J. Pharm. Pharmacol. 1985, 37: 854–862
Received February 26, 1985

Photon correlation spectroscopy of surface active cationic drugs

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Photon correlation spectroscopy (PCS) has been used to examine the aggregation in aqueous NaCl solution of a series of antidepressant and antihistamine drugs (hydrochlorides of imipramine, clomipramine, amitriptyline, butriptyline, protriptyline, doxepin, dothiepin, iprindole, diphenhydramine, bromodiphenhydramine, orphenadrine) propranolol hydrochloride and propantheline bromide. Critical micelle concentrations were measured by surface tension and PCS. Micellar sizes were investigated as functions of drug structure and drug and NaCl concentration. Generally, antidepressants formed the largest micelles. We propose that the antidepressants aggregate in a similar fashion to the phenothiazines by stacking with size increasing by addition of single monomers to stacks and by addition of more stacks to the aggregate.

A range of molecular structures occurs in the numerous classes of drugs exhibiting a surface active behaviour (e.g. Attwood 1979, 1983a; Attwood & Florence 1983). The tricyclic structured phenothiazines and antidepressants exhibit a micellar pattern of association (Florence & Parfitt 1971; Attwood & Gibson 1978) and drugs based on a diphenylmethane nucleus are also thought to associate by a micellar process (Attwood 1979). The drug critical micelle concentrations (CMCs) and micellar aggregation numbers were often obtained by the traditional method of light scattering. Developments in the area of photon correlation spectroscopy (PCS) have enabled the laser to be used to measure the size of micelles as small as the aggregates produced by surface active drug molecules. Phenothiazine micellar sizes have been related to molecular structure, counterion concentration and species (Atherton & Barry 1985). Here we report PCS measurements of micellar size and CMCs for the tricyclic antidepressants, diphenylmethane antihistamines, the β-adrenoceptor blocking agent, propranolol hydrochloride, and the antiacetylcholine drug propantheline bromide. Some preliminary results were presented by Atherton & Barry (1983).

MATERIALS AND METHODS

Materials

The hydrochloride salts of imipramine (APS), clomipramine (Ciba Pharmaceuticals), amitriptyline (Berk Pharmaceuticals), butriptyline (Ayerst Laboratories), protriptyline (MSD), doxepin (Pfizer), dothiepin (Boots Co. Ltd), iprindole (Wyeth Laboratories), diphenhydramine and bromodiphenhydramine (Parke Davis), orphenadrine (Gist Brocades Ltd), propranolol (ICI) and propantheline bromide (Searle) were of British Pharmacopoeial standard and were used as received.

Water, twice distilled from permanganate in an all-glass still, was of specific conductivity not greater than $2{\cdot}0 \times 10^{-6}$ ohm^{-1} cm^{-1}, surface tension was 72 $\pm$ 0·2 mNm^{-2}. Sodium chloride was of Analar grade.

Drug purity

The purity of each drug was assessed by differential scanning calorimetry (Du Pont 1091 Thermal Analyser, applications program PN 990481).

Surface tension

The Wilhelmy method with roughened platinum plate used an electrobalance (CI Electronics Ltd) connected to a pen chart recorder (Bryans 27000) at 25 $\pm$ 0·1 °C (double jacketed glass vessel) to provide steady state readings; the entire apparatus was enclosed in a perspex screen. Care was taken to minimize light exposure during measurements as many drug solutions photodegrade.

Photon correlation spectroscopy

A 2W Spectra Physics argon ion laser operating at 488 nm with a power of 50–200 mW was used in conjunction with a Malvern K7025, 128 channel correlator. The time decay of the autocorrelation function was analysed to estimate D, the micellar diffusion coefficient, by a linear least squares fit and by the method of cumulants (Koppel 1972), which also derived a value for polydispersity, Q. Values of

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Q less than 0·1 are generally taken as indicative of monodisperse solutions (Brown et al 1975). Both methods gave identical values for D within experimental error (1–5%), as the drug micelles appeared essentially monodisperse. We report the results from the method of cumulants.

Filtered (0·1 μm membrane filters, Sartorius) drug solutions were thermostatted to 25 ± 0·1 °C and measured at an angle of 90°. CMCs were determined using the method of Roe & Barry (1983) in which drug solutions increasing in 1 mM concentrations around an expected CMC were measured for 1000s, photon count approximately 4×10^5 Hz and sample time 1 μs. The CMC was approximated as the mean value between the lowest concentration for some correlation and the highest concentration for no correlation.

For size determinations, drug micellar solutions were measured at sample times of 1 or 2 μs and experimental duration 100–200 s, providing sufficient data for accurate, reproducible correlation. D was determined ten times for each solution. The mean micellar apparent hydrodynamic radius, $\bar{R}_h$, is related to D by the Stokes Einstein equation for spherical particles:

$$\bar{R}_h = kT/6\pi\eta D \qquad (1)$$

k is Boltzmann's constant, T is absolute temperature and η is solvent viscosity.

Refractive indices were measured with an Abbe 60 refractometer at 25 ± 0·1 °C and the solvent viscosities were 0·905 cp and 0·916 cp for 0·154 and 0·3 M NaCl solutions, respectively (Weast 1978).

RESULTS

The tricyclic antidepressants

Ring substitution in the molecular structure of the antidepressants (Table 1) markedly affected the micellar properties. CMC values measured in 0·154 M NaCl using surface tension and photon correlation spectroscopy (PCS) are shown in Table 1. Minima were obvious in all the surface tension plots, indicative of surface active impurities. Although the measured drug purities were high at approximately 99%, only traces of impurity are necessary to change markedly the surface tension profile and the resulting CMC. The CMC values were rough approximations taken as the lowest point in the dip and examples of the plots are shown in Fig. 1. The values obtained by PCS and surface tension

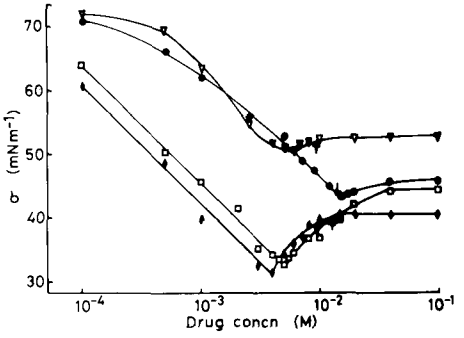
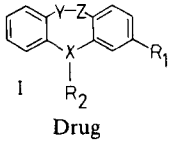


FIG. 1. Surface tension, σ, as a function of log molar concentration for —▽— dothiepin hydrochloride, —●— doxepin hydrochloride, —□— protriptyline hydrochloride, —◆— iprindole hydrochloride in 0·154 M NaCl. Arrows indicate CMC measurements by photon correlation spectroscopy.

Table 1. The critical micelle concentration of the antidepressant drugs at 25 °C in 0·154 M NaCl measured by photon correlation spectroscopy (PCS) and surface tension (ST).



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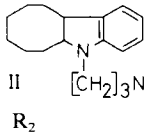


II

Drug	Structure	X	Y-Z	R_1	R_2	Critical micelle concentration (mM) PCS	ST	Literature[a]
Imipramine HCl	(I)	N	CH_2–CH_2	H	$(CH_2)_3N(CH_3)_2$	16·5	10	17·4, 22·1
Clomipramine HCl	(I)	N	CH_2–CH_2	Cl	$(CH_2)_3N(CH_3)_2$	6·5	3	4·27, 6·30
Amitriptyline HCl	(I)	C	CH_2–CH_2	H	$=CH(CH_2)_2N(CH_3)_2$	13·5	6	12·7, 17·5
Butriptyline HCl	(I)	C	CH_2–CH_2	H	$CH_2CH(CH_3)CH_2N(CH_3)_2$	10·5	7	—
Protriptyline HCl	(I)	C	CH=CH	H	$(CH_2)_3NHCH_3$	12·5	5	12·8, 13·3
Doxepin HCl	(I)	C	O–CH_2	H	$=CH(CH_2)_2N(CH_3)_2$	13·5	15	15·8, 25·3
Dothiepin HCl	(I)	C	S–CH_2	H	$=CH(CH_2)_2N(CH_3)_2$	9·5	6	—
Iprindole HCl	(II)	—	—	—	—	9·5	4	—

[a] Measurements at 20 °C, Thoma & Albert (1979).

were simlar to results published by Thoma & Albert (1979). Differences between the CMC values measured by PCS and surface tension were probably because of the presence of impurities which can noticeably lower surface tension and the CMC, and because the techniques measure different underlying phenomena.

Plots of the micellar apparent hydrodynamic radii, $\bar{R}_h$, as a function of drug concentration in 0·154 M NaCl are shown in Fig. 2a, b. The $\bar{R}_h$ values were only apparent, as the measured micellar diffusion coefficients, D, from which $\bar{R}_h$ values were calculated, can be affected by contributions from particle dissymmetry, hydration and interactions. Thus, the $\bar{R}_h$ value is representative of a roughly spherical particle that would diffuse in solution at the same rate as the measured diffusion coefficient. Trends shown by the $\bar{R}_h$ values for each drug with increasing drug concentration are complicated by the effects of repulsive and attractive forces upon D. Concentration dependence of D above the CMC is generally the result of the interplay of two effects; intermicellar interactions and change of micellar size. Measurement of D at drug concentrations very close to a CMC where these effects are minimal was not possible due to difficulties in preparing dust-free solutions at low drug concentrations, low number density of micelles and micellar size below accurate detection limits. The repulsive forces caused by electrostatic interactions between the poorly screened, charged micelles appear to predominate in 0·154 M NaCl solution resulting in an apparent decrease in micellar size with increasing drug concentration. Iprindole proved an exception, exhibiting an increase in $\bar{R}_h$ values with increasing drug concentration (Fig. 2b). Increasing electrolyte concentration shields micellar charge, reducing repulsive interactions and producing larger micelles. The bigger micellar sizes in 0·3 M NaCl are shown in Fig. 3a, b as a function of drug concentration. The growth in $\bar{R}_h$ with raised drug concentration is probably indicative of a greater micellar number and size as well as van der Waals' interactions. All drug solutions in 0·154 and 0·3 M NaCl appeared to be

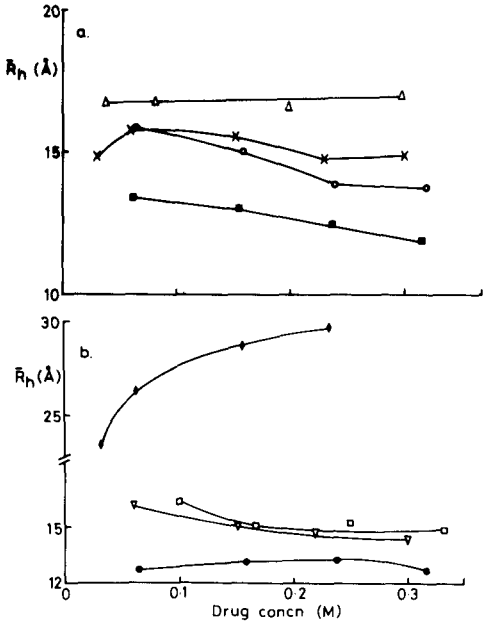


FIG. 2. Apparent hydrodynamic radii ($\bar{R}_h$) of (a) —△— clomipramine hydrochloride, —×— butriptyline hydrochloride, —○— amitriptyline hydrochloride, —■— imiprimine hydrochloride; (b) —◆— iprindole hydrochloride, —□— protriptyline hydrochloride, —▽— dothiepin hydrochloride, —●— doxepin hydrochloride in 0·154 M NaCl at 25 °C. Each point is mean ± s.d., n = 10 (s.d. within the size of the symbol).

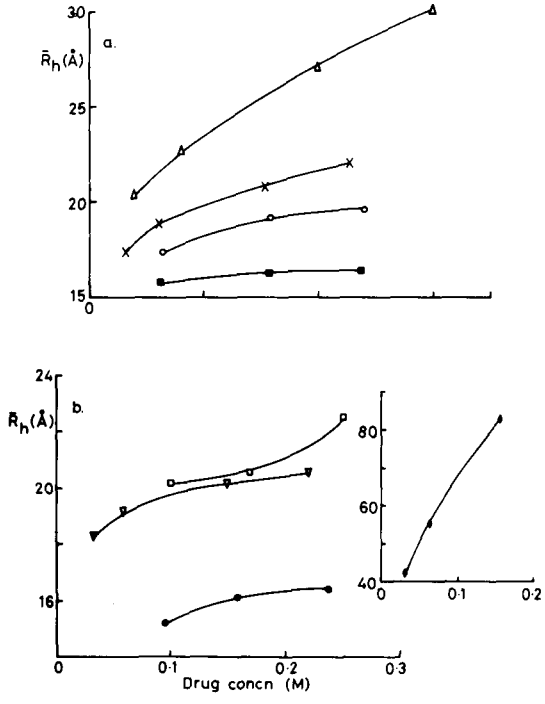
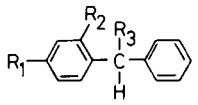


FIG. 3. Apparent hydrodynamic radii ($\bar{R}_h$) of (a) —△— clomipramine hydrochloride, —×— butriptyline hydrochloride, —○— amitriptyline hydrochloride, —■— imipramine hydrochloride at 25 °C; (b) —◆— iprindole hydrochloride, —□— protriptyline hydrochloride, —▽— dothiepin hydrochloride, —●— doxepin hydrochloride in 0·3 M NaCl at 25 °C. Each point is mean ± s.d., n = 10 (s.d. within the size of the symbol).

Table 2. The critical micelle concentration of the diphenylmethane antihistamines at 25 °C in 0·154 M NaCl measured by photon correlation spectroscopy (PCS) and surface tension (ST).



Drug	R_1	R_2	R_3	Critical micelle concentration (mM) PCS	ST	Literature	
Diphenhydramine HCl	H	H	$O(CH_2)_2N(CH_3)_2$	47	80	85[a]	77[b]
Bromodiphenhydramine HCl	Br	H	$O(CH_2)_2N(CH_3)_2$	17	8	20[a]	33[b]
Orphenadrine HCl	H	CH_3	$O(CH_2)_2N(CH_3)_2$	28	55	63[b]	

[a] Measurements at 30 °C, Attwood & Udeala (1975).
[b] Measurements at 20 °C, Thoma & Siemer (1976).

relatively monodisperse with the polydispersity index Q being less than 0·1 (but see Discussion).

The diphenylmethane antihistamines

CMC values in 0·154 M NaCl were measured using surface tension and PCS (Table 2). Minima were again apparent in the surface tension plots, indicative of surface active impurities (Fig. 4). The PCS results were significantly lower than the published values or those obtained by surface tension, with the exception of bromodiphenhydramine. This could be due to the presence of impurities which might enhance micellar or pre-micellar aggregation providing sufficient light scatter for apparent correlation. The drugs may also normally undergo premicellar aggregation.

The calculated apparent micellar hydrodynamic radii are shown in Fig. 5 as a function of drug concentration in 0·154 M NaCl. High diphenhydramine concentrations were necessary due to non-reproducible scattering at low drug concentration. The autocorrelation data analysis requires light scattering which behaves with Gaussian statistics. If the number density of scattering particles is too low (affecting the probability of detecting a diffusing particle) Gaussian behaviour is not observed and the results from the scattering data are inaccurate and non-reproducible. This could contribute to the difficulties encountered at low diphenhydramine concentrations. Also, the micelles are very small, pehaps too small for accurate size determination at low drug concentration. Micellar size remained relatively constant with increasing drug concentration for all the antihistamines. The initial rise in orphenadrine micellar size may be due to increasing size or, more probably, strengthening intermicellar interactions as more micelles formed when the drug concentration rose.

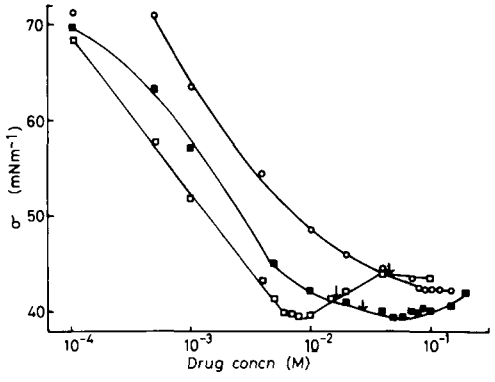


FIG. 4. Surface tension, σ, as a function of log molar concentration for —○— diphenhydramine hydrochloride, —■— orphenadrine hydrochloride, —□— bromodiphenhydramine hydrochloride in 0·154 M NaCl. Arrows indicate CMC measurements by photon correlation spectroscopy.

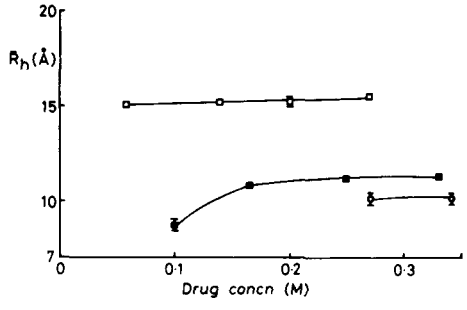


FIG. 5. Apparent hydrodynamic radii ($\bar{R}_h$) of —□— bromodiphenhydramine hydrochloride, —■— orphenadrine hydrochloride, —○— diphenhydramine hydrochloride in 0·154 M NaCl at 25 °C. Each point is mean ± s.d., n = 10 (s.d. normally within the size of the symbol).

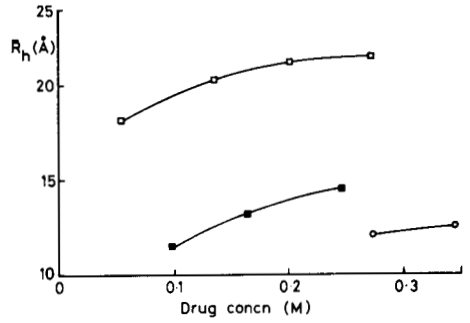


FIG. 6. Apparent hydrodynamic radii ($\bar{R}_h$) of —□— bromodiphenhydramine hydrochloride, —■— orphenadrine hydrochloride, —○— diphenhydramine hydrochloride in 0·3 M NaCl at 25 °C. Each point is mean ± s.d., n = 10 (s.d. within the size of the symbol).

Higher drug concentrations produced larger micelles for all the antihistamine solutions in the presence of 0·3 M NaCl (Fig. 6). This trend was also seen with the antidepressants (Fig. 4a, b) and may again result from the combination of an increase in micellar size and reduced repulsive interactions caused by shielding of the micellar charge. All drug solutions were *apparently* monodisperse (but see Discussion).

Propranolol hydrochloride and propantheline bromide

Propranolol with its diphenyl ring structure (Table 3) is thought to associate in a micellar manner thus exhibiting a true CMC (Elliott et al 1973). The CMC obtained by PCS was rather lower than the surface tension result (Table 3) which may indicate pre-micellar aggregation or increased correlation at the lower drug concentrations arising from the presence of surface active impurities (Fig. 7). Propantheline bromide is thought to aggregate by a continuous step-wise association process and therefore does not exhibit a true CMC. Attwood (1976), however, found that surface tension graphs were similar to those of conventional surfactants, showing apparent CMCs at distinct inflection points. Our results similarly showed a conventional surface tension graph (Fig. 7), the significant dip around the

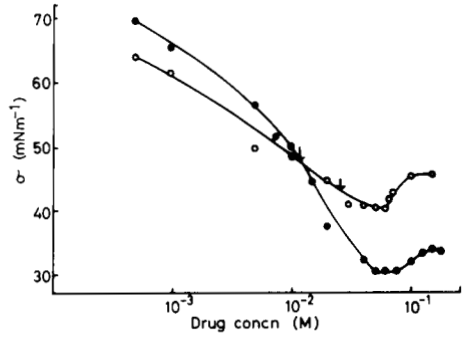
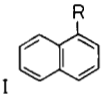


FIG. 7. Surface tension, σ, as a function of log molar concentration for —●— propantheline bromide, —○— propranolol hydrochloride in 0·154 M NaCl. Arrows indicate CMC measurements by photon correlation spectroscopy.

apparent CMC being indicative of impurities. Conventional light scattering permits measurement of a limiting monomer concentration, analagous with the apparent CMC derived from surface tension. The value obtained by PCS for the first appearance of correlation is rather low in comparison with our surface tension value for CMC (Table 3). This is not unexpected as the smaller aggregates produced initially during step-wise aggregation will scatter sufficient light for correlation. Such aggregates will

Table 3. The critical micelle concentration of propranolol hydrochloride and propantheline bromide at 25 °C in 0·154 M NaCl measured by photon correlation spectroscopy (PCS) and surface tension (ST).



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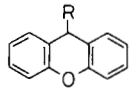

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Drug	Structure	R	Critical micelle concentration (mM) PCS	ST	Literature
Propranolol HCl	(I)	$OCH_2CH(OH)CH_2NHCH(CH_3)_2$	24	55	69·4 (0·2 M KCl)[a]
Propantheline Br	(II)	$COO(CH_2)_2\overset{+}{N}CH_3(CH(CH_3)_2)_2$	11	50	—

[a] Elliott et al (1973).

probably be produced at drug concentrations lower than the limiting monomer concentration or apparent CMC measured by surface tension.

The apparent micellar hydrodynamic radii for both drugs in 0·154 and 0·3 M NaCl as a function of drug concentration were calculated from measured diffusion coefficients (Fig. 8). Propranolol HCl was insoluble in 0·3 M NaCl. High concentrations of propantheline Br were necessary, in common with the antihistamine diphenhydramine, to produce accurate, reproducible correlation data. In 0·154 M

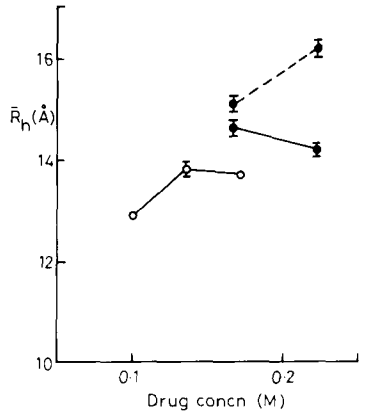

FIG. 8. Apparent hydrodynamic radii ($\bar{R}_h$) of —●— propantheline bromide in —— 0·154 M NaCl and – – 0·3 M NaCl, —○— propranolol hydrochloride in 0·154 M NaCl at 25 °C. Each point is mean ± s.d., n = 10 (s.d. within size of symbol where not indicated).

NaCl, increasing the drug concentration slightly reduced the propantheline apparent micellar size (Fig. 8). Raising the electrolyte concentration enhanced micellization with an apparent increase in $\bar{R}_h$ as the drug concentration rose. Propranolol micellar size in 0·154 M NaCl remained almost constant with changing drug concentration after an initial increase. The rise may result from intermicellar interactions at higher drug concentrations rather than a real change in micellar size.

DISCUSSION

Drug micellar properties were shown to differ within a class of drugs with the same basic structure and amongst classes with different basic structures. The tricyclic antidepressants were, in general, more surface active than the diphenylmethane antihistamines, exhibiting lower CMC values (Tables 1 and 2) and forming larger micelles in both 0·154 and 0·3 M NaCl (e.g. Figs 2a and 5). Micellar size as measured by PCS can only be apparent as the behaviour of charged molecules in solution is not ideal. The ions suffer attractive and repulsive forces which can decrease or increase the measured diffusion coefficient. The forces are themselves dependent upon salt and drug concentration. Theories have been developed to correct for intermicellar interactions (Rohde & Sackmann 1979, 1980; Corti & Degiorgio 1981; Dorshow et al 1982) but these concepts can only be used at present to correct data obtained for typical surfactants, i.e. surfactants forming spherical aggregates in a micellar fashion. For ideally behaving surfactant systems in low electrolyte concentration, plots of D against surfactant concentration are straight lines which appear to have a common intercept at infinite dilution. The value of D extrapolated to this common intercept corresponds to the micellar diffusivity in the absence of interactions, D_0. Linear plots are assumed to represent proportionality between the micellar volume fraction and surfactant concentration (Briggs et al 1982), the shape of the plots resulting solely from micellar interactions. This relation would occur if micelle size, spherical shape and aggregation number remained constant with a simple increase in the number of micelles of constant size. The non-linearity of our plots suggests that drug micelles grew and also suffered van der Waals' interactions. Drug aggregating behaviour is still relatively poorly understood and the mode of assembling is too ill-defined for us to be able to correct our data with inappropriate theories, as this could lead to wrong conclusions. The results shown are thus qualitative and indicative of trends.

Chemical modification of the drug structure changes the aggregating abilities of the drugs. The effectiveness of ring substitution in relation to the surface activity of a compound was clearly shown when different drugs within the same class were compared. Substitution of a chlorine atom into the basic ring structure of imipramine markedly increased the aggregation of the drug clomipramine, increasing the $\bar{R}_h$ values (Fig. 2a). There was also a noticeably different trend in the $\bar{R}_h$ values with increasing drug concentration in 0·154 M NaCl. Clomipramine micelles maintained a relatively constant $\bar{R}_h$ for the drug concentrations studied whereas imipramine micelles appeared to decrease in size with increasing drug concentration. The less hydrophobic drug, impiramine, therefore appeared to be more affected by repulsive electrostatic forces resulting in increased D and decreased $\bar{R}_h$. The relatively

constant micellar size of the more hydrophobic drug, clomipramine, suggests that interplay occurred between repulsive forces reducing $\bar{R}_h$, and micellar growth, raising $\bar{R}_h$. Increasing drug concentration in 0·154 M NaCl therefore appeared to have a minimal effect on imipramine micellar size but clomipramine micelles possibly enlarged with higher drug concentrations. Both drugs developed in micellar size with increasing drug concentration in 0·3 M NaCl, the change being larger for clomipramine (Fig. 3a). A similar rise in phenothiazine micellar size with drug concentration in strong NaCl has been examined by light scattering techniques (Attwood 1983b) and PCS (Atherton & Barry 1985).

A relatively constant micellar size, or apparent decrease, with increasing drug concentration in 0·154 M NaCl and evolving size in 0·3 M NaCl was also seen for the other tricyclic antidepressants. The basic tricyclic structure (Table 1) can be modified at the bridging group in the central seven membered ring (Y–Z), and at X, the position where the alkyl side chain is attached. The alkyl side chain stucture may also be altered. Amitriptyline, dothiepin and doxepin differ only at position Y–Z. This results in drugs with noticeably different surface activity. Comparing $\bar{R}_h$ plots (Figs 2a, b, 3a, b) indicated that hydrophobicity increased in the order O < CH_2 < S with dothiepin forming the largest micelles and doxepin the smallest. Iprindole was the most surface active of the antidepressants studied. The saturated, eight membered ring greatly enhanced the tricyclic ring structure hydrophobicity in spite of the central indole ring. Iprindole micellar size rose with increasing drug concentration in both 0·154 and 0·3 M NaCl solution (Figs 2b, 3b).

Measurement of diphenylmethane antihistamine micellar size was only possible at comparatively higher drug concentrations. In 0·154 M NaCl, size was relatively constant with drug concentration (Fig. 5). The $\bar{R}_h$ values reflect the relative hydrophobicity of the different chemical structures (Table 2). Diphenhydramine micelles exhibited the lowest $\bar{R}_h$ values and required the greatest drug concentration to produce sufficient reproducible light scatter for correlation. There is no ring substitution on the phenyl groups. Orphenadrine and bromodiphenhydramine were more surface active possessing, respectively, a methyl group at position R_2 and a bromine atom at position R_1. Hydrophobicity and hence the surface activity, of the molecule were enhanced in the order H < CH_3 < Br. All drugs showed micellar growth in 0·3 M NaCl (Fig. 6). Bromodiphenhydramine and orphenadrine $\bar{R}_h$ values increased with drug concentration whereas diphenhydramine micelles changed minimally.

High concentrations of propantheline bromide were necessary, in common with the antihistamine, diphenhydramine, to produce accurate, reproducible correlation data. In 0·154 M NaCl the limited data indicated a micellar size which decreased minimally with increasing drug concentration (Fig. 8). Raising the electrolyte concentration enhanced micellar size with an apparent increase in $\bar{R}_h$ values as the drug concentration rose. The increase in $\bar{R}_h$ could be due to an enhancement in micellar size or strengthened intermicellar interactions with greater micelle concentration in solution. Propranolol HCl micelles were smaller than propantheline bromide micelles in 0·154 M NaCl (Fig. 8), the size remaining relatively constant with changing drug concentration after an initial apparent rise in $\bar{R}_h$. This phenomenon may be due to intermicellar interactions at high drug concentration rather than a real alteration in micellar size. The tricyclic structure of propantheline enhances the hydrophobicity in comparison with the

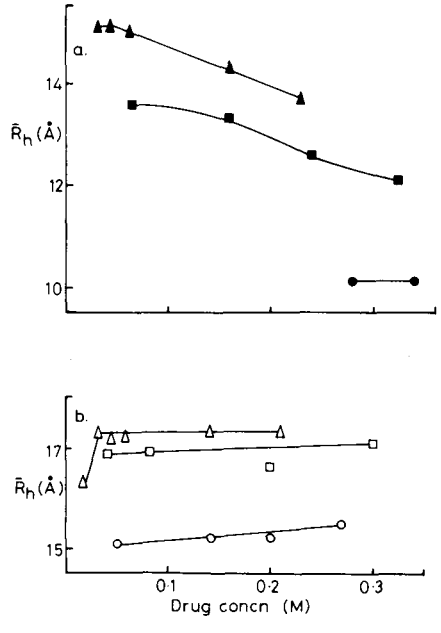

FIG. 9. Apparent hydrodynamic radii ($\bar{R}_h$) of (a) —▲— promazine hydrochloride, —■— imipramine hydrochloride, —●— diphenhydramine hydrochloride; (b) —△— chlorpromazine hydrochloride, —□— clomipramine hydrochloride, —○— bromodiphenhydramine hydrochloride in 0·154 M NaCl at 25 °C. Each point is mean ± s.d., n = 10 (s.d. within the size of the symbol).

diphenyl structure of propranolol. Bromide ions will also be present in propantheline Br solution which could also enhance micellization.

In general, the more hydrophobic drugs in each of the classes investigated formed the largest micelles in either 0·154 or 0·3 M NaCl. Increases in micellar size with higher drug concentration were also greater for these drugs. Comparing the micellar sizes for the three classes of drugs studied by PCS, the phenothiazines (Atherton & Barry 1985), antidepressants and diphenylmethane antihistamines, the largest micelles were formed by the phenothiazines (Fig. 9). This trend was the same whether the ring-substituted drugs, chlorpromazine, clomipramine and bromodiphenhydramine, or the ring-unsubstituted drugs, promazine, imipramine and diphenhydramine were compared. The tricyclic ring structure of the phenothiazines and antidepressants confers greater hydrophobicity on the overall drug structure compared with the diphenyl ring of the antihistamines. Phenothiazines are, in general, more surface active than the antidepressants due to the S atom which is replaced by less hydrophobic bridging groups in position Y–Z of the antidepressants.

The many similarities in structure between the phenothiazines and the antidepressants suggest a similar mode of aggregation by a stacking process. Both classes of drug show a definite CMC, usually indicative of a micellar pattern of association. Molecules which associate by a stacking process normally exhibit a non-micellar association, characterized by a lack of a definite CMC and a polydisperse micellar distribution (Mukerjee 1974). The polydispersity parameter, Q, was however significantly lower than 0·1, indicative of a relatively monodisperse solution. The reliability of the Q term as an indication of polydispersity is questionable for our micelles; Phillies (1982) has challenged the assessment of polydispersity as calculated by PCS because of the possible kinetic effects of the monomer-micelle reaction. The relevance of the Q term in relation to the possible mode of drug aggregation is therefore still uncertain. Previously we have proposed a mode of aggregation for the phenothiazines by 'stacking' with size increases by addition of single monomers to the stacks and by addition of more stacks. In this way the micelle would enlarge in all three axes which is more thermodynamically favourable than forming a long, narrow stack. The micelles would be spherical initially but would most probably undergo a sphere-to-rod transition as aggregation increased with rising electrolyte and drug concentrations.

Unlike the rigid tricyclic structure, the diphenylmethane aromatic rings are free to rotate around the central carbon atom. This free rotation may permit micellization by a similar mechanism to typical surfactants. Rate constants for micellization calculated from ultrasonic relaxations (Causon et al 1981) rose with increasing aggregation number suggesting that the mechanism of aggregation was unlikely to be base-stacking. Gettins et al (1976) found that ultrasonic relaxation times were not consistent with only one of the possible aggregation mechanisms taking place and therefore assumed that both phenomena occurred; initially base-stacking took place until a constant monomer concentration, the CMC, then micelle formation predominated. This behaviour would explain the apparently low CMC results obtained by PCS measurements. The small aggregates initially produced by stacking would be sufficient to scatter enough light for correlation.

The aggregating response of propranolol HCl and propantheline Br has not been studied in as great a depth as for the antidepressants and antihistamines. Our results show that propantheline and propranolol formed only small micelles in 0·154 M NaCl. Consideration of the basic drug structures suggested that a stacking mode could be possible. The long side chain of propranolol may, however, modify the procedure to that of a micellar association process, and ultrasonic relaxation studies by Causon et al (1981) suggested that base-stacking was unlikely.

Acknowledgements

The authors thank A.P.S., Ciba Pharmaceuticals, Berk Pharmaceuticals, Ayerst Laboratories, M.S.D., Pfizer, Boots Co. Ltd, Wyeth Laboratories, Parke Davis, Gist Brocades Ltd, ICI and Searle for the generous gifts of drugs, and the S.E.R.C. for a grant and for financial support for A. D. A.

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