Thermodynamics of Partitioning of the Antimalarial Drug Mefloquine in Phospholipid Bilayers and Bulk Solvents

Mei-Lin Go* and Tong-Lan NGIAM

Department of Pharmacy, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260.
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The antimalarial drug mefloquine binds avidly to phospholipids in biomembranes. The thermodynamics of the partitioning process in dimyristoylphosphatidylcholine (DMPC) bilayers was investigated to give some insight into the drug-phospholipid interaction. Thermodynamic parameters for the partition equilibria were evaluated from the equilibrium partition coefficients measured as a function of temperature. Negative values of ΔH and ΔS were obtained for the transfer of mefloquine from the aqueous to the gel phase of the phospholipid. The partitioning is enthalpy controlled which suggests that mefloquine interacts strongly with the phospholipid phase. In contrast, the partitioning of mefloquine into the liquid crystalline phase of DMPC is entropy controlled which is typical of a hydrophobic interaction between mefloquine and the aqueous phase. The partitioning of mefloquine into the bulk solvents octanol and hexane were found to be enthalpy and entropy controlled, respectively. The enthalpy dominated partitioning of mefloquine into gel phase DMPC and octanol is attributed to the occurrence of hydrogen bonding and van der Waals interactions between solute and solvent. The flat shape of mefloquine may further aid its interaction with the orderly domains of the lipidic/organic phase. This is apparent from a comparison of the partitioning characteristics of another structurally related but conformationally different molecule, quinine into DMPC and octanol.

Key words mefloquine; quinine; thermodynamics of partitioning; dimyristoylphosphatidylcholine bilayers; octanol

The antimalarial agent mefloquine is widely used for the treatment and prophylaxis of falciparum malaria.[1] Despite its wide usage, the mode of action of mefloquine is still unclear. Recent reports suggest that it may inhibit hemoglobin denaturation and iron release, thus causing inhibition of parasite growth,[2] or may exert its action *via* the formation of a complex with ferriprotoporphyrin IX.[3] Of late, there have been increasing reports of central nervous system adverse events associated with the use of mefloquine in malaria.[4] Such events range from mild symptoms like headache, dizziness and insomnia, to serious neurological and psychiatric events like affective and anxiety disorders, psychosis and acute brain syndrome.[5]

One of the most interesting properties of mefloquine is its high binding affinity to phospholipids.[6] It has also been shown to perturb lipid bilayers[7,8] and to accumulate within liposomes.[9] Little is known of its partitioning characteristics, however, other than some quantitative parameters cited by Mu and co-workers.[10] Of particular interest are the thermodynamics of the partitioning process, as this would give some insight into the nature of the drug-phospholipid interaction. The present investigation thus focuses on a study of the thermodynamics of partitioning mefloquine into the gel and liquid crystalline phases of 1,2-dimyristoyl-*sn*-glycero-3-phosphatidylcholine (DMPC) vesicles, and compares its transfer characteristics with those of mefloquine partitioning into a bulk solvent such as octanol. Similar studies were done on another quinolinemethanol antimalarial, quinine, for the purpose of comparison.

Experimental

Materials Quinine hydrochloride and DMPC (99%) were purchased from Sigma Chemical Company (St Louis, MO). (±) *erythro*-Mefloquine hydrochloride was a gift from Mepha Ltd. (Basel, Switzerland). All other reagents were of analytical grade.

Bulk Solvent-Buffer Partitioning The organic solvent (1-octanol or hexane) and phosphate buffer (0.1 M, pH 6.0) were mutually pre-equilibrated before use. Stock solutions (0.1 mM) of mefloquine or quinine were prepared in the same buffer solution and protected from light. Equal volumes (3 ml) of the buffer solution and organic solvent were placed together in a round bottom flask and agitated for 18 h at a preset temperature (11—45 °C) in a thermostated shaking water bath. The two phases were then separated, centrifuged (2000 rpm, 10 min) and the concentrations of solute in both octanol and aqueous phases were determined by UV spectroscopy at appropriate wavelengths. Distribution coefficients (D) were calculated from the mean of 8 determinations.

Liposome-Buffer Partitioning An aliquot (5 ml) of DMPC in $CHCl_3$ (2 mg/ml) was placed in a 25 ml Quickfit flask. Removal of solvent by rotary evaporation at 40 °C resulted in the deposition of a thin lipid film on the inside wall of the flask. An aliquot (5 ml) of phosphate buffer (0.05 M, pH 6) containing mefloquine or quinine at a concentration of 0.1 mM was added to the flask, allowed to stand at 50 °C for 15 min, followed by swirling on a vortex stirrer for another 15 min. The flask was then shaken for 20 h on a thermostated shaking water bath at a preset temperature (13—32 °C). The lipid and aqueous phases were separated by centrifugation (143000 × g, 40 min) on a Beckman L7 ultracentrifuge at the shaking temperature, except for temperatures above 24 °C in which centrifugation was carried out at 24 °C. The possibility of partitioning characteristics changing during this short period of centrifugation was considered negligible because the high speed of centrifugation quickly deposits the lipid phase as a small compact pellet with a limited interfacial area between the two phases. The concentration of mefloquine or quinine remaining in the aqueous buffer after centrifugation was determined by UV spectroscopy, while the concentration of liposomally-associated solute was calculated by mass balance. No less than 8 determinations were made for each compound at the selected temperature.

Determination of Distribution and Partition Coefficients Distribution (D) and partition (P) coefficients are defined as follows:

$$D = C_o/C_w \quad (1)$$

$$P = D(1 + 10^{pK_{a1} - pH} + 10^{pK_{a1} + pK_{a2} - 2pH}) \quad (2)$$

where C_o and C_w refer to the molar concentrations of solute in the organic and aqueous phases respectively, pH is that of the aqueous buffer (6.0) and pK_{a1} and pK_{a2} are the first and second ionization constants of mefloquine or quinine ($pK_{a1} > pK_{a2}$). Equation 2 is based on the assumption that partitioning of the ionic species into the organic phase is negligible.[11]

The partitioning of solute between DMPC liposomes and buffer is characterised by the molar distribution coefficient (K'_m)[12]:

* To whom correspondence should be addressed.

$$K'_m=(C_T-C_W)W_1/C_W W_2 \quad (3)$$

where C_T is the initial aqueous solute concentration before equilibrium, C_W is the final aqueous concentration after equilibrium and W_1, W_2 are the weights of the aqueous phase and phospholipid respectively. The partition coefficient was determined from Eq. 2 by replacing D with K'_m.

Estimation of Thermodynamic Parameters The free energy of partitioning ($\Delta G_{w\to l}$) at a given temperature is given by Eq. 4:

$$\Delta G_{w\to l}=-2.3RT\log P \quad (4)$$

The temperature dependence of partitioning (Eq. 5) was used to obtain the enthalpy ($\Delta H_{w\to l}$) of the process which was determined from the slope of the van't Hoff plot of $\log P$ *vs.* $1/T$:

$$\log P=\Delta S_{w\to l}/2.3R-\Delta H_{w\to l}/2.3RT \quad (5)$$

The change in entropy $\Delta S_{w\to l}$ is calculated from Eq. 6 using the known values of $\Delta H_{w\to l}$ and $\Delta G_{w\to l}$ at a given temperature:

$$\Delta S_{w\to l}=[\Delta H_{w\to l}-\Delta G_{w\to l}]/T \quad (6)$$

The determination of thermodynamic parameters in this way is based on certain assumptions, *viz.* that the variation of pK_a of solute with temperature is generally small as has been proposed by other investigators,[13-15] and that the mutual solubility of water in bulk solvents like octanol is not significantly affected by temperature.[13] The good linearity of the van't Hoff plots ($r=0.998$) obtained for mefloquine and quinine in octanol/buffer suggests that the latter is a valid assumption.

Conformational Determinations The geometries of mefloquine and quinine were fully optimized with the MMX force field for molecular mechanics calculations using PC Model Version 4 (Serena Software, Bloomington, U.S.A.) and the minimum energy conformations identified. Molecular volume (V_w) calculations were determined from minimum energy conformations using the SYBYL molecular modelling software, version 6.2 (Tripos Associates, St Louis, MO) run on a Silicon Graphics Indigo R4000 workstation.

Results and Discussion

Ionization, Polar and Conformational Characteristics of Mefloquine and Quinine Mefloquine and quinine are structurally related quinolinemethanols (Table 1). The pK_a values of quinine are 4.1 (quinolyl nitrogen) and 8.2 (quinuclidinyl nitrogen).[16] For mefloquine, only the pK_a (8.6) of the piperidinyl nitrogen has been reported.[10] The pK_a of the quinolyl nitrogen is assumed to be lower than that of quinine (<4.1) due to the presence of neighbouring trifluoromethyl substituents which are inductively electron withdrawing in nature. A pK_a value of 3.9 was assigned to the quinolyl nitrogen of mefloquine. Based on these pK_a values, mefloquine and quinine would exist mainly in the monocationic state ($\sim$98%) at pH 6.

Partitioning of the solute into bulk solvents would normally involve the non-ionized form. If the ionic species is extracted by the organic phase, it does so usually as an ion pair. This would result in greater partitioning into the organic phase as solute concentration increases.[15] The absence of such a trend in the partitioning of mefloquine and quinine into octanol or hexane suggests that only the non-ionized form is being partitioned (Fig. 1a, b).

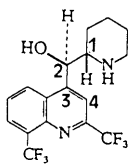
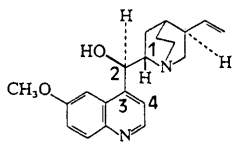
In contrast to bulk solvent partitioning, both ionized and non-ionized species of the solute have been shown to partition into the phospholipid bilayer.[17,18] Differential scanning calorimetry (DSC) studies on the interaction of mefloquine and quinine with dipalmitoyl phosphatidylcholine (DPPC) bilayers have shown that the mono-ionized species of both solutes do indeed partition into the phospholipid.[8] Their orientation within the bilayer is typical of catamphiphilic molecules, *viz.* with their cationic groups attracted to the anionic phosphate groups and the hydrophobic rings directed towards the fatty acid interior of the phospholipids. Therefore, it is reasonable to assume that both ionized and non-ionized species of mefloquine and quinine are partitioned into the DMPC bilayers.

El-Tayar and co-workers[19] have shown that $\log P$ can be factorized into a volume term V, expressing hydrophobic interactions, and a polarity term Λ which encodes polar interactions between solute and solvent. This is shown in Eq. 7, where a, b are constants describing the contributions made by volume (V) and polarity (Λ) to $\log P$:

$$\log P=aV+b\Lambda \quad (7)$$

Mefloquine and quinine have very similar size characteristics as seen from their van der Waals volume (Table 1). Therefore, differences in their partitioning properties must be attributed to their polar (Λ) characteristics which encompass H-bond donor acidity (α), H-bond acceptor basicity (β) and polarizability (π^*).

Table 1. Thermodynamic Parameters for the Partitioning of Mefloquine and Quinine into DMPC, Octanol and Hexane

		Mefloquine	Quinine
1.	Structure[a]		
2.	Van der Waals molecular volume	267.2	290.0
3.	Minimum energy conformations		
(a)	Planar conformation		
	Energy (Kcal/mol)	54.88	30.60
	τ N–C1–C2–C3	167.82	168.26
	τ C1–C2–C3–C4	−0.24	−0.16
(b)	Non-planar conformation	52.00	28.70
	Energy (Kcal/mol)		
	τ N–C1–C2–C3	62.55	173.28
	τ C1–C2–C3–C4	−96.6	−72.98
4.	DMPC liposome-buffer		
18 °C	$\Delta G_{w\to l}$ (kJ)	−33.8	−24.6
	$\Delta H_{w\to l}$ (kJ/mol)	−173.8	−28.5
	$\Delta S_{w\to l}$ (J/mol·K)	−481.4	−13.9
	$\log P$	6.1	5.8
29 °C	$\Delta G_{w\to l}$ (kJ)	−33.7	−25.0
	$\Delta H_{w\to l}$ (kJ/mol)	48.5	82.7
	$\Delta S_{w\to l}$ (J/mol·K)	272.2	356.8
	$\log P$	5.8	4.3
5.	Octanol-buffer		
24 °C	$\Delta G_{w\to l}$ (kJ)	−23.3	−18.5
	$\Delta H_{w\to l}$ (kJ/mol)	−46.3	20.2
	$\Delta S_{w\to l}$ (J/mol·K)	−77.0	130.7
	$\log P$	4.0	3.3
6.	Hexane-buffer[b]		
24 °C	$\Delta G_{w\to l}$ (kJ)	−9.5	
	$\Delta H_{w\to l}$ (kJ/mol)	43.1	
	$\Delta S_{w\to l}$ (J/mol·K)	176.9	
	$\log P$	1.7	1.3
7.	$\Delta \log P_{oct\text{-}hex}$	2.42	1.98

a) One enantiomer of the *erythro* racemate of mefloquine is shown. *b*) $\log P$ of quinine did not vary significantly with temperature change.

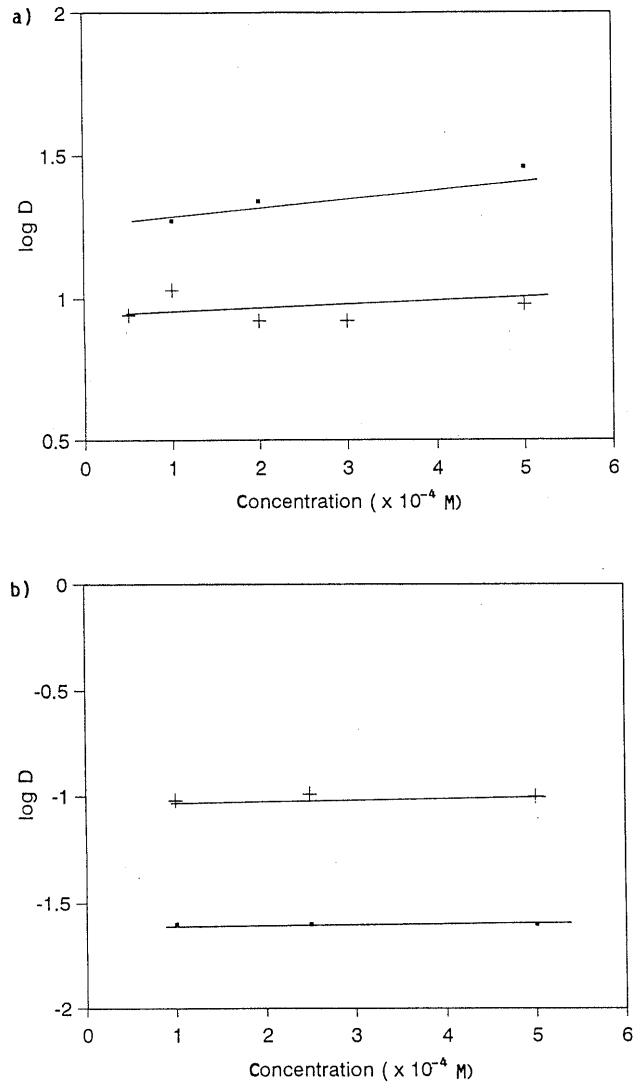


Fig. 1. Variation in log D with Concentration of Mefloquine (■) and Quinine (+) in (a) Octanol-buffer and (b) Hexane-buffer

For mefloquine, measurements were made at 30 °C, and 24 °C in octanol-buffer and hexane-buffer respectively. In the case of quinine, partitioning in octanol-buffer was carried out at 20 °C.

A consideration of the polar characteristics of the free base form of the two molecules does not reveal significant differences between them. Quinine is thought to be a net H-bond acceptor due to the greater number of H-bond acceptor groups (CH_3O–, quinoline and quinuclidine N) than donor groups (OH) in the molecule. Mefloquine should also behave similarly but it has a smaller number of H-bond acceptor groups (quinoline and piperidine N). The piperidinyl N is more likely to be an H-bond acceptor as amines are generally noted to be better H-bond acceptors than donors.[20] The quinolyl N in mefloquine is flanked by two electron withdrawing and bulky CF_3 groups which may reduce the ability of the quinolinyl N to participate in H-bonding with water.

Conformational studies have shown that the low energy states of mefloquine and quinine are non-planar (Table 1). However, the energy difference between the planar and non-planar conformations are small and not insurmountable at room temperature (2 Kcal/mol). Compared to mefloquine, the quinuclidine ring structure in quinine is bulky and causes the planar conformation of quinine to

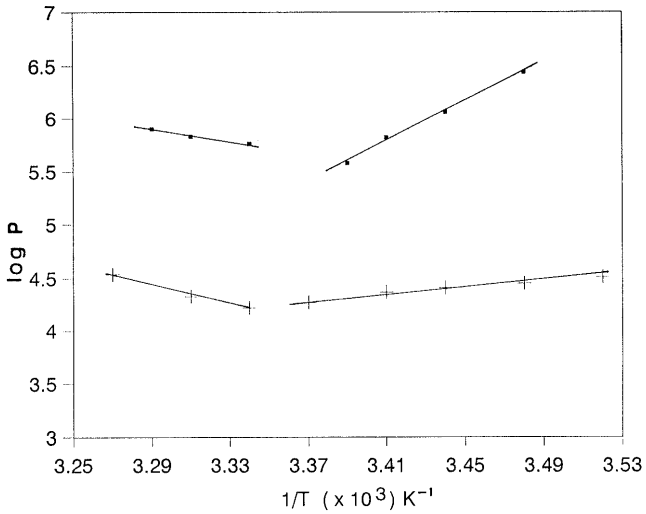


Fig. 2. Van't Hoff Plots of Mefloquine (■) and Quinine (+) in DMPC Liposome-buffer

be less flat compared to that of mefloquine. This appears to be an important structural difference between the two molecules.

Partitioning of Mefloquine and Quinine into DMPC Vesicles The partitioning of mefloquine and quinine into DMPC vesicles was investigated over a wide temperature range encompassing the gel and liquid crystalline states of the phospholipid which exists below, and above, the phase transition temperature T_m (24 °C) respectively. The thermodynamic parameters for solute transfer from the aqueous medium to the phospholipid were calculated from the van't Hoff analysis which is based on the dependency of partitioning coefficients to temperature change (Fig. 2, Table 1).

As seen from Fig. 2, the van't Hoff plot for each drug consisted of two fairly linear lines with different gradients, intersecting (upon extrapolation) at about the T_m (24 °C) of DMPC. The positive gradient of the line obtained at temperatures below T_m indicates that log P decreases with temperature up to approximately T_m. The negative gradient of the line obtained at temperatures above T_m is indicative of an opposite relationship. When considered in the light of Eq. 5, the positive gradient indicates that partitioning of the solute at temperatures below T_m (*i.e.*, into the gel phase phospholipid bilayers) proceeds with a loss of enthalpy ($-\Delta H_{w\to l}$). This would be the case when the energy gain from solute-phospholipid interaction is more than that needed to break the solute-water interactions in the aqueous phase and there is net bond-making upon partitioning. As seen from Table 1, the reduction in enthalpy is particularly large for mefloquine ($\Delta H_{w\to l} = -174$ kJ/mol) compared to quinine ($\Delta H_{w\to l} = -16$ kJ/mol). In contrast, the negative gradient of the van't Hoff plot which is observed as temperature increases beyond T_m suggested a different thermodynamic picture, *viz.* that the drugs partition into the less ordered liquid crystalline phase of DMPC with a gain in enthalpy ($+\Delta H_{w\to l}$).

Many investigators have also reported changes in the thermodynamic profile as solutes partition into phospholipids at temperatures above and below T_m.[14,15,21]

However, most reports have shown that partitioning of solutes into the gel phase of the phospholipid ($< T_m$) is accompanied by large gains in entropy and enthalpy ($+\Delta S, +\Delta H$),[14,15,21-23] and not losses in entropy and enthalpy ($-\Delta S$, $-\Delta H$), as shown in this study. The gains in entropy and enthalpy ($+\Delta S, +\Delta H$) have been explained by the disruption of the close packing of the hydrocarbon tails of the phospholipid upon the insertion of the solute molecules into the orderly crystalline array of the gel phase. Strong intermolecular forces have to be overcome ($+\Delta H$) and the resulting disorder gives rise to a gain in entropy ($+\Delta S$).

In this study, mefloquine partitioned into the gel phase phospholipid with a reduction in both enthalpy and entropy ($-\Delta S$, $-\Delta H$). The large enthalpy loss suggests that mefloquine forms strong bonding interactions with the ordered gel phase phospholipid array. Such interactions may take the form of charged interactions (e.g., protonated piperidinium nitrogen and anionic phosphate), H-bonding (OH group of mefloquine and the H-bond acceptor groups in the lipidic phase) and hydrophobic/van der Waals forces between the carbon skeleton of mefloquine and the hydrocarbon chains of the lipid. The flat shape of mefloquine may further enhance its interaction with the orderly array of phospholipid molecules in the gel phase. Although the minimum energy conformation of mefloquine is non-planar, the energy difference between the planar and non-planar forms is small (2 Kcal/mol). The enthalpy reduction resulting from optimum van der Waals interaction will more than compensate for the energy required for mefloquine to assume the planar conformation.

Compared to mefloquine, a smaller reduction in enthalpy was observed when quinine partitioned into the gel phase phospholipid. As pointed out earlier, quinine and mefloquine differ mainly in their shapes. The bulky quinuclidine ring structure may hinder the correct "fitting" of quinine into the highly ordered phospholipid matrix, thus resulting in fewer bonding interactions and a smaller enthalpy loss. DSC studies on the interaction of quinine with DPPC bilayers have also shown that quinine causes a smaller reduction in the phase transition temperature (T_m) of DPPC bilayers compared to mefloquine. This is in keeping with the lesser degree of partitioning of quinine into the bilayer and the formation of fewer intermolecular points of contact (and therefore, smaller $\Delta H_{w\to l}$) between quinine and phospholipid.

The reduction in enthalpy due to intermolecular interactions between mefloquine/quinine and the phospholipid array would impose a greater degree of orderliness to the latter. Thus, there is a net entropy loss ($-\Delta S_{w\to l}$) for the partitioning process, notwithstanding the expected entropy gain due to the release of "free water" surrounding the solute as the latter moves out of the aqueous phase into the non-polar phase.

The gains in enthalpy and entropy ($+\Delta H$, $+\Delta S$) when mefloquine and quinine partition into liquid crystalline DMPC ($> T_m$) are more consistent with the observations made by other investigators.[14,15,21] The gain in enthalpy indicates that bond breaking processes predominate as the drugs are partitioned from the aqueous phase to the less ordered liquid crystalline state of the phospholipid. It has been reported that a thermally induced change in the conformation of the phospholipid head group occurs, causing the polar head group to become increasingly submerged in the hydrocarbon core with increased temperature, increasing lateral head group repulsion and decreasing surface pressure.[24] The polar head group of the phospholipid would then be relatively inaccessible to ion/dipolar interactions with the solute, although weaker van der Waals interaction would still be possible. The weaker intermolecular interaction accounts for the gain in enthalpy ($+\Delta H$) and consequently does not impose a significant degree of orderliness to the phospholipid domain. The net $+\Delta S$ value is largely due to the release of "free water" from the solute as the latter moves from the aqueous phase into the phospholipid phase. The partitioning is thus entropy-driven.

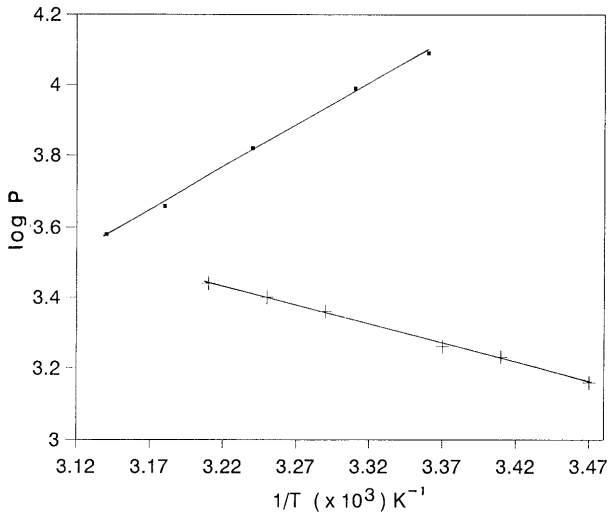


Fig. 3. Van't Hoff Plots of Mefloquine (■) and Quinine (+) in Octanol-buffer

Partitioning of Mefloquine and Quinine into Octanol

It has been suggested that partitioning of solutes into liposomes often involves large and compensatory changes in enthalpy and entropy due to alterations in liposomal structure.[22] These changes may even mask smaller changes in enthalpy and entropy due to the actual transfer of solute molecules. The enthalpy-driven partitioning of mefloquine into gel phase phospholipid is unusual and of particular interest. Confirmation that this is really due to solute transfer rather than liposomal changes can be deduced from the partitioning of mefloquine into a bulk solvent such as octanol which is known to have a highly ordered matrix.[25]

As seen from Fig. 3, the partitioning of mefloquine into octanol from the aqueous phase decreases with increasing temperature. The resulting van't Hoff plot is linear with a positive gradient ($-\Delta H$). A net loss in enthalpy and entropy ($-\Delta H$, $-\Delta S$) was observed. It is interesting to note that the partitioning of mefloquine into the highly ordered gel phase phospholipid and octanol show similar thermodynamic characteristics ($-\Delta H$, $-\Delta S$). The reduction in enthalpy indicates that there is a net release of energy (due to bond formation) upon transfer due to strong solute-octanol interactions. Octanol is a non-polar solvent

with a good capacity for hydrogen bonding and self association into aggregates.[25] It is widely considered to be a better proton acceptor than bulk water which is a net proton donor solvent.[26] Water saturated octanol consists of aggregates of four alcohol molecules surrounding a central water molecule and solute molecules partitioned into octanol have been postulated to replace one octanol molecule in the complex.[15]

The reduction in enthalpy ($-\Delta H$) associated with the partitioning of mefloquine into octanol can be explained by H-bonding and van der Waals interaction between solute and solvent. In addition, the relative flatness of the mefloquine molecule may allow it to fit into the ordered octanol matrix with minimal disruption. The reduction in entropy ($-\Delta S$) follows from the orderliness imposed upon mefloquine molecules in the octanol phase, compared to the relative freedom in the aqueous phase.

In keeping with this explanation, it is not surprising to find that the structurally bulkier quinine partitions into octanol with very different thermodynamic characteristics. This partitioning increases with temperature and the van't Hoff plot has a negative gradient ($+\Delta H$) (Fig. 3, Table 1). A net gain in enthalpy and entropy ($+\Delta H, +\Delta S$) was observed. The transfer of the solute from water would involve the release of "free" water and the bulkier quinine molecule may fit poorly into the highly ordered tetramic array of octanol molecules. The partitioning of quinine into octanol is entropy-driven.

Thus, there appears to be some similarity when mefloquine (but not quinine) partitions into the ordered phases of the gel phase phospholipid and octanol. Both partitioning processes are enthalpy-driven and characterized by net losses in enthalpy and entropy ($-\Delta H$, $-\Delta S$). This is notwithstanding the fact that ionized and non-ionized species are likely to be involved in solute partitioning into phospholipid bilayers, but that only non-ionized species are involved in octanol partitioning.

When the partitioning of mefloquine was investigated in hexane, a non-polar solvent with no H-bonding capacity and fixed liquid structure, a net gain in entropy and enthalpy was observed (Fig. 4, Table 1). Very little water is dissolved in hexane and H-bonding between mefloquine and hexane is non-existent. van der Waals interactions can occur between the carbon skeleton of mefloquine and hexane but, as seen from the results, the energy released by this process is clearly insufficient to offset the energy required to desolvate mefloquine from the aqueous phase. The release of "free water" and the resulting gain in entropy provides the main driving force for the partitioning of mefloquine from water into hexane.

Since the log P of mefloquine has been determined in octanol and hexane, the parameter $\Delta \log P_{\text{oct-hex}}$ could be obtained from the equation:

$$\Delta \log P_{\text{oct-hex}} = \log P_{\text{oct}} - \log P_{\text{hex}} \quad (8)$$

$\Delta \log P_{\text{oct-hex}}$ is a useful descriptor of the H-bonding capacity of the solute, in particular its H-bond donor capacity.[27] The value for mefloquine is 2.42 compared to 1.98 for quinine at 24 °C (Table 1). This means that mefloquine has greater H-bonding capacity than quinine, which may contribute to the thermodynamic characteristics ($-\Delta S_{w\to o}$, $-\Delta H_{w\to o}$) of its partitioning into gel phase phospholipid.

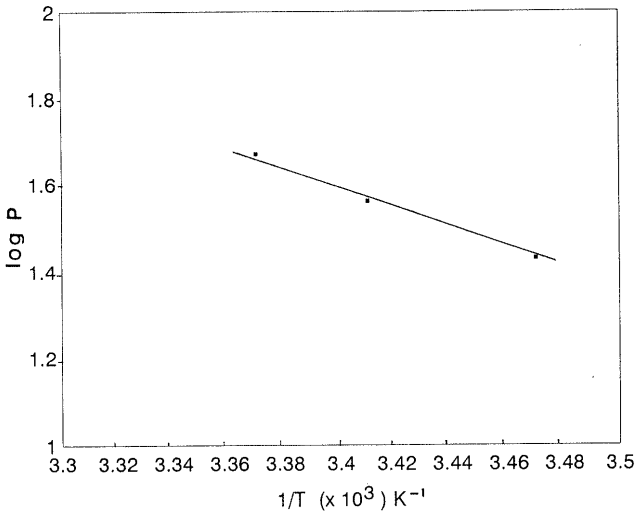


Fig. 4. Van't Hoff Plot of Mefloquine (■) in Hexane-buffer

Biological Significance of Results The present study has shown that the partitioning of mefloquine into the ordered phases of the gel phospholipid and the bulk solvent octanol is mainly driven by strong intermolecular forces between mefloquine and the lipidic phase. These interactions are made possible by the shape of mefloquine (flat and planar), and possibly, by the accessibility of its H-bond donor groups. The enthalpically favourable interaction of the drug and the lipidic phase of biomembranes would result in the localization of mefloquine within biomembranes. The various inhibitory properties reported for mefloquine, such as inhibition of human neutrophil protein kinase C[28] and inositol-1,4,5-phosphate (IP_3)-induced Ca^{2+} release from dog brain microsomes[29] may be the consequence of the presence of the drug within the lipidic phase. Thus, there is a possibility that many of the pharmacodynamic and pharmacokinetic properties of mefloquine are related to its localization within the phospholipid array.

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