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Thermodynamic properties of Clarithromycin, Azithromycin and Erythromycin antibiotic drugs in aqueous and nonaqueous solutions mixture from shear viscosity measurements

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ABSTRACT

Solution thermodynamics of Clarithromycin, Azithromycin and Erythromycin antibiotic drugs samples in 40% water- methanol, ethanol and dioxane mixture solvents have been investigated by viscometric studies at 20, 25, 30, 35, and 40°C. The drug absorption, transmission, activity and effect of drugs, structure making and breaking properties of ligands, solute-solute and solute-solvent interaction can be explain from thermodynamic parameters of drug. Taking all these things into consideration this research work was carried out. It was clear from the result that ligand with lower viscosity shows good results at higher temperature which favors the concept of pharmacokinetics and pharmacodynamics in pharmaceutical field.

Key words: Clarithromycin, Azithromycin, Erythromycin, antibiotic drugs, Thermodynamic properties, viscosity

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INTRODUCTION

The thermodynamic and transport properties of liquids and liquid mixtures [1] are used to study the molecular interactions between the various components of the mixture and also to understand engineering applications concerning heat transfer, mass transfer, and fluid flow. The density and viscosity data are so important that they contribute to theoretical and practical comprehension of the binary liquid mixtures pattern of behavior. Also, Viscosity is one of the physical properties of liquid, which measures viscous drug force between adjacent layers in the liquid[2]. Viscosity is directly related to the absorption of drug and metabolic and physiological activity in the body. The structure making and breaking properties of liquids have been considered as a measure of solute-solute and solute-solvent interactions [3-5]. Macrolide antibiotics, Because of its biological effect against both Gram-positive and Gram-negative bacteria and mycoplasma, are now extensively applied for prevention and treatment of bacterial infections in medical and veterinary practice, especially in stock animals, poultry and fish. For example erythromycin is an antibiotic that has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often used for people that have an allergy to penicillin. The term erythromycin is used for a group of antibiotics that include not only erythromycin but also those chemically related to or derived from erythromycin, such as azithromycin (Zithro-max) and clarithromycin (Biaxin). They are prescribed for a wide variety of infections caused by bacteria, including pneumonia, strep throat, bronchitis, ear infections, urinary tract infections, and tonsillitis. They also used to treat outbreaks of chlamydia, syphilis, acne, and gonorrhea [6,7]. The heterocyclic compounds play an immense role in medicinal, pharmaceutical, industrial and biochemical field[8-10].

The viscosity is directly related to the thermodynamic parameters ΔG*, ΔH* and ΔS*. The liquid possesses viscosity, which implies resistance to flow. Hence, in this work, we were studied the thermodynamic parameters of Clarithromycin, Azitromycin and Erythromycin antibiotic drugs in 40% percentage water – methanol, ethanol and 1,4-dioxan composition at different temperature by viscosity measurements.

MATERIALS AND METHODS

All the chemicals Drugs were prepared from shafa company. Densities of solutions were determined by a bicapillary pyknometer (±0.2%) having a bulb volume of about 25 $cm^3$and capillary having an internal diameter of 1 mm and calibrated with deionized doubly distilled water. The accuracy of density measurements were within ±0.1 Kg^{-3}. The viscosities were measured by means of Ostwald's viscometer thoroughly cleaned and dried. The viscometer was kept in Elite thermostatic water bath and temperature variation was maintained. For each measurement, sufficient time was allowed to attain thermal equilibrium between viscometer and water bath. The 0.02 M solution of ligand L1(Azithromycin), L2(Erythromycin) and L3(Clarithromycin) were prepared in 40% water – methanol, ethanol and 1,4-dioxan(from Merck) mixtures. The densities and viscosities of each ligand solution were at 20, 25, 30, 35 and 40^{o}C. The constant temperature was maintained with the help of elite thermostatic water bath (± 0.1^{o}C). For each measurement, sufficient time was allowed to attain the thermal equilibrium. In all cases the procedure was repeated at last three times and the resulting average values and corresponding deviations from the average are shown in the text and tables.

RESULTS AND DISCUSSION

According to Kauzman and Eyring [11] the viscosity of a mixture strongly depends on the entropy of the system which is in his turn dependent on the structure of the liquid as well as the enthalpy.

The absolute reaction rate theory of Eyring[12] relates the viscosity to the Gibbs energy ΔG* of activation flow:

$$\eta_{\text{mix}} = \frac{hN_A}{V} \exp\left(\frac{\Delta G^*}{RT}\right) \quad (1)$$

Where h, N_A and V are the Planck constant, Avogadro's number and the molar volume of the mixture, respectively. The ΔG* calculated values are reported in Table 1 for various temperatures. Using Eq.(2), one can determine for our mixture the enthalpy ΔH*and entropy ΔS*of activation of viscous flow activation parameters ΔH*:

$$\Delta G^* = \Delta H^* - T\Delta S^* \quad (2)$$

By assuming that the activation parameters ΔH* and ΔS* are independent of temperature [13].

In order to get these activation parameters, we have investigated the viscosity of ligand(L_1), ligand(L_2) and ligand(L_3) antibiotic drugs in 40% water- methanol, ethanol and 1,4- dioxane mixture in the whole range of compositions at five various temperatures. The values of viscosities are depicted in Table 1. From the Table 1, it is also observed that viscosities of all the ligand solutions have direct correlation with temperature. This correlation favors 'hole theory' of liquid. The liquid molecules keep on moving continuously into vacancies. The motion of liquid molecules need some energy to move into hole. At increasing temperature, the energy becomes increasingly available and so a liquid can flow more easily. Thus, the viscosity falls appreciably with rise in temperature. At the same time when the temperature increases the intermolecular force of attraction in the ligand also decreases this will directly affect the viscosity. This shows decrease in solute-solvent interactions which is the best property of drug. It means that drug effect is very advantageous. Also, the decrease is appreciable being about five percentage degree rise of temperature. The data obtained have been used to determine the thermodynamic parameters ΔG*, ΔH* and ΔS*. From this data, the structure breaking and making properties of liquids have been considered as a measure of solute-solute and solute-solvent interaction.

From the values of L_1, $L_2$and L_3 (table 1), it was observed that, the value of relative viscosity of L_1 with dioxan-water is greater than L_3 and L_2. Only the bulkiness of the group as substituent not only interfere the values of relative viscosity but the reactivity and stability and tautomeric properties also interfere the values of relative viscosities. It is clear from the result that, in L_1 a Nitrogen atom in great ring becomes more reactive which directly and easily involved in tautomeric conversion of whole molecule. Such type of greater interference of Nitrogen will

not involved in L_2 and L_3 but when we compare, relative viscosity of L_1 and L_2, the relative viscosity of bulkier group must be greater but in this investigation, the relative viscosity of L_1 is greater than that of L_2, this may be due to the donating capacity of –CH3 group to the amido molecule in ringe. As the amido molecule is highly electron rich moiety and –CH3 group is also electron donating group, hence in L_1 molecule there occur compactness in the bond which is greater than L_2 molecule. From this discussion, it is clear that bulky substituent on the molecule is not only factor in trend of relative viscosity but tautomeric conversion as well as electron donating nature, electron clouds, nature of hetero atom present in ligands and the compactness in the molecule will directly hampered results and trends in the relative viscosity. So ligand with lower viscosity shows good results at higher temperature which favors the concept of pharmacokinetics and pharmacodynamics in pharmaceutical field.

Table 1. Determination of relative viscosities and ΔG*, at 0.02 M concentration for ligand L1, L2 and L3 at 40% water-solvent mixture

Drug	Temp. (°C)	Time sec.	Density(g/cm3)	η	ΔG^*(KJ/mol)
	20	0.79	0.915	1.580	70.020
	25	0.64	0.913	1.215	70.947
Azithromycin	30	0.59	0.905	1.131	71.875
(Ethanol)	35	0.54	0.902	1.107	72.799
	40	0.49	0.860	0.904	73.726
	20	0.49	0.960	0.970	69.052
Azithromycin	25	0.46	0.902	0.863	69.951
(Methanol)	30	0.41	0.896	0.778	70.851
	35	0.37	0.8885	0.748	71.750
	40	0.32	0.8880	0.609	72.650
	20	0.65	1.051	1.493	69.711
Azithromycin	25	0.63	1.011	1.324	70.763
(1,4- Dioxane)	30	0.60	1.010	1.284	71.814
	35	0.56	1.007	1.282	72.866
	40	0.54	1.006	1.165	73.918
	20	0.67	0.905	1.325	70.274
Erythromycin	25	0.63	0.904	1.184	71.273
(Ethanol)	30	0.60	0.899	1.143	72.273
	35	0.55	0.892	1.115	73.272
	40	0.50	0.881	0.945	74.271
	20	0.44	0.908	0.873	68.702
Erythromycin	25	0.42	0.903	0.788	69.638
(Methanol)	30	0.37	0.902	0.707	70.575
	35	0.33	0.9018	0.676	71.511
	40	0.31	0.9017	0.599	72.447
	20	0.64	1.029	1.439	69.608
Erythromycin	25	0.61	1.022	1.296	70.642
(1,4- Dioxane)	30	0.58	1.018	1.251	71.676
	35	0.54	1.013	1.244	72.710
	40	0.51	0.99	1.093	73.744
	20	0.78	0.918	1.565	70.097
	25	0.72	0.908	1.359	71.093
Clarithromycin	30	0.66	0.905	1.265	72.089
(Ethanol)	35	0.60	0.902	1.231	73.084
	40	0.58	0.899	1.119	74.080
	20	0.44	0.905	0.870	68.757
Clarithromycin	25	0.42	0.8999	0.786	69.690
(Methanol)	30	0.37	0.8997	0.705	70.623
	35	0.33	0.897	0.673	71.557
	40	0.31	0.892	0.593	72.490
	20	0.59	1.028	1.326	69.457
Clarithromycin	25	0.55	1.027	1.174	70.438
(1,4- Dioxane)	30	0.52	1.022	1.126	71.420
	35	0.47	1.015	1.085	72.402
	40	0.43	1.010	0.932	73.383

Also, we can obtain thermodynamic parameters for each mixture composition by plotting ln η against 1/T. Using both graphical and least-squares fitting methods, the slope of the straight line is equal to ΔH*/R and the intercept is equal to $\ln(N_A h/V)\Delta S^*/R$. The obtained activation parameters ΔH* and ΔS* for the binary mixture are presented in Table 2 and are shown in Fig. 1, 2 and 3. No published work on the activation parameters was found for the present system with which to compare our results. Adding various solvents to water, activation Table 2 shows that the system exhibits a positive values of ΔH* and negative values of ΔS*. The negative values of ΔS* indicate that the greater degree of order is associated with the activation process for viscous flow.

Table 2. Determination of ΔH* and ΔS* at 0.02 M concentration for ligand L_1, L_2 and L_3 at 40% water- solvent mixture

Drug	Solvent	ΔH^0 (KJ/mol)	ΔS^0 (J/mol.k)
Azithromycin (L_1)	Ethanol	15.740	-185.259
	Methanol	16.337	-179.915
	1,4-Dioxane	8.068	-210.386
Erythromycin (L_2)	Ethanol	11.173	-199.869
	Methanol	13.836	-187.258
	1,4-Dioxane	9.007	-206.830
Clarithromycin (L_3)	Ethanol	11.756	-199.119
	Methanol	14.062	-186.673
	1,4-Dioxane	11.928	-196.345

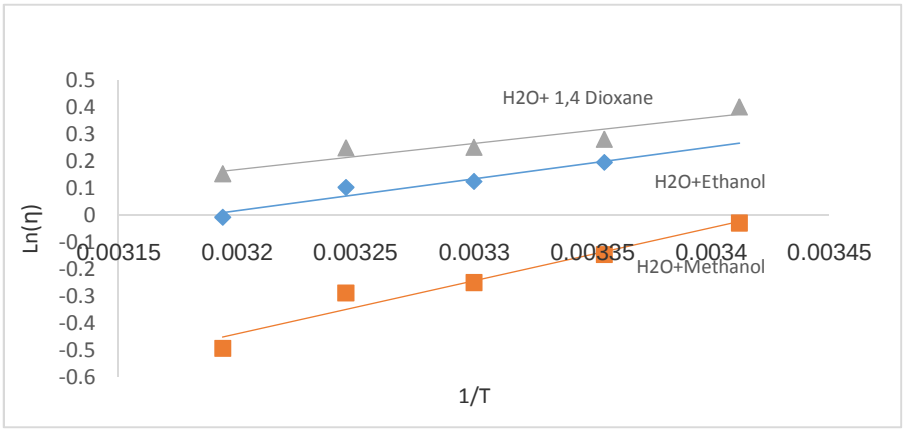

Fig. 1. ln η vs. l/T at 0.02 M concentration for ligand L_1 at 40% water- solvent mixture

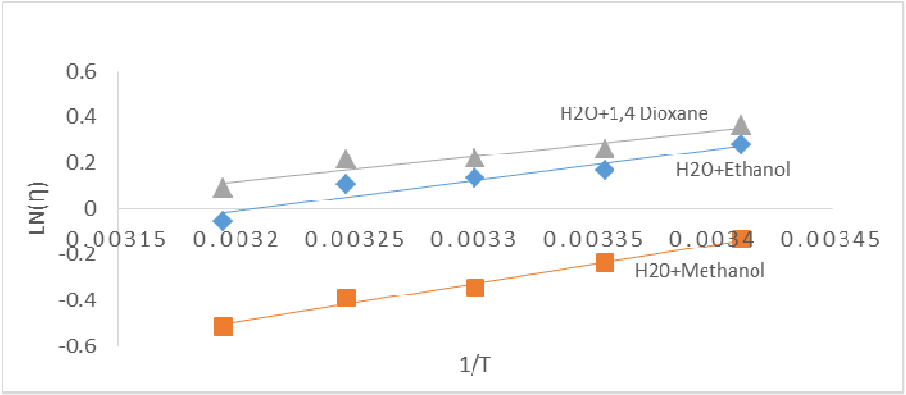

Fig. 2. ln η vs. l/T at 0.02 M concentration for ligand L_2 at 40% water- solvent mixture

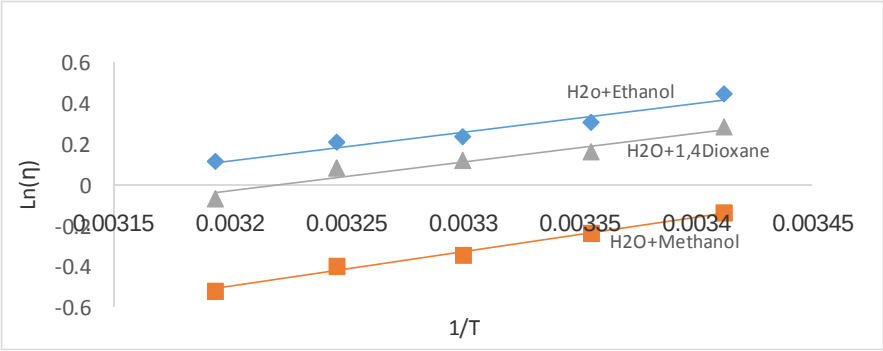

Fig. 3. ln η vs. l/T at 0.02 M concentration for ligand L_2 at 40% water- solvent mixture

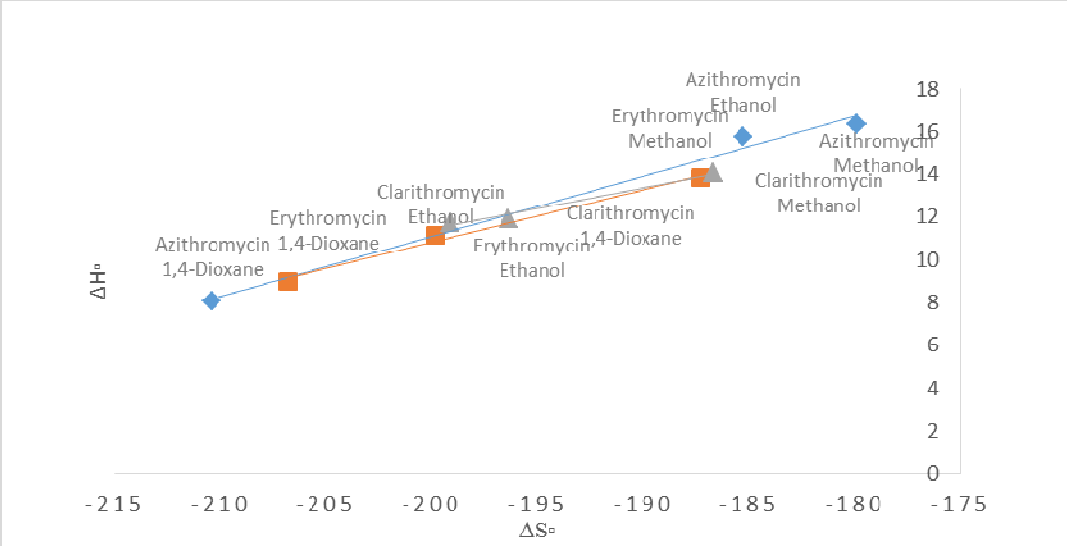

Fig. 4. Correlation between the entropy ΔS* and enthalpy ΔH* of activation of viscous flow for solvent + water mixtures versus various temperature of Drugs

In Figure 4, we have plotted ΔH*against ΔS* for each mixture composition (Azithromycin, Clarithromycin and Erythromycin) in 40% water – methanol, ethanol and 1,4-dioxan. A roughly linear relationship is observed between the values obtained in this work. Such a linear relationship bodes that the change in ΔH* is commensurate to the corresponding change in ΔS*. One can see from fig. 4 that ΔH* and ΔS* decrease and decline to a localized minimum for Azithromycin and Erythromycin in 1,4 - dioxane solvent mixture.

In fact, the negative values of ΔS*, suggest that structural order is not all the more destroyed by the activation process that many bonds are not broken between the associated molecules to form smaller units. These distinct behaviors are clearly revealed when the correlation between disorder and order is plotted in Fig. 4.

CONCLUSION

Hence from the above discussion, it was clear that bulky substituent on the molecule was not only factor in trend but tautomeric conversion as well as electron donating nature, electron clouds, nature of hetero atom present in compounds and compactness in the molecule will directly hampered results and trends in solubility. It means that at 60% percentage of methanol, the solute-solvent interactions i.e. interaction of compounds (drugs) and methanol shows good results with rise in temperature, which may be stabilize the drug activity. From this it can be concluded that the drug absorption, drug transmission and drug effect of compounds L_1, L_2, L_3 is more effective at higher temperature of methanol. This study may become a milestone in the drug, medicinal and pharmaceutical chemistry of macrolide antibiotics.

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