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Hydration of Thiourea and Mono-, Di-, and Tetra-*N*-Alkylthioureas at Infinite Dilution: A Thermodynamic Study at a Temperature of 298.15 K

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ABSTRACT: Molar enthalpies of solution in water, $\Delta_{\text{sol}}H_{\text{m}}$, of thiourea, methylthiourea, ethylthiourea, dimethyl-1,3-thiourea, diethyl-1,3-thiourea, and tetramethyl-1,1,3,3-thiourea were measured at T = (296.84, 302.45, and 306.89) K by isothermal calorimetry. Experimental results were used to derive molar enthalpies of solvation at infinite dilution (i.d.), $\Delta_{\text{solv}}H_{\text{m}}^{\infty}$, changes in heat capacity due to the solution process, $\Delta_{\text{sol}}C_{p,\text{m}}^{\infty}$, and partial molar heat capacities at i.d., $C_{p,2}^{\infty}$, at T = 298.15 K. The methylene group contributions to the enthalpy of solvation and partial molar heat capacity were $-4.5\ \text{kJ}\cdot\text{mol}^{-1}$ and $88.5\ \text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$, respectively, in good agreement with our earlier data for *N*-alkylureas and the literature data for various homologous series of alkyl-substituted compounds. The contributions of the functional groups to both $\Delta_{\text{solv}}H_{\text{m}}^{\infty}$ and $C_{p,2}^{\infty}$ were derived by employing additive schemes and compared with our earlier data for urea and corresponding *N*-alkylureas. Hydration behavior at the i.d. of thiourea, urea, and corresponding *N*-alkyl derivatives were compared and discussed.

INTRODUCTION

Biophysical structures achieve their spatial organization and functional properties in aqueous milieu through competing hydrophilic and hydrophobic interactions which rule most of biophysical processes such as protein folding/unfolding, biomembrane formation, lipid aggregation, selective recognition, in situ sensing of biological molecules, and so forth. Hydrophobic and hydrophilic moieties of biomolecules play therefore a crucial role in both the self-assembly and functionality of biomolecules. The thermodynamic studies of the hydrophobic effect initiated by Frank and Evans[1] in 1945 and continued by Kautzmann[2] showed that the entropic mechanism for association of nonpolar moieties is central for protein folding and stability. To better understand the complex interactions of biomolecules with their environment, the hydration of small model molecules has then been extensively studied.[3−7] In this context, properties and hydration of urea and its *N*-alkyl derivatives, as small model hydrophilic solutes, but also denaturants for proteins, have been widely investigated[8−11] in the past decade, while thiourea and *N*-alkylthioureas have been far less explored. However, great attention has been given to thiourea and its derivatives as enzyme inhibitors, in particular of HIV-1 reverse transcriptase,[12] potential receptors and ionophores for heavy metal cations,[13] and building blocks for anion receptors.[14,15] It was shown that hydrogen-bonding ability of the functional group −N(H)−C(=S)−N(H)− can be modulated by the insertion of hydrophobic alkyl substituents.[16,17] Moreover, the topography of hydrophobic moieties is expected to play an important role in determining their bonding/hydration as we found for urea and its *N*-alkyl derivatives.[18,19] As a consequence, thiourea and its derivatives are widely utilized in the field of molecular recognition,[20,21] while their employment in both crystal assembly and functionalization, as well as for the construction of nanostructured materials, is now explored.[22] This paper reports the results of a study on the thermodynamics of hydration at infinite dilution (i.d.) of thiourea, TU, and some of its *N*-alkylderivatives, namely, methylthiourea, MMTU, ethylthiourea, METU, dimethyl-1,3-thiourea, D(1,3)MTU, diethyl-1,3-thiourea, D(1,3)ETU, and tetramethyl-1,1,3,3-thiourea, T(1,1,3,3)MTU, as a continuation of our investigations on solute−solvent interactions of urea and its mono-, di-, tri-, and tetrasubstituted *N*-alkyl derivatives.[14,15] Thiourea enthalpies and entropies of both fusion and sublimation[23] and heat capacities in the solid state[24] were previously reported. In this paper we conclude the thermodynamic characterization of thiourea and *N*-alkyl derivatives by providing the hydration enthalpy and partial molar heat capacity, as well as the corresponding contributions of both polar and apolar moieties. A comprehensive picture of their thermodynamic cycle including fusion, sublimation, vaporization, and hydration is thus available.

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EXPERIMENTAL SECTION

Materials. Thiourea, TU (mass fraction purity 0.99), methylthiourea, MMTU (mass fraction purity 0.97), ethylthiourea, METU (mass fraction purity 0.99), dimethyl-1,3-thiourea, D(1,3)MTU (mass fraction purity 0.99), diethyl-1,3-thiourea, D(1,3)ETU (mass fraction purity 0.98), and tetramethyl-1,1,3,3-thiourea T(1,1,3,3)MTU (mass fraction purity 0.98) were from Aldrich. All compounds, except D(1,3)MTU, were purified by several successive crystallizations from either absolute ethanol (Fluka puriss, mass fraction purity >0.998) or (ethanol + water) solutions. The purification of T(1,1,3,3)MTU also included sublimation under vacuum. D(1,3)MTU was purified by recrystallization from anhydrous tetrahydrofuran (Sigma-Aldrich, mass fraction purity >0.999) and slowly precipitated by the addition of diisopropyl ether (Sigma-Aldrich, ACS reagent, mass fraction purity >0.99) to suppress the supercooling effect. All compounds were then dried to constant mass under reduced pressure at room temperature. Infrared spectra showed no traces of water in any of the purified compounds. Their final purity was always better than 0.995 mass fraction, as determined by the differential scanning calorimetry (DSC) peak profile method.[23,25]

Hexane, cyclohexane (Sigma-Aldrich, mass fraction purity >0.99), and urea (standard reference material from National Bureau of Standards) were employed in the calibration tests of the calorimeter without any further purification. Deionized bidistilled water HPLC grade from Sigma-Aldrich was used for solution preparation.

Calorimetric Measurements. Enthalpies of solution, $\Delta_{\mathrm{sol}}H_{\mathrm{m}}$, in water were measured at T = (296.84, 302.45, and 306.89) K with a CRMT-SETARAM rotating calorimeter (Tian-Calvet type). A glass ampule containing the sample was broken in a 100 mL cell, as already described.[26] 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 both the standard enthalpy of mixing of (hexane + cyclohexane)[27] and enthalpy of dilution of aqueous solutions of urea.[28] A conversion factor of $(7.36 \pm 0.04)\ 10^{-5}\ \mathrm{J \cdot mm^{-1} \cdot s^{-1}}$ was obtained in the experimental temperature range. Two out of three calibration tests 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 factor. The temperature was kept constant to ± 0.05 K as from the calibration made with certified thermocouples kindly supplied by the National Institute of Metrological Research (INRiM) in Turin. Three to four measurements of enthalpy of solution at different concentrations were performed for each sample. The final concentration of the solutes was in the range $(0.1 \text{ to } 2) \cdot 10^{-2}\ \mathrm{mol \cdot kg^{-1}}$.

RESULTS AND DISCUSSION

Enthalpy of Solution at Infinite Dilution (i.d.). Enthalpies of solution at i.d. at the three experimental temperatures were obtained by linear extrapolation to $m = 0$ of each set of data (Tables 1 and 2). The extrapolated molar enthalpies of solution were then fitted as a linear function of temperature:

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

where $a = \Delta_{\mathrm{sol}}H_{\mathrm{m}}^{\infty}$ at T = 298.15 K (Table 2). The value obtained for thiourea is in very good agreement with that previously reported by Taniewska-Osińska and Pałecz.[29] To the best of our knowledge, no previous data for the solution process of *N*-alkylthioureas are reported in the literature.

Enthalpy of Solvation. The molar enthalpy of solvation, $\Delta_{\mathrm{solv}}H_{\mathrm{m}}^{\infty}$, corresponding to the transfer of 1 mol of solute from the ideal gaseous phase to aqueous solution at i.d. was derived by combining molar enthalpy of solution at i.d., $\Delta_{\mathrm{sol}}H_{\mathrm{m}}^{\infty}$, and standard molar enthalpy of sublimation, $\Delta_{\mathrm{sub}}H_{\mathrm{m}}^{\circ}$, at 298.15 K:

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

The enthalpies of solvation at 298.15 K for thiourea and the five *N*-alkylthioureas together with the enthalpies of solution and sublimation[23] used for their derivation are presented in Table 3, columns 2 to 4. The enthalpies of solvation for urea and corresponding *N*-alkylureas obtained by us[18,19] are reported for comparison (column 6). $\Delta_{\mathrm{solv}}H_{\mathrm{m}}^{\infty}$ values progressively increase as a function of the alkyl chain length, displaying slightly higher values than those of *N*-alkylureas, except T(1,1,3,3)MTU. This behavior appears in agreement with the fact that thiourea and substituted thioureas have slightly higher dipole moments [(0.1 to 0.3) D units] than urea and substituted ureas as reported by Kumler and Fohlen.[30] These authors also show that *N*-alkylureas and *N*-alkylthioureas have dipole moments about 1 D unit higher than those of simple amides and ascribed this to the greater resonance energy of the two equivalent resonating forms with the separation of charge. Thiourea's moment, higher than for urea and in apparent contradiction with the electronegativity values of sulfur and oxygen atoms, was later explained by a quantum mechanical study by Orita et al.[31] and then confirmed by an ab initio molecular orbital theory study by Weiqun et al.[32] Both papers concluded that, in contrast to urea, the C—N bond is enhanced, while the polarity of C—S bond increases. It was also shown that, in spite of the common view that —S···H bonds are weaker than —O···H bonds, the total interaction energies are likely the same in the region of carbonyl and thyonil groups.[33] This feature is in agreement with an enhanced bonding ability of the sulfur atom brought about by the weakening of the C—S bond mentioned above.

As alkyl groups substitute the H atoms into thiourea, the hydrophobic character of the molecule and its nitrogen region progressively increases as a function of the number of alkyl carbon atoms, and the solvation enthalpy becomes more exothermic, as previously reported for ureas.[18,19] In Figure 1, a linear dependence of the solvation enthalpy on the number of C atoms of alkyl substituents for both *N*-alkylthioureas and *N*-alkylureas is depicted. The slopes, representing the solvation enthalpy of the methylene group, were $(-4.5 \pm 0.7)\ \mathrm{kJ \cdot mol^{-1}}$ and $(-3.0 \pm 0.4)\ \mathrm{kJ \cdot mol^{-1}}$,[15] respectively. $\Delta_{\mathrm{solv}}H_{\mathrm{m}}^{\infty}$ [CH$_2$] for thioureas appears thus in reasonable agreement with earlier results for various series of homologous alkyl compounds.[3,6,7,26,34−36] T(1,1,3,3)MTU was not considered for linearization since its solvation enthalpy strongly deviates from the linear plot (Figure 1). The considerably low value of $\Delta_{\mathrm{solv}}H_{\mathrm{m}}^{\infty}$ [T(1,1,3,3)MTU] should be attributed to both the steric hindrance provoked by bulky methylene groups and the intrinsic nitrogen atom inability to form hydrogen bonds with water. In fact, the hydration scheme reported for thiourea indicates a maximum number of only four water molecules directly bound to thiourea since the *trans*-NH bonds are not able to disrupt the water—water bonds, a situation different from that encountered in urea which binds five water molecules.[31] Ab initio studies on the interactions of water

Table 1. Experimental Molar Enthalpies of Solution in Water, $\Delta_{\mathrm{sol}}H_{\mathrm{m}}$, for Thiourea and Five *N*-Alkylthioureas at T = (296.84, 302.45, and 306.89) K for Different Molality, m, Values[a]

	m	$\Delta_{\mathrm{sol}}H_{\mathrm{m}}$
compound	10^{-3} mol·kg^{-1}	kJ·mol^{-1}
TU	T = 296.84 K	
	6.95	22.65
	9.10	22.55
	9.47	22.48
	11.58	22.59
	T = 302.45 K	
	4.86	22.84
	7.52	22.80
	9.60	22.86
	T = 306.89 K	
	2.76	22.95
	5.59	22.80
	5.82	22.88
	12.47	22.91
MMTU	T = 296.84 K	
	6.76	22.78
	7.95	22.92
	8.84	22.74
	10.90	22.89
	T = 302.45 K	
	7.80	23.34
	10.34	23.27
	11.60	22.54
	T = 306.89 K	
	8.96	23.15
	11.09	23.20
	11.71	23.10
D(1,3)ETU	T = 296.84 K	
	6.94	15.28
	8.45	15.24
	9.73	15.37
	T = 302.45 K	
	6.20	16.53
	8.49	16.32
	13.50	16.42
	T = 306.89 K	
	8.05	17.66
	8.25	17.61
	10.47	17.61
METU	T = 296.84 K	
	1.16	24.43
	2.31	24.50
	2.96	24.71
	4.01	24.75
	T = 302.45 K	
	1.94	24.65
	2.88	24.62
	3.45	24.48
	3.63	24.64
	T = 306.89 K	
	2.53	25.22
	13.62	25.24
	17.10	25.20
D(1,3)MTU	T = 296.84 K	
	10.77	13.74
	12.90	14.20
	16.63	13.65
	19.30	14.05
	T = 302.45 K	
	6.02	14.41
	6.50	14.25
	9.58	14.21
	T = 306.89 K	
	2.97	15.32
	3.75	15.28
	8.97	15.34
T(1,13,3)MTU	T = 296.84 K	
	1.90	15.94
	3.40	15.80
	5.67	15.90
	T = 302.45 K	
	2.67	17.21
	3.62	17.30
	4.09	17.22
	5.78	17.18
	T = 306.89 K	
	2.87	18.24
	3.92	18.22
	4.29	18.18
	5.40	18.04

[a] For measurement uncertainty, see the Calorimetric Measurements section.

with T(1,1,3,3)MTU and T(1,1,3,3)MU concluded that the nitrogen atom of T(1,1,3,3)MTU is no longer able to interact with the hydrogen atom of water, while the nitrogen atom of T(1,1,3,3)MU still form a hydrogen bond with water. Nonetheless, in the neighborhood of the carbonyl/thyonil group the total T(1,1,3,3)MU−water and T(1,1,3,3)MTU−water energies are nearly identical.[33]

The contribution of the functional group (FG) to the solvation enthalpy of *N*-alkylthioureas at T = 298.15 K was derived using a simple additivity scheme based on the subtraction from the

Table 2. Molar Enthalpies of Solution at Infinite Dilution in Water, $\Delta_{\text{sol}}H_{\text{m}}^{\infty}$, for Thiourea and Five *N*-Alkylthioureas at *T* = (296.84, 302.45, and 306.89) K, and Their Interpolated Values at 298.15 K from eq 1

	$\Delta_{\text{sol}}H_{\text{m}}^{\infty\,a}$/ kJ·mol^{-1}						
compound	N^b	*T* = 296.84 K	N^b	*T* = 302.45 K	N^b	*T* = 306.89 K	*T* = 298.15 K
TU	4	22.70 ± 0.23	3	22.81 ± 0.09	4	22.89 ± 0.08	22.73 ± 0.19 22.57[c]
MMTU	4	22.69 ± 0.29	3	22.98 ± 0.59	4	23.23 ± 0.36	22.76 ± 0.39
METU	4	24.28 ± 0.09	4	24.74 ± 0.20	3	25.23 ± 0.03	24.38 ± 0.13
D(1,3)MTU	4	13.81 ± 0.73	3	14.59 ± 0.28	3	15.28 ± 0.04	13.99 ± 0.62
D(1,3)ETU	3	15.04 ± 0.31	3	16.51 ± 0.26	3	17.73 ± 0.16	15.38 ± 0.30
T(1,1,3,3)MTU	3	15.90 ± 0.15	4	17.30 ± 0.10	4	18.43 ± 0.04	16.23 ± 0.14

[a] Data in columns 3, 5, and 7 are linearly extrapolated values at *m* = 0 with their uncertainties at a 95 % confidence level. Data in column 8 from eq 1 and associated uncertainties are calculated by the error propagation rule. [b] Number of experimental determinations. [c] Reference 29.

Table 3. Molar Enthalpies of Solvation in Water at Infinite Dilution at *T* = 298.15 K of Thiourea and *N*-Alkylthioureas from Equation 2 Compared with Urea and Corresponding *N*-Alkylureas

	$\Delta_{\text{sol}}H_{\text{m}}^{\infty}$	$\Delta_{\text{sub}}H_{\text{m}}^{\text{o}\,a}$	$\Delta_{\text{solv}}H_{\text{m}}^{\infty}$		$\Delta_{\text{solv}}H_{\text{m}}^{\infty}$
compound	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}	compound	kJ·mol^{-1}
TU	22.73 ± 0.19	112.0 ± 2	−89.3 ± 2	U	−81.8 ± 0.6[b]
MMTU	22.76 ± 0.39	112.9 ± 3	−90.1 ± 3	MMU	−85.0 ± 0.5[b]
METU	24.38 ± 0.13	118.8 ± 5	−94.4 ± 5	MEU	−89.0 ± 1.3[b]
D(1,3)MTU	13.99 ± 0.62	111.8 ± 3	−97.8 ± 3	D(1,3)MU	−87.7 ± 0.4[c]
D(1,3)ETU	15.38 ± 0.30	121.7 ± 3	−106.3 ± 3	D(1,3)EU	−94.7 ± 0.3[c]
T(1,1,3,3)MTU	16.23 ± 0.14	84.5 ± 3	−68.3 ± 2	T(1,1,3,3)MU	−90.6[c]

[a] Reference 23. [b] Reference 18. [c] Reference 19. Uncertainties of $\Delta_{\text{solv}}H_{\text{m}}^{\infty}$ calculated by the error propagation rule.

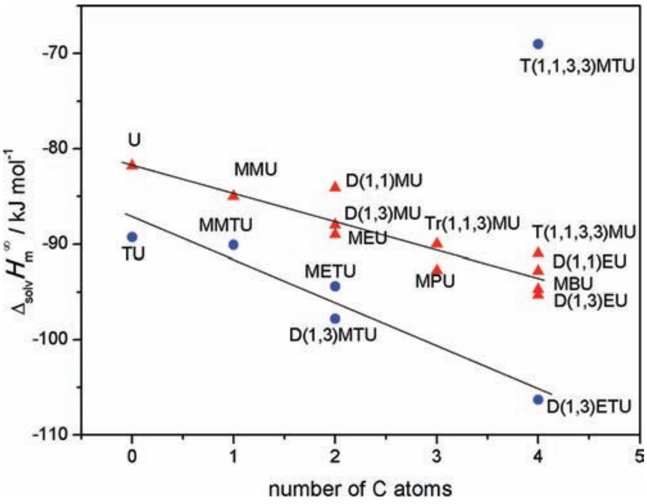

Figure 1. Molar enthalpies of solvation at i.d. as a function of the number of C atoms at *T* = 298.15 K for thiourea and *N*-alkylthioureas. Values for urea and mono-, di-, tri-, and tetra-*N*-alkylureas are plotted for comparison.

experimental $\Delta_{\text{solv}}H_{\text{m}}^{\infty}$ of each compound the sum of solvation enthalpies of the alkyl groups in the molecule:

$$\Delta_{\text{solv}}H_{\text{m}}^{\infty}[\text{FG}] = \Delta_{\text{solv}}H_{\text{m}}^{\infty}[N\text{-alkylthiourea}] - \sum \Delta_{\text{solv}}H_{\text{m}}^{\infty}[\text{alkylgroup}] \quad (3)$$

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

			$\Delta_{\text{solv}}H_{\text{m}}^{\infty}$ [FG]/ kJ·mol^{-1}	
N-alkyl derivatives	N^a	FG	X = S[b]	X = O[c]
monoalkyl	2	NH−CX−NH$_2$	−81.7	−77.0
1.3-dialkyl	2	NH−CX−NH	−81.0	−71.3
tetraalkyl	1	N−CX−N	−35.2	−57.5

[a] *N* = number of *N*-alkylureas. [b] Estimated by eq 3. [c] Reference 19.

where the enthalpy of solvation of the methylene group (−4.5 kJ·mol^{-1}) is from this paper and that of the methyl group (−8.28 kJ·mol^{-1}) is from Makhatadze and Privalov.[37]

$\Delta_{\text{solv}}H_{\text{m}}^{\infty}$ [FG] values listed in Table 4 are practically identical for monoalkylthioureas and 1,3-dialkylthioureas, unlike monoalkylureas and 1,3-dialkylureas, and more negative. These results are consistent with a prevailing role of the sulfur atom of the thiocarbonyl in the hydrophilic hydration of thioureas. By contrast, *N*-alkylureas display $\Delta_{\text{solv}}H_{\text{m}}^{\infty}[\text{FG}]$ values progressively lower from mono-, to di-1,3-, di-1,1,-, tri-1,1,3-, and tetra-1,1,3,3-alkylderivatives, suggesting a significant and modulated by alkyl groups topography contribution of the nitrogen atom to the hydrophilic hydration.[19] The enthalpy of solvation of the [N−CS−N] group, accounting for the hydrogen bonds in the thyonyl group region only, is

Table 5. Partial Molar Heat Capacities at Infinite Dilution, $C^{\infty}_{p,2}$, in Water at 298.15 K for Thiourea and *N*-Alkylthioureas from Equation 4

	$\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$	$C^{*}_{p,\mathrm{m}}(\mathrm{cr})$[a]	$C^{\infty}_{p,2}$		$\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$	$C^{\infty}_{p,2}$[b]
compound	$\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$	$\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$	$\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$	compound	$\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$	$\mathrm{J \cdot K^{-1} \cdot mol^{-1}}$
TU	18.9 ± 1.5 18.6 ± 0.9[c]	96.2 ± 0.2	115.1 ± 1.5	U	−18.95 ± 1.15[b]	74.2 ± 1.2[b]
MMTU	53.6 ± 2.6	115.4 ± 0.4	169.0 ± 2.6	MMU	27.85 ± 0.92[b]	143.9 ± 1.3[b]
METU	94.0 ± 4.9	150.4 ± 0.7	244.4 ± 4.9	MEU	75.59 ± 1.15[b]	227.1 ± 1.4[b]
D(1,3)MTU	146.0 ± 7.1	150.8 ± 0.7	296.8 ± 7.1	D(1,3)MU	136.3 ± 8[d]	269.6 ± 8[d]
D(1,3)ETU	267.4 ± 14.6	201.5 ± 0.2	468.9 ± 14.6	D(1,3)EU	233.7 ± 14[d]	452.7 ± 14[d]
T(1,1,3,3)MTU	251.7 ± 10.8	191.1 ± 0.3	442.8 ± 10.8	T(1,1,3,3)MU	171.1 ± 13[d]	400.7 ± 13[d]

[a] Reference 24. [b] Reference 18. [c] Reference 29. [d] Reference 19. Uncertainties of both $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ and $C^{\infty}_{p,2}$ are calculated by the error propagation rule.

much less negative compared to that of the [N−CO−N] group, as expected.

Partial Molar Heat Capacity. The partial molar heat capacity at infinite dilution at T = 298.15 K, $C^{\infty}_{p,2}$, was calculated by summing the heat capacity change due to the solution process, $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$, and the molar heat capacity of pure compounds at the same temperature:

$$C^{\infty}_{p,2} = \Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}} + C_{p,\mathrm{m}}(\mathrm{cr}) \tag{4}$$

where $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ for thiourea and *N*-alkylthioureas was obtained from the slope of eq 1:

$$b = (\partial \Delta_{\mathrm{sol}}H^{\infty}_{\mathrm{m}}/\partial T)_p = \Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}} \tag{5}$$

and $C_{p,\mathrm{m}}(\mathrm{cr})$ values were from an earlier paper[23] by some of us.

It should be noted that due to this method of calculating $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ significant uncertainty may affect the final values of $C^{\infty}_{p,2}$. In our case uncertainties of $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ values are 8 % or less. $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$, $C_{p,\mathrm{m}}(\mathrm{cr})$, and $C^{\infty}_{p,2}$ of thiourea and its *N*-alkyl derivatives are given in Table 5, columns 2 to 4, together with both the $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ and the $C^{\infty}_{p,2}$ values of urea and corresponding *N*-alkylureas, columns 6 and 7. Our $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ for thiourea is again in excellent agreement with the value reported by Taniewska-Osińska and Pałecz,[29] while no data for thiourea *N*-alkyl derivatives are available so far. It is worth noting that $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ is positive for thiourea ($19\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$) and negative for urea ($-19\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$),[18] whereas $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ of both *N*-alkylthioureas and *N*-alkylureas are all positive and progressively larger, the former displaying decisively higher values. It is known that $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ differentiates by sign between apolar groups (positive) and polar groups (negative).[38−40] It increases upon hydrophobic hydration of apolar compounds, while the hydration of polar compounds causes a decrease in heat capacity.[41−43] Our results are consistent with earlier thermodynamics,[16,44] dielectric spectroscopy,[10] and neutron scattering[8] studies, as well as molecular dynamics simulations[9] which conclude that urea and thiourea are characterized by weak solute−solvent interactions. In addition, the opposite sign of urea and thiourea solution heat capacity change values suggest that hydrophilic interactions are still prevailing in urea hydration, while hydrophobic interactions becomes predominating in thiourea hydration. In the view of the structure-making and structure-breaking model,[1] we can say that urea and thiourea oppositely act toward water structure. The thiourea low and positive $\Delta_{\mathrm{sol}}C^{\infty}_{p,\mathrm{m}}$ value confirms the intrinsic lower capability of thiourea's nitrogen region to form hydrogen bonds with water.[31−33] This feature, in turn, explains the slightly higher $C^{\infty}_{p,2}$ values of *N*-alkylthioureas.

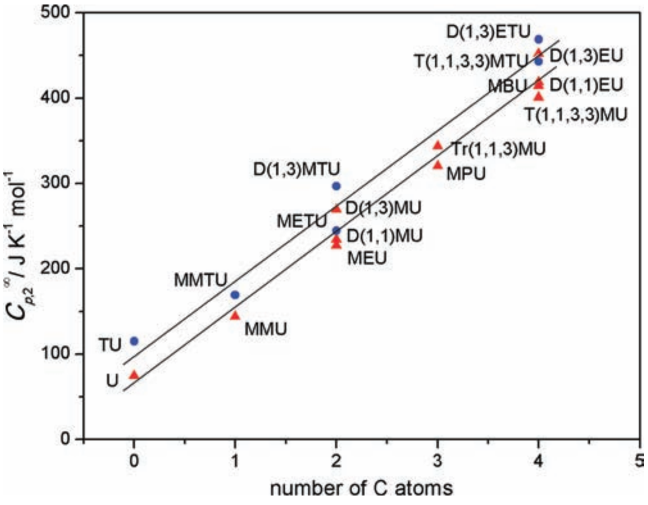

Figure 2. Partial molar heat capacities at i.d. as a function of the number of C atoms at T = 298.15 K for thiourea and *N*-alkylthioureas. Values for urea and mono-, di-, tri-, and tetra-*N*-alkylureas are plotted for comparison.

By plotting the $C^{\infty}_{p,2}$ of *N*-alkylthioureas as a function of the number of alkyl C atoms, a slope of $(88.5 \pm 6.8)\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$ was obtained, in very good agreement with that we previously found for mono-, di-, tri-, and tetra-*N*-alkylureas, $(88.9 \pm 2.3)\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$,[19] (Figure 2) as well as for *N*-acetylamino acid amines, $(89.3 \pm 0.6)\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$.[7] Similar average $C^{\infty}_{p,2}[\mathrm{CH_2}]$ values were reported for various monofunctional alkyl componds ($89.6\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$)[36,45] as well as for *N*-substituted alkylamides, carboxylic acids, and their sodium salts ($90.85\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$).[46] The increase of $C^{\infty}_{p,2}$ in *N*-alkylthioureas depends on both alkyl chain length and topography which determines a progressive increase of water-accessible surface area, steric hindrance of polar moieties, and inductive effects.[47]

The partial molar heat capacities of the functional groups were derived by means of the additive method used for evaluating their contribution to solvation enthalpies:

$$C^{\infty}_{p,2}[\mathrm{FG}] = C^{\infty}_{p,2}[N\text{-alkylthiourea}] - \sum C^{\infty}_{p,2}[\mathrm{alkylgroup}] \tag{6}$$

Table 6. Partial Molar Heat Capacity of the Functional Groups, $C_{p,2}^{\infty}$[FG], in Monoalkyl, 1,3-Dialkyl, and Tetraalkyl Derivatives of Thiourea Compared with Corresponding *N*-Alkylureas

			$C_{p,2}^{\infty}$ [FG]/ kJ·mol^{-1}	
N-alkyl derivatives	N^a	FG	X = S^b	X = O^c
monoalkyl	2	NH−CX−NH$_2$	5.7	−15
1,3-dialkyl	2	NH−CX−NH	−19.2	−43
tetraalkyl	1	N−CX−N	−185.2	−222

[a] *N* = number of *N*-alkylureas. [b] Estimated by eq 6. [c] Reference 19.

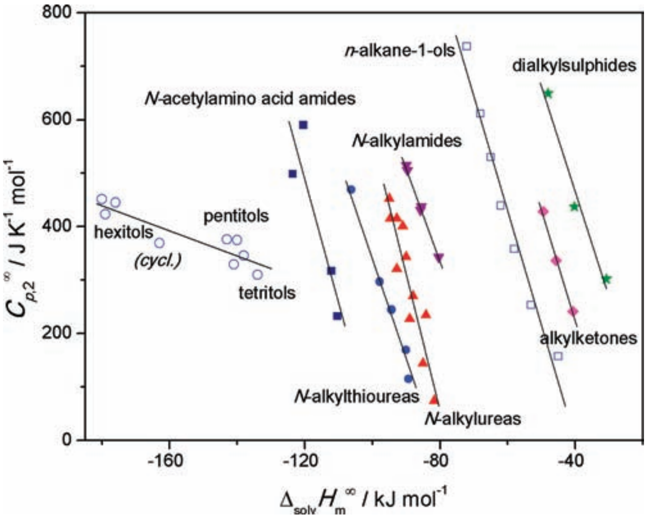

Figure 3. Interplay between partial molar heat capacity and molar enthalpy of solvation at i.d. at *T* = 298.15 K for *N*-alkylthioureas, blue ●, compared with *N*-alkylureas, red ▲, and other series of compounds bearing single or multiple hydrophilic functional groups: blue ○, polyhydric alcohols; blue ■, *N*-acetylamino acid amides; purple ▼, *N*-alkylamides; blue □, *n*-alkane-1-ols; pink ◆, alkylketones; green ★, dialkylsulfides.

where the partial molar heat capacitiy of the methylene group (89 J·K^{-1}·mol^{-1}) is from this paper and that of the methyl group (157 J·K^{-1}·mol^{-1}) is from Nichols et al.[45] Results are listed in Table 6 and compared with the values similarly obtained for *N*-alkylureas.[18,19] The substitution of hydrogen atoms by methylene groups progressively enhances the hydrophobic interactions and determines a structure-making propensity proportional to the number and length of alkyl substituents in both *N*-alkylureas and *N*-alkylthioureas. However, the less negative values of $C_{p,2}^{\infty}$[FG] in *N*-alkylthioureas are likely to be due to the less hydrophilic feature of the C−N bonds compared to *N*-alkylureas.[31−33]

Finally $C_{p,2}^{\infty}$ was plotted against $\Delta_{solv}H_m^{\infty}$ for both the *N*-alkylthioureas and the *N*-alkylureas[18,19] (Figure 3). These values fall on lines with slopes of (−0.019 ± 0.001) K^{-1} and (−0.026 ± 0.003) K^{-1}, respectively, comparable with those given by *N*-acetyl substituted acid amines, (−0.023 ± 0.007) K^{-1},[7] *N*-alkylamides, (−0.018 ± 0.006) K^{-1},[3,45] dialkylsulfides, (−0.020 ± 0.004) K^{-1},[34] alkylketones, (−0.021 ± 0.001) K^{-1},[26,48] and *n*-alkan-1-ols, (−0.022 ± 0.002) K^{-1},[35,45] reported in Figure 3, too. Moreover, these slope values are comparable with the average value found for *n*-alkanes, −0.022 K^{-1}.[49] Such behavior accounts for a prevailing hydrophobic hydration that promotes a smaller increase in $\Delta_{solv}H_m^{\infty}$ in comparison with that of $C_{p,2}^{\infty}$, a parameter highly correlated with first solvation shell structure of apolar solutes.[50] Polyhydric alcohols,[51] by contrast, display a much less steep plot (Figure 3) since their strong hydrophilic character determines a sharper increase of $\Delta_{solv}H_m^{\infty}$ and a much lower $C_{p,2}^{\infty}$ increase following the alkyl chain lengthening. It can be thus inferred that hydrophobic hydration is the prevailing effect in both *N*-alkylureas and *N*-alkylthioureas.

■ CONCLUSIONS

(i) The enthalpy of solvation and partial molar heat capacity at i.d. of thiourea and its mono-, di-, and tetraalkylderivatives display a linear dependence on the number of C atoms in the alkyl chains with slopes of $\Delta_{solv}H_m^{\infty}[CH_2]$ = −4.5 kJ·mol^{-1} and $C_{p,2}^{\infty}[CH_2]$ = 88.5 J·K^{-1}·mol^{-1}, respectively.

(ii) The enthalpies of solvation at i.d. of functional groups in mono- and di-*N*-alkylthioureas are a little more exothermic than those for urea and *N*-alkyureas, indicating a somewhat more efficient hydrogen bonding ability of thionyl group compared with a carbonyl group.

(iii) A comparison between the solvation enthalpies of [N−CS−N] and [N−CO−N] functional groups confirms the intrinsic inability of the T(1,1,3,3)TMTU nitrogen atoms to form hydrogen bonds with water already reported in the literature.[31−33]

(iv) The small, but with opposite sign, solution heat capacity changes, $\Delta_{sol}C_{p,m}^{\infty}$, of thiourea and urea indicate that the latter acts as a weak water structure-breaker, whereas thiourea appears to slightly enhance the water H-bond network.

(v) The large and positive $\Delta_{sol}C_{p,m}^{\infty}$ values of *N*-alkylthioureas confirm they act similarly to *N*-alkylureas, promoting water structuring around alkyl groups.

(vi) The interplay between partial molar heat capacity and molar enthalpy indicate that hydrophobic interactions prevails in *N*-alkylthiourea hydration as already reported for *N*-alkylureas.[18]

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Notes

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