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Ion Association and Solvation of Sulfathiazole Sodium in Aqueous and Partial Aqueous Media

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The electrical conductance of sulfathiazole sodium in water and different volume fractions of water + dimethyl sulfoxide (DMSO) and water + ethanol in the temperature range of (283 to 313) K has been measured. Kraus−Bray and Shedlovsky models of conductivity were used for analyzing the conductance data. The limiting ionic conductance, limiting molar conductance, and association constant, K_a, have been determined. On the basis of the viscosity of the solvent, the Walden product and Stokes molecular radius were also determined.

Introduction

The electrical conductivity study of electrolyte in mixed solvents is of importance as it gives information about the behavior of ions in solution, ion−solvent interaction, and solvent structural effects. The study of electrolytes in solvent mixtures is found to be useful for various electrochemical and technical investigations.[1−4]

The study of solvation behavior of medicinal compounds under varying biological conditions is an important field of studies as it reveals much information to medicinal chemists.[5−9] Moreover, these studies help in getting useful information regarding the ion−solvent interactions and also in determining the pharmacological properties of the drug molecules. Ion−solvent interactions are the controlling forces in dilute solutions where the ion−ion interaction is at a minimum. These considerations have influenced us to undertake a conductometric study to investigate the solvation behavior of the drug sulfathiazole sodium in aqueous and partial aqueous media.

Experimental Section

Materials and Methods. Sodium (4-aminophenyl)sulfonyl-(1,3-thiazol-2-yl)azanide (Sigma-Aldrich USA, CAS RN 144-74-1) was used as received. The structure of sulfathiazole sodium is given in Figure 1. Triply distilled water and purified[10] solvents (dimethyl sulfoxide, DMSO, and ethanol) of conductivity 10^{-6} $S^{1-}\cdot cm^{-1}$ at 298 K were used in the present work. Mixed solvents, $\phi_2 = 0.1$, $\phi_2 = 0.2$, $\phi_2 = 0.4$, and $\phi_2 = 0.8$, were prepared by mixing known quantities of water and nonaqueous solvents in volume ratios at laboratory temperature. Solutions of sulfathiazole sodium with a concentration range of (0.001 to 0.01) $mol\cdot L^{-1}$ were prepared in pure or mixed solvents as and when needed. The uncertainty in molar concentration was found to be less than $2.0\cdot 10^{-4}$ $mol\cdot dm^{-3}$. Work could not be carried out beyond the volume fraction $\phi_2 = 0.8$ of ethanol and DMSO due to solubility problems. The conductance measurements were carried out in a digital conductivity meter (CM-180, Elico India) using a calibrated[2] dip-type immersion conductivity cell having a cell constant = 0.998 cm^{-1} and having an uncertainty of ± 0.01 %. The solution of known concentration was placed in a double-walled vessel and kept in a thermostat or cryostat maintained at desired temperature (± 0.01 K) for approximately (20 to 30) min, and its specific conductivity was noted.

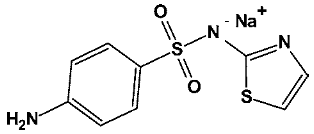

Figure 1. Structural formula of sodium (4-aminophenyl)sulfonyl-(1,3-thiazol-2-yl)azanide.

Results and Discussion

The specific conductance (κ) of solutions of sulfathiazole sodium in water (1) + DMSO (2) and + ethanol (3) were measured experimentally in the temperature range of (283 to 313) K. The specific conductance of sulfathiazole sodium increased with the increase in concentration and temperature. The experimental values of specific conductance in water (1) + DMSO (2) + ethanol (3) are presented in Tables SI 1a to SI 1e and SI 2a to SI 2d in the Supporting Information. After applying solvent corrections,[2] the molar conductance, λ_m, of it was estimated using eq 1

$$\lambda_m = \frac{\kappa}{c} \qquad (1)$$

where c is the concentration and κ is the specific conductance of sulfathiazole sodium solution. The resulted conductance data were analyzed initially by the Kraus−Bray equation.[11]

$$\frac{1}{\lambda_m} = \frac{1}{\lambda_m^o} + \frac{\lambda_m c}{\lambda_m^{o\,2} K_c} \qquad (2)$$

From the intercept and slope of the plot $1/\lambda_m$ versus $\lambda_m c$, the limiting molar conductance (λ_m^o) and the dissociation constant (K_c) were evaluated. However, this model does not include any

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Table 1. Ionic Conductance $\lambda_{\pm}^{o}$, Ionic Walden Product $\lambda_{\pm}^{o}\eta_{o}$, Ionic Radius $r_{\pm}$, and Ionic Mobility $\mu_{\pm}$ for Sulfathiazole Sodium in Water from T = (283 to 313) K

T	λ_{+}^{o}	λ_{-}^{o}	$\lambda_{+}^{o}\eta_{o}$	$\lambda_{-}^{o}\eta_{o}$	r_{+}	r_{-}	μ_{+}	μ_{-}
K	$S\cdot cm^2\cdot mol^{-1}$		$S\cdot cm^2\cdot mol^{-1}\cdot kg\cdot m^{-1}\cdot s^{-1}$		10^{-18} cm		10^{-4} $cm\cdot s^{-1}$	
T/K = 283	34.0	18.6	0.444	0.241	6.53	12.0	3.52	1.93
T/K = 293	44.0	22.0	0.445	0.222	6.33	12.6	4.55	2.28
T/K = 303	56.0	26.0	0.448	0.217	6.04	12.5	5.80	2.69
T/K = 313	68.0	31.0	0.446	0.203	5.88	12.6	7.04	3.21

Table 2. Limiting Molar Conductance λ_{m}^{o} for Sulfathiazole Sodium in Water (1) + DMSO (2) from T = (283 to 313) K

	$\phi_2 = 0.0$	$\phi_2 = 0.10$	$\phi_2 = 0.20$	$\phi_2 = 0.40$	$\phi_2 = 0.80$
property	DMSO	DMSO	DMSO	DMSO	DMSO
T = 283 K			$\lambda_{m}^{o}/(S\cdot cm^2\cdot mol^{-1})$		
λ_{m}^{o} (Kraus−Bray)	52.61	43.27	38.23	22.16	11.96
λ_{m}^{o} (Shedlovsky)	52.49	43.45	36.72	23.15	12.64
T = 293 K					
λ_{m}^{o} (Kraus−Bray)	65.90	54.97	43.18	28.63	14.97
λ_{m}^{o} (Shedlovsky)	65.65	53.15	44.49	29.61	15.58
T = 303 K					
λ_{m}^{o} (Kraus−Bray)	78.13	60.52	55.88	37.04	18.84
λ_{m}^{o} (Shedlovsky)	80.30	61.45	55.71	38.42	19.67
T = 313 K					
λ_{m}^{o} (Kraus−Bray)	98.76	78.42	61.91	44.55	23.08
λ_{m}^{o} (Shedlovsky)	99.50	80.72	63.91	46.29	23.61

Table 3. Limiting Molar Conductance λ_{m}^{o} for Sulfathiazole Sodium in Water (1) + Ethanol (2) from T = (283 to 313) K

	$\phi_2 = 0.0$	$\phi_2 = 0.10$	$\phi_2 = 0.20$	$\phi_2 = 0.40$	$\phi_2 = 0.80$
property	C_2H_5OH	C_2H_5OH	C_2H_5OH	C_2H_5OH	C_2H_5OH
T = 283 K			$\lambda_{m}^{o}/(S\cdot cm^2\cdot mol^{-1})$		
λ_{m}^{o} (Kraus−Bray)	52.61	38.61	29.70	22.48	20.08
λ_{m}^{o} (Shedlovsky)	52.49	39.21	31.77	22.11	21.71
T = 293 K					
λ_{m}^{o} (Kraus−Bray)	65.90	53.3	41.09	31.61	26.09
λ_{m}^{o} (Shedlovsky)	65.65	53.78	19.60	31.49	28.44
T = 303 K					
λ_{m}^{o} (Kraus−Bray)	78.13	68.93	53.68	43.46	33.24
λ_{m}^{o} (Shedlovsky)	80.30	66.66	55.95	41.53	35.39
T = 313 K					
λ_{m}^{o} (Kraus−Bray)	98.76	76.20	67.15	54.01	40.91
λ_{m}^{o} (Shedlovsky)	99.50	74.04	70.10	54.56	44.80

correction for interionic effects or for the activities of the ions. The Shedlovsky[12] model (eq 3) not only solves the above limitations but also provides absolute limiting molar conductance and association constant K_a.

$$\frac{1}{S\lambda_m} = \frac{1}{\lambda_m^o} + \frac{c\lambda_m S f_{\pm}^{\,2} K_a}{\lambda_m^{o\,2}} \tag{3}$$

$$S = \left[\frac{\beta\sqrt{c\lambda_m}}{2\lambda_m^{o\,3/2}} + \sqrt{1 + \frac{\beta^2 c\lambda_m}{4\lambda_m^{o\,3}}}\right]^2 \tag{3a}$$

$$\beta = \frac{8.204\cdot 10^5\ \lambda_m^o}{(\varepsilon T)^{3/2}} + \frac{82.5}{\eta(\varepsilon T)^{1/2}} \tag{3b}$$

$$\log f_{\pm} = \frac{-1.8246\cdot 10^6 (c\alpha)^{1/2}/(\varepsilon T)^{3/2}}{1 + 50.24\cdot 10^8 R(c\alpha)^{1/2}/(\varepsilon T)^{1/2}} \tag{3c}$$

$$\alpha = S\lambda_m/\lambda_m^o; R = q = e_0^2/2\cdot(4\pi\varepsilon_0\varepsilon kT) \tag{3d}$$

where c is the concentration, ε is the relative permittivity of the medium, ε_0 is the vacuum permittivity, R is the Bjerrum distance, k is the Boltzmann constant, T is absolute temperature, and η is the viscosity of the solvent. Required relative permittivity (ε) and viscosity (η) values were obtained from literature[13−15] and used while evaluating the Onsager slope, S and β, as shown in the above equations (eqs 3a and 3b). K_a is the association constant, and $f_{\pm}$ is the mean ionic activity coefficient of the electrolyte.

Limiting Ionic Conductance. Sulfathiazole sodium act as a good electrolyte in presence of solvents liberating sodium ion as

$$C_9H_8N_3NaO_2S_2 \leftrightarrow (C_9H_8N_{3O_2}S_2)^- + Na^+ \tag{4}$$

To have better insight into ion−solvent interactions and hydrophobic interactions, it is desirable to have single ion equivalent conductance values. The single ion conductance gives information regarding the diffusion of drug cations through the different solvent media. The limiting the ionic conductance of Na^+ in water at different temperatures was obtained[13] and was used to evaluate the limiting ionic conductance of the anionic species $(C_9H_8N_3O_2S_2)^-$. The ionic Walden product, ionic radius, and ionic mobility of both the cation and the anion species in water were also computed. These values are shown in Table 1.

Variation of Limiting Molar Conductance with Solvent Composition and Temperature. The calculated values of limiting molar conductance using Kraus−Bray and Shedlovsky models having an uncertainty of ± 0.05 % are presented in Tables 2 and 3. Limiting molar conductances were found to be high in greater relative permittivity region (water) and decreased sharply on adding nonaqueous solvents to it irrespective of the solvent specific property. The mixing of nonaqueous solvent to water brings variation in solvent−solvent interactions leading to variation in permittivity and production of bulky solvent mixture molecules. The addition of DMSO to water decreases the limiting molar conductance, probably due to the breakdown of the three-dimensional structure of pure water. The hydrogen bond formed between water and DMSO is stronger than in pure water due to dipole−dipole interaction,[16] which leads to the association of DMSO and water molecules, leading to reduction in ionic mobility. The addition of ethanol to water also increases the formation of hydrogen bonding and hence leads to the association of ethanol and water molecules. Therefore, both the ionic mobility and the λ_m^o values decrease for the addition of ethanol to water.

The limiting molar conductance of the solute under investigation increased with the increase in temperature from (283 to 313) K for all compositions. The increase in thermal energy breaks higher numbers of hydrogen bonds of water, decreasing the solvated ionic size, and hence increases the mobility of the species. This fact was proved by evaluating the mobility of the anion and cation.

Dissociation Constant/Association Constant. The dissociation constant K_c was obtained from the slope of the linear plot

Table 4. Association Constant K_a for Sulfathiazole Sodium in Water (1) + DMSO (2) + Ethanol (3) from T = (283 to 313) K

T/K	$\phi_2 = 0.0$	$\phi_2 = 0.10$	$\phi_2 = 0.20$	$\phi_2 = 0.40$	$\phi_2 = 0.80$
		Water + DMSO			
T/K = 283	16.84	19.74	21.05	24.59	26.59
T/K = 293	15.73	17.83	18.92	22.40	25.84
T/K = 303	14.89	15.52	16.43	19.38	23.03
T/K = 313	13.06	14.94	15.62	16.93	21.36
		Water + Ethanol			
T/K = 283	16.84	19.47	21.48	34.01	69.53
T/K = 293	15.73	17.16	19.59	32.43	64.54
T/K = 303	14.89	16.42	17.84	30.40	61.04
T/K = 313	13.06	14.98	16.06	28.48	58.15

$1/\lambda_m$ versus $\lambda_m c$ in water (1) + DMSO (2) and + ethanol (3) in between (283 and 313) K. These values are presented in Table SI 3 in the Supporting Information. The dissociation constant increased with the increase in temperature and decreased with the increase in volume of DMSO or ethanol in water.

The association constant, K_a, was determined from the slope of the Shedlovsky plot at all temperatures and compositions. The computed values are presented in Table 4. It increased with the increase in the volume of DMSO and ethanol in water at all studied temperatures, indicating the formation of associated ions. The variation in K_a from one composition to another is primarily due to the change in relative permittivity and also due to the formation of intermolecular hydrogen bonding, causing not only an increase in the thickness of the ionic atmosphere surrounding the polar species but also a reduction in the repulsion between them. The decrease in the hydration of the ions, due to the presence of solvent mixture molecules, leads to an increase in the association constant values. To identify this ionic association a plot of log λ_m versus log c was drawn on the basis of the Fuoss[2,15] equilibrium equation related to partially dissociated electrolytes. It was found to be linear, having a slope of approximately −0.5, indicating the formation of ion pairs in equilibrium with the ions.

Walden Product. If ion mobility is dependent on the bulk viscosity in accordance with the Stokes law, the Walden product[2,15] would be proportional to the reciprocal of the ionic or molecular radius of the species.

$$\lambda_m^o \eta_o = \frac{Ze_0F}{6\pi rT} \qquad (5)$$

where e_0 is the electronic charge, F is the Faraday constant, T is the absolute temperature, Z is the charge on the ion, and r is the effective Stokes molecular or ionic radius calculated using the following Stokes radius equation,[15]

$$r_i = \frac{0.820Z}{\lambda_m^o \eta_o} + 0.0103\varepsilon + 0.85 \qquad (6)$$

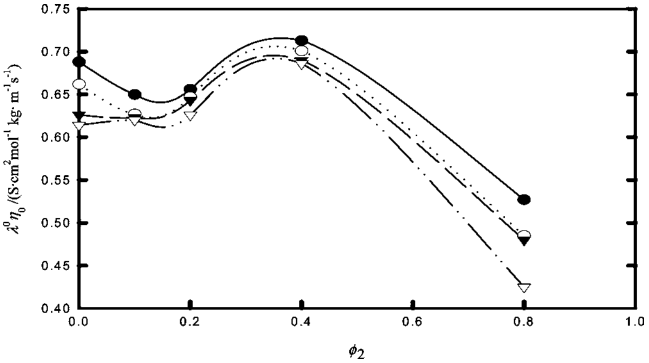

Figure 2. Plots of Walden product $\lambda_m^o\eta_o$/(S·cm²·mol⁻¹·kg·m⁻¹·s⁻¹) against volume fraction ϕ_2 for sulfathiazole sodium in water (1) + DMSO (2) from T = (283 to 313) K.

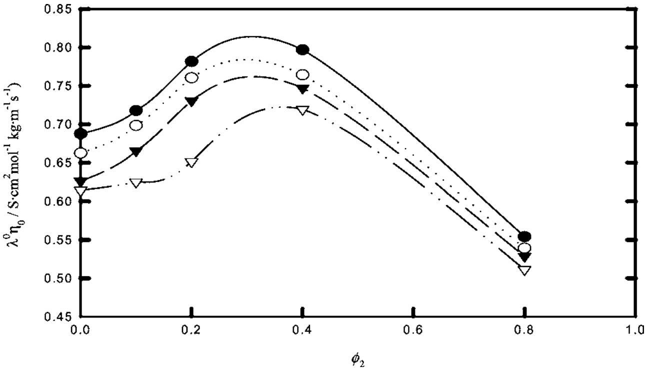

Figure 3. Plots of Walden product $\lambda_m^o\eta_o$/(S·cm²·mol⁻¹·kg·m⁻¹·s⁻¹) against volume fraction ϕ_2 for sulfathiazole sodium in water (1) + ethanol (2) from T = (283 to 313) K.

The calculated values of Stokes molecular radius r_i are presented in Table SI 4 in the Supporting Information. The Walden product was calculated for sulfathiazole sodium in different compositions of solvent mixtures at temperatures between (283 and 313) K and is depicted in Figures 2 and 3. The variation of the Walden product with solvent composition can be explained on the basis of the structure of water−ethanol and water−DMSO mixtures and the effect of ions on these structures. The addition of nonaqueous solvent initially enhances the structure of solvent. The structure enhancement of the solvent mixture appears to reach a maximum near $\phi_2 = 0.2$ to $\phi_2 = 0.3$ ethanol[17] and $\phi_2 = 0.4$ DMSO. The maxima in the Walden product at this region hint at the proposal that the Walden product should decrease with increased temperature because of the reduction in solvent structure at higher temperatures. Moreover, one might expect the effect of temperature on the Walden product to be larger near $\phi_2 = 0.3$ ethanol. Both of these predictions are in good agreement with the Walden product for the water + ethanol mixture as shown in the Figure 3.

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Supporting Information Available:

The measured specific conductance (κ), calculated values of dissociation constant (K_c), and corrected Stokes molecular radius (r_i) for sulfathiazole sodium in water (1) + DMSO (2) and + ethanol (3) from T = (283 to 313) K for all of the reported volume fractions. This material is available free of charge via the Internet at http://pubs.acs.org.

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