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The surface activity of some antihistamines at the air-solution interface

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The surface activity of some antihistamines at the air-solution interface has been examined. Change of the counterion associated with the drug from chloride to maleate or chloro-theophyllinate considerably decreased the critical micelle concentration and increased the surface activity. The effect on surface activity of changes in the nature of the hydrophobic and hydrophilic groups have also been evaluated.

The surface activity at the air-solution interface of a wide variety of drugs has been reported (see reviews by Florence, 1968; Felmeister, 1972). Apart from measurements on the phenothiazines (Seeman & Bialy, 1963; Patel & Zografi 1966; Zografi & Zarenda, 1966; Zografi & Munshi, 1970; Villalonga, Fried & Izquierdo, 1961), several of which have antihistamine properties, very little has been reported on the surface activity of the antihistamines. In a study of compounds known to prevent liver necrosis in rats, Bangham, Rees & Shotlander (1962) measured the surface tensions of the antihistamines, diphenhydramine hydrochloride and mepyramine maleate and correlated the surface activity and protective ability of these compounds.

In previous papers (Attwood 1972; Attwood & Udeala 1974, 1975a,b,) we have reported the properties of aggregates of antihistamines in aqueous solution. The nature of the counterion associated with the drug has been shown to influence the mode of aggregation, as determined by light scattering. The hydrochlorides of a series of antihistamines with a diphenylmethane hydrophobic group behaved as typical colloidal electrolytes with well-defined critical micelle concentrations (cmc). In contrast, light scattering studies on the maleates of other antihistamines, (arbitrarily characterized by their possession of a pyridine ring), indicated an apparently non-micellar mode of aggregation with no detectable cmc. Change of the counterion of such compounds to chloride induced typical micellar behaviour.

In the present investigation we have studied the surface activity of these antihistamines at the air-solution interface. Particular attention has been paid to the effect of a change of counterion on the surface properties and the influence of the chemical structure of the hydrophobic and hydrophilic groups of the drug molecules.

MATERIALS AND METHODS

Materials. The chemical structure of the antihistamines is given in Tables 1 and 2. The following compounds were used: tripelennamine hydrochloride (Ciba), thenyldiamine hydrochloride (Winthrop), pheniramine maleate (Hoechst) brompheniramine maleate (A. H. Robins), chlorcyclizine and cyclizine hydrochloride (Burroughs Wellcome), diphenhydramine and bromodiphenhydramine hydrochloride. (Parke-Davis), and dimenhydrinate (Searle). Tripelennamine maleate was a sample prepared as described previously (Attwood & Udeala, 1975b).

For compounds such as the antihistamines in which the non-ionized form has a very low water solubility, Zografi & Munshi (1970) have stressed the importance of comparing surface activities at pH values where all the drugs are in the ionized form. Control

Table 1. *Surface activity and cmc of antihistamines at 303K.*

Compound	R_1	R_2	Salt	Cmc mol kg^{-1}	Concn (mol kg^{-1} × 10^3) for π = 10mN m^{-1}	Area per molecule nm^2 × 10^2
Diphenhydramine	$-O CH_2CH_2NMe_2$	H	hydrochloride	0·122	3·0	84
Dimenhydrinate	"	H	chlorotheophyllinate	0·013	1·3	—
Bromodiphenhydramine	"	Br	hydrochloride	0·041	2·3	82
Cyclizine	$-NC_4H_8NMe$	H	"	—	0·14	96
Chlorcyclizine	"	Cl	"	0·039	1·0	61

of pH by electrolyte addition is clearly undesirable for these compounds, in view of the effect of counterions on the properties of the aggregates. Consequently measurements were made in electrolyte-free water. Marshall (1955) has reported pka values of between 8 and 10 for a series of antihistamines, including compounds investigated here. pH measurements on the solutions indicated that almost complete ionization could be assumed over the concentration range of the measurements, with the possible exception of dimenhydrinate, a saturated solution of which had a pH of approximately 7.

Water was distilled twice from alkaline permanganate in a glass apparatus and its surface tension checked against the literature value before use. Sodium chloride was of Analar grade.

Surface tension measurements. Measurements were made at 303K by the Wilhelmy plate method using a Cahn Electobalance Model R.G. Solutions were aged for 6–24 h until an equilibrium surface tension was attained.

RESULTS

Plots of surface tension, σ, as a function of the log molal concentration, m, are presented in Figs 1 and 2. The cmcs determined for diphenhydramine, bromodiphenhydramine and chlorcyclizine (Table 1) are in good agreement with those previously obtained from light scattering and conductivity methods. Cyclizine and dimenhydrinate had not previously been examined. The minimum in the surface tension curve of dimenhydrinate is characteristic of those normally noted at the cmc for surfactants containing surface active impurities. It is not clear whether this minimum is indicative of aggregation or merely a consequence of experimental error. Measurements in this concentration region were difficult due to the proximity of the solubility limit. Attempts were made to detect a cmc for dimenhydrinate by the dye solubilization technique. Solutions were shaken with an excess of the water-insoluble dye, Orange O.T., for 3 days. After centrifugation, the extinction of the supernatant solution was measured at the absorbancy peak of the Orange O.T. (498 nm). No

Table 2. *Surface activity and cmc of antihistamines at 303K.*

Compound	Structure	R_1	R_2	Salt	Solvent	Cmc mol kg^{-1}	Concn (mol kg^{-1} × 10^3) for π=10mN m^{-1}	area per molecule nm^2 × 10^2
Tripelennamine	I	C_6H_5	$-CH_2CH_2N Me_2$	HCl	H_2O	~0·20	10	~55
"	"	"	"	"	NaCl	~0·12	6·8	~55
"	"	"	"	maleate	H_2O	0·025	2·5	54
Thenyldiamine	I	C_4H_3S	"	HCl	"	0·18	20	~44
"	"	"	"	"	NaCl	0·10	7·7	~46
Pheniramine	II	$CH_2CH_2H(CH_3)_2$	H	maleate	H_2O	0·115	35	65
Brompheniramine	II	"	Br	"	"	0·038	10	57

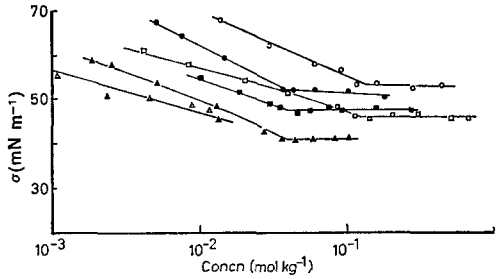

FIG. 1. Surface tension, σ, as a function of log molal concentration, m, showing effect of changes in nature of hydrophobic group for -○- pheniramine and -●- brompheniramine maleates; -□- diphenhydramine and -■- bromodiphenhydramine hydrochlorides; -△- cyclizine and -▲- chlorcyclizine hydrochlorides in H_2O at 303 K.

significant uptake of dye was detectable. Due to low solubility of this compound, only limited solubilization would, however, be possible if micelles were present and the results were regarded as inconclusive.

The surface tension plots for pheniramine, brompheniramine and tripelennamine maleate show clearly-defined inflections. This is in marked contrast to the light scattering behaviour of these compounds which indicated a continuous increase in aggregate size with increasing concentration, with no cmc. Appreciable minima, indicative of impurities, were observed in the surface tension curves of tripelennamine hydrochloride and thenyldiamine hydrochloride, both in water and salt solution. The cmc values quoted can only be regarded as rough approximations, although the values determined in salt solution are in reasonable agreement with those determined by light scattering. The curves have been included merely to illustrate the typical micellar behaviour of these compounds in electrolyte-free solutions, a fact which could not hitherto be established by light scattering methods, due to the low intensity of the scattered light.

Areas per molecule were calculated using the Gibb's adsorption equation

$$\Gamma = -\frac{1}{(x\ 2{\cdot}303\ RT)}\left[\frac{d\sigma}{d\ \log c}\right] \quad .. \quad .. \quad .. \quad (1)$$

x has a numerical value varying from 1, for ionic surfactants in dilute electrolyte-free

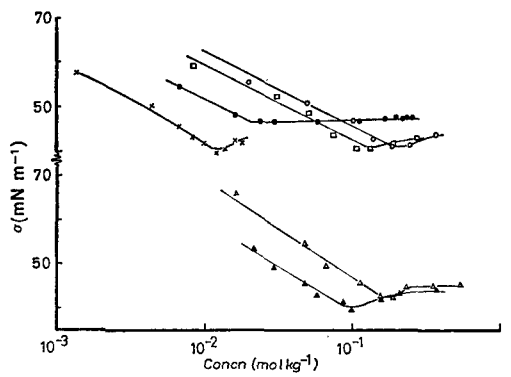

FIG. 2. Surface tension, σ, as a function of log molal concentration, m, showing effect of counterion for -○- tripelennamine hydrochloride in H_2O, -●- tripelennamine maleate in H_2O and -□- tripelennamine hydrochloride in 0·154 mol kg^{-1} NaCl; thenyldiamine hydrochloride in -△- H_2O and -▲- 0·154 mol kg^{-1} NaCl; -×- diphenhydramine 8-chlorotheophyllinate (dimenhydrinate) in H_2O. (see Fig. 1 for diphenhydramine hydrochloride in H_2O).

solution, to 2 for ionic surfactants in concentrated electrolyte-free solution (Pethica, 1954). In view of the uncertainty in the value of x, calculations were made using $x = 1$. It is realized that these values (see Table 1 and 2) may underestimate the true area per molecule.

DISCUSSION

The effect on the surface activity, of modifications of the chemical structure of the hydrophobic and hydrophilic groups and of altering the counterion, may be assessed by evaluating the relative surface activity of the drugs. In Tables 1 and 2 the relative surface activities have been compared in terms of the bulk concentrations of each drug required to produce a given surface pressure, π, (surface tension of solvent—surface tension of solution), as suggested by Zografi & Munshi (1970). Since the surface tension plots were similar in curvature for all drugs, the choice of a value of π was arbitrary and a value of 10 mN m^{-1} was used for the comparison. A similar comparison at a π value of 15 mN m^{-1} revealed essentially the same conclusions as those outlined below.

The significant hydrophobic effect of adding a -Br substituent to one of the phenyl rings of diphenydramine is apparent from the decrease in cmc and increased surface activity of bromodiphenydramine. A similar effect may be noted from a comparison of pheniramine and brompheniramine. The results for cyclizine are in apparent confliction, since this compound has a greater surface activity than chlorcyclizine. The reasons for this are not apparent.

The effect of the nature of the counterion on the surface activity may be illustrated by a comparison of diphenhydramine hydrochloride and dimenhydrinate. Replacement of the inorganic chloride associated with diphenhydramine by the very much bulkier organic chloro-theophyllinate ion, as in dimenhydrinate, produced a significant increase in hydrophobicity. This is evidenced by an apparent ten-fold decrease in the cmc and a much increased surface activity. A comparison of tripelennamine hydrochloride and tripelennamine maleate reveals a similar effect. Several workers have reported a greater depression of the cmc by organic counterions than by inorganic ions. For example, the replacement of the Na^+ counterion of the anionic surfactant, sodium dodecylsulphate, with a tetramethylammonium ion leads to an increase in micellar size (Mysels & Princen, 1959) and a decrease in the cmc (Goddard, Harva & Jones, 1953; Mukerjee, Mysels & Kapauan, 1967). Such effects have been explained in terms of the hydrophobic bonding between the micelle surface and the hydrocarbon exterior of the counterion. The intensity of the light scattering from tripelennamine maleate has been shown to be greater than that from tripelennamine hydrochloride and this is in agreement with the lower cmc determined for this compound. It is interesting to note that Zografi & Zarenda (1966) observed a similar increase in surface activity of some phenothiazine derivatives in the presence of phthalate, citrate and succinate ions.

An increase in the concentration of the counterion, rather than a change in its nature, produced a very much smaller effect on the surface activity and the cmc of tripelennamine and thenyldiamine hydrochloride. A lowering of the cmc and a slight increase in surface activity are, of course, well-established consequences of electrolyte addition to ionic surfactants.

A comparison of chlorcyclizine hydrochloride and bromodiphenhydramine hydrochloride illustrates the effect of changing the nature of the hydrophilic group, since the

-Cl and -Br substituents have similar hydrophobic effects. The greater surface activity and lower cmc of chlorcyclizine may possibly be a consequence of the extra number of carbon atoms in the side chain, although the situation is complicated by the two dissociable groups of the piperazine ring which make direct comparison difficult. A similar effect was noted by Zografi & Munshi (1970) in a comparison of prochloperazine, the side chain of which also contains a piperazine ring, and chlorpromazine, which has a propylamino side chain.

The well-defined cmc's observed for the antihistamines with maleate counterions are of interest, since these compounds previously gave no detectable inflections in light scattering or conductivity graphs. The situation is analogous to that noted for several non-ionic detergents. Light scattering studies (Attwood, 1968) on aqueous solutions of heptaoxyethylene glycol monohexadecyl ether (C_{16} H_7) have shown a pronounced concentration dependence of micellar size at low concentrations, with scattering curves of very similar appearance to those obtained for the antihistamine maleates studied here. Surface tension graphs for C_{16} H_7 (Elworthy & Macfarlane, 1962) similarly showed an abrupt change of slope at a clearly-defined cmc which was much lower than that estimated by extrapolation of the light scattering data. That such discrepancies between these techniques should occur is not unexpected in view of the different properties of the solution which influence each method. Thus, the surface tension of a solution is determined primarily by the monomer concentration, the conductivity is mainly dependent on the equivalent concentrations of both monomers and micelles and the intensity of light scattering is predominantly influenced by the size distribution of the micellar species. The failure to detect the cmc of these compounds by light scattering or conductivity methods is simply a consequence of the extreme polydispersity of micelle size.

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