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Aggregation of antihistamines in aqueous solution: micellar properties of some diphenylmethane derivatives

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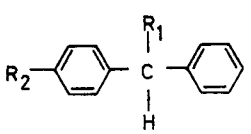
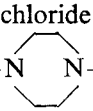
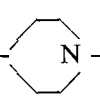
The micellar properties of the antihistamine drugs, diphenhydramine hydrochloride, bromodiphenhydramine hydrochloride, chlorcyclizine hydrochloride and diphenylpyraline hydrochloride, have been studied in aqueous solution. The zeta potentials of the micelles were calculated from their electrophoretic mobilities as determined by a dye-tracer technique. Estimates of the degree of ionization of the micelles using a combination of conductivity and electrophoresis data were in reasonable agreement with values previously determined by light scattering. The extent of micellar hydration has been calculated from viscosity data. The hydrophobic and electrical contributions to the free energy of micellization have been calculated and related to the chemical structure.

Many drugs have been shown to be surface-active and to form micelles in aqueous solution (Florence, 1968). The most extensive investigations of the colloidal behavior of the antihistamines have concerned the phenothiazine derivative, promethazine hydrochloride, the micellar properties of which have recently been reported (Florence & Parfitt 1970, 1971; Attwood, Florence & Gillan, 1974). In a preliminary communication (Attwood, 1972), it was established that the antihistamine drugs based on the diphenylmethane nucleus (I) also formed aggregates in solution.



(I)

This paper reports further investigations of the structure and charge characteristics of these compounds. The drugs investigated include diphenhydramine hydrochloride ($R_1 = OCH_2CH_2N(CH_3)_2 : R_2 = H$); bromodiphenhydramine hydrochloride ($R_1 = OCH_2CH_2N(CH_3)_2 : R_2 = Br$); chlorcyclizine hydrochloride ($R_1 =$  $: R_2 = Cl$) and diphenylpyraline hydrochloride ($R_1 =$  $: R_2 = H$).

MATERIALS AND METHODS

Materials. Chlorcyclizine hydrochloride B.P. and diphenhydramine hydrochloride B.P. were obtained from Burroughs Wellcome & Co., and Parke-Davis & Co., respectively. Bromodiphenhydramine hydrochloride was a gift from Parke-Davis

& Co. and diphenylpyraline hydrochloride a gift from Smith Kline & French Labs. Ltd. All drugs were used as received.

pK_a values have been determined for a series of proprietary antihistamines, including compounds investigated here (Marshall, 1955). Values ranged between 8 and 10 and consequently almost complete ionization may be assumed over the concentration range at which measurements have been made.

Electrophoretic mobility measurements. The electrophoretic mobilities of the micellar species were determined at 303K $\pm$ 0·5K by the dye-tracer method using an apparatus similar in design to that described by Hoyer, Mysels & Stigter (1954). The micelles were 'tagged' by shaking the solutions with the water-insoluble dye, Orange, O.T., for 3–4 days. The dye concentrations were determined spectrophotometrically at a wavelength of 498 nm.

Conductivity measurements. Measurements were made at 303K $\pm$ 0·01K using a Wayne Kerr Autobalance Universal Bridge Model B641.

Viscosity measurements. Measurements were made at 303 K $\pm$ 0·01K using a suspended-level dilution viscometer with a solvent flow time of approximately 200 s. The relative viscosities were referred to solutions at the critical micelle concentration (cmc).

Measurements of partial specific volume. The apparent specific volumes of the drug micelles were calculated from density measurements made using a Cahn Electrobalance Model R.G. at 303K $\pm$ 0·01K. 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

The conductivity data are presented as graphs of equivalent conductivity, Λ, as a function of $\sqrt{c}$, where c is the molar concentration (Fig. 1). The critical micelle

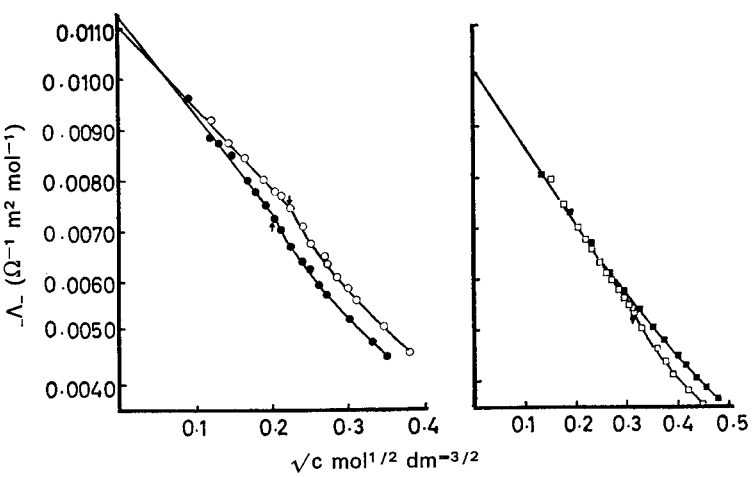


FIG. 1. Equivalent conductivity at 303K of aqueous solutions of –○– bromodiphenhydramine hydrochloride; –●– chlorcyclizine hydrochloride; –□– diphenylpyraline hydrochloride and –■– diphenhydramine hydrochloride. Arrows indicate critical micelle concentrations.

See Attwood, D. (1972) for the first part of this work.

concentrations determined from the inflection points of these graphs are in reasonable agreement with values previously determined by light scattering methods (see Table 1). Similar graphs were obtained by Farhadieh, Hall & Hammarlund (1967) for diphenhydramine hydrochloride and bromodiphenhydramine hydrochloride at 298K and a cmc of 0·052 mol kg^{-1} was obtained for the latter compound. This is close to the values determined at 303K and confirms previous indications that the cmc is not appreciably affected by temperature.

The degree of ionization, α, of the micelles was estimated from a combination of the conductivity and electrophoretic mobility measurements using an expression proposed by Stigter (1967):

$$\alpha = (\Lambda_m - I)/(F_u + Fu^0_c\, u/C_1\zeta) \quad .. \quad .. \quad .. \quad .. \quad (1)$$

F is the faraday and u^0_c is the average mobility of the counterions in the Gouy-Chapman double layer. The zeta potential, ζ, at the shear surface of a micelle with a hydrated radius, r_h (calculated from equation 6), was calculated from the experimentally determined electrophoretic mobilities, u (Fig. 2), using the numerical solu-

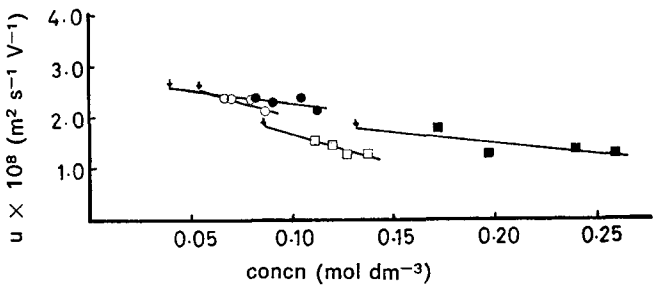


FIG. 2. Electrophoretic mobilities at 303K as a function of concentration. –○– bromodiphenhydramine hydrochloride; –●– chlorcyclizine hydrochloride; –□– diphenylpyraline hydrochloride and –■– diphenhydramine hydrochloride. Arrows indicate critical micelle concentrations.

tions of the Poisson-Boltzmann equation as tabulated by Loeb, Wiersema & Overbeek (1961). C_1 is the first coefficient in the virial expansion relating the electrophoretic mobility and the zeta potential (Wiersema, Loeb & Overbeek, 1966). The equivalent conductivity of the micellar species, Λ_m, was derived from plots of the differential equivalent conductivity $\Lambda_d = d\kappa/dc$ (where κ is the conductivity) as a function of concentration. The limiting value of Λ_d at high concentrations was related to Λ_m by the following expression (Stigter, 1954):

$$\Lambda_d = (\Lambda_m - A_u\Lambda_u)/(1 - A_u) \quad .. \quad .. \quad .. \quad .. \quad (2)$$

A_u represents the negative adsorption of monomeric drug, which for aqueous solutions is assumed to be of the order of 0·1 mol of un-associated drug per mol of micelles. Λ_u is the equivalent conductivity of the monomers at the cmc derived from Fig. 1. The term I of equation (1) is a correction factor for the influence of the liquid flow around the micelle in electrophoretic motion and is given by

$$I = (8\pi\rho_0 F/N)\int_a^\alpha v_r\, r^2 \sinh(e\psi/kT)dr \quad .. \quad .. \quad .. \quad (3)$$

The liquid velocity, v_r, at a distance r from the centre of the micelle was determined for a series of values of r from the potential-distance function, ψ_r, as interpolated from tables of Loeb & others (1961). T is the absolute temperature, ρ_0 is the concentration (number density) of counterions outside the double layer, k is the Boltzmann constant, e is the electronic charge and N is the micellar aggregation number. Values of α calculated from equation (1) are in good agreement with values previously obtained by light scattering (see Table 1).

Table 1. *Micellar properties of antihistamines in aqueous solution at 303K.*

	cmc (mol kg^{-1})					α		
	Conductivity	Lightscatt.*	N*	u$\times 10^8$ m^{2}s^{-1}V^{-1}	ζ mV	Light Scatt.*	Eq (1)	Eq (4)
Diphenhydramine	—	0·132	3	1·78	33·9	—	0·13	0·61
Bromodiphenhydramine	0·049	0·053	11	2·50	45·7	0·20	0·30	0·51
Chlorcyclizine	0·040	0·040	9	2·59	49·1	0·19	0·24	0·65
Diphenylpyraline	0·094	0·086	9	1·83	32·1	0·22	0·17	0·40

* Values from Attwood (1972).

An alternative method of estimating the degree of ionization involves a combination of the electrophoretic mobility and micellar size. The surface charge density, σ, was obtained from the relation between σ and ζ computed by Loeb & others (1961). The number of charges per micelle, Q, and consequently α were then derived from

$$\alpha = Q/N = 4\pi r_h^2 \sigma/Ne \quad .. \quad .. \quad .. \quad .. \quad .. \quad (4)$$

Values of α determined from equation (4) were higher than those from light scattering and from equation (1). A similar discrepancy has been reported by Stigter (1967) who placed a greater reliance on the conductance method of calculation at low onic strengths.

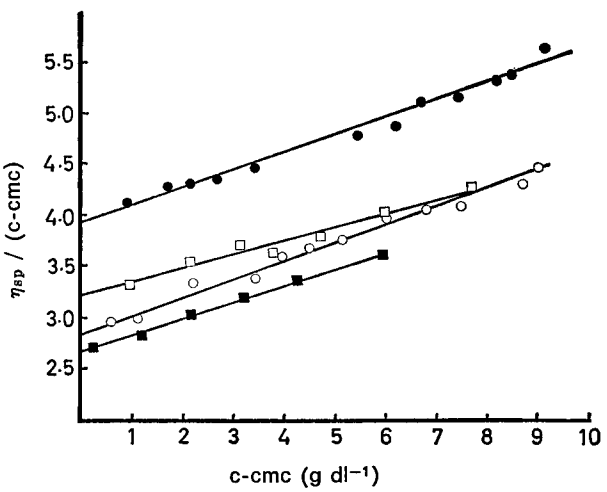


FIG. 3. Plot of reduced viscosity at 303K as a function of (c–cmc) for aqueous solutions of –○– bromodiphenhydramine hydrochloride; –●– chlorcyclizine hydrochloride; –□– diphenylpyraline hydrochloride and –■– diphenhydramine hydrochloride.

The viscosity data are presented as graphs of η_{sp}/c-cmc *vs* c-cmc (Fig. 3). Intrinsic viscosities, [η], derived by regression analysis, were corrected for the electroviscous effect using Booth's equation (Booth, 1950) which for spherical micelles of a univalent electrolyte may be written

$$\triangle[\eta] = 2{\cdot}5\pi\rho\mu b^2 (1 + b)^2 z\nu\zeta^2 \quad .. \quad .. \quad .. \quad .. \quad (5)$$

$\rho = \Sigma c_i \omega_i^{-1} / \Sigma c_i$ and $\mu = \Sigma c_i \omega_i / \Sigma c_i$ where c_i and ω_i are the concentration, and ionic mobility respectively of the ions at the cmc. b = xa where x is the reciprocal thickness of the double layer. z is a function of b evaluated by Booth.
$\nu = 4D^2 \epsilon^2_0 / \kappa\eta r^2_h$ where D and η are the dielectric constant and viscosity respectively of the solvent, ϵ_0 is the permittivity of a vacuum and κ refers to the conductivity at the cmc. The extent of hydration, δg of H_2O per g of drug, was determined from

$$[\eta] - \triangle[\eta] = 2{\cdot}5 (\bar{v} + \delta v_1^0) \quad .. \quad .. \quad .. \quad .. \quad (6)$$

where $\bar{v}$ is the partial specific volume of the micelle and v^0_1 is the specific volume of the solvent. Values of δ are given in Table 2. A hydration value was not calculated for diphenhydramine since the assumption of micellar sphericity which is implicit in the application of equation (6) is unlikely to be valid for a trimeric unit.

Table 2. *Viscosity data at 303K for antihistamines in aqueous solution.*

	[η]	$\triangle[\eta]$	$\bar{v}$ cm^{3}g^{-1}	δg H_2O g^{-1} drug
Diphenhydramine	2·66	0·30	0·86	—
Bromodiphenhydramine	2·85	0·38	0·74	0·25
Chlorcyclizine	3·93	0·47	0·81	0·58
Diphenylpyraline	3·23	0·28	0·86	0·32

DISCUSSION

Free energy of micellization. The standard free energy of micellization, $\triangle G_m$ (per mol of monomeric drug ion), was calculated using an expression derived from the application of the mass action law to the micellization process (Anacker, 1970).

$$\triangle G^0_m = -\frac{RT}{N} \ln \frac{F(M^{+Q})}{(D^+)^N (X^-)^{N-Q}} \quad .. \quad .. \quad .. \quad .. \quad (7)$$

F is a term involving the activity coefficients of the species present in solution. M^+, D^+ and X^- are the mol fractions of micelle, monomeric drug ions and free counterions respectively. Q is the number of unit charges per micelle, i.e. αN. By restricting the calculation to the region of the cmc, the term $1/N \ln F (M^{+Q})$ may be neglected and in the absence of added electrolyte equation (7) reduces to

$$\triangle G^0_m = (2 - Q/N) RT \ln (cmc) \quad .. \quad .. \quad .. \quad (8)$$

with cmc in mol fraction units.

Conceptually, the free energy of micellization may be divided into a hydrophobic

contribution, $\triangle G_h$, which is a measure of the extent of hydrophobic bonding, and an electrostatic contribution, $\triangle G_e$, which is the increase in electrical energy when $1/N$ mol of micelles of aggregation number N and the accompanying ionic atmosphere are formed from single ions. $\triangle G_e$ was calculated using an equation proposed by Verwey & Overbeek (1948)

$$\triangle G_e = \int_o^\sigma \psi_o' \, d\sigma' \quad .. \quad .. \quad .. \quad .. \quad (9)$$

ψ_0' and σ' are the surface potential and surface charge respectively at stages during the formation of a micelle with a final surface charge σ. Equation (9) was evaluated using the numerical computations of Loeb & others (1961). Free energy values calculated using equations (8) and (9) are given in Table 3. $\triangle G_h$ values were obtained from $\triangle G_h = \triangle G_m - \triangle G_e$.

Table 3. *Free energies of formation of micelles of antihistamines at 303K.*

	ΔG_m kJ mol^{-1}	ΔG_e kJ mol^{-1}	ΔG_h kJ mol^{-1}
Diphenhydramine	—28·49	1·63	—30·12
Bromodiphenhydramine	—30·68	1·24	—31·92
Chlorcyclizine	—32·64	1·55	—34·19
Diphenylpyraline	—29·53	0·92	—30·45

The insertion of a monomer into a micelle involves the transference of two phenyl rings from an aqueous to a non-polar environment. From the data of Kauzmann (1959), such a transfer should result in a free energy charge of —34 kJ mol^{-1}. This value is close to the experimental $\triangle G_h$ values of Table 3.

It is interesting to compare the free energies of micellization of diphenhydramine and bromodiphenhydramine, since these compounds differ by only a -Br group on one of the phenyl rings. The more negative $\triangle G_h$ of bromodiphenhydramine reflects the increase in hydrophobic bonding caused by this substituent. There is a similarity of structure of the hydrophilic chains of chlorcyclizine and diphenylpyraline. The main cause of the differences in the free energy of micellization of the latter compounds is attributable to the -Cl group of chlorcyclizine which significantly increases the hydrophobic bonding and hence the $\triangle G_h$ value.

Micellar structure. The calculated free energy of micellization of diphenhydramine suggests an almost complete removal of both phenyl rings from an aqueous environment. The most effective means of achieving this would be by a 'stacking' of the diphenhydramine molecules as in, for example, the phenothiazine derivatives (Florence & Parfitt, 1971). However, the hydrophobic regions of the diphenylmethane derivatives are non-planar and although a form of 'stacking' may be occurring with diphenhydramine, it is questionable whether 9 or 11 non-planar molecules could associate by this method. It is more probable that the micellization process for bromodiphenhydramine, chlorcyclizine and diphenylpyraline is similar to that of conventional ionic surfactants.

The viscosity data for these three compounds have been interpreted assuming that the departure from the theoretical value for spheres was due to hydration rather than

asymmetry. Apart from the solvent layer normally associated with ions in the monomeric state, the hydrophilic regions of the ions of these compounds contain oxygen and nitrogen atoms which readily form hydrogen bonds with the solvent. There is also a possibility that the relatively long hydrophilic chains will physically trap water molecules in a manner similar to that noted with the polyoxyethylene nonionic surfactants (Attwood, 1969). The calculated hydration values are not unreasonable in view of these considerations which suggests that, despite their very low aggregation numbers, the micelles of these three compounds do indeed assume the spherical or near spherical form typical of true ionic micelles. Further experimental evidence from, for example, nmr techniques is necessary to clarify the mode of packing in these micelles.

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