# Effect of Chemical Modification on the Surface Activity of Some Phenothiazine Derivatives

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**Abstract** □ The ability of some substituted phenothiazines to reduce the surface tension of aqueous solutions has been studied in order to evaluate their hydrophobic behavior. Particular emphasis was placed on utilizing conditions that would allow specific structural effects to be isolated quantitatively and to point out situations where this may be difficult to do. Substitution on the phenothiazine ring enhances surface activity in the order $CF_3 \gg Cl > H$. Changing the position of the chloro group on the ring significantly influences surface activity, the order being 3Cl > 2Cl > 1Cl. The effect on surface activity due to changes in the number of alkyl groups, the degree of branching, and the number of dissociable groups on the alkylamino portion of the molecule also has been evaluated.

**Keyphrases** □ Phenothiazine derivatives—surface activity □ Surface activity, phenothiazines—chemical modification effect □ Structure, phenothiazines—surface activity relationship □ Concentration, phenothiazines—surface activity

The fact that many drugs exhibit surface-active properties has led to numerous studies concerned with their relative surface and biological activity (1). In particular, for many drugs exhibiting an apparent action at biological membrane surfaces, *e.g.*, local anesthetics (2) and the substituted phenothiazines (3, 4), significant surface activity at a variety of interfaces has been reported. This is not to say that surface activity is solely responsible for pharmacological activity, but rather that it reflects hydrophobic characteristics of a drug molecule, known to influence availability as well as reactivity at a site of action.

In previous reports from this laboratory (5, 6), it has been suggested that measurement of surface-tension change at the air–solution interface is a convenient means of observing the hydrophobic behavior of chlorpromazine without the necessity of introducing more complex hydrophobic phases such as oils, solids, or specific reactants. Such studies have shown that factors tending to promote hydrophobic character, *e.g.*, decreasing the degree of ionization, increasing ionic strength, and the presence of counterions exhibiting some tendency to ion-pair, all increase surface activity, while substances tending to reduce hydrophobic behavior, such as urea and the tetraalkylammonium salts, decrease surface activity.

The present study was designed to evaluate the effect of chemical modification on the surface activity and, hence, hydrophobicity of several phenothiazine derivatives. Consideration was given to a means of choosing solution conditions and a point of reference that could be used for more meaningful quantitative comparisons.

## EXPERIMENTAL

**Materials**—The chemical structure of each phenothiazine studied is given in Table I along with reported pKa values for the protonated species. Chlorpromazine, its 1-chloro, 3-chloro, ethylamino, and butylamino analogs, as well as trimeprazine, prochlorperazine, and trifluoperazine (Smith Kline & French Laboratories), triflupromazine (E. R. Squibb & Sons), and promazine and promethazine (Wyeth Laboratories) were used. All buffer ingredients and inorganic compounds were of reagent grade, while the water used was double distilled.

**Surface-Tension Measurement**—Surface tension was measured by means of the drop volume method using equipment and procedures described previously (7). All studies were conducted at 25 ± 0.1°. Great care was taken to avoid contact with light because of possible photodecomposition exhibited by the phenothiazines (8). All surface-tension data are expressed in terms of surface pressure, $\pi$, which is the difference between the surface tension of the solvent and that of a given solution being measured. Thus as surface tension is reduced, the surface pressure increases.

## RESULTS AND DISCUSSION

**Considerations in Evaluating Relative Surface Activity**—In order to make meaningful comparisons of various drugs, an appropriate set of conditions and a point of reference must be chosen. Two conditions which must be chosen with care are the pH and ionic strength of the solution. Since the phenothiazines can exist as protonated and nonprotonated species, comparisons should be made where only one species is present or where the ratio of one species to the other is constant. Studies with the nonprotonated form of the phenothiazines are extremely difficult because of their very great water insolubility, as well as their tendency to adsorb on all materials with which they come in contact (9). Comparison at a constant ratio of protonated to nonprotonated species also is difficult because there is no assurance that the two species of a phenothiazine, both of which adsorb, will exhibit the same ratio of relative surface activity as that for another derivative. Uncertainties in exact pKa values (Table I) also make this approach difficult. Thus, for comparing such systems, probably it is best to choose a pH value where all drugs studied exist only in the protonated form. Figure 1 demonstrates that one should be at a pH of 5.0 or less to obtain pH independence for phenothiazines having pKa values close to that of chlorpromazine. In the present study, therefore, all experiments were carried out at a pH of 5.0 or less, depending on the pKa of the drugs in question.[1]

The use of a protonated species introduces an electrical contribution to the free energy of adsorption since work is required to overcome the electrical repulsion of those molecules already adsorbed. Increasing the ionic strength would be expected to increase surface activity significantly since these repulsive forces would be screened out by the higher concentration of ions in the vicinity of the surface. Figure 2 shows that such effects for chlorpromazine are significant; and since this was observed for all compounds, ionic strength was maintained at one value throughout the study.

Once standard conditions of pH and ionic strength are chosen for comparing the surface activity of drugs, it is desirable to choose some means of expressing the relative surface activity of each drug. Ideally, comparing the bulk concentration required to produce a given number of adsorbed molecules per unit area would be of value. Ordinarily the number of adsorbed molecules per unit area can be determined by measuring the change in surface tension or surface pressure with bulk solution activity and then applying the Gibbs adsorption equation (16). The major difficulty with this approach is not knowing the thermodynamic activity of the drug in solution.

[1] Previous studies have indicated buffer effects to be possible, presumably due to counterion binding (9). In such studies, however, acetate buffers at concentrations used in the present study were found to have no effect on surface activity so buffer effects were not considered as a variable in this study.

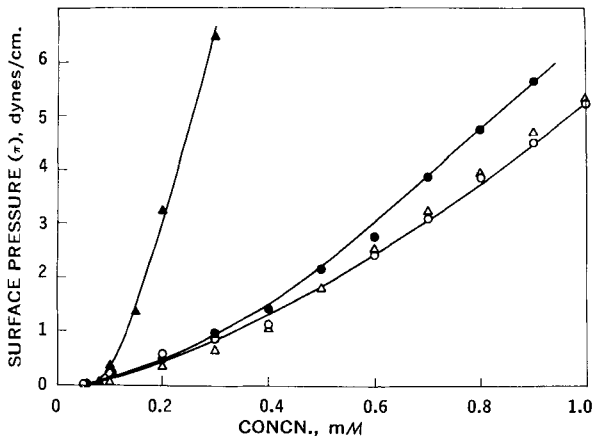



**Figure 1**—*Plot of surface pressure* versus *molar concentration for chlorpromazine at pH: 4.0* (○), *5.0* (△), *5.6* (●), *and 7.1* (▲) *at 25° and an ionic strength of 0.1.*

This is particularly applicable for the phenothiazines, where complex salt effects and aggregation have been noted (6, 9, 10).

In view of this and the need only to obtain relative surface activity under conditions which are identical except for the structural changes being considered, a much simpler approach can be used. What is done is to compare the bulk concentration of each drug required to produce a given surface pressure and to express this relative to one of the drugs. Solution concentration is kept as low as possible to minimize solution activity effects and, as stated earlier, all other conditions are maintained constant. Such a comparison, therefore, leads to a measure of the free energy change for adsorption relative to the drug chosen as the standard. If the $\pi$ *versus* concentration plot for the series of drugs is similar in curvature with about the same intercept, one can expect that the ratio of concentrations and hence the free energy change will be independent of the $\pi$ chosen for comparison. If, however, one merely chooses one arbitrary value without checking the complete curve or at least another surface pressure, results may be quite misleading (11, 12). As an extreme example, it is quite possible that some plots may intersect and give different relative values depending on where comparisons are made. To demonstrate this point, plots up to 5 or 6 dynes/cm. are presented and ratios are calculated at 3 and 5 dynes/cm.

**Comparison of the Various Phenothiazine Derivatives**—Figures 3 through 7 are presented to compare the surface activity of the various derivatives, each plot demonstrating the effect of one type of structural change. Based upon these results, the ratio of drug concentration required to produce 3 and 5 dynes/cm. surface pressure to the chlorpromazine concentration required to do this has been calculated and is presented in Table I. Values greater than one indicate less surface activity than chlorpromazine, while values less than one indicate a greater surface activity than chlorpromazine. The general agreement at 3 and 5 dynes/cm. seems to suggest that the free energy change for adsorption relative to chlorpromazine is independent of the surface pressure chosen at lower values of surface pressure.

Figures 3 and 7 and the ratios given in Table I illustrate the significant effect of changing the substituent on Position 2 of the

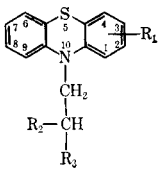
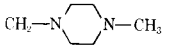
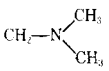
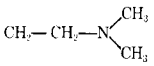
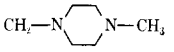
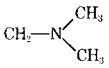
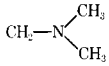
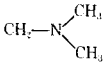
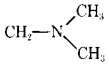
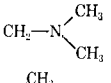


**Table I**—Phenothiazine Derivatives

| Drug | $R_1$ | $R_2$ | $R_3$ | Concn. Ratio, dynes/cm.[a] 3 | 5 | pKa[b] |
|---|---|---|---|---|---|---|
| Trifluoperazine | 2—$CF_3$ | H |  | 0.12 | 0.12 | 8.1, 8.4 |
| Triflupromazine | 2—$CF_3$ | H |  | 0.24 | 0.24 | 9.2 |
| Butyl chlorpromazine[c] | 2—Cl | H |  | 0.47 | 0.45 | 9.7 |
| Prochlorperazine | 2—Cl | H |  | 0.58 | 0.57 | 8.1, 7.5 |
| 3-Chlorpromazine[c] | 3—Cl | H |  | 0.62 | 0.63 | 9.2 |
| Chlorpromazine | 2—Cl | H |  | 1.0 | 1.0 | 9.3, 9.2 |
| 1-Chlorpromazine[c] | 1—Cl | H |  | 1.4 | 1.6 | 9.4 |
| Trimeprazine | H | $CH_3$ |  | 1.7 | 1.8 | — |
| Ethyl chlorpromazine[c] | 2—Cl | H |  | 2.2 | 2.2 | 8.6 |
| Promazine | H | H |  | 2.5 | 2.5 | 9.4, 9.5 |
| Promethazine | H | $CH_3$ |  | 2.7 | 2.6 | 9.1 |

[a] Concentration of drug required to produce a given surface pressure relative to concentration of chlorpromazine required. [b] Values are taken from *References 11* and *13–15*. [c] Actually only analogs of chlorpromazine without a generic name.

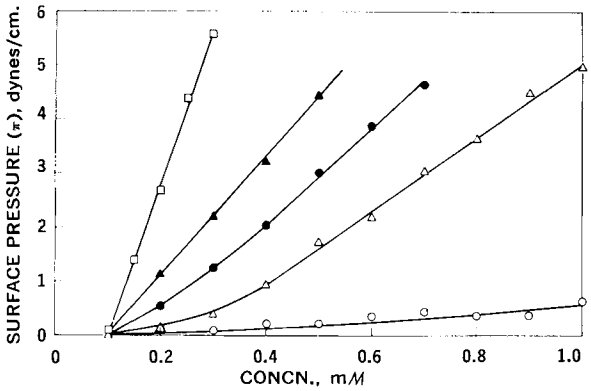



**Figure 2**—*Plot of surface pressure* versus *molar concentration for chlorpromazine at pH 5.0, 25°, and ionic strength: 0.01* (○), *0.10* (△), *0.15* (●), *0.20* (▲), *and 0.50* (□).

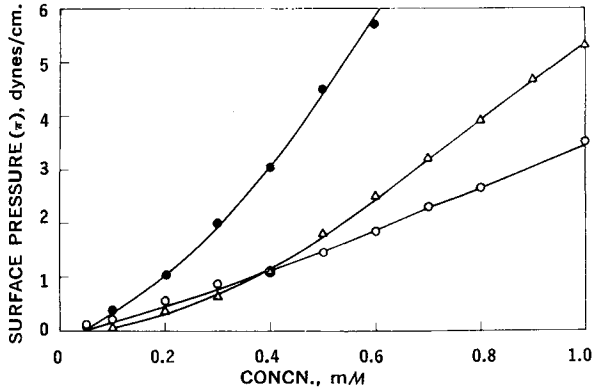



**Figure 4**—*Plot of surface pressure* versus *molar concentration at pH 5.0, ionic strength 0.1, and 25° for: 1-chlorpromazine* (○), *2-chlorpromazine* (△), *and 3-chlorpromazine* (●).

phenothiazine ring while holding other factors constant. Both compounds containing a —$CF_3$ group are many times more surface active than those containing a —Cl group, which in turn are more surface active than those containing only —H at that position. Picturing the phenothiazine molecules oriented at the interface with the ring toward the air and the alkylamino group directed toward the bulk aqueous phase, it is not surprising that changes in ring structure change surface activity so significantly. The strong contribution of the ring to the surface activity of the molecule, and hence its hydrophobic properties, is made apparent also by an earlier observation with chlorpromazine sulfoxide (5). Here, the addition of oxygen to the sulfur produces a hydrophilic species with a ratio of surface activity relative to chlorpromazine of about 100. Thus a polar group in the ring essentially eliminates any surface activity. The significant hydrophobic effect of adding the —$CF_3$ and —Cl group is made apparent further when one sees (Fig. 6) that trimeprazine, with four carbons in the alkylamino portion of the molecule but only —H on the ring, is significantly less surface active than any of the substituted propylamino derivatives which, of course, have only three carbons at that position.

Since the phenothiazine ring is the primary hydrophobic portion of the molecule, the ring position of substituent groups might be expected to have an effect on surface activity. Figure 4 compares chlorpromazine (2-chloro) with its 1-chloro and 3-chloro analogs. This figure and the ratios given in Table I indicate a fairly significant increase in surface activity as the chloro group is moved away from the vicinity of Position 10. It can be shown with molecular models that substitution at Position 1 definitely alters the orientation of the alkylamino group relative to the ring, restricting movement and limiting the number of possible orientations. No such effects are likely with the 2- and 3-chloro derivatives. In addition, intermolecular steric effects which also influence packing in the surface film may contribute to the difference between these compounds, although again little difference between the 2- and 3-chloro derivatives is noted with molecular models. In view of this, the significant increase in surface activity of the 3-chloro derivative may be more related to a change in the electronic structure of the phenothiazine ring. Evaluation with a wider variety of chemical structures would be extremely valuable in elucidating possible steric and electronic effects, but unfortunately the availability of just the right compounds is limited at the present time.

Figures 5–7 illustrate the effect of altering the nature of the alkylamino group at Position 10 of the ring. Comparing the ethyl, propyl, and butyl derivatives illustrates the well-known effect of increasing alkyl chain length on surface activity, an increase of one —$CH_2$— group giving about a twofold increase in activity. Comparison of the isomers, promazine and promethazine, indicates that the presence of a branched chain reduces surface activity relative to a compound with the same number of carbons. This agrees with the fact that branched chain hydrocarbons generally are less hydrophobic than their straight chain isomers. Examination of Fig. 7 illustrates the influence of adding a piperazine ring onto the propylamino group, namely, an increase in surface activity, presumably due to the extra carbons introduced into the molecule.

A closer analysis of the results with compounds differing at Position 10 demonstrates that great care must be taken in making simple correlations. It is apparent from Table I, for example, that the dissociation constant for the amino group is more sensitive to structural changes at this position. Thus it is especially important to compare these molecules at pH values much lower than the pKa value of the drug having the lowest pKa. Sometimes, as in the case of the piperazine compounds with two dissociable groups, this is not possible and quantitative correlation is made difficult. For example, as seen in Table I, the addition of only one —$CH_2$— group to chlorpromazine, giving the butyl derivative, produces a more surface-active molecule than prochlorperazine, with more $CH_2$ groups, because of the second ionized portion of the latter compound. Another situation where this factor apparently is important is when one compares the ratio of trifluoperazine to triflupromazine and that of prochlorperazine to chlorpromazine. If differences in surface activity are due only to the introduction of the same substituent, *i.e.*, the

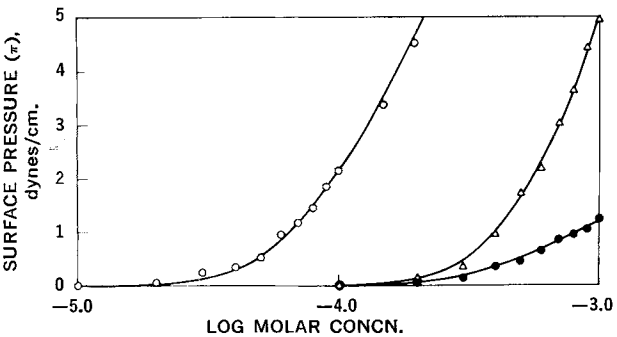



**Figure 3**—*Plot of surface pressure* versus *log molar concentration at pH 5.0, ionic strength 0.10, and 25° for: triflupromazine* (○), *chlorpromazine* (△), *and promazine* (●).

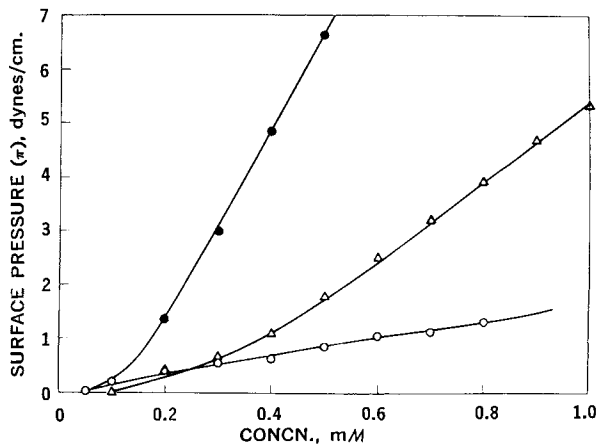



**Figure 5**—*Plot of surface pressure* versus *molar concentration at pH 5.0, ionic strength 0.1, and 25° for: ethyl chlorpromazine* (○), *propyl chlorpromazine* (△), *and butyl chlorpromazine* (●).

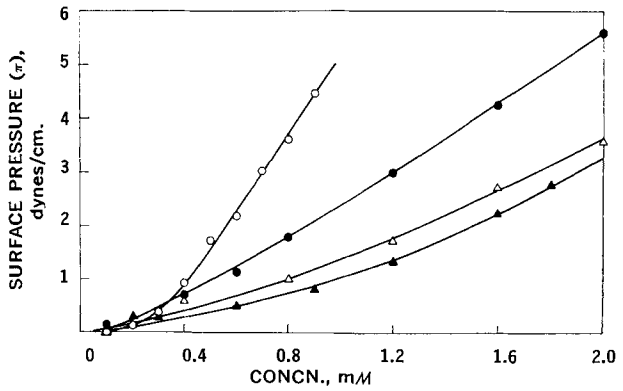



**Figure 6**—*Plot of surface pressure* versus *molar concentration at pH 5.0, ionic strength 0.1, and 25° for: chlorpromazine* (○), *trimeprazine* (●), *promazine* (△), *and promethazine* (▲).

piperazine ring, these ratios should be the same; however, the value for the $CF_3$ compounds is 0.50 and that for the Cl compounds is 0.59. What is happening, of course, is that at pH 4.0 all of these compounds are essentially completely protonated at one amino group, but the two piperazine derivatives have different second dissociation constants. Trifluoperazine has a dissociation constant of 3.9 while the value for prochlorperazine is 3.6. Hence at pH 4.0 the piperazine of trifluoperazine probably contributes more to the surface activity because it has introduced a lower degree of ionization to the molecule.

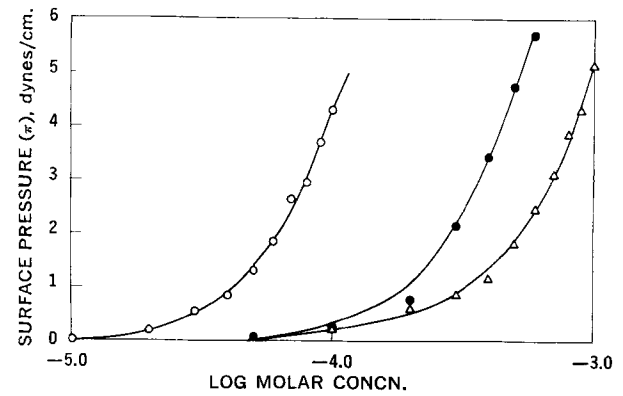



**Figure 7**—*Plot of surface pressure* versus *log molar concentration at pH 4.0, ionic strength 0.1, and 25° for: trifluoperazine* (○), *prochlorperazine* (●), *and chlorpromazine* (△).


## SUMMARY

The relative surface activity of various phenothiazine derivatives has been measured under solution conditions which for the first time allow meaningful comparison of structural effects.

Estimation of the concentration required to produce given changes in surface tension, relative to that produced by chlorpromazine, reveals significant effects due to substitution of H, Cl, and $CF_3$ groups on the phenothiazine ring. The position of a substituent on the ring has been shown to be another important factor.

The influence of changing the alkylamino group at Position 10 has been discussed in terms of changes in hydrophobicity due to the number and arrangement of alkyl groups. A primary factor to consider also is how substitution influences the dissociation constant(s) of the amino group(s) and hence the degree of ionization at the pH being utilized for comparison.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