

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Partial Molar Volumes, Jones-Dole Coefficients, and Molar Refractions of Sodium Naproxen in Water and its Computed Hydration Free Energy.

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ABSTRACT

In order to get the information regarding behaviour sodium naproxen in water, the physical properties of sodium naproxen in water have been determined at (298.15, 303.15, 308.15, and 313.15) K. Densities, viscosities, and refractive indices of sodium naproxen in water have been measured by using bi-capillary pycnometer, Ubbelohde viscometer, and Abbe's refractometer, respectively. Hydration free energy of sodium naproxen has also been computed using Gaussian G09 software. The calculated parameters from density, viscosity, and refractive index data are limiting apparent molar volume, solute-solute interaction parameter, Hepler's constant, Jones-Dole Coefficient, temperature derivative of Jones-Dole coefficient, and molar refraction. Strong sodium naproxen-water interactions exist in aqueous solutions of sodium naproxen. Sodium naproxen is water structure maker. In aqueous solutions of sodium naproxen, strength of dispersion forces increases with increase in the concentration of sodium naproxen. Hydration free energy of sodium naproxen is negative.

Keywords: *Sodium naproxen, aqueous solution, density, viscosity, and refractive index*

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INTRODUCTION

A Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are used to treat pain or inflammation caused by headache, toothache, back pain, arthritis, menstrual cramps or major injury. Our body produces certain natural substances which causes inflammation. NSAIDs like sodium naproxen works by blocking such production of certain natural substances.

There is need to study NSAIDs-water interactions because the major solvent medium required for the biochemical reactions that occur in our body is water. The physical properties such as conductivity, density, and viscosity of aqueous solutions of drug can be used to study the drug-water interactions. There are reports on conductometric study¹ of sodium naproxen in water. In biological and pharmaceutical sciences, solvation free energy serves as a characteristics property of various molecules. When solvent is water, the solvation free energy is called hydration free energy. Solvation model like Integral Equation Formalism Polarizable Continuum Model (IEPCM)²⁻³ can be used to compute the hydration free energy. All the computational work can be performed by the use of Gaussian G09 software. In previous publications, density, viscosity, ultrasonic velocity studies of sodium salicylate-water and sodium ibuprofen-water systems have been reported. In these publications, theoretical values of hydration free energies of sodium salicylate and sodium ibuprofen have also been reported. This paper reports computed value of hydration free energy of sodium naproxen and density, viscosity, and refractive index studies of Na-Naproxen-water system at (298.15, 303.15, 308.15, and 313.15) K.

MATERIAL AND METHOD

For present study, sodium naproxen (Sigma Aldrich, 98-102.0%) was used as received. Aqueous solutions of sodium naproxen were prepared in triply distilled deionized water by weight-by-weight method in airtight stoppered glass bottle. Dhona balance to an accuracy of $\pm 1 \times 10^{-5}$ g was used to record the masses. A bi-capillary pycnometer with a bulb volume of 15 mL was used for the density measurements due to its versatility and high accuracy i.e. 5 in 10^6 parts. To determine the density values at different temperatures bi-capillary pycnometer was kept in glass-walled water bath. The bi-capillary pycnometer was calibrated with triply distilled deionized water (conductivity 0.054 μ S) before the measurements of density. Dynamic viscosities (η) of aqueous solutions were measured by using Ubbelohde viscometer⁴⁻⁶. The advantages of Ubbelohde type viscometer are speed, accuracy, small sample size, low susceptibility to errors and cost effectiveness. An electronic digital stopwatch with an accuracy of ± 0.01 s was used for flow-time measurements. For each data point, the procedure was repeated three times and results were averaged. Kinetic energy corrections were not applied because all flow times were >300 s. To calculate the dynamic viscosity of liquids/solutions, following equation was used

$$\frac{\eta}{\eta_0} = \frac{\rho t}{\rho_0 t_0} \quad 1$$

where ρ , ρ_0 , t , t_0 , η , and η_0 are density, flow time, and viscosity of liquids/aqueous solutions and water, respectively. The uncertainty in the viscosity measurements was 0.03 mPa·s. Viscosity measurements were made at (298.15, 303.15, 308.15, and 313.15) K. Viscometer used for viscosity measurements was calibrated with triply distilled water and purified solvents. Uncertainties in the density, viscosity, and temperature measurements were 5.8×10^{-2} kg m⁻³, 4.71×10^{-4} mPa·S, and 0.006 K, respectively.

Abbes refractometer was used for the measurements of refractive indices of aqueous solutions. Refractive index range of refractometer was 1.3000 – 1.7000. Accuracy in the refractive index measurements was ± 0.0002 . Before the measurements refractive indices of aqueous solutions, the refractometer was calibrated with piece of glass of known refractive index provided with the instruments. To check the calibration, the refractive indices of distilled water were measured at different temperatures.

To calculate the values of standard free energy in the gas phase geometries of sodium naproxen were fully optimized and the frequencies were calculated in the gas phase using DFT RB3LYP⁷⁻⁸ method at 6-31++G(d, p) basis set. Optimized geometries were used to calculate the standard free energy of solute in water. Gaussian G09 Software used for computational work⁹.

RESULTS AND DISCUSSION

Densities of aqueous solutions sodium salt of naproxen are reported in Table 1. At fixed temperature, the density of sodium naproxen aqueous solution increases with increase in concentration of sodium naproxen. At fixed concentration of sodium naproxen, density of aqueous solution decreases with rise in the temperature. The thermodynamic property, apparent molar volume of sodium naproxen has been determined using the following equation¹⁰⁻¹¹.

$$V_{\phi} = \frac{M}{\rho} - \left\{ \frac{(\rho - \rho_0)}{(m\rho\rho_0)} \right\} \quad 2$$

where M , m , ρ_0 , and ρ are the molar mass of the solute, molality of the sodium cyclamate solution, density of solvent, and the density of the aqueous solution, respectively. The density values of water have been taken from the literature¹² for the calculation of apparent molar volumes. The uncertainty in the apparent molar volume ranges from $(0.1-0.05)10^{-6} \text{ m}^3 \cdot \text{mol}^{-1}$. Table 1 presents V_{ϕ} of sodium naproxen in water.

The variation of V_{ϕ} with square root of molality can be expressed using the following using the following equation¹³

$$V_{\phi} = V_{\phi}^0 + V_S m^{0.5} + V_b m \quad 3$$

The partial molar volume of the solute, V_{ϕ}^0 gives the information regarding solute-solvent interactions partial molar volume and solute-solute interaction parameter. V_S and V_b are constants. The least square method was used for calculations of V_{ϕ}^0 , V_S , and V_b . The values of V_{ϕ}^0 , V_S , and V_b are given in the Table 1. The reported¹⁴ value of V_{ϕ}^0 for sodium naproxen at 298.15 K is $182.14 \times 10^{-6} \text{ m}^3 \cdot \text{mol}^{-1}$. The experimentally observed value of V_{ϕ}^0 for sodium naproxen at 298.15 K is $180.77 \times 10^{-6} \text{ m}^3 \cdot \text{mol}^{-1}$. The difference between observed and literature value may due to model used for calculation and accuracy of density. Observed positive values of V_{ϕ}^0 suggests strong interaction between sodium naproxen and water. The V_{ϕ}^0 value increases with increase in the temperature. This result suggests that at higher temperature the electrostriction effect of water reduces and water molecules in secondary solvation layer release into the bulk of the water. This result leads to the expansion of the solution¹⁵. The experimentally observed values of V_S are positive. The positive value of V_S is due to the ion association. The V_S value decreases with temperature. In aqueous solutions of sodium naproxen, higher ion association at lower temperature has been already confirmed by conductometric study¹. Table 1 shows the positive values of V_b for sodium naproxen. The positive values of V_b confirms sodium ion-naproxen ion interactions¹⁶.

Table 1. Densities, apparent molar volumes and limiting molar apparent molar volumes for sodium naproxen-water system

m $\text{mol} \cdot \text{kg}^{-1}$	ρ $\text{kg} \cdot \text{m}^{-3}$				$10^6 (V_{\phi})$ $\text{m}^3 \cdot \text{mol}^{-1}$			
	298.15 K	303.15 K	308.15 K	313.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	0997.04	0995.64	0994.03	0992.21				
0.0881	1003.23	1001.77	1000.09	0998.20	181.48	182.33	183.32	184.35
0.1527	1007.61	1006.11	1004.39	1002.46	181.73	182.56	183.48	184.43
0.2203	1012.06	1010.53	1008.77	1006.80	181.96	182.73	183.62	184.54
0.2828	1016.07	1014.50	1012.72	1010.72	182.12	182.91	183.72	184.59
0.3469	1020.07	1018.47	1016.67	1014.64	182.30	183.06	183.82	184.67
0.4064	1023.69	1022.07	1020.25	1018.20	182.45	183.18	183.91	184.72
		$10^6 V_{\phi}^0$ $(\text{m}^3 \cdot \text{mol}^{-1})$				$10^6 V_b$		
	180.77	181.73	182.82	184.07	0.630	0.712	0.222	0.814
		$10^6 V_S$						
	2.229	1.826	1.513	0.326				

Figure 2 confirms nonlinear variation of partial molar volume with temperature. Following equation can be used to express the variation of V_{ϕ}^0 with temperature.

$$V_{\phi}^0 = a_0 + a_1 T + a_2 T^2 \quad 4$$

where a_0 , a_1 , and a_2 are constants and can be calculated using the least squares method.

The Hepler's constant¹⁷ provides the qualitative information regarding hydration of a solute from the thermal expansion of aqueous solutions. Following equation was used for calculations of Hepler's constant

$$\text{Hepler's constant} = \left[\frac{\partial^2 V_{\phi}^0}{\partial T^2} \right]_p = 2a_2 \quad 5$$

The values of the Hepler's constants for all temperatures are reported in Table 1. For structure making solute, the Hepler's constant should be positive¹⁷⁻¹⁸. The positive values of Hepler's constants suggest water structure making behaviour of sodium naproxen. Water structure making behaviour of sodium naproxen has also been reported previously¹⁴.

Viscosity data analysis provides valuable information regarding the strength of solute-solvent and solute-solute interactions. Viscosities of sodium naproxen in water are included in Table 2. The uncertainty in measured viscosity data was lower than 0.05%. It is observed that viscosity of aqueous solution of sodium naproxen increases with increase in the concentration of sodium naproxen at fixed temperatures. At fixed concentration, viscosity of aqueous solution of sodium naproxen decreases with increase in the temperature. Viscosity data can be analysed using the Jones-Dole Equation¹⁹ equation.

$$\frac{\eta}{\eta_0} = 1 + Am^{0.5} + Bm \quad 6$$

where η and η_0 are the viscosities of solution and solvent, respectively. Equation 6 can be rearranged as

$$\left[\frac{\frac{\eta}{\eta_0} - 1}{m^{0.5}} \right] = A + Bm^{0.5} \quad 7$$

Table 2. Viscosities, Jones-Dole Coefficients, and $\frac{dB}{dT}$ for sodium naproxen-water system

<i>m</i>	η mPa·s							
	298.15 K	303.15 K	308.15 K	313.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	0.890	0.797	0.719	0.653				
0.0881	0.959	0.855	0.768	0.695	0.2612	0.2452	0.2296	0.2167
0.1527	1.018	0.906	0.814	0.735	0.3680	0.3500	0.3381	0.3214
0.2203	1.081	0.962	0.862	0.778	0.4572	0.4411	0.4237	0.4078
0.2828	1.140	1.014	0.909	0.819	0.5282	0.5120	0.4969	0.4780
0.3469	1.205	1.070	0.958	0.863	0.6009	0.5816	0.5644	0.5460
0.4064	1.271	1.129	1.009	0.907	0.6715	0.6534	0.6327	0.6102
		B				A		
	1.190	1.184	1.168	1.145	-0.007	-0.025	-0.056	-0.068
		$\frac{dB}{dT}$						
		-0.003						

Equation 7 is similar to the equation of straight line ($y = mx + c$) with slope equal to B and intercept equal to A . Jones-Dole coefficient (B) was obtained by the use of least squares method. Table 2 includes the

values of B for sodium naproxen in water. Observed values of B are positive and large. The electrolytes containing large size organic ion have the high values of B . In literature²⁰, large values of B are reported for large organic ions (Bu_4N^+ and BPh^4). B value of the electrolyte is the sum of the analogous values of cation and anion. Therefore, B (Sodium Naproxen) is the sum of $B_{\text{Naproxen ion}}$ and $B_{\text{sodium ion}}$. Sodium naproxen on dissociation gives sodium cation and large naproxen anion. Therefore, the large values B in present study at all temperature are due to large size of naproxen ion. In case of large ions, the high values B are attributable to hydrophobic solvation. In aqueous solutions of sodium naproxen, presence of hydrophobic hydration by naproxen ion has already been reported¹⁴. The positive values B for sodium naproxen + water systems at all studied temperature suggest strong interactions between water and sodium naproxen. This information supports the conclusion drawn from density study.

The temperature derivative of B i.e. $\left(\frac{dB}{dT}\right)$ can also be calculated to get the information regarding structure making or structure breaking ability of solute in solvent²¹⁻²². Negative value of $\left(\frac{dB}{dT}\right)$ indicates structure making ability of the solute²³⁻²⁴. Table 2 shows negative value of $\left(\frac{dB}{dT}\right)$. The negative value of $\left(\frac{dB}{dT}\right)$ for sodium naproxen -water systems confirms structure making behaviour of sodium naproxen. Therefore, it can be concluded that sodium naproxen is water structure maker¹.

Table 3 shows the experimental values of refractive indices of sodium naproxen in water. It is clear that the refractive index of the solution varies linearly with molality. Experimental values of refractive indices were used for calculations of molar refraction (R_M). Lorentz-Lorenz equation²⁵⁻²⁶ was used for the calculations of the (R_M) values.

$$R_M = \frac{n^2 - 1}{n^2 + 2} \sum_{i=0}^3 \frac{x_i M_i}{\rho} \quad 8$$

where x_i and M_i are the mole fraction and molar mass of the i^{th} component of the mixture. Table 3 presents R_M values. It can be concluded from Table 4 that R_M increases with increase in the molality of the sodium naproxen solutions. R_M does not vary appreciably with temperature.

Table 3. Refractive indices, and molar refractions of sodium naproxen in water at different temperatures

m $\text{mol} \cdot \text{kg}^{-1}$	n				$10^{-6} \cdot R_M$ $\text{m}^3 \cdot \text{mol}^{-1}$			
	298.15 K	303.15 K	308.15 K	313.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	1.3330	1.3325	1.3320	1.3315	3.72	3.71	3.71	3.71
0.0881	1.3376	1.3370	1.3365	1.3360	3.82	3.82	3.82	3.82
0.1527	1.3409	1.3405	1.3400	1.3395	3.89	3.89	3.89	3.89
0.2203	1.3444	1.3440	1.3435	1.3429	3.97	3.97	3.97	3.97
0.2828	1.3479	1.3475	1.3470	1.3462	4.04	4.04	4.05	4.05
0.3469	1.3515	1.3510	1.3505	1.3498	4.12	4.12	4.12	4.12
0.4064	1.3551	1.3545	1.3539	1.3531	4.19	4.19	4.19	4.19

Dispersion forces operate in both polar and non-polar molecules. The strength of dispersion force depends on polarizability (α). R_M is related to the polarizability by the following equation.

$$R_M = \frac{4N\alpha\pi}{3} \quad 9$$

In aqueous solutions of sodium naproxen, the strength of dispersion force increases with increase in the concentration sodium naproxen.

Hydration free energy is the work required to transfer a molecule from gas phase into the solution phase. It is calculated by using following equation.

$$G_{\text{Solv}}^0 = G_S^0 - G_G^0 \quad 10$$

G_G^0 and G_S^0 indicate standard free energies of solute in the gas phase and in solvent, respectively. The computational work is carried out using the Integral Equation Formalism Polarizable Continuum (IEFPCM) Solvation Model. Computed value of hydration free energy of sodium naproxen is -30.49 kcal. Negative value of hydration free energy suggests existence of strong sodium naproxen - water interactions.

CONCLUSION

From density, viscosity, and refractive index studies of sodium naproxen water solutions, it can be concluded that strong interactions between sodium naproxen and water exists. Sodium naproxen is water structure maker. In aqueous solutions of sodium naproxen, strength of dispersion force increases with increase in the concentration of sodium naproxen. Computed value of hydration free energy of sodium naproxen is negative.

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