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ADSORPTION OF INHALATION ANESTHETICS ON THE AIR/WATER INTERFACE AND THE EFFECT OF WATER STRUCTURE

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The interaction of inhalation anesthetics with an air/water interface, and the effects of anions designated as water structure breaker (SCN^-) and water structure maker (F^-) upon anesthetic adsorption were studied. The values of the free energy of adsorption ($-\Delta G$) were in the order chloroform < halothane < enflurane < diethyl ether. The values of ΔS of the adsorption of the ether-type anesthetics differ markedly from those of the alkane-type anesthetics. According to our statistical mechanical theory, it was estimated that chloroform and halothane lose one degree of freedom of the rotation by the adsorption while enflurane and diethyl ether lose two and three degrees, respectively. These losses of the rotational degrees of freedom do not mean that the rotational motion is completely frozen; rather, it transforms into the vibrational mode with the resulting average frequencies in the order of the thermal vibration ($kT/h = 6 \cdot 10^{12}$ Hz). The larger number of the loss of the rotational freedom with the ether-type anesthetics suggests that the hydrophilic ether oxygen may be involved. The molar affinity potentials of the anesthetics to the interface were estimated to be; chloroform, 5.4; halothane, 5.6; enflurane, 8.7; and diethyl ether, 10.7 kcal/mol. These values are inversely correlated to the anesthetic potency of these drugs with correlation coefficient of 0.999. The interaction of anesthetics with the interface was stronger on 2 M KF subsolution than on 2 M KSCN. The ordered water structure is apparently favored for the interaction of anesthetics with water.

Introduction

It is known that the water molecules at the surface of macromolecules such as proteins and biological membranes assume a compact structure [1,2]. The existence of specific ion effects on biological system has been recognized in relation to the structure of water at the interfacial region [3,4]. The effects of anions on biological systems are often in order $SCN^- > I^- > Br^- > Cl^- > F^-$, in line with that of the Hofmeister series, which is related to the effect upon the water structure [5,6]. In this series, SCN^- is regarded as a water structure breaker, F^- as a structure maker [7].

So far, little attention has been focused on the interfacial action of anesthetics. Eyring et al. [8] and Ueda et al. [9] proposed that the interfacial water structure and its change by anesthetics may be the major determinant of the state of the membrane activity. We have also shown [10,11] that anesthetics tend to dehydrate the surface of non-ionic surfactant micelles and release counter-ions from the surface of ionic surfactant micelles.

The interaction of the vapor of inhalation anesthetics with the interfacial water can be studied by measuring the change of the surface tension of water. The present communication reports the relationship between the surface tension of water and the vapor

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pressure of inhalation anesthetics. The effects of SCN^- and F^- on the interaction of inhalation anesthetics with water surface is also reported.

Methods

Chloroform (Spectrograde) and diethyl ether (USP for Anesthesia) were obtained from Spectrum Chemical (Redond Beach, CA) and J.T. Baker (Phillipsburg, NJ), respectively. Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) and enflurane (2-chloro-1,1,2-trifluoro ethyl difluoromethyl ether) were gifts from Ayerst Labs (New York, NY) and Ohio Medical Products (Madison, WI), respectively. KF and KSCN were both reagent grade obtained from Fisher (Fair Lawn, NJ). These salts were dissolved in purified water at 2 M, and were treated with activated charcoal to remove surface-active contaminants. A 10 : 1 compression of the surface of the salt solutions by a dynamic surface tension balance, after being left to stand for 10 min, produced less than 0.1 dyne/cm change in surface tension.

Water was purified by distillation followed by passage through two mixed-bed ion-exchange columns, an activated charcoal column and an ultrafilter in a Millipore system (Bedford, MA). The specific resistance of the obtained water was maintained above 16 $M\Omega \cdot cm$, and the absence of surface active contaminants was checked by the dynamic surface tension measurement as described above.

The anesthetics were vaporized in the copper kettle of an anesthesia machine and diluted with nitrogen gas. The partial pressures of the anesthetics were estimated from the kettle temperature and the flows of the nitrogen gas and they were confirmed by gas-liquid chromatography. The surface tensiometer (Acoma, Tokyo, Japan) was enclosed in a box and the anesthetic vapors were administered into the gas phase at a flow rate of 3 l/min.

The anesthetic adsorption on the air/water interface was measured by the decrease of the surface tension using Langmuir's hanging plate method with a glass plate and a high-sensitivity force transducer (Shinkoh Co., Kanagawa, Japan) at 5.0, 12.0 and 19.0°C. The trough was milled from a Teflon block and its dimensions were 25 X 5 X 1 cm. The temperature was controlled by circulating water from a waterbath through a glass tube immersed in the trough, and was measured by a Digitec thermistor thermometer with 0.01°C resolution (Dayton, OH).

Results

Figs. 1 and 2 show the plot between the surface pressure and the anesthetic vapor pressure (π-P curves) for chloroform, halothane, enflurane and diethyl ether on distilled water at 5, 12 and 19°C. The surface pressure, π, is defined as

$$\pi = \gamma_0 - \gamma \quad (1)$$

where γ_0 is the surface tension of water in the absence of anesthetics and γ is that in the presence of anesthetics. The surface pressure of diethyl ether is very large compared to those of chloroform, halothane and enflurane. The π-P curves are comparable to those reported for aliphatic hydrocarbons [12,13].

Fig. 3 shows the π-P curves of four anesthetics adsorbed on 2 M KF and 2 M KSCN solutions at 12°C. The order of surface pressure at the same temperature and vapor pressure is 2 M KF > 2 M KSCN > distilled water.

From the surface pressure obtained as a function

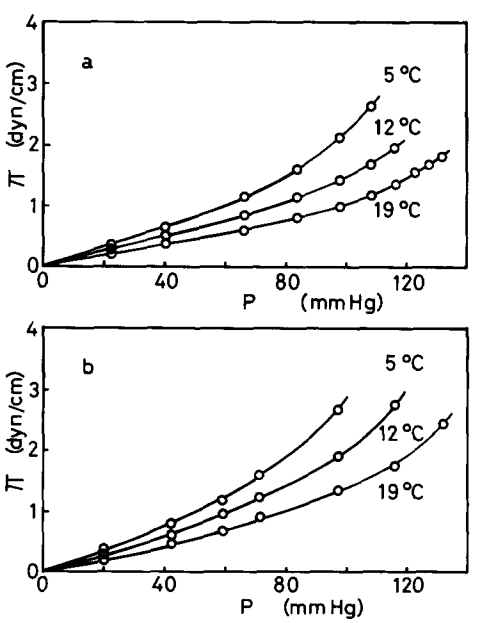

Fig. 1. π-P curves for the adsorption of chloroform (a) and halothane (b) on distilled water at 5.0, 12.0 and 19.0°C.

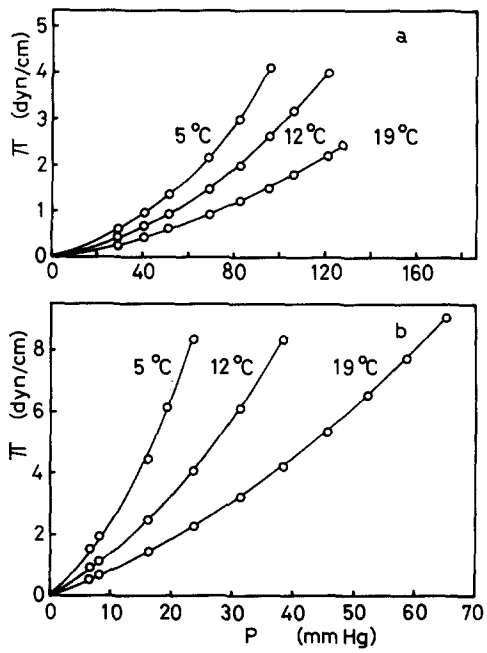

Fig. 2. π-P curves for the adsorption of enflurane (a) and diethyl ether (b) on distilled water at 5.0, 12.0 and 19.0°C.

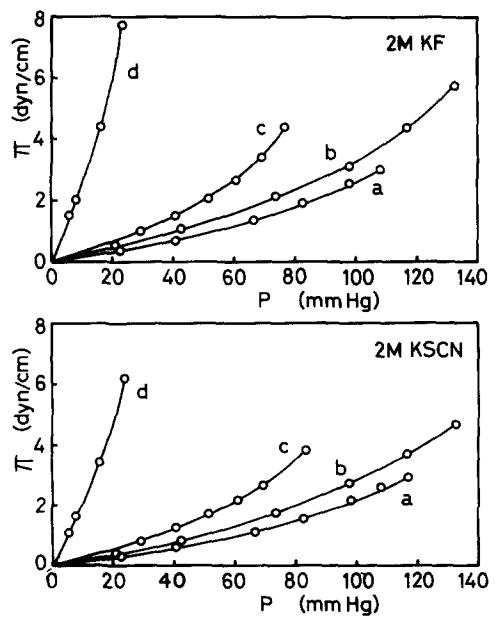

Fig. 3. π-P curves for the adsorption of chloroform (a), halothane (b), enflurane (c) and diethyl ether (d) on 2 M KF and 2 M KSCN subsolutions at 12°C.

of the vapor pressure of anesthestics, the adsorption excess, Γ, was estimated according to the Gibbs adsorption equation in the form of

$$\Gamma = \frac{1}{RT} \frac{d\pi}{d \ln P} \tag{2}$$

where R is the gas constant and T is the absolute temperature. The Γ-P curves of halothane on distilled water are shown in Fig. 4 as an example. It was found that, at a constant vapor pressure, the adsorption decreased with increasing temperature.

In all cases investigated, the adsorption isotherm followed the empirical equation

$$\Gamma = \frac{aP}{1 - bP} \tag{3}$$

where a and b are constants. This is an equation for a rectangular hyperbola. The curve passes the origin and is convexed to the P axis.

Fig. 5 shows the linear relationship obtained for halothane when Eqn. 3 is plotted in the form of Γ/P against Γ. The theory of multimolecular adsorption developed by Brunauer, Emmett and Teller [14] distinguishes five types of physical adsorption. The present form of adsorption isotherm is designated as type III, and occurs only when the forces of monomolecular adsorption are small.

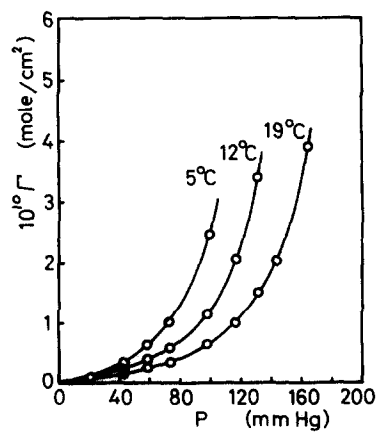

Fig. 4. Γ-P curves for the adsorption of halothane on distilled water at 5.0, 12.0 and 19.0°C.

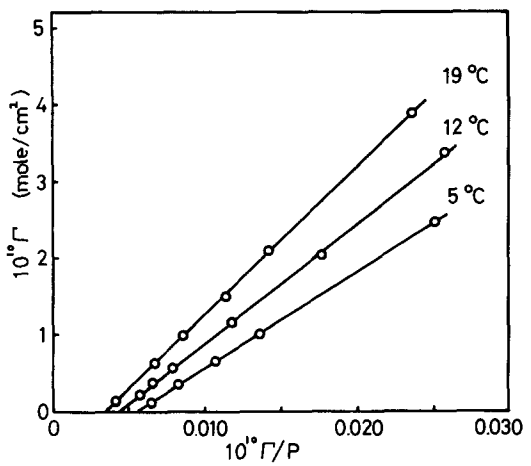

Fig. 5. Γ-Γ/P curves for halothane on distilled water at 5.0, 12.0 and 19.0°C.

The combination of the Volmer equation [15]

$$\pi(A - b) = kT \tag{4}$$

with the Gibbs equation by substitution followed by integration gives

$$\ln(P/\pi) = b\pi/kT + C \tag{5}$$

where b is the co-volume factor. In the present work linear relationships were obtained when $\ln(P/\pi)$ was plotted against π.

The free energy of adsorption was determined using the equation described by Kemball and Rideal [16].

$$-\Delta G = 2.303\, RT(4.0969 - C) \tag{6}$$

The value for the constant C can be obtained from the intercept of the plot between $\ln(P/\pi)$ and π.

Fig. 6 shows the relation between $\log(P/\pi)$ and π for enflurane and diethyl ether on distilled water. The free energy of adsorption for chloroform, halothane, enflurane and diethyl ether are shown in Table I. The enthalpy and entropy of adsorption were calculated from the dependence of the free energy of adsorption upon the temperature using the Gibbs-Helmholtz equation.

$$\Delta G - \Delta H = T(\partial \Delta G/\partial T) = -T\Delta S \tag{7}$$

The values of ΔH and ΔS are listed in Table I. The ΔH of adsorption is comparable to the ΔH of vaporization.

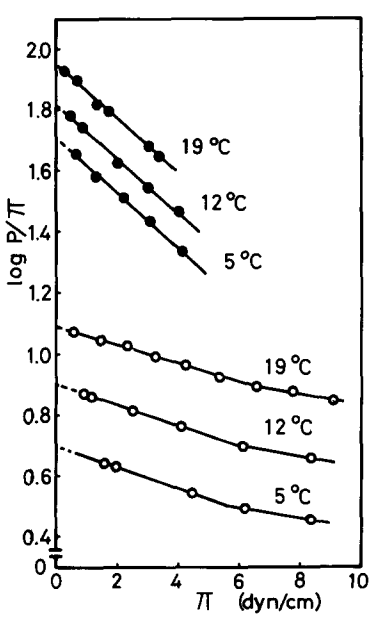

Fig. 6. $\log(P/\pi)$-π curves for enflurane (•) and diethyl ether (○) on distilled water at 5.0, 12.0 and 19.0°C.

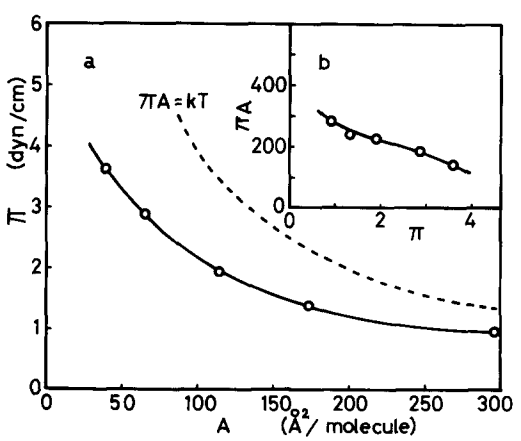

Fig. 7. π-A (a) and πA-π (b) curves for halothane on distilled water at 12.0°C.

TABLE I

THE ADSORPTION OF INHALATION ANESTHETICS UPON THE AIR/WATER INTERFACE AND THE EFFECTS OF 2 M KSCN AND 2 M KF

		$-\Delta G$ (cal/mol)			$-\Delta H$ (cal/mol)	$-\Delta S$ (entropy unit)
	Temperature (°C):	5.0	12.0	19.0		
Chloroform	H_2O	2833	2766	2700	5479	9.5
	KSCN	2940	2870	2807	5586	9.5
	KF	3004	2936	2867	5729	9.8
Halothane	H_2O	2940	2871	2806	5606	9.6
	KSCN	3144	3079	3008	5849	9.7
	KF	3195	3132	3061	5861	9.6
Enflurane	H_2O	3055	2962	2873	6676	13.0
	KSCN	3207	3118	3021	6907	13.3
	KF	3265	3197	3061	7323	14.6
Diethyl ether	H_2O	4329	4177	4030	10 277	21.4
	KSCN	4546	4399	4225	10 932	22.9
	KF	4609	4464	4279	11 174	23.6

Discussion

The values of the surface excess of the anesthetics were in the order of chloroform < halothane < enflurane < diethyl ether. The surface area per molecule, A, can be derived from the surface excess using the following relationship.

$$A = 1/\Gamma N_0 \qquad (8)$$

where N_0 is Avogadro's number.

Fig. 7 shows the π-A and πA-π relations for halothane at 12°C. The curve for an ideal gaseous film at the same temperature is also shown. The π-A curve is similar to the P-V curve for gas. The value of A for a given value of π is always less than that corresponding to the ideal gas equation. Clearly a correction is needed for the deviation for ideality. In the present case, the attractive term predominates. The deviation due to the attractive factor is more evident in the πA-π diagram, where the πA values fall increasingly below the ideal value as π increases. This is the usual finding for the adsorption of insoluble vapors on the water surface, and so far no case has been reported in which the slope of the curve assumed a positive value. Kemball and Rideal [16], however, reported a positive slope for the adsorption of insoluble vapors on the mercury surface, in which the deviation from the equation $\pi A = kT$ was opposite to that observed here. In their case, co-volume factor was the predominant correction term.

The free energies of adsorption of chloroform and halothane were smaller than those of n-alkanes. Jones and Ottewill [13] reported that the free energies of adsorption of n-hexane and n-heptane at 15°C were 3 054 and 3 420 cal/mol, respectively. From the plot of the free energy against the number of carbon atoms in the n-saturated hydrocarbons, they found that the increase of the free energy by each increment of carbon atom was about 420 cal/mol. The difference in the free energy of adsorption between chloroform and halothane was small, and about 100 cal/mol (Table I).

The free energies of adsorption of the ether-type anesthetics were larger than those of the alkane-type anesthetics. As shown in Fig. 6, a break is observed in the slope of $\log(P/\pi)$ against π for diethyl ether. The break probably corresponds to the change of the state of the film as the anesthetic vapor-pressure increases. These could be related to the relative changes in the attractive forces among anesthetic molecules and the co-volume factor.

The value of ΔS of the alkane-type anesthetics differ markedly from those of the ether-type anes-

thetics. The entropy change is analyzed by the following statistical mechanical theory. The surface pressure due to the adsorbed anesthetic is regarded as a result of the equilibrium between the gas phase and the surface under the present experimental conditions.

Let X and N be the total number of the anesthetics in the system and that of the adsorbed molecules on the surface, respectively. Then the partition function, Z, of the total system in written [17],

$$Z = \frac{1}{(X-N)!}(pf)_g^{X-N}\frac{1}{N!}(pf)_{ad}^{N}\exp(-\gamma_0 A_0/\boldsymbol{k}T) \tag{9}$$

where $(pf)_g$, $(pf)_{ad}$, γ_0 and A_0 are the molecular partition functions of the gaseous and the adsorbed anesthetics, the surface tension of pure water and the total surface area, respectively. The molecular partition functions are expressed in the forms of

$$(pf)_g = \frac{(2\pi m\boldsymbol{k}T)^{3/2}}{h^3}V\frac{1}{\pi}\left(\frac{8\pi^3 I\boldsymbol{k}T}{h^2}\right)^{3/2} \tag{10}$$

$$(pf)_{ad} = \frac{(2\pi m\boldsymbol{k}T)^{3/2}}{h^3}\Delta l(A_0 - Na)\frac{1}{\pi}\left(\frac{8\pi^3 I\boldsymbol{k}T}{h^2}\right)^{(3-n)/2} \times [1-\exp(-h\nu/\boldsymbol{k}T)]^{-n}\exp[(\epsilon_0+\epsilon x)/\boldsymbol{k}T] \tag{11}$$

where $I = (I_1 I_2 I_3)^{1/3}$, ν, V are the average moment of inertia of the molecule, the average frequency of the vibrations of the molecule in the interface and the total volume of the gas phase, respectively. The factors ϵ_0, ϵ and Δl are, respectively, the affinity potential of the anesthetics from the gas phase to the interface, the attractive energy parameter between the molecules in the interface, and the thickness of the interfacial domain where anesthetic molecules are adsorbed. The factor x is the packing fraction which is defined as

$$x = Na/A_0 \tag{12}$$

where a is the molecular area of the anesthetic (co-area) adsorbed on the interface. In Eqn. 11, it is assumed that n degrees of freedom on the rotation in the gas phase are frozen to become the same number of the vibrational modes with the average frequency ν. Although the two-dimensional translational motion may be restricted to some extent, we assume that there exists free translational motion at the interface, and also assume that there is some translational motion in the perpendicular direction to the interface with the translational free length Δl. The attractive energy, ϵ, is included so as to reproduce the usual van der Waals type equation of states.

Before we proceed, a discussion on the change of the degree of freedom on a molecule due to the adsorption is in order. In the study of the adsorption of benzene, toluene and n-heptane on the mercury surface, Kemball [16] completely froze the translational motion in the perpendicular direction on the mercury surface, while allowing the presence of a non-zero thickness (Δl = 6 Å) to estimate the area per molecule and the two-dimensional translational entropy. In order to avoid this inconsistency, we formulate that the total number of the degrees of freedom of a molecule stays unchanged when it is adsorbed on the interface from the gas phase. The theory satisfies the condition that the quantum effects must disappear in the high temperature range ($T \to \infty$).

The free energy, F, of the total system is defined as

$$F = -\boldsymbol{k}T\ln Z \tag{13}$$

and F is minimized by the change of the adsorbed number N to result

$$\frac{\partial F}{\partial N} = -\epsilon_0 - \epsilon x - \boldsymbol{k}T\ln\left[a\,\Delta l(1/x-1)\frac{X}{V}\right] + \frac{\boldsymbol{k}T}{1/x-1} - n\boldsymbol{k}T\ln[(8\pi^3 I\boldsymbol{k}T)^{1/2}/h\{1-\exp(-h\nu/\boldsymbol{k}T)\}] = 0 \tag{14}$$

Eqn. 14 determines the packing fraction x as a function of the concentration X/V in the gas phase.

The surface tension, γ, of water after the adsorption of anesthetics becomes, by definition

$$\gamma = \frac{\partial F}{\partial A_0} = \gamma_0 - \pi \tag{15}$$

where π is the surface pressure expressed as

$$\pi = \frac{1}{a}\left(\frac{\boldsymbol{k}T}{1/x-1} - \frac{\epsilon x^2}{2}\right) \tag{16}$$

When the anesthetic concentration is low, Eqn. 14 can be rewritten

$$-RT\ln\left(\frac{P_{ad}}{P_g}\right) = -N_0\epsilon_0 + nRT\ln\left[\frac{(8\pi^3 IkT)^{1/2}}{h} \times \{1 - \exp(-h\nu/kT)\}\right] \quad (17)$$

where $P_g = XkT/V$, $P_{ad} = xkT/\Delta la$ and N_0 are the partial pressure of the anesthetic in the gas phase, that at the interface in the limit of low concentration, and Avogadro's number, respectively.

The left-hand side of Eqn. 17 is identical to the free energy difference, ΔG, of Eqns. 6 and 7. Therefore, the enthalpy and the entropy changes of the previous section are expressed in the forms of

$$\Delta S = \frac{-\partial\,\Delta G}{\partial T} = -nR\ln\left[\frac{(8\pi^3 IkT)^{1/2}}{h}\{1 - \exp(-h\nu/kT)\}\right] + nR\left\{\frac{h\nu/kT}{\exp(h\nu/kT) - 1} - \frac{1}{2}\right\} \quad (18)$$

and

$$\Delta H = \Delta G + T\,\Delta S = -\epsilon_0 N_0 + nRT\left[\frac{h\nu/kT}{\exp(h\nu/kT) - 1} - \frac{1}{2}\right] \quad (19)$$

In Eqns. 18 and 19, there are four parameters, i.e., I, ν, n, and ϵ_0. For the calculation of the moment of inertia, I, the molecules are regarded spherical for simplicity. This approximation does not change the numerical values too much compared to those obtained by more precise estimation.

From the experimental data of ΔH and ΔS, we determine the three parameters, ν, n and ϵ_0. Because these values are estimated by the use of the two experimental data, we first fix the value of n to be 3 for all four anesthetics, and the results are shown in Table II. The obtained average frequencies are too small compared to that of the thermal frequency $\nu_t = kT/h = 6 \cdot 10^{12}$ Hz, except for diethyl ether. This result shows that the coupling force to produce the assumed vibrations of these molecules is very weak. Therefore, we infer that the rotational degrees of freedom of chloroform, halothane and enflurane

TABLE II

ANESTHETIC ADSORPTION ON WATER SURFACE

It is assumed that three degrees of freedom of rotation of the anesthetic molecules are transformed into vibrational modes with average frequency ν.

Anesthetics	n	ν ($\times 10^{12}$ Hz)	$N_0\epsilon_0$ (cal/mol)
Chloroform	3	0.36	6240
Halothane	3	0.26	6400
Enflurane	3	0.46	9030
Diethyl ether	3	3.1	10 700

molecules on the interface are partly frozen to become the vibrational motions.

Accordingly, the lowest possible values of n are chosen and the resulting parameters are shown in Table III. The frequencies are neither too small nor too large compared to the thermal frequency. From Table III, we can state that chloroform and halothane lose at least one degree of freedom of rotation, while enflurane and diethyl ether lose at least two and three degrees of freedom, respectively. The reason why too small frequencies of vibrational modes are considered to be unrealistic is discussed in the Appendix.

We postulate, therefore, that the rotational degrees of freedom are not completely frozen when anesthetic molecules are adsorbed on the water surface.

The extent of the adsorption of the anesthetics on 2 M KF and 2 M KSCN subsolutions was in the order of chloroform < halothane < enflurane < diethyl ether in accordance with that on distilled water. The adsorption was readily reversible by the wash-out of the anesthetic vapor with nitrogen gas. In Fig. 3 it is seen that, at the same vapor pressure, the surface pressure on the subsolution containing 2 M KF is higher than on 2 M KSCN.

Inorganic salts raise the surface tension of water, and the magnitude of the increase of the surface tension at the same concentrations follows the lyotropic series, i.e., $F^- > Cl^- > Br^- > I^- > SCN^- > (H_2O)$ for monovalent anions, and $Li^+ > Na^+ > K^+ > (H_2O)$ for monovalent cations. We have mentioned that F^- is regarded as water structure maker and SCN^- as water structure breaker.

The adsorption of hydrated ions on the air/water interface requires partial dehydration, and the work

required for this process is reflected in the positive $\Delta\gamma$. In other words, the increase of the surface tension of water due to the addition of inorganic salts is caused by the repulsive effects of the salt ions against the interface. According to the Gibbs equation, the concentration of such solute on the surface must be less than that in the bulk solution [18].

The result of the surface potential measurement by Frumkin [19] indicated that monovalent anions were repelled from the surface of water to a lesser degree than cations and the order of the decrease of surface potential was $F^- < Cl^- < Br^- < SCN^-$.

Frank and Evans [20] proposed a structural entropy term, S_{st}, which refers directly to the ability of the ion to alter the water structure. Thus, in terms of this criterion, it can be seen that the ions with more structure-disordering action show lower values of $\Delta\gamma$ (difference in surface tension between salt solution and pure water). Hence, the structure-breaker such as SCN^- ion is more easily accomodated at the interface than F^-, a structure-maker, due to the fact that the former introduces more disorder in the structured region at the air/water interface; there is a more favorable entropy contribution from SCN^- than from F^-.

It is shown in Table I that the interaction of anesthetics with interface of 2 M KF is stronger than that of 2 M KSCN. The structure-maker enhances the anesthetic adsorption, and the ordered water structure is apparently favored for the interaction of anesthetics with water at the surface.

It has been the general tendency to analyze the action of inhalation anesthetics on the air/water interface in the presence of lipid monolayers [21–23]. In this condition, the surface adsorption of anesthetics is a combined result including anesthetic-lipid and anesthetic-water interactions. When lipid membranes are present, positive correlations between the anesthetic potency and the increase of the surface pressure have been demonstrated [21–23].

TABLE III

ANESTHETIC ADSORPTION ON WATER SURFACE

Minimum degrees of rotational freedom are chosen which are transformed into the vibrational modes with resulting average frequency, ν, close to the thermal vibration ($kT/h = 6 \cdot 10^{12}$ Hz).

Anesthetics	n	ν ($\times 10^{12}$ Hz)	$N_0\epsilon_0$ (cal/mol)
Chloroform	1	9.1	5400
Halothane	1	6.2	5600
Enflurane	2	1.4	8700
Diethyl ether	3	3.1	10 700

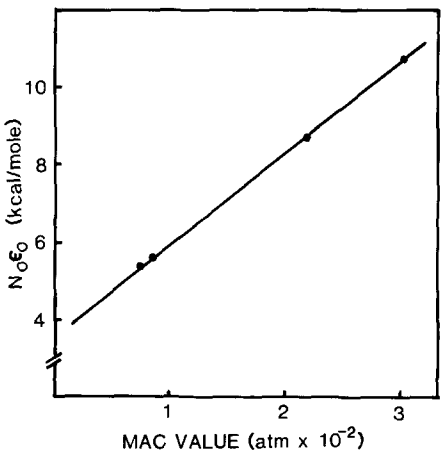

Fig. 8. Inverse correlation between the anesthetic potency expressed by the minimal alveolar concentration (MAC) and the affinity potential.

The present study separates the anesthetic-water interactions from the anesthetic-lipid interactions at the air/water interface. When the present adsorption data were corrected for the entropy change due to the loss of the degrees of rotational freedom, the affinity potential of these anesthetics (Table III) showed an inverse correlation to their anesthetic potencies with an excellent correlation coefficient, $r = 0.99997$ (Fig. 8). In this figure, the anesthetic potency is shown by the minimal alveolar concentrations (MAC) expressed by the partial pressure (atm) of these anesthetics required to induce a surgical stage of anesthesia in dogs [24]. The stronger affinities of these anesthetics to the aqueous phase at the interface decrease their tendency to penetrate into the cell membranes. This effect is enhanced by the structuring of the water molecules at the interfacial region.

Appendix

We discuss semiquantitatively the reason why too small frequencies of vibrational modes are considered

to be unrealistic. As an example, the following case is considered: a rotational degree of freedom of a molecule in the gas phase becoming a vibrational motion after binding to a surface. By denoting the angular variable as θ, the total energy E of the vibrational motion can be expressed as

$$E = \frac{I\dot{\theta}^2}{2} + \frac{\kappa\theta^2}{2} \tag{20}$$

where κ is the force constant of the vibrational mode. The vibrational frequency, ν, of this system is expressed as

$$\nu = \frac{1}{2\pi}\left(\frac{\kappa}{I}\right)^{1/2} \tag{21}$$

If the value of ν is known, the force constant can be estimated from Eqn. 21 by

$$\kappa = (2\pi\nu)^2 I \tag{22}$$

When the force constant is small, the amplitude, $\sqrt{\langle\theta^2\rangle}$ of the thermal motion is estimated from the relation

$$\frac{\kappa}{2}\langle\theta^2\rangle = \frac{kT}{2} \tag{23}$$

From Eqns. 22 and 23, we obtain

$$\sqrt{\langle\theta^2\rangle} = \sqrt{\frac{kT}{\kappa}} = \frac{1}{2\pi\nu}\sqrt{\frac{kT}{I}} \tag{24}$$

When we take the numerical values of ν, I and T to be $3 \cdot 10^{11}$ Hz, $1 \cdot 10^{-37}$ g $\cdot$ cm^2 and 12°C, respectively, the vibrational angle becomes

$$\sqrt{\langle\theta^2\rangle} = 0.33 \text{ rad} = 19° \tag{25}$$

When the radius, a, of the molecule is 3.5 Å, the amplitude, $a\sqrt{\langle\theta^2\rangle}$, of the surface becomes

$$a\sqrt{\langle\theta^2\rangle} = 1.2 \text{ Å} \tag{26}$$

These amplitudes expressed in Eqns. 25 and 26 appear to be too large for vibration of a molecule on a surface.

Acknowledgements

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