Micellar Properties of Drugs: Properties of Micellar Aggregates of Phenothiazines and Their Aqueous Solutions

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Abstract □ The solution properties of a series of phenothiazine hydrochlorides were studied using light-scattering, viscosity, conductivity, dialysis, and NMR techniques. The aggregates formed are considered to be true micelles, which in water are probably composed of about 10 monomers vertically stacked, with the alkyl side chain and nitrogen group alternating to form an approximately spherical unit in solution. In the presence of sodium chloride the micelles grow and it is thought that the conformation of the aggregate also changes. Calculations of the monomer concentration as a function of total drug concentration above the CMC's give good agreement with data obtained previously from NMR shift data. The free energy of inserting a monomer into a micelle was calculated, and the values obtained are discussed in the light of free energies of solution of the hydrophobic bases. The significance of aggregation, mixed micelle formation, and complexation in biological and pharmaceutical systems containing phenothiazines is discussed.

Keyphrases □ Micellar properties of drugs—symposium □ Micelle aggregates of phenothiazines—determination of properties by light scattering, viscosity, conductivity, dialysis, and NMR spectroscopy □ Phenothiazines—micellar aggregation properties determined by light scattering, viscosity, conductivity, dialysis, and NMR spectroscopy

The aggregation of four phenothiazines (chlorpromazine, promazine, promethazine, and thioridazine) was previously studied by NMR techniques (1, 2). Measurements of the changes in chemical shift produced in solutions of the four compounds by varying their concentration above and below their critical micelle concentration (CMC) allowed calculation of the proportion of monomer and micelles present in solution. Further work has been carried out to find out more about the nature of the aggregation process in solutions of phenothiazine derivatives and to compare the monomer–micelle ratios obtained using the mass action approach with those obtained from treatment of the NMR results. Aggregates composed of phenothiazine molecules stacked vertically with the *N*-alkyl side chain alternating were compatible with the magnitudes and directions of the chemical shifts.

The number of drugs observed to aggregate or to form micelles in aqueous solution continues to increase. This is not entirely a surprising observation because the structural requirements for surface activity or micelle formation are often similar to those for interaction of drug with receptor sites. Possession of a well-defined hydrophobic head provides opportunities for hydrophobic interactions, and the existence of a charged hydrophilic head group—often a nitrogen-containing group—provides the opportunities for hydrogen bonding interactions with receptor molecules. Discrete hydrophobic and hydrophilic regions are also prerequisites for surface activity and micelle-forming ability.

Although micellar concentrations of surface-active drugs are not frequently encountered *in vivo*, the actions of these drugs cannot be fully understood without a knowledge of the interactions that they can undergo. Micelle formation is the result of intimate interactions between the drug molecules. Micelle formation is primarily the result of hydrophobic bonding interactions. Hydrophobic bonding plays a part also in the binding of phenothiazines to bovine serum albumin (3) and in the interactions of phenothiazines and flavins (4), dyes (5), and erythrocytes (6). One can envisage instances, for example in pharmaceutical dosage forms, when the concentration of drug will exceed the CMC. In many experimental systems, high concentrations of drugs are used and anomalies caused by the aggregation of the solute may unwittingly be misinterpreted (7). There are instances where aggregation of drug molecules into micelles results in an alteration in biological activity. One can understand why this should be so: micelles have a larger radius and diffuse more slowly than the monomeric species, and the micellar solution has a lower thermodynamic activity than an ideal solution. A diminution in biological activity has been noted with surface anesthetics and bacteriostatic agents (8, 9); where the active species is the monomer, it is useful to know about the monomer–micelle equilibrium in detail.

MASS-ACTION TREATMENT

Scheme I describes the aggregation of j monomers, $[D^+]$, and $(j - Z)$ anions, $[X^-]$, to form positively charged micellar species $[M^{Z+}]$:

$$jD^+ + (j - Z)X^- \rightleftharpoons M^{Z+}$$

Scheme I

To utilize Scheme I, the values of j, from light-scattering or osmotic pressure measurements and of Z, the number of unit charges per micelle, are required.

If the micelle is considered to be monosized (10), the thermodynamic equilibrium constant for this reaction is:

$$K = \frac{M^{Z+}}{(D^+)^j(X^-)^{j-Z}} \qquad \text{(Eq. 1)}$$

or, in a more accessible form:

$$1 = \frac{(M^{Z+})^*}{(D^+)^{*j}(X^-)^{*j-Z}} \qquad \text{(Eq. 2)}$$

each concentration being divided here by $K_m^{1/(Z+1-2j)}$ and denoted by $(\,)^*$.

EXPERIMENTAL

Light Scattering—Measurements were made at a wavelength of 436 nm using an instrument fitted with an automatic scanning device and recording system, the cell being thermostatted to 34 ± 0.1°. The construction and calibration of the instrument were described previously (11). Solutions were clarified by ultrafiltration[1].

The Rayleigh ratios for the solutions were measured at 90° (R_{90}) to the incident beam, and the corresponding measurement for a solution at the CMC was subtracted to give the excess Rayleigh ratio, ΔR_{90}.

The specific refractive index increment, dn/dc, for the micellar species was determined with a Hilger-Rayleigh interference refractometer using Bauer's (12) technique for monochromatic light.

Micellar aggregation numbers, j, were evaluated by the method of Anacker and coworkers (13, 14). In a solution containing no added electrolyte:

$$p = \frac{M_0 S\,\mathrm{CMC} + (2M_0 S\,\mathrm{CMC})^{1/2}}{M_0 I(1 - M_0 I/2)} \qquad \text{(Eq. 3)}$$

$$j = \tfrac{1}{2}[p + 1/M_0 I] + \tfrac{1}{2}[(p + 1/M_0 I)^2 - p(p + 1)]^{1/2} \qquad \text{(Eq. 4)}$$

where p = effective thermodynamic charge[2]; M_0 = monomer molecular weight; I and S are the intercept and slope, respectively, of plots of $K(C - \mathrm{CMC})/\Delta S_{90}$ *versus* $(C - \mathrm{CMC})$, where $K = 2\pi^2 n_0^2 (dn/dc)^2 V_0/\lambda^4$; and the other symbols have their usual significance.

Electrophoretic Mobility—The electrophoretic mobilities of the micellar species were determined at 34 ± 0.5° by the dye-tracer method using an apparatus similar in design to that described by Hoyer *et al.* (15). The micelles were "tagged" by shaking the dispersions with the dye Orange O.T. for 3–4 days, and the dye concentrations were estimated from the E_{492}. The ζ-potential of the micelles was calculated from the experimentally obtained electrophoretic mobilities (Fig. 1) using the data computed by Wiersema *et al.* (16), which account for both electrophoretic retardation and relaxation effects. The micellar charge was estimated using the numerical solutions of the Poisson-Boltzmann equation obtained by Loeb *et al.* (17).

Conductivity—The conductivity of the solutions at 34 ± 0.01° was determined using a conductivity bridge[3]. CMC's were determined from plots of conductivity *versus* concentration (Fig. 2), the values agreeing well with those obtained from pH and NMR data (2). The effective micellar change, p, was estimated from the conductance data using an equation proposed by Evans (18):

$$\frac{p^2}{j^{1/3}}(1000\,S_1 - \Lambda_R) + \frac{p\Lambda_R}{j} = 1000\,S_2 \qquad \text{(Eq. 5)}$$

where Λ_R is the equivalent conductance of the counterion at infinite dilution, j is the aggregation number of the micelles, and S_1 and S_2 are the slopes of the specific conductance-concentration plots below and above the CMC, respectively.

Viscosity—Viscosity measurements were made at 25 and 34° (±0.01°) with a suspended-level dilution viscometer. The viscosities were obtained relative to water or 0.15 M NaCl as solvents, and corrections were made for the CMC. Measurements were made well above the CMC region, and there is little error in assuming that the monomer concentration is constant in the range studied. Intrinsic viscosities, $[\eta]$, were obtained by extrapolation of the reduced specific viscosities to zero micelle concentration, *i.e.*, where C_0 = CMC:

$$\lim_{(C - C_0) \to 0} \frac{\eta_{sp}}{C - C_0} = [\eta] \qquad \text{(Eq. 6)}$$

Dialysis[4]—The cells were of 10-ml capacity, and the solution and solvent sides were separated by a cellophane membrane[5]. The cells were rotated at 24 rpm along their vertical axis. Samples were taken from the solvent side at intervals and analyzed spectrophotometrically for phenothiazine. The rate of dialysis was constant up to 2 hr.

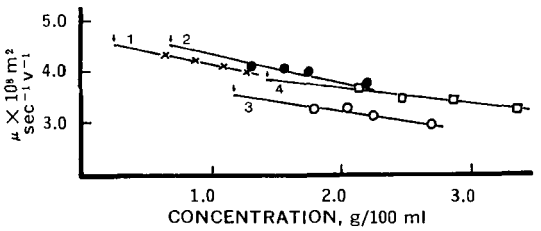

Figure 1—*Electrophoretic mobilities of the phenothiazine micelles as a function of concentration. Key: 1, thioridazine; 2, chlorpromazine; 3, promazine; and 4, promethazine. Arrows indicate CMC's. Temperature = 34°.*

Materials—The phenothiazines used were described previously (2). A commercial sample of triflupromazine was used as received. Sodium chloride was Analar grade material, and water was twice distilled from a glass apparatus.

RESULTS AND DISCUSSION

The light-scattering results (Table I) show that the aggregates formed by the phenothiazines are small. Those of chlorpromazine and promethazine have aggregation numbers of 11 ± 1, and the smallest aggregate, formed by thioridazine hydrochloride, consists of eight monomers. This is the order of magnitude expected from bulky molecules with relatively rigid hydrophobic ring systems in the absence of salt. A number of dyes with similar ring systems, *e.g.*, thionine and methylene blue, form only dimers in dilute solution (19). Sodium fusidate forms aggregates composed of only a few monomers (20), behaving like the structurally related cyclopentenophenanthrene derivative, sodium taurocholate, which is trimeric in 0.01 M NaCl (20). Similarly, the xanthone derivatives studied by Scholtan and Gonnert (21), with the exception of lucanthone hydrochloride which has an aggregation number of 445, form small micelles. While many drugs will be surface active, few will be capable of forming large micelles in water.

The relatively high CMC's (Ref. 2 and Figs. 2 and 3) are in the

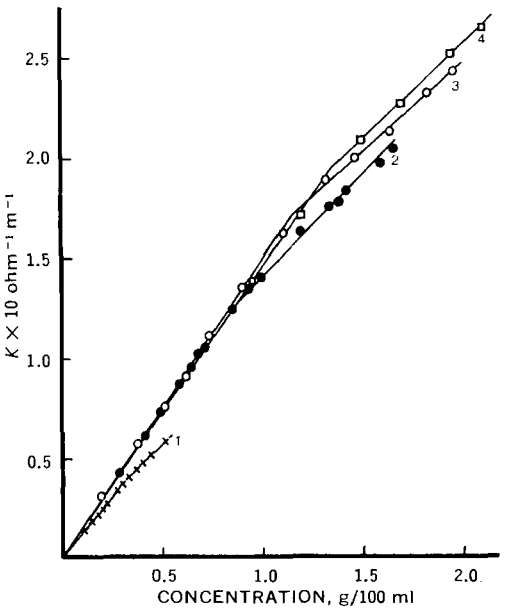

Figure 2—*Specific conductance of phenothiazine solutions as a function of concentration. Key: 1, thioridazine; 2, chlorpromazine; 3, promazine; and 4, promethazine. All show distinct breaks in the CMC region.*

[1] Millipore filters, 0.1 μm.

[2] Charge from light scattering is an effective thermodynamic charge, because ideality is assumed in its calculation. This charge is not the true charge at the shear plane of the micelle but its effective charge, taking into account all deviations from ideality [see K. J. Mysels, *J. Colloid Sci.*, **10**, 507(1955).] z is the micellar charge.

[3] L. K. B. Instruments Ltd., South Croydon, Surrey, United Kingdom.

[4] Dialysis cells were constructed from Gallenkamp filtration units.

[5] Visking.

Table I—Properties of Phenothiazine Micelles

Compound	Aggregation Number, j		Number of Unit Charges per Micelle, z			
			Experimental			
	Experimental: Light Scattering	Mass-Action Calculations	ζ-Potential Measurements	Conductivity Measurements	Mass-Action Calculations	ζ-Potential, mv
Thioridazine	8	8	6[a]	6	7	+88
Chlorpromazine	11	11	8	6	8	+83
Promazine	11	11	6[a]	6	11	+59
Promethazine	9	10	8	6	8	+70

[a] Value calculated using the simplified equation of Mysels and Stigter [K. J. Mysels and D. Stigter, *J. Phys. Chem.*, **57**, 104(1953)] was 7.

same region as found for sodium fusidate and sodium taurocholate (20). Therefore, one may assume that micellization of the phenothiazines and many other drug molecules is unimportant *in vivo*. What is important is the ability of the molecules to interact in the special way encountered in micelles. Interaction of the phenothiazines with various biological materials has been noted (4, 6). For example, Moriguchi *et al.* (22) recently reported the interaction of chlorpromazine with adenosine phosphate; the association of phenothiazines with bovine serum albumin (3, 23), caffeine, and riboflavin (27) was also reported.

The differences in the aggregation numbers j found for the four compounds cannot be regarded as significant, because the precision of the light-scattering technique allows measurement of j to ±1 monomer only. The authors are convinced, however, that the systems studied are in fact true micellar systems which are not behaving like the methylene blue systems investigated by Mukerjee and Ghosh (24). They interpreted the solution properties of methylene blue using a multiple equilibrium model for association from dimers to pentamers. Although the ring systems are similar, methylene blue differs from the phenothiazines in that the charge on the methylene blue monomer is delocalized due to resonance. Resonance cannot occur in the phenothiazines studied, and the compounds are more like conventional surfactants than dye molecules, having a fairly distinct separation of hydrophobic and hydrophilic groups. Methylene blue has hydrophilic groups on both sides of the ring.

Low concentrations of salt have a pronounced effect on the size of the aggregates formed. In 0.154 *M* NaCl, thioridazine micelles contain 57 monomers at 34°; pH measurements in water as a function of drug concentration at 20 and 34° show abrupt changes at the CMC and even more abrupt changes in the presence of sodium chloride (2). This behavior points to there being a true micellization phenomenon.

Mass-Action Calculations—Previously (2), the ratios of monomer to micelle in solutions of the phenothiazines were calculated from NMR data on the assumption that the observed chemical shift at any drug concentration, $\bar{\delta}$, was a numerical weight average of the resonance frequencies of the protons of the monomeric and micellar species (25). It was also assumed that the monomeric and micellar forms contributed shifts δ_{mon} and δ_{mic}, respectively, the latter value being obtained by an extrapolation procedure (2). The weight fractions, x, of the two species were obtained by substitution in the equation (25):

$$\delta_{mic} = \frac{\bar{\delta} - \delta_{mon}}{\delta_{mic} - \delta_{mon}} \qquad \text{(Eq. 7)}$$

To verify that this simple approach may be used, the authors sought to fit the results so obtained by calculating monomer and micelle concentrations using Eqs. 1 and 2 and Scheme I and solving graphically. The parameters j and Z were adjusted to give the best fit with experimental data points and compared with the values of j obtained by light-scattering measurements and Z values from ζ-potential and conductivity measurements (Table I). In Fig. 4 the continuous line is the calculated line (j, Z as in Table I), the points representing the NMR values. Very good fits were obtained when charge values and aggregation numbers close to those obtained experimentally were used in the calculations. Results for promazine do not match so well, but, in general, the agreement between the two sets of data lends weight to the use of NMR data and suggests that the extrapolations involved are valid. In addition, the view that these systems form true micelles with definite CMC's, which can be interpreted in the usual way, is strengthened.

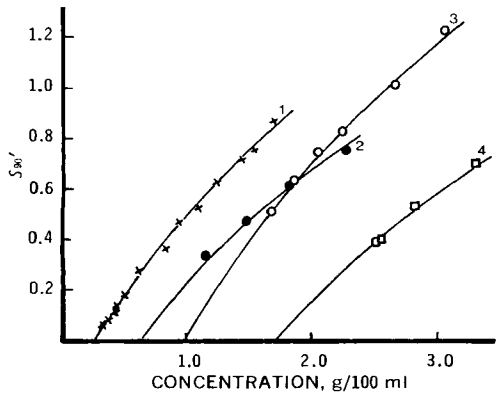

Figure 3—*Light-scattering results in water at 34°. Excess scattering at 90° to the incident beam, ΔS_{90}, plotted as a function of concentration. Key: 1, thioridazine; 2, chlorpromazine; 3, promazine; and 4, promethazine.*

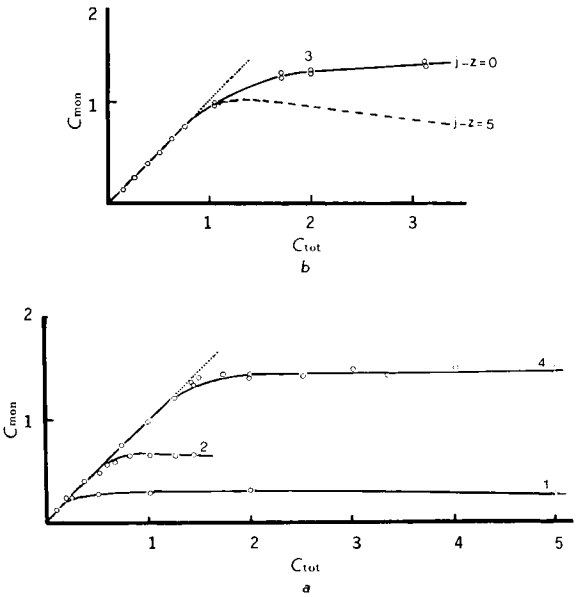

Figure 4—(a) *Monomer concentrations, C_{mon}, as a function of total concentration, C_{tot} (% w/v), for thioridazine (1), chlorpromazine (2), and promethazine (4). The continuous line is that calculated using Eq. 2 and the parameters recorded in Table I.* (b) *Results for promazine show best agreement between calculated line and NMR-derived results when* j − z = 0. *Conductivity and electrophoretic data indicate that* j − z *should be 5. The sensitivity of the calculated concentrations to* (j − z) *is shown in this diagram.*

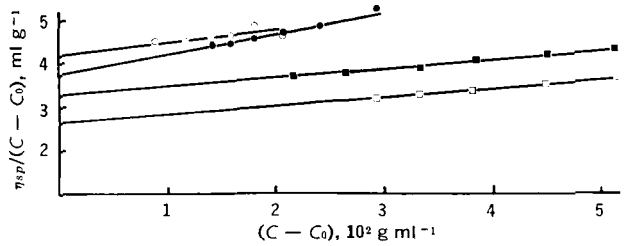

Figure 5—*Viscosity results for representative systems in 0.9% (0.154* M*) NaCl* $\eta sp/(C - CMC)$ *plotted as function of* $(C - CMC)$ *to obtain intrinsic viscosity,* $[\eta]$*, as intercept. Key:* ● *and* ○*, thioridazine at 25 and 34°, respectively; and* ■ *and* □*, chlorpromazine at 25 and 34°, respectively.*

Viscosity Results—Viscosity measurements (Fig. 5 and Table II) indicate that the phenothiazine micelles are spherical or nearly so, because the intrinsic viscosities, $[\eta]$, are close to the value expected for spherical units in solution, *i.e.*, 2.5/density. The intrinsic viscosities at 34° are lower than those at 20° in 0.154 *M* NaCl for chlorpromazine, promazine, and promethazine. With these compounds also, the intrinsic viscosities in the salt solutions are lower than those in distilled water, as would be expected from a reduction in the charge of nearly spherical units whose shape has not altered. The intercepts of 2.6 and 2.54 for chlorpromazine and promazine, respectively, must be an indication of their nearly spherical shape in solution. The micelles of thioridazine in a salt solution at 34° contain over 50 monomers, according to light-scattering results. The corresponding intrinsic viscosity is 4.35 ml g^{-1}, suggesting that some asymmetry is developing; 50 monomers cannot stack in a vertical mode without forming a very asymmetrical unit. The results of Scholtan and Gonnert (21) show that there is a marked decrease in micellar size with increasing temperature, and this probably explains the general decrease in intercept with rise in temperature. No such change should occur if the micelles are conventionally shaped spherical micelles. The difference in behavior between thioridazine and the other compounds may be related to the differences in the nature of the side-chain systems on these molecules. In a vertical stack, the side chains assume relatively little importance. Once larger, more intimate associations take place, the side chains should play a part in determining micelle size.

Transport across Membranes—Nonequilibrium dialysis measurements of the rate of transfer of thioridazine and chlorpromazine hydrochlorides indicate clearly the onset of aggregation. The results of transport rate—as a function of total concentration—can be explained using mass-action monomer–micelle ratio data and assuming simple partition of the monomeric species. The micelles are not expected to dialyze readily through the membrane, which has a pore size of 0.80-μm diameter; their rate of permeation is assumed to be sufficiently slow to allow one to account for the rates by considering the monomers alone. The results are shown in Fig. 6, where calculated points are superimposed on the experimental data.

Addition of salt (sodium chloride) to the system decreases the net rate of transport of the drug by inducing the formation of larger micelles and by depressing the CMC. Caffeine, sodium saccharin, and riboflavin decrease the rate of transport of chlorpromazine across dimethylpolysiloxane membranes (27), presumably as a result of complexation; micellization is one form of self-complexation, and both micelle formation and interactions with extraneous materials decrease the proportions of free drug available for passage through membranes. By addition of salt and by addition of surfactants to form mixed micelles, the rate of transport can be controlled. The pharmaceutical possibilities of this phenomenon have yet to be investigated.

Mixed Micelles in Phenothiazine Systems—A preliminary study was made of the aggregation of promethazine hydrochloride in the presence of the more hydrophobic compound chlorpromazine hydrochloride. It is well known that the addition of a more hydrophobic homolog to a lower surfactant homolog can result in the depression of the CMC of the latter (9). Measurement of the break in pH–concentration plots was used as a measure of the CMC in the mixed solutions. The results (Table III) suggest that the CMC of promethazine is depressed below the CMC of either component, a phenomenon not predicted by previous work (28) on straight alkyl chain ionic surfactants.

Table II—Intrinsic Viscosities of Phenothiazine Micelles (Milliliters Gram^{-1})

Phenothiazine	Solvent	25°	34°
Thioridazine	Water	—	3.8
	0.154 *M* NaCl	3.8	4.3_5
Chlorpromazine	Water	—	3.6_3
	0.154 *M* NaCl	3.2	2.6
Promazine	Water	—	3.8_8
	0.154 *M* NaCl	4.0_5	2.5_4
Promethazine	Water	—	3.5
	0.154 *M* NaCl	3.9	3.3_5

It is possible that there is a twofold effect here. The added chlorpromazine may be inducing easier micelle formation by the normal mechanism, but the free hydrogen chloride may be acting to reduce the charge on the protonated nitrogens of the alkyl side chains, with the result that the CMC is reduced. Further work with solutions of controlled ionic strength is required to confirm these results.

Thermodynamics of Aggregation Process—Since micelle formation is a relatively simple process, it should provide a clear indication of the energy, enthalpy, and entropy changes to be expected when micelle-forming drugs participate in interactions involving hydrophobic bonds. The free energy change on micellization per mole of monomer, ΔG_m, can be obtained from the CMC (mole fraction units). From the mass-action equilibrium (2):

$$\Delta G_m = (2 - z/j)RT \ln \text{CMC} \qquad \text{(Eq. 8)}$$

If j counterions are firmly bound to the micelle so that, when j is large, z is zero, Eq. 8 reduces to:

$$\Delta G_m = 2RT \ln \text{CMC} \qquad \text{(Eq. 9)}$$

If $z = j$, Eq. 9 becomes:

$$\Delta G_m = RT \ln \text{CMC} \qquad \text{(Eq. 10)}$$

which is the equation applicable to nonionic surfactants. More valuable from the biological point of view is gaining an understanding of the energy involved in adding a monomer to the "most probable" micelle. The incorporation of an additional surfactant ion into an aggregate containing j surfactant ions involves the equilibrium of $D^+ + M^{+j} = M^{+(j+1)}$, for which the free energy change can be written:

$$\Delta G_m = -RT \ln \frac{F(M^{+(j+1)})}{(D^+)(M^{+j})} \qquad \text{(Eq. 11)}$$

If equilibrium concentrations at the CMC are used and ln F is much smaller than ln CMC:

$$\Delta G_m = RT \ln \text{CMC} \qquad \text{(Eq. 12)}$$

This equation avoids complications arising from consideration of the formation of the double layer. There are conceptual difficulties with the definition of micellar standard state. In Eq. 12, the standard state has been taken to be the micelle at unit mole frac-

Table III—Apparent CMC of Promethazine in Presence of Chlorpromazine[a]

Concentration of Chlorpromazine $\times 10^2$ *M*	Apparent CMC of Promethazine $\times 10^2$ *M*	Promethazine–Chlorpromazine Molar Ratio
0	4.35	—
0.28	3.12	11.14
0.34	1.49	4.42
1.27	1.56	1.23

[a] CMC determined from break in pH *versus* concentration curve.

Table IV—Calculated Free Energies of Micelle Formation and Free Energy of Solution of Phenothiazines (kcal mole^{-1})

Compound	ΔG_m[a] (20°)	ΔG_m[a] (34°)	ΔG_m (0.154 *M* NaCl) (20°)	ΔG_m[b] (20°)	ΔG_{ma}[c] (20°)	ΔH_m[d]	ΔG_s (RT ln X_w)	ΔG_s[e] (RT ln X_w[corr])
Thioridazine	−5.25	−5.57	−6.0 (34°)	−10.5	−5.91	+1.5	+10.3	+7.4
Triflupromazine	−4.72			−9.44			+9.6	+7.2
Chlorpromazine	−4.66	−4.86	−5.46	−9.32	−5.93	−0.6	+9.3	+6.9
Promazine	−4.36	−4.45	−5.05	−8.72	−4.36[f]	−2.3	+8.2	+5.9
Promethazine	−4.15	−4.34	−4.98	−8.30	−4.98	−0.2	+8.15	+5.85

[a] RT ln CMC, with CMC in mole fraction units. [b] $2RT$ ln CMC. [c] $[2 - (j/z)]$ RT ln (CMC), using mass-action j and z values. [d] Calculated from limited data between 20 and 37°. [e] Solubility X_w in mole fraction units. Free energy of solution was corrected for side-chain contribution, using estimates based on data of G. Nemethy and H. A. Scheraga, *J. Phys. Chem.*, **66**, 1773(1962). Standard states are such that mole fractions are unity and solution properties are characteristic of infinitely dilute solution. In the case: drug (solid) → drug (solution) and drug (solution) → drug (micelle), the solution standard states will be identical. But while the micellar standard state represents a hydrated species, the solid standard state will be pure solid. The differences in magnitude between ΔG_{soln} and ΔG_m would represent the differences in those standard state conditions. [f] −6.34 if alternative j and z values in Table I are used.

tion, devoid of double layer. The values of ΔG_m obtained by the three main equations are quoted in Table IV.

Micelle formation involves the removal of the hydrophobic portion of the molecule completely or partially from the water. Hence, one would expect to obtain some indication of the energy involved in the aggregation process from the free energy of solution of the phenothiazines in their basic form. Solubilities of the bases were taken from Green's (29) data. By neglecting activity corrections (because of the extreme dilution), the free energy of solution, ΔG_s, was calculated from:

$$\Delta G_s = -RT \ln X_w \qquad \text{(Eq. 13)}$$

where X_w is the mole fraction solubility of the base (Table IV). Green's method involves precipitation of the base from its solution as the hydrochloride. The bases separate out as oils (see Ref. 29) so the equilibrium studied is base (oil) ⇌ base (solution). When ΔG_m is plotted as a function of ΔG_s, there is a linear relationship for the promazine derivatives (Fig. 7), but the thioridazine and promethazine values deviate from the line. The solubility values can predict the rank order of the CMC but not its absolute value.

The unitary free energy of dimerization of methylene blue (24), which involves the loss of two faces of the ring system and is therefore equivalent to the insertion of one molecule into a micelle, is −6.95 kcal mole^{-1}. After correcting for the positive free energy contribution due to electrical interaction, the hydrophobic contribution has been estimated to be approximately −8 kcal mole^{-1}. The methylene blue molecule differs from the phenothiazines in that its inner ring is aromatic; the phenothiazine inner ring is quinoid. A rough estimate of the corresponding value for the phenothiazine is, therefore, −5.3 kcal mole^{-1}, close to the values obtained experimentally, which range from −4.2 to −5.3 kcal mole^{-1} at 20°. This gives weight to the picture of the micelle containing the monomers stacked in an alternating mode, with the *N*-alkyl side chain still partially in an aqueous environment. Nevertheless, changes in the side chain (*cf.*, promazine and promethazine) do result in differences in ΔG_m.

The free energy of binding of chlorpromazine to serum albumin was found to be −5.83 kcal mole^{-1} (31). Kwant and Seeman (6) quoted a value of −9.4 kcal mole^{-1} for the energy of binding of chlorpromazine to hemoglobin-free erythrocyte ghost membranes. The interaction of the phenothiazine with the albumin is regarded to involve one benzene ring and part of the aliphatic side chain. The value obtained by Kwant and Seeman is close to the free energy of solution of chlorpromazine (−9.30 kcal mole^{-1}), suggesting that the ring system and aliphatic side chain are removed from water. The discrepancy between the solution free energies (from −8.15 to −10.3 kcal mole^{-1}) and the free energy of micelle formation (from ∼−5 to −7 kcal mole^{-1}) may be due to two factors in the case of the small drug aggregates encountered in water:

1. When the alternately stacked micelles form, the alkyl side chain is not completely removed from the water. Attempts to correct the solubility data to exclude the *N*-alkyl side-chain contribution (Fig. 7 and Table IV) bring the solubility and micellization energies closer, but only to within 1-2 kcal of each other.
2. The rings do not perfectly coincide in the stack.

The larger micelles formed in salt solutions have a more substantial hydrophobic core; the hydrophobic portions of the molecules are more completely removed from the water on micellization and, hence, ΔG_m is larger.

CONCLUSIONS

The aggregation process in phenothiazine solutions is akin to that observed in conventional surface-active agents and can similarly be described by the law of mass action. A CMC does exist, as demonstrated by nonequilibrium dialysis measurements of the transfer of a monomer across a membrane. The rate of transfer increases negligibly above the CMC region. The extreme hydrophobic character of the compounds and the sensitivity of the aggregation number to salt make the analysis of the transfer from

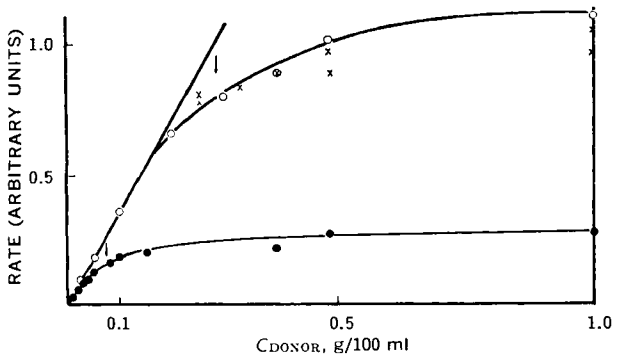

Figure 6—*Rate of dialysis of thioridazine across cellophane membranes as a function of drug concentration above and below the CMC in water* (○) *and 0.154* M *NaCl* (●) *at room temperature.* × = *calculated rates of transport assuming exclusive passage of monomer across the membrane, based on NMR data. Arrows denote CMC values.*

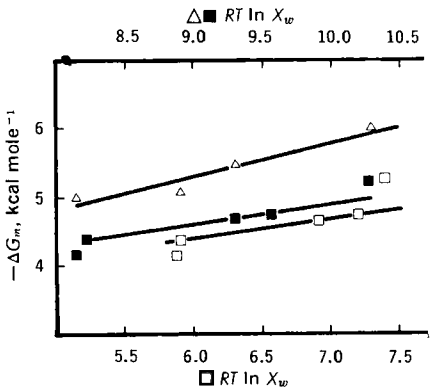

Figure 7—*Free energy relationships. The free energy of micelle formation as a function of the free energy of solution of the phenothiazine bases calculated from the solubility data of Green (29). Key:* ■, *from CMC values in water; and* △, *from CMC values in 0.9% NaCl. The corrected values for the free energy of solution represent data adjusted by subtracting an estimated contribution for the* N*-alkyl side chain* (□, *data points*).

water to a nonpolar environment difficult. Their surface-active properties and their ability to complex with other drugs having similar ring systems render doubtful the conclusions drawn by many workers as to the biological significance of enzyme inhibition studies and complexation with a variety of biological materials. While caution must be observed in interpreting such studies, it becomes clear that the colloidal properties of the drugs must be linked to their biological action. It should be no coincidence that a range of drugs with diverse structure, but with pharmacological properties similar to those of phenothiazines, was demonstrated to be surface active and to form micelles in solution.

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BOOKS

REVIEWS

The United States Dispensatory, 27th Edition. Edited by ARTHUR OSOL and ROBERTSON PRATT. Lippincott, East Washington Square, Philadelphia, PA 19105, 1973. xix + 1287 pp. 21 × 26 cm. Price $30.00.

This edition of the *Dispensatory* is about the same size as the 26th edition, which itself was much smaller than previous editions because of the deletion of hundreds of ineffective drugs and botanicals. As in the last edition, the collection of articles on individual drugs is arranged alphabetically (straight through from Acacia to Zinc Sulfate), with a number of more extensive articles on general classes of drugs interspersed.

Although the editors do not state the basis for the listing of the drugs in the book, it is apparent that the individual drug substances and pharmaceutic aids that are official in NF XIII and USP XVIII comprise the great majority of those covered in this edition. A number of other drugs, both old and new, are also included.

The articles on individual drugs (listed by nonproprietary name) typically contain information, where applicable and available, of the following types: chemical and brand name nomenclature; chemical structure; a summary of method of synthesis or other form of preparation or derivation; pharmacological actions; therapeutic uses; contraindications; untoward effects; warnings and precautions; drug interactions (a new feature for this edition); dosage for adults and children, including variations of dosage in different diseases; and dosage forms available.

The general articles, which usually provide more extensive information than is found in the individual drug articles, are titled as follows: Adrenergic Inhibiting Drugs; Adrenocortical Steroids; Analgesic Drugs; General Anesthetics; Local Anesthetics; Antibiotics; Antibiotics with Antineoplastic Activity; Anticoagulants;