

Micellar properties and surface activity of some bolaform drugs in aqueous solution

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The micellar properties of a series of dicationic drugs with structures resembling those of the bolaform electrolytes have been examined using light scattering, surface tension and conductivity techniques. The compounds investigated included, demecarium bromide, ambenonium chloride, dequalinium acetate, distigmine bromide and chlorhexidine acetate. Demecarium and dequalinium formed micelles at critical concentrations of 9×10^{-3} and 4×10^{-3} mol kg⁻¹ respectively. No significant association of chlorhexidine acetate could be detected, contrary to previous reports.

Although the association characteristics and surface properties of a wide variety of drugs have been reported (Attwood 1979) all of these compounds were typical amphiphiles with well-defined hydrophobic and hydrophilic regions. We report here the physicochemical properties of a series of medicinal compounds with structures resembling those of the bolaform electrolytes, that is, they are symmetrical molecules with two charge centres separated at a relatively large distance. Of the dicationic compounds investigated here only chlorhexidine has previously been examined in any detail. Heard & Ashworth (1968) have reported evidence from a variety of techniques for the association of both the acetate and gluconate salts of this compound. Perrin & Witzke (1971) have determined the critical micelle concentration (c.m.c.) of chlorhexidine gluconate from measurements of optical rotary dispersion.

In the present investigation, aqueous solutions of the bolaform drugs have been examined by light scattering, surface tension and conductimetric techniques. Critical micelle concentrations and micellar properties are reported.

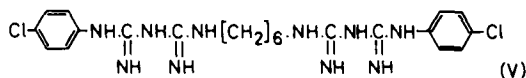
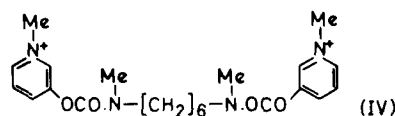
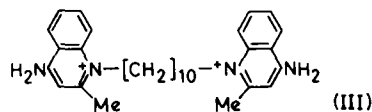
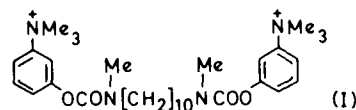
MATERIALS AND METHODS

Materials

The following drugs were used as received; demecarium bromide (I) (Astra Chemicals Ltd.); ambenonium chloride (II) (Winthrop Labs.); dequalinium acetate B.P. (III) (Glaxo Group Research Ltd.); distigmine bromide (IV) (Berk Pharmaceuticals Ltd.); chlorhexidine acetate B.P. (V) (ICI Ltd.). Melting point measurements, i.r.

and ¹H n.m.r. spectra indicated a satisfactory degree of purity of the drugs.

Water was distilled from alkaline permanganate in a glass apparatus and its surface tension checked against the literature value before use.



Light scattering measurements. Measurements were made at 303K with a Fica 42000 photogoniometer (ARL Ltd.). An incident wavelength of 546 nm was used for measurements on all compounds except demecarium bromide which fluoresced at this wavelength. No fluorescence was detected when solutions of this drug were excited with incident light at 436 nm and this wavelength was used for the light scattering measurements.

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Solutions were clarified by ultrafiltration through 0.1 μm Millipore filters until the ratio of light scattering at angles of 30° and 150° did not exceed 1.10. Refractive index increments determined using a differential refractometer were demecarium bromide 0.1271; ambenonium chloride, 0.1151; dequalinium acetate, 0.1410; distigmine bromide, 0.0996; chlorhexidine acetate, 0.1303 kg mol⁻¹.

Surface tension measurements. Measurements were made at 303K by the Wilhelmy plate method using a Cahn Electrobalance Model R.G. Solutions were aged until an equilibrium surface tension was attained.

Conductivity measurements. Measurements were made at 303 ± 0.01 K using a Wayne Kerr auto-balance universal bridge (Model B641).

RESULTS

The light scattering results are presented in Fig. 1 as graphs of the light scattering intensity at an angle of 90°, S₉₀, as a function of concentration, m.

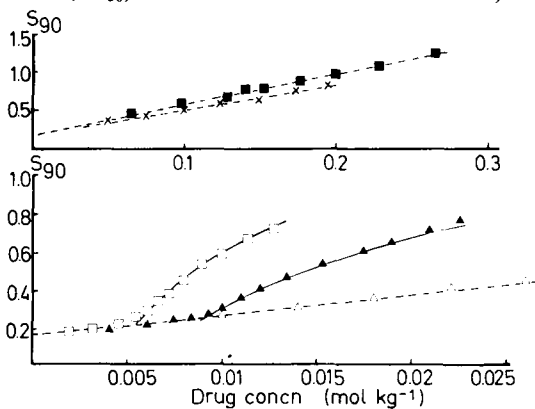


FIG. 1. Variation of the light scattering ratio S₉₀ with concentration for aqueous solutions of ▲, demecarium bromide; □, dequalinium acetate; ■, ambenonium chloride; ×, distigmine bromide and Δ, chlorhexidine acetate. (---) theoretical light scattering from unassociated monomers.

The curves for demecarium bromide and dequalinium acetate are similar in form to those noted for typical surfactants showing marked deviations from the theoretical scattering lines for unassociated monomers (calculated assuming thermodynamic ideality) at well-defined critical micelle concentrations. In contrast, the scattering data for distigmine bromide, ambenonium bromide and chlorhexidine acetate could be represented by the theoretical scattering plots for the respective monomers.

The micellar aggregation number, N, and charge, p, were calculated using a generalized light scattering theory recently proposed by Anacker & Jacobs (1974) which, unlike earlier theories, is applicable to multivalent surfactant and salt ions. In a solution containing no added electrolyte,

$$p = \frac{[\sigma\nu(\sigma + \nu)^3 \text{ cmcB}]^{\frac{1}{2}} + \sigma(\sigma + \nu)\text{cmcB}}{(\sigma + \nu - A)\nu A} \quad (1)$$

$$N = \frac{(p + p^2)Av}{\sigma(\sigma + \nu)\text{cmcB} + p\nu A^2} \quad \dots (2)$$

where A and B are the intercept and slope respectively of plots of Km₂/ΔR₉₀ against the molal concentration of micelles, m₂. ΔR₉₀ is the Rayleigh ratio of the solution in excess of that of a solution at the c.m.c.; σ and ν are the valency of the drug ion and counterion respectively; K = 2π²n₀²-(dn/dm₂)²V⁰/Lλ⁴; n₀ is the refractive index of the solvent; V⁰ is the volume of solution containing 1 kg of water; L is the Avogadro constant and λ is the wavelength of the incident light. The micellar properties calculated using eqn (1) and (2) are given in Table 1.

Table 1. Micellar properties of bolaform drugs in aqueous solution.

Compound	cmc (10 ³ mol kg ⁻¹)			N	p	α
	light scatt.	surf. tension	conduct.			
Demecarium bromide	0.88	0.82	1.04	10.5	5.2	0.49
Dequalinium acetate	0.55	0.41	0.33	15.9	8.0	0.50

The micellar nature of the association process for demecarium bromide and dequalinium acetate is further substantiated by the surface tension and conductivity results (see Figs 2 and 3). These techniques both gave inflections at similar concentrations to the c.m.c.s from light scattering (see Table 1). Surface tension and conductivity data for chlorhexidine acetate show clearly the lack of any significant association of this compound up to its solubility limit.

DISCUSSION

Several workers have discussed the aggregation characteristics of bolaform electrolytes in terms of the length of the -CH₂- chain between the terminal ionic groups. Brown et al (1949) noted a lack of association of diammonium salts with interionic chain lengths of less than 10 C atoms. Similarly

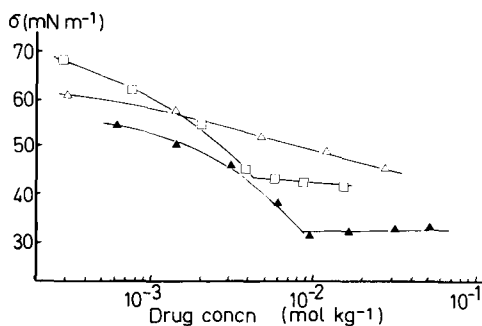


FIG. 2. Surface tension, σ (m N m^{-1}) as a function of log molal concentration for aqueous solutions of \blacktriangle , demecarium bromide; \square , dequalinium acetate and \triangle , chlorhexidine acetate.

Johnson & Fleming (1975) have concluded from determinations of apparent molal volume that hexamethonium (C_6) and decamethonium (C_{10}) bromides do not micellize in aqueous solution. Even compounds with 12C chains have been reported to form only loose aggregates rather than true micelles (Yiv et al 1976). Although demecarium and dequalinium have chains comprising only

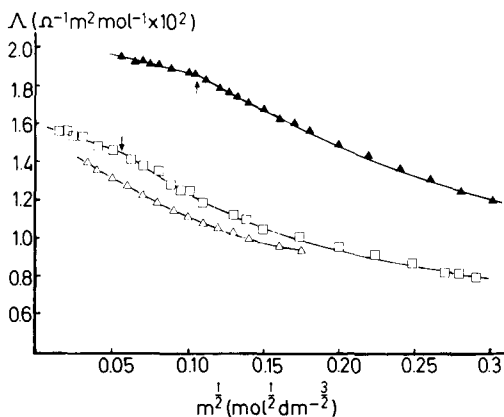


FIG. 3. Molar conductivity, Λ , ($\Omega^{-1} \text{ m}^2 \text{ mol}^{-1} \times 10^2$) of aqueous solutions of \blacktriangle , demecarium bromide; \square , dequalinium acetate and \triangle , chlorhexidine acetate.

10 $-\text{CH}_2-$ groups, which from the above considerations would seem insufficient to cause aggregation, both of these compounds have additional aromatic ring systems which increase the hydrophobicity sufficiently for association to occur. The remaining compounds have much shorter $-\text{CH}_2-$ chains and their failure to associate is not unexpected.

Our conclusion that chlorhexidine acetate does not form micelles is in conflict with the work of Heard & Ashworth (1968) who report a c.m.c. of 0.01 mol dm^{-3} . Although the apparent inflection points in the surface tension and conductivity data of these workers are unconvincing, these authors do demonstrate that this compound is capable of solubilizing water-insoluble dye. It is, however, well known that addition of dye can induce aggregation (Reeves 1975) and this method of c.m.c. determination may consequently lead to erroneous conclusions.

According to the data presented here, a proprietary preparation containing demecarium, Tosmilen eye drops (Sinclair), will contain a high proportion of the active ingredient in micellar form.

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