Micelle formation by some antihistamines in aqueous solution

Typical colloidal behaviour is exhibited by many drugs from several pharmacological groups of compounds including the local anaesthetics, antidepressives, tranquillizers, antibacterials and antibiotics (Florence, 1968; Felmeister, 1972). The consequences of surface activity on the biological activity of the drugs and the problems that arise in the formulation of surface-active drugs have been discussed. With the exception of the phenothiazine derivative, promethazine hydrochloride, the surface activity (Seeman & Bialy, 1963; Zografi & Zarenda, 1966) and micellar properties (Scholtan, 1955; Florence & Parfitt, 1970, 1971) of which have been studied extensively, the antihistamines have received little attention in this respect. Hammarlund & Pedersen-Bjergaard (1958) reported that bromodiphenhydramine hydrochloride appeared to form molecular aggregates in aqueous solution in concentrations in excess of 0·05 mol litre^{-1}. Johnson, Goyan & Tuck (1965) noted a similar tendency for aggregation in aqueous solutions of diphenhydramine hydrochloride. Farhadieh, Hall & Hammarlund (1967) used vapour pressure osmometry and conductivity measurements in an investigation of a series of medicinal amines that included both of the above diphenylmethane derivatives and also tripelennamine hydrochloride and mepyramine maleate, which are antihistamines based on the pyridine nucleus. Aggregation of each of these compounds was indicated.

I have used light scattering to study in more detail the micellization of the above two diphenylmethane derivatives and also to examine other antihistamines of this type for similar behaviour. Commercial samples of diphenhydramine hydrochloride, bromodiphenhydramine hydrochloride, chlorcyclizine hydrochloride and diphenylpyraline hydrochloride were used without further purification. Measurements were made at 30·0° with a Fica 42000 photogoniodiffusometer (A.R.L. Ltd.) using a wavelength of 546 nm. Clarification of the aqueous solutions was achieved by ultrafiltration through a 0·1 μm Millipore filter. The refractive index increment of the micellar species, dn/dc', was measured at 546 nm using a differential refractometer (P.C.L. Ltd.).

Critical micelle concentrations, cmc, were determined from the inflection points of graphs of the scattering at an angle of 90° to the incident beam, S_{90}, as a function of

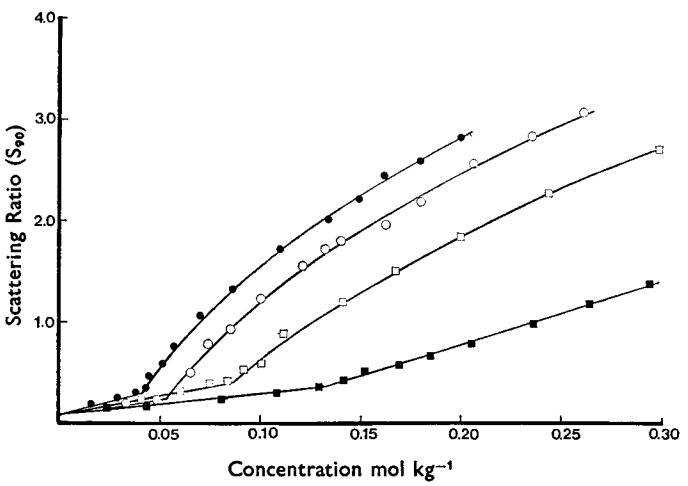

FIG. 1. Variation of the scattering ratio, S_{90}, with concentration for aqueous solutions of ●, chlorcyclizine hydrochloride; ○, bromodiphenhydramine hydrochloride; □, diphenylpyraline hydrochloride; ■, diphenhydramine hydrochloride.

Table 1. *Light scattering data for antihistamines in aqueous solution at* 30°.

Compound	dn/dc' kg mol^{-1}	cmc mol kg^{-1}	micellar weight	N	p	α
Diphenhydramine hydrochloride	0·0570	0·132	1020	3	—	—
Bromodiphenhydramine hydrochloride	0·0675	0·053	4240	11	2·2	0·20
Chlorcyclizine hydrochloride	0·0710	0·040	3000	9	1·7	0·19
Diphenylpyraline hydrochloride	0·0645	0·086	2800	9	2·0	0·22

the molal concentration, c (Fig. 1). The effective micellar charge, p, and the micellar aggregation number, N, were evaluated by the method of Anacker, Rush & Johnson (1964) and Anacker & Westwell (1964). In a solution containing no added electrolyte

$$p = [2\,B\,\text{cmc} + (8\,B\,\text{cmc})^{\frac{1}{2}}]A^{-1}\,(2 - A)^{-1}$$
$$\text{N} = p(p + 1)\,A\,(2\,B\,\text{cmc} + pA^2)^{-1}$$

A and B are the intercept and slope respectively of plots of $Kc'/\Delta R_{90}$ *vs* c'; ΔR_{90} is the Rayleigh ratio of the solution in excess of that of a solution at the cmc; c' is the micellar concentration i.e. $(c - \text{cmc})$; $K = 2\pi^2 n_0^2 (dn/dc')^2 V^0/L\lambda^4$; n_0 is the refractive index of the solvent; V^0 is the volume of solution containing 1 kg of water; L is Avogadro's number and λ is the wavelength of the incident light.

The results are summarised in Table 1 and indicate that micellization is occurring in each of the compounds studied. The cmc obtained for bromodiphenhydramine hydrochloride is in agreement with the value quoted by Hammarlund & Pedersen-Bjergaard from depression of freezing point measurements. It should be noted that the effective charge, p, refers to the equivalent charge under ideal conditions and is generally lower than the true value at the shear surface which is calculated from electrophoretic mobility measurements. Consequently the degree of ionization, α, as given by the ratio p/N, is likely to be an underestimation of the extent of ionization of the micelles.

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