Brief Communications

Effect of temperature on the H/D-isotope effects in the enthalpy of hydration of tetramethyl-bis-carbamide

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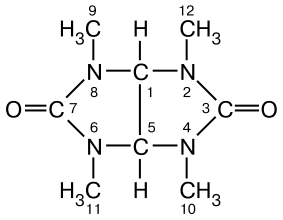
The heats of dissolution of tetramethyl-bis-carbamide (the pharmaceutical Mebicarum) in H_2O and D_2O were measured at 288.15, 298.15, and 318.15 K using a sealed microcalorimeter with an isothermal shell. The error of measurements did not exceed 0.2%. The limiting molar enthalpies of dissolution $\Delta_{sol}H_n^\infty$ and the H/D-isotope enthalpy effects of hydration $\delta\Delta_{hydr}H_n^\infty(H_2O \rightarrow D_2O)$ were determined. Different effects of temperature on the pattern of variation of $\delta\Delta_{hydr}H_n^\infty$ were found: when $T \leq 315$ K, this value is positive and decreases with T, while for $T \geq 315$ K, hydration of tetramethyl-bis-carbamide upon replacement of H_2O by D_2O progressively becomes less endothermic.

Key words: tetramethyl-bis-carbamide (Mebicarum), aqueous solutions, enthalpy of dissolution, hydration, H/D-isotope effects.

Tetramethyl-bis-carbamide (2,4,6,8-tetramethyl-2,4,6,8-tetraazobicyclo(3.3.0)octa-3,7-dione, below TM*b*U) is known, first of all, as the drug Mebicarum;[1] its molecular structure has been comprehensively studied.[2] However, data on the structure and thermodynamic properties of aqueous solutions of TM*b*U are virtually missing. These data would be useful for predicting the biological and physiological activities of TM*b*U and for targeted synthesis of other compounds of this class.



TM*b*U

Previously,[3] it was found that at 298.15 K the TM*b*U crystals dissolve in water with an endothermic effect ($\Delta_{sol}H_n^\infty \approx 3.67$ kJ mol^{-1}) that is ~2.6 kJ mol^{-1} greater than $\Delta_{sol}H_n^\infty(H_2O)$ for 1,3-dimethylcarbamide (1,3-DMU),[4] a molecular intermediate towards TM*b*U. Meanwhile, the difference between the standard enthalpies of dissolution in water of TM*b*U and hydrophobically hydrated 1,1,3,3-tetramethylcarbamide (TMU)[4,5] reaches 26 kJ mol^{-1}. These data attest to a predominantly hydrophilic nature of TM*b*U hydration, which should be even

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more obvious upon deuterium substitution in the solvent molecules, *i.e.*, with an increase in the degree of structurization.[6]

This communication reports the results of a calorimetric study of the enthalpy effects of TM*b*U dissolution in conventional and heavy (deuterated) water at 288.15—318.15 K.

The experimental measurements showed that the integral molar enthalpies of dissolution $\Delta_{sol}H_n^c$ in the high dilution region do not depend on the molal concentration c_m. Therefore, the arithmetic mean $|\Delta_{sol}H_n^c|_{av}$ values found from the results of four or five measurements were set equal to the limiting molar enthalpies of dissolution $\Delta_{sol}H_n^\infty$. The experimental data obtained for TM*b*U are summarized in Table 1.

It can be seen from Table 1 that dissolution of TM*b*U in the H/D-isotopomers of water is accompanied by heat absorption over the whole temperature range; with temperature rise, the dissolution becomes more endothermic.

A change in the isotope composition of the solvent as a whole has a slight influence on the $\Delta_{sol}H_n^\infty$ value. However, the sign of the H/D-isotope effect (IE) in the dissolution enthalpy of TM*b*U is inverted about 315 K (Fig. 1). At lower temperatures (T < 315 K), the IE value, $\delta\Delta_{sol}H_n^\infty(H_2O \rightarrow D_2O) = \Delta_{sol}H_n^\infty(D_2O) - \Delta_{sol}H_n^\infty(H_2O)$, is positive and decreases with an increase in T, whereas at higher temperatures (T > 315 K), the TM*b*U dissolution becomes less endothermic upon replacement of H_2O by D_2O.

The transfer function $\delta\Delta_{sol}H_n^\infty(H_2O \rightarrow D_2O)$ is identical, by definition, with the difference between the standard enthalpies of hydration ($\Delta_{hydr}H_n^\infty$) of the solute by usual and heavy water molecules. Hence, the transfer of TM*b*U molecules from H_2O to D_2O is accompanied by weakening of hydration at T < 315 K and by enhancement of hydration at T > 315 K.

Table 1. Limiting molar enthalpies of dissolution ($\Delta_{sol}H_n^\infty$) of tetramethyl-bis-carbamide in the H/D-isotopomers of water at various temperatures

Solvent	T/K	$c_m{}^a \cdot 10^4$ /mol (kg solvent)$^{-1}$	$\Delta_{sol}H_n^{\infty\,b}$ /kJ mol^{-1}
H_2O	288.15	6.6—9.4	1.96±0.13
	298.15	4.7—13.9	3.67±0.01
	318.15	6.2—13.1	7.03±0.03
D_2O	288.15	8.3—11.2	2.37±0.03
	298.15	4.6—6.7	3.87±0.01
	318.15	6.3—11.0	7.00±0.06

[a] Concentration ranges in which the $\Delta_{sol}H_n^c$ values for TM*b*U were averaged.

[b] The half-width of the confidence interval ($\pm\xi_m$) for the $\Delta_{sol}H_n^\infty$ was determined using the Peters formula[7] for the root-mean-square error with a correction for Student criterion $t_{0.95}$ = 2.78 (see Ref. 8): $\xi_m = 5t_{0.95}\sum_{i=1}^{n}|x_i - \bar{x}|\Big/\left[4n(n-1)^{1/2}\right]$, where n is the number of measurements, $x_i = \Delta_{sol}H_n^c$ and $\bar{x}_i = |\Delta_{sol}H_n^c|_{av}$.

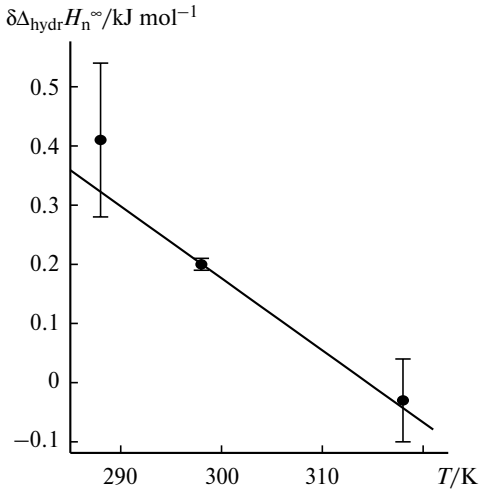

Fig. 1. Temperature dependence of the isotope effects in the enthalpy of hydration of tetramethyl-bis-carbamide (the vertical segments mark the confidence interval).

It is evident that different effects of temperature on the variation of the $\delta\Delta_{hydr}H_n^\infty(H_2O \rightarrow D_2O)$ value are directly related to the arrangement of the planar TM*b*U molecules in the structural matrix of water H- or D-isotopomer and their interaction with the molecules of the hydration environment. According to the recent NMR analysis[9] of the evolution of carbon chemical shifts (^{13}C) in H/D-isotope-substituted aqueous solutions of TM*b*U, the major contribution to the formation of TM*b*U...$H_2O(D_2O)$ hydrogen bonds is made by the C=O groups of the solute. The hydrogen atoms of the "glyoxal bridge" (*i.e.*, at the C(1) and C(5) atoms) are also capable of forming H-bonds with two water molecules.

The energy evolved upon the formation of these bonds and during hydrophobic hydration of the methyl groups (see Table 1) does not fully counterbalance the energy expenditure needed to destroy the crystal structure of TM*b*U during dissolution and to form the cavity in the structural matrix of the solvent. These effects are accompanied by rearrangement of the spatial H-bond network in water; this disturbance is enhanced at lower temperature.[6]

Weakening of TM*b*U hydration in D_2O at $T \leq$ 315 K (see Fig. 1) may be attributed to the higher degree of structuring of heavy water caused by the formation of stronger D-bonds.[10] As the temperature increases, the vibrational differences between water H/D-isotopomers is gradually leveled,[6,10] and at $T \geq$ 315 K, the enthalpy contribution to $\delta\Delta_{hydr}H_n^\infty(H_2O \rightarrow D_2O)$ due to the IE in the H-bond formation between TM*b*U molecules and water starts to play the predominant role. In particular, this conclusion is supported by the presence of tempera-

ture-dependent correlation between the IEs in the enthalpy of TM*b*U dissolution (see Fig. 1) and in the ^{13}C chemical shifts (see Ref. 9) corresponding to the structural transformations in the region of hydration of the CH_3 groups. Apparently, at $T \geq 315$ K, the structural base for the hydrophobic hydration disappears.

Experimental

Experiments were carried out with TM*b*U (Codex quality, JSC Automated Technologies, Vologda, Russia) purified by washing in diethyl ether followed by two recrystallizations from chloroform (according to the manufacturer´s quality certificate, the content of the basic material was 99.5±0.1% (w/w), m.p. 228±2 °C). The sample was additionally analyzed for the compliance with the quality indexes (based on the integral intensity of the key absorption bands) on a high-resolution AVATAR 360 FT-IR spectrometer. The content of the major concomitant impurity (1,3-DMU), for which the dissolution enthalpy in water at 298.15 K is close to $\Delta_{sol}H_n^c(H_2O; TMbU)$, was not more than 0.3%, which could not introduce a significant systematic error into the calorimetric data.

Prior to the measurements, the TM*b*U sample was dried in a vacuum oven at ~60 °C for 2 days and stored in a desiccator over P_2O_5. Water of the natural isotope composition was deionized and distilled two times to reach the specific electrical conductivity of the doubly distilled water $\kappa \approx 1.3 \cdot 10^{-5}$ S m^{-1}. Heavy water ($\kappa \approx 1.0 \cdot 10^{-5}$ S m^{-1}) was analyzed by densimetry for the content of deuterium, which corresponded to 99.90±0.01 at.%.

The enthalpy of dissolution $\Delta_{sol}H_n^c$ was measured at 298.15±0.005 K using a sealed isoperibolic calorimeter (ampoule type) with a ~60 mL reaction vessel. The error of measurements of single heats did not exceed 0.2%. The calorimeter was tested by determining (in a series of ten experiments) the dissolution enthalpy of KCl in water. The calorimetric setup was described in detail previously.[11,12]

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