Concentration Dependence of the Osmotic and Activity Coefficients of Imipramine and Clomipramine Hydrochlorides in Aqueous Solution

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Vapor pressure lowering of the two antidepressant drugs imipramine and clomipramine hydrochloride solutions in the concentration range 0−0.28 mol·kg^{-1} at 303.15 K were determined. For imipramine hydrochloride, measurements at 308.15 and 313.15 K were also made. From these results, the osmotic and activity coefficients for both compounds were calculated, and their concentration dependence was studied. An inflection point was detected for each substance, identified as a critical concentration.

Introduction

The association characteristics of the antidepressant drugs imipramine and clomipramine hydrochlorides have been examined by several workers (Attwood and Florence, 1983; Attwood et al., 1987). Discontinuities in the physicochemical properties of these drugs in aqueous solution (Attwood and Gibson, 1978) and in the presence of electrolyte (Thoma and Albert, 1979) have suggested micellar association, and the discontinuity was identified as the critical micelle concentration (cmc) of typical surfactant systems.

In the present work we report determinations of osmotic and activity coefficients for the antidepressant drugs imipramine and clomipramine hydrochlorides from vapor pressure lowering at the molality range of 0−0.28 mol·kg^{-1} and at 303.15 K. To study the temperature dependence of osmotic and activity coefficients, measurements for imipramine were also carried out at 308.15 and 313.15 K.

Materials and Methods

The hydrochlorides of imipramine, [5-(3-(dimethylamino)propyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine], and clomipramine, [3-chloro-5-(3-(dimethylamino)propyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine] (Sigma Chemical Co. Ltd., Nos. I-7379 and C-7291, respectively) were sufficiently well characterized and purified to be used as received. Both of compounds conformed to the purity requirements of the British Pharmacoepia and as such contained not less than 98.5% of the specified compound.

Osmotic coefficients were derived from vapor pressure measurements (Brady et al., 1951) on aqueous solutions of the drugs at 303.15 K, and also at 308.15 and 313.15 K in the case of imipramine, using a Knauer vapor pressure osmometer model 11.00 in combination with a digital meter and chart recorder. 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). At least six readings were taken at each molality. The error of the mean did not exceed ±3% at a 95% probability level, except at pre-cmc concentrations where measurements approached the limits of the precision of the technique.

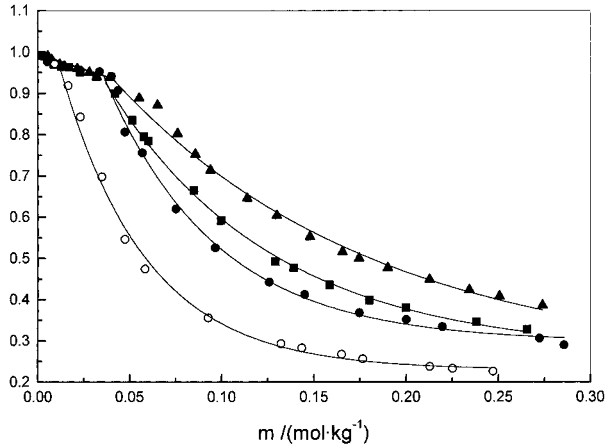

Figure 1. Variation of the stoichiometric osmotic coefficients, ϕ, with molality, m, for imipramine hydrochloride at (●) 303.15 K, (■) 308.15 K, and (▲) 313.15 K and for clomipramine hydrochloride at (○) 303.15 K.

Results and Discussion

The concentration dependence of osmotic coefficients, ϕ, determined by vapor pressure lowering for imipramine hydrochloride at 303.15, 308.15, and 313.15 K and for clomipramine hydrochloride at 303.15 K are given in Figure 1. This plot shows inflection points at the critical micelle concentrations, whose values are shown in Table 1. These values were obtained by fitting the experimental data of a gm vs m plot (where g is the rational osmotic coefficient and m is the molality) to two straight lines

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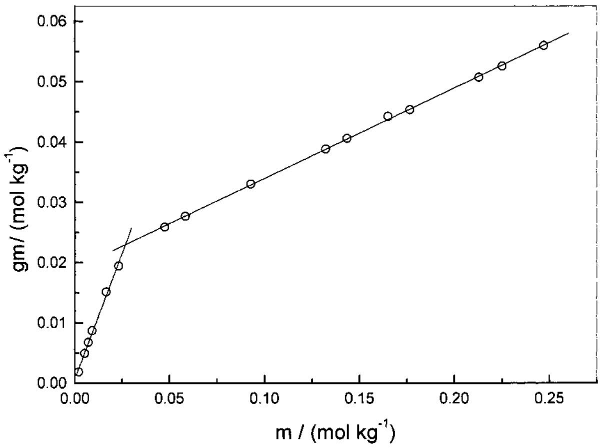

Figure 2. Plots of g vs m for clomipramine hydrochloride at (○) 303.15 K.

Table 1. Critical Micelle Concentrations (cmc) and Slope of *gm* vs *m* Plots above the cmc (*s*) for Imipramine and Clomipramine Hydrochlorides at 303.15, 308.15, and 313.15 K, Respectively

	imipramine		clomipramine	
T/K	cmc/(mol·kg^{-1})	s	cmc/(mol·kg^{-1})	s
303.15	0.042	0.188	0.027	0.150
308.15	0.056	0.169		
313.15	0.071	0.201		

Table 2. Rational Osmotic Coefficient (*g*), Stoichiometric Osmotic Coefficient (*ϕ*), and Activity Coefficient ($\gamma_\pm$) for Imipramine and Clomipramine Hydrochlorides at 303.15 K

imipramine				clomipramine			
m/(mol·kg^{-1})	g	ϕ	$\gamma_\pm$	m/(mol·kg^{-1})	g	ϕ	$\gamma_\pm$
0.0019	0.991	0.991		0.0019	0.007	0.991	
0.0051	0.977	0.977		0.0051	0.009	0.977	
0.0086	0.971	0.971		0.0070	0.015	0.975	
0.0135	0.965	0.965		0.0090	0.972	0.972	
0.0226	0.957	0.957		0.0165	0.919	0.919	
0.0335	0.953	0.953		0.0231	0.843	0.843	
0.0400	0.947	0.946		0.0348	0.698	0.698	0.662
0.0436	0.908	0.907	0.803	0.0474	0.547	0.547	0.509
0.0474	0.807	0.807	0.750	0.0583	0.475	0.475	0.427
0.0568	0.757	0.757	0.648	0.0927	0.357	0.356	0.288
0.0751	0.621	0.620	0.516	0.1321	0.294	0.294	0.213
0.0964	0.527	0.526	0.421	0.1434	0.283	0.283	0.199
0.1257	0.443	0.443	0.340	0.1649	0.268	0.268	0.176
0.1449	0.413	0.413	0.303	0.1764	0.257	0.257	0.167
0.1745	0.369	0.368	0.260	0.2127	0.239	0.238	0.142
0.2000	0.353	0.352	0.233	0.225	0.234	0.233	0.135
0.2195	0.335	0.335	0.216	0.2469	0.227	0.226	0.125
0.2722	0.307	0.306	0.181				
0.2855	0.291	0.290	0.175				

below and above the inflection point. Plot of gm vs molality is shown in Figure 2 for clomipramine as an exemple. Table 1 also shows the values of the slope of the gm vs molality plots above the critical concentration for both compounds. The introduction of a Cl atom into the dibenzazapine ring system causes a reduction in s, as seen by Attwood et al. (1989) for phenothiazine drugs. This decrease of s is an induction of closer packing of these molecules, confirmed by the lower critical concentration values for clomipramine than for imipramine.

It is necessary to remind the reader that the experimental variable obtained is g, the rational osmotic coefficient. For practical purposes, g may be defined as the observed vapor pressure lowering divided by the ideal vapor pressure lowering and is related to the stoichiometric osmotic coefficient by the equation (Lewis and Randall, 1961)

Table 3. Rational Osmotic Coefficient (*g*), Stoichiometric Osmotic Coefficient (*ϕ*), and Activity Coefficient ($\gamma_\pm$) for Imipramine Hydrochloride at 308.15 and 313.15 K

T = 308.15 K				T = 313.15 K			
m/(mol·kg^{-1})	g	ϕ	$\gamma_\pm$	m/(mol·kg^{-1})	g	ϕ	$\gamma_\pm$
0.0062	0.978	0.978		0.0053	0.990	0.990	
0.0087	0.970	0.970		0.0076	0.981	0.981	
0.0126	0.965	0.965		0.0119	0.970	0.970	
0.0170	0.963	0.963		0.0143	0.966	0.966	
0.0230	0.952	0.952		0.0214	0.960	0.960	
0.0320	0.941	0.941		0.0280	0.951	0.951	
0.0419	0.900	0.900		0.0320	0.940	0.940	
0.0514	0.835	0.835		0.0390	0.938	0.938	
0.0577	0.796	0.795	0.797	0.0551	0.889	0.889	
0.0602	0.785	0.785	0.769	0.0650	0.872	0.872	
0.0850	0.666	0.665	0.578	0.0759	0.803	0.803	0.777
0.0997	0.592	0.592	0.506	0.0857	0.754	0.753	0.705
0.1291	0.494	0.493	0.408	0.0938	0.715	0.714	0.656
0.1390	0.478	0.477	0.384	0.1138	0.646	0.646	0.562
0.1584	0.436	0.435	0.344	0.1298	0.605	0.604	0.506
0.1800	0.399	0.399	0.310	0.1478	0.554	0.553	0.456
0.1999	0.381	0.380	0.284	0.1654	0.517	0.516	0.417
0.2380	0.347	0.346	0.246	0.1744	0.501	0.500	0.400
0.2655	0.328	0.327	0.224	0.1899	0.478	0.477	0.374
				0.2126	0.450	0.449	0.341
				0.2341	0.424	0.423	0.316
				0.2505	0.409	0.408	0.300
				0.2738	0.387	0.386	0.279

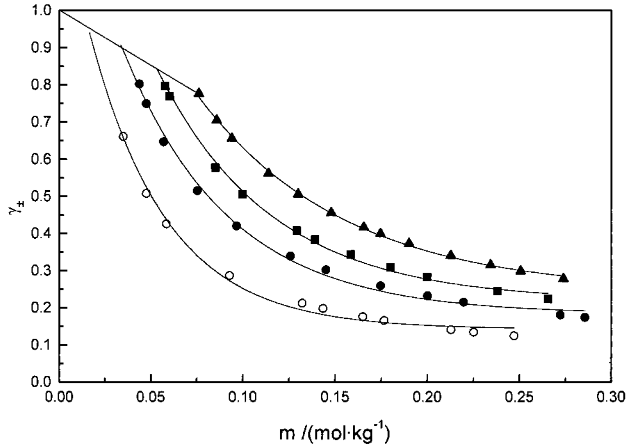

Figure 3. Concentration dependence of the mean activity coefficients, $\gamma_\pm$, for imipramine hydrochloride at (●) 303.15 K, (■) 308.15 K, and (▲) 313.15 K and for clomipramine hydrochloride at (○) 303.15 K.

$$g \ln x_1 = -\frac{\nu_2 m_2 M_1}{1000}\phi \qquad (1)$$

where M_1 is the molar mass of the solvent, m_2 is the molality of the solute, x_1 is the mole fraction of the solvent, and ν_2 is the number of ions produced by one molecule of the surfactant. Columns 2, 3, 6, and 7 of Tables 2 and 3 show the experimental results obtained for g and ϕ for imipramine and clomipramine at different temperatures, respectively. The apparent deviation of the osmotic coefficient in the pre cmc-region from values for sodium chloride at similar concentrations is thought to be a real effect and may indicate limited premicellar association. However, measurements in this region are taken at the limit of the precision of the technique and should be treated with caution.

The mean activity coefficients on a molality scale are given by the expression (Huff et al., 1951)

$$-\ln \gamma_{\pm} = (1 - g) + \int_0^m (1 - g)\, \mathrm{d} \ln m \qquad (2)$$

where $\gamma_{\pm}$ is the mean activity coefficient. In general, this expression must be evaluated by graphical integration, but in the region where the linear plot is valid it reduces to the simple expression

$$-\ln \gamma_{\pm} = -\ln \gamma_c + (\beta - 1) \ln (m_c/m) \qquad (3)$$

where γ_c is the activity coefficient at the critical concentration, β is the slope above the critical concentration in a gm vs molality plot, and m_c is the critical concentration value. γ_c may be taken equal to that of potassium chloride at the same concentration assuming both imipramine and clomipramine behave osmotically as simple electrolytes below the critical concentration.

The concentration dependence of the mean activity coefficients for imipramine in the range of temperature 303.15−313.15 K and for clomipramine at 303.15 K are shown in Figure 3. From this plot, an increase in the value of the mean activity coefficient with temperature can be observed. Columns 4 and 8 of Tables 2 and 3 give the experimental data of the mean activity coefficient for imipramine and clomipramine at different temperatures.

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