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Interaction studies of diglycine with aqueous solutions of sulphathiazole drug at different temperatures

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The interactions of diglycine with sulphathiazole drug as a function of temperatures have been studied using volumetric and acoustic parameters. Densities and speeds of sound of diglycine in (0.001, 0.002, 0.005 and 0.010) mol·kg^{-1} aqueous solutions of sulphathiazole drug have been measured at five different temperatures of (288.15, 293.15, 298.15, 303.15 and 308.15) K under 0.1 MPa pressure. From density data, the apparent molar volume, the partial molar volume and the standard partial molar volume of transfer for glycine from water to aqueous sulphathiazole solutions have been calculated. Partial molar isentropic compression and partial molar isentropic compression of transfer have been calculated from the speed of sound data. Transfer parameters by using cosphere overlap model have been explained on the basis of ionic-hydrophilic, hydrophilic-hydrophilic, hydrophilic-hydrophobic and hydrophobic-hydrophobic group interactions. To draw the conclusion from the volumetric and acoustic data, limiting apparent molar expansion as well as the hydration numbers have been studied. The calculated values of thermal expansion coefficient have small and positive values. All of these derived or calculated parameters are explained to understand the solvation behaviour and various types of interactions born in the ternary solutions of (dipeptide + drug + water) due to change in structure. We have also attempted to examine the temperature and concentration dependence of such interactions.

Keywords: Diglycine, Sulphathiazole, Apparent molar volume, Apparent molar isentropic compression

The interactions of water with the functional groups of proteins play important factor in determining the conformational stability of proteins[1,2]. The study of the solvent effect on the properties of model compounds such as amino acid/peptide is quite helpful in understanding water-protein interactions in solutions[3]. The partial molar volume and the related volumetric parameters of drug compounds in dilute aqueous solutions at different temperatures have been investigated by several authors[4–8]. Moreover, physico-chemical and thermodynamic investigations of drug molecule with amino acid/peptide is of much significance in order to understand the nature and the extent of the patterns of interaction in solutions and their variations with temperature and composition. Importance of studying low molecular weight model compounds lies in the fact that one can systematically alter the structure and therefore contribution of side chain groups of amino acid / peptide can be seen easily[9]. Drug can interact with small peptides to change the conformation of proteins either by stabilizing or destabilizing them. The recognition of drug-peptide interactions in aqueous solution has always been a matter of interest[10,11]. It is generally accepted that proteins stabilize because of hydrophobic effect[12], although there was a dispute reported by Makhatadze and Privalov[13] who predicts that binding model describes well but then Franks[14] strongly argued in the article "Protein stability" regarding involvement of hydrophobicity rather than binding which is responsible for solubilising and denaturing effects. Although no definite principle has been laid down in predicting the effect of solvent on the structure and reactivity of solutes, but much progress has been achieved[15-17]. Diglycine is a dipeptide made up of two glycine molecules joined by peptide linkage and is used in the synthesis of more complicated peptides. Whereas sulphathiazole used as a short-acting sulfa drug, is additionally significant class of heterocyclic compound, found in numerous powerful biologically active antimicrobial drug[18]. Sulfathiazole is effective against a wide range of gram positive and gram negative pathogenic microorganisms. It has a role as an antiinfective

agent. To study this class of compounds with small peptide are of potential interest that can provide valuable information regarding the conformational stability of proteins in these solutions, their solubility, folding/unfolding character, solute-solute and solute-solvent interactions[19,20].

There have been some source investigators in aqueous saccharide solutions[21-24] but very few in aqueous drug solutions[25-27] probably due to complex nature of their interactions. Our research group has attempted to quantify the bio-molecular interactions of biomolecules with drugs[28,29]. The systematic study of peptides with amphiphilic drug which enhances the probability of interactions with the biomolecules can provide valuable information about their behaviour in solutions and insight into the hydration of biological systems. For this purpose, it is necessary to investigate solutions of peptides with drugs. To this end, in the present paper, we report the density and speed of sound measurements of diglycine in aqueous drug solutions at T=(288.15 to 308.15) K and at atmospheric pressure from which the values for infinite dilution of apparent molar volumes are calculated with the help of least-square method[30]. The limiting apparent molar volumes, limiting apparent molar isentropic compression have been calculated in order to discuss the types of interactions i.e., solute-solute or solute-solvent and also their nature of interactions (hydrophilic-hydrophilic, hydrophilic-hydrophobic, and hydrophobic-hydrophobic), occurring in the ternary systems (dipeptide - drug-water) and its effect with temperature.

Materials and Methods

Diglycine (Loba Chemie Pvt. Ltd. Mumbai, minimum assay 99.0%) was used after drying over silica gel in a vacuum desiccator at room temperature. Sulphathiazole from Sigma Chemicals Co. was dried for 24 h in a vacuum desiccator before use. The structure of this drug is given in Fig. 1.

Freshly prepared triple distilled and degassed water having specific conductance less than 10^{-6} S cm^{-1} was used for the preparation of solutions. Solutions of diglycine in the concentration range of 0.002 to 0.01 mol·kg^{-1} were made by mass on the molality concentration scale with an accuracy of $\pm 1\times10^{-5}$. All the components were mixed together to form different concentrations using an analytical balance (Afcoset ER – 182A) having a precision of ± 0.01 mg. The standard uncertainty recorded in molality as per stated purities were in the range ± 2×10^{-5} mol kg^{-1}. To prevent the prepared mixtures from atmospheric moisture, cork was firmly applied on the glass vial just after the preparation. These mixtures were directly used to measure the density (ρ) and speed of sound (u) of the solutions by using vibrating–tube digital density and speed of sound analyzer (Anton Paar, DSA 5000 M, Austria) with a precision of ± 1×10^{-3} kg·m^{-3} and 1x10^{-2} m·s^{-1} at five different temperatures T = (288.15, 293.15, 298.15, 303.15 and 308.15) K and at atmospheric pressure.

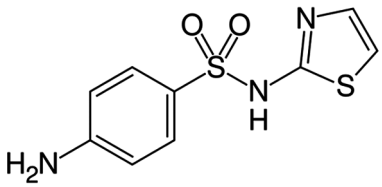

Fig. 1 — Structure of sulphathiazole drug

Before each series of measurements, the instrument was pre-calibrated with doubly distilled, deionised, degassed water, and dry air for the temperature range investigated. The maximal error in the measurements of density and speed of sound relative to water[31,32] is estimated to be less than ± 1.5×10^{-1} kg·m^{-3} and ± 5 $\times10^{-2}$ m·s^{-1}. Both the measured properties are extremely sensitive to temperature, so it was controlled to ± 1×10^{-2} K by a built-in solid state thermostat. The apparatus was also tested with the density of a known molality of aqueous NaCl using the data given by Pitzer *et al*.[33]. Further details of the measurements and calibration of instrument have been described in our previous papers[34,35].

Results and Discussion

Density, speed of sound and partial molar properties

The ρ and u values of diglycine in aqueous sulphathiazole (0.001-0.01 mol·kg^{-1}) solutions at T = (288.15 to 298.15) K have been reported in Table 1. The apparent molar volumes (V_ϕ) $\times10^6$ and the apparent molar isentropic compression ($K_{s,\phi}$) of diglycine in aqueous sulphathiazole solution have been calculated from the experimentally measured densities and speeds of sound using the following equations and are given in Table 2.

$$V_\varphi = \left(\frac{M}{\rho}\right) - \{1000(\rho - \rho_o)m_A\rho\rho_o\} \quad \ldots (1)$$

$$\mathrm{Ks},\phi = (\mathrm{M}\beta_s/\rho) - \{1000(\beta_{s,o}\rho - \kappa_s\rho_o)/m_A\rho\rho_o\} \quad \ldots (2)$$

Table 1 — Densities (ρ) and speeds of sound (u) of diglycine in aqueous solutions of sulphathiazole drug at different temperature (T)

m_A (mol kg^{-1})	T (K)									
	288.15		293.15		298.15		303.15		308.15	
	ρ·10^{-3} (kg m^{-3})	u (m s^{-1})	ρ·10^{-3} (kg m^{-3})	u (m s^{-1})	ρ·10^{-3} (kg m^{-3})	u (m s^{-1})	ρ·10^{-3} (kg m^{-3})	u (m s^{-1})	ρ·10^{-3} (kg m^{-3})	u (m s^{-1})
	0.001 m_B sulphathiazole + diglycine									
0.00000	0.999217	1466.56	0.998312	1482.90	0.997145	1497.10	0.995738	1509.56	0.994117	1520.23
0.00218	0.999314	1466.69	0.998408	1483.07	0.997239	1497.34	0.995831	1509.85	0.994208	1520.58
0.00569	0.999492	1467.28	0.998586	1483.72	0.997410	1498.31	0.996001	1510.97	0.994376	1521.82
0.00847	0.999652	1468.06	0.998746	1484.55	0.997564	1499.59	0.996154	1512.49	0.994527	1523.39
0.01000	0.999748	1468.63	0.998842	1485.12	0.997656	1500.48	0.996245	1513.58	0.994618	1524.48
	0.005 m_B sulphathiazole + diglycine									
0.00000	0.999728	1467.17	0.998818	1483.45	0.997640	1497.67	0.996233	1509.99	0.994607	1520.60
0.00212	0.999821	1467.28	0.99891	1483.61	0.997730	1497.89	0.996321	1510.25	0.994692	1520.90
0.00499	0.999961	1467.64	0.999049	1484.00	0.997866	1498.33	0.996455	1510.74	0.994823	1521.44
0.00801	1.000126	1468.26	0.999215	1484.65	0.998027	1498.99	0.996614	1511.41	0.994978	1522.18
0.01073	1.000293	1469.02	0.999379	1485.41	0.998187	1499.73	0.996773	1512.16	0.995135	1522.96
	0.01 m_B sulphathiazole + diglycine									
0.00000	1.000315	1468.52	0.999398	1484.50	0.998217	1498.74	0.996802	1510.71	0.995166	1521.69
0.00220	1.000409	1468.63	0.999491	1484.62	0.998307	1498.94	0.996891	1510.95	0.995252	1521.98
0.00516	1.000552	1468.76	0.999633	1484.78	0.998446	1499.20	0.997028	1511.27	0.995384	1522.40
0.00839	1.000730	1468.88	0.999811	1484.95	0.99862	1499.47	0.997198	1511.61	0.99555	1522.89
0.01003	1.000829	1468.93	0.999910	1485.04	0.998718	1499.60	0.997294	1511.78	0.995644	1523.16

m_A is the molality diglycine in water - drug solvent systems; m_B is the molality of drug in water; Standard uncertainties, U, are U(T) = ± 0.01 K, U(p) = ± 0.01 MPa, U(**ρ**) = ± 1.5×10^{-1} kg·m^{-3}, and U(u) = ± 5 ×10^{-2} m·s^{-1}

Table 2 — Apparent molar volume V_ϕ, and apparent molar isentropic compression $K_{\phi,s}$, of diglycine in aqueous solutions of sulphathiazole drug at different temperatures

m_A (mol kg^{-1})	T(K)									
	V_ϕ ·× 10^6 (m^3 mol^{-1})					$K_{\phi,s}$ ·×10^6 (m^3 mol^{-1}GPa^{-1})				
	288.15	293.15	298.15	303.15	308.15	288.15	293.15	298.15	303.15	308.15
	0.001 m_B sulphathiazole + diglycine									
0.00218	87.65	88.15	89.12	89.65	90.65	-17.6	-27.4	-44.3	-55.5	-68.4
0.00569	83.79	84.00	85.64	86.04	86.82	-63.5	-71.6	-108.0	-125.0	-138.0
0.00847	80.75	80.90	82.71	83.11	83.89	-98.3	-105.0	-159.0	-184.0	-193.0
0.01000	79.00	79.12	81.06	81.51	82.17	-119.0	-123.0	-186.0	-217.0	-224.0
	0.005 m_B sulphathiazole + diglycine									
0.00212	88.26	88.77	89.77	90.79	92.30	-12.2	-25.4	-39.7	-48.6	-56.3
0.00499	85.42	85.85	86.91	87.77	89.06	-41.6	-49.2	-59.3	-67.2	-74.2
0.00801	82.41	82.56	83.86	84.66	85.98	-70.9	-76.4	-81.4	-85.4	-93.0
0.01073	79.43	79.82	81.17	81.87	83.05	-96.7	-98.9	-99.9	-102.0	-108.0
	0.01 m_B sulphathiazole + diglycine									
0.00220	89.37	89.87	91.29	91.82	93.28	-10.0	-17.2	-31.6	-40.0	-50.1
0.00516	86.16	86.58	87.80	88.44	90.08	-12.0	-18.0	-33.4	-42.6	-56.1
0.00839	82.61	82.88	84.12	85.01	86.51	-14.1	-18.9	-35.4	-44.9	-62.2
0.01003	80.82	81.05	82.19	83.13	84.60	-14.8	-19.2	-36.2	-46.2	-65.8

where M/kg mol^{-1} is the molar mass of diglycine and ρ, ρ_o, β_S and $\beta_{S,0}$ are the densities in kg m^{-3} and coefficient of molar isentropic compression of solution and the solvent (drug+water) in Pa^{-1} and m_A is the molality of solute in kg mol^{-1}, that is, diglycine in solutions. The coefficient of molar isentropic compression has been calculated by the following Laplace- Newton's equation

$$\beta_s = (1/u^2\rho) \quad \ldots (3)$$

Since, for diglycine, a linear dependence of both the apparent molar volumes (V_ϕ) and the apparent molar isentropic compression ($K_{s,\phi}$) on the molality (m_A) was observed over the concentration range studied. Furthermore, both the values show an increase with the chain length i.e., from glycine[36] to diglycine at all the temperatures. Due to the presence of polar groups both on drug as well as on diglycine, the structure enhancing ability of peptide in the solution are improved.

The apparent molar volumes at infinite dilution (V_φ^0) and limiting apparent molar isentropic compression ($K_{s,\phi}^0$) are obtained by the linear regression analysis of the V_ϕ and $K_{s,\phi}$ data using the following equation

$$Y_\varphi = Y_\varphi^o + S_Q mA \quad \ldots (4)$$

where Y_φ^0 (denotes V_φ^0 or $K_{s,\phi}^0$) is the limiting value of the apparent partial molar property that is equal to the infinite dilution partial molar property and S_Q (denotes Sv or S_K) is the experimental or limiting slope indicative of solute-solute interactions. The V_φ^0 or $K_{s,\phi}^0$ at infinite dilution and Sv or S_K with standard errors obtained by the least square fitting of V_ϕ and $K_{s,\phi}$ data using Eqn.(4) are summarized in Table 3.

The V_ϕ and $K_{s,\phi}$ were found to be a linear function of m_A, in the concentration range studied. The V_ϕ and $K_{s,\phi}$ data have been used to see the effect of temperature and drug concentration on solute-solvent interactions occurring in the ternary mixtures of the present study. Table 3 reveals that diglycine studied here has large positive V_φ^0 values and negative $K_{s,\phi}^0$ (Ref 17) values in aqueous sulphathiazole solutions (except at lower temperature and at lower sulphathiazole concentrations), which indicates

Table 3 — Partial molar properties, V_ϕ^0 (m^3 mol^{-1}), $K_{\phi,s}^\circ$ (m^3 $mol^{-1}GPa^{-1}$) and their corresponding slopes, S_v (m^3 kg $mol^{-3/2}$) and S_K (kg m^3 $mol^{-2}GPa^{-1}$) of diglycine in aqueous solutions of sulphathiazole drug at different temperatures

Properties	T(K)				
	288.15	293.15	298.15	303.15	308.15
	Diglycine in water				
$V_\phi^0 \cdot \times 10^6$	74.14(± 0.02) [24]	74.63(± 0.03)*	75.24(± 0.05) [24]	75.57 (± 0.03)*	76.21(± 0.02) [24]
$S_v \cdot \times 10^6$	5.37(± 0.17)	5.40((± 0.02)	5.44(± 0.13)	5.32(± 0.02)	5.22(± 0.14)
$K_{s,\phi}^\circ \cdot 10^6$	-43.58(± 0.22) [22]	-41.64(± 0.25)*	-39.64(± 0.20) [22]	-37.54(± 0.18)*	-35.57(± 0.01) [22]
$S_K \cdot \times 10^6$	2.30(± 1.11)	6.74(± 1.04)	7.94(± 1.13)	8.46(± 0.64)	8.49(± 0.72)
	0.001 m_B sulphathiazole + diglycine				
$V_\phi^0 \cdot \times 10^6$	90.06(± 0.03)	90.62(± 0.07)	91.41(± 0.09)	91.93(± 0.03)	92.99(± 0.05)
$S_v \cdot \times 10^6$	-1103.64(± 5.31)	-1151.6(± 10.26)	-1030.3(± 13.64)	-1041.63(± 4.26)	-1080.56(± 6.93)
$K_{s,\phi}^\circ \cdot \times 10^6$	10.42(± 0.73)	-1.21(± 0.92)	-4.76(± 0.48)	-9.37(± 2.11)	-24.97(± 0.37)
$S_K \cdot \times 10^6$	-12911.2(± 101.1)	-12230.8(± 128.2)	-18156.3(± 67.07)	-20363.1(± 292.9)	-19874.2(± 51.6)
	0.005 $m_B$sulphathiazole + diglycine				
$V_\phi^0 \cdot \times 10^6$	90.48(± 0.124)	91.00(± 0.08)	92.38(±0.10)	92.96(±0.03)	94.50(± 0.10)
$S_v \cdot \times 10^6$	-1022.13(± 17.29)	-1044.98(± 11.09)	-1042.48(±13.97)	-1035.39(±4.31)	-1068.5(± 14.5)
$K_{s,\phi}^\circ \cdot 10^6$	8.00(± 0.86)	-6.97(± 0.75)	-24.66(±0.52)	-35.93(±0.63)	-43.9(± 0.86)
$S_K \cdot \times 10^6$	-9803(± 119.2)	-8588.09(± 103.8)	-7027.6(±72.04)	-6176.75(±87.81)	-6030.6(± 119.7)
	0.01 $m_B$sulphathiazole + diglycine				
$V_\phi^0 \cdot \times 10^6$	91.78(± 0.01)	92.37(± 0.03)	93.82(±0.04)	94.21(±0.08)	95.74(± 0.07)
$S_v \cdot \times 10^6$	-1092.78(± 2.20)	-1128.93(± 5.05)	-1159.15(±5.98)	-1103.27(±12.14)	-1106.51(± 10.10)
$K_{s,\phi}^\circ \cdot \times 10^6$	-8.71(± 0.21)	-16.64(± 0.07)	-30.32(±.106)	-38.38(±0.17)	-45.74(± 0.20)
$S_K \cdot \times 10^6$	-622.8(± 29.6)	-260.24(± 10.88)	-594.08(±14.98)	-782.68(±25.27)	-1986.12(± 31.70)

*Obtained through extrapolation; Expanded uncertainties, $U_{exp.}$ are $U_{exp.}(V_\phi) = \pm 0.05.10^{-6}$ m^3 mol^{-1} , and $U_{exp.}(K_{\phi,s}) = \pm 0.04.10^{-6}$ m^3 mol^{-1} GPa^{-1}; Corresponding references are given in the square bracket

the presence of strong dipeptide – drug-water[22] interactions. The V_φ^0 values increase from glycine[36] to diglycine with the order of the increase of the molar mass or peptide linkage. Further, the values increase with increasing temperature and also with increase in the concentration of sulphathiazole. This signifies that solute-solvent interaction increases[30,35] both with an increase in the concentration of sulphathiazole and temperature. This is due to the reduction in the electrostriction surrounding the zwitterion. This interaction results from the release of some water molecules from the loose solvation shell of the solute (diglycine) in the bulk solution. As a result, there is expansion in volume of the solution. That is, the maximum structure-breaking effect of diglycine takes place in higher concentrations of sulphathiazole and at higher temperature. Moreover, $K_{s,\phi}^0$, values are negative for diglycine but higher in magnitude than glycine[36] in aqueous sulphathiazole solutions. The negative $K_{s,\phi}^0$ values indicate that water molecules around the solute are less compressible than water present in the bulk. This feature is similar to that observed for diglycine in aqueous solutions of saccharides or cyclodextrin[17,22,24,30]. The experimental S_V values in Table 3 for diglycine in sulphathiazole are found to be negative but smaller than the V_φ^0 values, suggesting that solute-solute interactions are weaker than solute-solvent interaction in the system under study.

Partial molar properties of transfer

The transfer partial molar volume of transfer ($\Delta_{tr}V_\varphi^\circ$) and partial molar isentropic compression of transfer ($\Delta_{tr}K_{s,\varphi}^\circ$) of diglycine from water to aqueous solutions of sulphathiazole drug have been determined as

$$\Delta_{tr}Y_\varphi^\circ = Y_\varphi^0(in\ aqueous\ sulpatiazole\ solution) - Y_\varphi^0 \text{ (in water)} \quad \ldots (5)$$

The experimental values V_φ^0 and $K_{s,\phi}^0$ for diglycine in water have been taken from our previous works[22,24]. Table 4 and Figs. 2 and 3 show that $\Delta_{tr}V_\varphi^\circ$ are positive and $\Delta_{tr}K_{s,\varphi}^\circ$ are also positive (except for diglycine at higher concentrations of sulphathiazole and at higher temperatures). The $\Delta_{tr}V_\varphi^\circ$ value can further be explained on the basis of cosphere overlap model[37,38]. According to this model ionic-hydrophilic and hydrophilic - hydrophilic group interactions contribute positively, whereas hydrophilic-

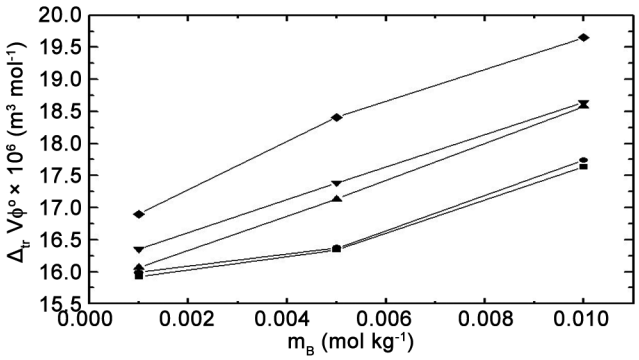

Fig. 2 — Plot of transfer partial molar volume, $\Delta_{tr}V_\varphi^\circ$at infinite dilution versus molality of sulphathiazole drug at T= (■, 288.15 K; ●, 293.15 K; ▲, 298.15 K; ▼, 303.15 K; ○, 308.15 K)

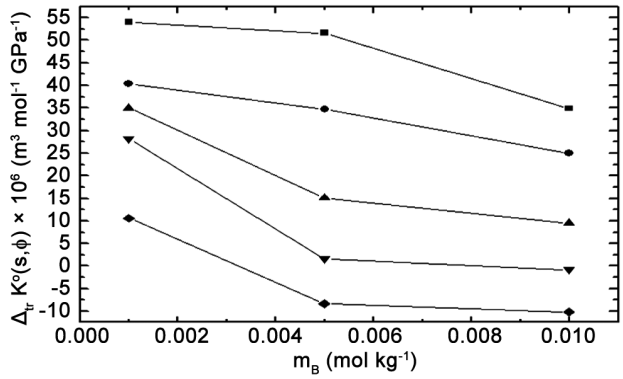

Fig. 3 — Plot of transfer partial molar isentropic compression,$\Delta_{tr}K_{s,\varphi}^\circ$ at infinite dilution versus molality of sulphathiazole drug at T= (■, 288.15 K; ●, 293.15 K; ▲, 298.15 K; ▼, 30315 K; ○, 308.15 K)

Table 4 — Transfer partial molar volumes, $\Delta_{tr}V_\phi^\circ$ and transfer partial molar isentropic compressions, $\Delta_{tr}K_{\phi,s}^\circ$ of diglycine in aqueous solutions of sulphathiazole drug at different temperatures

m_B (mol kg^{-1})	T(K)									
	$\Delta_{tr}V_\phi^\circ$ × 10^6 (m^3 mol^{-1})					$\Delta_{tr}K_{\phi,s}^\circ$ × 10^6 (m^3 mol^{-1} GPa^{-1})				
	288.15	293.15	298.15	303.15	308.15	288.15	293.15	298.15	303.15	308.15
	Sulphathiazole + diglycine									
0.001	15.92	15.99	16.07	16.36	16.90	54.00	40.43	35.04	28.17	10.6
0.005	16.34	16.37	17.14	17.39	18.41	51.58	34.67	15.14	1.61	-8.33
0.01	17.64	17.74	18.58	18.64	19.65	34.87	25.00	9.48	-0.84	-10.17

hydrophobic and hydrophobic- hydrophobic group interactions contribute negatively to the $\Delta_{tr}V_{\varphi}^{\circ}$ values. It can be seen in Table 4 and Fig. 2 that the positive transfer volume $\Delta_{tr}V_{\varphi}^{\circ}$ for diglycine increases with increasing concentration of drug and at all of the temperatures. It may be concluded that in the ternary solutions, the increased concentrations of drug lead to greater ionic-hydrophilic and hydrophilic-hydrophilic interactions between NH_3^+ and COO^- group of diglycine and sulfuric( )group of sulpha drugs that are not influenced by the hydrophilic-hydrophobic interactions. Thus, it promotes the structure making ability of solute in the solution due to hydrophilic interactions between them.

The $\Delta_{tr}K_{s,\varphi}^{\circ}$ values decrease both with increase in concentration of sulphathiazole drug and temperature. The positive value $\Delta_{tr}K_{s,\varphi}^{\circ}$ indicates the dominance of the charged end groups NH_3^+ and COO^-. The interactions between sulphathiazole drug and zwitterionic centre of diglycine increase with drug concentration. Increase in the concentration of drug leads to electrostriction decreases and structure making tendency of the ions increases[2]. That is, the release of water molecules to solvent bulk occurs due to disruption of hydration sphere of the charged end centers of diglycine and sulphathiazole drug. As a result, it leads to large decrease in the compressibility with increase in sulphathiazole concentration. Thus, $K_{s,\phi}{}^0$ values are negative and $\Delta_{tr}K_{s,\varphi}^{\circ}$ values are positive.

The pair and triplet interaction coefficients estimated from $\Delta_{tr}V_{\varphi}^{\circ}$ and $\Delta_{tr}K_{s,\varphi}^{\circ}$ values as given by McMillan *et al.*[39] and Millero *et al.*[40] by using the following equation,

$$\Delta_{tr}Y_{\varphi}^{\circ}(water\ to\ aqueous\ cosolute\ solution) = 2Y_{AB}m_B + 3Y_{ABB}m_B^2 \quad \ldots (6)$$

where, the constants Y_{AB} and Y_{ABB} are pairwise and triplet interaction coefficients. Here A denotes diglycine, B denotes the cosolute (drugs), and m_B is the molality of the cosolute. The $\Delta_{tr}Y_{\varphi}^{\circ}$ values have been fitted to Eqn. (6) to obtain Y_{AB} and $Y_{ABB.}$ The corresponding parameters V_{AB} and V_{ABB} for volumes and K_{AB} and K_{ABB} for isentropic compressions, estimated from $\Delta_{tr}V_{\varphi}^{\circ}$ and $\Delta_{tr}K_{s,\varphi}^{\circ}$ respectively, are listed in Table 5. The pair wise interaction coefficients V_{AB} are positive for sulpha drug at all temperatures whereas triplet interaction coefficient V_{ABB} is negative except at 288.15 K for diglycine. Positive values for V_{AB} strengthen our viewpoint that ionic/hydrophilic-hydrophilic interactions dominate over hydrophobic-ionic interactions between solute and cosolute molecules. The values of V_{AB} for diglycine increase with increase in temperature. The pairwise interaction coefficient K_{AB} corresponding to the isentropic compression is positive except at 308.15 K and it decreases with increase in temperature.

Apparent molar expansibilities

The temperature variation of V_{φ}^0 can be expressed as

$$V_{\varphi}^0 = a + b(T - T_m) + c(T - T_m)^2 \quad \ldots (7)$$

where T_m represents the midpoint temperature of the range used (T_m =298.15 K). Least-square fitting of Eqn. (7) was done to obtain a, b and c parameters. Differentiation of Eqn. (7) with respect to temperature at constant pressure was done to calculate partial molar isobaric expansions

$$E_2^o = (\partial V_{\varphi}^0/\partial T)_P = b + 2c(T - T_m) \quad \ldots (8)$$

It follows from Eqn. (8) that the quantity $b+2c(T-T_m)$ is equivalent to E_2^o. The calculated values of partial molar expansion (E_2^o) at different temperatures are included in Table 6.

Table 5 — Pair, Y_{AB} and triplet, Y_{ABB} interaction coefficients of diglycine in aqueous solutions of sulphathiazole at different temperatures

Temp. (K)	$V_{AB}\cdot\times 10^9$ ($m^3\ mol^{-2}\ kg$)	$V_{ABB}\times 10^{11}$ ($m^3\ mol^{-3}\ kg^2$)	$K_{AB}\cdot\times 10^9$ ($m^3\ mol^{-2}\ kg\ GPa^{-1}$)	$K_{ABB}\cdot\times 10^{11}$ ($m^3\ mol^{-3}\ kg^2\ GPa^{-1}$)
		Sulphathiazole + diglycine		
288.15	3.15	-1.54	11.0	-6.31
293.15	3.15	-1.54	7.68	-4.36
298.15	3.26	-1.58	4.58	-2.81
303.15	3.32	-1.62	2.20	-1.56
308.15	3.49	-1.70	-0.30	-1.67

Table 6 — Partial molar expansions, E_2^0 at infinite dilution and isobaric thermal expansion coefficient, α_2 of diglycine in aqueous solutions of sulphathiazole at different temperatures

m_B (mol kg^{-1})	$E_2^0\cdot\times 10^6$ ($m^3\ mol^{-1}\ K^{-1}$)				
	288.15	293.15	298.15	303.15	308.15
	Sulphathiazole + diglycine				
0.001	-0.018	0.015	0.049	0.083	0.117
0.005	0.056	0.080	0.103	0.127	0.150
0.010	0.087	0.094	0.100	0.107	0.113
	α_2 (K)				
	Sulphathiazole + diglycine				
0.001	-0.00021	0.00017	0.00054	0.00090	0.00012
0.005	0.00062	0.00088	0.00112	0.00136	0.00159
0.010	0.00095	0.00102	0.00107	0.00113	0.00118

The E_2^0values for any solute thought to be sensitive measure of solute-solvent interaction[41]. From Table 6, it has been seen that at each temperature E_2^0 values in aqueous drug solution are increasing regularly with rise in temperature, and with the concentration of sulphathiazole drug except at higher temperatures and higher concentrations. It may be noted that E_2^0 values are positive favouring the solute-solute interactions. The effect is that electrostricted water may be released from the loose salvation layer of diglycine. Removal of water molecules favours diglycine-drug or drug-drug interactions, indicating the value of partial molar expansibility gives information regarding the size of the solute and its hydrophobicity The values of V_φ^0 and E_2^o are further used to calculate the isobaric thermal expansion coefficient, α_2 using following relation[42]

$$\alpha_2 = E_2^0/V_\phi^0 \quad \ldots (9)$$

The α_2 value increases with increase in temperature as well as with increase in concentration of sulphathiazole drug (except at higher concentration and higher temperature) indicating that dipeptide - drug- water interaction increases as concentration of sulphathiazole drug increases. The calculated values of α_2 are included in Table 6.

Hydration Number

The partial molar volume of the peptide can be examined by a simple model[40]

$$V_\phi^0(\text{peptide}) = V_\phi^0(\text{int}) + V_\phi^0(\text{elect}) \quad \ldots (10)$$

where V_ϕ^0 (elect) is the electrostriction partial molar volume due to the hydration of the peptide and can be estimated from experimentally measured values of V_ϕ^0(peptide), and V_ϕ^0(int) is the intrinsic partial molar volume of the peptide and has been calculated from the following expressions[40]

$$V_\phi^0(\text{int}) = (0.7/0.6)\, V_\phi^0(\text{cryst}) \quad \ldots (11)$$

$$V_\phi^0(\text{int}) = (0.7/0.634)\, V_\phi^0(\text{cryst}) \quad \ldots (12)$$

where V_ϕ^0(cryst) (= M/d_{cryst}) is the crystal molar volume and M its molar mass, 0.7 is the packing density for molecules in organic crystals and 0.634 is the packing density for random packing spheres. The values of V_ϕ^0(int) for the peptide were estimated from Eqn. (11) and (12) using d_{cryst} values for diglycine determined by single crystal X- ray diffraction is 1.534 g cm^{-3} taken from the references[43,44].

The change in volume due to electrostriction can be related to the number of water molecules n_H hydrated to the diglycine by[45-47]

$$n_H = -V_\phi^0(\text{elect})/(V_{\phi,e}^0 - V_{\phi,b}^0) \quad \ldots (13)$$

where $V_{\phi,e}^0$ is the molar volume of electrostricted water and $V_{\phi,b}^0$ is the molar volume of bulk water (18.069 x 10^{-6} m^3 mol^{-1} at 298.15 K). The reported value[35,38] of ($V_{\phi,e}^0 - V_{\phi,b}^0$) is ≈–3.3 x 10^{-6} m^3 mol^{-1} at 298.15 K. Further, the number of water molecules n_H hydrated to the diglycine were calculated by using the method given by Millero *et al*.[40,48]

$$n_H = -K_{\phi,s}^0(\text{elect})/\, V_{\phi,b}^0\, K_{s,b}^0 \quad \ldots (14)$$

The values of n_H calculated from Eqn. (13) and (14) using the V_ϕ^0(elect) and $K_{s,\phi}^0$(elect) values determined are listed in Table 7. It can be seen that the n_H values calculated from partial molar volume data decrease with an increase in the concentration of sulphathiazole drug[30]. Similar results are observed between diglycine and sulpha drugs in aqueous solutions[44]. Again, this indicates that an increase in solute–cosolute interaction occurs with increase in concentration of antibiotic drug. This suggests that the interactions between the hydrophilic group of drugs and the charged end centers/polar groups of peptide become stronger with increase in the sulphathiazole concentrations. The values for the diglycine from compressibility data in the presence of sulphathiazole are less than in water and increases with the concentration of sulphathiazole. It again indicates the increase in the solute-cosolute interaction with increasing sulphathiazole drug concentrations as the number of solvent (water) molecules around solute goes on decreasing. Subsequently, solute-solvent

Table 7 — Hydration number, n_H of diglycine in aqueous solutions of sulphathiazole at 298.15 K

m_B (mol kg^{-1})	Hydration number (n_H)		
	From volume		From compressibility
	Using Eqn. 11	Using Eqn. 12	Using Eqn. 14
0.000	7.65	6.02	4.91
0.001	2.75	1.12	0.58
0.005	2.50	0.82	3.04
0.010	2.02	0.39	3.74

interaction decreases. This clearly shows that sulphathiazole drug have a dehydrating effect on diglycine in aqueous solutions. Also, we can classify diglycine as a structure- maker in aqueous solution of sulphathiazole.

Conclusions

In this paper, we have presented the volumetric and acoustic properties of diglycine in aqueous sulphathiazole drug solutions at different temperatures. The apparent molar volume values are positive and apparent molar isentropic compression values are negative in aqueous drug solutions, indicating the presence of strong solute-solvent interactions. The transfer volumes of peptide from water to aqueous drug solutions are positive, suggesting that ionic-hydrophilic and hydrophilic - hydrophilic group interactions play a dominant role in these systems. Positive value of partial molar expansibility and pair wise interaction coefficient indicate the presence of strong solute-solute interaction. These results also confirm the structure making behaviour of diglycine in aqueous drug solution. Hydration number calculated from values of partial molar volume decreases with increase in concentration of sulphathiazole drug, indicating an increase in solute-solvent interactions. Therefore, such a study has great importance in future for formulation development in the pharmaceutical industry, drug delivery and physiological action.

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