Factors Influencing the Surface Activity of Chlorpromazine at the Air–Solution Interface

Effect of Inorganic and Organic Electrolytes

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In a previous study it was observed that adsorption of chlorpromazine at the air-solution interface is influenced significantly by anionic buffer components. In view of this, the effect of a large number of inorganic and organic ions has been considered. Marked inhibitory effects were noted in the presence of organic cations *e.g.*, the tetraalkylammonium ions; the greater the chain length, the greater the inhibition. Inhibition was also noted in the presence of sodium methanesulfonate. On the other hand, bromide, iodide, propanesulfonate, benzenesulfonate, and naphthalenesulfonate ions all produced increased surface activity when compared to the system containing NaCl. The inhibitory effects appear related to factors influencing the structure of water, while the effect of anions appears due to interfacial ion-pair formation.

RECENT studies in this laboratory have been concerned with the possible relationship between surface activity at various interfaces and pharmacological activity of the phenothiazine drugs (1–3). The rationale for such studies is based upon many reports of phenothiazine involvement in metabolic processes controlled by the presence of biological membrane interfaces (4).

In a recent study (3) the surface activity of various phenothiazine derivatives was compared at the air–solution interface and found to reflect the relative nonpolarity and pharmacological activity of each compound. In addition, a significant effect due to the presence of buffer ingredients was noted at pH 5.0 and ionic strength 0.1. Phthalate, citrate, and succinate buffers markedly increased surface activity, while an acetate buffer decreased the tendency for surface pressure development. In contrast to acetate, studies with a phenylacetate buffer also showed a marked increase in surface activity (5). Dilution of all buffers, while maintaining pH and ionic strength constant, tended to restore surface activity to the value expected of the protonated form.[1]

It was suggested at that time (3) that increases in surface activity in the presence of the various buffer ingredients were due to specific interactions between the cationic drugs and the anionic buffer ingredients. The decrease in surface activity due to the acetate–acetic acid system suggested the possibility that the thermodynamic activity of these drugs was decreased by some change in water structure (18) or by a competing process at the interface. Since such factors could play an important role in determining the properties of these drugs at biological interfaces, the authors decided to examine more closely those factors influencing the surface. This first study is concerned with the influence of some inorganic and organic ions. The latter are comparable to the buffer ingredients utilized in the authors' earlier study; but, in addition, they are completely ionized at all pH values.

EXPERIMENTAL

Materials.—The hydrochloride, hydrobromide, and hydroiodide salts of chlorpromazine were obtained from the Smith Kline & French Laboratories, Philadelphia, Pa. They were all recrystallized twice from reagent grade isopropyl alcohol. All inorganic salts were reagent grade and, with the exception of NH_4Cl, were dried before use by heating to $200°$. The various tetraalkylammonium chlorides were obtained from Eastman Chemicals. The tetramethyl derivative was recrystallized from isopropyl alcohol, the tetraethyl and tetrapropyl derivatives from acetone, and the tetrabutyl derivative from benzene. Sodium-1-propanesulfonate, sodium benzenesulfonate, and sodium-2-naphthalenesulfonate were obtained from Eastman and recrystallized from absolute methanol. Sodium methanesulfonate was pre-

[1] Since the pKa values of all drugs studied are above 9.0 (6, 7), it is assumed that the drug is essentially 100% dissociated at pH 5.0. Therefore, the point of comparison for the protonated form, uninfluenced by buffer, is a solution of the hydrochloride brought to pH 2.0 and ionic strength 0.1 with HCl and NaCl.
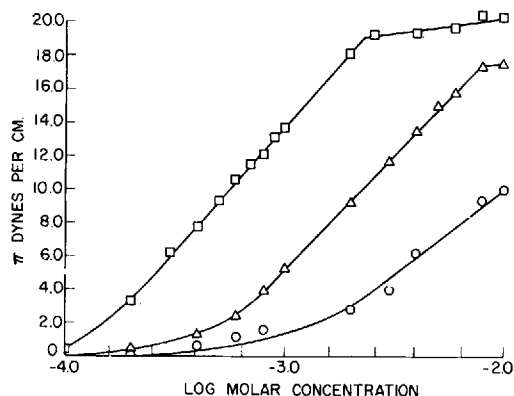
Fig. 1.—Plot of surface pressure, π, *vs.* log molar concentration for chlorpromazine at pH 5.0 and 25°. Key: ○, no salt; ▽, 0.1 *M* NaCl; □, 0.5 *M* NaCl.
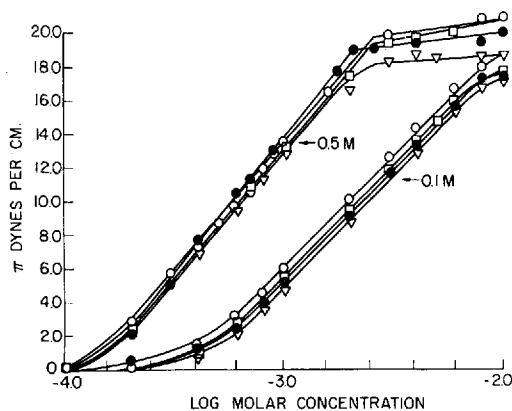
Fig. 2.—Plot of surface pressure, π, *vs.* log molar concentration for chlorpromazine at pH 5.0 and 25° in the presence of various inorganic electrolytes. Key: ○, LiCl; ●, NaCl; □, KCl; ▽, NH$_4$Cl.
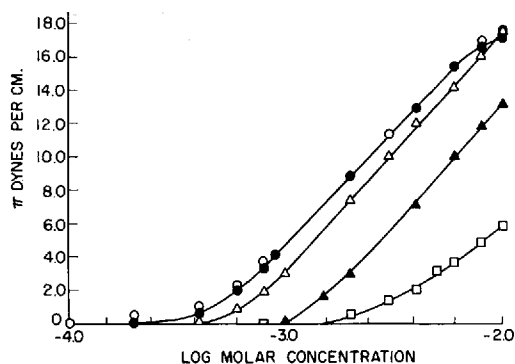
Fig. 3.—Plot of surface pressure, π, *vs.* log molar concentration for chlorpromazine at pH 5.0 and 25° in the presence of 0.1 *M* NH$_4$Cl and various tetraalkylammonium salts. Key: ○, 0.1 *M* NH$_4$Cl; ●, 0.1 *M* (CH$_3$)$_4$ N$^+$ Cl$^-$; △, 0.1 *M* (C$_2$H$_5$)$_4$ N$^+$ Cl$^-$; ▲, 0.1 *M* (C$_3$H$_7$)$_4$ N$^+$ Cl$^-$; □, 0.1 *M* (C$_4$H$_9$)$_4$ N$^+$ Cl$^-$.

pared by adding an equivalent amount of a sodium hydroxide solution to methanesulfonic acid (Eastman). The reaction mixture was treated with activated charcoal. All recrystallized materials were powdered and dried under vacuum at 60°.

Methods.—Surface tension measurements of all solutions were made at 25° utilizing the drop-volume apparatus, described previously (3, 8). Details for measuring the volume of drops and for calculating surface tension have been reported earlier (8). Values reported here are generally accurate to ±0.3 dyne/cm. Due to the possibility of chlorpromazine photodecomposition, all solutions were prepared just prior to measurement and were kept from any contact with light. The buffer utilized to maintain pH 5.0 was a 0.01 *M* acetate–acetic acid system, which did not exhibit any surface pressure beyond that of a blank solution and did not have any effect on the expected surface activity of the protonated drug. Unless otherwise stated, in all studies chlorpromazine hydrochloride was used as the drug. All pH measurements were made with a Beckman research pH meter.

RESULTS

In general, two criteria may be used to evaluate surface activity. The first, and perhaps the most important, is the concentration of drug required to achieve measurable surface pressures. The second involves estimating the surface excess or surface concentration at various bulk solution activities. This value requires measuring the change in surface pressure with changing solution activity and applying the appropriate form of the Gibbs adsorption equation (9). Unfortunately, in systems under study here bulk solution concentration cannot be easily equated or related quantitatively to solution activity. However, for the present, plots of surface pressure, π *versus* log C, will be given for the various systems studied, and it will be assumed that a greater slope at a given concentration *reflects* greater surface concentration.

Figure 1 indicates the relative tendency of chlorpromazine (CPZ) to develop surface pressure in the presence of buffer alone, and buffer plus 0.1 *M* and

0.5 *M* NaCl. The reduction in required concentration, the general increases in slope, and the appearance of an apparent critical micelle concentration (CMC) clearly indicate the strong tendency of chlorpromazine to exhibit marked surface activity once the apparent repulsive forces of the ionized polar group are reduced. The effect of different inorganic cations, as seen in Fig. 2, is relatively nonspecific except for small differences, particularly above the apparent CMC. At these higher drug concentrations, differences in hydration energies and ionic size may be accentuated.

Figures 3 and 4 demonstrate the inhibition of surface activity due to the presence of various tetraalkylammonium salts. It is interesting to note that 0.1 *M* tetramethylammonium ion acted exactly as an inorganic cation, while the 0.5 *M* solution offset the expected ionic strength effect by reducing surface activity. The surface pressure developed by these substances in the absence of drug was no greater than 1.0 dyne/cm. As can be seen, increasing the chain length of the four alkyl groups beyond one carbon greatly inhibits the surface activity, par-

ticularly 0.1 M tetrapropyl and tetrabutyl. The tetraethyl, tetrapropyl, tetrabutyl derivatives, at 0.1 M concentration without drug, exhibited surface pressures of 1.0, 5.0, and 10.0 dynes/cm., respectively. The 0.5 M solution of tetraethylammonium chloride exhibited a surface pressure of 2.0 dynes/cm. in the absence of drug.

A most interesting and revealing series of observations were made when the influence of various anions on surface activity was measured. Figure 5 illustrates the results with chlorpromazine hydrochloride plus 0.1 M NaCl, NaBr, and NaI. One can see that compared to NaCl a marked increase in surface activity occurs with a change in counter-ion. The iodide ion seems to exert the greatest effect and the bromide next. Note in particular the complete loss of curvature in the presence of iodide ion so that the plot of surface pressure *versus* log concentration is linear down to zero π. Under the conditions of this particular experiment, chlorpromazine hydrochloride was quite soluble (up to $10^{-2}M$) in the presence of excess bromide and chloride ion but separated as an oil at about $9 \times 10^{-3}M$ CPZ in the presence of iodide ion. The oil, upon standing, turned into a solid which, when collected and re-
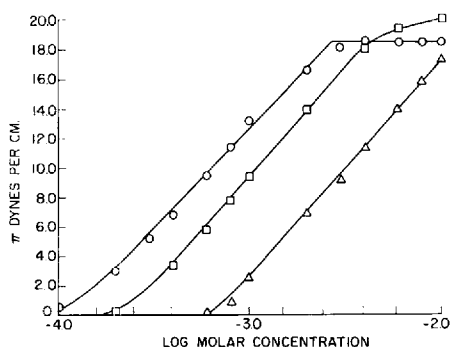
crystallized from isopropyl alcohol, was identified as chlorpromazine hydroiodide by comparison with a sample on hand.

Since both the hydrobromide and the hydroiodide of CPZ were available, a solution of each salt was prepared in a 0.1 M solution of NaCl and in 0.1 M of its own sodium halide salt. These were compared with the previous experiments and the results are given in Fig. 6. It is interesting to note that each salt of CPZ in the presence of 0.1 M NaCl exerts a small but significant effect as compared to CPZ–HCl. The rapidly rising curve for CPZ–HI appears particularly significant and suggests that the iodide ion is strongly interacted with CPZ. A comparison of CPZ–HCl and CPZ–HBr in 0.1 M NaBr indicates no significant difference except as one approaches upper limits of surface pressure. This would indicate that bromide ion can essentially replace Cl^-, so that the system is behaving as CPZ–HBr. An exaggerated example of Cl^- displacement was apparently seen with CPZ–HCl and 0.1 M NaI (Fig. 5), since marked surface activity occurred at much lower concentrations of CPZ. The results of experiments with the hydroiodide salt of CPZ in 0.1 M NaI were most interesting since no significant concentration of CPZ could be dissolved. Reduction of the concentration of the common ion (iodide) resulted in higher solubilities, but no concentrations approaching that of the hydrochloride in 0.1 M NaI could be reached. Apparently in the former case the oil produced *in situ* is more soluble than the crystalline salt. Such oil formation was also observed in the presence of the phthalate buffer in a previous study (3).

Since the buffer effects noted in a previous study appeared in the presence of organic anions, the authors chose to study a series of sulfonates which are completely dissociated over a wide range of pH values. Figure 7 shows the effect of adding 0.1 M solutions of sodium methane-, propane-, and benzenesulfonate. Compared to the hydrochloride, note the apparent increase in surface activity due to the latter two, while a significant decrease results in the presence of methanesulfonate ion. It is interesting that these results appear to parallel those seen

Fig. 4.—Plot of surface pressure, π, *vs.* log molar concentration for chlorpromazine at pH 5.0 and 25° in the presence of 0.5 M NH$_4$Cl, tetramethylammonium chloride, and tetraethylammonium chloride. Key: O, 0.5 M NH$_4$Cl; □, 0.5 M (CH$_3$)$_4$ N$^+$ Cl; △, 0.5 M (C$_2$H$_5$)$_4$ N$^+$ Cl.
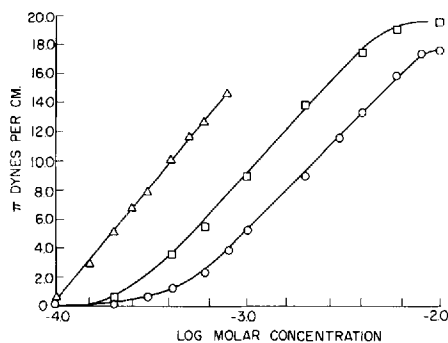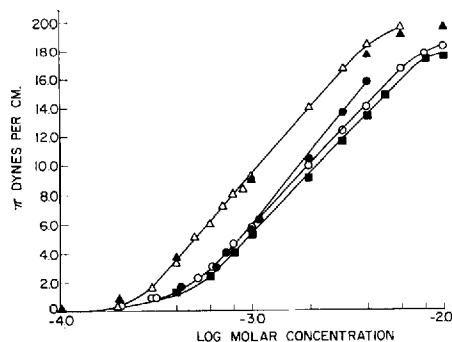
Fig. 5.—Plot of surface pressure, π, *vs.* log molar concentration for chlorpromazine at pH 5.0 and 25° in the presence of 0.1 M NaCl, NaBr, and NaI. Key: O, 0.1 M NaCl; □, 0.1 M NaBr; ∇, 0.1 M NaI.

Fig. 6.—Plot of surface pressure, π, *vs.* log molar concentration for various chlorpromazine halides at pH 5.0 and 25° in the presence of various sodium halides. Key: ▲, CPZ–HCl in 0.1 M NaBr; △, CPZ–HBr in 0.1 M NaBr; O, CPZ–HBr in 0.1 M NaCl; ●, CPZ–HI in 0.1 M NaCl; ■, CPZ–HCl in 0.1 M NaCl.
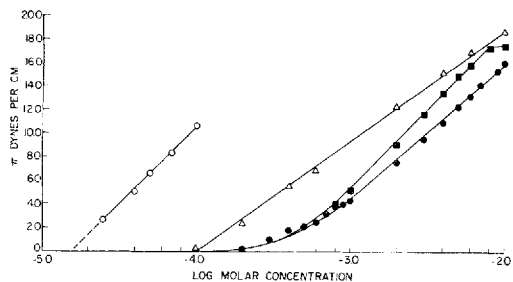
Fig. 7.—Plot of surface pressure, π, $vs.$ log molar concentration for chlorpromazine at pH 5.0 and 25° in the presence of various 0.01 M organic sulfonate solutions. Key: O, 0.1 M $C_6H_5SO_3Na$; $\triangle$, 0.1 M $C_3H_7SO_3Na$; $\bullet$, 0.1 M CH_3SO_3Na; $\blacksquare$, 0.1 M NaCl.

earlier with the buffers, in that the greatest increase in surface activity was seen with the aryl derivatives and an actual decrease was observed for the short chain species (3, 5). It may also be noted that, as in the case of iodide ion, there is complete loss of curvature for propane- and benzenesulfonate.

Figure 8 compares the same three sulfonates along with sodium-2-naphthalenesulfonate at a concentration of 0.01 plus 0.09 M NaCl. Here the marked surface activity due to the presence of the higher molecular weight anions may be noted. One can also observe that curvature is restored to the dilute propanesulfonate system and that there is no effect due to the methanesulfonate ion as compared to 0.1 M NaCl. As with the iodide system, oils were produced by the arylsulfonate system in the presence of CPZ but not by the aliphatics, but so far these oils have proved difficult to crystallize. Figure 9 indicates the effect of changing the benzenesulfonate concentration from 0.001 M to 0.1 M while maintaining an ionic strength of 0.1 with NaCl. Note the progressive reduction in concentration required for surface pressure development, the loss in curvature at higher concentrations of benzenesulfonate, and the fairly parallel slopes for all of the plots. Oil formation occurred at sulfonate concentrations of 0.01 M and higher.
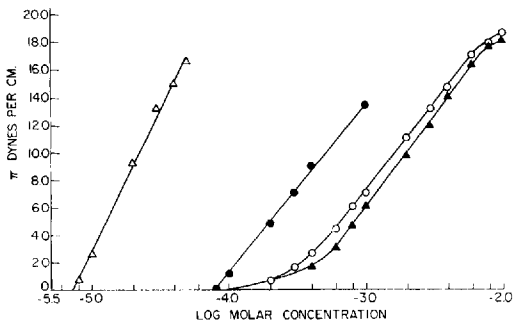

Fig. 8.—Plot of surface pressure, π, $vs.$ log molar concentration for chlorpromazine at pH 5.0 and 25° in the presence of various 0.01 M organic sulfonate solutions. Key: $\triangle$, 0.01 M 2-naphthalenesulfonic acid (Na$^+$); $\bullet$, 0.01 M benzene sulfonic acid (Na$^+$); O, 0.01 M propanesulfonic acid (Na$^+$); $\blacktriangle$, 0.01 M methanesulfonic acid (Na$^+$).

DISCUSSION

Factors Enhancing Surface Activity.—In general, it would appear that increases in surface activity in the presence of the various anions are due to some type of interaction with the CPZ cation. These interactions appear to be above and beyond the usual effects of electrolytes seen in Figs. 1 and 2. There, as seen with most ionic surfactants, the effect of increasing electrolyte concentration apparently produces penetration of the counterions between film molecules with a resulting increase in surface pressure (10). Additional electrolyte effects have been related to the hydration energies of the counterions (11) or, as the authors suspect with the anions considered here, to actual ion-pair formation of some type (12). Such interaction should produce a species which is more hydrophobic than the cation or anion alone. It is more than likely that the interactions involve secondary forces in addition to electrostatic forces since the increased hydrophobic nature and polarizability of the counterions appear to promote the effects we are seeing at the interface.
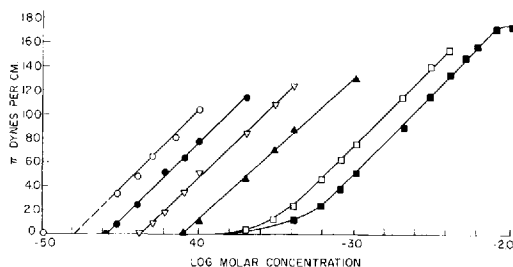

Fig. 9.—Plot of surface pressure, π, $vs.$ log molar concentration for chlorpromazine at pH 5.0 and 25° in the presence of various concentrations of benzenesulfonate. Key: O, 0.1 M $C_6H_5SO_3Na$; $\bullet$, 0.05 M $C_6H_5SO_3Na$; $\triangle$, 0.025 M $C_6H_5SO_3Na$; $\blacktriangle$, 0.01 M $C_6H_5SO_3Na$; $\square$, 0.001 M $C_6H_5SO_3Na$; $\blacksquare$, 0.1 M NaCl.

In all cases where marked increases in surface activity were noted the π *versus* log C curves appeared linear over the entire portion of the plot. Reduction of excess counterion concentration, while maintaining ionic strength, eventually restored curvature to the plots (Fig. 9, for instance) so that the degree of curvature seems related to the bulk solution state of the CPZ–anion pair. The linearity of such plots at concentrations just below the CMC has been reported for most common surfactants (13) but not over the entire plot. Such linearity implies a constant surface concentration, as seen when the Gibbs equation is applied, and it has been proposed that this is due to a hydration layer around the polar groups which prevents further increases in surface concentration (13). Elworthy and Mysels (14), however, have recently reported that constant surface concentration below the CMC, although thermodynamically possible, does not seem likely and does not occur as has been thought with sodium lauryl sulfate in water. Linear plots are believed to occur primarily because slight curvature is not easily detected and/or because corrections for activity coefficients and other bulk solution activity

effects are not included. In either case, therefore, in this region the linearity probably indicates that the change in surface concentration, if there is any, is very small and that the degree of surface coverage is very high. Fairly high surface coverage might be expected for the CPZ–anion systems since the anions probably produce fairly hydrophobic ion-pairs of rather large size; but, in order to prove this, radiotracer techniques (15) will be needed to directly measure surface concentration.

On the basis of the authors' experience with these systems, it is apparent that any situation producing a more hydrophobic form of chlorpromazine eventually produces an oil which appears to be more soluble than the crystalline form, at least in those cases where crystals have been isolated. This was seen also with the pure base as well as with the phthalate buffer in our earlier study (3). In addition, the solutions preceding the appearance of oil are quite surface active and yield the linear plots. In a sense, therefore, the solutions exhibiting linearity are in a supersaturated state which explains the apparent marked increase in thermodynamic activity. However, the exact state or degree of aggregation of the CPZ systems in this region remains unclear and is presently under study.

Factors Inhibiting Surface Activity.—The inhibition of surface activity by the quaternary ammonium salts and sodium methanesulfonate has raised many questions requiring more study. However, some clues related to the original observation of inhibition by the acetate buffer have been uncovered. If one only considers the effects of various quaternary ammonium ions, two major reasons for inhibition appear possible. Since they are cationic, as is CPZ, one might expect some competition at the air–solution interface. This could be a factor for the 0.1 M solutions of tetrapropyl and tetrabutyl derivatives since, in the absence of drug, they exhibited significant surface activity. However, the tetramethyl and tetraethyl derivatives are hardly surface active even at 0.5 M concentrations. Steigman *et al.* (16) have measured the effects of these quaternary ammonium ions on the CMC of hexadecyltrimethylammonium bromide with results similar to those reported here. Although some contribution was attributed to the surface activity of the short-chain compounds, the effects noted with the tetramethyl and tetraethyl derivatives caused them to consider an additional factor. This factor is the entropy change associated with the disorganization of water when molecules go to a surface or to a micelle. The authors feel that the presence of other alkyl groups tends to organize water structure in such a way as to reduce the tendency for nonpolar groups to leave an aqueous environment. Since alkyl anions such as methanesulfonate and acetate inhibit surface activity and yet cannot compete with CPZ, this mechanism seems quite plausible in the present case. Apparently beyond an anion

molecular size involving one or two carbons the interaction of the anion with CPZ offsets this tendency to cause inhibition. A stronger insight into this picture is seen with some preliminary data which indicate that urea, methyl urea, and 1,3-dimethyl urea, in increasing order, inhibit surface activity and CMC (5). The influence of urea and its derivatives on CMC and protein denaturation has been discussed (17); and, although a number of theories are proposed, they all evolve around alteration of water structure.

SUMMARY AND CONCLUSION

The surface activity of chlorpromazine at pH 5.0 at the air–solution interface was studied in the presence of a variety of inorganic and organic ions.

In addition to expected increases in surface activity due to increases in ionic strength, marked effects, apparently due to some type of interaction, were noted with bromide, iodide, propanesulfonate, benzenesulfonate, and naphthalenesulfonate ions. These results appear related to buffer effects observed previously.

Significant decreases in surface activity were observed in the presence of short chain quaternary ammonium ions and methanesulfonate ion. This strongly suggests the marked dependence of CPZ surface activity on the structure of water and the ability of environmental factors to influence the thermodynamic activity of this drug without necessarily interacting with it. This and other possible mechanisms will be the subject of future work.

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