C^{\infty}_{p,2}[CH_2] = (88.9 \pm 2.3)\ J\cdot K^{-1}\cdot mol^{-1}$, respectively, in very good agreement with the literature data.

(ii) Enthalpy of solvation at i.d. of the functional groups in *N*-alkylureas became less negative as a consequence of the decrease of N−H hydrogen bonds produced by the increase in the number of alkyl substituents. Asymmetrical di-*N*-alkylureas [D(1,1)MU and D(1,1)EU] displayed lower values than symmetrical isomers [D(1,3)MU and D(1,3)EU] due to steric hindrance effects.

(iii) Average solvation enthalpy of the N−CO−N group for MMU, D(1,1)MU, D(1,3)MU, Tr(1,1,3)MU, and T(1,1,3,3)MU was (−56.6 ± 2.1) $kJ\cdot mol^{-1}$, almost exclusively attributable to the hydration of the carbonyl group.

(iv) Partial molar heat capacity at i.d. of the various functional groups became more negative as the number of alkyl substituents increased in accordance with the corresponding decrease of their hydrophilicity. Asymmetrical di-*N*-alkylureas [D(1,1)MU and D(1,1)EU] displayed more negative $C^{\infty}_{p,2}$[FG] values than symmetrical isomers [D(1,3)MU and D(1,3)EU] in agreement with the decrease of their ASA.

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