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EFFECT OF SOLVENT H/D-ISOTOPE SUBSTITUTION AND TEMPERATURE ON SOME THERMODYNAMIC PROPERTIES OF TETRAMETHYLENEDIETHYLENETETRAMINE (PHARMACEUTICAL *TEOTROPINE*) IN AQUEOUS SOLUTIONS

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Keywords: *teotropine; standard volume and expansibility; standard enthalpy of dissolution; ordinary and heavy water; solvent H/D isotope effect*

Abstract. *The paper considers the measurements of densities the pharmaceutical "teotropine" or tetramethylenediethylenetetramine (TMDETA) solutions in heavy water (D_2O) with the solute molality from (0.01 to 0.12) mol·(kg solvent)$^{-1}$ at T = (278.15, 288.15, 298.15, 308.15, and 318.15) K and ambient pressure (p = 0.1 MPa). The uncertainty in density measured using the Anton Paar DMA 5000 M densimeter (equipped with oscillating U-tube) was 0.03 kg m^{-3} or lower. We obtain the standard (at infinite dilution) molar volumes and isobaric expansibilities of TMDETA as a solute in D_2O, along with the corresponding solvent D_2O–H_2O isotope effects (IEs). We define the isotope effects using the previously obtained data on volumetric properties of the system (H_2O + TMDETA). We also find that the insignificant IEs in the standard molar volume of TMDETA increase with increasing temperature. Based on the analysis of contributions to the standard molar volume of TMDETA in terms of the Scaled Particle Theory (SPT) we confirm that a bulkier molecule of this solute interacts with water (especially, in D_2O) actively than it does with a molecule of hexamethylenetetramine (HMTA) or pharmaceutical "urotropine" being the related aminal (cage-like) compound. The colloborating discussion of volume- and enthalpy-isotope characteristics of TMDETA (and HMTA) hydration within the scope of SPT led us to the conclusion that the structure matrix of D_2O is more efficient for incorporating the bulkier TMDETA molecule into it.*

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Introduction

The title heterocyclic compound named trivially as tetramethylenediethylenetetramine (TMDETA) is one of bioactive *adamanzanes* 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane or ([1^{4}.2^{2}]adamanzane) being analogous to adamantane with nitrogen at the nodal-branched position (see Fig. 1) [1]. The best-known related macrocyclic compound having a similar "cage-like" or *aminal* molecule structure is *urotropine* or hexamethylenetetramine (HMTA) [2] (see Fig. 1). Unlike it, TMDETA has two additional side-chain methylene groups in its molecular cycles (see Fig. 1).

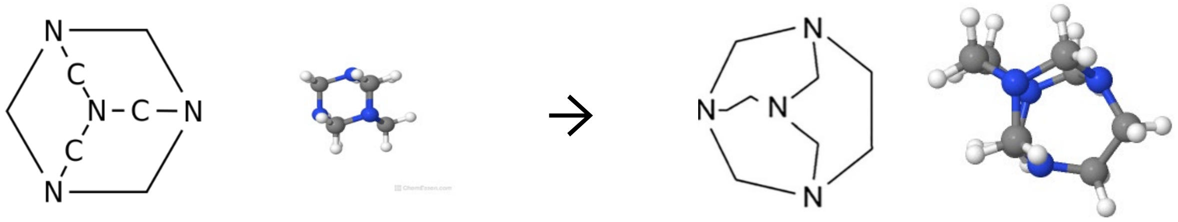


Fig. 1. The schematically simplified 2D- and 3D-structures of HMTA (left-handed) and TMDETA (right-handed) molecules

TMDETA has found useful applications as an effective antiseptic pharmaceutical *teotropine* [3,4] as well as a precursor in the synthesis of some technologically relevant *aza*-amino-derivatives. As similar to the widely used related drug *urotropine* (*hexamine*) based on the above-mentioned HMTA (1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane), TMDETA is of special interest as a hydrated solute in the solution physical chemistry [5-7]. It is due to a noticeable solubility in water [8] and a presence of hydrophilic and hydrophobic pharmacophore groups in TMDETA molecules (see Fig. 1), which have difference influence on the structure of aqueous environment. However, the existing information on structure-thermodynamic peculiarities of TMDETA hydration is still quite limited.

Previously [7, 9], the results of the calorimetric study of TMDETA solutions in ordinary (H_2O) and heavy (D_2O) water were comprehensively discussed. Two main points considered in the work [7] were: the connection of enthalpy-isotope effects in the dissolution process with the hydration behavior of TMDETA and their correlation with those derived for HMTA solutions in H_2O and D_2O [10]. It was found that the structure-making effects in aqueous media are enhanced when going from HMTA to TMDETA as a solute. Despite the formation of heterocomponent hydrogen ND(H)-O bonds in aqueous solutions of TMDETA, hydrophobic effects is the predominant part during the process of its hydration [7]. Indeed, the results [9] permit the classification of TMDETA on the enthalpy-hydration effects as a "mixed solute".

It is well-known that D bonds are stronger (but more susceptible to destruction under the influence of temperature) than H bonds, by virtue of the quantum (vibrational) nature of isotope effects (IEs), which causes changes in the donor-accepting ability of water molecules [7, 10, 11]. Hence, given the recent study on the {$H_2O(D_2O)$ + HMTA} systems [2], the important additional information on structure-packing effects induced by intermolecular interactions in the aqueous solutions of TMDETA can be obtained using an approach reasonably combining "non-perturbing" experimental methods of the $H_2O \to D_2O$ solvent isotope substitution and precision densimetry. But, the only densimetric study of H/D isotopically distinguishable aqueous systems under study was conducted at four "irregular" temperatures,

T = (293.15, 298.15, 300.15 and 305.15) K. by Romero and Mesa [6, 12]. Also, we have determined earlier [13] the temperature-dependent standard (at infinite dilution) molar volumes, V_2^{o}, and expansibilities, $E_{p,2}^{\mathrm{o}} = (\partial V_2^{\mathrm{o}}/\partial T)_p$, of TMDETA in ordinary water within the range of T = (278.15 to 318.15) K, with a step of 10 K.

At the same time, as we emphasized in previous papers [7, 13], the authentic nature of thermodynamic (including volume-related) IEs induced by TMDETA dissolution (solvation) in an aqueous medium remains uncertain. To derive more reliable and detailed data on the problem raised, we made an additional high-precise densimetric study of TMDETA solutions in D_2O at the same temperature range as in case of the (H_2O + TMDETA) system [13].

Main body

A detail description of the compounds employed in our experiments as well as the density measurement and solution preparation procedures are in the Experimental part.

The results of density measurements are compiled in Table 1. This table contains also the data on apparent molar volumes, $V_{\emptyset,2}$, for TMDETA in D_2O. The content of TMDETA was in the form of aquamolality, m_{aq}, which is determined by the number of solute moles per 55.50843 moles of D_2O or H_2O (for solutions in ordinary water m_{aq} coincides with molality, m) [14-16]. It is relevant for the interpretation of thermodynamic functions of transfer including the respective IEs [2, 15, 16]. The uncertainty in m_{aq} was assessed as ~$3{\cdot}10^{-5}$ mole per $55.50843M_1$, giving a number at the fifth decimal place of m_{aq} in Table 1.

Table 1. Experimental densities, $\rho_s/(\mathrm{kg{\cdot}m^{-3}})$, and apparent molar volumes, $V_{\emptyset,2}/(\mathrm{m^3{\cdot}mol^{-1}})$, for TMDETA solutions in D_2O at studied aquamolalities, $m_{\mathrm{aq}}[\mathrm{mol{\cdot}}(55.50843\ M_1)^{-1}]$, and temperatures, T (±0.01 K), and at p = (99.6 ±0.8) kPa

m_{aq}	T = 278.15 K		T = 288.15 K		T = 298.15 K		T = 308.15 K		T = 318.15 K	
	ρ_s	$10^6V_{\emptyset,2}$	ρ_s	$10^6V_{\emptyset,2}$	ρ_s	$10^6V_{\emptyset,2}$	ρ_s	$10^6V_{\emptyset,2}$	ρ_s	$10^6V_{\emptyset,2}$
0[a]	1105.543	–	1105.795	–	1104.380	–	1101.659	–	1097.869	–
0.01089	1105.719	137.56	1105.958	138.26	1104.539	138.96	1101.812	139.61	1098.022	140.28
0.02345	1105.922	137.53	1106.156	138.24	1104.721	138.94	1101.998	139.59	1098.198	140.26
0.04041	1106.184	137.50	1106.412	138.21	1104.972	138.91	1102.237	139.56	1098.433	140.23
0.05352	1106.408	137.47	1106.616	138.18	1105.166	138.89	1102.425	139.53	1098.620	140.20
0.06506	1106.587	137.45	1106.787	138.16	1105.335	138.87	1102.590	139.51	1098.780	140.18
0.07977	1106.820	137.42	1107.007	138.13	1105.549	138.84	1102.795	139.49	1098.980	140.16
0.08037	1106.826	137.42	1107.011	138.13	1105.549	138.84	1102.809	139.48	1099.002	140.16
0.09928	1107.141	137.38	1107.310	138.10	1105.834	138.80	1103.077	139.45	1099.260	140.12
0.10184	1107.180	137.38	1107.354	138.09	1105.870	138.80	1103.113	139.44	1099.304	140.12
0.11743	1107.428	137.35	1107.585	138.06	1106.104	138.76	1103.340	139.42	1099.515	140.09

[a] deuterium content is (99.93 ± 0.02) atom %.

To calculate $V_{\emptyset,2}$, the formula [2,15,17] expressing the *generic* volume of a binary solution, V_{s}, in the aquamolality scale, m_{aq}, was applied:

$$V_{\mathrm{s}}(m_{\mathrm{aq}}) = [55{,}50843M_1 + M_2m_{\mathrm{aq}}]/\rho_{\mathrm{s}} = V_1^* + V_{\emptyset,2}m_{\mathrm{aq}}, \qquad (1)$$

where $V_1^* = 55.50843M_1/\rho_1$ is the volume of a pure solvent (heavy water) in terms of the m_{aq} scale, M_1 and M_2 are the molar masses of components, and ρ_1 and ρ_s are the densities of a solvent and a binary solution, respectively.

According to works [2, 17],

$$V_{\mathrm{s}}^{\mathrm{E}}(m_{\mathrm{aq}}) = v_{22}m_{\mathrm{aq}} + v_{222}m_{\mathrm{aq}}^2 + \ldots, \tag{2}$$

where $V_{\mathrm{s}}^{\mathrm{E}}(m_{aq})$ is the excess volume of a binary solution per 55.50843 mole of water isotopologue; the adjustable v_{22} and v_{222} parameters in the virial expansion (2) can be considered as volume contributions to $V_{\mathrm{s}}^{\mathrm{E}}$ related to the solvent-mediated solute – solute interactions with formation of pair and triplet molecular aggregates.

On the other hand [2, 17],

$$V_{\mathrm{s}}^{\mathrm{E}}(m_{\mathrm{aq}}) = V_{\mathrm{s}}(m_{\mathrm{aq}}) - V_1^* - V_2^{\mathrm{o}}m_{\mathrm{aq}}. \tag{3}$$

Taking Eqs (1) to (3) into account, we can obtain the following:

$$V_{\emptyset,2}m_{\mathrm{aq}} = V_{\mathrm{s}}(m_{\mathrm{aq}}) - V_1^* = V_2^{\mathrm{o}}m_{\mathrm{aq}} + v_{22}m_{\mathrm{aq}}^2 + v_{222}m_{\mathrm{aq}}^3 + \ldots \tag{4}$$

According to Eq. (4), inferences concerning the interpretation of $V_{\mathrm{s}}^{\mathrm{E}}(m_{aq})$ are valid for $V_{\emptyset,2}(m_{aq})$, too. The LSM-statistical analysis based on *F*-testing showed that numerical values of the term v_{222} in Eq. (4) may be neglected.

The use of this (so-called "rational") procedure evidently has certain advantages over the "traditional" extrapolation procedure in the high dilution region. So, proceeding from Eq. (4), the experimental values of $V_{\emptyset,2}$ are in a narrow range of confidence intervals relative to the line intersecting the ordinate at a known preset point: V_1^*. The given fact allows us to exclude the influence of the so-called "gramophone horn" effect caused by the dramatic increase in uncertainty of $V_{\emptyset,2}$ as $m_{aq}\to 0$ [15, 16]. Also, it is important to highlight here that, unlike the "traditional" way of computing $V_{\emptyset,2}$ [13, 16], the experimental density value (ρ_{s}) in Eq. (1) is used only once. Being derived in such manner, the V_2^{o} and v_{22} values, together with the errors of their determination {as a half-width of the 95% confidence interval, $\pm\sigma(V_2^{\mathrm{o}})$ и $\pm\sigma(v_{22})$}, are collected in Table 2.

Table 2. Standard molar volumes, $10^6V_2^{\mathrm{o}}/(\mathrm{m^3{\cdot}mol^{-1}})$, and volume-related interaction parameters, $10^6v_{22}/(\mathrm{m^3{\cdot}55.50843}M_1\mathrm{{\cdot}mol^{-2}})$, for the ($H_2O$ + TMDETA) and (D_2O + TMDETA) systems at studied temperatures, *T* (±0.01 K), and at *p* = (99.6 ± 0.8) kPa

T/K	TMDETA in ordinary water [13]		TMDETA in heavy water		D_2O–H_2O isotope effect (δ)	
	$10^6V_2^{\mathrm{o}}$[a]	-10^6v_{22}	$10^6V_2^{\mathrm{o}}$[a]	-10^6v_{22}	$10^6\delta V_2^{\mathrm{o}}$	$-10^6\delta v_{22}$
278.15	137.41 ± 0.02	4.26 ± 0.06	137.57 ± 0.02	1.92 ± 0.05	0.16 ± 0.03	2.34 ± 0.08
288.15	138.06 ± 0.02	4.20 ± 0.06	138.28 ± 0.02	1.89 ± 0.06	0.22 ± 0.03	2.31 ± 0.09
298.15	138.65 ± 0.02 *137.53 ± 0.05*	4.19 ± 0.06	138.98 ± 0.02 *139.02 ± 0.05*	1.85 ± 0.09	0.33 ± 0.03	2.34 ± 0.11
308.15	139.30 ± 0.02	4.15 ± 0.06	139.63 ± 0.02	1.83 ± 0.08	0.33 ± 0.03	2.32 ± 0.10
318.15	139.95 ± 0.02	4.11 ± 0.06	140.30 ± 0.02	1.79 ± 0.06	0.35 ± 0.03	2.32 ± 0.08

[a] The data from Ref. 6 are highlighted in italics.

As we mentioned above, the only densimetric study of TMDETA solutions in H_2O and D_2O was carried out previously by the authors [6] at four irregular temperatures including *T* = 298.15 K (see Table 2). Comparing the V_2^{o} values taken from [6] with ours, we can conclude that there is excellent conformity between them in heavy water. At the same time, such quantities in ordinary water disagree by $1.1{\cdot}10^{-6}\ \mathrm{m^3{\cdot}mol^{-1}}$ [13] (see Table 2), a fact indicating that there are differences in the experimental procedures. As in our previous works [7, 13], here we attached primary importance of experimental approaches to measuring solution density and preparing solute and solvent samples with testing their quality. Therefore, thermodynamically the $H_2O \rightarrow D_2O$ substitution of is one of the "finest tools" in studying the properties of a binary aqueous solution [2, 7]. Hence, it was important to perform all the experiments and calculations under the same conditions.

The evolution of IEs $\delta V_2^o(H_2O \rightarrow D_2O)$ with increasing temperature in aqueous TMDETA is illustrated by the data in Table 2 and Fig. 2. The temperature-dependent volume-isotope effects for the same system from [6] as well as the previously derived $\delta V_2^o - T$ function for HMTA as a solute in water [2] can be found *ibidem*. Perhaps the most interesting fact here is that, unlike the sign-alternating $\delta V_2^o(T)$, the considered IE for TMDETA is positive and slightly increases with temperature in the *T*-range chosen. It does not comply with the conventional behavior of the predominantly hydrophobic solute [18]. Its molecules form "hydration complexes" in D_2O of a smaller volume than in ordinary water. Therefore, at $T = (308.15 \text{ to } 318.15)$ K, the volume-isotope differences between the aminal-containing aqueous systems compared virtually disappear (see Fig. 2).

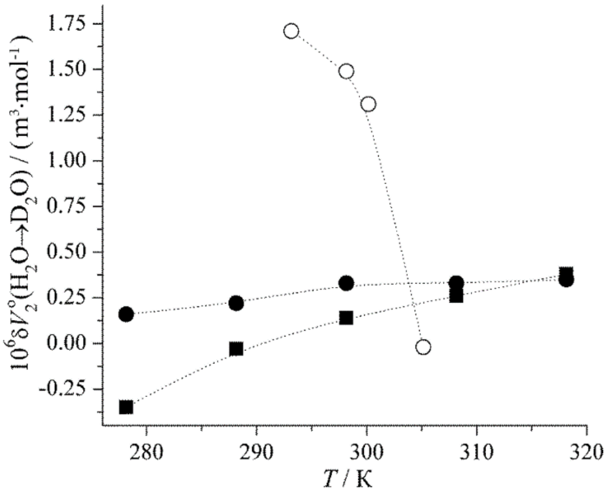


Fig. 2. H/D solvent isotope effects in the standard molar volume of TMDETA (●, our data from Table 2 and Ref. 13; ○, Ref. 6) and HMTA (▪, Ref. 2) in aqueous media as a function of temperature. Uncertainty in the assessment of the depicted value corresponds to the filled (or open) character size

As follows from Fig. 2, there are noticeable inconsistencies in the temperature-dependent changes in δV_2^o in aqueous TMDETA when the results reported by the authors [6] are compared with the ones we derived. Suffice it to say that the volume-isotope effects taken from [6] exceed ours (see Fig. 2) by $1 \cdot 10^{-6}$ $m^3 \cdot mol^{-1}$ and more at $T \leq 300$ K. But, when going to $T = 305$ K, this difference decreases dramatically and even becomes negative (in sign). Such an unusual situation is similar to the one we had observed previously when comparing the $\delta V_2^o(H_2O \rightarrow D_2O)$ *vs.* *T* functions for the aqueous HMTA plotted by Romero and Mesa [6,12], and E. Ivanov [2]. The corresponding IEs from [6] decrease sharply too as the temperature rises, with the only difference being that they have inexplicably higher (by a factor of 2 to 4) numerical values than they do in the aqueous TMDETA solution at $T < 305$ K (open circles for δV_2^o in Fig. 2). In contrast, our results (filled characters in the figure) point to quite insignificant influence of the H_2O-by-D_2O substitution on the volume hydration effects in the compared aminal-containing aqueous solutions {with the positive $(\partial \delta V_2^o / \partial T)_p$ derivative}. And the negative-to-positive sign inversion in the volume-isotope effect δV_2^{o} for HMTA at $T \approx 290$ K (see Fig. 2) is the most likely due to the isotopic distinctions in the thermal stability of $C_6H_{12}N_4{\cdot}6H_2O$ and $C_6H_{12}N_4{\cdot}6D_2O$ solvates of well-defined structure [19]. In ordinary water, such aggregates are overall stable up to $T \approx 287$ K [2, 19]. This inference does not contradict the results of studying the corresponding enthalpy-isotope effects, presuming the temperature-dependent *dualistic* character of hydration of this adamanzane solute [10]. In turn, data on thermodynamic IEs displayed in Fig. 2 and in our previous study [7] give reason to believe that the more hydrophobic in structure TMDETA does not form the similar hydrogen-bonded clathrate-type mixed aggregates with water in the temperature range chosen. However, other approaches must be also considered to confirm or refute the given conclusion.

We believe that the observed "discrepancy" in the δV_2^{o} *vs.* T functions (see Fig. 2) may be caused by a configuration factor, namely, by the different ability of aminal molecules to be built into the initial structural matrix of each of H/D isotopically distinguishable aqueous media [2, 7, 10]. Due to the formation of deuterium bonds heavy water has a more *openwork* (with a larger free volume) and less expansible structure [2, 11, 20]. Indeed, we can suggest that the structure of liquid D_2O is better one for incorporating a bulkier TMDETA molecule into it, and vice versa, if we deal with standard solutions of HMTA in heavy water at least up to temperatures being close to $T = 290$ K [2, 10]. In turn, at $T = (308.15$ to $318.15)$ K, the isotope differences in V_2^{o} between the aminal-containing aqueous systems compared are virtually disappeared (see Fig. 2). Also, the above inferences largely explain why IEs in the enthalpy of cavity formation $\delta\overline{H}_{\mathrm{cav}}(H_2O \rightarrow D_2O)$ in terms of Scaled Particle Theory (SPT) are negative for both TMDETA and HMTA [7].

The important additional information are data on the free or *excluded* volume in the specified hydration complexes, $d = V_{\mathrm{w},2}/V_2^{o}$ [13, 21], and the isobaric expansibility of their structures, $E_{p,2}^{\mathrm{o}} = (\partial V_2^{\mathrm{o}}/\partial T)_p$, as well. To calculate the *packing density* parameter (d), we assessed the Van der Waals volume of a solute, $V_{\mathrm{w},2} = v_{\mathrm{w},2}N_{\mathrm{A}}$, where N_{A} is the Avogadro constant, as a sum of mean-weighted volumes of atomic increments into a "molecule volume", $v_{\mathrm{w},2}$, using the Cambridge Structural Database [22]. The $V_{\mathrm{w},2}$ values assessed this way were *ca.* $92.5{\cdot}10^{-6}$ and $73.2{\cdot}10^{-6}$ $\mathrm{m^3{\cdot}mol^{-1}}$ for TMDETA and HMTA, respectively. The results of determining d for the H/D-isotopically distinguishable aqueous systems compared are shown in Table 3. The corresponding IEs, $\delta d(H_2O \rightarrow D_2O)$ from Table 3 are presented in Fig. 3.

Table 3. Packing density parameters, $d = V_{\mathrm{w},2}/V_2^{o}$, for standard solutions of TMDETA and HMTA in ordinary and heavy water at different temperatures (T)

T/K	TMDETA			HMTA [2]		
	H_2O	D_2O	$H_2O \rightarrow D_2O$	H_2O	D_2O	$H_2O \rightarrow D_2O$
278.15	0.6732	0.6724	−0.0008	0.6723	0.6745	0.0022
288.15	0.6700	0.6689	−0.0011	0.6670	0.6672	0.0002
298.15	0.6671	0.6656	−0.0015	0.6625	0.6617	−0.0008
308.15	0.6640	0.6625	−0.0015	0.6586	0.6570	−0.0016
318.15	0.6610	0.6593	−0.0017	0.6553	0.6530	−0.0023

An analysis of the d values shows that the fraction of excluded volume in the structural packing of the aminal-containing hydration complex decreases when going from HMTA to TMDETA, except for the corresponding transfer in D_2O at $T = 278.15$ K. This tendency is appeared in case of D_2O-by-H_2O substitution too, but not so evident (see Fig. 3). The differences in d become more transparent as the temperature increases. As for relatively packing of the solvation complex formed in D_2O (see Fig. 3), the nature of this unusual effect has not yet found a reasonable explanation. Obviously, this is due to the peculiarities of both the formation of longer and stronger (owing to the greater cooperative effect) D bonds and the solvent reorganization around bulkier hydrophobic molecules of TMDETA when the deuterium-substituted solvation complex is formed. As we assumed above, it may be related to a purely configurational factor of incorporating a more cyclic-branched aminal molecule into the structure of heavy water. Indeed, the fact of forming the denser aqueous structure around the TMDETA molecules, compared to HMTA those (see Table 3), is in compliance with trend of changing the enthalpy effects induced by solute – solvent interactions in terms of SPT {$\overline{H}_{\text{int}}$ and $\delta\overline{H}_{\text{int}}$ ($H_2O \rightarrow D_2O$)} [7]. According to [7], it is caused by strengthening of the solute ‑ solvent interaction, which is more evident in the D_2O medium.

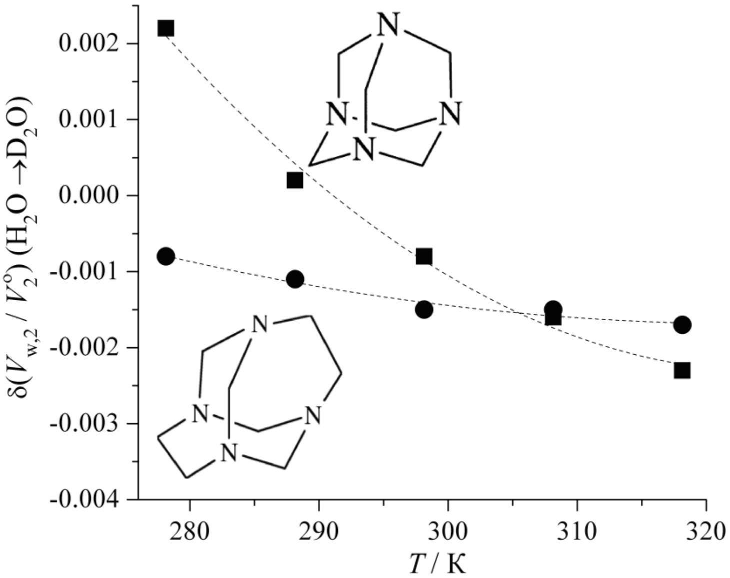


Fig. 3. H/D solvent isotope effects in the packing density parameter for standard aqueous solutions of TMDETA (●) and HMTA (▪) as a function of temperature. The error in the assessment of the depicted value corresponds to the filled character size

The presence of a rather strong water ‑ TMDETA interaction was confirmed previously by the results of a temperature-dependent study of the activity coefficients, γ, and partial molar Gibbs energies, $\overline{g}_2^{\text{E}}$, [5] in the binary aqueous system. As determined by the authors [5], the hydrophobic constituent plays a dominant role in the process of both TMDETA and HMTA hydration.

To obtain data on $E_{p,2}^{\text{o}}$, the $V_2^o - T$ function was approximated by the first-order equation [2]:

$$V_2^{\text{o}}(T) = V_2^{\text{o}}(T^*) + E_{p,2}^{\text{o}}(T - \theta), \tag{5}$$

where θ= 298.15 K is the *reference* (mean-weighted) temperature. It follows from Eq. (5) that $(\partial V_2^{\text{o}}/\partial(T-\theta))_p = E_{p,2}^{\text{o}}$. The temperature-independent $E_{p,2}^{\text{o}}(\theta)$ values for TMDETA were found to be (0.063 ± 0.002)·10^{-6} and (0.068 ± 0.002)·10^{-6} $m^3 \cdot mol^{-1}$ K^{-1} in ordinary and heavy water, respectively. The corresponding values of $E_{p,2}^{\text{o}}(\theta)$ obtained previously [2] for HMTA in H_2O and D_2O are (0.071 ± 0.001)·10^{-6} and (0.088 ± 0.005)·10^{-6} $m^3 \cdot mol^{-1}$ K^{-1}.

An analysis of $E^{o}_{p,2}$ shows that the hydration complex formed by TMDETA is thermally more stable than HMTA as a solute. The issue $E^{o}_{p,2}(D_2O) > E^{o}_{p,2}(H_2O)$ results from faster volume expansion of the spatial network of D bonds [2,18]. Indeed, if $\delta E^{o}_{p,2}(H_2O \rightarrow D_2O)$ for HMTA has a fairly high value close to $0.02 \cdot 10^{-6}$ $m^3 \cdot mol^{-1}$ K^{-1} {or ~20% of $E^{o}_{p,2}(D_2O)$}, the corresponding IE for TMDETA is only one-third of that. The relative comparability of $E^{o}_{p,2}(H_2O)$ and $E^{o}_{p,2}(D_2O)$ suggests that the temperature has a virtually identical influence on the structure packings of hydration complexes formed *via* H and D bonds. However, it may be due to mutual compensation of thermally induced contributions to the volume-isotope effect.

The special importance is the application of the well-known thermodynamic relation proposed by Hepler [23] to the analysis of both $E^{o}_{p,2} - T$ and $\delta E^{o}_{p,2} - T$ functions obtained in this work. Eq. (5) and according to [23], is

$$\left(\partial C_{p,2}/\partial p\right)_T = -T\left(\partial E^{o}_{p,2}/\partial (T-\theta)\right)_p, \qquad (6)$$

where $C_{p,2}$ is the standard (partial at infinite dilution) molar isobaric heat capacity of a solute.

In according with this approach {Eq. (6)}, the "structure-breaking" and "structure-making" solutes must have, respectively, negative and positive derivatives of $E^{o}_{p,2}$ or $\delta E^{o}_{p,2}$ relative to temperature. The issue when $\left(\partial E^{o}_{p,2}/\partial (T-\theta)\right) \approx 0$ (within the fitting error) can serve as an "indicator" that none of the above effects does not play the decisive role in the infinitely dilute TMDETA solution. Therefore, it can be concluded that hydrophobic and hydrophilic effects play an equally noticeable role in the process of TMDETA hydration. Nevertheless, the inferences derived only on the basis of "Hepler's criterion" or another volume-related property of a solute (including the corresponding IEs) seem to be rather overestimated, they depend on the extent to which the property is sensitive to long-range effects in the aqueous medium studied [2, 13]. Hence other approaches must be considered additionally, as we attempted to do it below applying the SPT expressions [24].

Of course, the possibility of using SPT to analyze the volume changes strongly associated (*via* hydrogen-bonding) liquids as aqueous solutions is fairly limited [7, 9, 24]. However, some difficulties can be avoided if to study the properties of a solute in H_2O and D_2O, and IEs derived then give useful information on the structure-dependent peculiarities of a solute – solvent interaction [7].

Similar to the molar enthalpy of solvation, $\Delta_{solv}H^{o}_{2}$ [7, 9], the V^{o}_{2} value within the scope of SPT can be decomposed into two main constituents, the volume associated with cavity formation, $\overline{V}_{\mathrm{cav}}$, and the contribution from solute – solvent interaction, $\overline{V}_{\mathrm{int}}$ [13]:

$$V^{o}_{2} = \overline{V}_{\mathrm{cav}} + \overline{V}_{\mathrm{int}} + \beta_{T,1}RT, \qquad (7)$$

where, the *correcting* term $\beta_{T,1}RT$ appares from the change in the standard state between gas and solution (R is the gas constant and $\beta_{T,1}$ is the isothermal compressibility coefficient for a pure water isotopologue [20]).

The volume contribution $\overline{V}_{\mathrm{cav}}$ to V^{o}_{2} is usually given by [13]:

$$\overline{V}_{\mathrm{cav}} = \beta_{T,1}RT\left[y/(1-y) + 3yz(1+z)/(1-y)^2 + 9y^2z^2/(1-y)^3\right] + \pi N_{\mathrm{A}} d_2^3/6, \qquad (8)$$

where $y = \pi N_{\mathrm{A}} d_1^3/(6V_1)$ is the *packing factor* for the solvent (H_2O or D_2O) molecules, d_1 and d_2 are the "scaled sphere diameters" for molecules of both solution components, $z = d_2/d_1$, and $V_1$is the solvent molar volume. The $d_2$value for TMDETA to be $8.35 \cdot 10^{-10}$ m is taken from our papers [7, 13]. The same is for the d_2(HMTA) quantity being 7.28·10^{-10} m. We realized the d_2 values do not depend on the temperature chosen. Indeed, the d_1 values assessed for water H/D isotopologues as the temperature-dependent *hard-sphere* diameters [7] are shown in Table 4 with V_1 and $\beta_{T,1}$values taken from the Kell's paper [20].

Table 4. Parameters of Eq. (8) to calculate $\overline{V}_{\text{cav}}$/(m^3·mol^{-1}) for the binary liquid systems {H_2O + TMDETA (HMTA)} and {D_2O + TMDETA (HMTA)} at different temperatures, *T* (± 0.01 K), and p≈0.1MPa

T /K	$10^6 V_1$/ (m^3·mol^{-1})		$10^{11}\beta^*_{T,1}$/ (Pa^{-1})		$10^{10} d_1$/ m^c	
	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O
278.15	18.016	18.114	49.28	51.55	2.724	2.716
288.15	18.031	18.110	46.78	48.42	2.730	2.723
298.15	18.069	18.134	45.24	46.48	2.733	2.727
308.15	18.123	18.178	44.42	45.38	2.731	2.726
318.15	18.193	18.241	44.15	44.90	2.729	2.725

Table 5 contains data on the temperature-dependent $\overline{V}_{\text{cav}}$ and $\overline{V}_{\text{int}}$ values calculated for each of the compared adamanzanes as a solute in H_2O and D_2O.

Table 5. Volume-related constituents of V_2^{o} calculated by Eqs (7) and (8) for solutions of TMDETA and HMTA in ordinary and heavy water at different temperatures, *T* (± 0.01 K), and p≈0.1MPa

T /K	Tetramethylenediethylenetetramine				Hexamethylenetetramine [2]			
	$10^6\overline{V}_{\text{cav}}$/(m^3·mol^{-1})		$-10^6\overline{V}_{\text{int}}$/(m^3·mol^{-1})		$10^6\overline{V}_{\text{cav}}$/(m^3·mol^{-1})		$-10^6\overline{V}_{\text{int}}$/(m^3·mol^{-1})	
	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O	H_2O	D_2O
278.15	264.98	265.71	128.71	129.33	184.68	185.26	76.94	77.92
288.15	264.67	264.98	127.73	127.86	184.44	184.68	75.81	76.12
298.15	264.83	264.93	127.30	127.10	184.57	184.65	75.20	75.17
308.15	264.90	264.89	126.74	126.42	184.62	184.62	74.61	74.37
318.15	265.67	265.60	126.89	126.49	185.22	185.17	74.68	74.27

The assessment of data in Table 5 shows that the $\overline{V}_{\text{cav}}$values are positive and more than two times higher than (in magnitude) the negative $\overline{V}_{\text{int}}$ values because $V_2^{\text{o}} \ll \overline{V}_{\text{cav}}$. As V_2^{o}, the "cavity volume" increases with the molecular size of an aminal solute. However, in contrast to $\overline{H}_{\text{cav}}$rising abruptly with thermal expansion of the solute structure [7], the temperature dependences of $\overline{V}_{\text{cav}}$ for both TMDETA and HMTA have characteristic features. Thus the $\overline{V}_{\text{cav}}$ (*T*) variations do not exceed ~ 0.8·10^{-6} m^3·mol^{-1} within the temperature interval studied. Herewith the $\overline{V}_{\text{cav}}$ *vs*. *T* curves for both adamanzanes exhibit a weak-pronounced minimum near $T \approx 290$ K in H_2O and shifting towards higher temperatures up to $T = 308$ K in D_2O, where a negative-to-positive sign inversion of IE in $\overline{V}_{\text{cav}}$ occurs (see Table 5). The same does the $\overline{V}_{\text{int}}$ values at higher temperatures (see Table 5).

This non-trivial behavior of $\overline{V}_{\text{cav}}$-*T* functions is related to the above-mentioned differences in properties of ordinary and heavy water. Consequently, we compare the ability of cage-like solute molecules to be built into the initial structural matrix of each of solvent. One of possible reasons is not only the more evident ability of heavy water molecules to form the hydrogen-bonded solvation complex with a TMDETA (HTMA) molecule [6, 7], but also the "isotope shift" between the regions of anomalous changes in V_1 and $\beta_{T,1}$ as well as d_1 forliquid H_2O and D_2O on the temperature scale (see Table 5). Since the quantities relate directly to the spatial distribution of H_2O and D_2O molecules in the structural packing of each of solvating media, this explanation seems to be quite reasonable. According to our previous conclusions [7], we can agree with the fact that $\delta\overline{H}_{\mathrm{cav}}(H_2O \rightarrow D_2O)$ values, which increase in magnitude when going from HMTA to TMDETA, are negative for both adamanzanes compared.

In case of $\overline{H}_{\mathrm{int}}$ [7,9,10], the negative sign at $\overline{V}_{\mathrm{int}}$ (see Table 5) means that the interactions of TMDETA – H_2O (D_2O) and HMTA – H_2O (D_2O) are more significant than the interactions between the molecules of water isotopologue. This is result of strengthening the aqueous structure around each of solutes. The trend of changing $\overline{V}_{\mathrm{int}}$ at the replacement of HMTA with TMDETA confirms the above conclusions about the more significant heterocomponent interaction in the hydration complex containing a bulkier adamanzane. The main increasing of the solvent structure around TMDETA as a solute in H_2O or D_2O shows the effect of hydrophobic hydration [5, 7-9]. The difference between two compared adamanzanes is caused by two additional $>CH_2$ groups in the cage-like molecule (see Fig. 1).

In accordance with the structure-dependent nature of thermodynamic (packing- and energy-related) solvation characteristics [18, 25], we can suggest that there is an obvious interrelation between the IEs in $\overline{V}_{\mathrm{cav}}$ and $\overline{H}_{\mathrm{cav}}$ as well as $\overline{V}_{\mathrm{int}}$ and $\overline{H}_{\mathrm{int}}$ for aqueous TMDETA or HMTA. Indeed, the "evolution picture" for each of such functions will noticeably vary when going from one temperature to another. The corresponding correlations are plotted in Figs 4, *a-b*.

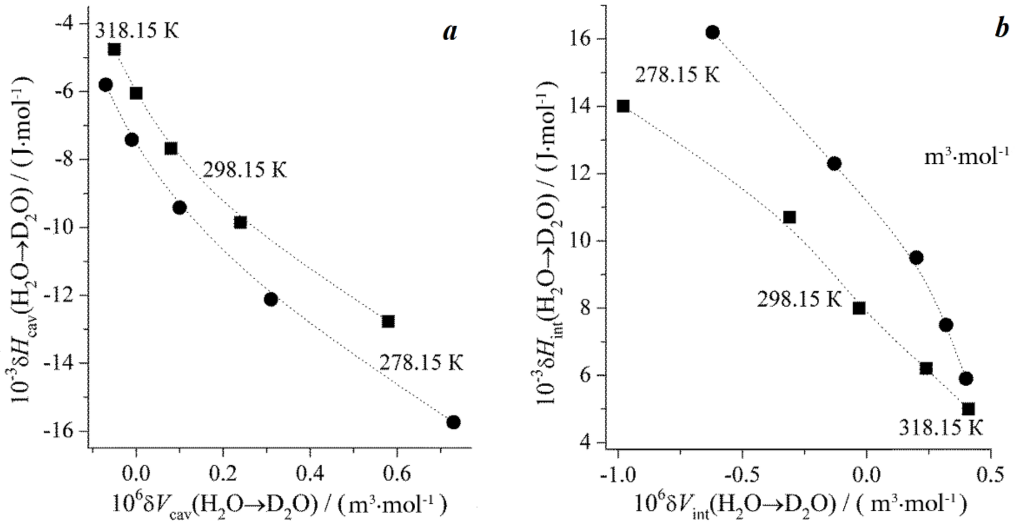


Fig. 4. Interrelations between volume-isotope and enthalpy-isotope effects in SPT-contributions from the cavity formation (***a***) and solute – solvent interaction (***b***) for aqueous solutions of TMDETA (●) and HMTA (▪) at all the temperatures considered. The uncertainty of each of values depicted corresponds to the filled character size

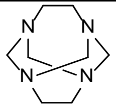
The results presented in Fig. 4, *a* demonstrate that the effect of H_2O-by-D_2O solvent isotope substitution on trends of changing the $\overline{H}_{\mathrm{cav}}(T) - \overline{V}_{\mathrm{cav}}(T)$ function is more noticeable in case of aqueous TMDETA at lower temperatures. But the different issue occurs in case of comparing the correlation dependences between $\delta\overline{H}_{\mathrm{int}}(T)$ and $\delta\overline{V}_{\mathrm{int}}(T)$. Unlike the evolution of the $\delta\overline{H}_{\mathrm{int}}$ ($H_2O \rightarrow D_2O$) values with temperature (see Fig. 4, *b*,) the variation range of the corresponding volume-isotope effect becomes narrow at replacement of HMTA by TMDETA. We possess, it is a result of the redistribution inconstituents of interaction-related thermodynamic effects during the deuteration of water molecules. As we noted above, this may be primarily due to an increase in hydrophobic effects at the expense of stronger D–O···D bonds [2, 7, 10, 18]. According to [7], the given circumstance most likely to be the reason why the $\delta\overline{H}_{\text{int}}(T)$ values are positive and increase when going to both adamanzane with abulkier molecule and lower temperatures (see Fig. 4, *b*). Therefore, the relative contribution of the N···H(D)–O-bonding to the structure-forming process seems to be greater in aqueous HMTA due to the packing-steric features manifested in the hydration process of this adamanzane [2, 10, 26].

The above-noted fact of more significant volume-isotope transformations induced by the interaction of HMTA with an aqueous environment corresponds to the ability of this solute to interact with solvent molecules through hydrogen-bonding. Being promoted by the substitution of H_2O with D_2O, the difference in $\delta\overline{V}_{\text{int}}$ between the aminals compared becomes decreasingly distinct with increasing temperature and it virtually disappears at T = 318.15 K (see Fig. 4, *b*).

Experimental part

A purified TMDETA sample (see Table 6) was dried at T = 323 K in a vacuum chamber for two days, then the crystalline product was crushed to powder and stored in a lightproof vacuum desiccator over phosphorous pentoxide. The sample melting point determined utilizing a Sanyo Gallenkamp capillary instrument was (456.0±0.5) K (literature data: 455.7 K [7] and 456.5 K [27], with a standard uncertainty of 0.5 K).

Table 6. Provenance and purity of the TMDETA sample examined

Characteristics	Solute (in the individual crystalline state)
Structure, molecular brutto-formula and molar mass, M_2 / (g·mol^{-1})	 $C_8H_{16}N_4$: M_2= 168.2420
CAS reg. no.	51-46-7
IUPAC name	1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane
Source	Original synthesis [7, 13, 28] performed by one of us (Dr. V. Baranov)
Initial mass fraction purity	≥ 0.98 (after synthesis)
Purification method	Double recrystallization from ethanol (Fluka: puriss) followed by final washing with cold diethyl ether (Fluka: ACS reagent) [2, 7, 13]
Final mass fraction purity	≥ 0.996 (with a content of residual water of <0.0001 m.f. by the Karl Fischer method)
Analysis method	High-performance Liquid Chromatography (HPLC)

The authenticity of the TMDETA specimen was also characterized by measuring the ^{1}H-NMR and ^{13}C-NMR spectra in DMSO-d_6 (relative to tetramethylsilane) at T = (300 ± 1) K using 300 MHz and 125 MHz Bruker AM devices (Germany), respectively. The results of our NMR-spectroscopic experiments were compared with those available in other sources. The chemical ^{1}H-shifts, δ /ppm, being 3.78 (s, 8H, 4CH$_2$) and 3.09 (s, 8H, 4CH$_2$), are in rather good agreement with the literature data: 3.98 (s, 8H) and 3.26 (s, 8H) [28], and 3.89 (s, 8H) and 3.17 (s, 8H) [29]. *The* ^{13}*C NMR spectrum*, having the values of δ /ppm to be 58.12 (CH$_2$) and 73.19 (CH$_2$), are also in a satisfactory agreement with the corresponding values from the works [28, 29]: 58.57 and 73.74 [28], and 58.58 and 73.54, respectively. The some discrepancies between our and other values of δ seem due to the procedure peculiarities in NMR measurements. To achieve reliable quantitative results, the adequate time was allowed between NMR scans in our experiments.

Ordinary water of natural isotopic composition was deionized and twice distilled up to a specific conductivity of $\kappa = 1.3 \cdot 10^{-6}$ S·cm^{-1} before experiments. Heavy water (Chemical Lines, Russia) with (99.93±0.02) mass % of D_2O and $\kappa = 3.0 \cdot 10^{-6}$ S·cm^{-1}(the manufacturer data) was used. The deuterium content in the D_2O sample was assessed using the additive scheme based on the comparison of experimentally obtained density data with those for the absolutely deuterium-substituted heavy water (*i.e.*, containing 100 at % D) at different temperatures [20]. The content of residual H_2O in heavy water was taken into account in the calculation of the D_2O molar mass, M_1, while preparing the H/D isotopically distinguishable aqueous solutions of TMDETA.

The TMDETA solutions of desired compositions in both H_2O and D_2Owere prepared by weighting with an uncertainty of $5 \cdot 10^{-5}$gusing the AND GH-202 analytical balance (Japan). For this purpose, we used hermetically sealed glass flasks (of a ~ 40 cm^3 volume) and a dry transparent glove-box.

The solution densities, ρ_s, were measured by an Anton Paar DMA 5000 M densimeter (Austria) equipped with a Pyrex-glass oscillating U-tube of ~2 cm^3 in volume. The measuring cell temperature was kept constant to 0.01 K. All densimetric experiments were conducted at the ambient pressure of p = (99.6±0.8) kPa. The experimental and calibration procedures were detailed in [2, 13, 15, 18]. All the density measurements were performed in the *isoplethal* mode caused by a temperature scanning over the particular solution filled in the densimeter cell with the repetition of the scan for next solution. The quality of the "local" water applied in the experiments was systematically checked by comparing its density with the "Ultra-pure water" density standard (from Anton Paar). During five-fold measurements, the $\rho_s(m_{aq})$values were reproducible to 0.005 kg·m^{-3}. The error in measuring ρ_s caused by the presence of trace impurities in solution components was assessed to be lower than 0.01 kg·m^{-3}. The same applies to the influence of uncertainties in preparing the desired solute concentration. Hence, given the influence of all factors, the overall uncertainty in measuring ρ_s did not exceed 0.03 kg m^{-3}, a fact that does not contradict in overall the recommendations [30] with respect to employing a similar setup to the densimetry experiments.

Conclusions

The main goal of this study was to derive additional information about volume-related characteristics of TMDETA (tetramethylenediethylenetetramine) or *teotropine*as a solute in heavy (D_2O) water using the results of high-precision densimetric experiments and the previously derived respective data on the (H_2O + TMDETA) system under the same conditions. It is established that in case of HMTA (hexamethylenetetramine) or *urotropine* – anadamanzane-type solute with a similar aminal (cage-like) molecular structure – the solvent H_2O-by-D_2O isotope substitution has insignificant influence on the standard molar volume of TMDETA in water. In contrast to the negative-to-positive sign inversion in the volume-isotope effect (IE) for

HMTAin water at $T \approx 290$ K, the corresponding IE for TMDETA was found as positive and increasing with temperature. This unusual effect does not comply with the conventional behavior of the predominantly hydrophobic solute whose molecules form hydration complexes in D_2O of a smaller volume than in ordinary water. Indeed, the volume-isotope differences between the aminal-containing aqueous systems compared virtually disappear near $T = 318$ K.

The effect of loosening the molecular packing of the TMDETA solvation complex formed in D_2O did not yet found a reasonable explanation. Obviously, this is due to the peculiarities of both the formation of stronger heterocomponent D bonds and the solvent reorganization around the bulkier hydrophobic molecules TMDETA. The fact of forming the denser aqueous structure around the TMDETA molecules, compared to HMTA those is in compliance with trend of changing the enthalpy effects induced by solute – solvent interactions in terms of Scaled Particle Theory (SPT): it may be by strengthening the solute – solvent interaction, which is more pronounced in the D_2O medium. The results of analyzing the contributions to the standard molar volume within the scope of SPT presume that the structure matrix of D_2O is better suited for incorporation of a bulkier TMDETA molecule. It happens in case of a HMTA molecule. Therefore, due to the redistribution in hydrophilic and hydrophobic constituents of the volume-solvation effect during deuteration of water molecules, structure transformations induced by the interaction of HMTA with an aqueous environment seem to be more pronounced.

The most interesting is the fact that IEs in the volume SPT-contribution from solute – solvent interaction undergo the negative-to-positive sign inversion nearby $T = 298$ K in the case of HMTA and at a higher temperature for TMDETA. This fact obviously related to the temperature range in which hydrogen-bonded aggregates of the HMTA·$6H_2O$ (or HMTA·$6D_2O$) composition lose in their stability, does not suggest the existence of similar cluster-type aggregates in aqueous solutions of a more hydrophobic aminal solute, which is TMDETA (at least at the chosen temperatures). Unfortunately, other information on whether there are any structure-ordered stable aggregates (solvates) in aqueous TMDETA is not currently available.

Also, one of the main unresolved problems so far is whether TMDETA really behaves as a predominantly hydrophobic solute, whether it forms strong hydrogen bonds with water and how these relate to those formed in aqueous solutions of HMTA. The additional experimental and theoretical information about the structural state of aqueous (hydrated) TMDETA will help us to support some of our claims. Therefore, our future investigation will allow us to obtain the temperature-dependent data on the enthalpies of dilution of TMDETA and HMTA solutions in H_2O and D_2O, with the subsequent estimation of enthalpy-related coefficients of the solute – solute pair interaction.

References

1. **Zwier, J.M., Brouwer, A.M., Buma, W.J., Troisi, A. & Zerbetto, F.** (2002) Structure and photophysics of an old, new molecule: 1,3,6,8-tetraazatricyclo[4.4.1.1(3,8)]dodecane, *J. Am. Chem. Soc.*, (124), pp. 149-158. DOI: 10.1021/ja016971b.
2. **Ivanov, E.V.** (2018) Temperature-dependent standard volumetric properties of hexamethylenetetramine in ordinary and deuterated water: A study resolving debatable issues being commented in the [Journal of Molecular Liquids, 248 (2017) 48-52], *J. Mol. Liq.*, (272), pp. 218-225. DOI: 10.1016/j.molliq.2018.09.046.

3. **Vasil'ev, D.A., Khairullin, I.N., Zolotukhin, S.N., Feoktistova, N.A. & Kuryanova, N.Kh.** (2011) Study of the bactericidal and bacteriostatic action of teotropine on microorganisms of various morphological structures, *Vestnik Ul'yanovskoi GSKhA*, 1(13), pp. 75-78 (in Russian).
4. **Balysheva, V.I., Nesterov, E.A., Lunitsin, A.V., Zhivoderov, S.P., Gorshkova, T.F., Lapteva, O.G., Balyshev, V.M. & Kolbasov, D.V.** (2013) Efficacy of a trivalent inactivated vaccine against bluetongue in both cattle and small ruminants, *Doklady Ross. akad. selskokhoz. nauk*, (39), pp. 516-518. DOI: 10.3103/S1068367413050030 (in Russian).
5. **Blanco, L.H. & Dávila, M.T.** (2010) Osmotic and activity coefficients of two macrocyclic aminals in aqueous solution at 288.15, 293.15, 298.15 and 303.15 K, *Fluid Phase Equil.*, (293), pp. 237-241. DOI: 10.1016/j.fluid.2010.03.012.
6. **Romero, C.M. & Mesa, H.J.** (2017) Effect of temperature on the partial molar volumes and viscosities of two macrocyclic aminals in water and deuterium oxide, *J. Mol. Liq.*, (242), pp. 244-248. DOI: 10.1016/j.molliq.2017.06.101.
7. **Ivanov, E.V., Batov, D.V., Lebedeva, E.Yu. & Baranov, V.V.** (2021) Some interaction-related thermodynamic properties of aqueous tetramethylenediethylenetetramine (drug *teotropine*) solutions: Effect of the solvent H/D isotope substitution and temperature, *J. Mol. Liq.*, (326), pp. 115274/1-115274/8. DOI: 10.1016/j.molliq.2020.115274.
8. **Blanco, L.H. & Sanabria, N.R.** (2007) Solubility of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) in water at temperatures between 275 K and 303 K, *J. Chem. Eng. Data*, (52), pp. 2288-2290. DOI: 10.1021/je700304z.
9. **Salamanca, Y.P., Blanco, L.H. & Vargas E.F.** (2013) Enthalpies of solution of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane in aqueous solution as a function of concentration and temperature, *J. Therm. Anal. Calorim.*, (114), pp. 451-455. DOI: 10.1007/s10973-012-2870-9.
10. **Ivanov, E.V. & Batov, D.V.** (2019) Unusual behavior of temperature-dependent solvent H/D isotope effects in the enthalpy and heat capacity of hexamethylenetetramine (*urotropine*) hydration, *J. Mol. Liq.*, (285), pp. 508-514. DOI: 10.1016/j.molliq.2019.04.104.
11. **Soper, A.K. & Benmore, C.J.** (2008) Quantum differences between heavy and light water, *Phys. Rev. Lett.*, (101), pp. 065502/1-065502/4. DOI: 10.1103/PhysRevLett.101.065502.
12. **Ivanov, E.V.** (2017) Some comments on the paper "Effect of temperature on the partial molar volumes and viscosities of two macrocyclic aminals in water and deuterium oxide" by Carmen M. Romero and Holman J. Mesa [Journal of Molecular Liquids, 242 (2017) 244-248], *J. Mol. Liq.*, (248), pp. 48-52. DOI: 10.1016/j.molliq.2017.09.125
13. **Ivanov, E.V., Lebedeva, E.Y., Baranov, V.V. & Kravchenko, A.N.** (2022) Volume properties of tetramethylenediethylenetetramine (pharmaceutical *teotropine*) in aqueous solutions between 278.15 and 318.15 K, *J. Mol. Liq.*, (174), pp. 106-860/1-106860/6. DOI: 10.1016/j.jct.2022.106860.
14. **Ansari, M.S. & Hafiz-ur-Rehman** (2011) Aquamolality: a useful concentration unit, *Phys. Chem. Liq.: Int. J.*, (49), pp. 743-745. DOI: 10.1080/00319104.2010.509723.
15. **Abrosimov, V.K. & Ivanov, E.V.** (2011) *Densimetry of solutions. Theoretical and Experimental Methods of Solution Chemistry*, Moscow: Prospekt (in Russian).
16. **Ivanov, E.V.** (2021) The solvomolality concept as a step in developing the ideas of structure-thermodynamic characteristics of solutions: dedicated to the anniversaries of the birth of G.A. Krestov and the foundation of the institute of solution chemistry of RAS being named after him, *Izv. Vuzov. Khimiya i Khim. Theknol.*, 64(10), pp. 6-15. DOI: 10.6060/ivkkt.20216410.6461 (in Russian).
17. **Wüzburger, S., Sartorio, R., Guarino, G. & Nisi, M.** (1988) Volumetric properties of aqueous solutions of polyols between 0.5 and 25°C, *J. Chem. Soc., Faraday Trans.*, 1(84), pp. 2279-2287. DOI: 10.1039/F19888402279.
18. **Ivanov, E.V., Lebedeva, E.Yu., Petrovskaya, S.G., Baranov, V.V., Kravchenko, A.N. & Ivanova, N.G.** (2017) Volume-related interaction parameters for dilute solutions of *Mebicaret* (2,4-dimethyl-6,8-diethylglycoluril) in normal and heavy water between 278.15 K and 318.15 K, *J. Mol. Liq.*, (242), pp. 160-167. DOI: 10.1016/j.molliq.2017.07.003.
19. **Mak, T.C.W.** (1965) Hexamethylenetetramine hexahydrate: a new type of clathrate hydrate, *J. Chem. Phys.*, (43), pp. 2799-2805. DOI: 10.1063/1.1697212.

20. **Kell, G.S.** (1977) Effect of isotopic composition, temperature, pressure, and dissolved gases on the density of liquid water, *J. Phys. Chem. Ref. Data*, (6), pp. 1109-1131. DOI: 10.1063/1.555561.
21. **Lepori, L. & Gianni, P.** (2000) Partial molar volumes of ionic and nonionic organic solvents in water: a simple additivity scheme based on the intrinsic volume approach, *J. Solution Chem.*, (29), pp. 405-447. DOI: 10.1023/A:1005150616038.
22. **Kuz'min, V.S. & Katser, S.B.** (1992) Calculation of the Van der Waals volumes of organic molecules, *Izv. RAN. Ser. khim.*, (41), pp. 720-729. DOI: 10.1007/BF01150899 (in Russian).
23. **Hepler, L.G.** (1969) Thermal expansion and structure in water and aqueous solutions, *Can. J. Chem.*, (47), pp. 4613-4617. DOI: 10.1139/v69-762.
24. **Pierotti, R.A.** (1976) A scaled particle theory of aqueous and nonaqueous solutions, *Chem. Rev.*, (76), pp. 717-726. DOI: 10.1021/cr60304a002.
25. **Ivanov E.V**. (2012) Thermodynamic interrelation between excess limiting partial molar characteristics of a liquid nonelectrolyte, *J. Chem. Thermodyn.*, 47, pp. 437-440. DOI: 10.1016/j.jct.2011.11.018.
26. **Malenkov, G.G. & Toryanik, A.I.** (1976) Molecular structure of aqueous solutions of hexamethylenetetramine, *Zhurn. strukt. khimii*, (17), pp. 46-49. DOI: 10.1007/BF00748391 (in Russian).
27. **Kuznetsov, A.I., Shukkur, A.H. & Kamara, K**. (2008) Synthesis of 4,5-dihydro-1,6:3,8-dimethano-1,3,6,8-benzotetrazecine, *Izv. RAN. Ser. khim.*, (57), pp. 1575-1577. DOI: 10.1007/s11172-008-0205-6 (in Russian).
28. **Peori, M.B., Vaughan, K. & Hooper, D.** (1998) Synthesis and characterization of novel *bis*-triazenes: 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes and 1,3-di-2-[(4-methoxyphenyl)-1-diazenyl] imidazolidine. The reaction of diazonium ions with ethylenediamine/formaldehyde mixtures, *J. Org. Chem.*, (63), pp. 7437-7444. DOI: 10.1021/jo981276g.
29. **Clavijo, J.A. & Blanco, L.H.** (2012) Effect of two macrocyclic aminals on the temperature of maximum density of water, *J. Solution Chem.*, (41), pp. 680-689. DOI: 10.1007/s10953-011-9736-9.
30. **Wagner, Z., Bendová, M., Rotrekl, J., Sýkorová, A., Čanji, M. & Parmar, N.** (2021) Density and sound velocity measurement by an Anton Paar DSA 5000 density meter: Precision and long-time stability, *J. Mol. Liq.*, (329), pp. 155547/-155547/17. DOI: 10.1016/j.molliq.2021.115547.

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