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Temperature effect on the volume properties of a bisurea aqueous solutions

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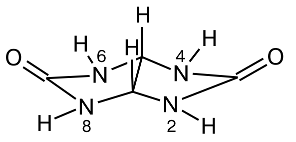
The densities of aqueous solutions of bisurea (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione) were measured using a vibrating-tube densimeter at 288.15, 298.15, 308.15, and 318.15 K in the concentration range up to $\sim 3 \cdot 10^{-3}$ moles of solute (1000 g of H_2O)$^{-1}$ with the error at most $\pm 5 \cdot 10^{-6}$ g cm^{-3} (reproducibility up to $2 \cdot 10^{-6}$ g cm^{-3}). The limiting partial molar volume and expansibility of bisurea in water were calculated. The bicyclic molecules under study form in aqueous solution H-bonded hydrate complexes with rather high structure-packing density. These complexes are more subjected to the destroying effect of temperature than the corresponding urea complexes. The hydration of bisurea weakens with the temperature increase.

Key words: bisurea, aqueous solutions, partial molar volumes and expansibilities, hydration.

Bisurea (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione) is a promising biologically active compound of the class of glycolurils, which are bicyclic bisureas of the octane series. Bisurea (hereinafter bU) is used as a precursor in the synthesis of drugs. Some of its alkylsubstituted derivatives (for example, the 2,4,6,8-*N*-methylated analog, or Mebicarum) have already found use as low-toxicity drugs of a wide therapeutic (psycho- and cardiotropic) effect.[1—4]



bU

Therefore, it is of interest to study the thermodynamic and structural characteristics of aqueous solutions of bU and peculiarities of hydration of its molecules. However, it is very difficult to study aqueous solutions of bU by calorimetry and spectral analysis because of the very low solubility ($\sim 5 \cdot 10^{-3}$ moles in 1 kg of H_2O at 298 K). Hence, we used precision densimetry.

In this report, we present the results of densimetric investigation of aqueous solutions of bU at 288.15, 298.15, 308.15, and 318.15 K and analyzed the volume effects of hydration of this compound.

Experimental

Bisurea (pharmacopoeia purity, Avtomatizirovannye Tekhnologii Co., Vologda, Russia) was purified by washing with diethyl ether followed by double recrystallization from chloroform and ethanol. The content of the major substance in the sample (according to the quality certificate presented by the producer) was ≥99.0 wt.%, m.p. 550±3 K (with decomp.). The compound was additionally analyzed for the presence of residual admixtures (urea, glyoxal, and others) by the integral intensity of absorption bands on an Avatar 360 FT-IR high-resolution IR spectrometer.

Solutions of bU in H_2O were prepared gravimetrically (weighing accuracy of at least $1 \cdot 10^{-5}$ g) from the degassed components by the dilution of the stock solution. The concentration of the solute was expressed in molality units $c_{m,2}$ (mole of bU (1000 g of H_2O)$^{-1}$).

The densities of solutions of bU in H_2O ($\rho_{1,2}$) were measured with the error at most $\pm 5 \cdot 10^{-6}$ g cm^{-3} (and reproducibility $\pm 2 \cdot 10^{-6}$ g cm^{-3} in a series of five measurements) on a precision vibrating-tube densimeter of original design.[5,6] The temperature of a measurement cell ~2 cm^3 in volume was maintained with an accuracy of $\pm 2 \cdot 10^{-3}$ K.

The regression analysis showed that the obtained dependences of $\rho_{1,2}$ on $c_{m,2}$ at all temperatures under study are adequately described by the first-order equation. The coefficients in the equation with the standard deviation values $\sigma_{0.95}$ are listed in Table 1.

Results and Discussion

The approximated $\rho_{1,2}$ values were used to calculate the limiting molar volume ($\bar{V}_2^{\infty}$) and expansibility ($\bar{E}_{p,2}^{\infty}$) of bU in water. For the estimation of $\bar{V}_2^{\infty}$, we applied the rational (original) procedure[6,8] that differs by an enhanced stability to the influence of errors in the determination of $\rho_{1,2}$ and $c_{m,2}$ in the region of high dilutions. The concen-

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Table 1. Coefficients in the equation $\rho_{1,2} = a_0(\equiv\rho_1) + a_1c_{\mathrm{sm},2}$ (ρ_1 is the water density[7]) at different temperatures[a]

T/K	n [b]	r [c]	a_0	a_1
			g cm^{-3}	
288.15	24	0.9927	0.999101 ($2.2\cdot10^{-6}$)	0.05394 ($1.40\cdot10^{-3}$)
298.15	26	0.9928	0.997047 ($1.9\cdot10^{-6}$)	0.05111 ($1.26\cdot10^{-3}$)
308.15	25	0.9942	0.994035 ($1.9\cdot10^{-6}$)	0.04924 ($1.11\cdot10^{-3}$)
318.15	27	0.9971	0.990216 ($1.3\cdot10^{-6}$)	0.04787 ($0.74\cdot10^{-3}$)

[a] The root-mean-square error of the approximation is given in parentheses.
[b] The number of the averaged experimental ρ values.
[c] The correlation coefficient.

tration dependence of the total volume of the solution $V_{1,2} = (n_1M_1 + n_2M_2)/\rho_{1,2}$ (n_1 = 55.50843 (amount of substance H_2O in 1 kg of water), $n_2 = c_{\mathrm{m},2}$, M_1 and M_2 are the molar weights of the components) was approximated by the equation

$$V_{1,2} - b_0\,(\equiv 55.50843V_1^*) =$$
$$= b_1(\equiv \bar{V}_2^\infty \equiv V_{\varphi,2}^\infty)c_{\mathrm{m},2} + b_2(\equiv B_V)c^2{}_{\mathrm{m},2}. \tag{1}$$

Here $V_1^* = M_1/\rho_1^*$ is the molar volume of the solvent at a given temperature, and B_V is the "slope parameter" ($(V_{1,2} - 55.50843V_1)/c_{\mathrm{m},2} = V_{\varphi,2}(c_{\mathrm{m},2})$). The results of calculation by Eq. (1) are listed in Table 2.

For water at T = 298 K, the van der Waals volume is $V_{\mathrm{w},1}$ = 11.4 cm^3 mol^{-1} (according to Bondi)[10] and the ratio is $V_1^*/V_{\mathrm{w},1}$ = 1.59. A comparison of these values with the data in Table 2 shows that the closest hydrate environment of a bU molecule has a higher packing density than that in the bulk solvent. The compact character of structural aggregates of this kind in the limiting and highly dilute aqueous solutions of bU increases appreciably with the temperature decrease. It is important that a comparison of the $\bar{V}_2^\infty/V_{\mathrm{w},2}$ values (see Table 2) with analogous ratios for usual urea (~1.55 and ~1.59 at 298 and 318 K, respectively)[11] shows resemblance in the degree of packing of the hydrate sphere around molecules of these substances. This fact suggests that, as in the case of typically hydrophilic urea, the nature of bU hydration is determined, to a great extent, by the ability of the donor and acceptor centers in a glycoluril molecule under study to specific interactions (through H-bonding) with H_2O molecules.

Table 2. Parameters in Eq. (1) and the characteristics of the structure packing of the bisurea—water solvate complex

T/K	$\bar{V}_2^\infty$ /cm^3 mol^{-1}	$\bar{V}_2^\infty/V_\mathrm{w}$ [a]	B_V /cm^3 mol^{-1}	$\bar{\alpha}_{p,2}^\infty\cdot10^3$ [b] /K^{-1}
288.15	88.2	1.48	11	3.6
298.15	91.1	1.53	0	2.8
308.15	93.1	1.56	–7	2.0
318.15	94.7	1.59	–8	1.2

[a] $V_{\mathrm{w},2} = v_{\mathrm{w},2}N_\mathrm{A}$, where N_A is Avogadro´s number, $v_{\mathrm{w},2} \approx 99.0\cdot10^{-24}$ cm^3 is the van der Waals volume of a bU molecule calculated by the earlier described method[9] taking into account the overlap of "valence" cospheres of the contacting atoms.
[b] The coefficient of partial volume expansion of the solute in the limiting dilute aqueous solution, whose values were calculated by the formula[5] $\bar{\alpha}_{p,2}^\infty = [\partial\ln\bar{V}_2^\infty/\partial(T - T_0)]_p = \bar{E}_{p,2}^\infty/\bar{V}_2^\infty$ using the equation $\bar{V}_2^\infty = e_0 + e_1(T - T_0) + e_2(T - T_0)^2$ (T_0 = 298.15 K) and the data in Table 1.

Based on the structure of the bU molecule, one can conclude that during hydration the molecule can act as an acceptor and a donor of four and six H-bonds, respectively, with water molecules. Similar specific contacts through the carbonyl and methine groups (protons at the C(1) and C(5) atoms) of glycolurils have been confirmed previously[12,13] by ^{13}C NMR spectroscopy when studying aqueous solutions of Mebicarum (tetramethylbisurea). The pronounced ability of the NH groups to H-bonding with the electron donor (adjacent oxygen atom) is predicted by the results of studies of the crystal structures of a series of bisureas.[2]

At the same time, since the heterocyclic framework is rigid and the five-membered rings are *cis*-coupled, the crystal structure of a bU molecule (as well as molecules of other achiral glycolurils) have the shape of a half-opened book (Fig. 1).[2,14,15] Sequences of this structure causing asymmetry of the electron density distribution[2,14] is the observed (see Fig. 1) sharp increase in $\bar{E}_{p,2}^\infty(H_2O)$ and the slope of the temperature plot of this characteristic on going from urea to bU. It cannot be excluded that the higher sensitivity of the molecular packing of an aqueous environment of bU to temperature and a decrease in the difference of the $\bar{E}_{p,2}^\infty(H_2O)$ values of the ureas with the temperature increase (Fig. 2) are caused, as a whole, by the higher strength of heterocomponent H-bonds formed in an aqueous solution of glycoluril. This assumption is favored, particularly, by the fact of obvious analogies in the character of changing the dependences of $\bar{E}_{p,2}^\infty$ on T (see Fig. 2) and those of solutions of Mebicarum and a series of the alkyl derivatives of ureas in H_2O and more structured D_2O.[11,16,17]

It is noteworthy that a more complicated character of the molecular structure and an almost twofold increase in the limiting partial molar volume of the solute when urea is replaced by bU (see Table 2)* is accompanied by a substantial rearrangement of the solvent structure around a hydrated particle and restriction of the accessibility of its donor-acceptor centers for water molecules. Probably, increasing steric hindrance to H-bonding of bU with H_2O

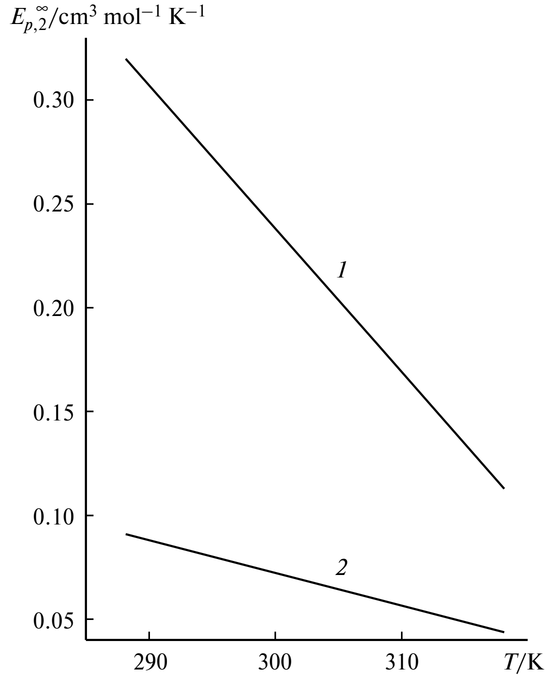

Fig. 1. Temperature plots of the limiting partial molar expansibilities of bisurea (*1*) and urea (*2*) in an aqueous solution.

molecules is one of the main reasons for the substantially higher endothermicity of dissolution of this glycoluril in water ($\Delta_{\text{sol}}H_2^{\infty} \approx 26.7$ kJ mol^{-1} at 298 K)**[18]** compared to the formation of limiting dilute aqueous solutions of urea ($\Delta_{\text{sol}}H_2^{\infty} \approx 15.3$ kJ mol^{-1})**[19,20]** and Mebicarum ($\Delta_{\text{sol}}H_2^{\infty} \approx 3.7$ kJ mol^{-1}) (see Refs 4 and 21).

A more detailed pattern of structure-packing transformations in the liquid system under question can be obtained on the basis of model concepts that make it possible to divide the total (integral) volume characteristics of hydration ($\bar{V}_2^{\infty}$) of bU into particular components. One of such approaches is the scaled particle theory**[22—24]** based on the statistical mechanical calculation of the compositions to $\bar{V}_2^{\infty}$ during the approximation of molecules of the components in the system by solid spheres or bodies of another geometric shape.** The procedure of hypothetical replacement of a "real" polyatomic molecule by a geometric body equivalent to this molecule in volume, which is a sphere with the diameter σ in this case, allows one to estimate reliably relative packing changes even in such systems, which are strongly associated through H-bonding, as aqueous solutions of the urea derivatives.**[17]**

According to the scaled particle theory, $\bar{V}_2^{\infty}$ takes the following form:

$$\bar{V}_2^{\infty} = \bar{V}_{\text{cav}}^{\infty} + \bar{V}_{\text{int}}^{\infty} + \beta_{T,1}RT, \qquad (2)$$

where $\bar{V}_{\text{cav}}^{\infty}$ and $\bar{V}_{\text{int}}^{\infty}$ are the contributions caused by the formation of the solvate cavity in the solvent medium and intermolecular interactions 1—2(1), respectively, and $\beta_{T,1}$ is the contribution that takes into account the change in the standard state of the system during the gas → liquid transition.

The $\bar{V}_{\text{cav}}^{\infty}$ value was calculated by the equation**[23—25]**

$$\bar{V}_{\text{cav}}^{\infty} = \beta_{T,1}RT\left[\frac{y}{1-y} + \frac{3yz(1+z)}{(1-y)^2} + \frac{9y^2z^2}{(1-y)^3}\right] + \frac{\pi\sigma_2^3 N_A}{6}, \qquad (3)$$

whose parameters are given in Table 3.

As can be seen from the data in Table 3, the absolute value of negative $\bar{V}_{\text{int}}^{\infty}$ decreases with the temperature increase. The difference in the $|\bar{V}_{\text{int}}^{\infty}|$ values at $T = 288$ and 318 K achieves 6 cm^3 mol^{-1}, which evidences in favor of weakening of bU hydration with the temperature increase. Earlier**[4,11]** we observed a similar tendency when studying the volume and enthalpy (including H/D-isotopic) effects of hydration of Mebicarum, which is a more "hydrophobic" tetra-*N*-methylated analog of bU. This suggests general regularities in the solvation behavior of bisureas of the series under study during the formation of their aqueous solutions. Despite the pre-destruction of the water structure that occurs with the temperature increase, the simultaneous enhancement of volume expansion of the H-bonding network of the solvent creates additional configuration hindrance for the specific interaction in the glycoluril hydrate complex that formed.

Table 3. Parameters in Eq. (3) and the volume characteristics (necessary for the calculation of the latter) for the components of an infinitely dilute aqueous solution of bisurea at different temperatures

T/K	*y* [a]	$\sigma_1 \cdot 10^8$ [b]	$\sigma_2 \cdot 10^8$ [c]	$\beta_{T,1}RT$ [d]	$\bar{V}_{\text{cav}}^{\infty}$	$-\bar{V}_{\text{int}}^{\infty}$
		cm		cm^3 mol^{-1}		
288.15	0.3493	2.713	5.739	1.12	98.5	11.4
298.15	0.3494	2.715	5.739	1.12	98.5	8.5
308.15	0.3481	2.715	5.739	1.14	98.6	6.3
318.15	0.3455	2.712	5.739	1.17	98.9	5.3

[a] The packing parameter estimated by the equation**[23]** $\beta_{T,1} = V_1(1-y)^4/[RT(1+2y)^2]$.

[b] The solid-sphere diameter of a solvent molecule calculated by the formula**[22]** $y = \pi\sigma_1 N_A/(6V_1)$.

[c] The solid-sphere diameter of a solute molecule**[25]** $\sigma_2 = [6V_{\text{w},2}/(\pi N_A)]^{1/3}$ (σ_2 is temperature-independent within the error of determination).

[d] The $\beta_{T,1}$ values are borrowed from Ref. 7.

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* The $\bar{V}_2^{\infty}(H_2O)$ value for urea at 298.15 K is**[17]** 44.25±0.02 cm^3 mol^{-1}.

** The analysis showed**[17]** that the relative change in the volume contribution depends weakly on the shape of a geometric body (sphere, oblong ellipsoid, cylinder) approximating a molecule of the solute or solvent.

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