Activity and Osmotic Coefficients of Promethazine and Chlorpromazine Hydrochlorides in Aqueous Solutions of Low Ionic Strength

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Osmotic and activity coefficients of amphiphilic drugs chlorpromazine hydrochloride and promethazine hydrochloride in aqueous solutions have been derived from vapor pressure measurements, in the presence of low concentrations of added electrolyte (0.000, 0.010, 0.025, and 0.050 mol kg^{-1} NaCl) at the temperature 303.15 K. From these results an inflection point was detected for both phenothiazine drugs identified as a critical concentration.

Introduction

The associations of the phenothiazine drugs have been examined by several workers (Attwood and Florence, 1983; Attwood et al., 1987, 1989). The presence of a discontinuity in the physicochemical properties of these drugs in aqueous solutions was assumed by early workers (Thoma and Arning, 1976; Scholtan, 1955) to be indicative of a micellar mode of association, and the discontinuity was identified with the critical micelle concentration (cmc) of typical surfactants systems.

In this paper we report determinations of osmotic and activity coefficients of chlorpromazine and promethazine hydrochlorides in the presence of low concentrations in the range (0.00–0.05) mol kg^{-1} of added electrolyte and at the temperature of 303.1 K.

Materials and Methods

Osmotic coefficients were derived from vapor pressure measurements (Brady et al., 1951) of aqueous solutions of the drugs at 303.1 K using a Knauer vapor pressure osmometer Model 11.00 in combination with a digital meter and chart recorder. The apparatus has been widely used to make these determinations as it is cited in the literature (Brady et al., 1951; Attwood et al., 1987, 1989; Bloor and Wyn-Jones, 1990; Attwood et al., 1991) The temperature was controlled with an Anton Paar probe OKT 100 with a precision of ±0.01 K. The length of the experiments was that necessary to reach the temperature of measurement. The instrument was calibrated with sodium chloride solutions of known molality by using the smoothed values of the osmotic coefficients reported by Herrington and Taylor (1982). The readings are time-dependent because it is not an equilibrium mesurement. However, with sufficient time the system reaches a steady state. This time is a function
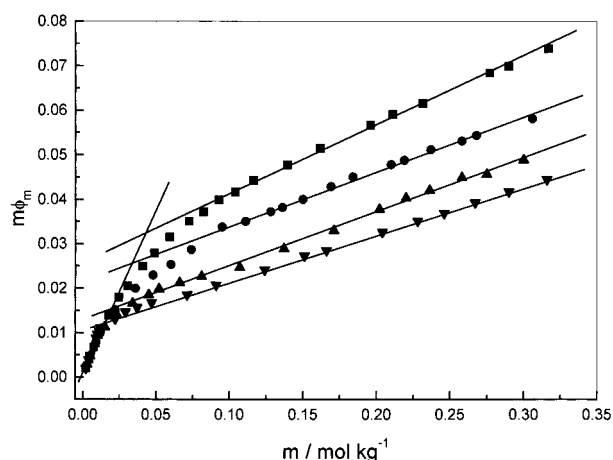
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Figure 1. Osmotic coefficients (ϕ_m) multiplied by molality (m), $m\phi_m$, as a function of m for promethazine hydrochloride in the presence of added electrolyte: (■) 0.00, (●) 0.01, (▲) 0.025, and (▼) 0.05 mol kg^{-1} NaCl.

of composition, so to avoid imprecisions, at least six readings were taken at each molality. The error of the mean did not exceed ±3%. When the vapor pressure measurements were made in the presence of electrolyte, the composition of the solvent droplet contained a fixed composition of sodium chloride in water and the solute droplet the drug and sodium chloride at the same composition. The hydrochlorides of promethazine [10-(2-(dimethylamino)propyl)phenothiazine], formula weight 320.9, and chlorpromazine [2-chloro-10-(3-(dimethylamino)propyl)phenothiazine], formula weight 355.3 (May & Baker), were sufficiently well characterized and purified to be used as received. Both of compounds conformed to the purity requirements of the British Pharmacopoeia as such contained more than 98.5% of the specific compound. Sodium chloride was of AnalaR grade.

Table 1. Activity, $\gamma_{\pm}$, and Osmotic, ϕ_m, Coefficients of Chlorpromazine Hydrochloride at $T = 303.15$ K in the Presence of Added Electrolyte

(a) 0.000 and 0.010 mol kg^{-1} NaCl

0.00 mol kg^{-1} NaCl			0.01 mol kg^{-1} NaCl		
m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m	m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m
0.002		0.991	0.003		0.960
0.004		0.981	0.005		0.952
0.005		0.977	0.008		0.942
0.009		0.974	0.010		0.935
0.010		0.967	0.015		0.754
0.011		0.940	0.023	0.629	0.617
0.012		0.927	0.034	0.446	0.489
0.013		0.835	0.045	0.349	0.412
0.022	0.534	0.597	0.052	0.310	0.382
0.029	0.419	0.507	0.066	0.249	0.322
0.037	0.337	0.424	0.081	0.208	0.280
0.047	0.273	0.358	0.107	0.163	0.231
0.071	0.187	0.262	0.137	0.131	0.211
0.091	0.151	0.228	0.171	0.108	0.193
0.124	0.114	0.195	0.202	0.0934	0.187
0.151	0.0954	0.181	0.220	0.0866	0.183
0.166	0.0877	0.172	0.236	0.0814	0.178
0.204	0.0730	0.160	0.258	0.0753	0.174
0.228	0.0659	0.154	0.275	0.0712	0.166
0.246	0.0616	0.150	0.300	0.660	0.163
0.267	0.0574	0.147			
0.290	0.0535	0.144			
0.316	0.0492	0.141			

(b) 0.025 and 0.050 mol kg^{-1} NaCl

0.025 mol kg^{-1} NaCl			0.05 mol kg^{-1} NaCl		
m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m	m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m
0.003		0.944	0.0022		0.939
0.005		0.942	0.0044		0.937
0.009		0.880	0.0075		0.896
0.012		0.833	0.0177		0.786
0.022		0.687	0.0246		0.731
0.036	0.712	0.556	0.0307		0.668
0.048	0.556	0.479	0.0409	0.812	0.610
0.060	0.458	0.423	0.0489	0.670	0.571
0.074	0.380	0.388	0.0593	0.592	0.532
0.095	0.307	0.356	0.0726	0.498	0.483
0.111	0.267	0.316	0.0823	0.448	0.452
0.128	0.236	0.291	0.0929	0.404	0.429
0.136	0.224	0.281	0.104	0.366	0.401
0.150	0.206	0.267	0.118	0.330	0.376
0.169	0.185	0.254	0.140	0.286	0.351
0.184	0.174	0.245	0.162	0.251	0.325
0.210	0.153	0.228	0.196	0.214	0.296
0.219	0.148	0.223	0.211	0.201	0.280
0.237	0.138	0.216	0.231	0.186	0.269
0.258	0.128	0.206	0.277	0.162	0.247
0.268	0.124	0.203	0.290	0.153	0.241
0.306	0.110	0.190	0.317	0.142	0.233

Table 2. Activity, $\gamma_{\pm}$, and Osmotic, ϕ_m, Coefficients of Promethazine Hydrochloride at $T = 303.15$ K in the Presence of Added Electrolyte

(a) 0.000 and 0.010 mol kg^{-1} NaCl

0.00 mol kg^{-1} NaCl			0.01 mol kg^{-1} NaCl		
m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m	m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m
0.006		0.957	0.0043		0.960
0.010		0.922	0.0063		0.950
0.020		0.867	0.0095		0.943
0.032		0.786	0.0105		0.939
0.041	0.902	0.725	0.0212		0.871
0.055	0.701	0.623	0.0337		0.785
0.061	0.635	0.564	0.0468	0.775	0.693
0.077	0.518	0.478	0.0545	0.678	0.641
0.089	0.454	0.429	0.0676	0.562	0.552
0.097	0.419	0.404	0.0897	0.483	0.460
0.106	0.390	0.383	0.105	0.381	0.415
0.112	0.371	0.367	0.114	0.355	0.400
0.122	0.343	0.345	0.126	0.326	0.375
0.138	0.308	0.321	0.138	0.300	0.343
0.145	0.294	0.312	0.151	0.278	0.330
0.148	0.288	0.309	0.161	0.262	0.317
0.165	0.260	0.284	0.168	0.253	0.313
0.177	0.246	0.273	0.181	0.237	0.290
0.186	0.235	0.266	0.192	0.225	0.284
0.205	0.215	0.247	0.214	0.205	0.263
0.218	0.204	0.235	0.234	0.189	0.258
0.230	0.194	0.237	0.250	0.178	0.247
0.247	0.182	0.221	0.259	0.173	0.241
0.260	0.173	0.215	0.270	0.167	0.239
0.276	0.164	0.211	0.281	0.161	0.228
0.293	0.156	0.203	0.301	0.152	0.227

(b) 0.025 and 0.050 mol kg^{-1} NaCl

0.025 mol kg^{-1} NaCl			0.05 mol kg^{-1} NaCl		
m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m	m (mol kg^{-1})	$\gamma_{\pm}$	ϕ_m
0.006		0.952	0.0062		0.934
0.010		0.950	0.0101		0.929
0.017		0.915	0.0210		0.892
0.0238		0.880	0.0307		0.828
0.029		0.832	0.0505		0.719
0.039		0.762	0.0601	0.848	0.663
0.050	0.785	0.680	0.0693	0.754	0.626
0.052	0.769	0.678	0.0857	0.633	0.566
0.061	0.670	0.618	0.0104	0.538	0.522
0.071	0.593	0.573	0.110	0.514	0.507
0.089	0.487	0.450	0.125	0.464	0.476
0.105	0.424	0.444	0.140	0.421	0.436
0.127	0.360	0.409	0.147	0.405	0.428
0.140	0.330	0.388	0.160	0.378	0.410
0.162	0.292	0.355	0.169	0.362	0.406
0.170	0.280	0.345	0.187	0.332	0.382
0.184	0.261	0.331	0.203	0.310	0.366
0.195	0.249	0.319	0.223	0.287	0.344
0.207	0.237	0.308	0.232	0.278	0.342
0.220	0.225	0.299	0.249	0.262	0.330
0.231	0.216	0.292	0.276	0.241	0.309
0.250	0.202	0.278	0.289	0.231	0.300

Table 3. Critical Micelle Concentrations (cmc) of Chlorpromazine and Promethazine Hydrochlorides in Aqueous Electrolyte Solution

	cmc/(mol kg^{-1})	
NaCl/(mol kg^{-1})	chlorpromazine	promethazine
0.000	0.022	0.055
0.010	0.021	0.049
0.025	0.019	0.043
0.050	0.017	0.040

Results and Discussion

Experimental results are given in Table 1a,b for chlorpromazine hydrochloride and Table 2a,b for and promethazine hydrochloride. The first columns show the molality, m, of the drug solutions, and the osmotic coefficient, ϕ_m, is listed at the second columns. Plots of the $m\phi_m$ term as a function of m show break points at the critical micelle concentration, whose values are shown in Table 3. These values were obtained by fitting the experimental data of $m\phi_m$ vs m plot to two straight lines above and below the break point. Figure 1 shows these plots for promethazine. Similar plots were obtained for chlorpromazine. Clearly the cmc decreases as electrolyte concentration increases. Numerous studies have been reported of the effect of added electrolyte on the micellar properties of ionic surfactants (Mukerjee and Mysels, 1971; Corrin and Harkins, 1974; Kratohvil, 1980). Addition of electrolyte causes a reduction in the thickness of the ionic atmosphere surrounding the polar headgroups and a consequent decreased repulsion between them. These effects are manifest as a reduction in the cmc.
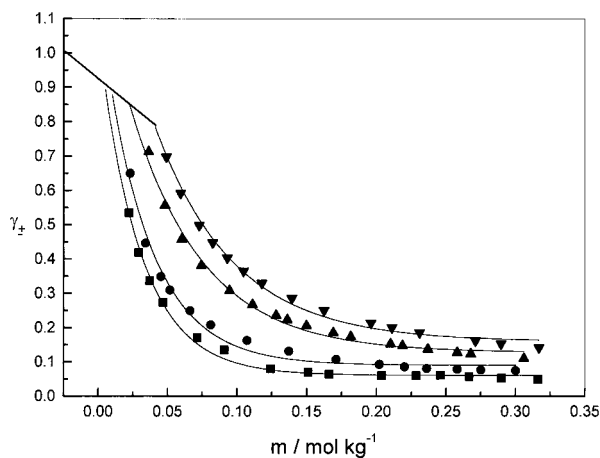
Figure 2. Variation of the activity coefficient, $\gamma_\pm$, with molality, m, for chlorpromazine hydrochloride in the presence of added electrolyte: (■) 0.00, (●) 0.01, (▲) 0.025, and (▼) 0.05 mol kg^{-1} NaCl.
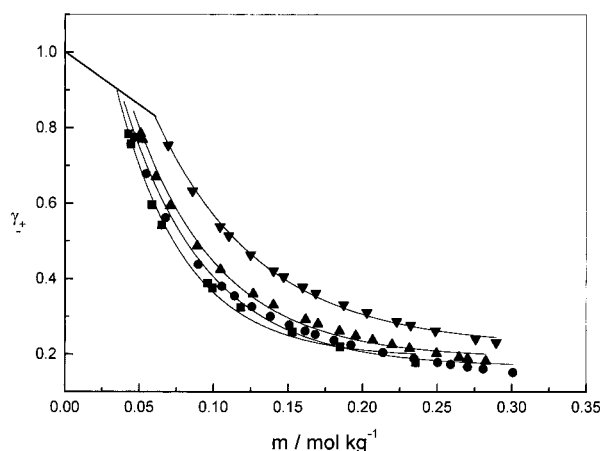

Figure 3. Variation of the activity coefficient, $\gamma_\pm$, with molality, m, for promethazine hydrochloride in the presence of added electrolyte: (■) 0.00, (●) 0.01, (▲) 0.025, and (▼) 0.05 mol kg^{-1} NaCl.

The mean ion activity coefficients, $\gamma_\pm$, were obtained from the equation (Huff et al., 1951)

$$- \ln \gamma_\pm = (1 - \phi_m) + \int_0^m (1 - \phi_m) \, \mathrm{d} \ln m \qquad (1)$$

In general, this expression must be evaluated by graphical integration, but in the region where the linear plot is valid, it reduced to the espression

$$- \ln \gamma_\pm = - \ln \gamma_c + (\beta - 1) + \ln\left(\frac{m_c}{m}\right) \qquad (2)$$

where γ_c is the activity coefficient at the critical concentration, m_c is the critical concentration, and β is the slope above the critical concentration, i.e., the fraction of counterion bound to the micelle.

Experimental values of the mean activity coefficients for chlorpromazine and promethazine hydrochlorides at different electrolyte concentrations, obtained from eq 2, are listed in Tables 1a,b and 2a,b, respectively. An increase in the value of the mean activity coefficient with electrolyte concentration can be observed. Figures 2 and 3 show their concentration dependence.

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