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Ultrasonic, Volumetric, and Viscometric Studies of Tetracycline and Its Allied Compound

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Ultrasonic velocity, density, and viscosity of aqueous and nonaqueous solutions of tetracycline (TC) and its derivative 7-chlorotetracycline (aureomycin) (CTC) have been measured at 298.15 and 313.15 K (±0.01 °C). An ultrasonic interferometer, Ostwald-type viscometer, and bicapillary pycnometer, respectively, were used for these measurements. The thermodynamic property, viz., compressibility lowering, calculated by the difference in compressibilities of solution and solvent, for both TC and CTC, according to the density-velocity relation, $\beta_s = U^{-2}\rho^{-1}$, throws light on the type of solute-solvent interaction in solution.

The tetracyclines, a group of broad-spectrum antibiotics having a hydronaphthacene skeleton, are well-known for their prophylactic and therapeutic values. These are active against the majority of Gram-positive organisms and some Gram-negative bacteria, but by and large they have no significant action against viruses (*1*). Clive (*2*) has given a full review on the chemistry of tetracyclines including their mode of action (*3*) and biogenesis (*4-7*). However, the exact mechanism of their drug action is not clearly understood. The tetracyclines form coordination complexes with metal ions in vitro (*8-10*). Sachan et al. (*11*) have carried out thermodynamic studies on tetracyclines and their complexes with indium(III) in aqueous medium. The great clinical potential of these antibiotics, along with their interesting molecular structure, prompted us to study the molecular interaction in aqueous and nonaqueous media of the two most important members of this group, tetracycline itself and its 7-chloro derivative, i.e., aureomycin. Recently (*12*) we have reported the ultrasonic and thermodynamic studies on these compounds, and the results were discussed in the light of apparent molar volume, apparent molar compressibility, and the Jones-Dole (*13*) and Vand equations (*14*) of viscosity (*15-17*).

Experimental Section

Materials. Analytical grade TC and CTC were obtained from Cynamide India Limited (Ledereley Division) as hydrochlorides and used as such. These antibiotics were kept in a vacuum desiccator for about 48 h before use, and their melting points have been checked.

Preparation of the Aqueous Solutions. Stock solutions (10^{-3} M) of TC and CTC were prepared in double-distilled water. Nine solutions of different concentrations ranging from 1×10^{-4} to 9×10^{-4} M were prepared from the stock solutions and used in the experiments.

Preparation of the Nonaqueous Solutions. Stock solutions (10^{-3} M) of TC and CTC were prepared in double-distilled water and in 1,4-dioxane. Solutions of different concentration have been prepared from the stock solutions by varying the weight percentage of dioxane with respect to water.

Methods. All the measurements have been carried out on a water bath thermostatically controlled within ±0.01 °C. Bath temperature was set and monitored by a Beckman thermometer which had been set with a thermometer calibrated against a NBS certified standard.

Ultrasonic Velocity and Compressibility Measurements. Ultrasonic velocity measurements and calibration of the instrument have been carried out with a variable path ultrasonic interferometer having a frequency of 2 MHz. The procedure of the technique used is detailed elsewhere (*18*). The estimated error has been found to be ±0.07%. The adiabatic compressibility has been calculated from the well-known relation $\beta_s = U^{-2}\rho^{-1}$ (*19,20*).

Table I. Values of Ultrasonic Velocity, Viscosity, and Density of Various Pure Liquids at 303.15 K

	U, m·s^{-1}		ρ, kg·L^{-1}		$10^3\eta$, kg·m^{-1}·s^{-1}	
liquid	this work	ref *21*	this work	ref *21*	this work	ref *21*
CCl_4			1.5738	1.5740	0.840	0.843
C_6H_6	1277.8	1278	0.8681	0.8680		
$CHCl_3$			1.4700	1.4706		
1,4-dioxane	1341.0	1342			1.088	1.087
water	1510.0	1510			0.796	0.797

Density Measurements. The density measurements have been performed with the help of a bicapillary pycnometer. The procedure of the technique has been detailed elsewhere (*18*). The estimated error in the density measurements was found to be ±0.04% while uncertainity of weighing is about ±0.0001%.

Viscosity Measurements. A modified Ostwald-type viscometer has been used to measure the viscosity of aqueous and nonaqueous solutions of tetracycline hydrochloride and chlorotetracycline at 298.15 and 313.15 K ± 0.01 °C. The procedure of the technique has been detailed in another paper (*18*). Uncertainity in the measured viscosity has been found to be ±0.53%.

The accuracy of estimations has been calculated by direct comparison of the values obtained by us with those reported in the literature (*21*), in terms of percentage deviation. Both values are recorded in Table I for comparison, and thus the calibration of the instrument has been made before final use.

Results and Discussion

The experimental values of ultrasonic velocity, density, viscosity, and compressibility lowering (*18, 22-24*) calculated by the relation $\Delta\beta_s = (\beta_s^\circ - \beta_s)$ using the density-velocity relation, $\beta_s = U^{-2}\rho^{-1}$, for aqueous solutions of tetracycline hydrochloride (TC) and 7-chlorotetracycline (CTC) have been recorded in Table II and for their nonaqueous solutions in Table III. It is evident from Table II that the values of ultrasonic velocity, density, viscosity, and compressibility lowering (*18, 22-24*) increase with increasing concentration of tetracycline hydrochloride and 7-chlorotetracycline, with temperature remaining constant. The effect of temperature on these parameters is interesting with the exception of ultrasonic velocity, which increases with increase in the temperature. The values of all other parameters decrease with the rise of temperature, with concentration remaining constant.

In the ternary mixture water + dioxane + tetracycline hydrochloride/7-chlorotetracycline (Table III), the gradation of the value of these parameters is more complicated and depends mainly on the weight percentage of dioxane in the solution. The viscosity increases consistently with the increase in weight percentage of dioxane, while ultrasonic velocity, density, and

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Table II. Ultrasonic Velocity, Density, Viscosity, and Compressibility Lowering ($\Delta\beta_s$) of Aqueous Solutions of Tetracycline and Its Allied Compound

concn × 10^4, mol·L^{-1}	U, m·s^{-1}		ρ, kg·L^{-1}		$10^3\eta$, kg·m^{-1}·s^{-1}		$10^{12}(\Delta\beta_s)$, Pa^{-1}	
	298.15 K	313.15 K	298.15 K	313.15 K	298.15 K	313.15 K	298.15 K	313.15 K
			Tetracycline Hydrochloride + Water					
1.0000	1498	1519	0.9972	0.9941	0.9076	0.7219	1.7	1.3
1.9881	1501	1522	0.9974	0.9942	0.9229	0.7372	3.6	3.1
2.9929	1508	1528	0.9978	0.9944	0.9442	0.7585	7.9	6.6
4.0000	1513	1534	0.9983	0.9946	0.9644	0.7787	11.6	10.0
5.0176	1518	1539	0.9988	0.9949	0.9823	0.7966	14.1	12.9
5.9536	1524	1545	0.9993	0.9951	1.0002	0.8145	17.8	16.3
6.9696	1530	1551	0.9998	0.9954	1.0216	0.8359	21.3	19.7
8.0089	1536	1558	1.0003	0.9957	1.0373	0.8516	24.9	23.6
9.0000	1542	1564	1.0008	0.9960	1.0462	0.8605	28.4	26.9
			Chlorotetracycline + Water					
1.0000	1497	1518	0.9973	0.9942	0.9195	0.7470	1.2	0.8
1.9881	1501	1520	0.9976	0.9944	0.9348	0.7623	3.7	2.0
2.9929	1508	1523	0.9979	0.9946	0.9561	0.7836	7.9	3.8
4.0000	1514	1526	0.9982	0.9949	0.9763	0.8038	11.6	5.7
5.0176	1520	1530	0.9986	0.9952	0.9942	0.8217	15.2	8.1
5.9536	1526	1534	0.9990	0.9955	1.0121	0.8431	18.8	10.4
6.9696	1532	1539	0.9995	0.9958	1.0282	0.8588	22.3	13.3
8.0089	1538	1543	0.9999	0.9962	1.0430	0.8697	25.8	15.7
9.0000	1544	1548	1.0003	0.9965	1.0524	0.8796	29.3	18.5

Table III. Ultrasonic Velocity, Density, and Compressibility Lowering ($\Delta\beta_s$) of Nonaqueous Solutions of Tetracycline and Chlorotetracycline

compn, mole fraction			U, m·s^{-1}	ρ, kg·L^{-1}	$10^3\eta$, kg·m·s^{-1}	$10^{12}(\Delta\beta_s)$, Pa^{-1}
X_1	X_2	X_3				
Tetracycline Hydrochloride + Dioxane + Water						
298.15 K ± 0.01 °C						
0.0040	0.0228	0.9732	1575	1.0036	1.1348	46.8
0.0145	0.0816	0.9039	1576	1.0063	1.2282	48.1
0.0301	0.1687	0.8012	1581	1.0160	1.4055	54.0
0.0556	0.3111	0.6333	1565	1.0093	1.5012	42.5
0.1047	0.5861	0.3092	1521	0.9798	1.6583	4.5
313.15 K ± 0.01 °C						
0.0041	0.0227	0.9732	1544	0.9999	0.8599	18.9
0.0145	0.0813	0.9042	1553	1.0021	0.9217	27.8
0.0301	0.1682	0.8017	1562	1.0102	0.9898	40.2
0.0556	0.3103	0.6341	1570	1.0016	1.0640	48.1
0.1046	0.5853	0.3101	1545	0.9717	1.1545	36.1
Chlorotetracycline + Dioxane + Water						
298.15 K ± 0.01 °C						
0.0040	0.0228	0.9732	1541	1.0054	1.1001	29.7
0.0147	0.0816	0.9037	1562	1.0098	1.1873	42.2
0.0302	0.1687	0.8011	1573	1.0150	1.3305	49.5
0.0558	0.3311	0.6331	1556	1.0285	1.4678	55.8
0.1049	0.5859	0.3092	1529	0.9742	1.5673	6.5
313.15 K ± 0.01 °C						
0.0041	0.0227	0.9732	1544	1.0019	0.8414	19.7
0.0146	0.0813	0.9041	1554	1.0038	0.8942	28.9
0.0302	0.1681	0.8017	1563	1.0080	0.9613	39.7
0.0557	0.3103	0.6340	1568	0.9968	1.0156	34.5
0.1052	0.5849	0.3099	1545	0.9635	1.0160	32.1

compressibility lowering increase until the weight percentage of dioxane is 50%; after this there is consistent decrease. The effect of temperature is also guided by the proportion of dioxane in the mixture. In general, the values of all these parameters decrease with increase in temperature. However, this relation holds good for velocity and compressibility lowering only up to 50 wt % dioxane, after which the values are incoherent. In the case of compressibility the values start rising after the solution of tetracycline hydrochloride + dioxane + water has 50% dioxane while for the mixture of chlorotetracycline + dioxane + water, it is found to show an increment only when solution has 90% dioxane. In the case of density and viscosity, the values decrease consistently with increase in temperature. These observations clearly indicate the significance of the role played by the solvent in the mode of intermolecular interactions in these ternary mixtures because of the bulky size of the dioxane molecules. The size of the dioxane molecules appears to produce a hindrance during the accommodation in the structure of the solution, and thus it may cause a breakdown of the three-dimensional water structure. The above observation concludes that the solute-solvent interaction becomes less in the dioxane-water mixture, which is supported by the formation of hydrogen bonds with the oxygen of dioxanes and the chlorine atom of chlorotetracycline by the water molecules.

Glossary

TC	tetracycline hydrochloride (achromycin)
CTC	7-chlorotetracycline (aureomycin)
U	ultrasonic velocity of the solution, m·s^{-1}
ρ_s	density of the solvent, kg·L^{-1}
ρ	density of the solution, kg·L^{-1}
β_s	isentropic compressibility of the solution, Pa^{-1}
$\beta_s{}^{\circ}$	isentropic compressbility of the solvent, Pa^{-1}
η	viscosity of the solution, kg·m^{-1}·s^{-1}
T	temperature, K
X	mole fraction
M	molar concentration

Registry No. TC, 60-54-8; CTC, 57-62-5.

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Studies on Solvent Extraction of Resorcinol

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Liquid–liquid equilibrium data and distribution coefficients have been generated to ascertain the effect of associated constituents on the recovery of resorcinol from the neutralized fusion mass. Butyl acetate has been found to be a better solvent than butanol, and the distribution coefficient of resorcinol has been found to be 50% greater in a mixed solvent comprising 40% butanol and 60% butyl acetate by weight than in butyl acetate alone. The presence of salt increases the distribution coefficient whereas that of phenol decreases its value. The combined presence of the associated constituents, such as phenol and salt, in the composite feed favors the distribution coefficient of resorcinol in the mixed solvent. The effects of revolutions per minute, solvent to feed ratio, and number of stages on the solvent recovery and extraction time have been analyzed, and a correlation constant, *K*, has been determined for scale-up. It is observed that 99% recovery of resorcinol can be achieved in three stages with the mixed solvent for the selected feed composition.

Introduction

Solvent extraction is a key step in the manufacturing process of resorcinol as it controls the overall economics not only by its maximum recovery but also by minimizing the amount of pollutants released. In view of the expanding demand for resorcinol, a systematic study has been carried out for the selection of a better solvent and the generation of some process parameters for extraction of resorcinol from the neutralized fusion mass, a typical composition of which is given in Table I. LLE data have been generated for various systems with a view to ascertaining the individual effects of various associated constituents on the distribution coefficient of resorcinol prior to studying their combined effect. An attempt has also been made to study the performance of the extractor to analyze the effects of certain parameters needed for the process design.

Solvent Selection

The selection of solvent for extraction is based on several criteria, such as selectivity, distribution coefficient, capacity, solubility, and physical and chemical properties, besides its cost. The distribution coefficient at infinite dilution is often used as the basis for preliminary screening of the solvent, as has been considered by Won and Prausnitz (*1*). For the extraction of both phenol and resorcinol, ketones and esters are considered better solvents than alcohols and ethers. Polar solvents are better than nonpolar solvents, but then they have the problem of miscibility with water, which increases the cost of solvent recovery. An interesting possibility is the use of mixed solvents (*2*), when one of them is hydrogen-bonding acceptor, e.g., ketones, esters, or ethers, and another is a donor, e.g., alcohols, with the result that the solubility of solute in the organic phase increases. Medir and McCay (*3*) observed that the mixed solvent comprising octanol and butyl acetate gave the highest distribution coefficient of phenol. A preliminary investigation reveals that butyl acetate is better than butanol as a single solvent for the extraction of resorcinol. Binary combinations of mixed solvents comprising butyl acetate, 1-butanol, Diisopropyl ether (DIPE), and *n*-octane have been selected for the present investigation. The physical properties of these solvents are presented in Table II.

Table I. Composition of Neutralized Fusion Mass

component	composn (w/v), g/100 cm^3
Na_2SO_4	15
resorcinol	8
phenol	0.4
tarry mass	1.0
water	75.6

Experimental Section

With a view to ascertaining the domain of immiscibility and LLE behavior, the binodal curve was determined by the turbidity method, as described in the textbook by Alders (*4*), while maintaining a constant temperature at 35 °C. The binodal compositions were plotted against density for the calibration of the tie-line compositions. For generation of the tie-line data, several heterogeneous mixtures of known composition were prepared and shaken for about 4 h and later settled for the same amount of time at 35 °C. After careful separation of the clear phases, volumes and densities of these phases were measured. The tie-line compositions were determined from the knowledge of their densities and the binodal composition vs density calibration. The reliability of the tie-line compositions was verified by checking the validity of the material balance. However, for concentrations of less than 10% resorcinol in the aqueous phase, the tie-line compositions were determined iodimetrically by the chemical analysis method of Willard (*5*), in which the sample containing about 0.05 mg of resorcinol was mixed with 50 mL of acetate buffer (acetic acid–sodium acetate) solution and 50 mL of 0.1 N iodine solution in potassium iodide. After 1 min, excess iodine was titrated with the standard 0.1 N sodium thiosulfate solution using starch as the indicator. The percentage of resorcinol in the sample was calculated according to the stoichiometry of the prevailing chemical reaction. The amount of resorcinol in the extract phase was

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