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Report

Thermodynamics and Mathematical Modeling of the Partitioning of Chlorpromazine Between *n*-Octanol and Aqueous Buffer

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The distribution of chlorpromazine (CPZ) between aqueous buffer solutions and 1-octanol was studied over a wide range of pH, buffer concentration, and temperature. A mathematical model was developed to simulate the distribution profiles. It is assumed that only monomers of CPZ exist in the organic phase, whereas in the aqueous phase, association equilibria were assumed to occur. The model predicted the formation of dimers and no higher aggregates over most of the concentration range covered in this study. Thermodynamic parameters for the partition equilibria were evaluated from the equilibrium partition coefficients measured as a function of temperature. Positive values of ΔH and ΔS were obtained for the transfer of CPZ from the aqueous to the organic phase. The process is entropy controlled indicative of a hydrophobic interaction between CPZ and the aqueous solvent.

KEY WORDS: chlorpromazine; partition coefficients; association equilibria; ion pairing, hydrophobic effect; thermodynamics.

INTRODUCTION

Chlorpromazine (Fig. 1) and other phenothiazine drugs are fat soluble and surface active. Their amphiphilic nature is responsible for their ability to bind to biological membranes and to modify their physical properties (1–8). Previous studies have reported on the micelle forming properties of chlorpromazine (9,10), its surface activity (11–15), and "liquid membrane" formation (16,17).

The oil/water partitioning properties of chlorpromazine showed strong functions of pH and concentration. Association and micelle formation have been inferred from these studies (18–20).

The objective of the present study is to report partition measurements of chlorpromazine between aqueous acetate buffer and 1-octanol as a function of the concentration of the drug in the aqueous phase, the concentration of the buffer species, pH, and temperature. These data are rationalized in terms of a mathematical model describing the associative properties of chlorpromazine in the aqueous phase and the partition equilibria of all species. Thermodynamic parameters for the partition process are also developed. Studies were also undertaken to investigate the contributions from the nature of the buffering species and the capacity and ionic strength of the buffers toward the partitioning of CPZ between 1-octanol and aqueous media (23).

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MATERIALS AND METHODS

Materials

Chlorpromazine hydrochloride (CPZ · HCl) was purchased from Sigma Chemical Company (St. Louis, MO) and used as obtained. The water used throughout the study was deionized and glass-distilled. Buffer agents used in the partitioning study and in the high-performance liquid chromatography (HPLC) solvent system were glacial acetic acid, sodium acetate, and potassium acetate. Glacial acetic acid was obtained from Mallinckrodt Inc. (Paris, KY); sodium acetate and potassium acetate were obtained from Fisher Scientific Company (Fair Lawn, NJ) and used as received. Acetonitrile used for HPLC was HPLC grade and was obtained from Fisher Scientific Company (Fair Lawn, NJ). Benzil received from UIC Inc. (Joliet, IL) was used as the reference compound for the calibration of the vapor pressure osmometer.

Methods and Procedures

Partition Coefficient Measurements

1-Octanol was used as the organic phase and acetate buffer was used as the aqueous phase. To minimize volume changes due to mutual miscibility of the solvents, the aqueous and organic phases were presaturated with each other at each of the temperatures studied before being used.

Equal volumes of the two solvents with given amounts of CPZ · HCl dissolved in aqueous phase (2×10^{-5} to 10^{-1} *M*) were placed together and shaken for at least 2 hr in a

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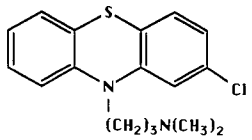

Fig. 1. Structure of chlorpromazine.

thermostated water bath. The temperature of the water bath was controlled to within ±0.5°C. Care was taken in order to exclude light throughout the equilibration process. The two phases were then separated by centrifugation. The concentration of CPZ in both phases was analyzed by HPLC. The partition coefficient of CPZ (K_{app}) was calculated from the equation $K_{app} = C_{org}/C_{aq}$, where C_{org} is the concentration of CPZ in the organic phase and C_{aq} is the concentration of CPZ in the aqueous phase. The pH of the aqueous phase for each sample was always measured before and after partitioning.

High-Performance Liquid Chromatographic Analysis of CPZ

The concentration of CPZ in both phases was analyzed by HPLC. The liquid chromatographic system consisted of a Waters Associated (Milford, MA) Model 6000A pump, a U6K variable-volume injector, and a Model 440 fixed ultraviolet absorbance detector at 254 nm. A 20-μl aliquot was injected and separated with a Shandon CPS (cyanopropyl silica) Hypersil 5-μm (150 × 4.6-mm) column. All analyses were performed at ambient temperature. The mobile phase consisted of 30% 50 m*M* potassium acetate buffer (pH 4.0) and 70% acetonitrile. For samples containing high concentrations of CPZ appropriate dilutions of the samples were accomplished by using the mobile phase.

pH Measurements

Measurements of pH were accomplished using a Corning Digital Model 112 pH meter (Corning, NY) equipped with a Cole Parmer combination pH electrode (Chicago, IL).

Vapor Pressure Osmometry

The determination of the state of association of chlorpromazine in the organic phase was accomplished by a UIC Inc. Knauer vapor pressure osmometer (Joliet, IL) with a universal thermistor probe. The probe was applicable to the temperature range from 25 to 70°C.

In this method, the temperature difference between a reference solution (benzil/1-octanol) or a sample solution (CPZ · HCl/1-octanol) and the pure solvent (1-octanol) at steady state is determined. Thermistors are employed as temperature sensors, and their electric resistance ΔR is measured with a Wheatstone bridge. The resulting ΔR values are proportional to the osmolal concentration of the solute (21,22).

RESULTS AND DISCUSSION

The partition profiles of CPZ between 1-octanol and sodium acetate buffer, pH 4.76, and 25°C are shown in Fig. 2 at acetate concentrations varying from 0.025 to 0.2 *M*. No attempt was made to control ionic strength because preliminary experiments had shown that all anions strongly affected the values of K_{app}, presumably due to specific ion association with CPZ. The pH's of the aqueous phases were measured after equilibration and were found to remain constant at pH 4.76 for all CPZ concentrations below 3×10^{-4} *M*. At higher concentrations of CPZ, the pH of the aqueous phase after partitioning decreased. Increasing the acetate concentration in the aqueous phase increases the partition into the organic phase as observed previously by Murthy and Zografi (21). In view of the strong effect of counterion concentration on the partition coefficient, measurements of K_{app} were performed at a constant acetate concentration (0.0125 *M*) with varying pH. The results of this study are shown in Fig. 3.

In order to determine the thermodynamic parameters for the partition process, the effect of temperature on K_{app} was determined. As seen in Fig. 4, increasing the temperature increases the affinity of CPZ for the organic phase for concentrations of CPZ less than 10^{-3} *M*. At higher concentrations a reversal in the order is observed.

DEVELOPMENT OF A MATHEMATICAL MODEL FOR THE PARTITION PROCESS

Previous studies and the data from this investigation show that the partition of CPZ between aqueous solutions and a less polar medium is influenced by several variables including the pH, counterion concentration in the aqueous phase, and temperature. A complete description of the partition equilibria is also complicated by the association of CPZ as dimers and higher oligomers. A model for describing these phenomena is shown in Fig. 5.

According to this model, it is assumed that (a) CPZ partitions between the two phases as free base (B) and as ion pairs of the protonated species (BH^+X^-); (b) only the monomeric form of CPZ (i.e., B and BH^+X^-) partitions into the organic phase; (c) CPZ does not self-associate in the organic phase; (d) self-association of CPZ (B and BH^+) in the aqueous phase is an equilibrium involving monomers → dimers; and (e) there is no distinction between the ionized (BH^+) and the nonionized (B) forms of CPZ in the equilibria of association in the aqueous phase.

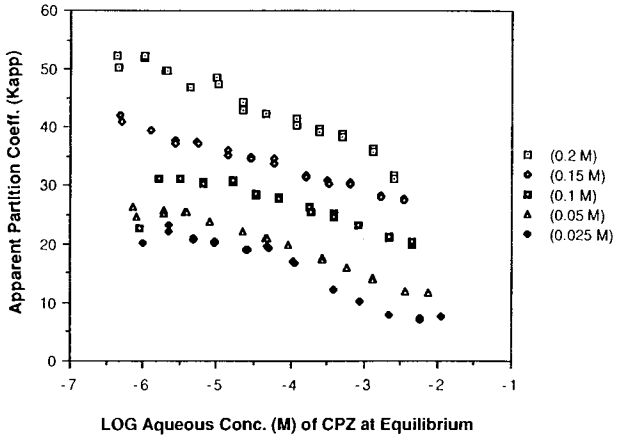

Fig. 2. Distribution profile of chlorpromazine hydrochloride between 1-octanol and sodium acetate buffer at 25°C. Effect of varying buffer concentration at pH 4.76.

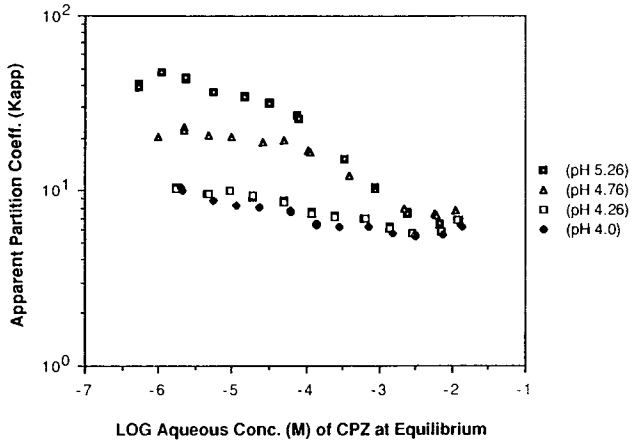

Fig. 3. Distribution profile of chlorpromazine hydrochloride between 1-octanol and sodium acetate buffer at 25°C. Effect of varying pH of the acetate buffer at constant acetate ion concentration (0.0125 *M*).

The assumption that CPZ present in the 1-octanol phase was not associated was tested by vapor pressure osmometry (21,22). The osmolalities of a test solution ($m_s \cdot \varnothing_s$) and the reference solution ($m_r \cdot \varnothing_r$) are related to the measured resistance ratio from the vapor pressure osmometer by the equation

$$\frac{m_s \cdot \varnothing_s}{m_r \cdot \varnothing_r} = \frac{\Delta R_s}{\Delta R_r}$$

where

m = molality
$\varnothing$ = osmotic coefficient
ΔR = change in resistance

The subscripts "s" and "r" refer to the test and reference solutions, respectively.

Benzil (diphenylethanedione), a non-self-associating molecule, was used as a reference solute for vapor pressure studies in 1-octanol. A deviation from unity in the ratio of the osmotic coefficient of the sample to the reference solute ($\varnothing_s/\varnothing_r$) represents the extent of association of the sample molecules in the chosen solvent. Table I shows the ratio of the osmotic coefficients of CPZ to that of benzil ($\varnothing_{cpz}/\varnothing_{benzil}$) at 35, 45, and 55°C.

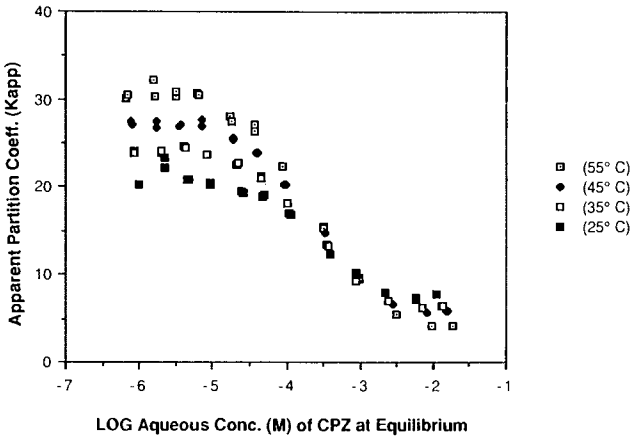

Fig. 4. Distribution profile of chlorpromazine hydrochloride between 1-octanol and pH 4.76 sodium acetate buffer (0.025 *M*). Effect of varying the temperature.

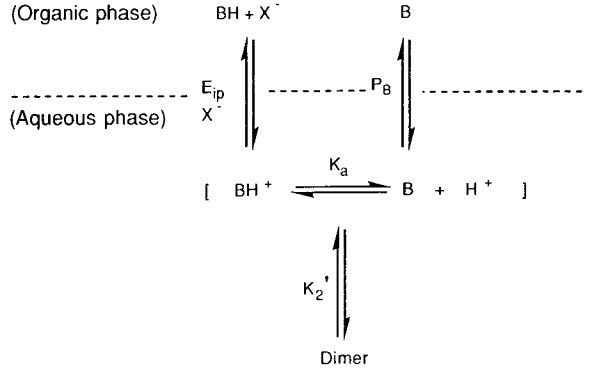

Fig. 5. A schematic representation of the possible equilibria involved in the partitioning of CPZ between 1-octanol and aqueous acetate buffer.

The ratios presented in Table I are fairly close to unity, suggesting that in the range of concentration investigated CPZ exists as monomers in the 1-octanol phase at each of the temperatures investigated.

Measurements were attempted at 25°C, but these were not reproducible due to the low vapor pressure of 1-octanol.

At low equilibrium concentrations it is assumed that CPZ exists only as monomers in both phases. Considering that CPZ may partition in the monomeric form as two different species, namely, the neutral free-base species (B) and as the ion pair (BH^+X^-) of the protonated species, then at equilibrium the following relationships apply:

$$C_{aq} = [BH^+]_{aq} + [B]_{aq} = [M]_{aq} \quad (1)$$
$$C_{org} = [BH^+X^-]_{org} + [B]_{org} \quad (2)$$
$$C_{org} = K^\circ_{app} \cdot [M]_{aq} \quad (3)$$

and the intrinsic partition coefficient K°_{app} can be expressed as

$$K^\circ_{app} = \frac{C_{org}}{M_{aq}} \quad (4)$$

where C_{aq} is the total concentration of CPZ in the aqueous phase; C_{org} is the total concentration of CPZ in the organic phase; K°_{app} is the intrinsic partition coefficient of CPZ monomers at a given pH in the infinitely dilute solution; $[BH^+]_{aq}$ is the concentration of protonated species of CPZ present in the aqueous phase; $[B]_{aq}$ is the concentration of CPZ present as the free base in the aqueous phase;

Table I. Vapor Pressure Osmometric Determination of $\varnothing_{cpz}/\varnothing_{benzil}$ Ratio in 1-Octanol

CPZ · HCl concentration (*M*)	$\varnothing_{cpz}/\varnothing_{benzil}$		
	35°C	45°C	55°C
0.0028	0.90	0.94	0.96
0.0053	0.92	0.91	0.94
0.0124	0.93	0.93	0.94
0.0217	0.89	0.93	0.95

$[BH^+X^-]_{org}$ is the concentration of ion pairs of the protonated CPZ (BH^+) with appropriate counter ion (X^-) present in the organic phase; $[B]_{org}$ is the concentration of CPZ present as the free base in the organic phase; and $[M]_{aq}$ is the total concentration of monomer present in the aqueous phase.

The fraction of the ionized species (f_{BH^+}) and nonionized species (f_B) of CPZ, the extraction constant (E_{ip}) of the ionized species into the organic phase, and the partition coefficient (P_B) of the nonionized species are expressed by the following relationships:

$$f_{BH^+} = \frac{[H^+]}{[H^+] + K_a} \tag{5}$$

$$f_B = \frac{K_a}{[H^+] + K_a} \tag{6}$$

$$E_{ip} = \frac{[BH^+X^-]_{org}}{[BH^+]_{aq} \cdot [X^-]_{aq}} \tag{7}$$

$$P_B = \frac{[B]_{org}}{[B]_{aq}} \tag{8}$$

where K_a is the dissociation constant of the protonated CPZ.

Substituting Eq. (1) and Eq. (2) for C_{aq} and C_{org}, respectively, and using the relations from Eqs. (5)–(8) in Eq. (4) results in Eq. (9).

$$K^\circ_{app} = E_{ip}[X^-]_{aq} \cdot f_{BH^+} + P_B \cdot f_B \tag{9}$$

$[X^-]_{aq}$ is the concentration of the counter ion present in the aqueous phase at equilibrium. If the medium contains more than one counter ion, then

$$E_{ip}[X^-]_{aq} = \sum_{n=1}^{N} (E_{ip,n}[X^-]_{aq,n})$$

For low concentrations of CPZ, the total equilibrium concentration of CPZ in the organic phase $[M]_{aq}$ may be obtained using Eq. (3).

At higher concentrations if CPZ self-associates in the aqueous phase, then according to mass action and assuming that the formation of different sizes of aggregate from the monomer are independent of each other, the total equilibrium concentration of CPZ in the aqueous phase may be expressed as

$$C_{aq} = [M]_{aq} + 2K'_2[M]^2_{aq} + 3K'_3[M]^3_{aq} + \cdots \tag{10}$$

where K'_2 and K'_3 represent composite association constants for the neutral (B) and protonated (BH^+) forms of CPZ.

The experimentally determined apparent partition coefficient (K_{app}) of CPZ is expressed as

$$K_{app} = \frac{C_{org}}{C_{aq}} \tag{11}$$

Introducing Eq. (3) for C_{org} and Eq. (10) for C_{aq}, we may write

$$\frac{K^\circ_{app}}{K_{app}} = 1 + 2K'_2[M]_{aq} + 3K'_3[M]^2_{aq} + \cdots \tag{12}$$

Since the degree of self-association is markedly dependent on the concentration of the associating species, it may be expected that in relatively dilute solutions dimerization would be the primary equilibrium, and as the concentration is increased the tendency to form higher aggregates would be more pronounced. With this consideration a rather simple test for the proposed model can be made.

If, at low concentration of CPZ, the formation of dimers is the primary equilibrium, then Eq. (12) can be reduced to

$$\frac{K^\circ_{app}}{K_{app}} = 1 + 2K'_2[M]_{aq} \tag{13}$$

where $[M]_{aq}$ is obtained from Eq. (3). A straight-line relationship expressed by eq. (13) for the experimental data would show that only dimers exist in the system. If higher aggregates form, Eq. (12) with additional terms $K'_3, K'_4, \ldots,$ would be required (22).

In order to be able to use Eq. (13) for testing of the proposed model, the values of K°_{app} and $[M]_{aq}$ for each data point need to be known.

Since CPZ can partition into 1-octanol as ion pairs of the protonated form (21), the equilibrium concentration of the counter ion species remaining in the aqueous phase $[X^-]_{aq}$ would be unknown for each data point. Thus, to calculate K°_{app} and $[M]_{aq}$, and to test further the model as well as to calculate K'_2, it was necessary to obtain $[X^-]_{aq}$ for each data point.

Since acetate ion was present as a buffer species in this partition study it was not possible to ascertain the influence of the chloride ion on the partitioning of CPZ. Chloride ion was always introduced into the system by CPZ · HCl salt. Murthy and Zografi (21) reported very similar extraction constants for chloride and acetate ions ($E_{ip,OAc^-} = 213$, $E_{ip,Cl^-} = 197$). Hence, it is assumed that chloride and acetate have similar capabilities of forming ion pairs with CPZ and partitioning into the organic phase (i.e., assuming $E_{ip,OAc^-} = E_{ip,Cl^-}$). Therefore, for the purpose of simplifying the mathematical treatment of the data the two counter ions (acetate and chloride) present in the system were considered as a single species of counter ion. Mathematically the above assumption may be expressed as

$$E_{ip,Cl^-} \cdot [Cl-]_{aq} + E_{ip,OAc^-} \cdot [OAc^-]_{aq} = E_{ip} \cdot [X^-]_{aq}$$

and

$$[BH^+Cl^-]_{org} + [BH^+OAc^-]_{org} = [BH^+X^-]_{org}$$

Substituting the value of K°_{app} from Eq. (9) into Eq. (10) gives

$$C_{org} = (E_{ip} \cdot [X^-]_{aq} \cdot f_{BH^+} + P_B \cdot f_B) \cdot [M]_{aq} \tag{14}$$

and

$$\begin{aligned} [X^-]_T &= [X^-]_{buffer} + [X^-]_{cpz} \\ &= [BH^+X^-]_{org} + [X^-]_{aq} \\ [X^-]_T &= (E_{ip} \cdot [X^-]_{aq} \cdot f_{BH^+}) \cdot [M]_{aq} + [X^-]_{aq} \end{aligned} \tag{15}$$

where $[X^-]_T$ is the total concentration of the counter ion present in the system. By solving Eqs. (14) and (15) simultaneously, the values of $[X^-]_{aq}$, $[M]_{aq}$, and then K°_{app} for each of the data points could be calculated.

However, to be able to solve the above two simultaneous equations, values of E_{ip} and P_B had to be determined.

According to Eq. (9), K°_{app} would be a function of the

total anion concentration in the aqueous phase $[X^-]_{aq}$ and the pH of the aqueous medium only if the extraction constant, E_{ip}, and intrinsic partition coefficient of the neutral species, P_B, were invariant with both $[X^-]_{aq}$ and pH of the aqueous medium.

A plot of K°_{app} versus f_B for a fixed $[X^-]_{aq}$ concentration would give a linear relationship. E_{ip} and P_B could then be obtained, respectively, from the intercept and slope of such a plot. To obtain E_{ip} and P_B a series of experiments was conducted at different pH values using acetate buffer at a fixed acetate ion concentration (Fig. 3). Under these experimental conditions and at very low concentrations of CPZ, the total counter ion concentration, $[X^-]_T$, could be considered to be derived only from the acetate ion of the buffer. Also, under these experimental conditions the equilibrium acetate concentration in the aqueous phase could be considered to be not significantly different from the initial acetate ion concentration of the buffer. Therefore,

$$[X^-]_T = [X^-]_{buffer} = [X^-]_{aq}$$

From the plot of K°_{app}, which is obtained at the lowest CPZ concentrations, versus the fraction of the neutral form of CPZ, (f_B) values of both E_{ip} and P_B were calculated from the intercept and slope and determined to have the values of 554 M^{-1} and 4.123×10^5, respectively (Fig. 6).

In the solution of Eqs. (14) and (15), the values of f_{BH^+} and f_B were fixed by the choice of the buffer pH. The total counter ion concentration present in the system was calculated by adding the free acetate ion concentration obtained from the buffer to the chloride ion concentration obtained from the hydrochloride salt of CPZ, and the concentration of CPZ in the organic phase was determined by HPLC.

Making use of these values of E_{ip}, P_B, $[X^-]_T$, C_{org}, f_{BH^+}, and f_B, the values of $[X^-]_{aq}$ and $[M]_{aq}$ for each experimental point were calculated by solving the simultaneous Eqs. (14) and (15). The K°_{app} value for each experimental point was then estimated by using Eq. (9). In these studies the pH was kept constant and as a result, K°_{app} was only a function of $[X^-]_{aq}$.

From the estimated values of $[M]_{aq}$ and K°_{app}, calculated for each point, the aggregation number of CPZ in the aqueous phase was determined using Eq. (13). This testing of the mathematical model was conducted for the data obtained from the experiments which were performed at different pH, with a fixed concentration of the acetate ion. A linear relationship was found only with Eq. (13), suggesting that dimerization was the predominant aggregation process for CPZ in the aqueous phase (Fig. 7). The dimerization constants (K'_2), calculated for the aggregation of CPZ in acetate buffer at different pH values, each containing a constant acetate ion concentration (0.0125 M), are listed in Table II. Atwood *et al.* (24) reported the existence of an aggregate of 11 monomers in water and Nichol *et al.* (25) reported the occurence of 35-mer aggregates in a 0.15 μM solution of sodium chloride. In this study the aggregates of CPZ were predicted to exist predominantly as dimers over a wide range of concentration. This observation of aggregation in an aqueous phase in equilibrium with an organic phase was significantly different from previous reports in the literature for self-association of CPZ.

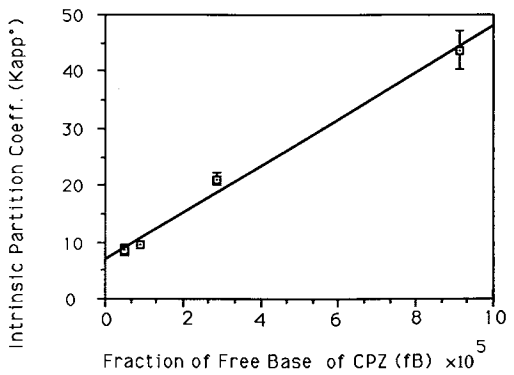

Fig. 6. Calculation of the extraction coefficient (E_{ip}) for the chlorpromazine ion pair ($CPZH^+X^-$) and the intrinsic partition coefficient (P_B) for the free base (CPZ) using data from Fig. 3 and the relationship $K^\circ_{app} = E_{ip} \cdot [X^-]_{aq} \cdot f_{BH^+} + P_B \cdot f_B$.

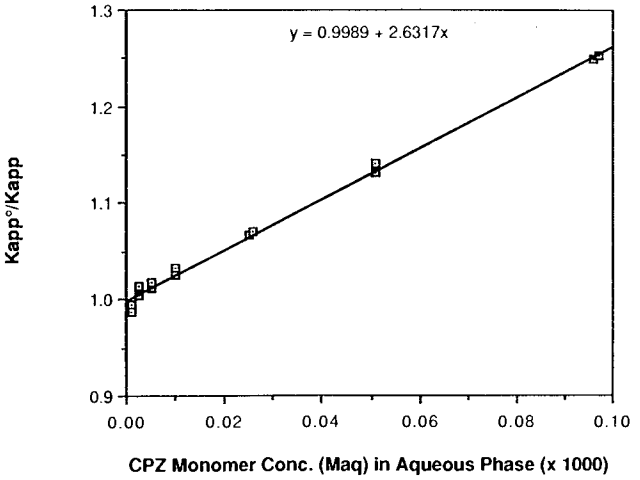

Fig. 7. Plot testing the occurrence of CPZ dimers in the aqueous phase at 25°C according to the equation $(K^\circ_{app}/K_{app}) = 1 + 2K'_2[M]_{aq}$.

The calculated values of K°_{app}, $[M]_{aq}$, and K'_2 were used to simulate the distribution profiles of CPZ between 1-octanol and acetate buffer with constant acetate ion concentration using Eqs. (3), (11), and (16),

$$C_{aq} = [M]_{aq} + 2K'_2[M]^2_{aq} \qquad (16)$$

Figures 8 to 10 show the model generated partition isotherms together with the experimental data for each study. The model was found to be appropriate as is evident by the good agreement obtained for the three pH values shown in Figs. 8 to 10. Using the mathematical relationships developed for modeling the partition behavior of CPZ, the distribution pro-

Table II. The Calculated Values for the Dimerization Constant (K'_2) of Chlorpromazine in Sodium Acetate Buffer at Different pH's with a Constant Acetate Ion (OAc^-) Concentration (0.0125 M) in the Buffer

pH	K'_2 (M^{-1})
4.00	1.45×10^3
4.26	1.75×10^3
4.76	1.32×10^3

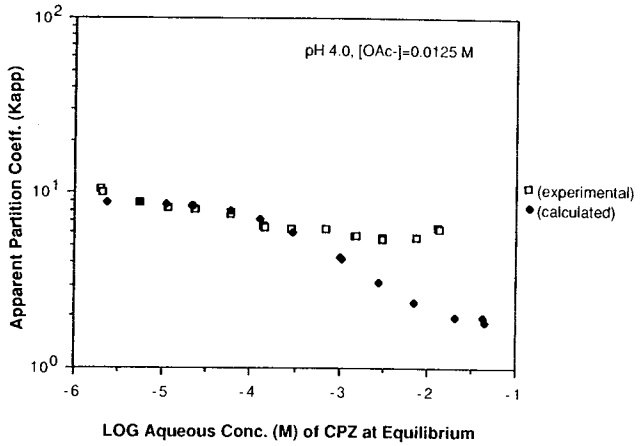

Fig. 8. Experimental and simulated distribution profiles of chlorpromazine hydrochloride between 1-octanol and sodium acetate buffer with a constant acetate ion concentration (0.0125 *M*) and varying the pH of the buffer. I. pH 4.0 acetate buffer (0.0839 *M*) at 25°C.

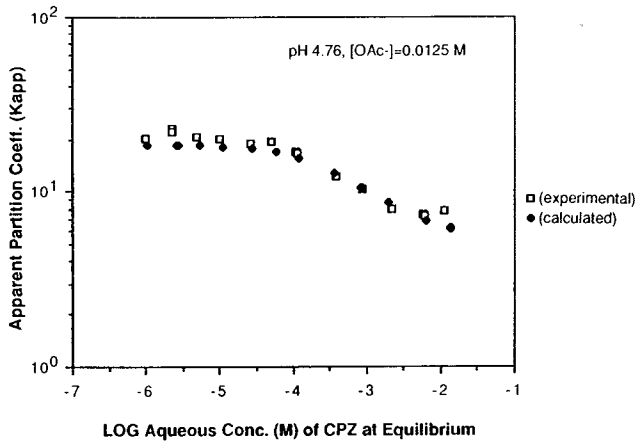

Fig. 10. Experimental and simulated distribution profiles of chlorpromazine hydrochloride between 1-octanol and sodium acetate buffer with a constant acetate ion concentration (0.0125 *M*) and varying the pH of the buffer. III. pH 4.76 acetate buffer (0.025 *M*) at 25°C.

files for the monomeric and dimeric species were generated. Figure 11 shows the distribution profiles of the monomers and dimers as a function of the equilibrium concentrations of CPZ in the aqueous phase.

The model was applied to partition data obtained with acetate buffer concentrations exceeding 0.0125 *M*. The agreement of one model-generated partition isotherms to the data was much poorer, suggesting that activity corrections and specific interaction between buffer components and chlorpromazine species may be important at higher ionic strengths.

Thermodynamics of the Partitioning of CPZ

From the study of the temperature dependency of the partitioning of CPZ (Fig. 4), the thermodynamic functions of the transfer process could be calculated. The enthalpy of transfer process (ΔH°_{tr}) can be found from the van't Hoff plot of $\ln(K^\circ_{app})$ versus the reciprocal of the absolute temperature (Fig. 12), where the slope of the line is $-\Delta H^\circ_{tr}/R$. Similarly, the free energy for the transfer process (ΔG°_{tr}) is related to the intrinsic apparent partition coefficient (K°_{app}) by the equation

$$\Delta G^\circ_{tr} = -RT\ln(K^\circ_{app})$$

Therefore, ΔS°_{tr}, the entropy for the transfer process, can be calculated from the expression

$$\Delta G^\circ_{tr} = \Delta H^\circ_{tr} - T\Delta S^\circ_{tr}$$

Table III lists thermodynamic quantities for the transfer process of CPZ from aqueous phase into 1-octanol phase.

It should be pointed out that the calculation of thermodynamic parameters does not take into account the variation of the mutual solubility of 1-octanol and water. At each temperature both phases were presaturated with the other phase. It is assumed in the following discussion and in the

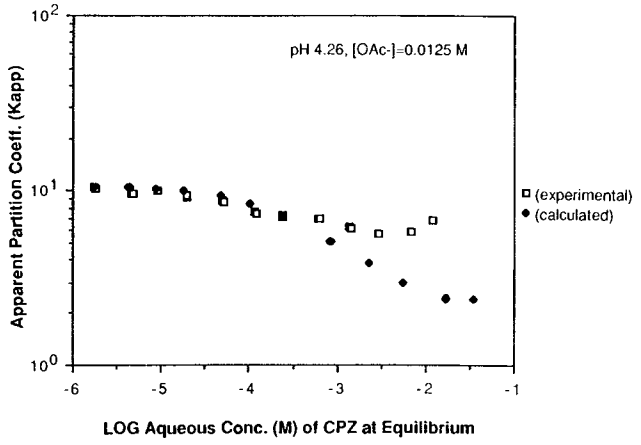

Fig. 9. Experimental and simulated distribution profiles of chlorpromazine hydrochloride between 1-octanol and sodium acetate buffer with a constant acetate ion concentration (0.0125 *M*) and varying the pH of the buffer. II. pH 4.26 acetate buffer (0.0518 *M*) at 25°C.

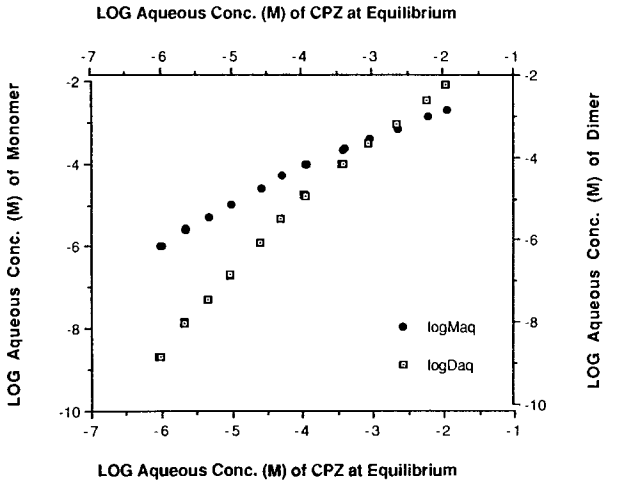

Fig. 11. Distribution profiles of monomer and dimer of chlorpromazine hydrochloride in pH 4.76 sodium acetate buffer (0.025 *M*) at equilibrium after partitioning (25°C).

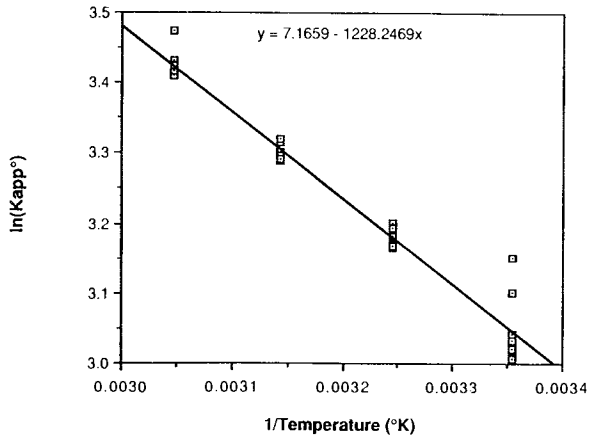

Fig. 12. The van't Hoff plot for the partition of chlorpromazine hydrochloride between 1-octanol and 0.025 *M* sodium acetate buffer, pH 4.76.

listing of parameters in Table III that the variation of properties with temperature is not substantially affected by the variation of the solubility of 1-octanol in the buffer and the solubility of water in 1-octanol. The justification for this assumption is the apparent linear behavior of the Arrhenius plot (Fig. 12). Nevertheless, the interpretation of the thermodynamic parameters is limited to some qualitative remarks.

Positive values obtained for the enthalpy and entropy for partitioning of CPZ from the aqueous phase into the organic phase are consistent with the expectations based on the hydrophobic character of CPZ molecule. In an aqueous solution of CPZ, the water molecules in the vicinity of the nonpolar molecule are more strongly hydrogen bonded and exist in a higher local order than in pure water. As CPZ partitions out from the aqueous phase, the normal hydrogen-bonded structure of water is restored as a consequence of the decrease in the less ordered state of hydrogen-bonded water. These processes are characterized by an increase in enthalpy and entropy and indicate that energy is required to break hydrogen bonds as a result of a loss in ordered structure of water molecules. The self-association of CPZ in the aqueous phase may be attributed to contributions from the "hydrophobic efffect." From the values of the thermodynamic parameters, it can be concluded that the partitioning of CPZ from the aqueous phase into 1-octanol is an entropically dominated process.

Table III. The Intrinsic Apparent Partition Coefficient ($K°_{app}$) and the Thermodynamic Values for the Transfer Process of Chlorpromazine Hydrochloride Between 1-octanol and 0.025 *M* Sodium Acetate Buffer, pH 4.76

Temp. (°C)	$(K°_{app})$	$\Delta G°_{tr}$ (kcal/mol)	$\Delta H°_{tr}$ (kcal/mol)	$\Delta S°_{tr}$ (cal/mol · K)
25	21.08	−1.81	2.44	14.25
35	24.04	−1.95		14.25
45	27.20	−2.09		14.24
55	30.72	−2.23		14.23

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