Surface and Bulk Properties of Two Amphiphilic Phenothiazine Drugs in Different Aqueous Media

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Surface behavior and bulk properties of two phenothiazine drugs, fluphenazine and trifluoperazine dihydrochlorides, are reported. Surface activity studies for both amphiphilic drugs were carried out in aqueous solutions at 20 °C by surface tension measurements. The volumetric and compressibility properties of the drugs were derived from density and ultrasound velocity measurements. Critical concentrations were determined by surface tension and ultrasound data. The experiments were realized in aqueous and buffered (pH 3.0, 5.5, and 9.2) media at 20 °C. The buffered media were chosen below and above the different pK_a's that the drug molecules present (pK_{a1} and pK_{a2} of 3.90 and 8.10, respectively).

Introduction

The hydrophobic character of the aromatic ring of some amphiphilic drugs is useful in probing the relationship between molecular architecture and physicochemical properties.[1] There are many types of amphiphilic drugs with different actions. The pharmacological groups of tranquilizing and antipsychotic drugs based on the phenothiazine ring system are surface active and exhibit self-association in aqueous solution.[2] It has been established from earlier studies on these compounds that aggregates of approximately 8 to 10 monomers are formed in water by a closed association process at well-defined concentrations and that some of them present a second aggregation concentration in aqueous solutions.[3–5] Although the pharmacological effect of drug molecules is usually manifest at low concentrations where self-association is not important, it is likely that accumulation of drug molecules at certain sites in the body may cause a localized high concentration resulting in aggregation and subsequent changes in biological activity due to decreased transport rates or decreased ability to pass through biological barriers.[1] All such interactions are influenced by changes in the surrounding medium: pH, temperature, ionic strength, etc. In this work, we study two piperazine drugs with important antipsychotic activity: fluphenazine and trifluoperazine dihydrochlorides. Trifluoperazine dihydrochloride has a structure similar to that of fluphenazine dihydrochloride (see Figure 1), differing only in the structure of the side chain attached radical. Previous studies[6–8] have also shown that the micellar properties of drugs which contain a piperazine moiety (opipramol, thiopropazate, flupenthixol, clopoenthixol) show considerable pH dependence. We report the properties on the surface and in the bulk of the solution of these two drugs at 20 °C at different pH. The surface activity studies in water solutions were carried out by surface tension measurements. Density and ultrasound measurements let us calculate volumetric and compressibility properties of the drugs in water and at different pHs (3.0, 5.5, and 9.2), below and above the pK_a's of the drugs[9,10] (pK_{a1} = 3.90; pK_{a2} = 8.10, see Figure 1).

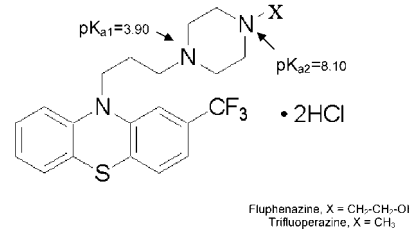

Figure 1. Chemical structures of fluphenazine and trifluoperazine dihydrochlorides.

Materials and Methods

Materials. Fluphenazine dihydrochloride [$C_{22}H_{26}F_3N_3OS.2HCl$] and trifluoperazine dihydrochloride [$C_{21}H_{24}F_3N_3S.2HCl$] with molecular weights of 510.5 g·mol^{-1} and 480.43 g·mol^{-1}, respectively, were obtained from the Sigma Chemical Company. Solutions for surface tension, density, and ultrasound velocity experiments were made up by weight at room temperature, using a METTLER AT20 balance with a precision of 0.001 mg and double-distilled, deionized, and degassed water. For bulk properties (density and ultrasound velocity), the buffer solutions used were glycine + HCl (I = 0.01 M) for pH 3.0, sodium acetate−acetic acid for pH 5.5 (I = 0.01 M), and glycine + NaOH for pH 9.2 (I = 0.01 M), respectively, to evaluate the drug aggregation process at the different ionization states of the drug. To avoid concentration gradients, all solutions were stirred before the measurements. All the glassware and the Teflon troughs were cleaned using an alkaline detergent and repeatedly rinsed in double-distilled water.

Surface Tension Measurements. Measurements of dilute water solutions of fluphenazine and trifluoperazine were made by the Wilhelmy vertical platinum plate technique using a Kruss K-12 surface tension instrument equipped with a processor to acquire the data automatically. The instrument was connected to a HETO circulating water bath with a proportional temper-

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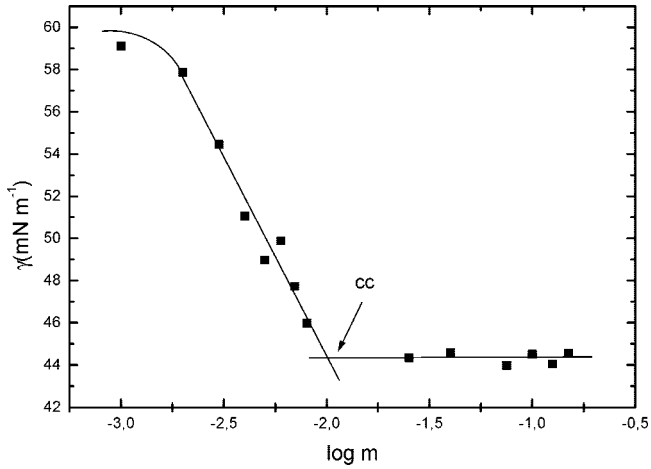

Figure 2. Surface tension vs log m for fluphenazine dihydrochloride in water at 20 °C. The arrow denotes the critical concentration, cc.

ature controller to keep the temperature of the experiments at 20.0 ± 0.1 °C.

Drug solutions of known molality were progressively diluted with water solutions using an automatic pump (Dosimat 665 Metrohm). Techniques were followed to ensure that the plate and glassware used in the measurements and preparation of the solutions were scrupulously clean. The plate was cleaned by washing with doubly distilled water followed by heating in an alcohol flame between each reading, and the tensiometer was calibrated using doubly distilled water after each of the five readings. Surface tension shows time dependence, so equilibrium was considered to be obtained when successive values taken at 5 min intervals agreed to within ± 0.1 mN·m^{-1}. It is well-known that critical concentrations derived from surface tension techniques are particularly sensitive to traces of impurities.[11] Figure 2 shows an example that shows that there is no evidence of minima in the regions of the critical concentration, cc.

The value of the critical concentration (cc) was determined from the inflection point in the $\gamma-\log m$ curve. The maximum excess surface concentration of drug, Γ_2, was calculated according to the Gibbs adsorption isotherm[11]

$$\Gamma_2 = -\frac{1}{2.3RTx}\left(\frac{\mathrm{d}\gamma}{\mathrm{d}\log m}\right) \quad (1)$$

where R is the gas constant; T is the temperature in Kelvin; and m is the concentration expressed in moles per kilogram. The variable x is introduced to allow for the simultaneous adsorption of cations and anions. The expression used in the calculation of x was proposed by Matijevic and Pethica,[12] $x = 1 + m/(m + m_s)$, where m_s is the concentration of the added electrolyte. Thus, x has a value of 2 in water and approaches 1 in the presence of excess inert electrolyte.

Changes in the minimum surface area per molecule must be obtained from the maximum excess surface concentration at the air–solution interface, A (nm^2·molecule^{-1}), and were evaluated from[12]

$$A = \frac{1}{N_A\Gamma_2} \quad (2)$$

where N_A is the Avogadro constant.

Density and Ultrasound Velocity Measurements. To obtain apparent molal volumes and adiabatic compressibilities of the drugs with good precision, we need high-precision density and ultrasound measurements. Measurements were realized using a commercial density and ultrasound velocity measurement apparatus (Anton Paar DSA 5000 densimeter and sound velocity analyzer) equipped with a new generation stainless steel cell. Temperature control was maintained by the Peltier effect with a precision of ± 0.001 °C, giving rise to precision of ca. ± 1·10^{-6} g·cm^{-3} and ± 0.01 m·s^{-1} in density and ultrasound velocities, respectively. The densimeter and the ultrasound equipment were calibrated using deionized and doubly distilled water whose densities and velocities were taken from the literature.[11]

The apparent molal volumes of the drugs were calculated from density data by means of the equation

$$V_\varphi = \frac{M}{\rho} - \frac{10^3(\rho - \rho_0)}{m\rho\rho_0} \quad (3)$$

where M is the molecular weight of the solute; ρ is the density of the solution; ρ_0 is the density of the solvent; and m is the concentration expressed in moles per kilogram. Values of ρ_0 in water, pH 3.0, 5.5, and 9.2 were 0.998203, 0.999538, 0.999899, and 1.000111, respectively. By differentiating the equation of the volume[13] with respect to m at constant ρ a probable error in V_φ of $(M/\rho - V_\varphi)(\delta m/m)_\rho$ is obtained that gives a maximum error of ± 0.25 cm^3·mol^{-1} in the concentration range studied for both antidepressants. If the equation of the apparent molal volume is now differentiated with respect to ρ at constant m, a probable error in V_φ of $(1000/m\rho_0 + V_\varphi)(\delta\rho/\rho)_m$ is obtained

Table 1. Surface Tension Data of Fluphenazine and Trifluoperazine Dihydrochlorides in Water at 20 °C

m (mol·kg^{-1})	γ (mN·m^{-1})
Fluphenazine Dihydrochloride	
0.001	59.1
0.002	57.9
0.003	54.5
0.004	51.1
0.005	49.0
0.006	49.9
0.007	47.7
0.008	45.9
0.025	44.3
0.040	44.6
0.075	44.0
0.100	44.5
0.125	44.1
0.150	44.6
Trifluoperazine Dihydrochloride	
0.003	58.1
0.004	55.1
0.005	51.4
0.006	51.1
0.007	49.6
0.008	47.7
0.009	47.7
0.010	46.5
0.025	46.0
0.050	46.5
0.075	45.9
0.100	46.6
0.125	46.5
0.150	45.9

Table 2. Critical Concentration, cc, Maximum Surface Excess Concentration, Γ_2, Minimum Area per Molecule, A, of Fluphenazine and Trifluoperazine Dihydrochlorides in Water at 20 °C

	cc[a] (mol·kg^{-1})	Γ_2 (10^{-6} mol·m^{-2})	A (nm^2)
fluphenazine	0.011	1.67	1.00
trifluoperazine	0.010	1.95	0.86

[a] Uncertainty cc to ± 5 %.

Table 3. Densities, ρ, Ultrasound Velocities, u, Apparent Molal Volume, V_φ, and Isentropic Apparent Molal Compressibility, $K_{\varphi(S)}$, of Fluphenazine Dihydrochloride in Water and at pHs 3.0, 5.5, and 9.2 Solutions and at 20 °C

M	ρ	u	V_φ	$K_{\varphi(S)}$	M	ρ	u	V_φ	$K_{\varphi(S)}$
mol·kg^{-1}	g·cm^{-3}	m·s^{-1}	cm^3·mol^{-1}	cm^3·bar^{-1}·mol^{-1}	mol·kg^{-1}	g·cm^{-3}	m·s^{-1}	cm^3·mol^{-1}	cm^3·bar^{-1}·mol^{-1}
				Water					
0.00605	0.999199	1484.09	345.85	−0.0086	0.05060	1.006170	1492.82	350.60	−0.0036
0.00716	0.999381	1484.62	345.89	−0.0084	0.05999	1.007589	1494.39	351.09	−0.0032
0.00794	0.999509	1484.81	345.89	−0.0083	0.08030	1.010637	1496.89	351.64	−0.0020
0.00898	0.999679	1485.08	345.95	−0.0082	0.10002	1.013527	1499.05	352.24	−0.0011
0.01001	0.999848	1485.31	345.95	−0.0079	0.12483	1.017051	1501.52	353.22	−0.0003
0.01999	1.001437	1487.53	347.93	−0.0064	0.14900	1.020451	1503.83	353.68	0.0003
0.02935	1.002910	1489.30	348.82	−0.0053	0.17517	1.023979	1506.32	354.58	0.0008
0.04000	1.004555	1491.48	349.81	−0.0048					
				pH 3.0					
0.00699	1.000640	1483.99	349.97	−0.0115	0.09967	1.014476	1499.49	355.23	−0.0018
0.00803	1.000806	1484.32	349.99	−0.0115	0.12453	1.018040	1502.07	355.30	−0.0009
0.00903	1.000966	1484.63	349.95	−0.0113	0.15015	1.021622	1504.61	355.54	−0.0002
0.01009	1.001135	1484.99	349.97	−0.0114	0.17536	1.025079	1507.07	355.76	0.0003
0.01994	1.002672	1488.02	351.41	−0.0107	0.19966	1.028411	1509.46	355.63	0.0007
0.02936	1.004110	1489.96	352.67	−0.0084	0.22463	1.031625	1511.68	356.24	0.0011
0.03988	1.005705	1492.51	353.32	−0.0076	0.24955	1.034867	1514.24	356.36	0.0013
0.05258	1.007602	1493.69	354.02	−0.0049	0.27456	1.038074	1516.81	356.44	0.0014
0.06009	1.008729	1495.21	354.08	−0.0047	0.29990	1.041229	1519.02	356.65	0.0017
0.08010	1.011665	1497.42	354.67	−0.0029					
				pH 5.5					
0.00622	1.000865	1483.64	354.38	−0.0113	0.07986	1.011841	1497.33	356.69	−0.0029
0.00705	1.000994	1483.91	354.39	−0.0127	0.10005	1.014729	1499.49	356.97	−0.0018
0.00799	1.001140	1484.20	354.39	−0.0124	0.12515	1.018287	1502.14	357.00	−0.0008
0.00895	1.001289	1484.50	354.38	−0.0121	0.15000	1.021726	1504.48	357.19	−0.0001
0.01010	1.001467	1484.87	354.42	−0.0120	0.17509	1.025180	1507.04	357.08	0.0004
0.01994	1.002979	1487.84	354.81	−0.0107	0.19956	1.028498	1509.47	356.99	0.0007
0.02917	1.004370	1489.58	355.52	−0.0080	0.22530	1.031869	1514.48	357.19	0.0012
0.03990	1.005987	1492.49	355.70	−0.0078	0.25030	1.035221	1511.92	356.79	0.0010
0.05377	1.008040	1493.28	356.16	−0.0044	0.27490	1.038358	1516.89	356.88	0.0014
0.05989	1.008944	1495.01	356.22	−0.0047	0.29980	1.041534	1519.23	356.78	0.0016
				pH 9.2					
0.00792	1.001349	1484.79	360.42	−0.0180	0.10000	1.014910	1499.42	357.73	−0.0018
0.00900	1.001511	1485.28	360.31	−0.0180	0.12500	1.018463	1502.09	357.53	−0.0009
0.00997	1.001657	1485.65	360.18	−0.0177	0.14950	1.021901	1504.49	357.30	−0.0002
0.01992	1.003151	1489.38	359.44	−0.0156	0.17480	1.025374	1507.17	357.24	0.0002
0.03016	1.004680	1490.61	359.10	−0.0096	0.20010	1.028803	1509.71	357.11	0.0006
0.03997	1.006133	1492.28	358.99	−0.0075	0.22360	1.031935	1512.05	357.03	0.0009
0.04780	1.007300	1493.70	358.61	−0.0058	0.24947	1.035299	1514.56	357.08	0.0012
0.06005	1.009092	1494.86	358.59	−0.0045	0.27460	1.038531	1517.05	357.05	0.0013
0.08000	1.012008	1497.19	358.17	−0.0028	0.29865	1.041579	1519.42	357.00	0.0015

that will cause a maximum error of about ± 0.01 cm^3·mol^{-1} in the range of data measured.

To obtain the value of the apparent molal volume at infinite dilution, V_φ^0, it was assumed that the amphiphilic antidepressants behave as 1:1 electrolytes in solution at concentrations up to the critical concentration. The apparent molal volumes at concentrations below the cc may then be described taking into account the ionic strength of the buffer solution by the equation[14]

$$V_\varphi = V_\varphi^0 + \frac{A_v}{2b}\ln(1 + b(m + I_{buff}))^{1/2} + B_v m + \cdots \quad (4)$$

where A_v is the Debye–Hückel limiting law coefficient, values of which were taken from the literature[14–16] for selected temperatures; b has a value of 1.2 kg$^{1/2}$·mol$^{-1/2}$ for all electrolytes;[17] I_{buff} is the ionic strength of the buffer solution; and B_v is an adjustable parameter related to pair interactions and equivalent to the second virial coefficient which measures the deviation from the limiting law due to nonelectrostatic solute–solute interactions. B_v is generally negative except for hydrogen-bonding interactions.[18]

Density and ultrasound velocity measurements were combined to calculate adiabatic compressibilities using the Laplace equation[19]

$$k_s = -\frac{1}{V}\left(\frac{\partial V}{\partial p}\right)_S = \frac{10^6}{\rho u^2} \quad (5)$$

where V, p, and S refer to volume, pressure, and entropy, respectively; k_s is the adiabatic compressibility coefficient, expressed in bar^{-1} when u is expressed in cm·s^{-1} and the density in g·cm^{-3}.

The isentropic apparent molal compressibility, $K_{\varphi(S)}$, can be calculated from ultrasound measurements[20]

$$K_{\varphi(S)} = \frac{1000(k_s - k_s^0)}{m\rho_0} + k_s V_\varphi \quad (6)$$

where k_s and k_s^0 are the adiabatic compressibilities of the solution and solvent, respectively. The maximum error obtained in the range of concentration studied was about ± 0.00005 cm^3·bar^{-1}·mol^{-1}. The same method as that used to calculate the volume error was used to calculate the error of $K_{\varphi(S)}$, using now the variables ρ, m, and u.

Table 4. Densities, ρ, Ultrasound Velocities, u, Apparent Molal Volume, V_φ, and Isentropic Apparent Molal Compressibility, K_φ, of Trifluoperazine Dihydrochloride in Water and pHs 3.0, 5.5, and 9.2 Solutions and at 20 °C

m / mol·kg^{-1}	ρ / g·cm^{-3}	u / m·s^{-1}	V_φ / cm^3·mol^{-1}	K_φ / cm^3·bar^{-1}·mol^{-1}	m / mol·kg^{-1}	ρ / g·cm^{-3}	u / m·s^{-1}	V_φ / cm^3·mol^{-1}	K_φ / cm^3·bar^{-1}·mol^{-1}
				Water					
0.00790	0.999369	1484.08	334.62	−0.0024	0.09979	1.012031	1498.32	337.53	−0.0007
0.00895	0.999513	1484.27	334.62	−0.0024	0.12479	1.015253	1500.56	338.30	0.0002
0.01100	0.999803	1484.65	334.78	−0.0024	0.14957	1.018448	1502.94	338.65	0.0007
0.01547	1.000449	1485.45	334.83	−0.0024	0.17372	1.021445	1505.11	339.08	0.0011
0.02109	1.001241	1486.44	335.16	−0.0023	0.19936	1.024628	1507.29	339.31	0.0015
0.02860	1.002310	1487.75	335.48	−0.0022	0.22448	1.027651	1509.52	339.62	0.0018
0.03996	1.003909	1489.76	336.17	−0.0021	0.24940	1.030555	1511.66	340.09	0.0020
0.04920	1.005180	1491.32	336.60	−0.0020	0.27490	1.033523	1513.57	340.31	0.0023
0.06004	1.006672	1493.04	336.76	−0.0018	0.29980	1.036298	1515.78	340.46	0.0024
0.07991	1.009393	1496.16	337.14	−0.0015					
				pH 3.0					
0.00760	1.000640	1483.81	335.80	−0.0043	0.09950	1.013036	1498.68	340.27	−0.0013
0.00920	1.000865	1483.65	335.83	−0.0045	0.12500	1.016316	1501.10	340.59	−0.0003
0.01090	1.001109	1484.02	335.86	−0.0045	0.15030	1.019499	1503.30	340.91	0.0004
0.01324	1.001440	1484.51	335.92	−0.0044	0.17460	1.022534	1505.60	340.98	0.0008
0.01423	1.001587	1484.72	335.84	−0.0044	0.20070	1.025727	1507.96	341.11	0.0012
0.02020	1.002431	1486.01	336.33	−0.0044	0.22490	1.028587	1510.08	341.36	0.0015
0.03970	1.005107	1490.24	338.36	−0.0042	0.24840	1.031406	1512.20	341.42	0.0017
0.06020	1.007863	1494.41	339.41	−0.0039	0.27450	1.034452	1516.74	341.43	0.0014
0.07966	1.010455	1496.72	339.77	−0.0024	0.29990	1.001587	1514.49	341.45	0.0025
				pH 5.5					
0.00810	1.001025	1483.50	341.05	−0.0067	0.08000	1.010666	1496.54	342.18	−0.0023
0.00947	1.001215	1483.86	341.04	−0.0067	0.10020	1.013299	1498.72	342.13	−0.0013
0.01011	1.001304	1484.02	341.00	−0.0067	0.12490	1.016484	1501.11	341.99	−0.0004
0.01190	1.001551	1484.53	341.05	−0.0066	0.15033	1.019676	1503.48	342.13	0.0003
0.01996	1.002661	1486.40	341.12	−0.0061	0.17518	1.022797	1505.08	341.91	0.0010
0.02897	1.003890	1488.58	341.43	−0.0060	0.20023	1.025829	1508.04	342.08	0.0011
0.03997	1.005369	1491.12	341.73	−0.0056	0.22459	1.028762	1510.25	342.06	0.0014
0.04900	1.006580	1492.81	341.90	−0.0050	0.24965	1.031734	1512.58	342.04	0.0016
0.05524	1.007411	1493.89	341.89	−0.0044	0.27429	1.034579	1514.82	342.15	0.0018
0.06000	1.008041	1494.49	341.97	−0.0041					
				pH 9.2					
0.00599	1.000922	1483.48	344.73	−0.0131	0.10012	1.013446	1498.01	342.65	−0.0009
0.00698	1.001056	1483.84	344.69	−0.0131	0.12517	1.016624	1500.54	342.82	−0.0001
0.00814	1.001214	1484.25	344.52	−0.0129	0.15007	1.019809	1502.84	342.40	0.0005
0.00905	1.001325	1484.52	345.84	−0.0125	0.17534	1.022924	1505.26	342.49	0.0009
0.01201	1.001736	1485.59	344.54	−0.0126	0.19959	1.025868	1507.83	342.53	0.0012
0.02024	1.002851	1488.04	344.09	−0.0111	0.22549	1.028951	1510.21	342.63	0.0015
0.03000	1.004184	1489.83	343.24	−0.0081	0.24940	1.031862	1512.46	342.23	0.0016
0.03993	1.005496	1491.70	343.69	−0.0066	0.27495	1.034803	1514.75	342.35	0.0019
0.05996	1.008185	1494.14	342.98	−0.0038	0.29919	1.037516	1516.88	342.57	0.0020
0.07994	1.010808	1496.01	342.93	−0.0019					

Results and Discussion

1. Surface Properties. Figure 2 shows a representative plot of surface tension, γ, against the logarithm of molality, m, for fluphenazine dihydrochloride in water. A similar plot was obtained for trifluoperazine dihydrochloride. The surface tension data of both drugs in water at 20 °C are presented in Table 1. The values obtained of the critical concentrations are shown in Table 2, as well as values of Γ_2 and A. Comparison of the cc values of both drugs indicates that trifluoperazine is more hydrophobic than fluphenazine due to the different substituent in the molecular structure. Values of the different magnitudes obtained are in good agreement to those reported for other phenothiazine drugs[2,21] and tricyclic antidepressant drugs.[16]

2. Bulk Properties. Densities and ultrasound velocities have been applied to study the bulk properties of the drugs trifluoperazine and fluphenazine in water and at different buffered solutions at 20 °C. Experimental data are shown in Table 3 and Table 4 along with volumetric and compressibility results obtained using the methods described in the preceding section.

The dependence of the sound velocity, u, on the concentration, m, of fluphenazine dihydrochloride in water is shown in Figure 3. Two inflection points are clearly visible in the plot, which correspond to two different critical concentrations, cc_1 and cc_2. The inflection points were determined by the intersection of

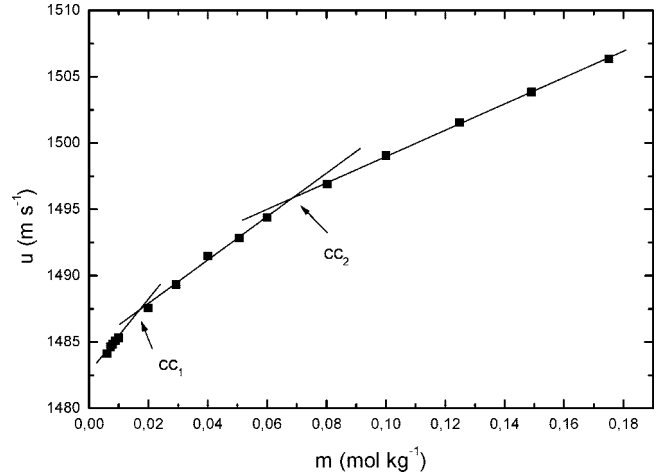

Figure 3. Ultrasound velocity, u, vs concentration, m, for fluphenazine dihydrochloride in water at 20 °C. The arrows denote the critical concentrations, cc_1 and cc_2.

Table 5. Ultrasound Calculation of the Critical Concentrations, cc_1/cc_2, of Fluphenazine and Trifluoperazine Dihydrochlorides in Different Media at 20 °C[a]

	fluphenazine	trifluoperazine
	mol·kg^{-1}	mol·kg^{-1}
water	0.016/0.070	0.015/0.067
pH 3.0	0.014/0.066	0.013/0.061
pH 5.5	0.013/0.065	0.012/0.058
pH 9.2	0.011/0.061	0.009/0.047

[a] Uncertainty cc to ± 5 %.

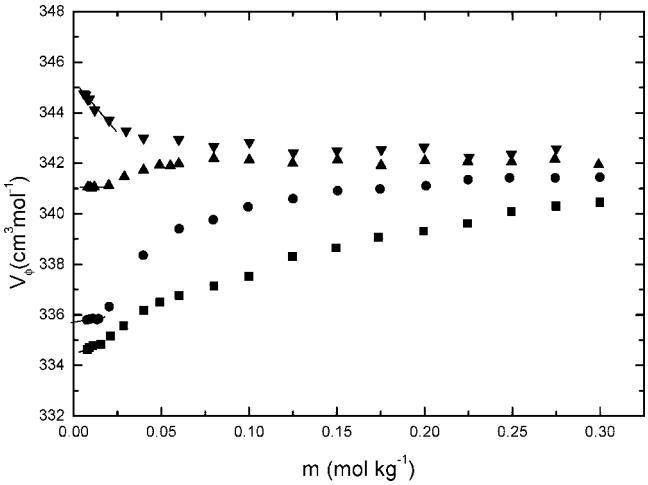

Figure 4. Apparent molal volumes, V_φ, vs concentration, m, for trifluoperazine dihydrochloride in ■, water and at pHs: ●, 3.0; ▲, 5.5; and ▼, 9.2 at 20 °C.

the three straight lines of the plot and also by means of a numerical method based on the combination of the Runge–Kutta integration method and the Levenberg–Marquardt fitting algorithm.[16] Similar plots were obtained at different pH and for trifluoperazine dihydrochloride (not shown). The presence of several critical concentrations for the drug systems suggest a rearrangement of the aggregates as previously reported for other phenothiazine drugs.[3] Values of cc_1 and cc_2 for both drugs in different media are presented in Table 5. As can be seen there, the value of cc_1 for the drugs in water is in reasonable agreement with the value obtained by surface tension at 20 °C. In addition, the critical concentrations decrease as the pH increases as a result of the lower ionization of drug molecules when the solution pH approaches their pK_a, favoring hydrophobic interactions.

Figure 4 shows the apparent molal volumes, V_φ, against the concentration of trifluoperazine dihydrochloride in water and at different pHs. Table 6 presents the results obtained for V_φ^0 and B_v derived by fitting to eq 4. Experimental points fit this equation fairly well (χ^2 lower than $5 \cdot 10^{-4}$ in all cases). Both drugs have a positive B_v in water and pH of 3.0, possibly as a consequence of nonelectrostatic solute–solute interactions such as hydrogen bonding, which has been related to the presence of dimers and trimers in the preaggreation region.[18] Positive B_v values have also been obtained for other phenothiazine drugs.[22] In addition, V_φ^0 values of the drugs increase as the solution pH increases as a consequence of the larger hydration layer around the drug molecules at high pH, provided that the drugs become more hydrophobic due to their decrease in ionization state. Table 6 also shows the values of apparent molal volume of monomers in aggregates, V_φ^m, obtained by linear fit of the volume well above the cc_1, assuming the phase separation model of micellization.[22] The change in apparent molal volume associated with the formation of a stable aggregate

Table 6. Apparent Molal Volumes at Infinite Dilution, V_φ^0, Apparent Molal Volume of Monomers in Aggregates, V_φ^m, Change in Apparent Molal Volumes upon Aggregation, ΔV_φ^m, and B_v Parameter of Fluphenazine and Trifluoperazine Dihydrochlorides in Water at 20 °C

	V_φ^0	V_φ^m	ΔV_φ^m	B_v
	cm^3·mol^{-1}	cm^3·mol^{-1}	cm^3·mol^{-1}	cm^3·kg·mol^{-2}
		Flupherazine		
water	345.68	354.90	9.22	26.22
pH 3	349.93	355.46	5.43	4.4
pH 5.5	354.38	356.81	2.43	−0.59
pH 9.2	360.85	357.17	−3.64	−62.69
		Trifluoperazine		
water	334.44	339.80	5.36	19.59
pH 3	335.80	341.99	5.12	2.31
pH 5.5	341.04	342.16	0.88	−7.12
pH 9.2	345.18	342.24	−2.57	−82.13

[a] Uncertainty: V_φ^0, V_φ^m, ΔV_φ^m to ± 1 %, B_v to ± 10 %.

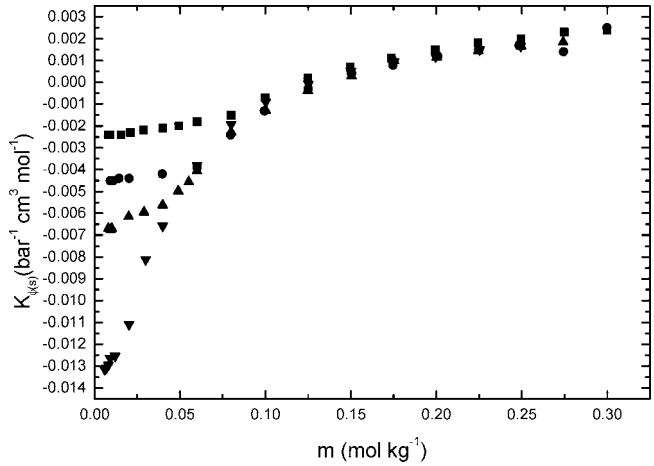

Figure 5. Apparent molal compressibilities, $K_{\varphi(S)}$, vs concentration, m, for trifluoperazine dihydrochloride in ■, water and at pH: ●, 3.0; ▲, 5.5; and ▼, 9.2 at 20 °C.

of the drugs was taken as $\Delta V_\varphi^m = V_\varphi^m - V_\varphi^0$. The volume change for the formation of the aggregate for both drugs passes from positive to negative as the solution pH increases indicating the lack of release of structured water in the hydration shell of the monomers when the aggregates are formed.

The isentropic apparent molal compressibility data at infinite dilution, $K_{\varphi(S)}^0$, in contrast with apparent molar volume at infinite dilution, V_φ^0, which consists of the contributions from the intrinsic volume of the solute molecule and that of the hydration shell, provide insight into the compressibility of the hydration layer around the solute molecule, provided that the solute intrinsic compressibility is assumed to be zero. When the amphiphilic molecules form micelles, the hydrophobic hydration around the alkyl chains disappears and the compressibility of the aggregate becomes the dominant factor. Figure 5 is an example of the behavior of the isentropic apparent molal compressibility against the concentration for trifluoperazine dihydrochloride in water and at different pHs. Values of $K_{\varphi(S)}^0$ were calculated by extrapolation to the ordinate. As is shown in Table 7 for both drugs, values of the isentropic apparent molal compressibilities at infinite dilution, $K_{\varphi(S)}^0$, are negative as a consequence of a higher resistance to pressure of the structured water and buffer salts. These values become more negative as the solution pH increases suggesting the existence of a larger amount of structured water around the drug monomers due to the increase of drug molecule hydrophobicity as their electrical charge diminish. On the other hand, the hydrophobic character

Table 7. Apparent Molal Compressibilities at Infinite Dilution, $K^0_{\varphi(S)}$, Apparent Molal Compressibilities of Monomers in Aggregates, $K^m_{\varphi(S)}$, and Changes in Apparent Molal Compressibilities upon Aggregation, $\Delta K^m_{\varphi(S)}$, of Flupherazine and Trifluoperazine Dihydrochlorides in Different Media at 20 °C[a]

	$10^{-3}K^0_{\varphi(S)}$ / $cm^3 \cdot bar^{-1} \cdot mol^{-1}$	$10^{-3}K^m_{\varphi(S)}$ / $cm^3 \cdot bar^{-1} \cdot mol^{-1}$	$10^{-3}\Delta K^m_{\varphi(S)}$ / $cm^3 \cdot bar^{-1} \cdot mol^{-1}$
		Fluphenazine	
water	−8.8	0.8	9.60
pH 3.0	−11.7	1.8	13.50
pH 5.5	−13.4	1.6	15.00
pH 9.2	−18.2	1.7	19.90
		Trifluoperazine	
water	−2.4	1.7	4.10
pH 3.0	−4.6	1.6	6.20
pH 5.5	−6.7	1.7	8.40
pH 9.2	−13.4	1.4	14.80

[a] Uncertainty: $K^0_{\varphi(S)}$, $K^m_{\varphi(S)}$, $\Delta K^m_{\varphi(S)}$ to ± 0.005 %.

of the aggregates of both drugs is indicated by the positive values of the apparent molal adiabatic compressibility of the aggregates, $K^m_{\varphi(S)}$.

The change in the partial molal isentropic compressibility of aggregation, $\Delta K\varphi^m{}_{(S)}$, can be evaluated from

$$\Delta K_{\varphi(S)} = K^m_{\varphi(S)} - K^0_{\varphi(S)} \quad (7)$$

and is given in Table 7. $\Delta K_{\varphi(S)}$ is positive for both drugs. Positives values of $\Delta K_{\varphi(S)}$ were also previously found for the antidepressant drugs clomipramine and imipramine and nortriptyline[23,24] indicating the decrease of hydrophobic hydration in the aggregation process due to dehydration of aromatic rings during association.

In summary, thermodynamic and surface properties such as apparent volumes, isentropic compressibilities, and surface tension data allow identification of changes in the aggregation and hydration states of amphiphilic drugs under changes in the molecule ionization state through variation in the solution conditions.

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