Thermodynamic Study of Phenyl Salicylate Solutions in Aprotic Solvents at Different Temperatures†

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Phenyl salicylate is employed as a nervous system depressant as well as an intestinal antiseptic owing to its antibacterial activity upon hydrolysis in the small intestine. Various partial molar quantities, namely, apparent molar volume (V_ϕ), partial molar volume ($V°_m$), thermal expansion coefficient (α_2), and ($\partial^2 V°_m/\partial T^2$), of phenyl salicylate in aprotic solvents, i.e., acetonitrile, dimethyl sulfoxide, tetrahydrofuran, and 1,4-dioxane, at $T =$ (293.15 to 313.15) K have been determined. The density and viscosity data were obtained with the help of a vibrating-tube densimeter and viscometer in a concentrarion range of ($9.6 \cdot 10^{-3}$ to $33.0 \cdot 10^{-3}$) mol·kg^{-1}. The viscosity data have been analyzed using the Jones−Dole equation and the derived parameter B has also been interpreted in terms of solute−solvent interactions.

Introduction

Physicochemical properties of drugs are of interest to know drug action at the molecular level. The action of a drug must be regarded as the vital outcome of physicochemical interactions between the drug and functionally important molecules in the living organism. Most drugs are organic molecules with both solvophilic and solvophobic groups due to which these molecules show specific as well as electrostatic interactions. Hence, knowledge of the physicochemical properties of drugs plays an important role in understanding their physiological actions which are highly dependent upon the solution behavior. Volumetric data of drugs can provide clues to the interactions occurring in cellular fluids. Viscosity B-coefficients along with partial molar volume have been interpreted in terms of various interactions.

Study of the volumetric properties of nonsteroidal anti-inflammatory drugs (NSAIDs) has been the subject of interest because they exhibit analgesic, anti-inflammatory, antipyretic, and platelet inhibitory properties. However, these drugs have serious side effects such as gastrointestinal (GI) toxicities, gastric mucosal ulcerations, and hemorrhage.[1] This work is a continuation of the systematic investigation of volumetric and transport properties of biochemical processes involving drug−macromolecular interactions in various solvents.[2−4] The literature survey reveals that the volumetric properties of phenyl salicylate with the above-mentioned solvent systems are not available and that viscosity measurements of drugs are not very common.

Experimental Section

Materials and Methods. Phenyl salicylate (99 %) was supplied by Aldrich. The structural formula of phenyl salicylate is shown in Scheme 1. The solvents used were acetonitrile (99.5 %, Sigma-Aldrich), dimethyl sulfoxide (99.8 %), tetrahydrofuran (99.9 %), and 1,4-dioxane (99.5 %) (all supplied by Riedel-da Haen). The solvents were used without further purification.

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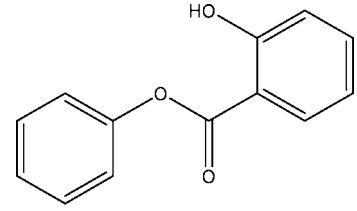
Scheme 1. Structure of Phenyl Salicylate



Solutions of the drug compound were prepared immediately prior to density measurements in a concentration range ($9.6 \cdot 10^{-3}$ to $33.0 \cdot 10^{-3}$) mol·kg^{-1}. Molar solutions were prepared on mass basis. The precision of balance was ± 0.001 g. The densities of solutions were measured by an automated vibrating-tube densimeter (Anton Paar DMA 5000) with an uncertainty of ± 10^{-5} g·cm^{-3} which was calibrated with deionized and doubly distilled water for the temperature range investigated. The density measurements are performed at different temperatures $T =$ (293.15 to 313.15) K ± 0.01 K.

The viscosities were measured by means of an Anton Paar SVM 3000 viscometer at the desired temperatures. The viscometer was calibrated with deionized and doubly distilled water. The uncertainty of viscosity measurements was ± 0.003 mPa·s. The viscosities were measured at different temperatures $T =$ (293.15 to 313.15) K ± 0.01 K. All experiments were repeated three times.

Results and Discussions

From the density values, apparent molar volume, V_ϕ, is calculated using the following equation[5]

$$V_\phi = \frac{1000(\rho_o - \rho)}{c\rho\rho_o} + \frac{M_2}{\rho} \quad (1)$$

where ρ and ρ_0 are the densities of the solution and solvent, respectively; M_2 is the molar mass of the drug; and c is the concentration.

The apparent molar volume, V_ϕ, of phenyl salicylate is plotted against the concentration, c, in different aprotic

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Table 1. Density, ρ, of Molality $10^{-3}\cdot c$ and Apparent Molar Volume, V_ϕ, of Phenyl Salicylate in Acetonitrile at T = (293.15 to 313.15) K

T/K	c/mol·kg^{-1}	ρ/g·cm^{-3}	V_ϕ/cm^3·mol^{-1}	T/K	c/mol·kg^{-1}	ρ/g·cm^{-3}	V_ϕ/cm^3·mol^{-1}
313.15	0.0	0.760702		310.15	0.0	0.763991	
	9.9	0.761351	168.17		9.8	0.764642	166.44
	13.2	0.761545	171.05		13.1	0.764835	169.82
	16.5	0.761711	175.69		16.4	0.765015	173.18
	19.8	0.761849	181.23		19.7	0.765153	179.06
	23.1	0.762019	182.76		23.0	0.765331	180.26
	26.4	0.762135	187.45		26.3	0.765465	184.02
	33.0	0.762341	195.35		32.9	0.765629	194.68
308.15	0.0	0.766217		303.15	0.0	0.771674	
	9.8	0.766875	165.07		9.7	0.772334	163.20
	13.1	0.767071	168.35		13.0	0.772545	164.90
	16.4	0.767241	172.34		16.2	0.772724	168.53
	19.7	0.767385	177.80		19.5	0.772856	175.54
	23.0	0.767558	179.52		22.7	0.773025	177.34
	26.3	0.767695	183.14		26.0	0.773165	180.95
	32.9	0.767859	193.89		32.6	0.773351	190.80
298.15	0.0	0.777099		293.15	0.0	0.782499	
	9.7	0.777771	160.80		9.6	0.783179	157.94
	12.9	0.777981	162.26		12.8	0.783379	161.30
	16.1	0.778151	167.23		16.0	0.783559	165.34
	19.4	0.778309	172.11		19.2	0.783709	170.57
	22.6	0.778451	176.29		22.4	0.783871	173.42
	25.8	0.778609	178.40		25.7	0.784031	175.68
1	32.3	0.778835	186.24		32.1	0.784222	185.69

solvents, i.e., acetonitrile, dimethyl sulfoxide, tetrahydrofuran, and 1,4-dioxane, according to the following equation[6]

$$V_\phi = V^\circ_m + S_v c \quad (2)$$

where V°_m is the partial molar volume of the solute molecule in the specific solvent. S_v is a semiempirical parameter which depends on solvent, solute, and temperature, its value for large organic solutes is not of much significance, and c is the concentration. The values of V°_m are estimated by the least-squares fitting of the apparent molar volume data in eq 2. The temperature dependence of V°_m for drugs can be expressed by the following relation[7]

$$V^\circ_m = \propto + \beta T + \gamma T^2 \quad (3)$$

where $\propto$, β, and γ have been estimated by least-squares fitting of V°_m in eq 3 and T is the temperature.

From the partial molar volume, V°_m data, the isobaric thermal expansion coefficient α_2 of solute is also calculated by the following equation

$$\alpha_2 = \frac{1}{V^\circ_m}\left[\frac{\partial V^\circ_m}{\partial T}\right] \quad (4)$$

The change in partial molar volume of a solute from solvent I to another solvent II is referred to as the transfer volume ΔV°_m and is defined by the following equation[8]

$$\Delta V^\circ_m(\mathrm{I.II}) = V^\circ_m(\mathrm{II}) - V^\circ_m(\mathrm{I}) \quad (5)$$

where V°_m(II) is the partial molar volume for phenyl salicylate in water and V°_m(I) is the partial molar volume for phenyl

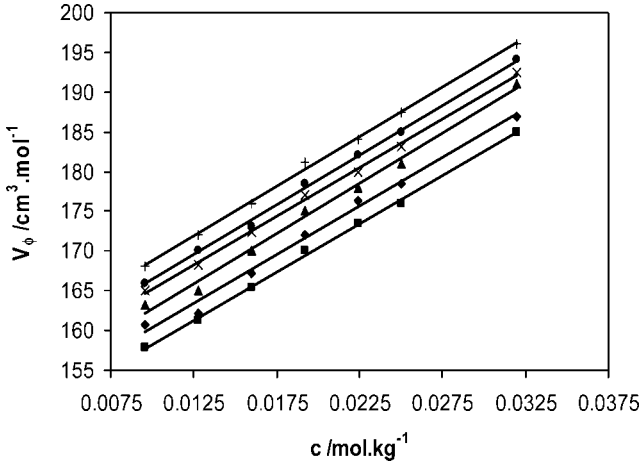

Figure 1. Apparent molar volumes, V_ϕ, as a function of concentration, c, of phenyl salicylate in acetonitrile at ■, 293.15 K; ♦, 298.15 K; ▲, 303.15 K; ×, 308.15 K; ●, 310.15 K; and +, 313.15 K.

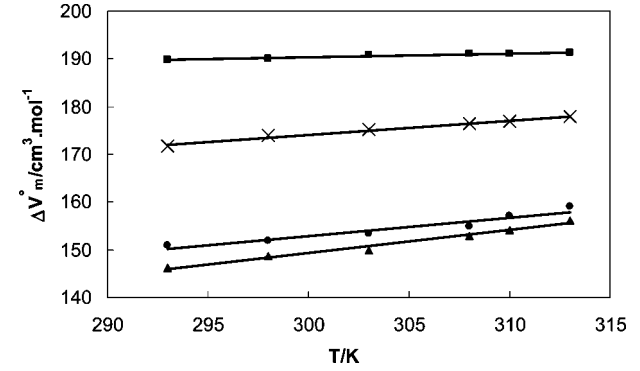

Figure 2. Plot of the transfer volumes ΔV°_m of phenyl salicylate in ×, acetonitrile; ■, dimethyl sulfoxide; ▲, 1,4-dioxane; and ●, tetrahydrofuran, at T = (293.15 to 313.15) K.

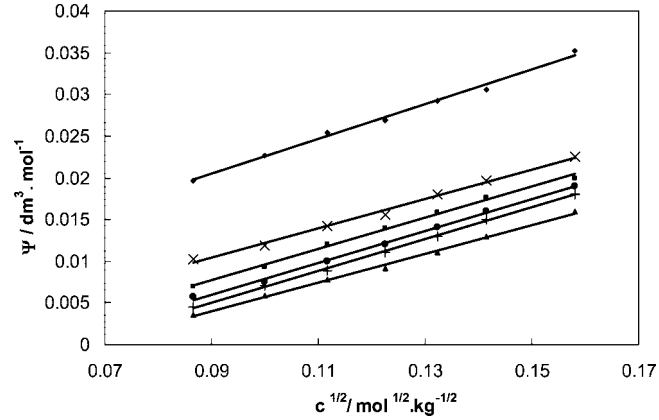

Figure 3. Plot of Ψ versus $c^{1/2}$ of phenyl salicylate in acetonitrile at T = ■, 293.15 K; ♦, 298.15 K; ▲, 303.15 K; ×, 308.15 K; ●, 310.15 K; and +, 313.15 K.

Table 2. Partial Molar Volumes, V°_m, Isobaric Thermal Expansion Coefficients, α_2, B/V°_m, Viscosity *B*-Coefficients, and Hepler's Constant $(\partial^2 V^{\circ}_m/\partial T^2)$ of Phenyl Salicylate in Aprotic Solvents at $T = (293.15$ to $313.15)$ K

T	V°_m	$10^3 \cdot \alpha_2$		B	$(\partial^2 V^{\circ}_m/\partial T^2)$	V°_m	$10^3 \cdot \alpha_2$		B	$(\partial^2 V^{\circ}_m/\partial T^2)$
K	$cm^3 \cdot mol^{-1}$	K	$10^3 \cdot B/V^{\circ}_m$	$dm^3 \cdot mol^{-1}$	$m^6 \cdot mol^{-2} \cdot K^{-2}$	$cm^3 \cdot mol^{-1}$	K	$10^3 \cdot B/V^{\circ}_m$	$dm^3 \cdot mol^{-1}$	$cm^6 \cdot mol^{-2} \cdot K^{-2}$
			Acetonitrile					Dimethyl sulfoxide		
293.15	146.12	2.27	1.53	0.223	0.023	123.76	5.09	1.68	0.208	0.010
298.15	148.58	2.23	1.35	0.200		126.39	4.99	1.50	0.190	
303.15	149.94	2.21	1.26	0.190		129.57	4.86	1.39	0.180	
308.15	152.60	2.17	1.18	0.180		132.45	4.76	1.28	0.170	
310.15	154.24	2.15	1.10	0.170		134.65	4.68	1.12	0.151	
313.15	156.19	2.13	1.02	0.160		136.15	4.62	1.04	0.141	
			1,4-Dioxane					Tetrahydrofuran		
293.15	171.76	2.83	1.05	0.181	0.003	151.32	1.91	1.13	0.170	0.0018
298.15	173.98	2.79	0.92	0.161		152.44	1.88	0.99	0.151	
303.15	175.25	2.77	0.86	0.150		153.30	1.87	0.92	0.141	
308.15	176.40	2.75	0.80	0.140		154.42	1.86	0.88	0.137	
310.15	177.46	2.74	0.73	0.131		156.09	1.84	0.77	0.121	
313.15	178.93	2.72	0.62	0.111		157.04	1.83	0.66	0.105	
			Water							
293.15	161.79	0.3034			0.001					
298.15	161.98	0.3031								
303.15	162.21	0.3027								
308.15	162.47	0.3022								
310.15	162.59	0.3019								
313.15	162.77	0.3017								

Table 3. Transfer Volumes, ΔV°_m, for Phenyl Salicylate in Water and Aprotic Solvents at $T = (293.15$ to $313.15)$ K

	$\Delta V^{\circ}_m/cm^3 \cdot mol^{-1}$					
solvents	T/K = 293.15	T/K = 298.15	T/K = 303.15	T/K = 308.15	T/K = 310.15	T/K = 313.15
acetonitrile	20.45	18.29	16.53	14.91	12.98	11.35
dimethyl sulfoxide	64.77	60.14	55.90	52.60	49.71	47.82
1,4-dioxane	−0.17	−2.54	−3.82	−5.16	−6.27	−7.73
tetrahydrofuran	17.46	15.31	13.49	11.79	9.41	9.47

salicylate in acetonitrile, dimethyl sulfoxide, tetrahydrofuran, and 1,4-dioxane.

The viscosity data are analyzed by using the Jones−Dole equation[9]

$$\frac{\eta_r - 1}{c^{1/2}} = \psi = A + Bc^{1/2} \tag{6}$$

where $\eta_r = \eta/\eta_o$ and η and η_o are viscosities of the solution and solvent, respectively, and c is the concentration. The linear plots for ψ versus $c^{1/2}$ are obtained for phenyl salicylate in all the solvents used here. Figure 3 shows a linear plot for ψ versus $c^{1/2}$ for phenyl salicylate, and viscosity A and B coefficients have been obtained using the least-squares method. A is a constant independent of concentration, and B is a Jones−Dole coefficient and is related to the effect of the drug on the structure of solvents.

The densities (ρ) of phenyl salicylate in aprotic solvents at different temperatures are included in Table 1. Variations of ρ of phenyl salicylate in aprotic solvents with molal concentration (c) of phenyl salicylate at different temperatures are depicted in Figure 1. Apparent molar volumes of phenyl salicylate in acetonitrile increases with concentration at constant temperature. A similar behavior is observed for all the other solvents and water.

Values obtained for V°_m are shown in Table 2. The values for partial molar volume V°_m represent the volume behavior of a solute at infinite dilution which provides information concerning solute−solvent interaction. Positive values of partial molar volume suggest that strong solute−solvent interactions between the drug and solvent promote the structure making effect of the studied drug. Thus, the values of B support the behavior of partial molar volume for the present drug. Partial molar volume increases with an increase in temperature due to releases of some solvent molecules from the loose solvation layers of the solute in the solution.

The values of Hepler's Constant $(\partial^2 V^{\circ}_m/\partial T^2)$ are listed in Table 2. The positive values of $(\partial V^{\circ}_m/\partial T^2)$ suggest that phenyl salicylate is a structure maker in all the solvents used. The values of isobaric thermal expansion coefficient, α_2, as shown in Table 2 tend to decrease with increasing temperature. The highest value of α_2 in aprotic solvents is obtained for dimethyl sulfoxide and the lowest in tetrahydrofuran.

The transfer volumes ΔV°_m are listed in Table 3. The transfer volume is positive for all the solvents investigated here except for 1,4-dioxane at all the studied temperatures. This trend can be discussed in terms of higher solvation of the drug in various organic solvents compared to that in aqueous medium. This also implies a solvophobic character of the drug. An examination of ΔV°_m indicates that the ΔV°_m is highest for dimethyl sulfoxide and lowest for 1,4-dioxane at all temperature ranges. Positive transfer volume ΔV°_m indicates the dominant role of ion−solvophilic and solvophilic−solvophilic interaction. The ΔV°_m for 1,4-dioxane is negative indicating that solvophobic−solvophilic interactions are dominant. Figure 2 shows the transfer volume to be dependent on temperature.

The solvation of any solute can be judged from the magnitude of B/V°_m.[10] The values of B/V°_m are given in Table 2. A value between 0 and 2.5 indicates an unsolvated spherical species, and any higher value is an indication of solvated ones. Phenyl salicylate in dimethyl sulfoxide has the highest value of B/V°_m but the lowest value in 1,4-dioxane showing that in dimethyl sulfoxide it is more solvated forming a primary solvation shell around the drug molecule whereas it is least solvated in 1,4-dioxane.

Figure 3 shows a representative plot (ψ versus $c^{1/2}$) for phenyl salicylate in acetonitrile over the temperature range analyzed in this study. Almost similar plots in all the other solvents have been obtained. A-coefficients of viscosity are found to be close to zero representing very weak solute−solute interactions, and therefore their values have not been reported here. A precise estimation of viscosity B-coefficient is important because it is a measure of drug−solvent interactions and is directly dependent on the size, shape, and charge of the solute molecule. Positive values of B-coefficients indicate that the large size of moving molecules is decreasing with the temperature increase. This can be attributed to the breakup of the solvation shell due to the

thermal motion. Table 2 shows that the values of B for phenyl salicylate in all of the solvents employed here are positive and large which also decrease with a rise in temperature. This indicates the structure promoting tendency (hydrophobic and H-bond making action) of phenyl salicylate drug molecule on the solvents.[11]

Conclusions

In summary, using density and viscosity data, apparent molar volume, partial molar volume, isobaric thermal expansion coefficient, and viscosity B-coefficient have been computed. Viscosity is an important parameter that affects the permeation of drug through biological membranes. It is indicative of the structure promoting tendency of phenyl salicylate in all the solvents used here.

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