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Enthalpies of solution of tetramethyl-bis-urea (*Mebicarum*) in amides and acetone at 298.15 K

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Abstract

The enthalpies of solution of 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione or tetramethyl-bis-urea (the drug *Mebicarum*) in formamide, *N*-methylformamide, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, *N*,*N*,*N*′,*N*′-tetramethylurea, and acetone were measured at 298.15 K. Standard enthalpies of solution and transfer from one solvent to another were computed. The enthalpies of solution of the solute were found to be endothermic and weak depending on the nature of methylation in an amide molecule. It was concluded that the solvent proton-donor ability and existing steric hindrances for H-bonding and other interparticle interactions play the key role in solvation of tetramethyl-bis-urea.

Keywords: Tetramethyl-bis-urea; Formamide and its methyl-substituted analogues; Tetramethylurea; Acetone; Enthalpies of solution

1. Introduction

Tetramethyl-bis-urea (Fig. 1), referred to below as TMbU, plays an important role among alkyl-substituted bicyclic derivatives of urea (the octane-derived bis-ureas or glycolurils) [1,2]. This is determined by the fact that TMbU is used in medicine as a polyfunctional pharmaceutical (known as the *Mebicarum*) [2,3]. Interest in TMbU also stems from peculiarities of its hydration (solvation). Previously [4–7], it was ascertained that the crystalline TMbU dissolves in water with an endothermic effect ($\Delta_{sol}H^{\circ} = 3.67 \pm 0.02$ kJ mol^{-1} at 298.15 K), and its hydration should be treated as a superposition of two mechanisms, hydrophobic and hydrophilic, with the latter predominating.

Meanwhile, some questions important for biochemistry concerning the state of this compound in solution, solvation, and the structure of the solvation environment still remain unanswered. Up to now, virtually no data on the specific features of solvation of TMbU molecules by organic solvents (except for low-molecular-weight alkanols [4,8]), in particular amides, are available, although some of the amides can be regarded as molecular intermediates towards the solute in question. First of all, it is tetramethylurea that has four methyl groups (like TMbU, see in Fig. 1) and properties of a methyl-substituted amide due to the presence of a $OCN(CH_3)_2$ grouping in its molecule [9,10].

This paper reports experimental molar enthalpies $\Delta_{sol}H^{m}$ (and standard those $\Delta_{sol}H^{\circ}$) of solution of TMbU in formamide (hereinafter, FA), *N*-methylformamide (NMF), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), *N*,*N*,*N*′,*N*′-tetramethylurea (TMU), and acetone (as a comparison solvent) at 298.15 K.

2. Experimental

TMbU or 2,4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0] octane-3,7-dione (Codex quality, $M = 198.23$ g mol^{-1}, m.p. 501 ± 2 K) synthesized at JSC Automated Technologies (Vologda, Russia) was purified by washing with diethyl ether, with subsequent double recrystallization from a (chloroform + ethanol) mixture according to [4,5]. The check of the preparation purity, carried out using an Avatar 360 high-resolution FT IR spectrometer, showed that the TMbU content in the sample was at list 99.5 wt%. Before each measurement, the TMbU sample was dried *in vacuo* at *ca.* 343 K for 2 days and then stored in a vacuum dessicator over P_2O_5.

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Table 1
Sources, purities, densities (ρ, g cm^{-1}) and refractive indexes (n_D) of solvents used at 298.15 K

Solvent	Source	Purity/water impurity (wt%)[a]	ρ		n_D	
			Expt.	Lit. [11]	Expt.	Lit. [11]
FA	Merck	99.5 ± 0.03	1.12915	1.1292	1.4465	1.4468
NMF	Aldrich	99.0 ± 0.02	0.99892	0.9988	1.4308	1.4300
DMF	Aldrich	99.5 ± 0.03	0.94393	0.9440	1.4276	1.4282
DMA	Aldrich	99.8 ± 0.02	0.93650	0.9366	1.4360	1.4356
TMU	Fluka	99.0 ± 0.02	0.96211	0.9619	1.4494	1.4493
Acetone	Fluka	99.9 ± 0.01	0.78465	0.7844	1.3563	1.3560

[a] The content of water dissolved in a solvent is maximal.

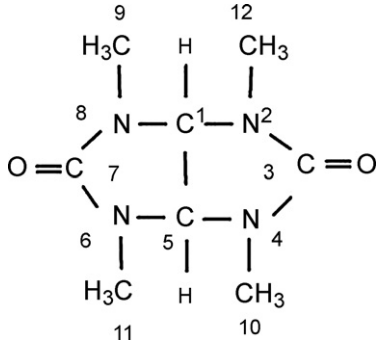

Fig. 1. Tetramethyl-bis-urea (*Mebicarum*) molecule.

Characterization data for solvents under study are listed in Table 1. FA, DMF, DMA and acetone were used without further purification. NMF and TMU were dried on 4 Å molecular sieves (which had been dried in vacuum above 473 K for more than 15 h) for 2 days and fractionally distilled at reduced pressure of about 20 mmHg. The water content of these liquids (see in Table 1) was determined with a Karl Fisher titration. Purity of each solvent was checked by measuring the density and refractive index at 298.15 K. Densities were measured using a precise vibrating-tube densimeter [6,12] with an accuracy of $\pm(1 \times 10^{-5})$ g cm^{-3}. Refractive indexes were measured with a Pulfrich refractometer (PR 2). The accuracy of n_D measured is on the order of ±0.0001. Table 1 shows that our results agree with values obtained from the literature [11]. All solvents were stored in brown glass bottles under air-tight conditions.

The experimental enthalpies of solution $\Delta_{sol}H^m$(TMbU) were measured at 298.15 ± 0.005 K using an isoperibol (ampoule-type) hermetic calorimeter fitted with a 60 cm^3 reaction vessel and electrical calibration. The thermometric and thermal sensitivities of the apparatus were, respectively, 10^{-5} K and 2×10^{-3} J/mm of the recording scale. The relative random error of measurements did not exceed 0.5%. The calorimeter was tested by measuring (in a series of 10 experiments) the enthalpies of solution of potassium chloride (KCl) in water at 298.15 K according to [13–15]. The agreement between our ($\Delta_{sol}H^m$ ($m = 0.111$ mol kg^{-1}) = 17.60 ± 0.04 kJ mol^{-1} and $\Delta_{sol}H^\circ$ = 17.23 ± 0.07 kJ mol^{-1})[1] and recommended literature values (17.56 ± 0.02 [13]/17.58 ± 0.02 [14] kJ mol^{-1} and 17.22 ± 0.04 kJ mol^{-1} [13,15], respectively) was found to be excellent. The calorimeter setup and experimental procedure were described in detail previously [16–18].

3. Results

The calorimetric measurements showed that the $\Delta_{sol}H^m$ values in the high dilution region do not depend (within the experimental error) on m those ranging between 0.004 and 0.0075 (see footnote 1). Therefore, the molar enthalpies of TMbU dissolution at infinite dilution, i.e., the limiting or standard molar enthalpies of solution ($\Delta_{sol}H^\circ$) have been calculated as average values $|\Delta_{sol}H^m|_{av}$ in the range of our measured results. The confidence interval half with ($\pm\,\xi_n$) of the $\Delta_{sol}H^\circ$ value was determined by the Peters formula [19] for the root-mean-square error with correction for a Student criterion of $t_{0.95} = 2.78$: $\xi_n = t_{0.95}4/5\sum_{i=1}^{n}|x_i - \tilde{x}_i|/[n(n-1)^{1/2}]$, where n (=5) is the number of runs, $x_i = \Delta_{sol}H^m$, and $\tilde{x}_i = |\Delta_{sol}H^m|_{av}$. The experimental data obtained for TMbU are summarized in Table 2.

4. Discussion

According to the data in Table 2, the dissolution of TMbU in all the solvents studied, like that in water (see above) and alkanols (C_1–C_4) [4,8], is endothermic. However, unlike the latter case, the endothermicity of the given process in amides and acetone as a whole is lower. The difference in $\Delta_{sol}H^\circ$ (TMbU) is the largest between FA and acetone and becomes noticeably smaller on going from the latter to methyl-substituted amides except

Table 2
Standard enthalpies of solution of tetramethyl-bis-urea in amides and acetone at 298.15 K

Solvent	m[a] (× 10^3 mol (kg solvent)$^{-1}$)	$\Delta_{sol}H^\circ$[b] (kJ mol^{-1})
Formamide	4.39–5.32	7.88 ± 0.05
N-Methylformamide	4.66–5.41	17.45 ± 0.09
N,*N*-Dimethylformamide	3.91–5.86	14.69 ± 0.04
N,*N*-Dimethylacetamide	4.84–7.14	15.49 ± 0.08
N,*N*,*N*′,*N*′-Tetramethylurea	4.87–5.56	15.61 ± 0.08
Acetone	6.22–7.53	17.87 ± 0.08

[a] Concentration ranges in which the $\Delta_{sol}H^m$ values for TMbU were averaged.
[b] The arithmetic mean $|\Delta_{sol}H^m|_{av} = \Delta_{sol}H^\circ$ values found from the results of five measurements.

[1] Here m is the solution molality [moles of the solute (TM*b*U) per 1 kg of the solvent (amide or acetone)].