Short Articles

Volumetric and Viscometric Studies of Antidepressant Drugs in Aqueous Medium at Different Temperatures†

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Notriptyline hydrochloride and trimipramine maleate are used as antidepressants and analgesics. The density and viscosity of the aqueous solutions of these compounds are measured in a range of molality, $m = (9.7 \cdot 10^{-6}$ to $32.5 \cdot 10^{-6})$ mol·g^{-1}, at $T = (293.15$ to $313.15)$ K using a commercial densimeter and viscometer. The apparent molar volume (V_ϕ), partial molar volume (V_m^0), partial molar expansivity (E_2^0), thermal expansion coefficient (α_2), and Hepler's constant ($\partial^2 V_m^0/\partial T^2$) are calculated from the density data. The values of the *B*-coefficient and hydration number (H_n) are computed from the viscosity data.

1. Introduction

Characterization of antidepressant drugs in aqueous solutions has been a subject of interest because they exert their activity by interaction with biological membranes. The detailed literature survey reveals that although studies regarding thermodynamics and self-aggregation aspects of a few antidepressants have been reported,[1] information is scant on the volumetric and viscometric characteristics of antidepressants that play an important role in understanding their drug action.

In the present study, the density and viscosity of the aqueous solutions of two antidepressant drugs, namely, notriptyline hydrochloride and trimipramine maleate salt, are determined at different temperatures in the range $T = (293.15$ to $313.15)$ K. A number of useful parameters, namely, apparent molar volume (V_ϕ), partial molar volume (V_m^0), Hepler's constant ($\partial^2 V_m^0/\partial T^2$), partial molar expansivity (E_2^0), isobaric thermal expansion coefficient (α_2), Jones−Dole viscosity *B*-coefficients, and the hydration number (H_n) have been reported.

2. Materials and Methods

Notriptyline hydrochloride and trimipramine maleate salt of high purity (>0.99 mass fraction) were obtained from Aldrich and were used as received. Deionized water with a specific conductance of $< 10^{-6}$ S·cm^{-1} was used for the preparation of solutions at room temperature in a molality range of $(9.7 \cdot 10^{-6}$ to $32.5 \cdot 10^{-6})$ mol·g^{-1}. The precision of balance used was ± 0.001 g.

The density was measured with an uncertainty of ± 10^{-5} g·cm^{-3} using an Anton Paar (DMA 5000) densimeter that was precalibrated with doubly distilled deionized water for the temperature range investigated. The solution viscosities were measured with an uncertainty of ± 0.003 mPa·s with a precalibrated viscometer (Anton Paar SVM 3000). The density and viscosity measurements were performed at $T = (293.15$ to $313.15)$ K. The uncertainty in the temperature measurements was ± 0.01 K. All of the experiments were repeated thrice.

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3. Results and Discussion

3.1. Density Measurements. Experimental values of density of the aqueous solutions of antidepressants are used to calculate the apparent molar volume, V_ϕ, using the following equation

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

where M_2 represents the molar mass of the drug compound, m is molality, and ρ and ρ_o are the densities of solution and the pure solvent, respectively. The values for ρ and V_ϕ at different solution concentrations are listed in Tables 1 and 2. The values of the partial molar volume of the solute (V_m^0) are computed by the least-squares fitting of the linear plots of V_ϕ against the molality, m, in accordance with the following equation

$$V_\phi = V_m^0 + S_v m \quad (2)$$

The plots are shown in Figures 1 and 2.

Calculated values of V_m^0 for notriptyline hydrochloride and trimipramine maleate salt are positive, as shown in Table 3. Trimipramine maleate salt has a higher partial molar volume than that of notriptyline hydrochloride, indicating a linear dependence of the V_m^0 on their molar masses. Because the nature of the interacting groups in the two solute molecules is different, the hydrophobic effect is also different. Because of the release of some of the water molecules from loose hydration layers, the value of V_m^0 increases with the increase in temperature.

The temperature dependence of V_m^0 can be expressed by the following relationship[2]

$$V_m^0 = a_0 + a_1 T + a_2 T^2 \quad (3)$$

We estimated the coefficients a_0, a_1, and a_2 by plotting partial molar volume data at different temperatures by the least-square fitting method. Qualitative information on the hydration of the solute molecules can be retrieved from the values of the Hepler's

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Table 1. Density (ρ), Viscosity (η), and Apparent Molar Volume (V_ϕ) of Notriptyline Hydrochloride of Molality (m) at T = (293.15 to 313.15) K

T / K	$m/10^{-6}$ / mol·g^{-1}	ρ / g·dm^{-3}	$V_\phi \cdot 10^{-3}$ / dm^3·mol^{-1}	η / mPa·s	T / K	$m/10^{-6}$ / mol·g^{-1}	ρ / g·dm^{-3}	$V_\phi \cdot 10^{-3}$ / dm^3·mol^{-1}	η / mPa·s
293.15	7.5	0.998486	266.14	1.0347	298.15	7.6	0.997322	266.81	0.9368
	10.0	0.998545	268.73	1.0351		10.0	0.997382	269.52	0.9370
	12.5	0.998599	270.92	1.0356		12.5	0.997428	272.00	0.9374
	15.2	0.998645	272.70	1.0360		15.2	0.997469	273.99	0.9376
	17.5	0.998668	275.29	1.0366		17.5	0.997499	276.04	0.9379
	20.0	0.998705	276.53	1.0371		20.0	0.997521	278.09	0.9382
	25.0	0.998721	280.68	1.0381		25.0	0.997545	281.66	0.9388
303.15	7.6	0.995904	267.95	0.8338	308.15	7.6	0.994285	269.03	0.7279
	10.0	0.995959	270.96	0.8339		10.0	0.994335	272.05	0.7281
	12.5	0.996001	273.55	0.8342		12.5	0.994379	274.35	0.7283
	15.2	0.996045	275.14	0.8345		15.2	0.994409	276.99	0.7285
	17.5	0.996065	277.79	0.8348		17.5	0.994435	278.95	0.7286
	20.0	0.996085	279.66	0.8349		20.0	0.994455	280.73	0.7289
	25.0	0.996105	283.15	0.8356		25.0	0.994465	284.51	0.7293
310.15	7.6	0.993565	270.41	0.6925	313.15	7.6	0.992443	271.61	0.6556
	10.0	0.993621	272.53	0.6928		10.0	0.992499	273.51	0.6557
	12.5	0.993659	275.25	0.6929		12.5	0.992539	275.94	0.6558
	15.2	0.993689	277.77	0.6931		15.2	0.992571	278.26	0.6560
	17.5	0.993712	279.83	0.6932		17.5	0.992592	280.41	0.6562
	20.0	0.993730	281.63	0.6935		20.0	0.992601	282.72	0.6564
	25.0	0.993741	285.23	0.6938		25.0	0.992609	286.28	0.6568

Table 2. Density (ρ), Viscosity (η), and Apparent Molar Volume (V_ϕ) of Trimipramine Maleate Salt of Molality (m) at T = (293.15 to 313.15) K

T / K	$m/10^{-6}$ / mol·g^{-1}	ρ / g·dm^{-3}	$V_\phi \cdot 10^{-3}$ / dm^3·mol^{-1}	η / mPa·s	T / K	$m/10^{-6}$ / mol·g^{-1}	ρ / g·dm^{-3}	$V_\phi \cdot 10^{-3}$ / dm^3·mol^{-1}	η / mPa·s
293.15	7.5	0.998499	375.27	1.0349	298.15	7.6	0.997329	376.88	0.9370
	10.0	0.998566	377.82	1.0354		10.0	0.997396	379.12	0.9373
	12.5	0.998625	379.70	1.0358		12.5	0.997455	380.83	0.9376
	15.2	0.998675	381.55	1.0362		15.2	0.997499	382.97	0.9379
	17.5	0.998715	383.45	1.0369		17.5	0.997535	385.11	0.9382
	20.0	0.998745	385.50	1.0375		20.0	0.997569	386.67	0.9385
	25.0	0.998799	388.48	1.0400		25.0	0.997601	390.39	0.9393
303.15	7.6	0.995919	377.55	0.8339	308.15	7.6	0.994296	378.91	0.7339
	10.0	0.995981	379.91	0.8342		10.0	0.994355	381.38	0.7341
	12.5	0.996031	382.29	0.8345		12.5	0.994401	383.91	0.7343
	15.2	0.996081	384.06	0.8348		15.2	0.994455	385.24	0.7346
	17.5	0.996105	386.65	0.8350		17.5	0.994475	387.98	0.7348
	20.0	0.996141	387.99	0.8354		20.0	0.994515	389.03	0.7351
	25.0	0.996175	391.56	0.8361		25.0	0.994535	393.01	0.7355
310.15	7.6	0.99358	379.83	0.6928	313.15	7.6	0.992458	381.16	0.6561
	10.0	0.993638	382.24	0.6930		10.0	0.992506	384.35	0.6564
	12.5	0.993681	384.89	0.6932		12.5	0.992551	386.51	0.6566
	15.2	0.993721	387.04	0.6934		15.2	0.992589	388.59	0.6568
	17.5	0.993749	389.11	0.6937		17.5	0.992609	390.96	0.6571
	20.0	0.993769	391.06	0.6939		20.0	0.992615	393.55	0.6573
	25.0	0.993799	394.29	0.6943		25.0	0.992635	396.76	0.6579

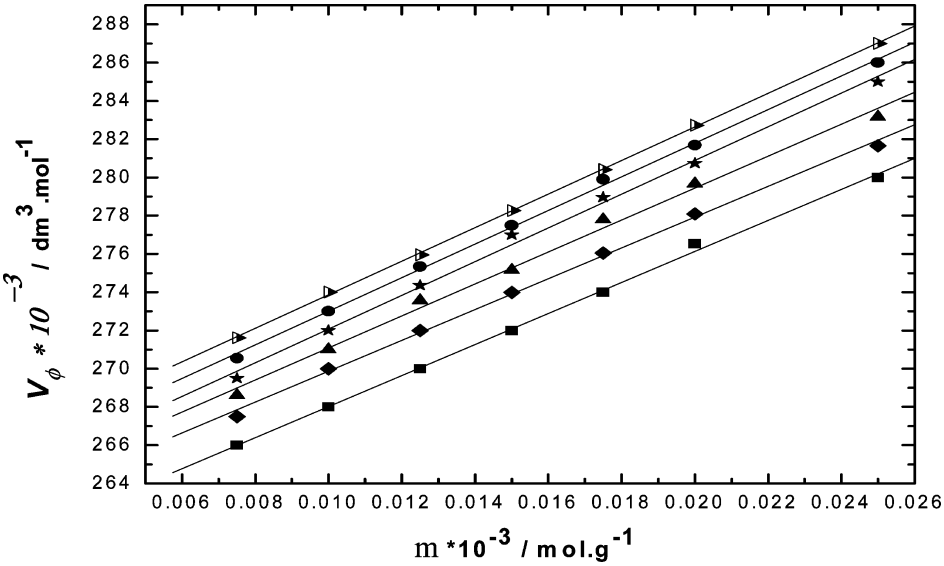

Figure 1. Apparent molar volumes, V_ϕ, as a function of concentration, m, of notriptyline HCl in aqueous media at T = ■, 293.15 K; ◆, 298.15 K; ▲, 303.15 K; ★, 308.15 K; ●, 310.15 K; open/solid tilted triangle, 313.15 K. Standard deviation is ± 0.01.

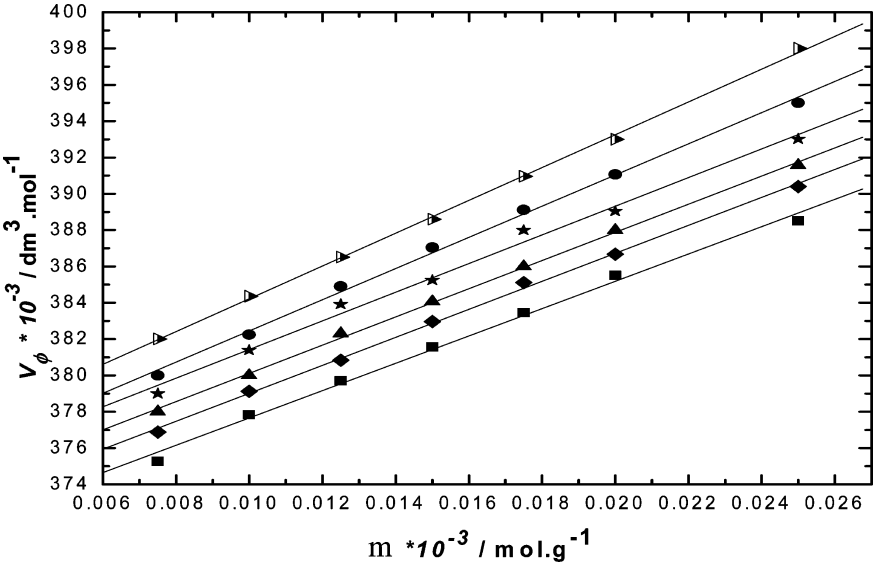

Figure 2. Apparent molar volumes, V_ϕ, plotted as a function of concentration, m, of trimipramine maleate salt in aqueous media at T = ■, 293.15 K; ◆, 298.15 K; ▲, 303.15 K; ★, 308.15 K; ●, 310.15 K; open/solid tilted triangle, 313.15 K. Standard deviation is ± 0.02.

Table 3. Partial Molar Volumes (V^0_m), Isobaric Thermal Expansion Coefficient (α_2), Partial Molar Expansivity (E^0_2), and Hepler's Constant ($\partial^2 V^0_m/\partial T^2$) of Notriptyline Hydrochloride and Trimipramine Maleate Salt in Aqueous Solutions from T = (293.15 to 313.15) K

T / K	$V^0_m \cdot 10^{-3}$ / dm^3·mol^{-1}	$\alpha_2 \cdot 10^{-4}$ / K	$E^0_2 \cdot 10^{-3}$ / dm^3·mol^{-1}·K^{-1}	$\partial^2 V^0_m/\partial T^2 \cdot 10^{-6}$ / dm^6·mol^{-2}·K^{-2}	B ± *s.d.* / g·mol^{-1}	H_n
			Notriptyline Hydrochloride			
293.15	260.50	9.10			0.20 ± 0.01	0.767
298.15	261.20	9.07			0.17	0.650
303.15	262.33	9.04			0.16	0.609
308.15	263.24	9.00	0.23	0.010 ± 0.04	0.14	0.531
310.15	264.48	8.96			0.12	0.453
313.15	265.00	8.94			0.10	0.377
			Trimipramine Maleate Salt			
293.15	370.20	6.65			0.24 ± 0.02	0.648
298.15	371.30	6.63			0.20	0.538
303.15	372.05	6.62	0.25	0.012 ± 0.05	0.18	0.483
308.15	373.49	6.59			0.16	0.428
310.15	374.14	6.58			0.14	0.374
313.15	375.30	6.56			0.12	0.319

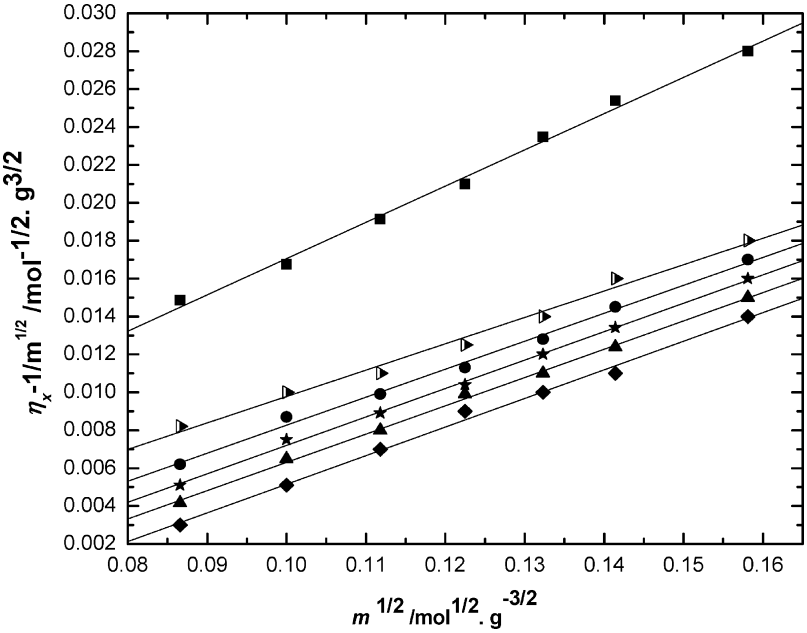

Figure 3. Plot of Ψ versus molality $m^{1/2}$ of notriptyline hydrochloride in water at T = ■, 293.15 K; ◆, 298.15 K; ▲, 303.15 K; ★, 308.15 K; ●, 310.15 K; open/solid tilted triangle, 313.15 K. Standard deviation is ± 0.00012.

constant ($\partial^2 V_m^0/\partial T^2$). Inspection of Table 3 reveals that positive values of ($\partial^2 V_m^0/\partial T^2$) are associated with the structure-making nature of the drug molecules because of their hydrophobicity. The partial molar volume data at different temperatures are used to calculate the partial molar expansivity (E_2^0) using the following equation

$$E_2^0 = \left[\frac{\partial V_m^0}{\partial T}\right]_p \tag{4}$$

The values of V_m^0 and E_2^0 are further used to calculate the isobaric thermal expansion coefficient, α_2, using following relation

$$\alpha_2 = \frac{E_2^0}{V_m^0} \tag{5}$$

The positive values of E_2^0 that are obtained for the two compounds under investigation indicate the predominance of hydrophobic hydration over the electrostriction of water molecules around the solute molecules. The values of E_2^0 and α_2 are higher for trimipramine maleate than for notriptyline hydrochloride owing to the greater hydrophobicity of trimipramine maleate salt. The calculated values of E_2^0 and α_2 are listed in Table 3.

3.2. Viscosity Measurements. The experimental values of viscosity (η) measured at different temperatures for the two antidepressant solutions under investigation are reported in Tables 1 and 2. The viscosity data of aqueous solutions of the antidepressants are plotted in accordance with the well-known Jones−Dole equation

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

Where, $\eta_r = \eta/\eta_o$, η and η_o are viscosities of the solution and water, respectively, and m is the molality. The plots for ψ versus $m^{1/2}$ are linear for both of the drugs, as shown in Figures 3 and 4. The values of the B-coefficient are calculated using the least-squares fitting method. The positive B values denote the structure-making effect[3] of both notriptyline

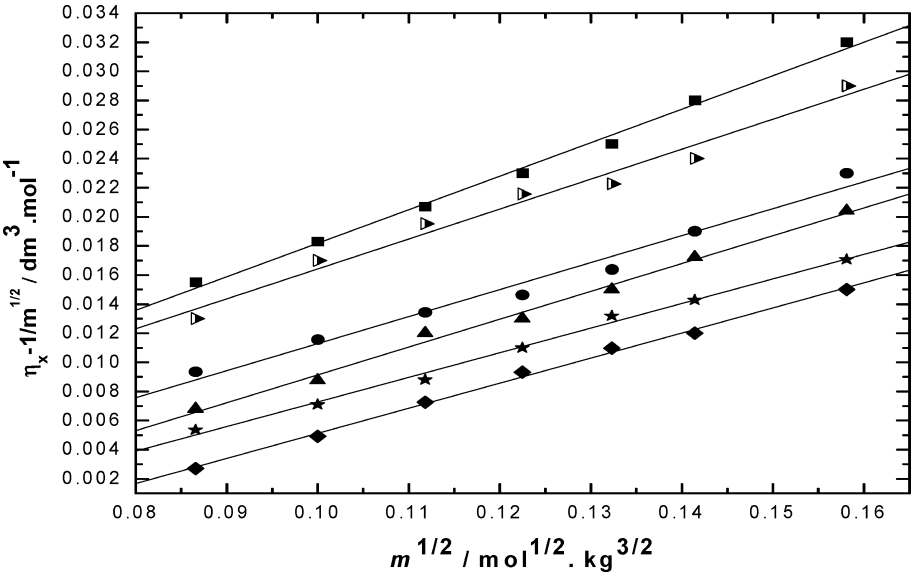

Figure 4. Plot of $\Psi = \eta_r - 1/m^{1/2}$ versus molality $m^{1/2}$ of trimipramine maleate salt in water at $T =$ ■, 293.15 K; ◆, 298.15 K; ▲, 303.15 K; ★, 308.15 K; ●, 310.15 K; open/solid tilted triangle, 313.15 K. Standard deviation is ± 0.00007.

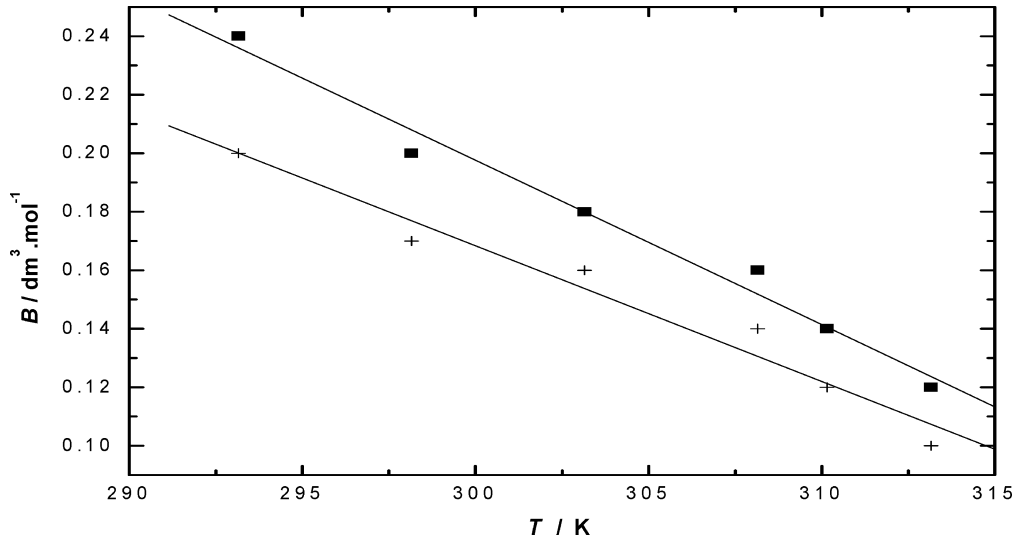

Figure 5. Plot of viscosity B-coefficients versus temperature for: +, notriptyline hydrochloride; ■, trimipramine maleate salt in aqueous media. Standard deviation is ± 0.01.

hydrochloride and trimipramine maleate. The values of *B*-coefficient decrease with the increase in temperature, as illustrated in Figure 5 to indicate the structure-promoting tendency of the compounds.

The hydration of solute is judged from the value of the hydration number, H_n, which can be calculated by the following expression[4]

$$H_n = \frac{B}{V_m^0} \tag{7}$$

The observed values of $H_n < 2.5$ at low temperatures (Table 3) indicate that notriptyline hydrochloride and trimipramine maleate salt are not very hydrated because a value higher than $H_n = 2.5$ is an indication of hydrated spherical species.[4]

4. Conclusions

In summary, we have presented volumetric and viscometric properties of two antidepressant drugs, namely, notriptyline HCl and trimipramine maleate salt. The values of the partial molar volume in dilute aqueous solutions are positive, indicating strong solute−solvent interactions that may have implications for the permeation of these molecules through the biological membranes. Also, Jones−Dole viscosity *B*-coefficients of these drugs are positive, indicating a structure-promoting tendency.

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