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PARTITION EQUILIBRIUM OF INHALATION ANESTHETICS AND ALCOHOLS BETWEEN WATER AND MEMBRANES OF PHOSPHOLIPIDS WITH VARYING ACYL CHAIN-LENGTHS

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From the depression of the phase-transition temperature of phospholipid membranes, the partition coefficients of inhalation anesthetics (methoxyflurane, halothane, enflurane, chloroform and diethyl ether) and alcohols (benzyl alcohol and homologous *n*-alcohols up to C = 7) between phospholipid vesicle membranes and water were determined. The phospholipids used were dimyristoyl-, dipalmitoyl- and distearoylphosphatidylcholines. It was found that the difference in the acyl chain length of the three phospholipids did not affect the partition coefficients of the inhalation anesthetics and benzyl alcohol. The actions of these drugs are apparently directed mainly to the interfacial region. In contrast, *n*-alcohols tend to bind more tightly to the phospholipid vesicles with longer acyl chains. The absolute values of the transfer free energies of *n*-alcohols increased with the increase of the length of the alkyl chain of the alcohols. The increment was 3.43 kJ per each carbon atom. The numerical values of the partition coefficients are not identical when different expressions for solute concentrations (mole fraction, molality and molarity) are employed. The conversion factors among these values were estimated from the molecular weights and the partial molal volumes of the phospholipids in aqueous solution determined by oscillation densimetry.

Introduction

Phospholipid membranes undergo thermotropic phase transition between solid gel and liquid crystalline states. It is well documented that anesthetics decrease the phase-transition temperature [1–8]. Thermodynamically, the depression of phase-transition temperature does not occur if the solute molecules are not expelled from the frozen solvent.

The partition coefficients of anesthetics between the phospholipid and water can be estimated from the depression of the phase-transition temperature. Hill [1,2], Ueda et al. [3] and Tashiro and Ueda [4] reported the methods to obtain the partition coefficients of anesthetics by utilizing the van't Hoff equation.

We will report here a revised method of calculating the lipid/water partition coefficient of anesthetics by modifying the van't Hoff equation in which the phospholipid concentration is held constant and the anesthetic concentration is varied. The partition coefficients are expressed as the ratio of anesthetic mole fractions in the two phases. The transfer free energy (ΔG°) from water to the lipid membrane is computed from the obtained partition coefficients.

It came to our attention that the partition coefficients so far reported are computed arbitrarily using either mole fraction [9], molality [10], molarity [11,12], a combination of these [13] or with the authors' own definition [1,2]. Because of the lack of uniformity in the expressions, these data are not readily comparable.

Abbreviations: DMPC, dimyristoylphosphatidylcholine; DPPC, dipalmitoylphosphatidylcholine; DSPC, distearoylphosphatidylcholine.

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It appears to be a general contention to assume that the concentration units are not important in derivation of the partition coefficients, because the property is the ratio of the solute concentrations in the two phases and the units cancel out. We will show that the numerical values of partition coefficients differ considerably among those obtained by using different expressions of the solute concentrations. The relationships of these values are discussed, and the conversion factors for these values are presented by using the measured partial molal volumes of dimyristoyl-, dipalmitoyl- and distearoylphosphatidylcholine in the aqueous solution.

Theory

The activity, a, of a phospholipid in the membrane relates to the phase-transition temperature, T, expressed by the absolute temperature as follows

$$\left(\frac{\partial \ln a}{\partial T}\right)_P = \frac{\Delta H}{RT^2} \tag{1}$$

where H is the enthalpy change associated with the phase-transition and R is the gas constant. Integration of Eqn. 1 under the condition that ΔH is independent of the temperature, one obtaines

$$\ln\left(\frac{a}{a_0}\right) = \frac{\Delta H\, \Delta T}{RT_0 T} \tag{2}$$

where $\Delta T = T - T_0$ and the subscript zero denotes the absence of anesthetics.

The activity of the phospholipid in the lipid phase is written

$$a = X_L f_L \approx (1 - X_A) f_L \tag{3}$$

where X_L and X_A are the mole fractions of phospholipid and anesthetics, respectively. If we choose the liquid crystalline phase for the standard chemical potential of phospholipid, $a_0 = 1$, then Eqn. 2 becomes

$$\ln(X_L f_L) = \ln(1 - X_A)\, f_L = \frac{\Delta H\, \Delta T}{RT_0 T} \tag{4}$$

When X_A is sufficiently small, f_L approaches unity due to the convention for the standard chemical potential.

The partition coefficient K of the anesthetic between the bulk solution and the lipid phase is

$$K = X_A / Y_A = \exp(-\Delta G^\circ / RT) \tag{5}$$

where Y_A is the mole fraction of the anesthetic in the bulk solution and ΔG° is the standard free energy change for the partitioning process.

From Eqns. 4 and 5, we obtain

$$\ln(1 - KY_A) = \frac{\Delta H\, \Delta T}{RT_0 T} \tag{6}$$

Eqn. 6 indicates that the partition coefficient can be obtained from a knowledge of the depression of the phase-transition temperature and the concentration of the anesthetic in the water phase (Y_A). Under the condition of $KY_A \ll 1$ and $T_0 \approx T$, Eqn. 6 is rewritten as

$$-\Delta T = \frac{KRT_0^2}{\Delta H} \cdot Y_A \tag{7}$$

It is expected from Eqn. 7 that the depression of the phase-transition temperature is directly proportional to the anesthetic concentration in the water phase.

Let us assume that m_L mol of a phospholipid and m_A mol of an anesthetic are dissolved into m_W mol of water. If we take 1 000 g water (55.5 mol), m_L and m_A become molality. At the partition equilibrium, m'_A moles of the anesthetic molecules are transferred from the bulk solution to the lipid phase. Therefore, the mole fractions of the anesthetic in the lipid phase and in the bulk solution are written as follows.

$$X_A = \frac{m'_A}{m_L + m'_A} \tag{8}$$

and

$$Y_A = \frac{m_A - m'_A}{m_W + m_A - m'_A} \tag{9}$$

Here, m'_A can be determined from the experiment of the phase-transition temperature by Eqns. 4 and 8, as

$$m'_A = m_L \left\{ \exp\left(-\frac{\Delta H\, \Delta T}{RT_0 T}\right) - 1 \right\} \tag{10}$$

The partition coefficient, K, is expressed as

$$K = \frac{m'_A}{m_L + m'_A} \Big/ \frac{m_A - m'_A}{55.5} \tag{11}$$

where $(m_A - m'_A) << m_W = 55.5$.

Materials and Methods

Synthetic dimyristoylphosphatidylcholine (1,2-ditetradecanoyl-*sn*-glycero-3-phosphorylcholine, DMPC), dipalmitoylphosphatidylcholine (1,2-dihexadecanoyl-*sn*-glycero-3-phosphorylcholine, DPPC) and distearoylphosphatidylcholine (1,2-dioctadecanoyl-*sn*-glycero-3-phosphorylcholine, DSPC) were obtained from Sigma. Their purities were checked by thin-layer chromatography and confirmed to show a single spot. Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), enflurane (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) and methoxyflurane (2,2-dichloro-1,1-difluoroethyl methyl ether) were gifts from Ayerst Laboratories (New York, NY), Ohio Medical Products (Madison, WI) and Abbott Laboratories (North Chicago, IL), respectively. All other chemicals were reagent grade. Water was purified by triple distillation, once from alkaline potassium permanganate solution. The absence of surface active impurities was ascertained by measuring the dynamic surface tension of water by the Wilhelmy hanging plate method with a Cahn RG electrobalance (Paramount, CA) equipped with a dynamic surface tension device as previously reported [14].

The phospholipid vesicles were prepared by sonication for 20 min under nitrogen gas in water at $1 \cdot 10^{-3}$ molal concentration using a Bransonic ultrasonic disruptor (Danbury, CT) at the temperature several degrees above the phase transition. The lipid suspension was centrifuged at low speed (1 100 g) for 5 min to remove metal particles liberated from the sonicator tip.

Anesthetics and a homologous series of *n*-alcohols were added to the vesicle suspension in glass ampules with microsyringes under nitrogen gas. The amount of added anesthetics was determined by weighing the ampules using an analytical balance. The ampules were closed by fusing with a flame. The gas space in the ampule was made as small as possible to prevent the escape of the volatile anesthetics into the gas phase. The ampules were incubated at above the phase-transition temperature for 24 h in a shaking water bath.

The turbidity change of the lipid suspension was measured with a Perkin-Elmer MPF-44B fluorescence spectrophotometer (Norwald, CT) in the 90° light-scattering mode at 350 nm. The photometer output was recorded together with the temperature signal on an *X-Y* recorder. The temperature of the sample was monitored by a Digitec thermometer (Dayton, OH) with 0.01 K resolution and a filament thermistor probe with the response time of 0.1 s. The thermistor tip was inserted into the lipid suspension through a tight-fitting cover of the cuvette. The distance between the thermistor tip and the light path was within 2 mm. The cuvette temperature was raised at a rate of 1 K per 30 s by circulating water from a water bath. The sudden change of the light scattering accompanying the phase-transition was followed. The midpoint where the beginning of the decrease in the light scattering and the point where the scattering reached its plateau during heating process was taken as the phase-transition temperature.

The partial molal volumes of the phospholipids in water suspension were measured to $\pm 1.5 \cdot 10^{-6}$ g $\cdot$ cm^{-3} using a Mettler-Paar DMA 60/601HT oscillation density meter (Hightstown, NJ) at 2 K above the phase-transition temperature. The temperature was controlled ±0.01 K at the desired level by circulating water from a Hotpak constant-temperature water bath. The principle of the method of fluid oscillation densimetry is to measure the number of vibrations of a U-shaped tube filled with the test fluid as described by Elder [15]. It has been reported [16] that this method suffers experimental errors when the fluid viscosity is extremely high. The concentration of the phospholipids presently employed was much lower than those which interfere with the density measurement.

From the obtained density data of the phospholipid vesicle suspension, the apparent molal volume (ϕ_V) was calculated by the following equation.

$$\phi_V = \frac{1}{m}\left(\frac{1000 + Mm}{d} - \frac{1000}{d_0}\right) \tag{12}$$

where M is the molecular weight of the phospho-

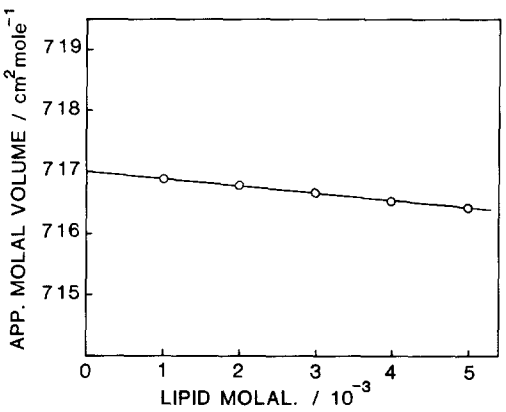

Fig. 1. The apparent partial molal volume, ϕ_V, of dipalmitoylphosphatidylcholine in the aqueous solution is plotted against its molal concentration. Extrapolation to the infinite dilution gives the partial molal volume, $\bar{V}^\circ$.

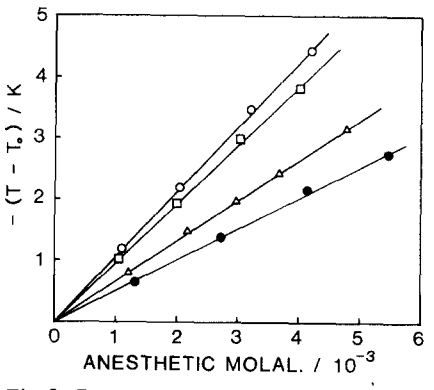

Fig. 2. Depression of the phase-transition temperature of $1 \cdot 10^{-3}$ molal dipalmitoylphosphatidylcholine vesicle membranes by halothane (○), methoxyflurane (□), enflurane (△) and chloroform (●).

lipid, m is the molality of the phospholipid, d_0 is the density of water and d is the density obtained. The density was measured at several concentrations of the phospholipid, and the value at the infinite dilution was obtained by extrapolation, which equals the partial molal volume, V° (Fig. 1).

The partition coefficients, K, of general anesthetics (halothane, methoxyflurane, enflurane, chloroform and diethyl ether), benzyl alcohol and a homologous series of n-alcohols up to C = 7 were determined according to Eqns. 10 and 11 using the reported ΔH values for DMPC (22.6 kJ · mol^{-1}), DPPC (36.4 kJ · mol^{-1}) and DSPC (44.4 kJ · mol^{-1}) by Mabrey and Sturtevant [17].

Results

Without anesthetics, the phase-transition temperatures of DMPC, DPPC and DSPC were 297.7 ± 0.1, 314.7 ± 0.1 and 327.7 ± 0.1 K, respectively. Addition of anesthetics depressed the phase-transition temperatures linearly in a dose-dependent fashion as expected from Eqn. 7. The relationships between ΔT and the concentrations of halothane, methoxyflurane, enflurane, chloroform, diethyl ether and benzyl alcohol with DPPC are shown in Figs. 2 and 3.

The partition coefficients and the transfer free energies, ΔG°, for the inhalation anesthetics and benzyl alcohol with DMPC, DPPC and DSPC are summarized in Table I. The same parameters for the n-alcohols with DPPC are listed in Table II.

The partial molal volumes of DMPC, DPPC and DSPC in the liquid-crystalline states were 662.1, 717.0 and 810.6 cm^3 · mol^{-1} at 299.7, 316.7 and 329.7 K, respectively.

Discussion

One of the advantages of the present method is that the experiment is easier than other methods provided that the enthalpies of the phase transition are known. The use of the mole fraction for the solute concentration eliminates the problem with the temperature-dependent quantity such as molal

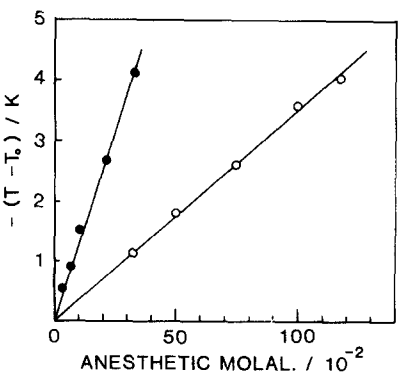

Fig. 3. Depression of the phase-transition temperature of $1 \cdot 10^{-3}$ molal dipalmitoylphosphatidylcholine vesicle membrane by diethyl ether (○) and benzyl alcohol (●).

TABLE I

PARTITION COEFFICIENTS, K, AND TRANSFER FREE ENERGIES, ΔG°, OF INHALATION ANESTHETICS AND BENZYL ALCOHOL BETWEEN PHOSPHOLIPID VESICLES AND WATER

	DMPC		DPPC		DSPC	
	K	$-\Delta G^\circ$ 297.7 K	K	$-\Delta G^\circ$ 314.7 K	K	$-\Delta G^\circ$ 327.7 K
Halothane	2050	18.58	2570	20.25	2200	20.71
Methoxyflurane	2760	19.46	2350	20.04	2700	21.25
Enflurane	1760	18.33	1680	19.20	1450	19.66
Chloroform	1060	17.03	1220	18.45	1220	19.16
Diethyl ether	35.8	8.28	77.5	11.17	68.9	11.25
Benzyl alcohol	329	14.10	305	14.85	330	15.73

volume. It is also unnecessary to consider the volume of the non-solvent water associated with vesicles as in the case of the direct measurement of the partition coefficients with tracer-labeled anesthetics. Katz and Diamond [11] used tritiated water and ^{14}C-labeled phospholipids to estimate the volume of the non-solvent water.

In this experiment, the partition coefficient was calculated using the reported values for ΔH [17] assuming that ΔH associated with the phase-transition is not affected by the presence of anesthetics. This assumption is based on the report of Jain et al. [7] who studied the phase-transition of DPPC membranes with differential scanning microcalorimetry. They used general and local anesthetics and uncoupling agents of oxidative phosphorylation. All drugs decreased the phase-transition temperature. The heat-flow profile changed when these drugs were added but the total area under the curve (ΔH) remained constant.

When a fixed amount of anesthetics is dissolved into the lipid suspension, lesser amounts of anesthetics will distribute to each lipid vesicle when the lipid concentration is higher, and the depression of the phase-transition temperature becomes smaller. This lipid concentration effect is magnified when anesthetics with higher lipid/water partition coefficients are employed. This phenomenon was used to calculate the partition coefficients of octanol and nonanol by Hill [1,2], and those of anesthetics by Ueda et al. [3] and Tashiro and Ueda [4]. Fig. 4 shows the theoretical plotting for this method. The partition coefficients are derived from the spread of the fan-like lines. The spread becomes smaller (group E) when the partition coefficient becomes low, and the estimation of the partition coefficient becomes difficult.

The partition coefficients obtained by the present method showed reasonable agreement with the values reported previously (Table IV). The DPPC/water partition coefficient of benzyl alcohol was smaller than the value reported by Colley and Metcalfe [18] and that calculated from the data of Ebihara et al. [8] according to the present theory. In the latter paper, benzyl alcohol was dissolved in saline solution. We tested the possibility that benzyl alcohol might be salted out into the lipid phase. It was found that the DPPC/water and the DPPC/saline partition coefficients were same.

The partition coefficients of the inhalation anesthetics and benzyl alcohol with DMPC, DPPC and DSPC showed similar values and are independent

TABLE II

PARTITION COEFFICIENTS, K, AND TRANSFER FREE ENERGIES, ΔG°, OF n-ALCOHOLS WITH DPPC

n-Alcohols	K	$-\Delta G^\circ$ 314.7 K
Ethanol	2.53	2.43
n-Propanol	19.0	7.66
n-Butanol	61.6	10.63
n-Pentanol	278	14.60
n-Hexanol	963	17.87
n-Heptanol	4060	21.38

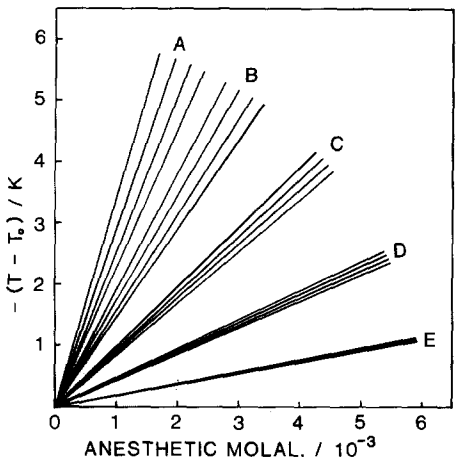

Fig. 4. The theoretical plot of the depression of the phase-transition temperature (ordinate) as a function of the total anesthetic concentration, M_A, in the bulk solution (abscissa). The letters A–E indicate hypothetical partition coefficients of 10 000, 5 000, 2 500, 1 200 and 500, respectively. Each group includes four lines representing the dipalmitoylphosphatidylcholine concentrations of $1 \cdot 10^{-3}$, $2 \cdot 10^{-3}$, $3 \cdot 10^{-3}$ and $4 \cdot 10^{-3}$ molal, respectively from the upper most. The slopes of the lines decrease as the partition coefficients become smaller and the lipid concentrations become larger.

of the acyl chain length of the phospholipids. This indicates that the site of anesthetic adsorption in the membrane may be the region where the change of the acyl chain length has the least effect. The site may be the head region of the phospholipids at the interface, and the anesthetics may not penetrate into the lipid core at the concentrations employed in the present experiment. This finding supports the results of our NMR studies reported by Shieh et al. [19] and Yokono et al. [20] who found that the actions of inhalation anesthetics upon the phase-transition of DPPC membranes were mainly directed to the interfacial choline protons at the clinical concentrations. Although the $\Delta G°$ values appear to show some correlation between the acyl chain length of the phospholipid and the partition coefficient, these values are not readily comparable because the temperatures at which the $\Delta G°$ values were calculated were not identical.

We obtained 662.1 $cm^3 \cdot mol^{-1}$ for the partial molal volume of DMPC at 299.7 K (above the phase-transition temperature) from the density measurement. It agrees well with the dilatometric data by Wilkinson and Nagle [21] who reported 0.939 $ml \cdot g^{-1}$ (630 $cm^3 \cdot mol^{-1}$) at 294.1 K (below the phase-transition temperature). These two values differ by the ΔV associated with the phase transition plus the thermal expansion.

The increase of the absolute value of $\Delta G°$ with the increase of the carbon chain length of the *n*-alcohols was nearly constant: 3.43 kJ per one carbon chain (Table II). It has been reported [22] that transfer of *n*-alcohols from water to sodium dodecyl sulfate micelles accompanies an increase of $\Delta G°$ by 2.51 kJ per one carbon chain. In this respect, the carbon chain of alcohols has higher affinity to the phospholipid vesicles than to the micelles.

The lipid/water partition coefficients of anesthetics have been reported with various definitions using a number of expressions for the concentrations of the drugs. Simon et al. [9] reported partion coefficients of halothane between various phospholipids and saline solutions employing mole fractions. Jain and Wray [10] reported DPPC/water partition coefficients of long-chain alcohols defining the partition coefficients as '(g of solute)/(g of DPPC) divided by (g of solute)/(g of aqueous phase)' which becomes a ratio of molality. Hill [1,2] presented a method of calculating DPPC/water partition coefficients of alcohols and general anesthetics by measuring the depression of the phase-transition temperature. He expressed the partition coefficient, P, by 'the moles of solute in one mole of DPPC divided by the moles of solute in one mole of water' which may be designated as mole ratio, and is not mole fraction. When the drug concentration in the membrane is much smaller than unity, which was the case, P approaches K. Miller and Yu [13] reported lipid/buffer partition coefficients of pentobarbital using radioassay and ultrafiltration methods. The partition coefficients were expressed by 'the moles of pentobarbital in 1 g of the phospholipid divided by the moles of pentobarbital in 1 ml of buffer' which is a combination of molal and molar concentrations. Trudell et al. [12] reported the partition coefficients of lidocaine between the membranes of several phospholipids and water. They apparently used the molar concentration unit for the local anesthetic but the method of estimation of the membrane volume to derive the concentration was not mentioned.

The variations of the expressions of solute concentrations in deriving partition coefficients may arise from the idea that the expression of the solute concentration is not important because the partition coefficient is a dimensionless property and the expression of the units of concentration are cancelled out during computation. From thermodynamics, the partition coefficient computed from mole fraction, K, molality, $K_{(m)}$, and molarity, $K_{(c)}$ are not identical.

The chemical potential of ith species can be written by using mole fraction, molality and molarity,

$$\mu_i = \mu_i^\circ + RT \cdot \ln(X_i f_i) \quad (13)$$

$$\mu_i = \mu_{i(m)}^\circ + RT \cdot \ln(m_i \gamma_i) \quad (14)$$

$$\mu_i = \mu_{i(c)}^\circ + RT \cdot \ln(c_i \alpha_i) \quad (15)$$

where, μ_i, $\mu_{i(m)}^\circ$ and $\mu_{i(c)}^\circ$ are the standard chemical potentials represented by the mole fraction (X_i), molality (m_i) and molarity (c_i), respectively, and f_i, γ_i and α_i are the activity coefficients. When the same solution is represented by different expressions of the concentration, the standard chemical potentials are not numerically identical. They are related to each other by the following equations [23].

$$\mu_{i(m)}^\circ = \mu_i^\circ + RT \cdot \ln(M_1/1\,000) \quad (16)$$

$$\mu_{i(c)}^\circ = \mu_i^\circ + RT \cdot \ln(V_1/1\,000) \quad (17)$$

where M_1 and V_1 are the molecular weight and the molal volume of the solvent.

Now, let us consider the transfer of the solute (anesthetic) from the water phase (W) to the lipid phase (L). Since the chemical potentials of the solute in the two phases are equal,

$$\Delta G^\circ = \mu_i^\circ(L) - \mu_i^\circ(W) = -RT \cdot \ln K \quad (18)$$

According to Eqns. 14 and 16, the standard free energy of transfer, ΔG_m° by the molality partition coefficient K_m is written as follows.

$$\Delta G_{(m)}^\circ = -RT \cdot \ln K_{(m)} = \Delta G^\circ + RT \cdot \ln(M_L/M_W) \quad (19)$$

where M_L and M_W are the molecular weight of the phospholipid and water, respectively. Likewise, from Eqns. 15 and 17, one can also obtain the standard free energy of transfer $\Delta G_{(c)}^\circ$ by the molarity partition coefficient $K_{(c)}$.

$$\Delta G_{(c)}^\circ = -RT \cdot \ln K_{(c)} = \Delta G^\circ + RT \cdot \ln(V_L/V_W) \quad (20)$$

where V_L and V_W are the molal volumes of phospholipid and water, respectively. From Eqns. 19 and 20, the relationships among K, $K_{(m)}$ and $K_{(c)}$ are written as

$$K = (M_L/M_W) \cdot K_{(m)} = (V_L/V_W) \cdot K_{(c)} \quad (21)$$

In dealing with the DPPC/water partition coefficients, the following conversion factors are required for (M_L/M_W) and (V_L/V_W).

$$K = 40.6 \cdot K_{(m)} = 42.5 \cdot K_{(c)} \quad (22)$$

The conversion factors for the three phospholipids are listed in Table III.

In order to compare the reported partition coefficient data, $K_{(m)}$ and $K_{(c)}$ for the general anesthetics and alcohols were computed from K using Eqn. 22 and shown in Table IV. Although M_L/M_W and V_L/V_W in Table III are numerically close, these values will deviate significantly when a wide temperature range is employed due to the greater thermal expansion of lipid as compared to water, plus the volume change associated with the phase transition. Therefore, molality and molarity should not be used interchangeably unless the numerical values of M_L and V_L are sufficiently close enough and the temperature is maintained constant.

The standard free energy of transfer is thermo-

TABLE III

CONVERSION FACTORS AMONG PARTITION COEFFICIENTS EXPRESSED BY MOLE FRACTION, MOLALITY AND MOLARITY

	M_L/M_W	V_L/V_W	(Temp.)
DMPC	37.5	36.6	(299.7 K)
DPPC	40.6	42.4	(316.7 K)
DSPC	43.7	44.3	(329.7 K)

TABLE IV

DPPC/WATER PARTITION COEFFICIENTS OF INHALATION ANESTHETICS AND *n*-ALCOHOLS CALCULATED FROM THE CONCENTRATIONS USING DIFFERENT EXPRESSIONS

References: a, Simon et al. [9], b, Hill [2], c, Colley and Metcalfe [18], d Ebihara et al. [8] and e, Jain and Wray [7].

	K	$K_{(m)}$	$K_{(c)}$	Comparison
Halothane	2570	63.3	60.6	4000 [a], 3790 [b]
Methoxyflurane	2350	57.9	55.4	
Enflurane	1680	41.4	39.6	
Chloroform	1220	30.0	28.8	962 [b]
Diethyl ether	77.5	1.92	1.83	65.2 [b]
Benzyl alcohol	305	7.51	7.19	12.7 [c], 9.52 [d]
Ethanol	2.53	0.062	0.060	4.25 [b]
n-Propanol	19.0	0.47	0.45	22.7 [b]
n-Butanol	61.6	1.52	1.45	114 [b]
n-Pentanol	278	6.58	6.56	336 [b], 4.8 [e]
n-Hexanol	963	23.7	22.7	1770 [b], 25.2 [e]
n-Heptanol	4060	100.0	95.8	5070 [b], 50.4 [e]

dynamically defined as the difference of the standard chemical potentials of the anesthetics in the two phases expressed by mole fraction. ΔG° may be calculated from the partition coefficients derived from molality or molarity after transforming the values into those of mole fraction by using the conversion factors shown in Table III.

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References

1 Hill, M.W. (1974) Biochim. Biophys. Acta 356, 117–124
2 Hill, M.W. (1975) Biochem. Soc. Trans. 3, 149–152
3 Ueda, I., Tashiro, C. and Arakawa, K. (1977) Anesthesiology 46, 327–332
4 Tashiro, C. and Ueda, I. (1977) Jpn. J. Anesthesiol. 26, 513–518
5 Kamaya, H., Ueda, I., Moore, P.S. and Eyring, H. (1979) Biochim. Biophys. Acta 550, 131–137
6 Trudell, J.R., Payan, D.G., Chin, J.H. and Cohen, E.N. (1975) Proc. Natl. Acad. Sci. USA 72, 210–213
7 Jain, M.J., Wu, N.Y. and Wray, L.V. (1975) Nature 255, 494–496
8 Ebihara, J.E., Hall, J.E., MacDonald, R.C., McIntosh, T.J. and Simon, S.A. (1979) Biophys. J. 28, 185–196
9 Simon, S.A., McIntosh, T.J., Bennett, P.B. and Shrivastav, B. (1979) Mol. Pharmacol. 16, 163–179
10 Jain, M.K. and Wray, L.V. (1978) Biochem. Pharmacol. 27, 1294–1296
11 Katz, Y. and Diamond, J.M. (1974) J. Membrane Biol. 17, 87–100
12 Trudell, J.R., Nelson, C. and Mastrangelo, C.J. (1979) Anesthesiology 51, S13
13 Miller, K.W. and Yu, S-C.T. (1977) Br. J. Pharmacol. 27, 1294–1296
14 Ueda, I., Shieh, D.D. and Eyring, H. (1974) Anesthesiology 41, 217–225
15 Elder, J.P. (1978) Am. Lab. 10(4), 75–81
16 Bernhard, J. and Pauly, H. (1980) J. Phys. Chem. 84, 158–162
17 Mabrey, S. and Sturtevant, J.M. (1976) Proc. Natl. Acad. Sci. USA 73, 3862–3866
18 Colley, C.M. and Metcalfe, J.C. (1972) FEBS Lett. 24, 241–246
19 Shieh, D.D., Ueda, I., Lin, H.C. and Eyring, H. (1976) Proc. Natl. Acad. Sci. USA 73, 3999–4002
20 Yokono, S., Shieh, D.D. and Ueda, I. (1981) Biochim. Biophys. Acta 645, 237–242
21 Wilkinson, D.A. and Nagle, J.F. (1979) Biochemistry 18, 4244–4249
22 Hayase, K. and Hayano, S. (1977) Bull. Chem. Soc. Jpn. 50, 83–85
23 Kirkwood, J.F. and Oppenhaim, I. (1962) in Chemical Thermodynamics, Ch. 11, McGraw-Hil, New York