Oil–Water Partitioning of Chlorpromazine and Other Phenothiazine Derivatives Using Dodecane and *n*-Octanol

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Abstract □ The apparent partition coefficients of chlorpromazine and some other phenothiazine derivatives in dodecane–water and *n*-octanol–water systems were measured at 30°. Results in the dodecane system at various pH values demonstrated that only the free base form partitions. Intrinsic partition coefficients for all derivatives, except the very polar metabolite chlorpromazine sulfoxide, range from 10^4 to 10^5, indicating the remarkable hydrophobicity of these molecules. Partitioning measurements in *n*-octanol indicate significant extraction of these drugs as ion-pairs, as well as higher intrinsic partition coefficients than in dodecane. Measurement of partitioning at various salt concentrations, utilizing different anions, allowed the calculation of extraction constants. Correlations between intrinsic partition coefficients in dodecane and extraction constants in *n*-octanol are presented. From these studies, it is clear that quantitative studies involving the phenothiazines in heterogeneous systems such as membranes must consider their extreme hydrophobicity and the various factors that influence such behavior.

Keyphrases □ Chlorpromazine, oil–water partitioning—dodecane, *n*-octanol □ Phenothiazine, oil–water partitioning—dodecane, *n*-octanol □ Partition coefficients, apparent—phenothiazines □ Electrolyte, pH effects—apparent partition coefficients, phenothiazines □ Extraction constants—phenothiazines

Previous studies have suggested significant hydrophobic behavior for chlorpromazine and other phenothiazines which appears to be related to their pharmacological activity (1, 2). Such behavior is demonstrated by the very low water solubility of the free base form (3), an apparently high cyclohexane–water partition coefficient (4), significant surface activity at various interfaces (5–7), and accumulation at various biological membranes *in vitro* (8). Measurement of surface activity at charged lipid monolayer surfaces (9, 10), binding to red blood cell ghost membranes at various pH values (11), significant protein binding (12), and accumulation in intestinal membranes during the absorption process (13) all indicate that the ionized form of these drugs participates in hydrophobic interactions when its charge is suitably neutralized by appropriate anions.

In view of these observations, it appeared important to evaluate quantitatively the hydrophobic properties of the phenothiazines so as to characterize the effect of chemical modification and the relative behavior of ionized and free base forms. For this purpose, the influence of variables such as pH, ionic strength, and specific anions on partitioning into dodecane and *n*-octanol was studied.

EXPERIMENTAL

Materials—The chemical structure of each phenothiazine studied is given in Table I. Chlorpromazine (CPZ);[1] chlorpromazine sulfoxide (CPZ-O);[1] 1-chloro, 3-chloro, ethylamino, and butylamino analogs of CPZ;[1] trifluoperazine (TFP);[1] triflupromazine (TPZ);[2] and promazine (PZ)[3] were studied. All buffer ingredients, electrolytes, and urea were of reagent grade. Sodium methane sulfonate and sodium ethane sulfonate were prepared by adding an equivalent amount of sodium hydroxide to the corresponding alkyl sulfonic acid, followed by recrystallization from absolute methanol. The *n*-dodecane and *n*-octanol[4] were a spectrally pure grade.

Determination of Apparent Partition Coefficients—In *n*-octanol–aqueous systems, *n*-octanol saturated with buffer and buffer saturated with *n*-octanol were used to minimize volume changes due to mutual miscibility. Equal volumes of the two solvents with given amounts of solute were placed together and shaken for at least 8 hr., the time required to ensure equilibrium. The two phases were then separated in a separator, and the aqueous phase was analyzed. The difference in amount of solute present before and after equilibration was taken as the amount partitioning into *n*-octanol. Occasional assay of the lipid phase confirmed the validity of this procedure.

For experiments in dodecane–aqueous systems, no presaturation of the two solvents was necessary and solute was analyzed in both phases. Analysis of the phenothiazines was performed spectrophotometrically (Hitachi UV spectrophotometer), employing 95% ethanol as the solvent, following the procedure of Warren *et al.* (14). The wavelengths of maximum absorption are given in Table I. Care was taken to avoid any decomposition of these drugs by eliminating contact with light. Concentrations of solute in the range 10^{-5} to 10^{-4} *M* were chosen to avoid any effects due to micellar aggregation noted earlier for these compounds (15). Temperature was maintained at 30°. In dodecane–water systems, ion strength was always adjusted with KCl; ions used in the *n*-octanol–water system varied and will be specified with the results. When referring to partition coefficients, the ratio of concentration in oil to that in water will always be used.

RESULTS

Partitioning in Dodecane—Dodecane was chosen as a typical hydrocarbon solvent after it had been shown that the oil–water partition coefficients in *n*-octane, *n*-decane, *n*-dodecane, *n*-tetradecane, and *n*-hexadecane did not differ significantly. The choice of dodecane was advantageous since it is readily available in a high quality grade and since mutual miscibility with water is negligible (16). Partition coefficients were found to be independent of: (*a*) the final aqueous concentration of drug up to 10^{-3} *M*; (*b*) the concentration and type of buffer; (*c*) the ionic strength over a range of 0.06 to 0.35; (*d*) different specific counterions used to adjust ionic strength, *e.g.*, Cl^-, Br^-, NO_3^-, and various alkyl sulfonates.

In view of the lack of effect by any of these parameters, particularly ionic strength and counterions, it would appear that only the free base form partitions into dodecane. This agrees with the conclusions of Reese *et al.* (4) concerning CPZ partitioning into cyclohexane and the work of others with many drugs (17–19).

To evaluate this quantitatively, apparent partition coefficients were determined over a pH range of 2.0 to 7.6 (Table II). If the free base is the only form partitioning, then the apparent partition coefficient, P_a, can be expressed in terms of P_t, the true or intrinsic partition coefficient of the free base, and f_B, the fraction of drug present as the free base. Thus,

$$P_a = f_B P_t \qquad \text{(Eq. 1)}$$

[1] Supplied by Smith Kline & French Laboratories.

[2] Supplied by Squibb Co.

[3] Supplied by Wyeth Pharmaceutical Co.

[4] Matheson, Coleman and Bell.

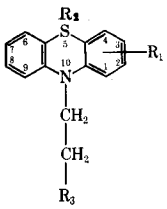

Table I—Chemical Structures of Phenothiazines

Drug	R_1	R_2	R_3	Wavelength of Maximum Absorbance,[a] mμ
Chlorpromazine	2-Cl	—	$-CH_2-CH_2-N(CH_3)_2$	257
Chlorpromazine sulfoxide (CPZ-O)	2-Cl	O	$-CH_2-CH_2-N(CH_3)_2$	239
Promazine (PZ)	H	—	$-CH_2-CH_2-N(CH_3)_2$	254
Triflupromazine (TPZ)	2-CF_3	—	$-CH_2-CH_2-N(CH_3)_2$	259
1-"Chlorpromazine"	1-Cl	—	$-CH_2-CH_2-N(CH_3)_2$	259
3-"Chlorpromazine"	3-Cl	—	$-CH_2-CH_2-N(CH_3)_2$	258
Ethyl "chlorpromazine"	2-Cl	—	$-CH_2-CH_2-N(CH_3)(CH_3)$	255
Butyl "chlorpromazine"	2-Cl	—	$-CH_2-CH_2-CH_2-N(CH_3)_2$	257
Trifluoperazine (TFP)	2-CF_3	—	$-CH_2-CH_2-N\langle\rangle N-CH_3$	260

[a] Solvent is 95% ethanol.

The value of f_B may be determined as

$$f_B = \frac{K_a}{K_a + [H_3O^+]} \qquad \text{(Eq. 2)}$$

where K_a is the dissociation constant of the conjugate acid of these drugs.

From Table II, it is apparent that the change in P_a with each unit of pH is about 10-fold, as predicted by combining Eqs. 1 and 2. Therefore, values of P_t were obtained from the slope of P_a *versus* f_B plots. Values for CPZ and a number of derivatives are listed in Table III, along with calculated values of P_a at pH 7.0. Since TFP has two dissociable groups, the fraction of free base was calculated by taking the two dissociation constants into account (20).

It should be pointed out that there is some uncertainty in the values of pKa for the phenothiazines, except for CPZ-O (Table III), since their significant water insolubility does not allow simple titration in aqueous solution. Thus, techniques such as influence of pH on solubility of the free base (3) and titration in mixed solvent systems (21) must be used. Although both methods agree fairly well, the very high partition coefficients of these compounds dictate that a small error in the choice of pKa will give a significantly different answer for P_t. For example, using a pKa of 9.3 for CPZ gives a P_t of 73,100; at 9.2, one obtains a value of 59,300.[5] Even small differences in pKa due to activity coefficient changes, therefore, will have an effect. For this reason, the authors chose to use values obtained by the same method (3, 23), thus ensuring more consistency when comparing relative hydrophobic properties of the various molecules (Table III). The value of 9.3 for CPZ was confirmed in the laboratory by solubility measurement, and the value for CPZ-O was determined by titration in water since its free base is sufficiently water soluble.

Table II—Effect of pH of the Aqueous Phase on the Apparent Partition Coefficient, P_a, of CPZ between Dodecane and Water at 30°

pH	P_a
2.0	0.003
3.6	0.120
4.0	0.320
5.0	3.80
5.6	13.80
6.6	137.0
7.6	1388

Partitioning in *n*-Octanol—In contrast to the dodecane studies, measurement of P_a in *n*-octanol was significantly influenced by the nature of the aqueous solution. For example, at pH 3.9 in a 0.1 *M* acetate buffer, the addition of 0.125 *M* KCl changed the P_a of CPZ from 4.6 to 32.4, while in 0.125 *M* KBr the value increased to 56.8. Altering the acetate buffer concentration up to 1.0 *M* increased the value to 23.3. These results and comparison of pH dependency with that seen in dodecane suggest that the free base has a higher intrinsic partition coefficient in *n*-octanol and that the ionic species is partitioning as an ion-pair. This can be seen in Table IV; the values of 32.4 and 32.8 mainly represent ionic species partitioning, while values at pH 6.6 and higher represent the free base contribution primarily. Exact analysis of pH data to obtain P_t values is not possible since each value is dependent on the buffer, its concentration, and the concentration of KCl used to adjust ionic strength. It may be assumed, however, that apparent partition coefficients obtained at pH values in excess of 6.6 are essentially due to the free base. Utilizing the value of P_a at pH 6.6 and a pKa of 9.3, a P_t for CPZ of about 250,000 was obtained. This is in good agreement with a value of 220,000 reported by Hansch (24), utilizing a P_a obtained at pH 6.8. Unfortunately, large amounts of drug were needed at such high pH values, and a limited supply of other derivatives did not allow the determination of the exact P_t values in *n*-octanol.

The effect of various electrolytes on the apparent partition coefficient of CPZ at pH 3.9 is presented in Table V by comparing the effect of 0.125 *M* concentrations of electrolyte, all other factors being equal. It may be concluded that inorganic counterions have a significant effect, whereas no differences are noted between the inorganic cations. It is interesting to note a reduced P_a for the methane and ethane sulfonates compared to Cl^- and this will be discussed later. Note also the significant reduction in partitioning when the tetraalkylammonium chlorides are used: the longer the alkyl chain length, the lower the value of P_a. In all cases, except for the tetraalkylammonium ions, increasing the electrolyte concentration increased partitioning; the opposite effect occurred with increasing organic cation concentration. This latter observation suggested a "water-structure" effect, so urea was added to a solution containing KCl. As seen in Table V, urea also decreases the value of P_a significantly.

The effect of counterions on the value of P_a can be measured quantitatively by determining an extraction constant, E_{X^-}, for each anion, X^-. Such a constant may be written for a 1:1 ion-pair

[5] Such large partition coefficients are usually expressed as logarithms (22); in this form, these values are 4.86 and 4.77, respectively.

Table III—Partition Coefficient for Various Phenothiazine Derivatives between Dodecane and Water at 30°

Compound	pKa	P_t	P_a at pH 7.0
CPZ	9.3	73,100	366
CPZ-O	9.0	0.75	0.0075
PZ	9.4	10,400	42
TPZ	9.2	137,000	863
1-CPZ	9.4	61,200	245
3-CPZ	9.2	46,300	292
Ethyl-CPZ	8.7	28,200	553
Butyl-CPZ	9.7	116,000	232
TFP	3.9, 8.1	12,900	97

as follows:

$$E_{X^-} = \frac{(CPZH^+X^-)_{org.}}{(CPZH^+)_{aq.}(X^-)_{aq.}} \quad \text{(Eq. 3)}$$

If one assumes the ion-pair, $CPZH^+X^-$, forms only in the organic phase and, therefore,

$$P_a = \frac{(CPZH^+X^-)_{org.}}{(CPZH^+)_{aq.}} \quad \text{(Eq. 4)}$$

then:

$$P_a = E_{X^-}(X^-)_{aq.} \quad \text{(Eq. 5)}$$

Equations can be written for the possible equilibria involving ion-pairing which occur with divalent anions ($SO_4^=$) or when two positive charges exist on TFP. However, since these constants are dependent on higher powers of drug or anion concentration, no meaningful comparisons independent of drug concentration are possible. Thus, no extraction constants are given for sulfate-ion extraction of CPZ or for chloride-ion extraction of TFP. Figures 1 and 2 show typical plots for 1:1 ion-pair partitioning. Tables VI and VII contain E_{X^-} values obtained from the slopes of these plots as predicted by Eq. 5. This equation predicts a zero intercept. However, in all cases, intercepts due to the acetate ion of the buffer were present. In all cases of 1:1 ion-pairing, no drug concentration dependence was observed for the E_{X^-} values obtained.

DISCUSSION

Partitioning of the Free Base—As was suspected from the earlier evidence of hydrophobic behavior, the intrinsic and apparent partition coefficients of the phenothiazine derivatives in dodecane and *n*-octanol are many orders of magnitude greater than those usually observed with acidic and basic drugs (17–19). The high intrinsic partition coefficient of the free base form demonstrates the need to consider its role when one assesses the effects of these drugs *in vitro* and *in vivo*, even 3–4 pH units below the apparent pKa. Because of these very high partition coefficients, it is important also to recognize the remarkable changes in hydrophobicity that can occur with very small changes in pH. This appears especially true in the pH range of 6–8 where so many *in vitro* and *in vivo* processes are studied. Likewise, at interfaces many steric and electrical factors can produce local pH changes which will alter partitioning without apparently influencing the bulk solution. This suggests, therefore, that any model system, or even a biological system such as a membrane, can produce significant selectivity with these molecules merely on the basis of free base partitioning.

Partitioning of the Ion-Pair—In view of the marked hydrophobic behavior of these molecules in very nonpolar hydrocarbon solvents as the free base, it is not surprising that the ionic species will partition when it can be effectively neutralized by an appropriate anion and solvated by a polar oil phase such as *n*-octanol. The need for solvation of the ion-pair in the oil phase has been studied by Higuchi *et al.* (25), utilizing pharmaceutical amines and mixtures of cyclohexane with chloroform, pentanol, or *p-tert*-butyl phenol. In each case, the proton-donating tendencies of the polar solvent were essential for partitioning of the ion-pair. Enhanced partitioning of tetracycline into cyclohexane when *n*-octanol is added presumably is due also to such a mechanism (26).

Table IV—Effect of pH on CPZ Partitioning in *n*-Octanol

pH	P_a
3.9	32.4
4.2	32.8
5.2	64.0
5.9	135.9
6.6	613.4

Table V—Apparent Partition Coefficient of CPZ into *n*-Octanol in the Presence of Various Salts at 0.125 *M* Concentration

Salt	P_a
Sodium chloride	32.3
Potassium chloride	32.4
Potassium bromide	56.8
Potassium nitrate	50.0
Sodium methane sulfonate	14.8
Sodium ethane sulfonate	25.1
Sodium propane sulfonate	54.5
Ammonium chloride	31.0
Tetramethylammonium chloride	26.1
Tetraethylammonium chloride	18.8
Tetrapropylammonium chloride	16.1
Potassium chloride + 2.0 *M* urea	12.8
Sulfate	15.0

What is most significant in the present study is the very large partition coefficient obtained for these drugs in the presence of very common inorganic ions at commonly encountered ionic strengths (Tables V and VII). These values are much greater than those found in *n*-octanol for most acids and bases in nonionized form (18), zwitterionic form (27), and as ion-pairs (23, 28). The effects of specific ions such as Cl^-, Br^-, NO_3^-, and $SO_4^=$ appear to follow an order expected for counterion binding to amines: the greater the polarizability and hydrophobicity of the anion, the greater this effect. The relatively small value of P_a for the sulfate ion appears to reflect the difficulty of ion-pairing when two CPZ molecules must interact with each sulfate ion to neutralize completely the partitioning species. When this is compared to other amine systems that show no tendency to partition in the presence of sulfate ion (29), the authors again conclude that the phenothiazines indeed are quite hydrophobic.

Comparison of extraction constants for the organic anions, such as acetate, and the alkylsulfonates reveals a significant reduction relative to that due to chloride ion. Likewise, whereas sodium, potassium, and ammonium ion exhibit no influence on partitioning, the tetraalkylammonium ions markedly reduce partitioning. These results may be interpreted by considering the various thermodynamic factors associated with partitioning of hydrophobic ions. In the oil phase, factors tending to promote partitioning will be the

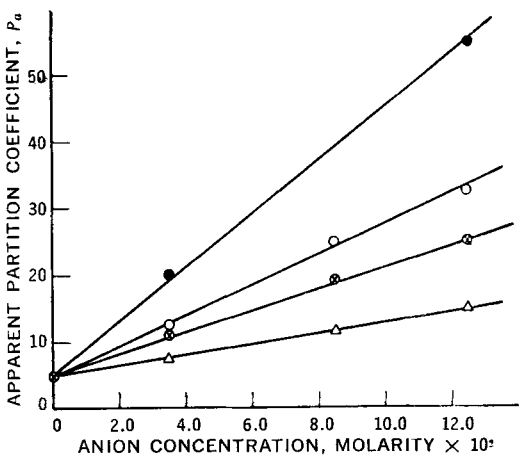

Figure 1—*Apparent partition coefficients for CPZ between* n*-octanol and aqueous buffers, pH 3.9, in the presence of various anions at 30°. Key: ○, chloride; ●, propane sulfonate; ⊗, ethane sulfonate; and △, methane sulfonate.*

Table VI—Extraction Constants for Various Anions with CPZ in *n*-Octanol

Anion	E_{X^-}
Chloride	197
Bromide	383
Nitrate	362
Acetate	213
Methane sulfonate	68
Ethane sulfonate	163
Propane sulfonate	374

electrostatic attraction of the ions (their size, shape, and charge) and the interaction of the ion-pair with the solvent, as already discussed. In the aqueous phase, the hydrophobic drug produces an increase in water structure in its vicinity and hence a decrease in water entropy, the process of transfer, therefore, being favored because of the resultant increase in water entropy after transfer. In the presence of tetraalkylammonium ions, however, partitioning of drug is reduced because a major proportion of water structuring now occurs around the added alkyl groups, reducing the entropy increase ordinarily produced by transfer.[6] This process, a form of salting in, has been noted for micelle formation (30) and surface tension reduction by CPZ (31), and has been discussed theoretically by Diamond (32). It also is presumed that the retarding effect of urea on partitioning into *n*-octanol and dodecane[7] is caused by water-structure effects.

The results obtained with acetate ion and the alkylsulfonates suggest a reduced tendency to partition when compared with chloride ion, which agrees with earlier observations that these substances reduce the surface activity of CPZ (31). It is possible that solvation of the ion-pair in *n*-octanol is not complete, but another factor must be operating since similar effects are seen at the air–solution interface. Again, water-structuring effects should be examined. One possibility is that acetate and the alkylsulfonates work like the tetraalkylammonium ions (32). Another possibility is the formation of an ion-pair in water with a reduced tendency to partition into oil. Diamond (32) has described the tendency of large hydrophobic ions to combine in water as "water-structure-enforced" ion-pairs, which lower the overall free energy of the aqueous phase without the necessity to expel the ion-pair. Whatever these

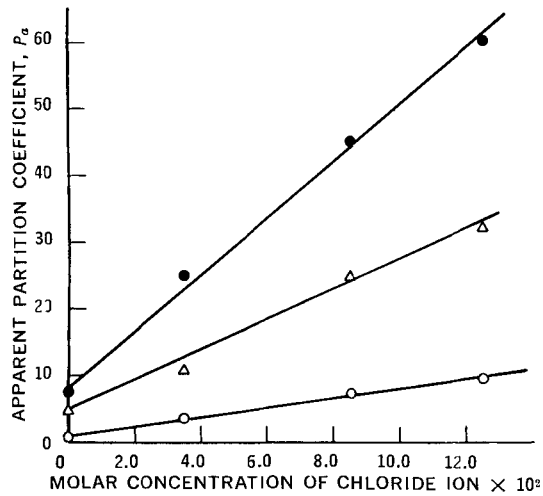

Figure 2—*Apparent partition coefficients for three phenothiazine derivatives between* n-*octanol and aqueous buffer, pH 3.9, in the presence of chloride ion at 30°. Key:* ○, *promazine;* △, *chlorpromazine; and* ●, *triflupromazine.*

[6] The possibility that the tetraalkylammonium ions could partition into octanol, and thus reduce the chloride ion available for CPZ partitioning, exists. However, no detectable partitioning of the tetramethyl- and tetraethylchlorides could be measured, while less than 1% of the tetrapropyl derivative appears to partition.

[7] The value of P_a for CPZ into dodecane at pH 4.0 is reduced in the presence of 2.0 *M* urea from 0.32 to 0.17.

Table VII—Partitioning of Various Derivatives in *n*-Octanol in Presence of KCl

Drug	E_{X^-}	P_a (0.125 *M* KCl)
CPZ	197	32.4
TPZ	384	60.0
PZ	58	8.1
CPZ-O	1.5	0.22
1-CPZ	114	17.0
3-CPZ	430	61.3
TFP	—	49.3

mechanisms are, it is clear that the nature of the aqueous phase must be considered significant in controlling the value of P_a. Furthermore, in the choice of buffers and electrolytes in any study with these drugs, one should keep these phenomena in mind.

Chemical Modification—The influence of chemical modification on the partitioning behavior of the phenothiazine derivatives would, of course, be of great interest when attempting to compare structure to biological activity. The approach used by Hansch *et al.* (22) to correlate *n*-octanol–water partition coefficients with such activity is well known. But, as stated earlier, no attempt was made here to determine values in *n*-octanol because of: (*a*) the limited supply of enough phenothiazines with appropriate substituent group variation, (*b*) the effects of ion-pairing due to buffers and salts present, (*c*) the uncertainty of exact pKa values, and (*d*) the necessity to work at pH values very much lower than the pKa of each drug because of very high intrinsic partition coefficients. However, a number of conclusions should be pointed out concerning structural effects which should be helpful in evaluating phenothiazine structure–activity data obtained in various *in vitro* and *in vivo* studies.

From the data presented in Tables III and VII, it is apparent that comparisons made in dodecane represent the behavior of the free base, while those made in *n*-octanol at low pH represent the ionic species. In both systems the hydrophobic properties of the drug are the major factors contributing to differences between molecules but, in addition, factors controlled by the nature of the ion-pairing mechanism are important in the case of partitioning into octanol. Thus, for example, the P_t values for the 1-, 2-, and 3-Cl derivatives of CPZ in dodecane are close and appear to show a maximum with the 2-Cl compound, whereas the order of extraction constants increases significantly from the 1- to 3-Cl position. The authors suggest that, in the latter case, steric and electronic effects on the ion-binding process are being seen in addition to hydrophobic behavior which occurs in the dodecane system. This latter order of behavior is seen also for adsorption of the ionic species of these derivatives to the air–solution interface (33). Following this reasoning helps to explain the reasonably consistent agreement between the two solvent systems when comparing TPZ and CPZ (about a twofold difference), since now all effects due to position on the ring should be the same. The somewhat poorer quantitative agreement when comparing the relative values of PZ may reflect an additional effect due to differences in size between the hydrogen atom and the other substituents.

Looking at some specific structural effects in both solvents, it is clear that substitution on the phenothiazine ring exerts a significant effect. The marked reduction in hydrophobicity when going from CPZ to CPZ-O clearly indicates why CPZ-O exhibits very little of the physical, chemical, and biological properties of CPZ (1, 9). A relatively large increase in hydrophobicity is also seen when Cl and CF_3 are placed on the aromatic ring, in good agreement with the results of biochemical and pharmacological structure–activity relationships (1, 2). From the results with the ethyl and butyl CPZ analogs and TFP, it is apparent also that the nature of the alkylamino portion is important: the greater the number of alkyl groups, the greater the partitioning tendency. Note, however, in Table III that substitution of this portion of the molecule has the greatest effect on pKa changes. Hence, comparisons near pH 7.0, for example, should be made with great caution so as not to attribute effects to the wrong species.

Finally, the behavior of TFP is interesting because its partitioning is not as great as expected, *i.e.*, the presence of a CF_3 group and more $-CH_2-$ groups than TPZ. The explanation in *n*-octanol centers on the presence of a second dissociated group for a sig-

nificant number of molecules at pH 3.9, which should increase polarity and reduce the ease of ion-pair formation. The presence of the polar nitrogen group also appears to reduce the partitioning tendency of TFP in dodecane, which agrees with the reported reduced water solubility of free base when going from CPZ to TFP (3). It also helps to explain the significantly lower accumulation of TFP relative to CPZ in rat intestinal membrane during drug absorption at pH 6.0 (13).

CONCLUSIONS

Based upon the results of this study, it is clear that studies designed to evaluate the behavior of phenothiazines *in vitro* and *in vivo* must consider the extreme hydrophobicity of these molecules. This study has demonstrated also that great variation in hydrophobicity exists between closely related compounds, as well as between different ion-pairs of the same compound. In biological systems, *in vitro* and *in vivo*, any number of membrane phases and anionic species may exist. Therefore, structure–activity studies must take into account the type of phenomena discussed in this paper when dealing with hydrophobic molecules such as the substituted phenothiazines.

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