

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.

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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 ($\Delta_{\text{sol}}H^\circ = 3.67 \pm 0.02 \text{ kJ mol}^{-1}$ 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 $\text{OCN}(\text{CH}_3)_2$ grouping in its molecule [9,10].

This paper reports experimental molar enthalpies $\Delta_{\text{sol}}H^m$ (and standard those $\Delta_{\text{sol}}H^\circ$) 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, $M = 198.23 \text{ g mol}^{-1}$, m.p. $501 \pm 2 \text{ K}$) 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⁻³) 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.

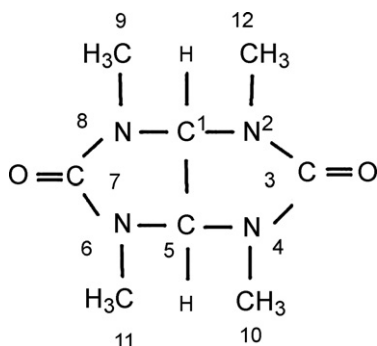


Fig. 1. Tetramethyl-bis-urea (*Mebicarum*) molecule.

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 $\Delta_{\text{sol}}H^m$ (TMbU) were measured at 298.15 ± 0.005 K using an isoperibol (ampoule-type) hermetic calorimeter fitted with a 60 cm³ 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 ($\Delta_{\text{sol}}H^m$ ($m = 0.111$ mol kg⁻¹) = 17.60 ± 0.04 kJ mol⁻¹ and $\Delta_{\text{sol}}H^\circ = 17.23 \pm 0.07$ 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 $\Delta_{\text{sol}}H^m$ 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 ($\Delta_{\text{sol}}H^\circ$) have been calculated as average values $|\Delta_{\text{sol}}H^m|_{\text{av}}$ in the range of our measured results. The confidence interval half with ($\pm \xi_n$) of the $\Delta_{\text{sol}}H^\circ$ 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, $x_i = \Delta_{\text{sol}}H^m$, and $\tilde{x}_i = |\Delta_{\text{sol}}H^m|_{\text{av}}$. 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 (C₁–C₄) [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 $\Delta_{\text{sol}}H^\circ$ (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 ($\times 10^3$ mol (kg solvent) ⁻¹) | $\Delta_{\text{sol}}H^{\circ b}$ (kJ mol ⁻¹) |
|-----------------------------------|--|--|
| Formamide | 4.39–5.32 | 7.88 ± 0.05 |
| <i>N</i> -Methylformamide | 4.66–5.41 | 17.45 ± 0.09 |
| <i>N,N</i> -Dimethylformamide | 3.91–5.86 | 14.69 ± 0.04 |
| <i>N,N</i> -Dimethylacetamide | 4.84–7.14 | 15.49 ± 0.08 |
| <i>N,N,N',N'</i> -Tetramethylurea | 4.87–5.56 | 15.61 ± 0.08 |
| Acetone | 6.22–7.53 | 17.87 ± 0.08 |

^a Concentration ranges in which the $\Delta_{\text{sol}}H^m$ values for TMbU were averaged.

^b The arithmetic mean $|\Delta_{\text{sol}}H^m|_{\text{av}} = \Delta_{\text{sol}}H^\circ$ values found from the results of five measurements.

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

for NMF. Noteworthy is the comparability of the enthalpies of TMbU dissolution in DMA and TMU as well as in NMF and acetone.

A positive sign at the $\Delta_{\text{sol}}H^\circ$ value suggests that TMbU–amide and TMbU–acetone interactions are weaker than the interaction between molecules in the individual (crystalline) medium of the solute. Meanwhile, the quantity considered does not provide a complete information on the energy changes in the solvent structure induced by the solvation of TMbU molecules.

On the other hand, by definition, the limiting (standard) molar enthalpy of solution does not contain a contribution from the interactions between the solute molecules. Since the energy spent to destroy the crystal lattice of TMbU remains unaltered, the changes in $\Delta_{\text{sol}}H^\circ$ observed on going from one solvent to another are numerically equal to those in the standard enthalpy of solvation $\Delta_{\text{solv}}H^\circ(\text{TMbU})$, i.e., in the energy of the solute–solvent interaction upon replacement of the dissolving medium. For this reason, caused by the solvation of TMbU the degree of the solute–solvent molecular affinity in FA is substantially higher than that in each of the methyl-substituted amides including TMU, as well as in acetone (Table 2), showing the hydrogen-bonding effects play the decisive role in the solvation (amide-based) environment of the solute.

To facilitate the comparison procedure we have schematically depicted the data on $\Delta_{\text{sol}}H^\circ$ as the enthalpies of transfer $\Delta_{\text{tr}}H^\circ \equiv \delta\Delta_{\text{sol(v)}}H^\circ$ of TMbU from one solvent to the others (see Fig. 2). As follows from Fig. 2, the change in $\Delta_{\text{solv}}H^\circ$ caused by the transfer of TMbU from FA to NMF differs significantly from that induced by the transfer of this solute from NMF to DMF. Introduction of one methyl group on the *N*-proton position of FA, to form NMF, entails a rather sharp weakening of the solute solvation (the endothermicity of TMbU dissolution increases by *ca.* 9.6 kJ mol⁻¹, i.e., more than twice!). Conversely, solvation is enhanced going from NMF to DMF although in the given case the change in $\Delta_{\text{solv}}H^\circ$ (TMbU) is far less pronounced.

It is well known that FA and NMF are strongly self-associated through CO···HN hydrogen-bonding but DMF (and other *N,N*-

methyl-substituted amides) has no NH-group having that ability [20–22]. The energy of hydrogen bonds in NMF is slightly lower than that in FA because of the flexibility of the *N*-site-methylated chain structure of the former [21]. Intermolecular dipole–dipole and van der Waals interactions are prevailing in the pure DMF [21,22] although the dimerization of its molecules at the expense of CO···HC specific contacts also takes place [20,23].² However, there is a possibility that DMF molecules form strong hydrogen bonds with a proton-donor dissolved in the medium under consideration [21,22]. According to Fig. 1, the solute molecule has a bicyclic structure containing the >C(H)–C(H)<(bis) grouping or “glyoxal bridge” and two carbonyl groups (within the five-membered rings) capable of strong specific interaction through H-bonding. The hydrogen atoms connected at the glyoxal-bridge carbon atoms (i.e., methyne groups) also form hydrogen bonds both in TMbU crystals [2] and in amphiprotic media (such as water and alkanols [4,8]).

Considering of the results presented in Fig. 2 from this point of view led us to the conclusion that such a significant increase in the endothermicity of TMbU dissolution due to the replacement of FA with NMF can be explained mainly by a decrease in the proton-donating capacity of the amide and an increase in the effect of steric hindrances for H-bonding. The fact that FA has two acidic protons may allow it to hydrogen bond to a TMbU molecule without breaking H bonds between the solvent molecules. This would make the forming solvent–solute interactions the dominant factor and account for the large negative value of $\Delta_{\text{tr}}H^\circ$ in the case of TMbU transfer from acetone to FA (see Fig. 2). In contrast, a NMF molecule must break a solvent–solvent hydrogen bond for each solute–solvent hydrogen bond formed. This could explain the large difference between the values of $\Delta_{\text{solv}}H^\circ$ for FA and NMF. Besides the relatively minor difference in $\Delta_{\text{solv}}H^\circ$ for TMbU solutions in acetone and NMF suggests that CO···HN(HC) interactions in the latter system occur against the background of the more pronounced configurational rearrangements. It makes sense that the number of solvent molecules hydrogen-bonded to the electron-donor/acceptor sites of TMbU in NMF is smaller than in FA.

As regards DMF, the steric or configurational factor that complicates the formation of strong H-bonds in TMbU–NMF (FA) solvation complexes does not play the key role in this solvent (see Footnote 2). We are inclined to believe that the positive-to-negative sign inversion of $\Delta_{\text{tr}}H^\circ$ in FA → NMF → DMF transitions (see Fig. 2) is most likely due to superposition of several mutually cancelling enthalpic contributions in $\delta\Delta_{\text{sol(v)}}H^\circ$, that first of all are caused by decreasing of the steric hindrances for TMbU–solvent interactions and, as a consequence, by reducing of the energy expenditure at creating of the solvation cavity.

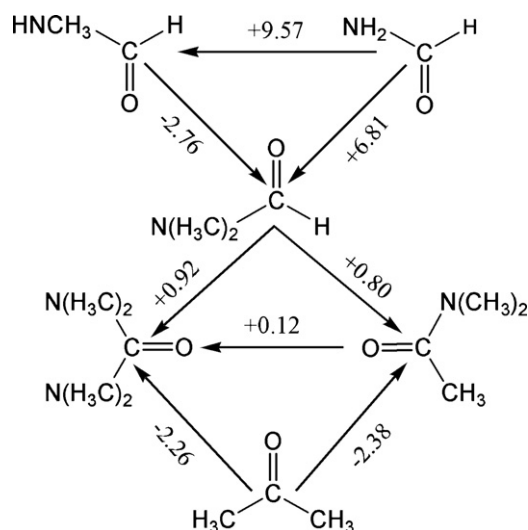


Fig. 2. Enthalpies of transfer of TMbU from one solvent to the other (energies are in kJ mol⁻¹).

² According to X-ray diffraction data [23], the two crystallographically independent molecules in DMF form four-membered centrosymmetric rings held together by C–H···O intermolecular interactions, two *via* the formyl protons, C···O (*ca.* 329.42 pm), and two involving methyl protons, C···O (*ca.* 341.42 pm). At the same time the structure of liquid DMF can, despite the strong hydrogen bond acceptor properties of the oxygen atom, be described without hydrogen bonding.

Further methylation of DMF, to form DMA, causes only insignificant weakening of TMbU solvation (a positive shift in $\Delta_{\text{sol(v)}}H^\circ$ of *ca.* 0.8 kJ mol⁻¹). Most interesting is the fact that the values of $\Delta_{\text{tr}}H^\circ$ for DMF \rightarrow TMU (DMA) transitions are close to each other (Fig. 2) despite obvious differences in the structural and solvating properties of DMA and TMU [11]. That is, DMF as a solvating medium for TMbU exhibits off-beat selectivity with respect to other amides containing a OCN(CH₃)₂ grouping. The given circumstance suggests that the molecular packing of DMF should be best suited for incorporating into it a TMbU molecule (having a “half-open book” conformation [1,2]), revealing the presence of additional steric incompatibilities during the formation of TMbU–DMA (TMU) solvation complexes of similar type.

It is possible that, when placed in DMF, a bicyclic TMbU molecule interacts with the solvation environment by means of both methine and carbonyl groups (i.e., through the H-formyl atom of the solvent molecule, as it is shown above). This is favored by the electron-accepting (proton-donating) ability of DMF being higher than that of DMA and TMU [24]. Based on the distribution schemes displayed in Fig. 2, one can also conclude that, on the whole, the nature of methyl-substitution in an amide molecule has a weak effect on the TMbU solvation. The van der Waals intermolecular contacts are not likely to be considered the main reason of structural changes in amides under the action of TMbU molecules. The given inference seems true for the N···O donor–acceptor interactions between the solute and solvent molecules, too.

Unfortunately, the data on the heats of TMbU dissolution in acetamide and *N*-methylacetamide at 298.15 K, which could confirm or reject the above assumptions, are lacking because of higher melting points of these amides. However, we believe that the configurational (steric) factor is the most important in the formation of a solvate shell around a TMbU molecule dissolved in each of the amides studied, as in infinitely dilute solutions of this solute in branched alkanols [8]. In addition to the above-mentioned data, it is illustrated both by the trends of $\Delta_{\text{sol(v)}}H^\circ$ (TMbU) changes in the acetone \rightarrow DMA \rightarrow TMU transitions (Fig. 2) and by the comparability of the $\Delta_{\text{sol}}H^\circ$ (TMbU) values for NMF and acetone (Table 2). In the former case, the replacement of both one and simultaneously two acetone methyl group(s) with amino group(s) results in the same change in $\Delta_{\text{sol(v)}}H^\circ$ (increase in $\Delta_{\text{sol}}H^\circ$ or decrease in $|\Delta_{\text{sol}}H^\circ|$) which is only about 2.4 kJ mol⁻¹. In the latter case, the $\Delta_{\text{sol(v)}}H^\circ$ values do not differ almost from each other (as can be seen from Table 2, a shift in $\Delta_{\text{sol}}H^\circ$ at TMbU transfer from NMF to acetone is *ca.* 0.4 \pm 0.1 kJ mol⁻¹ at 298.15 K) although the structure characteristics and solvating abilities of the solvent compared are significantly different [11,20,24].

5. Conclusion

From the aforesaid, we may claim that configurational (steric) effects are important in structure packings not only for pure amides (FA, NMF, DMF, DMA, and TMU) and acetone but also for TMbU solutions in the solvents specified. The solute molecules cause significant structural changes in the solvat-

ing media under comparison. These changes appearing in the enthalpic effects of TMbU dissolution are associated with the changes in intermolecular, basically, specific interactions (*via* H-bonding). The nature of methylation in an amide molecule has a weak effect on the TMbU solvation, as the whole, reflecting the stronger interaction to the more polar amides.

Meanwhile, despite the analysis of the experimental data performed using even such a structure-sensitive thermodynamic method as a solution calorimetry, we failed to find unambiguous answers to all the questions. One of them, perhaps the most important, was formulated in the beginning of Section 4. It is related to the establishment of a substantiated correlation between the energy characteristics or affinity parameters of the amide–amide and TMbU–amide (acetone/TMbU–acetone) interactions. This problem likely should be substantiated by performing additional studies based on experimental and theoretical approaches more informative regarding the structure of solutions.

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