

# Aggregation of antihistamines in aqueous solution. The effect of electrolyte on the micellar properties of some diphenylmethane derivatives

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The effect of sodium chloride on the micellar properties of the antihistamines, diphenhydramine hydrochloride, bromodiphenhydramine hydrochloride, chlorcyclizine hydrochloride and diphenylpyraline hydrochloride in aqueous solution has been investigated by light scattering and viscometric methods. The drugs behaved as typical ionic surfactants showing an increase in aggregation number and decrease in critical micelle concentration as the electrolyte concentration was increased over the range 0.05 to 0.154 mol kg<sup>-1</sup>. A linear relation between log critical micelle concentration and log counterion concentration was established, from which values of the degree of ionization and the free energy of micellization were calculated. The intrinsic viscosity was decreased by the addition of electrolyte and this has been attributed to a decrease in micellar hydration due to a removal of hydrogen-bonded water.

The antihistamines, diphenhydramine hydrochloride, bromodiphenhydramine hydrochloride, chlorcyclizine hydrochloride and diphenylpyraline hydrochloride, all of which contain a diphenylmethane group, have been shown to micellize in aqueous solution (Attwood, 1972; Attwood & Udeala, 1974). This is in contrast to antihistamines in which the hydrophobic region contains a single phenyl ring, some of which are thought to form aggregates by a nonmicellar process (Attwood & Udeala, 1975). The micellar properties of the diphenylmethane derivatives have previously been examined in aqueous solution. We now report an investigation of the effect of electrolyte on the physico-chemical properties of these compounds.

## MATERIALS AND METHODS

*Materials.* Diphenhydramine hydrochloride B.P. (2-diphenylmethoxy-*NN*-dimethylethylamine hydrochloride) and chlorcyclizine hydrochloride B.P. [1-(*p*-chlorodiphenylmethyl)-4-methyl piperazine hydrochloride] were obtained from Parke-Davis and Company and Burroughs Wellcome and Company respectively. Bromodiphenhydramine hydrochloride [2-( $\alpha$ -*p*-bromophenyl- $\alpha$ -phenylmethoxy)-*NN*-dimethylethylamine hydrochloride] and diphenylpyraline hydrochloride (4-diphenylmethoxy-1-methylpiperidine hydrochloride) were gifts from Parke-Davis and Company and Smith, Kline and French Laboratories Limited respectively.

*Light scattering measurements.* A Fica 42000 photogonioidiffusometer (A.R.L. Ltd) was used to measure the light scattered by aqueous solutions of the compounds in the presence of increasing amounts of sodium chloride over the range 0.05-0.154 mol kg<sup>-1</sup>.

Measurements were made at 303K using light of wavelength 546nm. Solutions were clarified by ultrafiltration through 0.1  $\mu\text{m}$  Millipore filters until the ratio of the light scattering at angles of 30° and 150° did not exceed 1.10. The refractive index increments of the micellar species in the presence of electrolyte were measured at 546 nm using a differential refractometer (P. C. L. Limited).

*Viscosity measurements.* Measurements were made on solutions of the compounds in 0.154 mol kg<sup>-1</sup> NaCl at 303 K  $\pm$  0.01 K. A suspended-level viscometer with a solvent flow time of approximately 200 s was used. The relative viscosities were referred to solutions at the critical micelle concentration (cmc).

*Measurement of partial specific volume.* The apparent specific volumes of the micelles in the presence of 0.154 mol kg<sup>-1</sup> NaCl were calculated from density measurements made using a Cahn Electrobalance Model R.G. at 303 K  $\pm$  0.01 K. No dependence of apparent specific volume on concentration was observed within the accuracy of our measurements, for solutions with concentrations exceeding the cmc. The partial specific volumes were therefore equated with the mean values of apparent specific volume for each compound.

#### RESULTS

Representative light scattering graphs, showing the effect of electrolyte on the scattering from chlorcyclizine hydrochloride solutions, are shown in Fig. 1. The effective thermodynamic micellar charge,  $p$ , and the micellar aggregation number,  $N$ , were evaluated using equations proposed by Anacker & Westwell (1964).

$$p = [2fm_3B \pm (8m_3B)^2] A^{-1} (2-fA)^{-1} \quad \dots \quad (1)$$

$$N = p(p + 1)A (2m_3B + pA^2)^{-1} \quad \dots \quad (2)$$

$A$  and  $B$  are the intercept and slope respectively of plots of  $Km_2 / \Delta R_{90}$  against the molal concentration of micelles,  $m_2$ .  $\Delta R_{90}$  is the Rayleigh ratio of the solution in

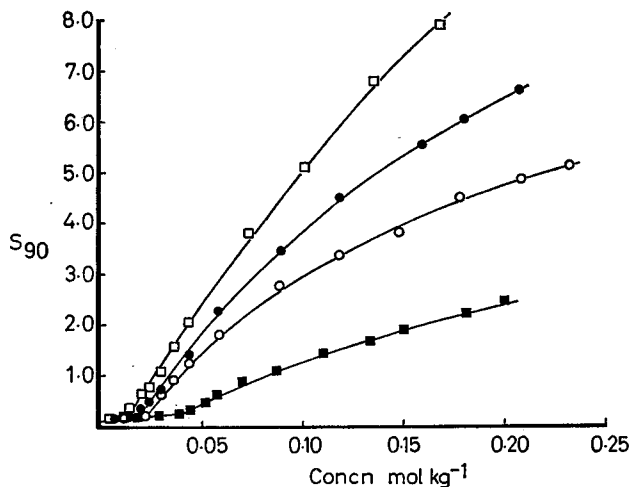


FIG. 1. Variation of the scattering ratio,  $S_{90}$ , with concentration for chlorcyclizine hydrochloride in ■ H<sub>2</sub>O; ○ 0.05 mol kg<sup>-1</sup> NaCl; ● 0.10 mol kg<sup>-1</sup> NaCl and □ 0.154 mol kg<sup>-1</sup> NaCl. Values for  $S_{90}$  in H<sub>2</sub>O are taken from Attwood (1972).

Table 1. Effect of electrolyte on the micellar properties of antihistamines at 303 K.

	NaCl concn (mol kg <sup>-1</sup> )	(dn/dm <sub>2</sub> ) <sub>m<sub>3</sub></sub> (kg mol <sup>-1</sup> )	cmc (mol kg <sup>-1</sup> )	p	N	α
Diphenhydramine	0.000*	0.0570	0.132	—	3	—
	0.050	—	0.112	—	4	—
	0.100	—	0.095	—	4	—
	0.154	0.0610	0.085	—	6	—
Bromodiphenhydramine	0.000*	0.0675	0.053	2.2	11	0.20
	0.050	—	0.033	4.0	16	0.25
	0.100	—	0.026	4.4	18	0.25
	0.154	0.083	0.020	6.7	29	0.23
Chlorcyclizine	0.000*	0.0710	0.040	1.7	9	0.19
	0.050	—	0.023	4.3	19	0.22
	0.100	—	0.018	4.3	21	0.21
	0.154	0.0722	0.012	4.4	24	0.18
Diphenylpyraline	0.000*	0.0645	0.086	2.0	9	0.22
	0.050	—	0.073	3.4	10	0.33
	0.100	—	0.060	3.5	12	0.29
	0.154	0.0652	0.044	3.5	14	0.25

\* Values in the absence of electrolyte are taken from Attwood (1972).

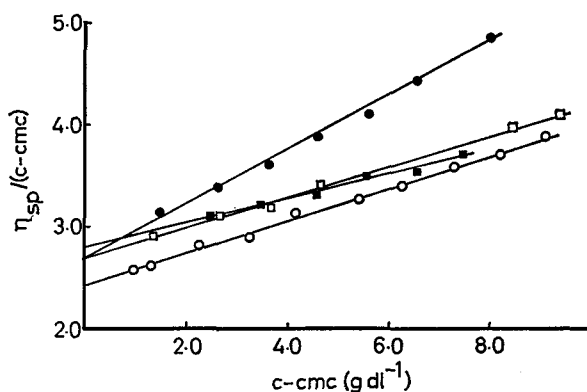


FIG. 2. Plot of reduced viscosity in 0.154 mol kg<sup>-1</sup> NaCl as a function of (c-cmc) for ○ bromodiphenhydramine hydrochloride, ● chlorcyclizine hydrochloride, □ diphenylpyraline hydrochloride and ■ diphenhydramine hydrochloride.

excess of that of a solution at the cmc;  $K = 2\pi^2 n_0^2 (dn/dm_2)_{m_3}^2 V^0/L\lambda^4$ ;  $n_0$  is the refractive index of the solvent,  $V^0$  is the volume of solution containing 1 kg of water,  $L$  is the Avogadro number;  $\lambda$  is the wavelength of the incident light,  $m_3$  is the molality of supporting electrolyte and  $f = (dn/dm_3)_{m_2}/(dn/dm_2)_{m_3}$ . Micellar properties are summarized in Table 1 and include critical micelle concentrations determined from the discontinuities in the light scattering plots.

The viscosity data are presented as graphs of  $\eta_{sp}/(c-cmc)$  vs (c-cmc), where  $c$  is the total weight concentration of the solution and  $\eta_{sp}$  is the specific viscosity (Fig. 2). Intrinsic viscosities,  $[\eta]$  are given in Table 2. These values have not been corrected for the electroviscous effect, which is generally considered to be negligible in solutions with electrolyte concentrations exceeding 0.1 mol kg<sup>-1</sup>.

Table 2. Viscosity data for antihistamines in 0.154 mol kg<sup>-1</sup> NaCl at 303K.

	$[\eta]$	$\bar{v}$ cm <sup>3</sup> g <sup>-1</sup>	$\delta$ g H <sub>2</sub> O g <sup>-1</sup> drug*	
Diphenhydramine	2.82	0.88	—	(—)
Bromodiphenhydramine	2.42	0.74	0.23	(0.25)
Chlorcyclizine	2.71	0.82	0.26	(0.58)
Diphenylpyraline	2.70	0.88	0.20	(0.32)

\* Values in parentheses are taken from Attwood & Udeala (1974).

## DISCUSSION

The increase in aggregation number and corresponding decrease in the cmc observed with addition of electrolyte is typical of the behaviour of ionic surfactants. The apparent lack of dependence of the degree of ionization,  $\alpha$ , as given by the ratio  $p/N$ , on the electrolyte concentration has been noted with other ionic micelles (Stigter & Mysels, 1955). According to equation 3, which is derived by the application of the mass-action law to the micellization process, plots of  $\log$  cmc vs  $\log$  counterion concentration,  $X^-$ , should be linear (Anacker, 1970).

$$\log \text{cmc} = -(1-\alpha) \log X^- + \Delta G_h^\circ / 2.303 RT + 1/N \log F (M^{+p}) \dots \dots (3)$$

$\Delta G_h^\circ$  is the hydrophobic contribution to the standard free energy of micellization (per mol of monomeric drug ion),  $M^{+p}$  is the mol fraction of micelles and  $F$  is a term involving the activity coefficients of all species present in solution. The cmc data for antihistamines are plotted in accordance with equation 3 in Fig. 3. Values of  $\alpha$  derived from the slopes of such plots (Table 3) are in agreement with values derived from light scattering. If the concentration of micelles at the cmc is assumed to be negligible, the intercept obtained on extrapolation to  $\log X^- = 0$  may be equated with  $\Delta G_h^\circ / 2.303 RT$ , thus enabling approximate  $\Delta G_h^\circ$  values to be calculated. Table 3 shows reasonable agreement between  $\Delta G_h^\circ$  values calculated by this method and those derived previously from a knowledge of the charge characteristics of the micelle.

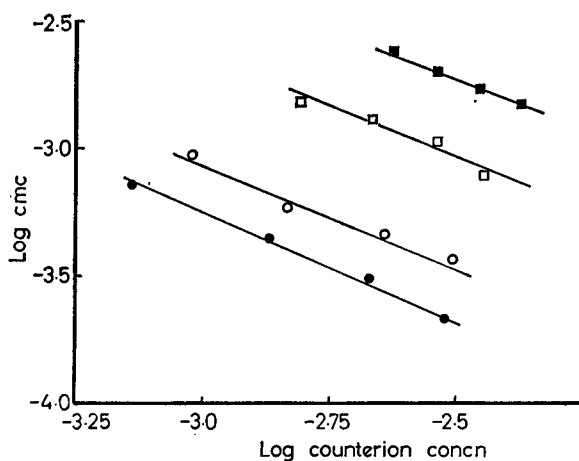


FIG. 3. Log cmc against log counterion concentration for  $\circ$  bromodiphenhydramine hydrochloride,  $\bullet$  chlorcyclizine hydrochloride  $\square$  diphenylpyraline hydrochloride and  $\blacksquare$  diphenylpyraline hydrochloride. Concentrations are expressed as mol fractions.

Table 3. Degree of ionization and free energy of micellization of antihistamines as calculated from equation 3.

	$\Delta G_h^*$ kJ mol <sup>-1</sup>	$\alpha$
Diphenhydramine	-26.6 (-30.1)	0.3
Bromodiphenhydramine	-31.4 (-31.9)	0.2
Chlorcyclizine	-33.3 (-34.2)	0.2
Diphenylpyraline	-28.8 (-30.5)	0.2

\* Values in parentheses are taken from Attwood & Udeala (1974).

With the exception of diphenhydramine hydrochloride, the intrinsic viscosities shown in Table 2 are lower than those previously determined in the absence of electrolyte (Attwood & Udeala, 1974). This suggests that the increase in micellar size on the addition of electrolyte was not accompanied by a corresponding increase in micellar asymmetry. A deviation of  $[\eta]$  from the theoretical value for spheres may be interpreted in terms of micellar hydration using equation 4.

$$[\eta] = 2.5 (\bar{V} + \delta V_1^\circ) \quad \dots \quad (4)$$

$\delta$  is the hydration expressed as g of H<sub>2</sub>O per g of drug,  $V_1^\circ$  is the specific volume of the solvent and  $\bar{v}$  is the partial specific volume of the micelles. These  $\delta$  values are compared with similar values determined in the absence of electrolyte, in Table 2. Calculations have not been made for diphenhydramine hydrochloride since the assumption of micellar sphericity is unlikely to be valid for such low aggregation numbers. The apparent decrease in  $\delta$  on the addition of electrolyte is a possible consequence of a decrease in the amount of water, hydrogen-bonded to the N and O atoms in the concentrated electrolyte solutions.

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