A COMPARATIVE STUDY OF THERMODYNAMIC PROPERTIES OF STRUCTURALLY RELATED PHENOTHIAZINE DRUGS IN AQUEOUS SOLUTION

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ABSTRACT

Association characteristics of amphiphilic phenothiazine drugs Fluphenazine and Trifluperazine dihydrochloride in water have been examined and their thermodynamic parameters have been calculated using conductometry. The electrical conductivity was measured as a function of concentration at various temperatures and cmc was calculated in the temperature range of 20-50°C. Thermodynamic parameters i.e. standard free energy of micellization, ΔG_m°, standard enthalpy of micellization, ΔH_m° and standard entropy of micellization, ΔS_m° were calculated from cmc value using closed association model.

INTRODUCTION

A large number of drugs exhibit colloidal behavior and their properties mainly depend on the nature of aromatic ring system of hydrophobic moiety. They are useful in probing the relationship between molecular structure and physicochemical properties. One of the mechanisms to serve this purpose is to study the thermodynamics of their aggregation and the factors governing this process[1]. The tricyclic antidepressant drugs are the family of structurally related compounds suited ideally for exploration of this relationship. They possess an almost planar ring system with a short hydrocarbon chain carrying a terminal, charged nitrogen atom[2].

Phenothiazine compounds are commonly used in clinical medicines as antipsychotic and tranquilizing drugs. They have interesting physicochemical properties associated with their ability to self aggregate forming "micelle-like" structure as well as properties to change natural and model biomembranes. Their unusual association characteristics derive from their rigid tricyclic hydrophobic group. The flexibility of hydrophobic group, for example, in the drugs with diphenyl methane structure is conductive to closed or micellar association. However linkage of aromatic rings in the form of rigid, planar nucleus leads to open or continuous association. The rigidity and planarity of aromatic groups, although an important requirement for latter is not the only structural feature influencing the mode of association, playing also alkyl side chain attached to it, a key role. We have already examined thermodynamic properties of Phenothiazine drug thioridazine hydrochloride[3] butriptyline and doxepine hydrochloride[4], warfarine sodium salt[5], promazine and triflupromazine hydrochlorides[6], certizine hydrochloridel[7], Dexamethasone Sodium Phosphate[8] and Citalopram Hydrobromide[9] in aqueous solution.

In this article we intend to discuss the thermodynamic properties of structurally related phenothiazine drugs in aqueous solution which have the following chemical structure.
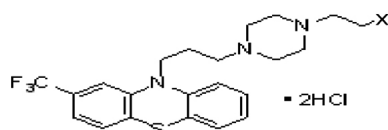
Fluphenazine, X= CH₂-CH₂-OH

Trifluperazine, X=CH₃

Scheme 1. Chemical structure of Fluphenazine and Trifluperazine dihydrochloride

EXPERIMENTAL

Reagents

Fluphenazine dihydrochloride [C22H26F3N3OS.2HCl] and trifluperazine dihydrochloride [C21H24F3N3OS.2HCl] with Molar mass 510.5gmol⁻¹ and 480gmol⁻¹ respectively were purchased from Sigma Chemical Co. and were used as received. Solutions were made up by weight at room temperature using a METTLER AT20 balance with a precision of 0.001mg and double-distilled, deionized water. To avoid concentration gradient, all solutions were stirred before the measurements. All the glassware and Teflon troughs were cleaned using alkaline detergent and rinsed in double distilled water.

Apparatus:

Specific Electric conductivity measurements: Conductivities were measured with an HP 4285A Precision LCR meter equipped with an HP 5050A colloid dielectric probe. The probe is especially designed to measure conductances and to avoid polarization that occur when probe is constructed from place condenser plates. Specific conductivities were measured at (20-50) °C with 10° increment. The measuring cell was immersed in a thermostat bath keeping the temperature control within ±.01°C, and was calibrated with aqueous solution of KCl over appropriate concentration range using the molar conductivity data of Schedlovsky[10] and Chambers et al[11].

RESULTS AND DISCUSSION

The self aggregation study of Fluphenazine and Trifluperazine dihydrochlorides is carried out by a fundamental quantity, the critical micelle concentration, the concentration where micellization just starts. Since this process is very complex hence it is very difficult to pinpoint the concentration where it actually does happen. That's why people are still trying to make an easy way available to determine this concentration which is very important in many biological and industrial phenomenons [12]. The experimental determination of specific conductivities provides an efficient and sensitive technique to detect cmc. It helps to detect second and even third critical concentration (if any). At each temperature concentration dependence of electrical conductivity shows a gradual increase of slope.

The inflection points were made visible by employing Origin program. In agreement with Phillips[13], the critical micelle concentration is defined as

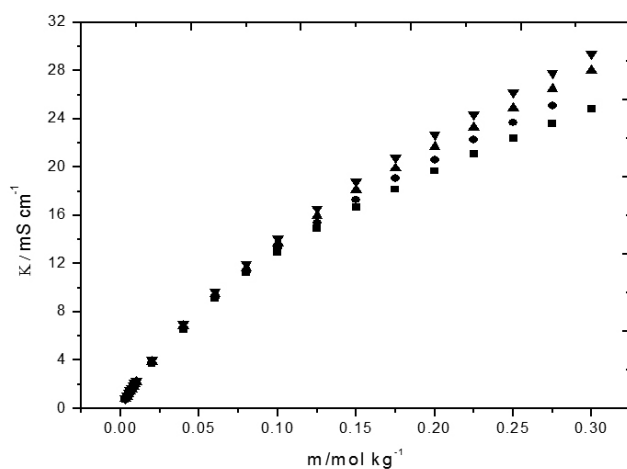$$\left(\frac{d^3k}{dc^3}\right) = 0 \qquad (1)$$

Figure 1. The plot of specific Conductivity (mS) versus molality, m, (mol/Kg), for aqueous solution of Trifluperazine 2HCl at 293K (■), 303K (●), 313K (▲) and 323K (▼).
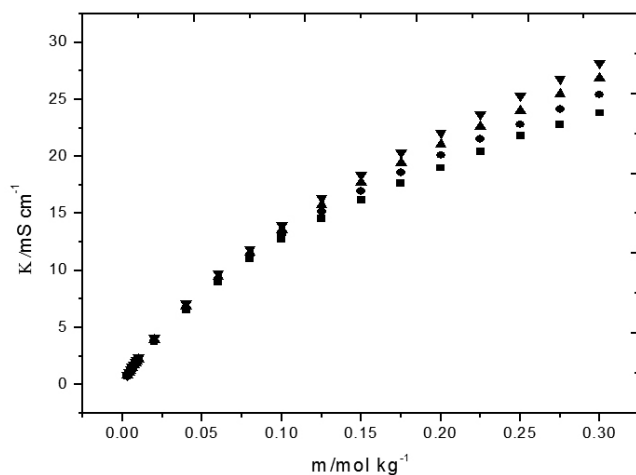

Figure 2. The plot of specific Conductivity (mS) versus molality, m, (mol/Kg), for aqueous solution of Fluphenazine 2HCl at 293K (■), 303K (●), 313K (▲) and 323K (▼).

Where k denotes the conductivity and c the critical micelle concentration (cmc). The cmc can also be determined by the intersection of two straight lines of concentration-conductivity plot, above and below the cmc. The precision of measurement depends on the width of concentration range over which the change in physical properties are observed. Two inflection points are obtained in the conductivity plot for both drugs. They are indicated as cc_1 and cc_2. The cc_1 is taken as cmc because it has reasonable agreement with the value obtained by surface tension data of these drugs[14]. There is again a change in slope of conductivity-concentration plot at cc_2 which may be related with structural rearrangement of aggregates previously formed in order to minimize the energy of solution, as occurred for number antidepressant and phenothiazine amphiphilic drugs. Its value doesn't have any clear temperature dependence[4].

The value of cmc increases with temperature because the degree of hydrophillic dehydration, at high temperature, is greater than that of hydrophobic dehydration which enhances the repulsion among hydrophilic groups and renders micellization difficult consequently increasing the cmc value[14]. The cmc of Trifluperazine 2HCl has lower value than that of Fluphenazine 2HCl because the former is more hydrophobic as -OH group reduces hydrophobicity of Fluphenazine 2HCl.. The value of cmc helps to calculate value of thermodynamic parameters of drugs i.e. ΔG_m°, ΔH_m° and ΔS_m° These parameters are called standard free energy of micellization, standard enthalpy of micellization and standard entropy of micellization respectively. In this case we are using cmc in term of mole fraction rather than molality or molarity. We

need to define standard state for thermodynamic parameters to be calculated for micellization process. The hypothetical standard state for surfactants in the aqueous phase is taken to be the solvated monomer at unit mole fraction with properties of infinitely dilute solution. For the surfactant in the micellar state, the micellar state is itself considered to be the standard state[16].
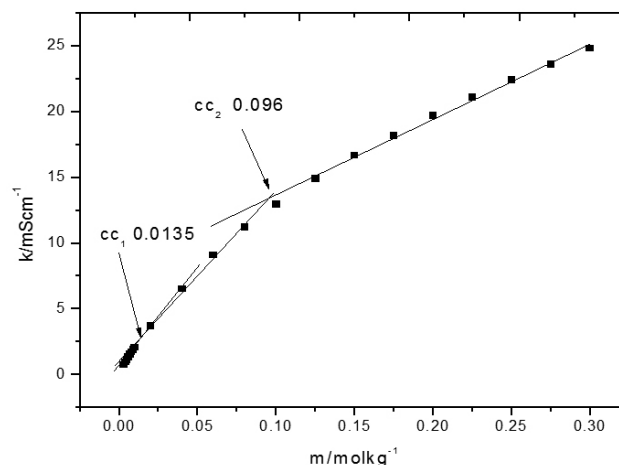

Figure 3. The plot of specific Conductivity (mS) versus molality, m, (mol/Kg), for aqueous solution of Trifluperazine 2HCl at 293K.

The thermodynamic parameters e.g. Gibbs free energy of micellization, ΔG_m° was calculated from equation 2, while Enthalpy of micellization, ΔH_m° and Entropy of micellization, ΔS_m° were calculated from conductivity data using equation 3 and 4 respectively.

$$\Delta G_m^0 = (1+\alpha)RT \ln X_{cmc} \qquad (2)$$

$$\Delta H_m^\circ = -RT^2 \left[\frac{\partial(1+\alpha)(\ln X_{cmc})}{\partial T} \right]_P \qquad (3)$$

$$\Delta S_m^\circ = \frac{\Delta H_m^\circ - \Delta G_m^\circ}{T} \qquad (4)$$

Here Xcmc is cmc in term of mole fraction while α is degree of counter ion binding. An approximate value of α is calculated as

$$\alpha = 1 - \beta = 1 - \frac{S_2}{S_1} \qquad (5)$$

Where β is degree of ionization while S2 and S1 are slopes of conductivity-concentration plot after and before cmc respectively.

Table 3 and 4 show the value of thermodynamic parameters along with the values of cc1,cc2, degree of counter ion binding (α) and degree of ionization (β) for both Phenothiazine drugs.

Table 1: Various parameters calculated from specific conductivity measurements for Fluphenazine 2HCl.

$\dfrac{T}{K}$	$\dfrac{cmc}{mmolkg^{-1}}$	$\dfrac{c_2}{mmolkg^{-1}}$	$\dfrac{\Delta H_m}{KJmol^{-1}}$	$\dfrac{\Delta G_m}{KJmol^{-1}}$	$\dfrac{\Delta S_m}{JK^{-1}mol^{-1}}$	α	β
293	17±0.65	110±4.2	-5.60±0.73	-26.8±0.84	72.15±0.95	0.590	0.407
303	17.5±0.35	118±2.3	-5.98±0.49	-27.9±0.51	72.44±1.03	0.600	0.400
313	19.3±0.2	140±4.2	-6.38±0.37	-28.75±0.39	71.47±1.01	0.606	0.393
323	20.0±0.31	140±3.2	-6.80±0.53	-29.7±0.47	70.87±0.93	0.610	0.390

Table 2: Various parameters calculated from specific conductivity measurements for Trifluperazine 2HCl.

$\dfrac{T}{K}$	$\dfrac{cmc}{mmolKg^{-1}}$	$\dfrac{c_2}{mmolKg^{-1}}$	$\dfrac{\Delta H_m}{kjmol^{-1}}$	$\dfrac{\Delta G_m}{kjmol^{-1}}$	$\dfrac{\Delta S_m}{JK^{-1}mol^{-1}}$	α	b
293	13.5±0.37	96±1.52	-20.70±0.53	-28.24±0.59	25.70±0.45	0.618	0.382
303	14.9±0.20	109±2.08	-22.15±0.31	-29.50±0.44	24.29±0.35	0.619	0.381
313	17.5±0.45	122±1.2	-23.64±0.55	-30.18±0.59	20.88±0.51	0.631	0.369
323	18.4±0.33	122±2.1	-25.17±0.36	-31.33±0.52	19.07±0.39	0..636	0.364

At higher temperature the value of cmc increases while that of ΔGm becomes more negative. It apparently seems contradicting but actually it is not so because ΔG is not only dependent on cmc but also on the degree of counter ion binding and temperature. Published data for a number of amphiphiles makes it clear that process of micellization may be more spontaneous even if cmc is increasing. The increase in cmc means delay in micellization process and increase in negative value of ΔG is indicative of spontaneity of process[6].

The large negative value of ΔG_m° indicates that micellization is a thermodynamically favorable process. The values of ΔG_m° become more negative with temperature showing more spontaneity of process at higher temperature. The positive values of ΔS_m° and negative value of ΔH_m°, at each temperature, connotes that micellization is a both entropy and enthalpy driven process[15] where, in addition to hydrophobic, electrostatic interactions play a vital role. The negative values of ΔH_m° also let us know about exothermic nature of process. The decrease in value of ΔS_m° and increase in value of ΔH_m° with temperature displays that hydrophobic interactions become weaker while electrostatic ones become stronger. The ΔH_m° is the sum of change in enthalpies arising from hydrophobic interactions, electrostatic interactions, hydration of polar head groups and counter ion binding to micelles. A negative value of ΔH_m° may occur when hydration of water molecules around hydrophilic heads groups become more important than destruction of water structure around hydrophobic groups of monomers. The increase in temperature causes dehydration of hydrophilic groups, thus making electrostatic repulsion stronger. The positive values of ΔS_m° are due to transfer of hydrophobic chains of drugs from aqueous environment to micelle core[16]. It is accepted that in the immediate vicinity of hydrophobic groups there is strengthening of hydrogen bonding between water molecules. This hydration of hydrophobic groups is quite different than the usual solvent-solute interaction and is termed as hydrophobic hydration. The water molecules in neighborhood of hydrophobic groups are more attracted by nearby water molecules. This corresponds to tightening of water structure around hydrophobic groups[2]. A consequence of this situation is that internal torsional vibrations of chains are restricted in solution. The more ordered structure of water molecules around hydrophobic chains and restriction in vibrations of hydrophobic groups leads to decrease in entropy of system. The removal of hydrophobic groups from aqueous environment is entropically favourable leading to disruption of highly organized water structure and removal of mobility constraints on hydrocarbon chain[16]. The dehydration of hydrophobic parts causes a plunge in ΔS_m° values with temperature. The comparison of ΔG_m° values of both drugs indicates

that Trifluperazine 2HCl is more hydrophobic than Fluphenazine 2HCl due to presence of different substituents in molecular structure. The micellization of the former is, thus, more spontaneous. These values are in good agreements to those reported for other drugs[4, 5, 6].

CONCLUSION

The comparative study of thermodynamic properties of Fluphenazine and Trifluperazine dihydrochlorides has been carried out from specific conductivity measurements. The value of cmc is obtained by employing Origin Program. The value of cmc increases with increase in temperature because at high temperature the degree of hydrophobic dehydration is less than hydrophilic dehydration. This phenomenon opposes micellization and hence increases the cmc. Trifluperazine 2HCl has lower value of cmc and more negative value of ΔG_m° than Fluphenazine 2HCl because it has more hydrophobic character. The ΔG_m° values of both drugs are negative and become more negative at high temperature showing that the process of micellization becomes more spontaneous with temperature. The positive value of ΔS_m° and negative value of ΔH_m° indicates that micellization is both entropy as well as enthalpy driven and is equally supported by both hydrophobic and electrostatic interactions. The positive value of ΔS_m° is due to removal of hydrophobic parts of drugs from aqueous environment to micellar core which destroys ordered water structure around them and enables them to get rid of mobility constraints. The negative value of ΔH_m° displays that hydration of hydrophilic groups is more important than destruction of water structure around hydrophobic groups.

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