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Solvation of Oxytetracycline Hydrochloride in Ethanol-Water Mixed Solvents.

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Research Article

ABSTRACT

The aim of this study was to determine the thermodynamic functions, Gibbs energy, enthalpy and entropy for the solution processes of oxytetracycline hydrochloride in the mixed solvent (ethanol+water) from solubility values obtained at temperatures ranging from 293.15 K to 308.15 K. The respective thermodynamic functions for mixing and solvation processes as well as the activity coefficients for the solute were calculated. The experimental results enable us to estimate the value of thermodynamic solubility product, $K_{sp(th)}$, of oxytetracycline hydrochloride in the mixed solvent. In addition, Gibbs energy, enthalpy, entropy for the solution processes and free energies of transfer of oxytetracycline hydrochloride from water to ethanol solutions.

INTRODUCTION

The solubility of solutes of all kinds in mixed solvents is of great practical importance, since many industrial process as well as laboratory procedures [1]. Most physicochemical properties of ionic solutions are influenced by ionic strength and the dielectric constant of the solvent. Indeed, in the context of solution chemistry, solvent polarity, the dielectric constant of the solvent, and the ionic strength of the medium are of great interest as a measure of the solvent ability to stabilize charges or dipoles. As an example, the dissolution of an ionic salt in a solvent or in a mixed solvent depends on the relative permittivity and the polarity of the solvent as well as on the lattice energy of the solute and the ionic strength of the medium [2,3,4].

The solvation of dissolved ions determines many of the properties of electrolyte solutions [5,6,7], including their redox, complexation, and kinetic behavior. Its particular importance to solubilities, the central topic of the International Symposium on Solubility Phenomena, is illustrated by the thermodynamic cycle in Fig. 1. As shown, the (standard) Gibbs energy of solution, $\Delta_{soln}G°$, is seen to be the sum of (the negative of the) lattice energy of the salt, $\Delta_{latt}G°$, and the solvation energies of the ions, $\Delta_{solv}G°$. This cycle makes it clear that the only reason that salts dissolve in solvents is because the very large lattice energies that are lost upon dissolution are compensated by the even larger solvation energies of the ions.

$$MX(s) \underset{-\Delta_{latt}G}{\rightleftharpoons} M^+(g) + X^-(g)$$

$$\Delta_{sln}G \qquad \Delta_{solv}G$$

$$M^+(sln) + X^-(sln)$$
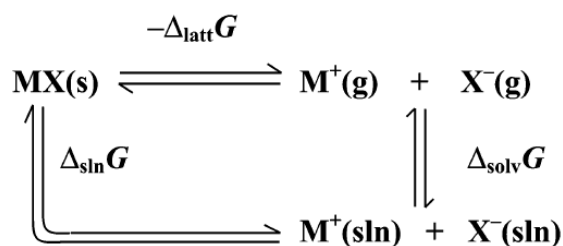
Born–Haber cycle for dissolution of the salt MX.

Because both $\Delta_{latt}G°$ and $\Delta_{solv}G°$ are very large (negative) quantities, typically of the order of −1000 kJ/mol, it follows that relatively small changes in either, for example, arising from minor changes in the nature of the solvent or the salt, can result in dramatic changes in solubility. Given that

$$\Delta_{sln}G^O = -RT\ln K_{sp}^o = 2.303 \; RT \; pK_{sp}^o \qquad (1)$$

where R and T have their usual meanings and K_{sp}^o is the (standard) solubility product of the salt:

In turn, most of the theories that have been used to predict the extend of solubility of an ionic compound in a given solvent or in a mixed solvent and related ion association are based on changes in the electrostatic properties of the solvent, solute and ion solvation as well as on the ionic strength of the medium [8,9,10,11,12,13,14,15].

## MATERIALS AND METHODS

Chemicals and Reagents

Oxytetracycline hydrochloride and ethanol were purchased from Merck Company with high degree of purity and used without further purification.

Preparation of mixed solvent and saturated solutions

The mixed solvent, (ethanol + water , 0, 20, 40, 60, 80 and 100% by volume), were prepared from bidistilled water and fairly pure ethanol. Then, saturated solutions of oxytetracycline hydrochloride were prepared by dissolving different amounts in closed test tubes containing different (ethanol + water) mixtures. These mixtures were then saturated with nitrogen gas as an inert atmosphere. The tubes were placed in a shaking thermostat (Model Gel) for a period of four days till equilibrium reached. The solubility, S (mole/Kg.solvent), of barium oxytetracycline hydrochloride in the mixed solvent at different temperature was determined gravimetrically by the solvent evaporating method. All the solubility experiments were repeated at least three times and the average were taken.

RESULTS AND DISCUSSION

For an ionic compound, with the formula AB, we may consider the following equilibrium in its saturated solution at a given constant temperature.

$$AB\,(s) \quad \leftrightarrow \quad A^+\,_{(aq)} + B^-\,_{(aq)}, \qquad K_{sp(th)} = a_+ \cdot a_- \qquad (2)$$
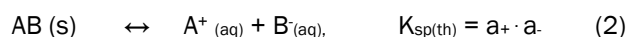
Where $K_{sp(th)}$ denotes the thermodynamic solubility product constant and a_+ and a_- refer to activity of A^+ and B^- in the solution, respectively. If the solubility of AB is very low, it may replace the activity of each ion by its concentration, so,

$$K_{sp(th)} = 2S_o^2 \qquad (3)$$

Where S_o represents the molarity of BA in the very dilute solution. The electrostatic interaction becomes very small and the ion association phenomenon may be negligible (the activity coefficient $\gamma_\pm \sim 1$) [16,17,18,19,20,21].

At low concentration, the activity coefficient may be determined by using the Debye-Hückel limiting law:

$$\log \gamma_\pm = -Z_+ Z_- A\sqrt{I} \quad \text{applicable for I} < 10^{-2}\,M \qquad (4)$$

Where Z_+ and Z_- are the charges of ions in solutions, A= $1.823\times10^6(\varepsilon.T)^{-3/2}$, the ionic strength, I, defined as, $I = \frac{1}{2}\sum_i m_i Z_i^2$ (Z_i is the charge on ion i, and Where , m_i is the molality of ion i) and the ionic strength, I emphasizes the charges of ions because the charge numbers occur as their squares. The values of dielectric constant (ε) for ethanol-water mixtures were taken from previous publications [22].

On the other hand, it can be considered that at high concentration, the solubility product constant (K_{sp}) is given by:

$$K_{sp} = 2S^2 \gamma_\pm^2 \qquad (5)$$

where S is the molal solubility of AB and $\gamma_\pm$ is the mean molal activity coefficient. There are several theoretically-based expressions that can be used to estimate single ion activity coefficients [15]. At relatively high concentration, the electrostatic interaction becomes very large [23,24,25,26]. The activity coefficient may be determined using the extended Debye-Hückel law:

$$\log \gamma_\pm = -\frac{Z_+ Z_- A\sqrt{I}}{I + Br^\circ \sqrt{I}} \qquad \text{for} \quad I < 10^{-1}\,M \qquad (6)$$

Where $B = 50.29\,(\varepsilon.T)^{-\frac{1}{2}}$, and r° is the solvated radius.

At high concentrations, activity coefficients of electrolyte solutions can be determined by using the Davies equation [27] which is an empirical extension of Debye–Hückel theory. The final form of the equation gives the mean molal activity coefficient, $\gamma_\pm$, of an electrolyte which dissociates into ions having charges Z_+ and Z_- as a function of ionic strength, I.

$$\log \gamma_\pm = -Z_+ Z_- A \left(\frac{\sqrt{I}}{I + \sqrt{I}} - 0.3I \right) \qquad (7)$$

The second term, 0.3 I, goes to zero as the ionic strength equal to zero, so the equation reduces to the Debye–Hückel equation at low concentration. However, as concentration increases, the second term becomes increasingly important, so the Davies equation can be used for solutions too concentrated to allow the use of the Debye–Hückel equation.

The molal solubility, S (mole/Kg.solvent), of oxytetracycline hydrochloride in the mixed solvent at different temperature was determined gravimetrically by the solvent evaporating method. The solubility values and activity coefficients are cited in Table (1).

The solubility of saturated solution of oxytetracycline hydrochloride in mixed solvents found to decrease with the increase the mole fraction of EtOH in the mixed solvents and increase with increase temperature depends primarily on the solvation of the solutes or their constituent ions by the components of the solvent mixtures. The saturated solution of oxytetracycline hydrochloride salt in the mixed solvent is perfectly non-ideal. The non-ideality is partly due to the mean activity coefficient of ions in the solution and partly due to the ion association phenomenon. The solubility product was calculated by the use of equation (8)

$$\mathbf{pK_{sp}} = -4(\log S^3 + \log \gamma_\pm^{\,3}) \text{......... .... (8)}$$

solubility product (pK_{sp}) data are given in Table (2), the Gibbs free energies of solvation and the transfer Gibbs free energies from water to mixed solvents were calculated by using equations (8) and (9) [28,29,20,31,32]. Their values are tabulated also in Table (2) and Table (3).

$$\Delta G^\circ = 2.303\,RT\,pK_{sp} \qquad (9)$$
$$\Delta G_t = \Delta G_s - \Delta G_w \qquad (10)$$

Where (s), (w) denote solvent and water, respectively.

The enthalpies change of solvation (ΔH)$_s$ were calculated from the plots of log $K_{sp.}$ versus $\frac{1}{T}$ as shown in Figs. 1, where the slope equals $-\Delta H/2.303\,R$ using van 't Hoff equation [33]:

$$\log K = -\frac{\Delta H^{\circ}}{2.303R}\left(\frac{1}{T}\right) + cons\tan t \qquad (11)$$

From equation (10) , the values of $(\Delta G)_s$ and $(\Delta H)_s$ can be used to calculate the values of $T\Delta S$ at different temperatures according to Gibbs-Helmholtz equation (12) [32] and all the results are reported in Table (3).

$$(\Delta G)_s = (\Delta H)_s - (T\Delta S)_s \qquad (12)$$

The magnitude of $\Delta G_{t\,(solute,\,w\,\rightarrow\,w\,+\,s)}$ as shown in Figs. 2 is a measure of the overall change in the solvation (energy) of an ion upon its transfer from water to an organic–aqueous mixture. Such quantities are usually "well behaved" in the sense that they vary smoothly as a function of solvent composition, even though they may show great diversity.

It was concluded that the Gibbs free energies of transfer increase in negativity by increasing the mole fraction of EtOH in the mixed EtOH -H_2O solvents indicating the decrease in spontaneous nature of oxytetracycline hydrochloride solubilization. This is due to more solvation behaviour in water than that of the mixed solvents where the Gibbs free energy values provide information on whether the process conditions favor or disfavor oxytetracycline hydrochloride solubilization in the aqueous carrier solution. Positive Gibbs free energy values indicate disfavourable conditions.

Figure 1: Plots of log $K_{sp.}$ for oxytetracycline hydrochloride versus $\frac{1}{T}$ at different vol % of EtOH
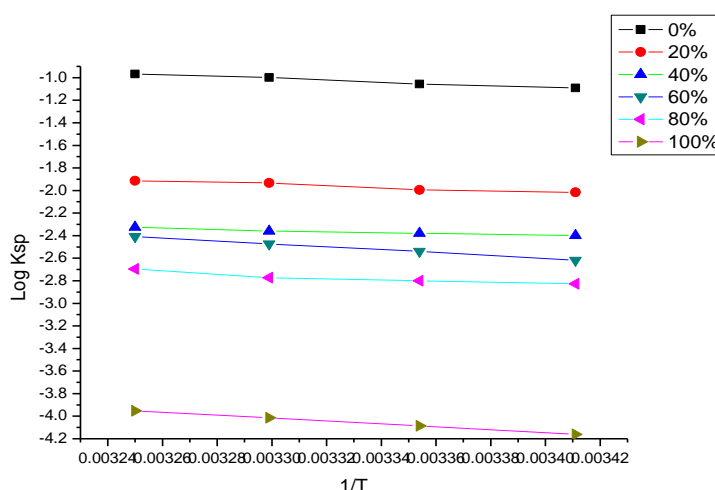

Figure 2: Gibbs free energies of transfer (ΔG_t) for oxytetracycline hydrochloride versus the mole fraction (X_s) of EtOH at different temperature.
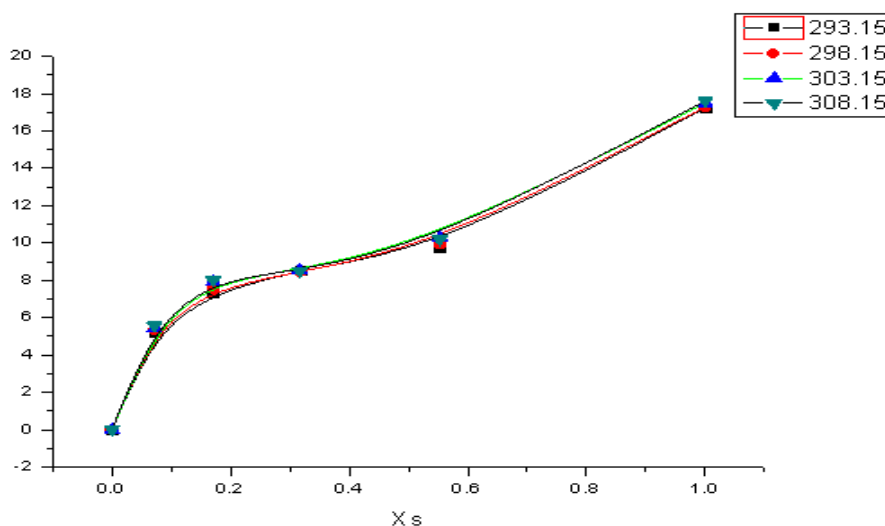
Table 1: Solubility and molal activity coefficients for oxytetracycline hydrochloride in mixed EtOH-H2O solvents at different temperature.

EtOH% By vol.	X_s, EtOH	S, mol/kg solvent				$\log \gamma_\pm$			
		293.15K	298.15K	303.15K	308.15K	293.15K	298.15K	303.15K	308.15K
0	0	0.3887	0.4057	0.4352	0.4527	0.135	0.137	0.138	0.141
20	0.0717	0.1298	0.1341	0.145	0.1494	0.123	0.126	0.13	0.133
40	0.1708	0.0829	0.0852	0.0876	0.092	0.121	0.124	0.127	0.131
60	0.3166	0.0663	0.0733	0.0801	0.087	0.137	0.141	0.148	0.151
80	0.5527	0.0565	0.0592	0.0617	0.0691	0.18	0.187	0.193	0.203
100	1	0.0152	0.0179	0.0205	0.0232	0.294	0.333	0.36	0.386

Table 2: Solubility product and Gibbs free energies of solvation for oxytetracycline hydrochloride in mixed EtOH-H$_2$O solvents at different temperature.

X_s, EtOH	pK_{sp}				ΔG_s, KJ/mol			
	293.15K	298.15K	303.15K	308.15K	293.15K	298.15K	303.15K	308.15K
0	1.091	1.057	0.999	0.968	6.1225	6.0329	5.7971	5.7098
0.0717	2.017	1.994	1.933	1.913	11.322	11.381	11.222	11.288
0.1708	2.398	2.38	2.36	2.325	13.458	13.586	13.7	13.72
0.3166	2.618	2.539	2.474	2.408	14.694	14.497	14.358	14.207
0.5527	2.828	2.801	2.773	2.695	15.871	15.99	16.097	15.902
1	4.161	4.086	4.014	3.953	23.357	23.326	23.301	23.322

Table 3: Transfer Gibbs free energies, enthalpy and entropy of solvation for oxytetracycline hydrochloride in mixed EtOH-H$_2$O solvents at different temperature.

X_s, EtOH	ΔG_t, kJ/mol				ΔH_s, kJ/mol	$(T\Delta S)_s$, kJ/mol			
	293.15K	298.15K	303.15K	308.15K		293.15K	298.15K	303.15K	308.15K
0	0.000	0.000	0.000	0.000	14.291	8.169	8.258	8.494	8.582
0.0717	5.199	5.348	5.425	5.578	12.497	1.175	1.116	1.275	1.209
0.1708	7.336	7.553	7.903	8.010	7.833	-5.626	-5.754	-5.868	-5.887
0.3166	8.572	8.464	8.560	8.497	12.162	-2.532	-2.335	-2.195	-2.045
0.5527	9.749	9.957	10.299	10.192	14.001	-1.870	-1.990	-2.096	-1.901
1	17.235	17.293	17.504	17.612	108.438	85.081	85.112	85.137	85.117

CONCLUSIONS

The solubility of saturated solution of oxytetracycline hydrochloride in mixed solvents found to decrease with the increase the mole fraction of EtOH in the mixed solvent and increase with increasing the temperature. In addition, Gibbs energy, enthalpy, entropy for the solution processes and free energies of transfer were also calculated in order to estimate the contribution of solute-solvent interactions related ion association are based on changes in the electrostatic properties of the solvent, solute and ion solvation as well as on the ionic strength of the medium. The saturated solution of oxytetracycline hydrochloride salt in the mixed solvent is perfectly non-ideal. The non-ideality is partly due to the mean activity coefficient of ions in the solution and partly due to the ion association phenomenon. By choosing a suitable model for estimating the mean activity coefficient and using the iteration calculations, we obtained the value of ion-pair concentration and the activity coefficient contribution and ion association contribution to the solubility of the considered ionic compound in the considered mixed solvent at different temperature.

ACKNOWLEDGEMENTS

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