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COMMUNICATIONS

Micellar properties of chlorpromazine hydrochloride in concentrated electrolyte solutions

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Recent interest has been shown in the effect of high concentrations of added electrolyte on the association of surfactants, with particular emphasis on the association of sodium dodecyl sulphate (Mazer et al 1976, 1977; Young et al 1978; Missel et al 1980; Hayashi & Ikeda 1980; Ikeda et al 1981) and of the cationic surfactants, dodecyldimethylammonium chloride (Ikeda et al 1980), dodecyltrimethylammonium bromide (Ozeki & Ikeda 1982) and cetylpyridinium bromide (Porte & Appell 1981). Both classical and quasielastic light scattering studies have shown a pronounced increase in micellar size and polydispersity with increase in surfactant concentration in solutions of high salt content. Corresponding increases in the dissymmetry of the angular dependence of the light scattering from these solutions has led to the idea of micellar growth accompanied by a transition from spherical to rod-like micelles.

Despite the large number of studies into the micellar properties of the phenothiazine tranquillizers which have been reported (see Attwood 1983) there have been only limited reports of the effect of electrolyte on the solution properties (Thoma & Arning 1976) and these have been restricted to low concentrations of added electrolyte. Although the association pattern of the phenothiazines resembles that of typical surfactants, it is thought (Florence & Parfitt 1971) that the aggregates form by stacking of the planar molecules rather than by the intertwining of the hydrophobic moieties as in spherical surfactant micelles. It is of interest therefore to extend the examination of the solution properties of these drugs to include solutions of high electrolyte content.

In this present work we have used classical light scattering techniques to investigate the association of chlorpromazine hydrochloride (May & Baker) in aqueous solutions of sodium chloride (Analar grade) up to 0·6 mol dm^{-3}. Measurements were made at 303K with a Fica 42000 photogoniodiffusometer using a wavelength of 546 nm. The aqueous solutions were clarified by ultrafiltration through 0·1 μm Millipore filters. The refractive index increments of the micellar species were measured at 546 nm using a differential refractometer.

Fig. 1 shows the light scattering intensity at an angle of 90°, S_{90}, plotted as a function of the molar concentration of chlorpromazine hydrochloride for systems containing electrolyte concentration of up to 0·6 mol dm^{-3}. Inflections were noted in all curves at well defined critical micelle concentrations (cmc). At concentrations below the cmc the scattering data were well represented by theoretical lines calculated assuming solution ideality for unassociated monomers. Cmc values were also derived from inflections in pH–log concentration plots as determined at 303 ± 0·01K using a Pye Model 290 pH meter fitted with a combined glass-silver chloride electrode (see Table 1).

At low electrolyte concentration, plots of $(m_2/\Delta S_{90})$ against the molality of the micellar species m_2, (where $\Delta S_{90} = S_{90} - S_{90cmc}$) were linear with positive slopes (Fig. 2). Treatment of the data using the theory of Anacker & Westwell (1964) yielded the values of aggregation number, N, given in Table 1. Degrees of ionization, α, of 0·17 and 0·19 were calculated in water and 0·1 mol dm^{-3} NaCl respectively. For systems of higher electrolyte concentration such plots are clearly anomalous showing a pronounced increase in the mean size of the aggregates with increasing solution concentration above the cmc. The size of the primary micelles formed at the cmc was estimated from the intercept

Table 1. Micellar properties of chlorpromazine hydrochloride at 303K in aqueous solutions containing added sodium chloride.

NaCl concn (mol dm^{-3})	cmc (mmol dm^{-3})		Aggregation number at cmc
	light scatt.	pH	
0·000	22·0	—	12
0·100	7·0	6·2	35
0·165	5·2	5·4	27
0·200	4·1	4·4	28
0·250	3·5	3·7	30
0·400	2·8	2·5	~30
0·600	2·3	2·0	~30

* Correspondence.

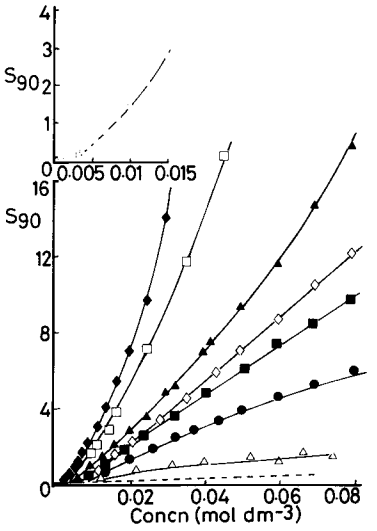

FIG. 1. Variation of the scattering ratio, S_{90}, with concentration for chlorpromazine hydrochloride in $\triangle H_2O$; and in the presence of ● 0·1; ■ 0·165; ◇ 0·2; ▲ 0·25; □ 0·4 and ◆ 0·6 mol dm^{-3} sodium chloride at 303K. – – Monomer line. Insert: detailed graph of data close to cmc in 0·4 mol dm^{-3} NaCl.

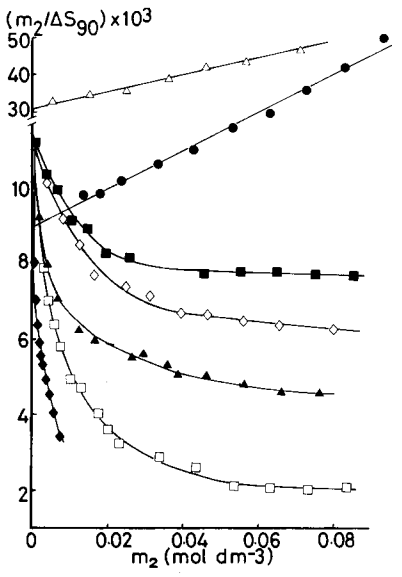

FIG. 2. $m_2/\Delta S_{90}$ plotted against micellar concentration m_2 for chlorpromazine hydrochloride in $\triangle H_2O$; and in the presence of ● 0·1; ■ 0·165; ◇ 0·2; ▲ 0·25; □ 0·4 and ◆ 0·6 mol dm^{-3} sodium chloride.

obtained by extrapolation of these plots to the cmc using an assumed value of p = 0·19N. (Table 1). Although careful measurements were made in the region of the cmc (see insert to Fig. 1) the extrapolation in high electrolyte concentration was uncertain and the estimated micellar size in these systems is approximate.

The standard free energy of micellization (per mole of monomeric drug ion), ΔG_m^θ, was calculated from a plot of log cmc against log counterion concentration, X^-, according to (Anacker 1970)

$$\log \text{cmc} = -(1 - \alpha) \log X^- + \Delta G_m^\theta/2{\cdot}303RT + 1/N \log F(m^{+p}) \quad (1)$$

In equation (1), which is derived by application of the mass action law to the micellization process, m^{+p} is the mole fraction of micelles and F is a term involving the activity coefficients of all species present in solution. The cmc data are plotted in accordance with equation 1 in Fig. 3. The value of α derived from the slope of the linear plot was 0·24. Extrapolation to log $X^- = 0$ yielded a value of $\Delta G_m^\theta = -34{\cdot}4$ kJ mol^{-1}.

In a previous paper (Attwood et al 1974) we have calculated a value of +38·9 kJ mol^{-1} for the free energy of solution, ΔG_s^θ, of chlorpromazine using the data of Green (1968) for the solubility of chlorpromazine base. Since the micellization process involves removal of the hydrophobic portion from an aqueous environment, some measure of agreement between the values of ΔG_s^θ and ΔG_m^θ might be expected, although it is recognized that the two free energy changes relate to different standard states; the micellar standard state represents the hydrated species, that of the solid will be the pure solid. Differences will also arise between the two ΔG^θ values if the side chains are not completely removed from the aqueous environment on micellization. Bearing in mind these potential causes of discrepancy the agreement between Δ_m^θ and Δ_s^θ is reasonable. The ΔG_m^θ value obtained here is appreciably higher than previously determined for chlorpromazine (Attwood et al 1974) which suggests a more complete removal of the hydrophobic portions from the aqueous environment than was possible with the much smaller micellar units in the systems of low electrolyte concentration studied previously.

It is clear from the evidence presented that, in salt concentrations in excess of approximately 0·165 mol dm^{-3}, the aggregation of chlorpromazine no longer conforms to that of typical micelle association. On the other hand, the association process is not a continuous association process of the type reported for some drug molecules (Attwood 1983) since unlike these systems, aggregation does not commence until a critical concentration is reached. The form of the plots of $m_2/\Delta S_{90}$ against m_2 suggests that the micelles formed at the cmc undergo a concentration-dependent increase in size. Similar behaviour has been reported for sodium dodecyl sulphate (Hayashi & Ikeda 1980), dodecyldimethylammonium bromide (Ikeda et al 1980) and dodecyltrimethylammonium bromide (Ozeki & Ikeda 1982) and has been interpreted in terms of micellar growth involving a sphere-to-rod transition. No explicit information regarding changes in the shape of the

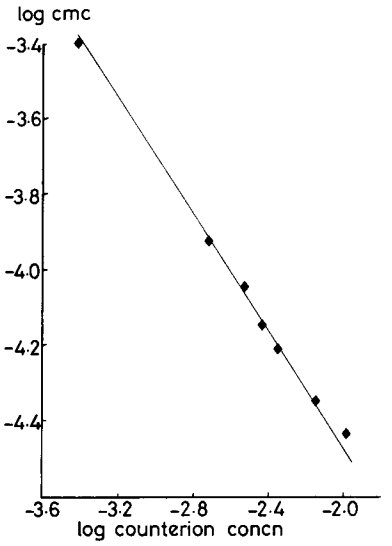

FIG. 3. Log cmc against log counterion concentration for chlorpromazine hydrochloride in the presence of added sodium chloride. Concentrations are expressed as mole fractions.

micelles was provided by the light scattering data, any increases in micellar asymmetry were not sufficient to induce significant distortion of the symmetry of the scattering envelope. In this respect it should be noted that dissymmetry of the angular scattering envelope occurs only when the dimensions of the scattering particles exceed approximately $\lambda/20$ and the symmetrical envelopes noted here do not rule out the possibility of asymmetric micelles in these solutions.

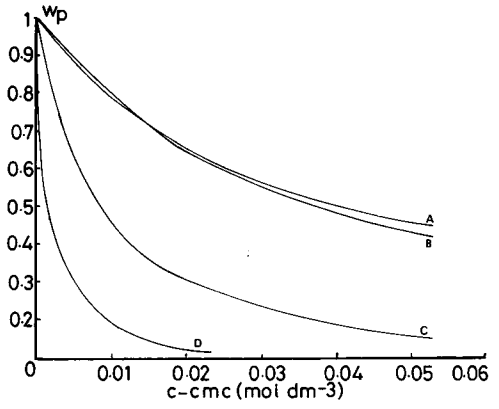

FIG. 4. Variation of weight fraction of primary micelles, w_p, with micelle concentration for chlorpromazine hydrochloride in aqueous solutions containing A, 0·165; B, 0·2; C, 0·4 and D, 0·6 mol dm^{-3} sodium chloride.

Some indication of the extent of micellar enlargement may be derived from the calculation of changes in the weight fraction of the primary micelle, w_p, with increase in drug concentration in solutions of high electrolyte content. This may be assessed using Steiner's procedure for continuously associating systems (Steiner 1952).

$$\ln w_p = \int_0^{\text{c-cmc}} \left[\frac{N_p}{N} - 1\right] d \ln(\text{c-cmc}) \qquad (2)$$

In equation 2, N_p is the aggregation number of the primary micelle and N the apparent aggregation number at a weight concentration of c-cmc. N was calculated using the Anacker & Westwell (1964) theory assuming a value of p = 0·19N at all concentrations. Fig. 4 shows clearly the very pronounced increase in micellar size and polydispersity in solutions of high electrolyte concentration.

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REFERENCES

Anacker, E. W., Westwell, A. E. (1964) J. Phys. Chem. Ithaca 68: 81—93

Anacker, E. W. (1970) in: Jungermann, E. (ed.) Cationic surfactants. New York, Marcel Dekker p 217

Attwood, D. (1983) in: Wyn-Jones, E., Gormally, J. (eds) Aggregation Processes in Solution. Elsevier, The Netherlands, Chpt. 9.

Attwood, D., Florence, A. T., Gillan, J. M. N. (1974) J. Pharm. Sci. 63: 988–993

Florence, A. T., Parfitt, R. T. (1971) J. Phys. Chem. Ithaca 75: 3554–3560

Green, A. L. (1968) J. Pharm. Pharmacol. 19: 10–16

Hayashi, S., Ikeda, S. (1980) J. Phys. Chem. Ithaca 84: 747–751

Ikeda, S., Hayashi, S., Imae, T. (1981) Ibid. 85: 106–112

Ikeda, S., Ozeki, S., Tsunoda, M-A (1980) J. Coll. Interface Sci. 73: 27–37

Mazer, N. A., Benedek, G. B., Carey, M. C. (1976) J. Phys. Chem. Ithaca 80: 1075–1085

Mazer, N. A., Carey, M. C., Benedek, G. B. (1977) in: Mittal K. L. (ed.) Micellization, Solubilization and Microemulsions, Vol 1, Plenum Press, New York, pp 359–381

Missel, P. J., Mazer, N. A., Benedek, G. B., Young, C. Y., Carey, M. C. (1980) J. Phys. Chem. Ithaca 84: 1044–1057

Ozeki, S., Ikeda, S. (1982) J. Coll. Interface Sci. 87: 424–435

Porte, G., Appell, J. (1981) J. Phys. Chem. Ithaca 85: 2511–2519

Steiner, R. F. (1952) Arch. Biochem. Biophys. 39: 333–354

Thoma, K., Arning, M., (1976) Arch. Pharm. 309: 837–850

Young, C. Y., Missel, P. J., Mazer, N. A., Benedek, G. B., Carey, M. C. (1978) J. Phys. Chem. Ithaca 82: 1375–1378