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Apparent molar volumes and adiabatic compressibilities of aqueous solutions of amphiphilic drugs

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Abstract: The apparent molar volumes and adiabatic compressibilities of aqueous solutions of the amphiphilic tricyclic drugs, chlorpromazine, promethazine, promazine and imipramine have been determined from measurements of density and ultrasound velocity. Positive deviations of the apparent molar volume from the Debye–Hückel limiting law in dilute solution indicate possible premicellar association. The changes of molar volume and compressibility accompanying aggregate formation were appreciably smaller than those of typical surfactants, suggesting a more tightly packed aggregate. The magnitude of the increase in molar compressibility on micellisation of imipramine decreased with temperature rise between 20 and 35 °C. The results are discussed in terms of the structure and hydration of the drug aggregates.

Key words: Apparent molar volume – adiabatic compressibility – micelles – drugs – micellar properties

Introduction

The drugs under investigation are amphiphilic in nature, possessing an almost planar tricyclic ring system with a short hydrocarbon chain carrying a terminal, charged N atom (see below for structures). In the absence of electrolyte, aggregates of approximately 10 monomers form in aqueous solution at a critical concentration, which can be detected by a discontinuity of the concentration dependence of the physicochemical properties of the solution [1]. Evidence from NMR studies [2] on the phenothiazine drugs chlorpromazine, promethazine and promazine suggests the stacking of molecules within the aggregate in the manner of the tricyclic dyes. Although some workers have identified this critical concentration with the critical micelle concentration (CMC) of a typical surfactant system, there is recent evidence from calorimetry [3, 4] and osmometric studies [5] on these drugs that limited association occurs below the critical concentration. Such studies suggest that, at this concentration, the small primary units formed in dilute solution increase in size by, for example, the hydrophobic bonding of the short stacks to form larger aggregates of stable size. Recently, we demonstrated [6] a second discontinuity in the light scattering data for aqueous solutions of several phenothiazine drugs in the concentration region 0.20 to 0.27 mol kg^{-1} suggesting a complex association pattern.

We have recently reported on temperature dependent changes of the apparent molar volume and adiabatic compressibility of the phenothiazine drug, chlorpromazine hydrochloride [7]. Treatment of data was simplified by the use of a pseudophase model which assumed that the drug was in monomeric form below the critical concentration [8]. In the present work we present a more detailed examination of the concentration dependence of apparent molar volume and adiabatic compressibility of several phenothiazine drugs and also of the antidepressant drug,

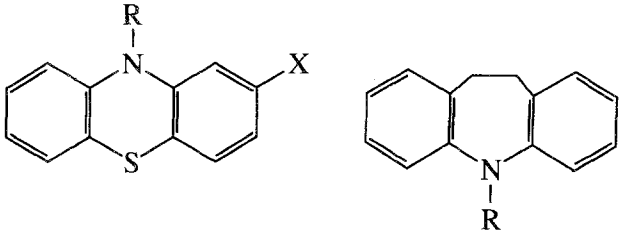
imipramine. Extensive measurements were carried out in the concentration region below the critical concentration and deviations from the Debye–Hückel limiting law were interpreted in terms of association at these concentrations. Measurements were restricted to the concentration region below any second inflection point.

Experimental section

Materials

The hydrochlorides of chlorpromazine (I) [2-chloro-10-(3-dimethylaminopropyl)-phenothiazine], promethazine (II) [10-(2-dimethylaminopropyl)-phenothiazine], promazine (III) [10-(3-dimethylaminopropyl)-phenothiazine] and imipramine (IV) [5-(3-dimethylaminopropyl)-10, 11-dihydro-5H-dibenz[b, f]azepine] (Sigma Chemical Co) conformed to the purity requirements of the British Pharmacopoeia and as such contained not less than 98.5% of the specified compound.

Water was double-distilled and degassed before use.



I: R = $-CH_2CH_2CH_2N(CH_3)_2$, X = Cl

II: R = $-CH_2CH(CH_3)N(CH_3)_2$, X = H

III: R = $-CH_2CH_2CH_2N(CH_3)_2$, X = H

IV: R = $CH_2CH_2CH_2N(CH_3)_2$

Ultrasound velocity measurements

Ultrasound velocity was measured at 25 °C at a frequency of 2 MHz using a Nusonic model 6380 concentration analyser (Nusonics Inc.), with a temperature transducer connected to a Hewlett-Packard digital microvoltimer 3455A. The sound velocity transducer was connected to a Hewlett-Packard multimeter 3437A, giving an accuracy in the velocity of $\pm$ 0.01 m s^{-1}. Each datum point is the mean of 100 measurements of velocity. Temperature control was to $\pm$ 0.005 °C giving rise to uncertainties in measurements of ultrasound velocity of ca $\pm$ 0.05 m s^{-1} in this study.

Density measurements

Density was measured at 25 °C using a Paar DMA 60/602 densimeter with a resolution of 10^{-6} g cm^{-3}. Temperature control was within $\pm$ 0.005 °C giving rise to uncertainties in density of ca. $\pm 3 \times 10^{-6}$ g cm^{-3}.

Results and discussions

Plots of ultrasound velocity, u, as a function of molality, m, (Fig. 1) show clear inflection points at the concentrations, c', given in Table 1, which are similar to values from light scattering techniques.

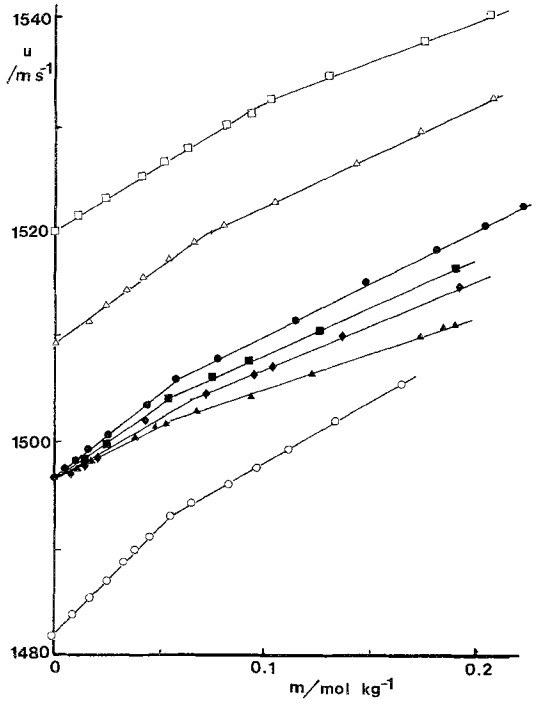


Fig. 1. Concentration dependence of ultrasound velocity, u in aqueous solution of ▲, chlorpromazine; ◆, promazine and ■, promethazine at 25 °C and imipramine at ○, 20°; ●, 25°; △, 30° and □, 35 °C

Table 1. Critical concentrations and apparent molar properties

	Temp °C	c' mol kg^{-1}	ϕ_v^0 cm^3 mol^{-1}	ϕ_v^{mic} cm^3 mol^{-1}	ΔV_m cm^3 mol^{-1}	B_v cm^3 kg mol^{-2}	ϕ_K^0 10^{-3} bar^{-1} cm^3 mol^{-1}	ϕ_k^{mic} 10^{-3} bar^{-1} cm^3 mol^{-1}	ΔK_m 10^{-3} bar^{-1} cm^3 mol^{-1}
Chlorpromazine	25	0.043(0.027)[a]	269.7	271.5	1.8	19	+ 1.9	3.9	2.0
Promazine	25	0.044(0.035)[a]	259.6	260.3	0.7	19	+ 0.3	2.9	2.6
Promethazine	25	0.056(0.058)[a]	255.9	257.0	1.1	11	− 0.6	2.1	2.7
Imipramine	20	0.052	273.4	272.7	− 0.7	2.6	− 2.0	2.1	4.1
	25	0.054	274.7	273.7	− 1.0	2.8	+ 0.2	3.4	3.2
	30	0.065(0.047)[b]	275.6	275.0	− 0.6	3.5	+ 1.3	3.7	2.4
	35	0.094	276.9	276.1	− 0.8	3.7	+ 3.3	4.5	1.2

Values in parenthesis are from light scattering data at 30 °C [a] ref [6] [b] ref [23]

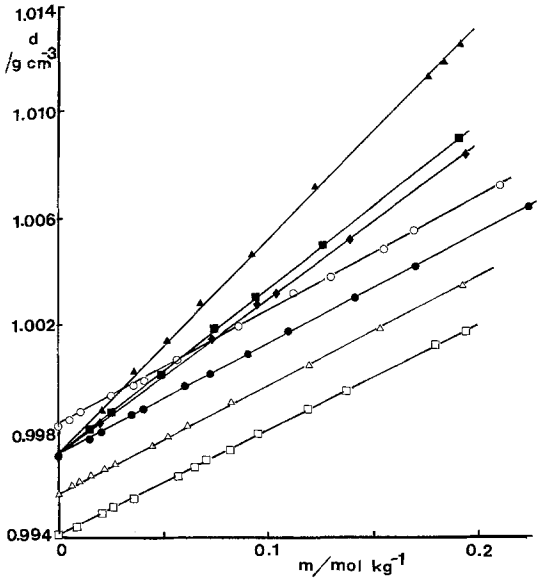


Fig. 2. Density, d, of aqueous solutions of ▲, chlorpromazine; ◆, promazine and ■, promethazine at 25 °C and imipramine at ○, 20°; ●, 25°; △, 30° and □, 35 °C as a function of molality, m

Figure 2 shows plots of density, d, against molality. The densities at concentrations below c' were fitted to the empirical equation [9]

$$d = d_0 + (Am + Bm^{3/2} + Cm^2 + Dm^{2/5})/10^3 , \quad (1)$$

where d_0 is the density of pure water at each temperature (0.998020, 0.997043, 0.995645 and 0.994030 g cm^{-3} at 20, 25, 30 and 35 °C respectively). Values of the least squares parameters, A, B, C, and D are given in Table 2, together with the variance for the fits.

Apparent molar volumes, ϕ_v, were determined from the density values using

$$\phi_v = \frac{M}{d} - \frac{10^3(d - d_0)}{mdd_0} , \quad (2)$$

where M is the molecular weight. Figure 3 shows the apparent molar volumes of each drug plotted against $c^{1/2}$, where c is the molar concentration calculated from molality using the measured densities.

The gradient of such plots approaches zero at high drug concentration and many workers have subjectively chosen the approximately constant or limiting values as the apparent molar volume of the micelles, ϕ_v^{mic}. An alternative approach [10] is to fit these data to the function

$$\phi_v/\phi_v^{mic} = m/(a + m) , \quad (3)$$

where a is an empirical constant. Rearrangement to

$$\phi_v = -a(\phi_v/m) + \phi_v^{mic} \quad (4)$$

enables ϕ_v^{mic} to be derived from plots of ϕ_v against ϕ_v/m. The values of ϕ_v^{mic} determined in this manner are given in Table 1.

In the concentration region $c \leq c'$, ϕ_v for a 1:1 electrolyte may be described by the equation [11]

$$\phi_v = \phi_v^0 + A_v c^{1/2} + B_v c , \quad (5)$$

where A_v is the Debye–Hückel limiting law coefficient (1.780, 1.865, 1.952 and 2.040 cm^3 kg$^{1/2}$ mol$^{-3/2}$ for a 1:1 electrolyte at 20, 25, 30 and 35 °C respectively). B_v is an adjustable parameter which measures the deviations from the limiting law and ϕ_v^0 is the apparent

Table 2. Parameters of Eq. (1)

	Temp °C	A	B	C	D	$10^{12}\sigma^2$
Chlorpromazine	25	83.16	104.15	− 1204.8	3986.49	0.19
Promazine	25	62.27	− 6.55	− 43.92	130.78	1.17
Promethazine	25	69.81	− 112.56	879.18	− 2370.42	0.30
Imipramine	20	20.74	474.62	− 3162.96	6693.89	1.23
	25	69.05	− 648.33	5039.47	− 12644.55	4.92
	30	52.98	− 258.57	2011.52	− 5237.40	1.70
	35	17.62	434.83	− 2688.10	5310.61	1.10

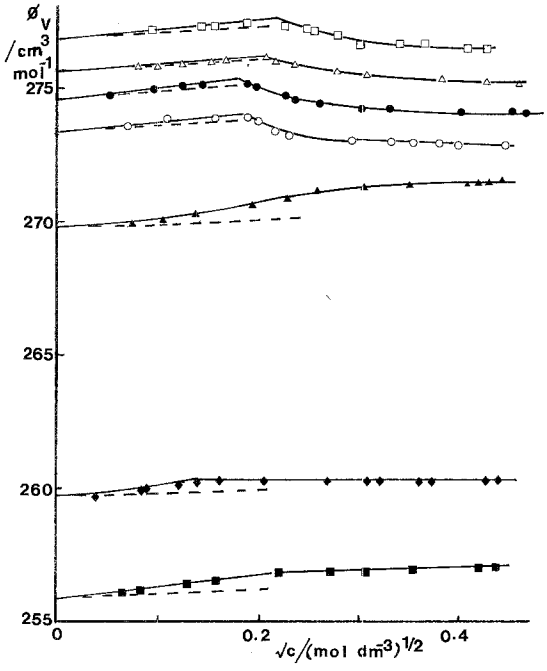


Fig. 3. Apparent molar volume, ϕ_v, as a function of $c^{1/2}$ for aqueous solution of ▲ chlorpromazine; ◆, promazine and ■, promethazine at 25 °C and imipramine at ○, 20°; ● 25°; △, 30° and □, 35 °C. Dotted lines are values from the Debye–Hückel limiting law

molar volume at infinite dilution. The dotted lines of Fig. 3 are the limiting law values for each drug and it is clear from this figure and from the B_v values of Table 1 (derived by computer simulation of the ϕ_v against $c^{1/2}$ curves) that positive deviation from the predicted values occurs at these concentrations.

It is instructive to compare these results with those from studies on cationic and anionic surfactants [12–14] which show a negative deviation for these hydrophobic solutes. A possible exception to this generalisation was reported with sodium octyl sulphate [12] and it was suggested that the observed positive deviation might be a consequence of the reported dimerization of this compound in the pre CMC region [15]. Of greater relevance to the present work is the study by Djavanbakht et al. [16] which showed positive deviations from the Debye–Hückel limiting law for potassium cholate and sodium deoxycholate. This behaviour was attributed to continuous association of these bile salts in a manner similar to a stacking process. Evidence from calorimetric [3, 4] and osmotic techniques [5] has shown limited association of the phenothiazine drugs at concentrations below the inflection point at c'. The positive B_v values indicated in this present study provide further confirmation of such behaviour.

The change in volume associated with the formation of the stable aggregate from monomeric drug was taken to be $\Delta V_m = \phi_v^{\text{mic}} - \phi_v^0$. The ΔV_m value for chlorpromazine determined in this way is in reasonable agreement with that derived previously [7] at 25 °C by the application of a pseudophase model. The use of such a model, although simplifying data treatment, provides no information on any changes in ϕ_v at low concentration. The ΔV_m values of the drugs (see Table 1) are appreciably lower than values determined for typical surfactants (for example, sodium dodecyl sulphate = 10.8 $\text{cm}^3\,\text{mol}^{-1}$ at 25 °C) [12] and in the case of imipramine are negative. These results suggest that there is less free space in the interior of the aggregates compared to typical micelles as might be expected for a stacked aggregate. Since the drugs have similar ionic head groups, any differences in their ΔV_m values will be a consequence of differences in their hydrophobic groups. The higher ΔV_m for chlorpromazine reflects

a greater hydrophobic hydration of this drug, resulting from the Cl substituent on the phenothiazine ring. Similar increases in ΔV_m with hydrophobicity have been reported for homologous series of both anionic and cationic surfactants [12, 17]. Since the drugs have identical counterions, differences in the ϕ_v^0 values arise from structural differences of the drug cations. Comparison of chlorpromazine and promazine shows a contribution to the volume of $+10\,cm^3, mol^{-1}$, arising from the Cl substituent. Atherton and Barry [18] have reported ϕ_v values for a series of phenothiazine drugs in the presence of added electrolyte at concentrations in excess of the critical concentrations. Since these authors noted no significant dependency of ϕ_v on concentration of added electrolyte over the range 0.05 to 0.30 mol dm^{-3} NaCl, their values may be compared with those of the present study. The reported values at 25 °C in 0.05 mol dm^{-3} NaCl at concentrations close to the critical concentration were 270 (270.7), 259 (260.3) and 257 (256.9) cm^3 mol^{-1} for chlorpromazine, promazine and promethazine respectively, in good agreement with the values obtained here in the absence of electrolyte (given in parenthesis for identical drug concentrations).

Apparent molar expansivities $\phi_E = (\partial\phi_v^i/\partial T)_p$ calculated for the monomer ($i = 0$) and micelle ($i = m$) of imipramine from linear plots of ϕ_v^i as a function of temperature were 0.225 and 0.230 cm^3 mol^{-1} K^{-1} respectively. The concentration dependence of ϕ_E at concentrations below c', as calculated using the derivative of Eq. (5)

$$\phi_E = \left(\frac{\partial\phi_v}{\partial T}\right)_p = \left(\frac{\partial\phi_v^0}{\partial T}\right)_p + \left(\frac{\partial A_v}{\partial T}\right)_p^{m^{1/2}} + \left(\frac{\partial B_v}{\partial T}\right)_p^{m} \quad (6)$$

was

$$\phi_E = 0.225 + 0.018m^{1/2} + 0.078m\,. \quad (7)$$

The concentration dependence of the adiabatic compressibility of the solutions, β, as calculated from $\beta = 1/u^2\rho$ is shown in Fig. 4. Apparent molar compressibilities, ϕ_K, were determined from these data using

$$\phi_K = 10^3 c^{-1}(\beta - \beta_0) + \beta_0\phi_v \quad (8)$$

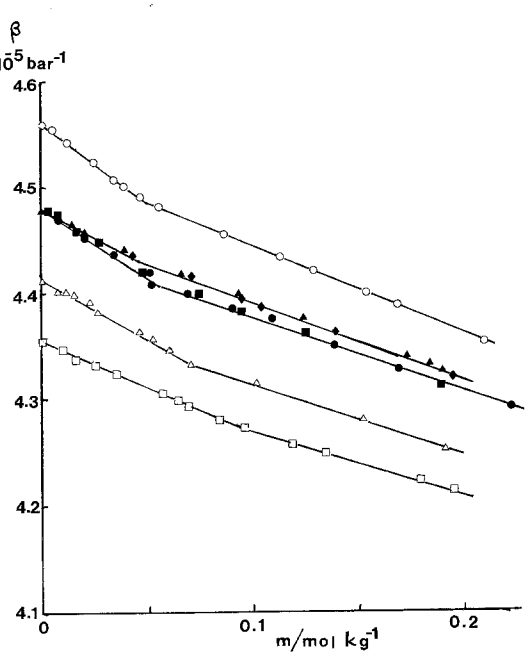


Fig. 4. Adiabatic compressibility, β, of aqueous solutions of ▲ chlorpromazine; ◆, promazine and ■, promethazine at ○, 20°; ●, 25°; △, 30° and □, 35 °C as a function of molality, m

where β_0 is the adiabatic compressibility of the solvent. Plots of ϕ_K as a function of concentration are given in Fig. 5.

Within a homologous series of tetra-*n*-alkylammonium salts [19] and alkyltrimethylammonium bromides [17], the apparent molar compressibility of the surfactant monomers decreased with increasing chain length, due to an increase in the amount of structured water in the vicinity of the hydrocarbon chains, which is less compressible than bulk water. It might therefore be expected that the drug cations would have lower compressibilities than these surfactants because of their larger hydrophobic groups. The compressibilities at infinite dilution, ϕ_K^0, of the drugs are, however, significantly higher (see Table 1) than those of the alkyltrimethylammonium bromides (for example, the ϕ_K^0 value of dodecyltrimethylammonium bromide is -42×10^{-4} cm^3 mol^{-1} bar^{-1} at 25 °C) [17]. The reason for these higher ϕ_K^0 values may be that there is a more significant contribution to the observed compressibility arising from the intrinsic molecular compressibility of the very much bulkier hydrophobic group of the drugs. The uncertainty in measurements at very low solution

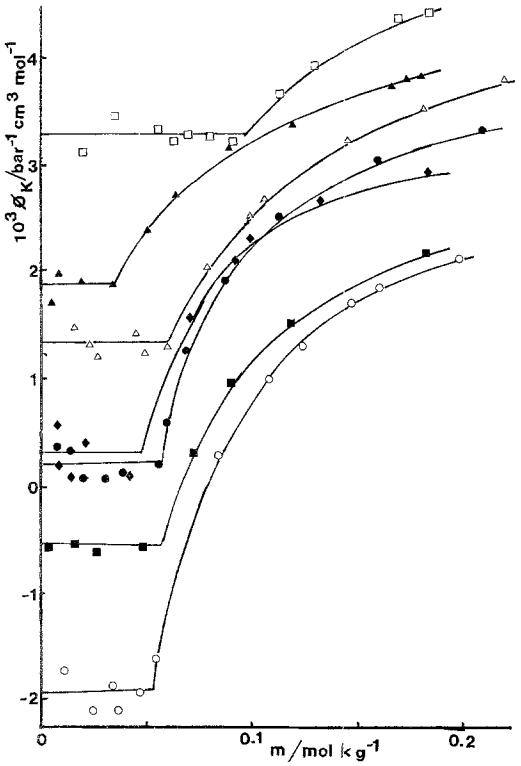


Fig. 5. Apparent molar compressibility, ϕ_K, of aqueous solutions of ▲ chlorpromazine; ◆, promazine and ■, promethazine at 25 °C and imipramine at ○, 20°; ●, 25°; △, 30 ° and □, 35 °C as a function of molality, m

concentrations made it impossible to determine whether deviation from the ϕ_K against c behaviour of typical surfactants [20] occurred below the critical concentration.

The increases of compressibility, ΔK_m, on the formation of aggregate, taken to be the difference between the ϕ_k values at high concentration (equated with the micellar compressibility, ϕ_K^{mic}) and ϕ_K^0, were appreciably smaller than for typical surfactants (ΔK_m for dodecyltrimethylammonium bromide = 16.2×10^{-3} mol^{-1} bar^{-1} at 25 °C) [17]. The low compressibility of the drug aggregates which is partially responsible for the low ΔK_m values is an expected characteristic of a stacked aggregate which does not possess the looseness of structure associated with the micelles of typical surfactants.

Inspection of Table 1 shows that both ϕ_K^0 and ϕ_K^{mic} values for imipramine increase with increasing temperature. The changes in ϕ_K^0 are larger, resulting in a net decrease of ΔK_m with temperature. Similar tendencies have been reported previously for sodium decanoate [21] and for a series of alkyltrimethylammonium bromides [17]. Negative values of ϕ_K^0 have been interpreted [22] as a consequence of a higher resistance to pressure of the structured water around the surfactant monomer compared to that of bulk water. The gradual loosening of water struture around the monomer with increase of temperature is responsible for the corresponding increase of ϕ_K^0. The increases of ϕ_K^{mic} can be attributed to similar temperature induced changes in water structure of the hydration shell around the polar head groups of the aggregated drug molecules.

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