

some commercial samples of quaternary ammonium bromides containing up to seven components (Barry, Morrison & Russell, 1970) were measured by light scattering. Table 1 shows good agreement between theoretical and experimental values of M.

Table 1.

| Commercial surfactant               | Temperature<br>°C | M from light<br>scattering<br>data $\times 10^{-4}$ | M from eqn<br>(1) $\times 10^{-4}$ |
|-------------------------------------|-------------------|---|------------------------------------|
| Cetrimide B.P.                      | 25                | 2.53  | 2.68                               |
| Dodecyltrimethylammonium bromide    | 25                | 2.09  | 2.15                               |
| Tetradecyltrimethylammonium bromide | 25                | 2.73  | 2.60                               |
| Hexadecyltrimethylammonium bromide  | 30                | 3.33  | 3.62                               |

The temperature dependence of the cmc of these mixtures was determined and an estimate of the effect of temperature upon the degree of counterion binding to the micelle was deduced. These values were used to calculate the thermodynamic parameters  $\Delta G$ ,  $\Delta H$ ,  $\Delta S$ , and  $\Delta C_p$  at different temperatures from equations based on the phase separation and mass action models of micellization. Values obtained from the former model were more negative since this model does not consider the extent of counterion binding to the micelle. Trends in all parameters were explained with regard to the structural changes in water. Results showed that the thermodynamic parameters of micellization of mixtures of surfactants of known composition yield as valuable information as those of single surfactants which are often difficult to prepare pure.

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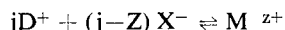
**Monomer concentrations in micellar drug systems**

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Some drugs in the local anaesthetic, tranquillizer and antibiotic classes are surface-active and may exert their action by interaction with membranes. Many of these surface-active drugs form micelles (Florence, 1968) and if the active species is the monomer, it is important that the concentration of monomer in the micellar system is known. Monomer concentrations can be obtained by interpretation of concentration dependent shifts of nuclear magnetic resonance (nmr) spectra (Corkill & others, 1969). The method is relatively simple and requires no assumptions about micellar charge or size, but the method requires independent means of verification.

The Law of Mass Action was applied to four systems containing phenothiazines in an attempt to confirm nmr data obtained previously (Florence & Parfitt, to be published). Application of the Law to the micellization process,



where the phenothiazine micelle consists of  $j$  monomers ( $D^+$ ) with  $(j-Z)$  firmly bound anions necessitates a knowledge of  $j$  and  $Z$ . Aggregation numbers for chlorpromazine, promazine, promethazine and thioridazine hydrochlorides in aqueous solution have been obtained by light-scattering. These are in the range 8 to 11. The number of unit charges per micelle determined by dye-tracer electrophoresis and also by conductivity techniques are high (6 to 8) indicating that few anions are tightly bound to the micelle surfaces. Using this experimental information in the mass-action calculations of monomer concentration, good agreement was obtained with the values derived from nmr, thus substantiating the validity of the latter method and the findings i.e. that at any given phenothiazine concentration above the cmc the amount of monomers in the system can vary by a factor of 5 in the series studied, being lowest for thioridazine and highest for promethazine. In all systems studied the concentration of monomers does not change appreciably above the cmc.

Determinations of the rate of dialysis of chlorpromazine across Visking membranes qualitatively agree with these observations in that the rate of transport decreases as the drug concentration is increased above the cmc. This phenomenon may have applications in sustained release technology.

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**The use of methylene chloride and chloroform for the extraction of tertiary alkaloids from *Strychnos* species**

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When strychnine is extracted with chloroform a crystalline quaternary salt may separate out (Von Klemperer & Warren, 1955; Caws & Foster, 1956). Chloroform itself does not react with strychnine and it has been thought that methylene chloride, which is present as an impurity, is responsible (Caws & Foster, 1957). Strychnine refluxed with methylene chloride for 10 h gives the chloromethochloride which is not identical with the quaternary salt formed when chloroform is used. This salt is strychnine chloromethobromide formed from chlorobromethane another impurity in chloroform (Caws & Foster, 1957).

Chloroform and methylene chloride are both useful solvents for strychnine and related alkaloids which tend to be relatively insoluble in many common organic solvents. During the screening of *strychnos* material it was noted that a few alkaloid-rich extracts gave needle crystals which proved to be quaternary salts formed from strychnine-type alkaloids and methylene chloride. Although the indications from the literature (Caws & Foster, 1957) are that this is a slow reaction (see above) the present work shows that strychnine and brucine solutions in methylene chloride can form heavy crops of quaternary salt crystals within 2 h at laboratory temperature. Each of these salts gives two major spots on t.l.c. In order to study the behaviour of these compounds more closely the following quaternary salts of strychnine and brucine were prepared:—(a) chloromethochloride, (b) chloromethobromide, (c) bromomethochloride, (d) bromomethobromide.

T.l.c. of the mother liquors of the quaternary salts formed on allowing strychnine to stand in chloroform reveals the presence of three other major alkaloidal constituents. Two of these have been characterized as strychnine *N*-oxide and pseudostrychnine. Although this may cast doubt on whether these compounds occur naturally, control experiments have indicated that during normal extraction procedures only very small amounts of these compounds are formed.

Pseudostrychnine, pseudobrucine, icajine, novacine and vomicine do not appear to form quaternary salts with chloroform or methylene chloride.

It is clear from the work discussed above and from preliminary experiments with other alkaloids that the use of chloroform and methylene chloride may lead to considerable changes in the nature of alkaloids and their extracts. Hence when these solvents are used for alkaloid extraction care should be taken to determine whether or not the alkaloids remain chemically unchanged.

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