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INTERACTIONS OF SMALL NONPOLAR MOLECULES WITH BIOLOGICAL MEMBRANES: AN EXACTLY SOLVABLE MODEL

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An exactly solvable model of the interaction of small nonpolar molecules with biological membranes is developed. This model, which is based upon a "decorated dimer model" extension of Nagle's membrane model, is demonstrated to qualitatively reproduce many of the changes in the order-disorder phase transition seen when biological membranes are exposed to anesthetic gases. The decorated dimer model is itself interesting because it provides an example of an exactly solvable monomer-dimer model in which phase transitions can occur in the presence of monomers.

1. Introduction

One theory of general anesthesia is based upon the hypothesis that general anesthetics shift the order-disorder phase transition to lower temperatures, increasing the fraction of membrane lipids in the "melted" state, increasing the membrane volume, and increasing the cation permeability. That small hydrophobic molecules can cause such changes is well established experimentally, as is the fact that the changes may be reversed by increasing the pressure [1,2,3]. Although classical thermodynamic relationships have been considered to explain this behavior [1], this approach is aesthetically unsatisfying because it fails to account for the many ways in which biological membranes differ from ordinary fluids. The lipid bilayer is highly anisotropic, consisting of an ordered arrangement of hydrocarbon chains. The lipid molecules are held together predominantly by hydrophobic interactions, and to some degree, by electrostatic effects. At low temperatures most chains are in all trans states; the number of gauche rotations increases only slightly with increasing temperature until, at the transition temperature T_m, a cooperative phase transition results in a predominantly "gauche" membrane.

Nagle [4–8] has described a series of models of the melting transition in which excluded volume effects are accounted for by transforming a chain polymer model of the membrane to an exactly solvable dimer model. These models account for many aspects of the membrane phase transition. In this paper we generalize one of Nagle's models to include an interaction with small hydrophobic molecules, such as the noble gases. The principal theoretical tool employed in this generalization is the concept of a "decorated dimer model" which is in many ways similar to the decorated lattice gas (Ising) models used by Widom [9], Mermin [10], Wheeler [11] and others. Using this theoretical tool we show how the general nature of membrane interactions with small nonpolar molecules, such as inhalation anesthetics, may be described in a mathematically tractable and qualitatively accurate way.

2. The Nagle dimer model

In fig. 1 we show several hydrocarbon chains placed on a lattice corresponding to Nagle's membrane model A. The first chain is in an all gauche state. Each gauche rotation is associated with an energy ϵ of approximately 0.5 kcal/mole. The fourth chain is in an all trans configuration. Links joined in trans conformations are associated with an energy α which is taken to be zero. The chains are held together by an interaction of the form

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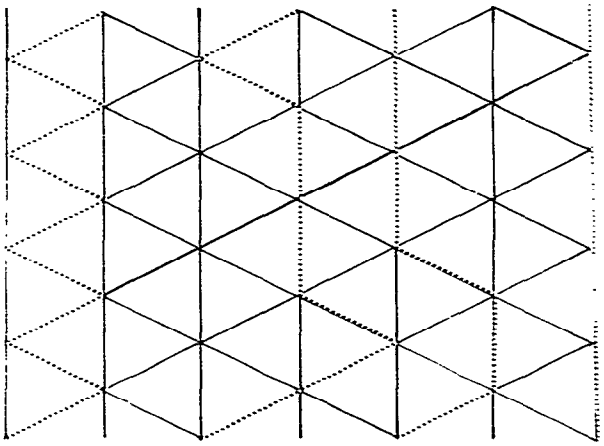

Fig. 1. Hydrocarbon chains (dotted lines) on a lattice corresponding to Nagle's model A (ref. [4]). The first chain is in an all-gauche state, while the fourth is in an all-trans state.

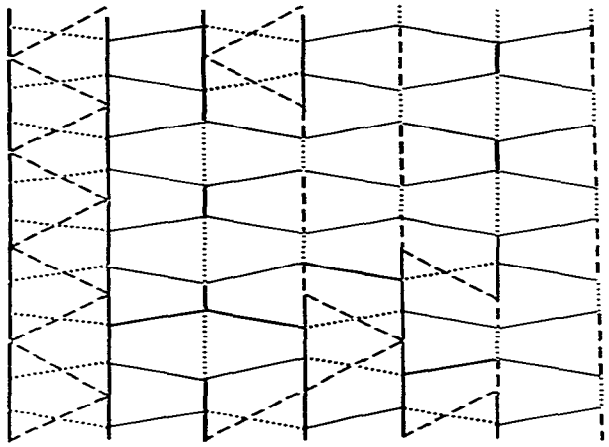

Fig. 2. Dimer model corresponding to the chain placement shown in fig. 1 illustrating dimer model A. Dotted lines represent the dimers; dashed lines correspond to the hydrocarbon chains; solid lines represent the underlying trapezoidal lattice.

$$G = U_{\text{configuration}} - TS_{\text{configuration}} + a\rho^{3/2} + P/\rho, \quad (1)$$

where ρ is the overall chain density and $a\rho^{3/2}$ is the contribution of the van-der-Waals interaction to the free energy. We will not here justify the form of this model. For a complete explanation of the original model and its assumptions, the reader is referred to Nagle's original paper [2]. As formulated above, the method for exactly calculating the partition function of this system is not obvious. However, Nagle showed how the model may be transformed to a dimer model for which the method of solution is well known [12,13].

Following Nagle, we decorate the original lattice with two new vertices placed one third of the way from either end of each vertical link (fig. 2). Each new vertex is joined by new edges to the four closest new vertices. Each state on the original lattice thus transforms to a unique state on the dimer lattice according to the rules:

1) Place a dimer on each horizontal edge of the new lattice which crosses a horizontal chain link.

2) Cover each vertical link of the chain with a dimer placed on the corresponding short vertical edge.

3) Cover any vertex on the new lattice which is not already covered by a dimer, by placing a dimer on the long vertical edge incident to that vertex.

In this model the chains are not allowed to fold back on themselves; hence the model is only reasonable when the membrane density is fairly high. Fortunately, this is usually the case in biomembranes.

The activity x of the horizontal dimers is given by

$$x = \exp(-\epsilon/kt),$$

where ϵ is the energy of gauche rotation given earlier. The activities y of the long vertical dimers and w of the short vertical dimers are given by

$$y = \exp(-\delta/kt)$$

and

$$w = \exp(-\alpha/kt)$$

where δ is an adjustable parameter reflecting the presence of "vacuum" in the membrane, and α is the energy of the trans rotation. The activity w is usually 1, corresponding to a zero energy state for an all trans molecule.

The model thus given is slightly more general than in Nagle's presentation, so some details of calculating the partition function are given in the appendix. We will not consider them further for the moment, but will rather consider how the presence of small molecules in the biological membrane may be incorporated in the model described above.

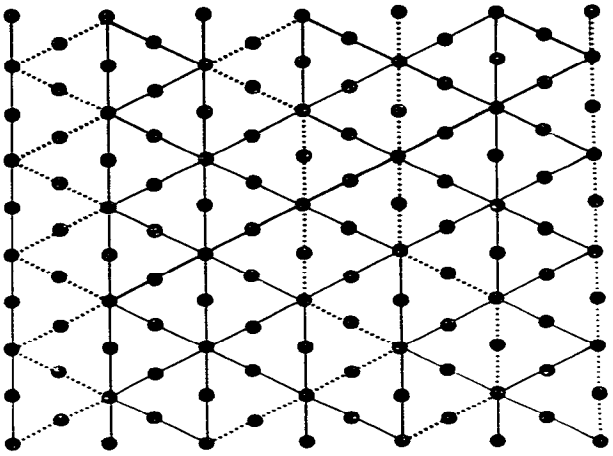

Fig. 3. Lattice based on Nagle's model A (ref. [4]) decorated with interstitial sites (•) used for the enumeration of monomer configurations within the membrane.

In order to account for the effects of monomers on the membrane model, we decorate the original lattice again, this time placing a secondary site at each vertex on the primary lattice and midway between vertices on the primary lattice (fig. 3). The secondary lattice thus contains twice as many sites as the primary lattice. This secondary lattice is left unchanged during transformation of the primary chain model to the dimer model. Hence, every bond in the resulting dimer model is associated with a secondary lattice site. The small molecule can thus interact with only one dimer at a time; similarly it cannot interact with more than a single chain at any one time. We will see later that this assumption, though physically somewhat unrealistic, gives qualitatively satisfactory results. In principle interactions with the vacuum can occur with interaction energies ϵ_v which are positive, negative, or zero. Interaction energies ϵ_c with the polymer chains are assumed to be more unfavorable than the interactions with the vacuum.

The following section is devoted to a formal definition of the decorated dimer model.

3. The decorated dimer lattice model

In order to account for the presence of monomers, we decorate the rectangular lattice generated by the dimer membrane analog by placing an interstitial site midway between each pair of vertices. Monomers with activity z may occupy interstitial sites of this decorated lattice, while the dimers are confined to the primary lattice. The activity z is assumed to have the form

$$z = 2\pi mkTA \exp[\mu/kT]/h^2.$$

μ is the chemical potential and A is the area of an interstitial site. Thus it is linearly related to the pressure of an ideal gas in equilibrium. We see that there are a total of $n(m-1)$ horizontal interstitial sites and $m(n-1)/2$ vertical interstitial sites of each type. As in other exactly solvable dimer models, we must require that all primary sites be covered by dimers. The monomers interact with primary lattice bonds according to table 1. This decoration is identical to that described in the last section on the untransformed primary lattice.

Table 1
Interaction energies for monomers in the decorated dimer model [a]

Type of bond	Status of bond	Energy
Horizontal	covered	ϵ_{xc}
Horizontal	uncovered	ϵ_{xu}
Short Vertical	covered	ϵ_{wc}
Short Vertical	uncovered	ϵ_{wu}
Long Vertical	covered	ϵ_{yc}
Long Vertical	uncovered	ϵ_{yu}

[a] This form for the energies of interaction is given for generality. In the remainder of the paper, we will assume that $\epsilon_{xc} = \epsilon_{yu} = \epsilon_{wc} = \epsilon_c$ and $\epsilon_{xu} = \epsilon_{yc} = \epsilon_{wu} = \epsilon_v$ i.e. that all interactions with the polymer have the same energy, and all interactions with the "vacuum" have the same energy.

Following Wheeler [11] we may write the partition function for the overall system as

$$Z = \sum_{\text{all sites}} g(N_x, N_y, N_w) x^{N_x} y^{N_y} w^{N_w} \times (1 + z\eta_{xu})^{v_{xu}} (1 + z\eta_{xc})^{v_{xc}} (1 + z\eta_{yu})^{v_{yu}} \times (1 + z\eta_{yc})^{v_{yc}} (1 + z\eta_{wu})^{v_{wu}} (1 + z\eta_{wc})^{v_{wc}}, \quad (2)$$

where

$$\eta_{ab} = \exp[-\epsilon_{ab}/kT].$$

We find that v_{xc}, the number of dimer covered horizontal interstitial sites which may be occupied by monomers, is clearly $v_{xc} = N_x$, while the number of uncovered horizontal bonds available to monomers is $v_{xu} = n(m-1) - N_x$. Similar relationships hold for the vertical dimers. Hence we have for the partition function

$$Z = \sum_{\text{all states}} Kg(N_x, N_y, N_w)\lambda^{N_x}\xi^{N_y}\Delta^{N_w}, \tag{3}$$

where

$$\lambda = x(1 + z\eta_{xc})/(1 + z\eta_{xu}),$$

$$\xi = y(1 + z\eta_{yc})/(1 + z\eta_{yu}),$$

$$\Delta = w(1 + z\eta_{wc})/(1 + z\eta_{wu}),$$

$$K = (1 + z\eta_{xu})^{n(m-1)} \times (1 + z\eta_{yu})^{m(n-1)/2}(1 + z\eta_{wu})^{m(n-1)/2}.$$

Hence

$$\ln(Z_{n,m}) = n(m-1)\ln(1 + z\eta_{xu}) + 0.5\, m(n-1)\ln(1 + z\eta_{yu}) + 0.5\, m(n-1)\ln(1 + z\eta_{wu}) + \ln(Z_{ref}[\lambda, \xi, \Delta, N_x, N_y, N_w]), \tag{4}$$

where Z_{ref} is the partition function for the reference dimer system. The per-site partition function Z is given by

$$\ln(Z) = \lim_{n,m\to\infty} \frac{1}{nm}[\ln(Z_{n,m})] = \ln(1 + z\eta_{xu}) + 0.5\ln(1 + z\eta_{yu}) + 0.5\ln(1 + z\eta_{wu}) + \ln(Z_{ref}). \tag{5}$$

The densities ρ_x, ρ_y and ρ_w for the decorated lattice dimer model are given by

$$\rho_x = \frac{d[\ln(Z)]}{d[\ln(x)]} = \frac{d[\ln(Z)]}{d[\ln(\lambda)]}\frac{d[\ln(\lambda)]}{d[\ln(x)]} = \rho_\lambda,$$

$$\rho_y = \frac{d[\ln(Z)]}{d[\ln(y)]} = \frac{d[\ln(Z)]}{d[\ln(\xi)]}\frac{d[\ln(\xi)]}{d[\ln(y)]} = \rho_\xi,$$

$$\rho_w = \frac{d[\ln(Z)]}{d[\ln(w)]} = \frac{d[\ln(Z)]}{d[\ln(\Delta)]}\frac{d[\ln(\Delta)]}{d[\ln(w)]} = \rho_\Delta.$$

These relationships (and those in the appendix) are all we need to apply the decorated dimer concept to the membrane model. Other thermodynamic quantities are readily obtained from the reference dimer model by taking the appropriate derivatives.

The rational for using a decorated dimer model rather than a model in which both dimers and monomers sit on the same lattice is simple: the latter model has no phase transition when monomers are present [14]. The present model does not suffer from that disadvantage and as a result, may be useful in understanding not only this system but other monomer-dimer systems which are known to undergo phase transitions.

4. Relationship on the polymer model to the dimer model

We may summarize the relationships between the dimer model and the biomembrane model as follows. The density of hydrocarbon chains ρ is given by

$$\rho = 0.5 - \rho_y.$$

The internal energy of the chain model per link is $(U_{dim} - \delta\rho_y)/\rho - a\rho^{3/2}$, where $U_{dim} = -kT\ln(Z) + TS$. Overall, the Gibbs free energy per link is therefore

$$G_c = -kT\ln(Z) + \delta\rho_y - a\rho^{3/2} + P/\rho.$$

The thermodynamically stable state of the membrane is found by minimizing G_c for fixed x, w, and z. Nagle has found that the order–disorder phase transition of the undecorated model occurs at density $\rho = 0.5$. This is unchanged in the decorated model. The phase transitions occur when

$$4\,kT_m\ln(1 + z\eta_{xu}) + 2\,kT_m\ln(1 + z\eta_{yc}) + 2\,kT_m\ln(1 + z\eta_{wu}) - 2\,kT_m\ln(1 - 2\lambda/\Delta) = 4P + 3a/2\sqrt{2}, \tag{6}$$

where T_m is the phase transition temperature. For the case $w = 1$ ($z = 0$) the model is identical to Nagle's and the phase transitions occur at the same points. These are summarized in table 2 for several values of

Table 2
Phase transitions in the basic membrane model

P	a	T_m	$\Delta\rho$ (5°)
0.001	1.0	234	0.0710
0.001	2.6	312	0.0095
0.001	4.0	341	0.0033
0.001	5.2	351	0.0015
0.010	1.0	237	0.0590
0.010	2.6	312	0.0098
0.010	4.0	342	0.0032
0.010	5.2	353	0.0016
0.100	1.0	259	0.0280
0.100	2.6	322	0.0077
0.100	4.0	346	0.0026
0.100	5.2	355	0.0014

the pressure P and a. As nonpolar molecules with activity z are added to the secondary lattice, the phase transition temperature decreases at a rate depending on the values of the interaction energies ϵ_v and ϵ_c.

If we consider the nature of the monomer–membrane interaction several things are immediately apparent. First of all, in general the interaction with the hydrocarbon chains themselves is expected to be unfavorable (characterized by a positive value for ϵ_c). A molecule sitting within a region of "vacuum" in the model might be expected to contribute an energy

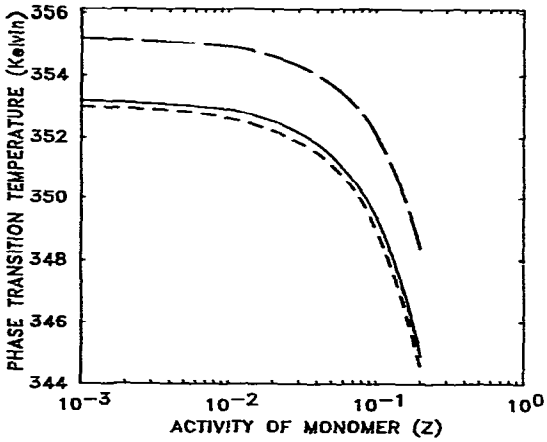

Fig. 4. Phase transition temperature plotted as a function of monomers at activity z interacting with a membrane characterized by $a = 5.2$ at pressures $P = 1$ atm (short dashes), $P = 10$ atm (solid lines) and $P = 100$ atm (long dashes).

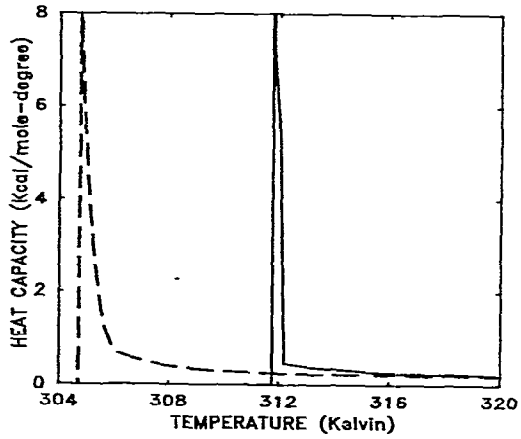

Fig. 5. Heat capacity plotted as a function of temperature for monomers at activity $z = 0.0$ (solid lines) and $z = 0.04$ (dashed lines) interacting with a membrane with $a = 2.6$ at pressure $P = 1$ atm, $\epsilon_v = 0.0$, $\epsilon_c = 0.5$.

which is favorable, zero, or unfavorable, but in any event the interaction should be more favorable than if the molecule were sitting in the region of a bond. In fig. 4 we show the behavior of the phase transition temperature as a function of monomer activity for three different pressures. Monomers interacting with the hydrocarbon chain are assumed to interact with an energy of 0.5 kcal per mole, while monomers in the vacuum contribute 0.0 kcal/mole. It is apparent that the effect of the monomers is to decrease the phase transition temperature, and that this effect is completely reversed by raising the pressure. The effect on the phase transition temperature is dependent only on the energy of interaction with sites not near the polymer chain. It is not dependent on the interaction with the polymer chains themselves. There is a broadening of the phase transition, as measured by the C_p curve (fig. 5). Changes in the interaction energies which result in a more potent effect in depressing the phase transition temperature also result in an increased solubility of the molecule at any given temperature above the phase transition (fig. 6). If, indeed, general anesthesia results from fluidization of the membrane due to a depressed phase transition temperature, this would correspond to the Meyer–Overton rule, which relates the potency of general anesthetics to their solubility in olive oil.

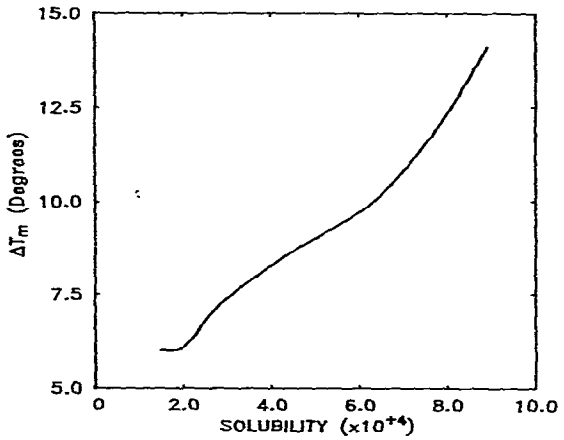

Fig. 6. Change in the membrane phase transition temperature induced by a monomer with activity $z = 0.05$, plotted as a function of solubility of the monomer within the membrane.

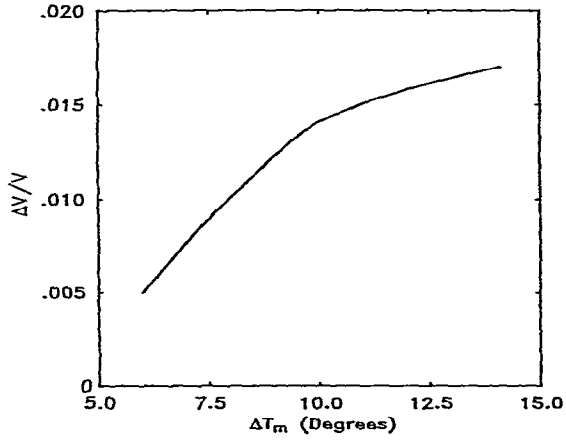

Fig. 7. Change in the membrane volume at 317° of a membrane with $a = 2.6$ induced by a monomer at activity $z = 0.05$, plotted as a function of solubility in the membrane.

5. Discussion

Many authors have presented models of biological membranes which show phase transitions occurring as a result of positional or orientational cooperative phenomena. Some of these models [15,16] could in principle be generalized to include interactions with monomers in the membrane, possibly by using decoration techniques similar to those employed here. Nagle's model has the advantage that the partition function of both the basic and decorated lattice models may be obtained exactly. For this reason information about the phase transitions of the model is not degraded by approximation procedures.

The interaction of small molecules with biological membranes is of particular interest in understanding the mechanism of general anesthesia. The fact that general anesthetics lower the phase transition temperatures for biomembranes led Trudell et al. to postulate that the disorder resulting from this interaction was the fundamental molecular event responsible for the neuronal transmission defect. Hill [1,17,18] applied classical solution theory to this aspect of membrane-anesthetic interactions. Unfortunately, such theories are suspect as they do not account for the anisotropy of the membrane. Unlike Hill's theory, the present theory is valid in principle for both small and large concentrations of anesthetics, and predicts a nonlinear dependence of the phase transition temperature on the small molecule concentration. This nonlinearity may become quite severe for certain combinations of the interaction energies. It is not necessary to have solubility information to determine the anesthetic effect in the present theory – the nature of the interactions describes the solubility. The pressure reversal of anesthesia is shown to be complete if the membrane pressure is increased without increasing the number of monomers present in the membrane. These characteristics have been demonstrated experimentally [3].

Meyer and Overton [19] correlate lipid solubility with anesthetic potency. Trudell [3,22] asserts that this correlation exists because the physiologic change responsible for anesthesia is enhancement of membrane fluidity by anesthetic molecules. Others [20,22] assert that the fundamental change occurring in anesthesia is membrane volume expansion. Our calculations show that for the model membrane these changes do not occur in isolation. A molecule which interacts with the membrane in such a way as to be highly soluble will be more effective at decreasing the phase transition temperature (fig. 6), and hence expanding the membrane (fig. 7), than a molecule which interacts unfavorably with the membrane. Thus, the theory outlined here unifies several concepts frequently discussed in theories of general anesthesia.

At high pressure small molecules are more easily ex-

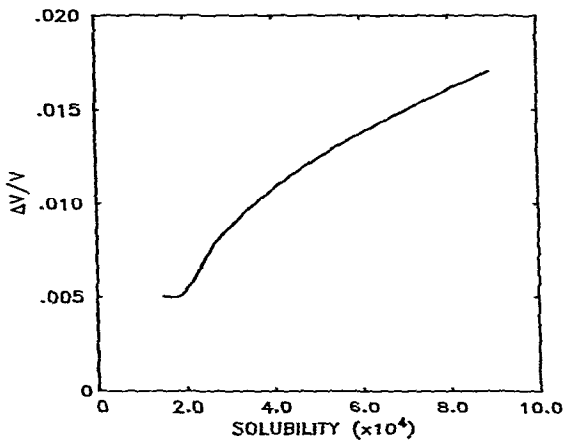

Fig. 8. Change in the membrane volume at 31.7° of a membrane with $a = 2.6$ induced by a monomer at activity $z = 0.05$, plotted as a function of the change in phase transition temperature induced by the monomer.

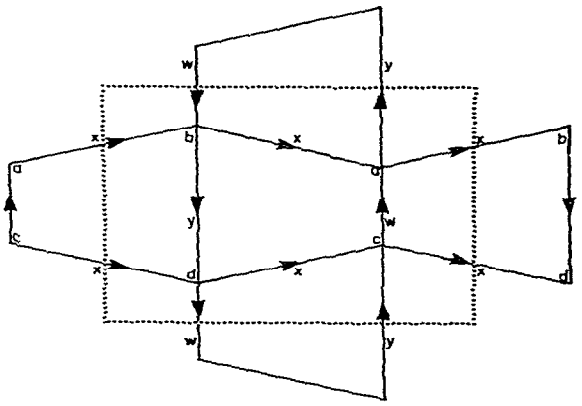

Fig. 9. Unit cell for the dimer model generated by Nagle's model A.

cluded from the membrane than they are at low pressure. Anesthetic-induced increases in membrane fluidity and volume are reversed if the pressure is increased sufficiently. In addition, the width of the phase transition is decreased, again reversing the effect of anesthetics. The anesthetic monomers may thus be regarded as decreasing the effective pressure. Pressure and monomers thus have opposite effects, and it is as reasonable to regard their complementary interactions as anesthesia reversal of pressure as it is to regard them as pressure reversal of anesthesia.

The model does not accurately reproduce the shape of the C_p curve, and the changes of the curve which result from anesthetics. Experimentally, anesthetic gases tend to broaden the curve and to decrease its maximum [23]. This broadening occurs mostly on the low temperature side of the curve, tending to skew it. In the model employed here, however, the excluded volume interactions result in an infinitely steep C_p curve at the beginning of the phase transition, irrespective of the presence of monomers. Hence, the model is incapable of reproducing this experimentally observed broadening. Instead, monomers produce a small but real broadening on the high temperature side of the curve (fig. 5). Models which do not assume such hard interactions would not be expected to have such a steep C_p curve. In addition, eq. (6) assumes that the lateral spreading pressure of the membrane is zero, which is probably not completely accurate [5]. In spite of its shortcomings, however, the two-dimensional model proposed here forms a reasonable framework for understanding the effects of small molecules on the primary order-disorder phase transition occurring in lipid monolayers and bilayers.

Appendix

The unit cell for the Nagle dimer model is shown in fig. 9. Following Montroll [13] we see that

$$\ln(Z) = 0.25\,(1/2\pi)^2\,\mathrm{Re}\int_0^{2\pi} d\phi_1 \int_0^{2\pi} d\phi_2 \ln[g(\phi_1,\phi_2)], \qquad g(\phi_1,\phi_2)^2 = \det M(\phi_1,\phi_2),$$

where

$$M(\phi_1,\phi_2)=\begin{bmatrix} 0 & x(1-\exp[-i\phi_1]) & w-y\exp[i\phi_2] & 0 \\ -x(1-\exp[i\phi_1]) & 0 & 0 & y-w\exp[i\phi_2] \\ w-y\exp[-i\phi_2] & 0 & 0 & x(1-\exp[-i\phi_1]) \\ 0 & -y-x\exp[-i\phi_2] & -x(1-\exp[i\phi_1]) & 0 \end{bmatrix}$$

Hence, for the densities we have

$$\rho_x=\left(\frac{x}{2\pi}\right)^2\int_0^{2\pi}d\phi_1\int_0^{2\pi}\frac{(1-\cos\phi_1)d\phi_2}{2x^2(1-\cos\phi_1)-w^2\exp[i\phi_2]-y^2\exp[-i\phi_2]+2wy},$$

$$\rho_y=0.5\,y\,(1/2\pi)^2\int_0^{2\pi}d\phi_1\int_0^{2\pi}\frac{(w-y\exp[i\phi_2])d\phi_2}{g(\phi_1,\phi_2)},$$

$$\rho_w=0.5\,y\,(1/2\pi)^2\int_0^{2\pi}d\phi_1\int_0^{2\pi}\frac{(y-w\exp[i\phi_2])d\phi_2}{g(\phi_1,\phi_2)},$$

where $\rho_x+\rho_y+\rho_w=0.5$.

There are three regions of differing analytic behavior of the model.

In region A $y\leqslant w-2x$

$\rho_x=0;\quad \rho_y=0;\quad \rho_w=0.5$

$N\ln Z=0.5\ln(w)$

In region B $y\geqslant w+2x$

$\rho_x=0;\quad \rho_y=0.5;\quad \rho_w=0.0$

$N\ln Z=0.5\ln(y)$

In region C $w-2x\leqslant y\leqslant w+2x$

$\rho_x=0.5-(1/2\pi)\cos^{-1}[1-(w+y)^2/2(x^2+wy)]$

$\rho_y=0.25-0.5\,\rho_x\mp(1/4\pi)\cos^{-1}[1-(w-y)^2/2x^2]$

$\rho_w=0.25-0.5\,\rho_x\pm(1/4\pi)\cos^{-1}[1-(w-y)^2/2x^2]$

where the upper sign is used if and only if $w\leqslant y$.

The ln (Z) integral is very difficult to obtain analytically in this region, and has not been obtained. It is readily obtained by numerical integration of ρ_y, however.

References

[1] M.W. Hill, Ann. NY. Acad. Sci. 138 (1978) 101.
[2] J.M. Vanderkooi, R. Landesberg, H. Selik and G.G. McDonald, Biochim. Biophys. Acta 464 (1977) 1.
[3] J.R. Trudell, D.G. Payan, J.H. Chin and E.N. Cohen, Proc. Nat. Acad. Sci. USA 72 (1975) 210.
[4] J.F. Nagle, J. Chem. Phys. 58 (1973) 252.
[5] J.F. Nagle, J. Chem. Phys. 63 (1975) 1255.
[6] J.F. Nagle, J. Memb. Biol. 27 (1976) 233.
[7] J.F. Nagle, Phys. Rev. Letters 34 (1975) 1150.
[8] J.F. Nagle, Proc. R. Soc. A 337 (1974) 569.
[9] B. Widom, J. Chem. Phys. 46 (1967) 3324.
[10] N.D. Mermin, Phys. Rev. Letters 26 (1971) 169.
[11] J.C. Wheeler, Ann. Rev. Phys. Chem. 28 (1977) 411.
[12] P.W. Kasteleijn, J. Math. Phys. 4 (1963) 287.

[13] E. Montroll, Applied combinatorial mathematics, ed. E.F. Bechenbach (Wiley, New York, 1964) chapter 4.
[14] O.J. Heilman and E.H. Lieb. Phys. Rev. Letters 24 (1970) 1412.
[15] H.L. Scott, Biochim. Biophys. Acta 406 (1975) 329.
[16] H.L. Scott, J. Chem. Phys. 62 (1975) 1347.
[17] M.W. Hill, Biochem. Soc. Trans. 3 (1975) 149.
[18] M.W. Hill, Biochim. Biophys. Acta 356 (1974) 117.
[19] K.H. Meyer, Trans. Faraday Soc. 33 (1937) 1062.
[20] L.S. Mullins, Chem. Rev. 54 (1954) 289.
[21] B. Wardley-Smith and M.S. Halsey, Br. J. Anaesthesia 51 (1979) 619.
[22] K.W. Miller, W.D.M. Paton, R.A. Smith and E.B. Smith, Molec. Pharm. 9 (1973) 131.
[23] D.B. Mountcastle, R.L. Biltonen and M.J. Halsey, Proc. Nat. Acad. Sci. USA 75 (1978) 4906.