

Theory of Cooperative Phenomena in Lipid Systems

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I. Introduction

The behavior of insoluble films at fluid interfaces has been the subject of active scientific investigation for a



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large part of this century. Yet, the recent literature reflects a change from the study of often ill-defined materials to the study of highly purified compounds and an experimental precision not previously obtained. The



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Lawrence John Dunne graduated from Imperial College, University of London, specializing in physical chemistry and mathematics. He obtained a Masters degree in physical chemistry from the University of Newcastle upon Tyne and obtained his Ph.D. in biophysics/theoretical physics from the University of London in 1976. After 2 years as postdoctoral fellow at Chelsea College, University of London, working with Professor G. M. Bell on the statistical mechanics of biophysical systems, he took up a Science Research Council (U.K.) overseas postdoctoral fellowship for 2 years at the Quantum Chemistry Group, University of Uppsala, under the supervision of Professor Per Olov Löwdin. At the present time he is a European Molecular Biology Organization (EMBO) postdoctoral fellow in the Theoretical Chemistry Department at Aarhus University (Denmark) (Professor Jan Linderberg, Director). His research interests lie in the areas of chemical physics and molecular biology.

main impetus for the growth of activity in lipid monolayer research has, without doubt, been the hope that the results obtained would have considerable relevance for biomembrane structural studies. To extract fundamental insight from the surface pressure/area isotherms of naturally occurring lipids at the air/water or oil/water interface demands an understanding of such behavior for less complex organic molecules. Cadenhead¹ has published an article on the relationships of monomolecular films and membrane structure where he outlines assumptions made in considering a monolayer as a model membrane system. Thus systematic monolayer studies of substituted aliphatic carboxylic acids (spin labeled, mono- and bipolar substituted) and highly purified phospholipids have a pertinent place in the recent relevant literature. These systematic studies have exposed certain novel features of monolayer behavior which, through the novelty of the trends observed, have encouraged development on the theoretical side. A fundamentally incorrect theory is unlikely to qualitatively reproduce novel experimental trends whereas the agreement between novel theoretical and experimental results at the level of trends is mandatory for the survival of the chosen theoretical model.

Two general classes of compounds form insoluble monolayers. The first class (I) has been widely studied and consists of molecules which have sufficient attraction for the subphase so that surface spreading and dispersing may occur. Generally, molecules studied in this class are long-chain alcohols or fatty acids on a water subphase. The polar groups confer the water solubility while the hydrocarbon chain portion is hydrophobic. A balance then is attained which is a function of chain length. Valeric acid (C_4H_9COOH) has a solubility of 3 g/100 mL of water at room temperature while stearic acid ($C_{17}H_{35}COOH$) has a solubility of about 0.003 g/1000 g of water. Other systems in this class would include long-chain hydrocarbons on a mercury surface where there is sufficient dispersion interaction to allow a film of molecules to be formed flat on the surface. Generally, however, by subphase attraction one means the polar group attraction to the water subphase. The second class (II) of compounds which form monolayers consists of polymeric materials that are positively adsorbed at the liquid-gas interface.

Molecules in monolayers can exist in different states as a function of density. The "gaseous monolayer" state is the one in which the molecules are far apart from each other and exert little influence on each other. An ideal gas type equation can be utilized for a description of them ($\pi A = kT$) with various modifications of it to allow for subphase interactions. At the other density extreme is the condensed film region in which the molecules are arranged in a nearly close-packed arrangement. Harkins² refers to the most compressible, lower pressure condensed phase as "liquid-condensed". At an intermediate density is the expanded monolayer state or "liquid-expanded" as denoted by Adam³ and Harkins.² High molecular weight polymers (class II) do not show transitions between phases, but molecules of class I do show such transitions, and it is a study of factors influencing such transitions to which we address ourselves. Possible class I π vs. molecular area curves are given in Figure 1.

Our aim here is to review theoretical work on critical

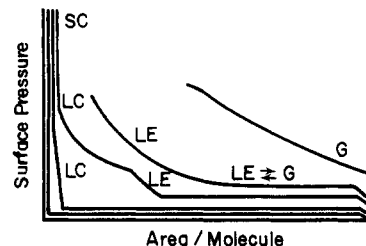


Figure 1. Schematic representation (not to scale) of the various physical states of monomolecular films: SC for solid condensed, LC for liquid condensed, LE for liquid expanded, and G for gaseous. (Reproduced from "Structure of Biological Membranes" by permission. Copyright 1977, Plenum Press.)

or cooperative phenomena in monolayers of molecules with a hydrophilic head group at the water interface and a carbon chain "tail". One methodological difficulty is that a number of authors regard an aqueous "bilayer" as simply two monolayers back to back, and some of these study what is essentially a monolayer model with a view to comparison with experimental bilayer rather than monolayer phenomena. The relation between monolayers and bilayers has been discussed by, among others, Chapman,⁴ Cadenhead,¹ Nagle,⁵ and Nagle and Scott.⁶ We shall give most emphasis to authors who have some specific interest in monolayers. The topics chosen for discussion reflect our own knowledge and interests, and we apologize in advance to the authors of any work which has been omitted or insufficiently emphasized. For reasons of space we do not include the interesting theoretical work done on lipid mixing with cholesterol and protein.

II. Phase Transitions in Monolayers

Monomolecular films spread on liquid surfaces and gases adsorbed on the surfaces of solids have long been used as model systems for the study of the behavior of matter in two dimensions. The question of the occurrence of phase transitions in two dimensions is of considerable fundamental interest. Lipid monolayer phase behavior is most usually characterized experimentally by measuring surface pressure/area isotherms. The corresponding surface potential data are often also measured. Surface potentials are expected to contain information on conformational changes in lipid monolayers with changes in surface area or temperature, but an adequate theory for such interpretations is lacking.

Most experiments have been performed by using a Langmuir trough or Wilhemy plate.⁷ Recent advances in instrumentation have enabled some old measurements to be repeated with increased accuracy, enabling certain critical exponents to be reliably estimated. A point of considerable interest which will be returned to later is the observation that at least one of the critical exponents for certain gaseous expanded carboxylic acid monolayers is in accord with that predicted by mean field theory.⁸⁻¹⁰ This observation may give some insight into the range of intermolecular interaction in monolayers. Many lipid monolayers show a clear first-order transition at high surface areas and a higher order or continuous phase transition which shows up as a "kink" point in the plot of surface pressure against area at lower surface areas (Figure 1). The exact order of these transitions, in the sense of Ehrenfest,¹¹ has not been

established although they have been loosely described as second-order transitions. It has been known since Onsager's solution¹² of the two-dimensional Ising model that Ehrenfest's classification scheme is in some senses inadequate, and hence as Fisher¹³ has pointed out it is more consistent to simply describe phase changes which are not first order in Ehrenfest's scheme as continuous phase transitions. At low temperatures most lipid monolayer phase transitions appear to become first order. The continuous nature of such phospholipid monolayer phase changes has been questioned by Nagle,¹⁴ but his criticism seems to be unjustified in view of the large measure of agreement among experimentalists concerning the shape of most π/A isotherms. Gershfeld¹⁵ has discussed the possibility that metastable lipid films above the equilibrium spreading pressure are not describable by the usual procedures of minimizing the free energy in statistical mechanics. Goddard¹⁶ takes much the same point of view. He stresses the fact that in many systems the surface pressure at the continuous transition is greater than the spreading pressure and that the transition thus occurs in a region of phase space where the molar free energy of the monolayer is greater than that of a crystal of the same substance. However, both experimentally and theoretically, amphipathic monolayers above the spreading pressure are metastable systems well defined by the "constraint condition" that the head groups are situated in the surface region of the substrate. Although well-defined metastable states do not correspond to a global minimum in the free-energy surface, they do correspond to a local minimum. For this to be physically significant there must be a high-energy barrier between the local minimum and the global minimum leading to a relaxation time much greater than experimental time scales. In fact the molecules of spread monolayers are not expected to regress to the crystalline state, and when surface pressure becomes too large the film collapses into a noncrystalline multilayer state. Goddard himself points out that the transition points are reproducible and not much affected by compression speed. Hence it is perfectly meaningful to use whatever methods of statistical mechanics available to find the local free-energy minimum, subject to the constraint condition, and to compare the results with experiments. "Permanent" metastable states are well-known in physics and everyday life. For instance, glass and diamond are metastable.

It is worthwhile to briefly sketch for the benefit of surface chemists and others working with the experimental aspects of critical phenomena in lipid systems the ideas underlying universality and scaling which have played such a prominent role in critical phenomena generally in the last 20 years or so. An excellent introduction is given in the book by Stanley.¹⁷ The essential observation is a striking similarity between some critical phenomena in many apparently unrelated and distinct systems. In particular, one has in mind the critical behavior of magnetic crystals, normal fluids, and superfluids. The critical behavior of a magnet is partly characterized by its (M, H, T) surface, where M denotes the magnetization, H is the magnetic field, and T is the absolute temperature. A further variable is the specific heat C , which is measured either at constant field or constant magnetization, and from the field dependence

of the magnetization the magnetic susceptibility χ may be specified. It is found both experimentally and theoretically that

$$\begin{aligned} C &\sim (T - T_c)^{-\alpha}_{T \rightarrow T_c^-}, & \chi &\sim (T - T_c)^{-\gamma}_{T \rightarrow T_c^-}, \\ M &\sim (T_c - T)^{\beta}_{T \rightarrow T_c^-} \end{aligned} \quad (1)$$

where α , β , and γ are termed critical exponents and T_c is the phase transition temperature. Similarly for normal fluids one has

$$\begin{aligned} C &\sim (T - T_c)^{-\alpha}, & \rho &\sim (T_c - T)^{\beta}, \\ \chi &\sim (T - T_c)^{-\gamma} \end{aligned} \quad (2)$$

where ρ is the density gap. It is found experimentally that for almost all systems α , β , and γ are very similar. For a lipid monolayer the analogous variables are

$$\begin{aligned} C &\sim (T - T_c)^{-\alpha}, & \rho_s &\sim (T_c - T)^{\beta}, \\ \chi_s &\sim (T - T_c)^{-\gamma} \end{aligned} \quad (3)$$

where ρ_s is the surface density gap and χ_s is the monolayer compressibility. Thermodynamically these exponents satisfy certain inequalities, which become equations in renormalization group theory. A value of an exponent given by experiment or accurate theory is usually regarded as differing from the classical value as derived from mean field theory by an amount which depends on $4 - d$, d being the dimension of the space. For instance, $\beta = 1/2$ classically for all d ; in Onsager's solution, the $d = 2$ Ising model, $\beta = 1/8$; and for $d = 3$, $\beta \sim 3/8$. Renormalization theory indicates that the classical exponent values would only be attained for $d = 4$. It is remarkable therefore that some experiments⁸⁻¹⁰ indicate that $\beta \sim 1/2$ for the liquid-vapor transition in simple fatty acid monolayers at the air/water surface. One might hope that this indicates that mean field theories of the zero-order (Flory-Huggins) or first-order (Bethe) type give reasonable results for monolayers. Any general comment must be highly speculative, but possibly this peculiar result has some connection with the range of the forces. At least it adds to the interest which the strange cooperative phenomena in lipid monolayers should have for the theoretical physicist.

Although many experiments have been performed to investigate fatty acid monolayer phase behavior over many years, little fundamental insight at the molecular level has been achieved, we believe, until fairly recently. The description of novel behavior is more demanding of a theoretical model than more mundane behavior, but it also allows inadequate theories to be discarded and enables a refinement to be made in terms of the adequacy of models to describe the novelties of a phenomenon. It is perhaps useful in this context to sketch the nature of the monolayer behavior which led us to our present viewpoint. Cadenhead and Müller-Landau¹⁸ studied the π/A characteristics of certain spin-labeled stearic acids and their esters. Spin-labels are stable paramagnetic nitroxides which have been very widely used for electron spin resonance studies of biological systems. Cadenhead and Müller-Landau¹⁸ observed a phenomenon which has been termed "isotherm reversal".¹⁹ The normal behavior where surface area increases with increasing temperature is reversed over a range of temperature between about 273 and 323 K,

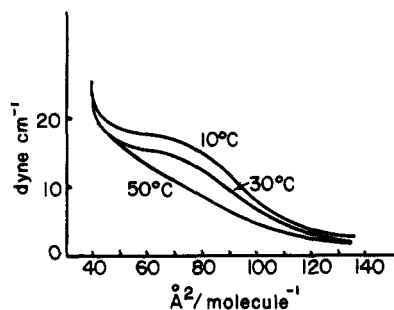


Figure 2. Sketch of isotherm reversal phenomenon in stearic acid 12-nitroxide monolayers after the experimental results of Cadenhead and Müller-Landau. (Reproduced from *J. Chem. Soc., Faraday Trans. 2*, 1978, 74, 149, by permission. Copyright The Royal Society of Chemistry.)

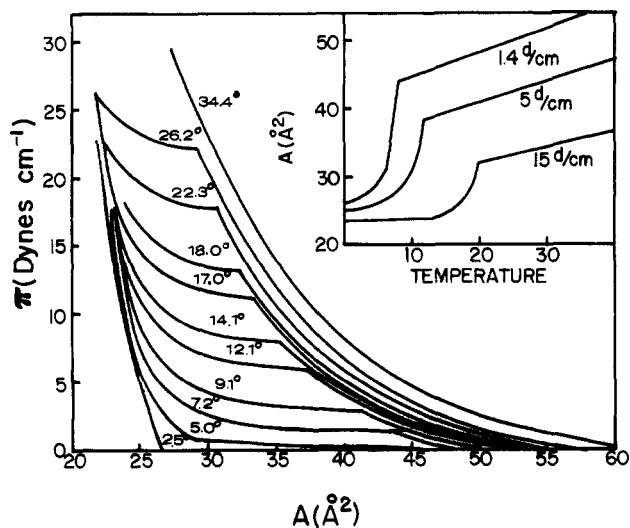


Figure 3. π/A diagrams for myristic acid spread on 0.01 N HCl at various temperatures (reproduced from *Proc. R. Soc. London, Ser. A*, 1926, 112, 364 by permission).

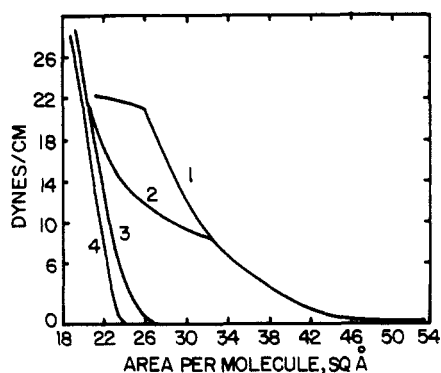


Figure 4. π/A curves of normal saturated fatty acids at 25 °C and pH 2 with 1 = myristic acid, 2 = pentadecylic acid, 3 = palmitic acid, 4 = arachidic acid (adapted from *J. Am. Chem. Soc.*, 1939, 61, 1182 by permission).

as shown in Figure 2. Many lipids such as myristic acid show "kinks" in the π/A curve, as depicted²⁰ in Figure 3. The "kink" points in Figure 3 are continuous-phase transitions whose interpretation at the molecular level is the central purpose of this review. The temperature dependence of such behavior is difficult to account for and is far from being satisfactorily described by the equation of state for an ideal two-dimensional gas. Increasing molecular chain length has an effect similar to lowering the temperature where the π/A curves become more condensed,²¹ as shown in Figure 4. Rather

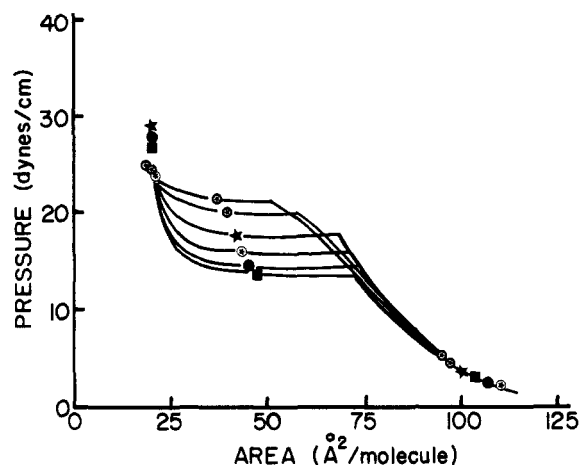


Figure 5. Temperature dependence of the π/A isotherms of 9-hydroxyhexadecanoic acid on 3 M NaCl. The nearly linear portions of the curves are, from bottom to top, respectively, 8.4 °C, 15.4 °C, 22.0 °C, 28.0 °C, 37.4 °C, 42.6 °C. (Reproduced from *J. Colloid Interface Sci.*, 1978, 63, 452 by permission. Copyright 1978, Academic Press.)

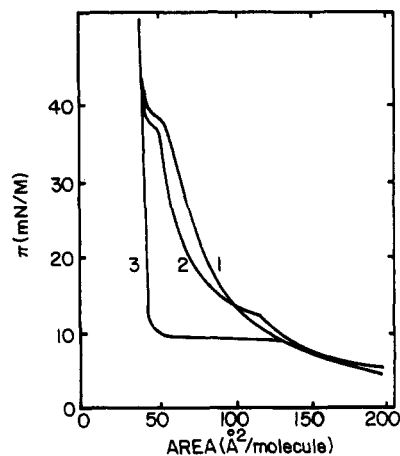


Figure 6. Surface pressure–area isotherms for two phosphatidylcholines and their mixture at the heptane–water interface. Temperature 20 ± 0.1 °C, NaCl concentration 0.1 M, pH 5–6. Monolayers are spread from dilute solutions in heptane–ethanol (90:10, v/v). (3) Didocosanoylphosphatidylcholine; (2) dihexadecanoylphosphatidylcholine; (1) equimolar mixture (adapted from *Biochim. Biophys. Acta*, 1973, 323, 157).

similar behavior is observed in phospholipid monolayers at the air/water interface.

Monolayer studies of a series of bipolar hydroxyhexadecanoic acids have revealed an intermediate behavior, so to speak, between the "isotherm reversal" property of spin-labeled monolayers and the "normal" behavior of long-chain aliphatic carboxylic acids. This phenomenon²² is depicted in Figure 5.

Monolayers of lipid mixtures have been the subject of intense study, particularly because of the better approximation such model systems make to real and complicated biological membranes. Binary mixtures of certain phospholipids appear to exhibit two kink points in their π/A curves at the oil/water interface although the sharpness of both transitions is a matter as yet undecided. The transition points depend on the nature of the polar head group and on chain length. As an example, Figures 6 and 7 show the π/A curves for 1:1 mixture of phosphatidylcholines at the heptane/water interface.²³ The detailed interpretation of such behavior is likely to be rewarding with respect to understanding intermolecular forces between different lipid species.

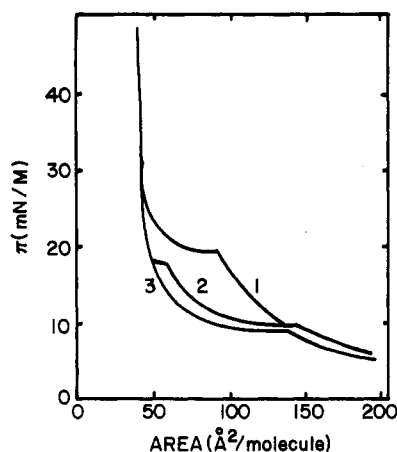


Figure 7. Surface pressure–area isotherms for phosphatidylethanolamine, phosphatidylcholine, and their mixture at the iso-octane–water interface. Temperature 1 °C, NaCl concentration 0.1 M, pH 5–6. Monolayers are spread from dilute solutions in various iso-octane–ethanol mixtures. (3) Dihexadecanoylphosphatidylethanolamine; (2) dihexadecanoylphosphatidylcholine; (1) 1:1.4 mixture of the phosphatidylcholine and phosphatidylethanolamine (adapted from *Biochim. Biophys. Acta*, 1973, 323, 157.)

The ultimate understanding of the phase transitions of cell membranes requires such information.

The phase separation at very high surface areas observed in certain monolayers is most likely attributable to the clustering of molecules in extended conformations. Such a transition should be fairly well described by a Flory–Huggins type approximation which has been shown²⁴ to be quite accurate for the calculation of the pressure in monomer–dimer lattice fluids. The experimental observation that some of the critical exponents for the above transition are in accord with those predicted by mean-field theory lends support to the suitability of the Flory–Huggins approximation for describing certain aspects of the theory of critical phenomena in lipid systems.

III. Intermolecular Forces between Chains

The calculation of intermolecular forces is conceptually quite simple compared to chemical bond calculations. One is concerned only with interactions due to permanent, induced, and correlated instantaneous charge distributions which can be expanded in powers of $1/R$; that is, they are long-range forces. Chemical bond interactions have an R dependence of essentially $e^{-\alpha R}$; that is, they are short-range forces. One would thus expect perturbation theory to be the method of choice for intermolecular force calculations and some variational procedure to be preferred for chemical bond calculations. It will be shown here that for hydrocarbon interactions this conclusion is true. However, it will also be obvious that even though intermolecular energy calculations are conceptually simpler than chemical bond calculations, the problem is still very complicated. It is well to be reminded that, except for very simple systems, chemical bond calculations done exactly are still impossible!

It is not the intention of this section to give a complete review of intermolecular force calculations for that would require at least one large book, and several already exist.^{25–30} Considerable work has been done by

numerous authors on the theory of intermolecular forces between small systems (H, He, Ne, Ar, N₂, H₂, CO₂, H₂O) because these are small enough for the variables to be reasonably handled by ab initio principles—although even these cannot, of course, be treated exactly. A recent survey of some results as related to the importance of various contributions to intermolecular forces as computed by ab initio methods on small molecules has been reported by Lischka.³¹ He concludes that such calculations can only be performed with extended basis sets. Several polarization functions are necessary to obtain the required accuracy. Also a good bit of work has been done on rather large systems by more qualitative and semiempirical methods. The world of ordinary molecules is somewhat of a “no-man’s land” due to the complexity of the systems and their lack of sufficient long-range order to be amenable to some of the approximate techniques. In this section will be discussed some of the methods used to determine the intermolecular forces between molecules appropriate to this general review. Although the intent is to survey theoretical techniques, a few experimental procedures will also be mentioned.

The initial concept of correlating van der Waals forces with polarization was developed by Debye³² in a set of classical electrostatic calculations. The extension of this concept utilizing quantum mechanics was performed by London³³ so that now all physical chemistry students learn about London–van der Waals forces. London’s applications were to crystals of atoms or simple molecules. Müller^{34,35} made the first applications of London’s theories to a paraffin crystal. London’s method dealt with simple systems so that each lattice point could be treated as a single center of force. Müller’s treatment of the chain molecules was to consider them as made of subunits of such size that the nearest approach distance between neighboring molecules was relatively large so that each subunit could be considered a point center of attraction and repulsion and London’s law could then be utilized. He considered three different ways of dividing the molecules into subunits: atoms, bonds, and CH₂ units. For all cases he assumed pair additivity and did not consider any orientational effects. For the attraction potential he used Kirkwood’s expression³⁶ for the van der Waals potential

$$V_{\text{VDW}} = 6mC^2\chi_1\chi_2/[(\chi_1/\alpha_1) + (\chi_2/\alpha_2)] \quad (4)$$

where χ is the diamagnetic susceptibility and α is the polarizability. The experimental values to be used for α and χ are averages obtained for anisotropic media whereas the above equation is for isotropic systems. To easily convey the structure of a long-chain saturated hydrocarbon, Müller introduced the nomenclature illustrated in Figure 8a. The chain axis is W and the figure to the right is a projection of the molecule on a plane perpendicular to W. The dark circles imply the first CH₂ set encountered as one looks down the molecule so the orientation is perfectly clear by the figure to the right. Figure 9 shows a cross section through the unit cell of the crystal considered. The angle ϕ is the setting angle defining the positions of the molecules relative to the a axis of the crystal. This was taken to be 30°, which is approximately what is found in the crystals.

The application of the VDW potential to a crystal

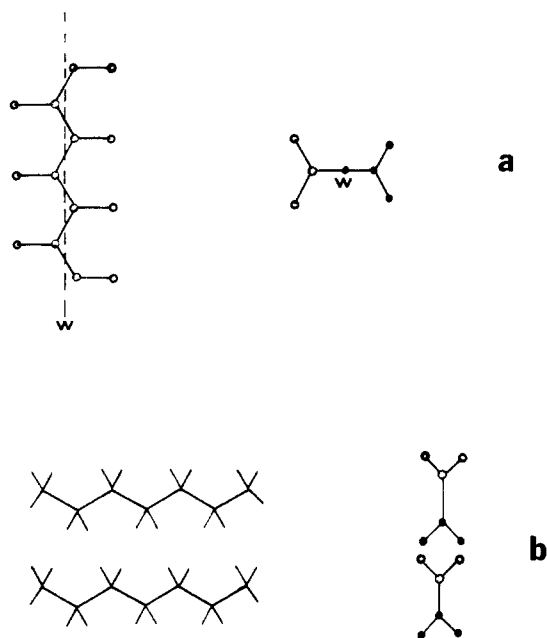


Figure 8. (a) Müller's method³⁴ of showing a straight chain molecule in a simple figure. (b) A 1:1 dimer conformation using Müller's technique.³⁴

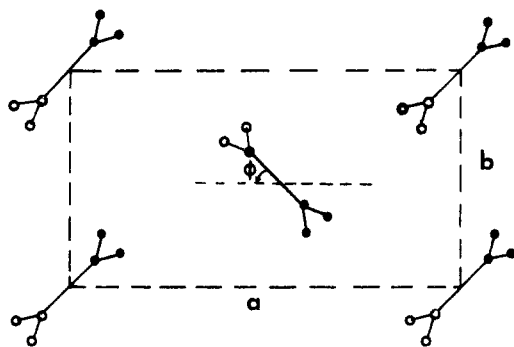
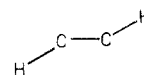


Figure 9. Müller's drawing of unit cell occupancy in the paraffin crystal (reproduced from *Proc. R. Soc., London, Ser. A, 1936, 154, 624.*)

involves a summation between a center of one type in one molecule and all other centers of the same type in surrounding molecules, a summation over the distances between centers of two different types, and a summation over centers of the second type. These were done with tables, a 20-in. slide rule, and integration. The repulsion forces were calculated by replacing the CH₂ group with a fictitious helium atom at the extreme end of the C-H bond since he reasoned that most of the repulsion is due to the hydrogen atoms. By these calculations, his lowest energy value for $\Delta H_{\text{sublimation}}$ is obtained from the subunits being atoms and is 1.83 kcal/mol per CH₂, which is in excellent agreement with experiment.

Salem³⁷ determined the dispersion interaction between long saturated chains using an assumption of locally additive forces between basic subunits in the same spirit as Müller.³⁴ The intermolecular distance must be large in comparison with the dimensions of the subunits so London's inverse sixth-power distance law holds. The basic units are CH₂ groups so that intermolecular distances as small as about 4 Å may be studied. To keep units centered on the chain axis and to consider only bond-bond interaction, he considers the basic unit to be actually



Considering bond-bond interactions rather than atom-atom interactions allows for consideration of anisotropy of molecular polarizabilities. Using mean polarizabilities (determined experimentally) of the interacting bonds,³⁸ Salem effectively has an expression for the bond-bond interactions which is an average over all orientations of the total dispersion interaction:

$$W_{\text{bond-bond}} = -(e^2/d^6) \frac{\bar{\alpha}\bar{\alpha}'}{\bar{\alpha}/\langle(\sum_i \bar{r}_i)^2\rangle + \bar{\alpha}'/\langle(\sum_i \bar{r}'_i)^2\rangle} \quad (5)$$

The denominator is calculated a priori by assuming that in the C-H bond the two electrons occupy the molecular orbital

$$\psi = (2 + 2\Delta)^{-1/2} (t_c + 1S_H)$$

$$\Delta = \int 1S_H t_c dy \quad (6)$$

where t_c is a tetrahedral hybrid centered on the carbon atom. The C-C single bond is described by a molecular orbital built from two carbon tetrahedral orbitals. The ethylenic bond is composed of a σ orbital and a π orbital of common type. He thus arrives at

$$W_{\text{CH}_2\text{-CH}_2} = -[1.34 \times 10^3/d^6] \text{ kcal/mol} \quad (7)$$

where d is the distance between centers of interacting units in Å. This then gives for the total attraction between two parallel and opposed paraffin chains of N carbon atoms separated by D Å

$$W = -1.24 \times 10^3(N/D^5) \text{ kcal/mol} \quad (8)$$

Applying this to a lattice arrangement, he obtains an attractive component of 2.09 kcal/mol per CH₂. The repulsion energy he calculated semiempirically to give a repulsion contribution of 0.38 kcal/mol per CH₂. This gave a calculated heat of sublimation of 1.71 kcal/mol per CH₂, in comparison with an experimental value of 1.84 kcal/mol per CH₂.

Zwanzig³⁹ was intrigued by these approximations and in particular by the approximations of pairwise additivity and isotropy so he examined them in some detail. He based his calculations on a Drude model (dispersion oscillator model) for the interaction between two parallel linear lattices of dispersion oscillators as a model for the interaction between long parallel hydrocarbon chains. He concludes that these assumptions are not valid for a Drude model. However, he states that Salem's procedure leads to essentially correct numerical results due to the use of an experimentally determined bond polarizability and to the neglect of interactions between groups in the quantum mechanical calculation of $\langle(\sum_i \bar{r}_i)^2\rangle$. Note that the first of these allows for interactions and the second does not, so that mutual compensation results.

Before proceeding to discussions of relatively recent computations, several important pioneer calculations should be mentioned. The van der Waals attraction between anisotropic particles was contributed by Vold.⁴⁰ The calculation of the London-van der Waals potential between two cylindrical molecules was done by Sparnaay.⁴¹ De Rocco and Hoover⁴² include attractive and

TABLE I. Minimum Energy Predictions (kcal/mol)^a

| <i>N</i> | 1 | 2 | 4 | 8 | 10 | 79 | 199 | 499 |
|------------|-------|-------|------|------|------|-------|-------|-------|
| $-E_0^a$ | 0.16 | 0.53 | 1.4 | 3.2 | 4.1 | 36 | 90 | 230 |
| $-E_0^a/N$ | 0.16 | 0.27 | 0.35 | 0.40 | 0.41 | 0.456 | 0.452 | 0.46 |
| $-E_0^s$ | 0.044 | 0.17 | 0.49 | 1.2 | 1.5 | 14 | 34 | 86 |
| $-E_0^s/N$ | 0.044 | 0.086 | 0.12 | 0.15 | 0.15 | 0.177 | 0.171 | 0.172 |

^a s for symmetrical polarization; a for asymmetrical polarizability.

repulsive forces in a Lennard-Jones potential to calculate the interaction energies between two thin rod molecules.

Ohki and Fukuda⁴³ proposed a method for calculating the dispersion energy between separate C₂H₄ subunits based upon a bond polarizability approximation method by Smith and Mortensen.⁴⁴ Their interest was in the elucidation of the stability of lipid bilayer membranes which led to the necessity of calculating the interaction energy of oriented hydrocarbon molecules. They divided the calculation of interlayer interaction into three parts: dispersion interaction between two oriented monolayers, dipole-induced dipole interaction between one oriented monolayer and one permanent dipole layer in the surface of the other monolayer, and dipole-dipole interaction between two permanent dipole layers. Their deductions show that the energy from dipole-dipole interactions is repulsive for thin membranes of finite size. For small dimensions of this bilayer sheet, a net repulsive force exists between the permanent dipole layers which can be greater than the sum of the attractive dipole-induced dipole and dispersion forces. This study does not then offer an explanation for the stability of lipid bilayers.

The follow-up to the above study is reported by Shapiro and Ohki;⁴⁵ they allow each aliphatic hydrocarbon chain to rotate freely around its molecular axis. They use second-order perturbation theory as in their first paper⁴³ to develop the dispersion interaction energy, $W_{\alpha\alpha}^{ij}$, in the bond polarizability method using Denbigh's⁴⁶ bond polarizability estimates. To allow free rotation, the polarizability is rotationally averaged. The repulsive energy, W_{rr}^{ij} , contribution is determined by a method due to Kihara⁴⁷ which uses the general form of the Lennard-Jones potential and assumes spheroidal molecules. The total energies are based upon the pairwise additivity approximation where pair interactions are taken between C₂H₄ groups. For two chain groups then the total interaction energy, W_c , between any pair of molecular subunits (C₂H₄), W_{ij} , is formed as the sum of $W_{\alpha\alpha}^{ij}$ and W_{rr}^{ij} and then this is summed over all N^2 combinations of interacting molecular subunits:

$$W_c = \sum_{i=1}^N \sum_{j=1}^N W_{ij} \quad (9)$$

This work is extended to a hexagonally packed array to treat the monolayer case by summing W_c over k nearest neighbors where the maximum k treated is 12. For this treatment to be applicable to phospholipids which have more than one fatty acid chain per molecule, a mutual interaction energy between the two chains on the same molecule must be included. Table I gives the minimum interaction potential energy for some N values (number of C₂H₄ units) considered. Fitting these results to a standard Lennard-Jones n - m type interaction, they find $n \approx 5$ and $m \approx 11$. For the monolayer case for 18 carbon atoms, they determine E_0 to be -26.8

kcal/mol at a predicted separation of 5.0-Å separation. These calculations appear in quite reasonable agreement with experiment, but the basic model of a rotationally free state will require further elaboration.

Lochmann and co-workers⁴⁸⁻⁵⁶ have been actively investigating the application of the perturbative configuration interaction with localized orbitals (PCILO) method⁵⁷⁻⁶¹ to the study of intermolecular interactions. The form of PCILO employed by them uses the complete neglect of differential overlap (CNDO) method⁶² of integral parameterization, and this is probably one of the most valid criticisms against the general method. Other theoretical problems exist with the method, and it has not received the wide application the self-consistent-field (SCF) methods have, probably partly because it is somewhat more difficult to use and interpret. There is an integral parameterization based on intermediate neglect of differential overlap (INDO)⁶² currently available. The short-range repulsion is represented in CNDO/2 procedures by a deliberate artifact, namely, the replacement of the exact nuclear attraction integrals by Coulomb integrals. However, this repulsion is still underestimated. In the CNDO-SCF method, there is no correlation energy and hence the dispersion energy is underestimated. In the PCILO method, correlation terms are included via the second-order perturbation term. However there is an underestimation due to a restriction in the basis of excited states in the method (only one virtual localized orbital for each bond localized orbital). The electrostatic long-range energy is correctly evaluated. One would expect from these comments that the interaction energies between nonpolar molecules would be underestimated.

Four of Lochmann's papers are of particular significance to the present discussions, so some brief comments on them now follow. These calculations are all in the supermolecule context where the intermolecular interaction energy is given by $\Delta E = E(r) - E(\infty)$ where $E(r)$ is the energy of the total system with a distance r between the subsystems. Lochmann and Weller⁴⁸ calculated the interaction energy curves for the dimers of propane, butane, pentane, and nonane with only one relative orientation between the dimers considered, as illustrated in Figure 8b in the same manner as Müller.³⁴ This is a 1-1 interaction to mean that both monomers of the dimer have the same spatial orientation. The 1-2 dimer results when one of the monomers is rotated about its molecular axis by 180°. They also use the CNDO/2 method to calculate the interaction energy of the ethane dimer, but they do not do the CNDO/2 calculation at large separation. From these calculations they predict an equilibrium separation for the dimers of 4.75 Å and an intermolecular interaction energy of 0.09 kcal/mol per methylene group. Lochmann⁵⁴ calculated interaction energies for the butane dimer and the nonane dimer with and without polarity optimizations. The results were the same with both techniques, which is not surprising for nonpolar molecules.

Lochmann and Holza⁵⁵ calculated intermolecular interactions for the ethane, propane, butane, pentane, and nonane dimers in three different mutual orientations. The orientations were 1-1, head-to-head, and T-shaped. No structure optimization was performed; the monomers were rigid during mutual approach. The 1-1 orientation was found to be energetically preferred for these dimers.

Frischleder and Lochmann⁵⁶ used a PCILO-crystal calculation (PCILOCC) method⁵⁰ and an empirical potential function to calculate intermolecular interactions for phospholipids in a two-dimensional lattice. Their results show the same type crystal structure as predicted by X-ray crystallography with a crystal stabilization energy of -36.6 kcal/mol. The crystal stabilization is due to intermolecular interactions, especially of the hydrogen-bond type. The stabilizations of the conformation of the subunits is due to intramolecular hydrogen bonding between the ammonium and the phosphate group.

Morris⁶³ has used an "exp-6" type atom-atom potential

$$AR^{-6} + B \exp(-CR) \quad (10)$$

to study the intermolecular forces between anthracene monomers. He uses several methods to calculate the individual terms of the total potential energy. The extended Hückel and the CNDO/2 techniques were used to calculate quadrupole interaction terms. He finds that the quadrupole moment interactions actually determine the structure of the stable dimer so are certainly not negligible. A reliable estimate of the dispersion energy was particularly difficult to obtain due to contributions from high-energy and multiple electron transitions and uncertainties in the behavior of atomic orbitals at large distances from the nuclei. He states that it seems we will be forced to use experimentally determined polarizabilities and quadrupole moments for some time yet.

Amos and Crispin⁶⁴ have used a version of uncoupled Hartree-Fock perturbation theory to find the long-range forces between large molecules which is one of the main problems in treating intermolecular forces between large molecules. They demonstrate that for large molecules with localized electrons the long-range interaction is the sum of individual interactions between the localized charged distributions which can be divided into electrostatic, induction, and dispersion terms. The electrostatic and induction contributions are obtained from electric moments and polarizabilities of the localized charge distributions. The dispersion term is calculated by a method they introduce which involves the frequency-dependent polarizabilities of the local distributions. They use a minimal basis set *ab initio* Hartree-Fock procedure to obtain the parameters needed for water, methane, and ethane. The angular dependence is naturally treated in this approach, and interactions between pairs of these molecules are used to demonstrate such dependence.

Rabinowitz, Swissler, and Rein⁶⁵ have studied interaction energies for large molecules using the CNDO method⁶² and an iterated extended Hückel theory (IEHT).⁶⁶ The interaction energies are calculated by writing the electrostatic energy of two charge distributions using Coulomb's law and expanding in Taylor

series to express the interaction energies in multipole-multipole terms. They include up to quadrupole-quadrupole terms and use both a molecular expansion and a segmental expansion (decompose the molecular charge distribution into atomic segments). The molecular expansions are not convergent to quadrupole terms for the intermolecular distances in this study between adenine and thymine at one relative orientation (not given). The segmental expansion to quadrupole is convergent at a distance between mass centers of 15-20 Å. They conclude that the IEHT wave functions give better segmental moments for use in an interaction theory than CNDO wave functions.

Parsegian and Ninham⁶⁷ developed a method for calculating van der Waals forces in condensed media based upon the Lifshitz theory⁶⁸ and applied it to the interaction of two planar parallel lipid slabs in an aqueous medium. In this study they conclude that the van der Waals energy of a system is not the sum of $(1/r^6)$ interactions between small elements of the interacting species and that van der Waals forces in lipid-water mixtures increase with temperature and exhibit only weak retardation forces.

Phillips⁶⁹ et al. have investigated the role of dipole interactions in monomolecular layers with the conclusion that these effects are much smaller than dispersion interactions and generally only play a minor role in determining molecular packing in insoluble lipid monolayers at the air/water interface.

Sudhindra⁷⁰ has presented a review of some methods of determining intermolecular forces between large molecules. His emphasis is on energy decomposition and methods of evaluating the resultant components of the total energy.

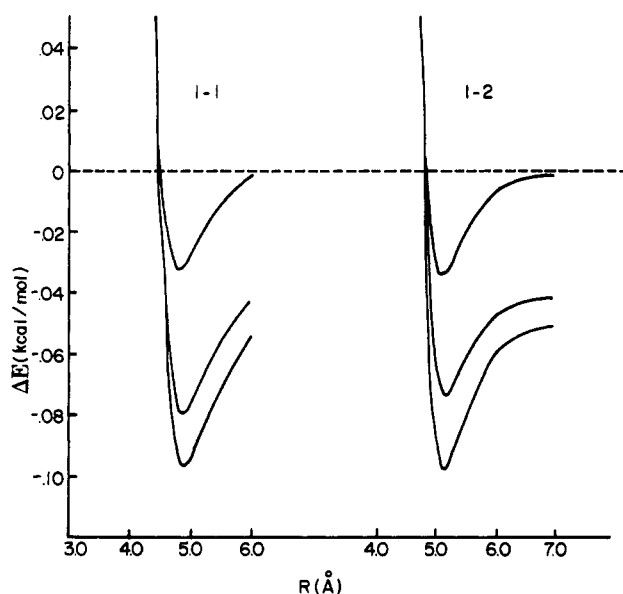
Several means of experimentally determining internal energies of lipid films have been developed.¹⁵ One method is surface vaporization—dissociation of condensed films to gaseous films.⁷¹ A second method involves a sequence of processes such as going from condensed surface film to gaseous surface film and then to liquid vapor.⁷² Thus for liquid-expanded and liquid-condensed surface films, the energies obtained per CH₂ are 1.3 and 1.6 kcal/mol. Another method is to measure surface pressure as a function of occupied area of the spread film.⁷³ When the material is compressed, the molecular separation is decreased, and the orientation of the molecules changes, which affects the variation in the surface pressure. This measurement of surface pressure in a monomolecular film can give information about orientation of the film and molecular interaction.

Gabrielli, Puggelli, and Faccioli⁷⁴ studied binary mixtures of poly(methyl methacrylate) (PMMA) and poly(ethyl methacrylate) (PEMA) at different molar ratios at the water/air interface and compared their data with that obtained from the separate pure polymers. The mixture was found to be very stable due to the attractive forces between the rigid segments. They determined that the polymers behave essentially rigid whether in a mixture or pure and that there is no change in the fraction of submersed polymeric fraction at the various mole fractions considered. The minimum in the excess free energy of mixing was obtained at a molar ratio of 1/1 and a net attractive interaction of 2.68 kcal/mol.

Clint and Walker⁷⁵ have studied the interaction en-

TABLE II. Calculated Energies, Experimental Work of Adhesion, and Separations^a

| | E , m cal/m ² | W , m cal/m ² | D , nm |
|--|-------------------------------|-------------------------------|----------|
| CH ₃ /CH ₃ | 9.58 | 9.3 | 0.347 |
| CH ₃ /C ₇ F ₁₅ | 6.19 | 6.9 | 0.385 |
| C ₇ F ₁₅ /C ₇ F ₁₅ | 4.25 | 4.3 | 0.423 |

^a Reference 75.Figure 10. Inter-molecular interactions for planar dimers as calculated by INDO for C₃, C₅, and C₆ dimers respectively, top to bottom.

ergies between layers of alkyl and partially fluorinated alkyl chains experimentally and theoretically. The attractive energy component was obtained as sums of London dispersion forces due to combinations of various layers in adjacent oriented molecules from refractive index data. The sums were taken over 21 layers on each side of the reference layers. The repulsive contribution was taken as the repulsive part of a Lennard-Jones potential appropriate to the second virial coefficients of CH₄ and CF₄. The calculated energies (E) were compared to the work of adhesion (W), and some of the data they obtained are in Table II, with d being the separation distance ($n - m$) calculated. For behenic acid, they extended their calculations to sum over 42 layers on each side rather than 21. The increase in interaction energy was found to be less than 1%. The major interaction energy came from the contacting terminal groups, so they deduced that extensive summations are not required past the first monolayer.

Combs and Dunne⁷⁶ have also studied the applicability of the PCILO method and the INDO method for calculating intermolecular interactions. Their applications were to the dimers of ethane, propane, pentane, heptane, and nonane. The INDO method greatly overestimates the intermolecular attraction at large internuclear separations and underestimates it at smaller separations (see Figure 10). Additionally, the INDO method is considerably slower than the PCILO method. For all dimers they studied the 1-1 and 1-2 conformations in two different angles of approach, the effect of optimizing polarities, and the effect of geometry optimization. They found, as did Lochmann and Weller, that polarity optimization does not affect the interaction energy or the distance at which energy

TABLE III. Propionic Acid (1-1) Dimer Calculations by PCILO Method

| R , Å | $-E$, kJ/mol | ΔE , kJ/mol |
|---------|---------------|---------------------|
| 3.6 | 329890.5649 | 88.9439 |
| 3.8 | 329939.0428 | 40.4660 |
| 4.0 | 329962.9380 | 16.5707 |
| 4.2 | 329974.0746 | 5.4342 |
| 4.4 | 329978.8648 | 0.6439 |
| 4.6 | 329980.6677 | -1.1590 |
| 4.7 | 329981.0150 | -1.5062 |
| 4.8 | 329981.1631 | -1.6544 |
| 4.9 | 329981.1903 | -1.6815 |
| 5.0 | 329981.1468 | -1.6380 |
| 5.5 | 329980.6707 | -1.1619 |
| 6.0 | 329980.3133 | -0.8046 |

TABLE IV. Propionic Acid(1-2) Dimer Calculations by PCILO Method

| R , Å | $-E$, kJ/mol | ΔE , kJ/mol |
|---------|---------------|---------------------|
| 4.9 | 329948.1559 | 31.3528 |
| 5.0 | 329966.5174 | 12.9913 |
| 5.1 | 329972.7972 | 6.7116 |
| 5.2 | 329973.9578 | 5.5509 |
| 5.3 | 329973.3612 | 6.1476 |
| 5.4 | 329972.4775 | 7.0312 |
| 5.5 | 329971.8420 | 7.6668 |
| 5.7 | 329971.6579 | 7.8509 |
| 5.9 | 329972.3198 | 7.1889 |
| 6.4 | 329974.6231 | 4.8857 |
| 6.9 | 329976.2406 | 3.2681 |
| 7.9 | 329977.8757 | 1.6330 |

minimization occurs. The dimer energies are lowered by about 5 kcal/mol by optimizing the polarities, but the monomer energies are similarly shifted so that the changes cancel. Geometry optimizations were only performed on the isolated monomers and at one dimer formation distance. The geometry optimization lowers the interaction energy by about 0.4 kcal/mol for the C₉ dimers, but they reason that this may be artificial since structure optimization was not done at all separation distances (an approach deemed too expensive for the possible rewards). The two angles of approach for dimer formation were such that all carbon atoms remain in the same plane during approach (planar dimers) and when the carbon atoms of the separate monomers were not in the same plane during approach (paraffin dimers). Since they were interested in application to fatty acid monolayers, they did calculations on the 1-1 and 1-2 planar dimers of propionic acid and found that the 1-2 dimer has no net attractive region due to the polar head group repulsions of the lone-pair electrons (see Tables III and IV). The propionic acid 1-1 planar dimer has a stabilization energy of 0.4019 kcal/mol at 4.9 Å whereas the propane dimer's corresponding values are 0.217 kcal/mol and 4.6 Å. The major point in such calculations as these is in being able to successfully extrapolate to an energy per CH₂ group because such calculations cannot be done on extremely long-chain molecules. However, if such data are safely extrapolatable, then such calculations can be very helpful in understanding the energetics of intermolecular interactions.

To demonstrate the usefulness of such calculations to long-chain molecules beyond the practical capability of computer systems, consider pairs of CH₃(CH₂)₁₁C-O₂H molecules in the 1-1 and 1-2 planar conformation. If we consider that the energy for such a molecule is decomposable into a sum of interactions from two long

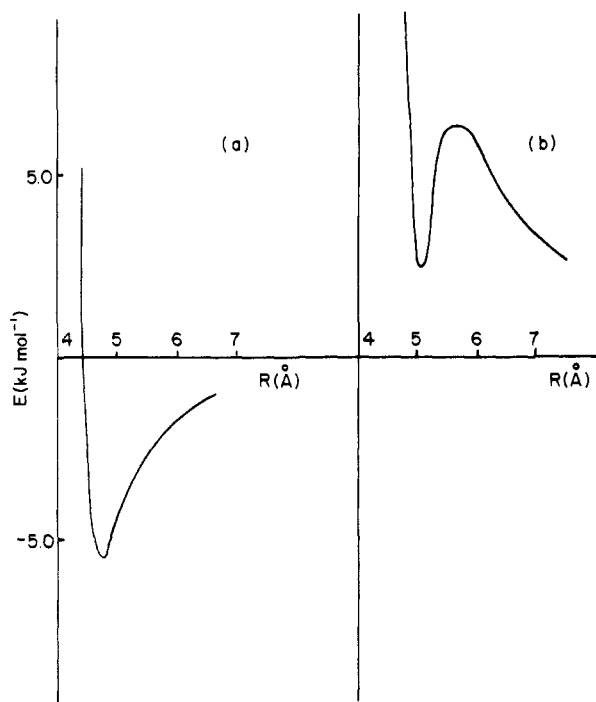


Figure 11. Intermolecular interactions for $\text{CH}_3(\text{CH}_2)_{11}\text{CO}_2\text{H}$ dimers in the 1:1 (a) and 1:2 (b) planar conformations as calculated by PCILO assuming an energy decomposition.

paraffin chains and two short fatty acid molecules, then the potential-energy diagram for these systems constructed by a sum of their parts is as shown in Figure 11. These predicted interaction energies are in reasonable agreement with the required parameters of the monomer-dimer model as discussed in another section.

In studying intermolecular forces between large molecules, it must be remembered that dispersion energy between large molecules (in contrast to small molecules) decays rather slowly with distance. One must also remember that a knowledge of the intermolecular interaction between two large molecules may give us little information on an ensemble of such particles. Thus a statistical mechanical treatment is essential to a proper understanding of assemblies of molecules of biological importance. An example would be a system which exhibits a two-phase equilibrium of large micelles and lipid monomers at equilibrium in solutions. Obviously, the statistical mechanical treatment also requires an intermolecular force study to obtain information pertaining to the most energetically favorable mutual orientation of molecules in the system. An SCF method is too time consuming and too inaccurate at a semiempirical level, and so it seems that a perturbation method approach is the most promising for such studies.

IV. Influence of Molecular Shape on Structure at Interfaces

If one is interested in adsorption phenomena or any type of interfacial study, he must be concerned with the conformation of the molecules at the interface for the conformation affects the inter- and intramolecular forces, the relative orientation of molecules adsorbed at the interface, and hence the physical and chemical properties at the interface. Some literature examples will be mentioned to demonstrate the wide range of

topics affected; these will also show that this is an area of study which requires considerably more study.

Tennyson Smith⁷⁷ has studied the theoretical equations of state and the molecular configuration of alkanes, alcohols, and carboxylic acids on the mercury surface by measuring surface tension and surface potential. He found that at low surface density the molecules reside with their long axis adjacent to the surface and exhibit a great deal of lateral interaction. He found that as the partial monolayer is compressed, a two-dimensional liquid is produced. When the close-packed horizontal orientation is further compressed, the chains begin to kink and portions of the chains are now erect. These erect portions then begin to cluster into micelles. Fatty acids with the number of carbon atoms (m_c) greater than 15 were found to orient with the carboxyl head group adjacent to the substrate and the tail pointing out. Fatty acids with m_c less than 15 were found to orient with the carboxyl group in the outer surface and the tail pointed toward the substrate.

Newman⁷⁸ has studied molecular reorientation in stearic acid monolayers at the paraffin-water interface by the Langmuir-Blodgett method over the pH range 2-9. It is generally accepted that the amphipathic lipid components of biological membranes are preferentially oriented with their polar groups in the outer bilayer. The work supports the suggestion that under certain conditions a reorientation occurs with the hydrocarbon tails facing the aqueous phase.

Nakahara and Fukuda⁷⁹ have studied molecular orientation in multilayers of chain anthraquinone derivatives by polarized infrared spectra. The multilayers were built up on calcium fluoride plates. Their main purpose was to elucidate the different types of orientations of the anthraquinone chromophore in the multilayers. They found the orientations to depend quite strongly on the numbers and relative positions of the long-chain substituents.

The conformational states of macromolecules adsorbed at solid-liquid interfaces has been studied by Eirich⁸⁰ with about 20 different polymeric systems. Most were found to form monolayers, with most of these consisting of individual macromolecules. Unless multisite adsorption or chain stiffness forces the molecules to lie flat on the surface, the macromolecules will exhibit properties both of the adsorbed and the solution states.

Two polymers may be incompatible in the bulk phase but due to special spatial orientation of the individual polymers at the interface they may become compatible at the interface. This can lead to special chemical and physical properties at interfaces with mixed polymer monolayers which would not have been predicted on the basis of the bulk properties of the polymers. Some aspects of this feature have been examined experimentally by Wu and Huntsberger.⁸¹

Takenaka⁸² has utilized resonance Raman spectra to study the effect of electrolytes on the molecular orientation of monolayers adsorbed at the liquid-liquid interface. He found that sodium chloride and barium chloride affect the amount of adsorbed molecules, the degree of orientation, and the type of molecular orientation (uniaxial or other).

A liquid crystal study by Proust and Ter-Minassian-Saraga⁸³ showed that the orientation of hexa-

decyltrimethylammonium bromide (I) on glass changed from parallel to perpendicular to the glass as δ (mol/cm²) increased. Then they showed that the orientation of *N*-(*p*-methoxybenzylidene)-*p*-butylaniline (II) adhered to I on the glass varied from planar to perpendicular as δ of I varied from $(4.5-9) \times 10^{13}$ mol/cm² to $(9-17) \times 10^{13}$ mol/cm².

Multilayer adsorption of solutions of methyl, ethyl, propyl, butyl, and amyl alcohols in toluene were studied by Oscik and Goworek.⁸⁴ They studied the dependence of the molecular areas occupied by the alcohol molecules and their orientation in the adsorbed phase on the length of the carbon chain.

Maelstaf and Bothorel⁸⁵ used depolarized Rayleigh scattering to study molecular orientation correlations in various hydrocarbons which form the hydrophobic part of usual tensioactive compounds. The correlations were weak and suggested an important molecular disorder at an interface such as water-tensioactive compound-oil which could contribute to the falling of interfacial tensions caused by the addition of tensioactive compounds.

Vilallonga, Garret, and Hunt⁸⁶ have been involved in a series of studies on the kinetics and mechanisms of monolayer interactions. They found that the free energies of adsorption of C₁₋₁₄ alkanols at air/water interfaces were linear functions of chain length for the 1-alkanols. However, from C₃₋₈, the 2- and 3-isomers gave lower free energies of adsorption than the corresponding 1-isomers. Similar observations were obtained by Meister, Rang, and Eisen⁸⁷ on a system of C₆₋₁₀ alkenes and alkynes adsorbed on carbon black. They calculated the changes of differential internal energy of adsorption ($\Delta\bar{U}$) and noted that $\Delta\bar{U}$ increased linearly with an increase in number of carbon atoms of the adsorbate. They also observed that $\Delta\bar{U}$ increased as the position of the double bond changed from the middle to the end of molecules with the same number of carbon atoms. Most certainly orientational changes are involved in both these systems as the positions of the double bond change. Does the energy of attraction change the orientation or does a change of orientation change the energy of attraction? It would seem that yes is the appropriate answer, for surely the effects complement each other. The effect of orientation of the same molecules on different surfaces has been examined by Rao and Nayar.⁸⁸ The molecules studied were diethylamine, dipropylamine, acetone, diethyl ketone, and dipropyl ketone. They determined the molecules adsorbed on silica gel (Stantocel C) to be oriented perpendicular to the surface whereas they were oriented parallel and perpendicular to a glassy silica gel surface. Here the energy of attraction affects the orientation.

Anesthetic action has been studied by Richards et al.⁸⁹ as possibly being caused by a degenerate perturbation of protein structure. They found that anesthetic effects and changes in bilayer physical properties were unrelated and concluded that anesthetics probably do not perturb the bilayer regions of membranes, but directly interact with target proteins. However, Koch and Combs⁹⁰ do not completely agree with this conclusion. They contend that it is possible that penetration of the bilayer region by anesthetics could occur to such an extent as not to disrupt the physical properties of the bilayer but yet alter chemical processes. Certainly this area needs further research, and orientation effects

could still be a factor in anesthetic actions. Baranova et al.⁹¹ studied the structure of adsorption layers of surfactant molecules and found the nonpolar parts of the molecules which interacted with the surface of hydrophobic solid adsorbents to be oriented parallel to the surface.

Certainly electrical effects are important, and they will be considered in more detail in another section. However, to show orientational ordering, a few more general references are in order here also. Kinoshita et al.⁹² found that adenine or deoxyadenosine molecules undergo a rearrangement from parallel to the surface to perpendicular to the surface when there is a sudden sharp decrease in capacitance centered at -0.6 V. Their studies were performed at pH 9 at mercury electrodes by capillary electrometer and differential capacitance measurements. This rearrangement was not observed by monodeoxynucleotides, which suggests a conformational flexibility factor to be involved in the rearrangement as well as differences in multisite adsorption by each molecule. Solution electrolyte effects were studied by Skripnik and Strazhesko.⁹³ They studied the effects of phenols and carboxylic acids on the adsorption of strong electrolytes (Kl, HCl, Hg, NO₃⁻) from dilute aqueous solutions on carbon to elucidate the orientation of aromatic compounds at the solution-carbon interface. It was found that the phenols affected adsorption the least and the aromatic carboxylic acids caused the largest decrease in adsorption, with picric acid causing a 96% decrease.

The nature of the medium certainly affects the orientation and configuration of the adsorbed species, and considerable research has been done on the effect of water on molecules adsorbed at interfaces. A review of the state of water and hydrated ions at interfaces has recently been published by Conway⁹⁴ with particular emphasis to double-layer and charged surface effects. There has been considerable debate about how far from the interfacial structure order exists in the water itself. Klier and Zettlemyer⁹⁵ published an article on recent advances on the structure and dynamics of water-inorganic systems. From a molecular orientation profile at 4 °C, Croxton⁹⁶ states that a degree of molecular orientation extends over a range of about 35 Å. Some have maintained⁹⁷ that structure enhancement by a boundary surface extends from 100 to 1000 Å. Conway⁹⁴ states that thermodynamic evidence is inconsistent with the water having any special properties in layers more than 1-2 molecules in thickness. The superficial excess entropy is positive and not consistent with long-range structuring. Also the magnitude of the force field required to maintain an ordered, oriented surface over a long distance seems to argue against such an effect due to the large dielectric constant of water which acts as a screening effect. Edelhoch⁹⁸ has recently written a review on protein-lipid interaction and the role of water. He states that the association of lipids to form micelles and bilayers, and proteins to form oligomers and organelles, and lipids and proteins to form lipoproteins and membranes can be understood solely from the interaction of nonpolar groups with water (the hydrophobic effect). Water certainly seems unique as the solvent which can produce the folding of a polypeptide chain to form the active structure. Strong binding of small or large molecules to proteins requires proper pairing of polarities and close fitting of ligands,

and water uniquely affords the medium for the proper molecular conformations to be free energy preferred.

A number of theoretical studies have been made on the question of orientation and configuration changes during adsorption by lattice gas models and by Monte Carlo simulation experiments. Lal, Tarpin, Richardson, and Spencer⁹⁹ studied the configurational behavior of isolated chain molecules adsorbed from athermal solutions with a Monte Carlo computer simulation method. For strongly interacting systems, standard Monte Carlo methods possess difficulties pertaining to sample convergence. One objective of their study was to develop a more efficient sampling scheme which favors high density regions of phase space. The adsorption sites were the lattice points of a two-dimensional lattice. Standard bond angles were chosen and fixed for a 100-segment length molecule with the configuration studied as a function of $-\Delta\epsilon_2(\text{segment/surface binding energy})/kT$. They found that at low $\Delta\epsilon_2$ only a small fraction of the segments is bound to the surface and the configurational behavior of the molecule is much the same as in solution. At increased $\Delta\epsilon_2$, however, the number of segments bound to the surface are significant. The major contributor to the thickness of the adsorbed layer though was due to the orientational behavior of the end segments rather than to segments of the center of the molecule being above the surface. This was a simple model, but they concluded that their Metropolis sampling method was sound.

The follow-up to the above was published in 1977 by Clark and Lal¹⁰⁰ in a more realistic model. Although this work is not strictly applicable to short-chain systems, it does speak to orientational effects which are relevant. The same sampling was used, but now a trans/gauche bond conformational energy of $1.0kT$ was introduced and the athermal condition was relaxed. The solvent condition was defined by intersegmental interactions given by a square-well potential, the depth of which ($\Delta\epsilon_s$) was varied. All interactions were assumed to be pairwise additive. The expected changes in polymer structure from more elongated to more spherical were observed as the solvent changed from "good" to "poor". If $\Delta\epsilon_s/kT > -0.4$, the isolated chains assume positive excluded volume, and if $\Delta\epsilon_s/kT < -0.4$, the excluded volume is negative. They anticipate changes in the application of their sampling method to allow the calculation of free energies for a thermodynamic study of these systems in later publications.

Brown, Everett, Powell, and Thorne¹⁰¹ have published a preliminary study of adsorption and structuring at the solid/liquid interface. They reviewed evidence for structural solidlike layers at interfaces between a graphitized carbon surface and liquid alkanes, alkanols, and their mixtures. As temperature increases, a breakdown in monolayer structure occurs smoothly for alkanes, but a steeper transition is observed for alkanols. Configurational effects contributing to these changes are mentioned, and the need for a theory of the structure of the monolayers at the interface is mentioned.

Order-disorder transitions are also observed in studies of adsorption of straight-chain aliphatic molecules such as 1-octanol on graphite substances.¹⁰² Specific heat measurements for a slurry of graphon in 1-octanol show a clear λ transition which may suggest that well-defined two-dimensional arrays of hydro-

carbon chains will exhibit transitions in which higher order derivatives of certain thermodynamic quantities change discontinuously.

A one-dimensional lattice model of adsorption considering the reorientation of adsorbed molecules as a function of number density was performed by Vernov and Lapatkin.¹⁰³ They found that changes in the interaction parameter affected the degree of coverage and the thermodynamic properties.

An interesting study by Kharkats¹⁰⁴ was concerned with the question of paired phase transitions in reorientation of a system of adsorbates on surfaces with two different orientations of interacting particles. He found a critical condition for the production of the bitransitions.

V. Role of Conformation Changes in Phase Changes in Monomolecular Films

The interpretation of lipid monolayer behavior in molecular terms requires certain assumptions to be made, or postulates put forward, concerning the significant conformations which monolayer molecules adopt. The chemical nature of the lipid species and the substrate are important in this respect. The demand that a theoretical model should describe both molecular trends and have a realistic temperature dependence enables the significant conformers to be identified. At any given surface area and temperature any one or several conformers may be significantly contributing to the monolayer behavior (see Figure 12). The influence of molecular shape on structuring at interfaces is discussed in section IV of this review. Also, some insight into the general problem of structuring at interfaces is to be gained by studying the literature on adsorption at the liquid/solid interface. Here, a typical experiment investigates the adsorption of, for example, heptane on a graphitized carbon black. Everett¹⁰⁵ has reviewed the recent experimental and theoretical status of that problem. The role of the polar carboxylic acid head group is also an important consideration and has been initially studied^{106,107} based upon the BMT model.¹⁰⁸ The unusual temperature behavior has been qualitatively discussed by Cadenhead and Müller-Landau^{109a,b} and will be treated in section VIII.

In most theoretical treatments of the monolayer phase diagram, one or the other of two main types of conformational change in groups of monolayer molecules are regarded as mainly responsible for the observed phenomena. The first of these is chain isomerism or "bending". In the lowest energy state of a saturated hydrocarbon chain, each successive carbon-carbon bond is at the "trans" angle with the previous bond, which implies that all carbon atoms of the chain are coplanar. The all-trans state is thus conducive to the closest packing of an assembly of chains. However, a bond can rotate from the trans angle to one of two gauche angles with an energy absorption of about 0.5 kcal/mol (other angles are possible but demand too much energy to occur significantly at normal temperatures). After trans-gauche rotations the carbon atoms of a chain are no longer coplanar; the chain is "bent" and takes up a larger monolayer area. Hence, in a closely packed group of erect chains, the isomerization of one chain disorders the positions of the other chains and creates free space. This makes the effect cooper-

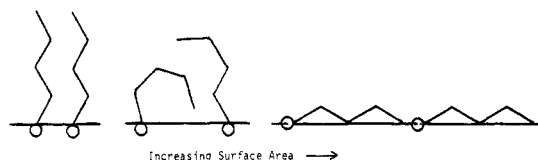


Figure 12. A sketch of the behavior of a pair of molecules on a surface as a function of increasing surface area.

ative since it is then easier for the other chains to isomerize. In a very interesting model of Nagle^{5,14,117} similar cooperative behavior results in a first-order "melting" transition from the state of closest packing to a more disordered state which is less dense by a few per cent. We discuss the relation of this model to monolayer behavior and also a number of other theories based on chain isomerism¹²⁹⁻¹³⁰ in section VI.

Pethica, Glasses, and Mingins^{110a} investigated chain conformations in dilute monolayers by comparing second virial coefficients derived from experimental isotherms, especially those of Kim and Cannell⁹ for pentadecylic acid, with calculated second virial coefficients. For the latter they use Salem's³⁷ estimate of interaction potentials for parallel straight hydrocarbon chains. They conclude that chain coiling or flexing is infrequent at high dilutions. Although attempts to improve the fit by incorporating bulk water effects on the interactions are stated to be not helpful, the straight chains are interpreted as lying stretched along the water surface.

Considerable insight into the effects of chain conformations relative to the water surface is obtained from phenomena observed with monolayers, at the air/water interface, of bipolar molecules (i.e., molecules with a second polar group attached to the carbon chain and separated by at least a few links from the head group). These phenomena take their most remarkable form with nitroxide spin-labeled fatty acids or derivatives^{145,146} where there is negative thermal expansion over a large region of the surface pressure-area plane, causing "isotherm inversion" (i.e., an isotherm lying above rather than below isotherms for higher temperatures). In another case¹⁴⁶ isotherms are effectively coincident over a range of 27 °C. The explanation given^{145,146} is that the second polar group can form a bond to the water surface which is weaker than the head-group bond. Hence, as the temperature increases, the proportion of molecules which are extended along the water surface decreases. Statistical mechanical theories based on this idea are reasonably successful.^{19,24} Since liquid condensed-liquid expanded transitions are absent in these systems, the bulky spin-label groups must interfere with whatever ordering process is responsible. However, certain other monolayers of bipolar molecules display isotherm inversion in conjunction with liquid condensed-liquid expanded transitions. These include 9-hydroxyhexadecanoic acid¹⁴⁸ where the inversion is on the low density side of the transition and estradiol diacetate¹⁴⁷ where it is on the high density side. Bipolar monolayers are discussed at greater length in section VIII.

The other main type of conformational effect, which is basic to a number of theories, is change in the relative orientation of neighboring pairs of monolayer molecules. This orientation is usually defined in terms of rotation about an axis normal to the interface, and orientational theories depend on lack of rotational symmetry of the

whole amphipathic molecule about any such axis. Such asymmetry would seem to be obvious for the phospholipids with their bulky complicated head groups and double chains. It now seems to be accepted that in hydrated bilayers, the head-group zwitterions are parallel or nearly parallel to the bilayer planes.^{110b} The same physical factors causing this type of behavior are likely to operate in monolayers, at least at high densities. Finite dipoles parallel to the interface would, through their electrostatic interaction, produce strong orientational effects. It should be noted that the position in the surface pressure-area plane of the liquid condensed-liquid expanded transition point depends on the nature of the head group as well as the chain length.^{4,119,120} Again in certain bilayer systems parallel all-trans carbon chains are regarded as tilted rather than perpendicular to the bilayer plane.^{110b} Such tilting relative to the interface normal would result in steric interference with rotation about the normal. Some of these factors, for instance the head-group dipolar effect, are present for single-chain molecules. Also, recent experiments by Vaz et al.^{110c} indicate hindrance to the rotation of a single all-trans chain about its long axis in a close-packed state.

As far as we are aware, the earliest theory in which the liquid condensed-liquid expanded transition is regarded as between orientationally long range ordered and disordered states is by Kirkwood,¹¹³ which appeared as long ago as 1963. Kirkwood regarded the molecules as occupying a regular two-dimensional lattice of sites, and his work is fully discussed in section VI. More recent theories have incorporated orientational effects into lattice fluid models in which there are vacant sites (holes) as well as occupied sites. Such theories have the advantage that, with suitable interaction parameter values, both first-order liquid-vapor transitions and continuous liquid condensed-liquid expanded transitions can be derived. This is the case with the theory of Bell, Mingins, and Taylor¹⁰⁸ who use the simplest possible type of orientational interaction by treating the monolayer as an Ising model diluted by "holes". Since in this model all molecules are "monomers" occupying one site only, they must be regarded as in an erect state with chains perpendicular to the interface. Dunne and Bell¹⁴³ modified this model to incorporate lateral extension as well as orientational effects by including an additional extended state in the molecule occupying two lattice sites. Firpo et al.^{143c} envisage a lattice fluid with each molecule represented by a "ring rod" occupying p sites, and they compare theoretical results with those observed for monolayers in the case $p = 4$. The liquid condensed-liquid extended transition is steric in nature, and the rods tend to line up parallel to one another in the liquid condensed state. This is an attractive idea but comes up against the difficulty that the liquid condensed state often persists to densities so high that the molecules must be in erect conformations taking up the minimum monolayer area. A recent treatment by Kaye is intermediate between that of Firpo et al. and Bell et al., respectively, in that all molecules occupy two sites but interaction energies tending to make the molecules line up are postulated. Lattice fluid models are discussed in more detail in section VII.

In conclusion we may mention a review article by Wiegand and Kox¹¹¹ which covers the literature up to about the middle of 1978. It differs from the present

work in accepting that the liquid condensed-liquid extended transition is classically first order.

VI. General Models for Cooperative Phenomena in Amphipathic Monolayers

The earliest attempt known to us to construct a theory of the liquid-condensed/liquid-expanded transition in monolayers was due to Langmuir¹¹² in 1933. This very eminent physicist was stimulated by the experimental discoveries of such workers as Adam and Jessop²⁰ in the previous decade. He attributed the transition to the formulation of micelles or complexes of amphipathic molecules. He envisaged the micellization process as beginning suddenly at the transition density. However, while, if there were a tendency to micellization, the proportion of molecules in micelles will obviously increase with density, this increase would normally be continuous. The micellization process could be regarded as similar to the formation of nuclei or droplets which precedes a vapor/liquid transition, but in this case a different type of transition is in question. This takes place in an assembly which has in many cases already passed through a vapor/liquid transition at a lower density. Furthermore Langmuir uses an expression proportional to $(A - A_0)^{-1}$ for the surface pressure exerted by the micelles, and this is inappropriate in states approaching closest packing.

The next important theory for the transition region was developed by Kirkwood¹¹³ in 1943. He assumed that the head groups form a regular two-dimensional lattice parallel to the interfacial plane while the carbon chains, in what would now be termed an all-trans configuration, are perpendicular to this plane. Kirkwood regarded the free energy of a nearest-neighbor pair of chains as minimized when the planes of the carbon atoms in each chain are parallel. He postulated a free energy of relative rotation in the form

$$-\frac{1}{2}\omega_0 \cos 2(\phi - \phi') \quad (11)$$

where ϕ is the angle between the "long-diagonal" of the cross section of one chain and a fixed reference line parallel to the interface and ϕ' is the corresponding quantity for the other chain. He defined an angular distribution function $g(\phi)$ and a parameter α where

$$\int_0^{2\pi} g(\phi) d\phi = 1, \quad \alpha = \frac{1}{2}z\omega_0/kT \quad (12)$$

z being the coordination number of the lattice. He then gives an integral equation

$$\ln(\lambda g) = \alpha \int_0^{2\pi} \cos 2(\phi - \phi') g(\phi') d\phi' \quad (13)$$

for $g(\phi)$, stating that it is derived from an extension of his theory of three-dimensional rotational transitions. By analogy with the latter we can write for the free energy per molecule

$$f_c = kT \int_0^{2\pi} g(\phi) \ln g(\phi) d\phi - \frac{1}{4}\omega_0 z \int_0^{2\pi} \int_0^{2\pi} g(\phi) \cos 2(\phi - \phi') g(\phi') d\phi d\phi' \quad (14)$$

This free energy is minimized with respect to the function $g(\phi)$ and the integral eq 13 results from varying $g(\phi)$ to $g(\phi) + \delta g$ and equating the resulting variation

in f_c to zero. The parameter λ is related to the Lagrange multiplier used to incorporate the normalization relation of (12), which acts as a "constraint" on $g(\phi)$. The solution of (13) takes the form

$$g(\phi) = \lambda^{-1} \exp(\alpha s \cos 2\theta) \quad (15)$$

and it is easy to show from (13) that the order variable s is the mean value of $\cos 2\phi$. When $s = 0$ all orientations are equally probable, but when $s > 0$ the chain planes are tending to parallel alignment. With a little manipulation it can be shown from (12), (13), (14), and (15) that

$$f_c/kT = -\ln \lambda + \frac{1}{2}\alpha s^2 = -\ln \left(\int_0^{2\pi} e^{\alpha s \cos 2\phi} d\phi \right) + \frac{1}{2}\alpha s^2 \quad (16)$$

From (12), (15), and certain standard Bessel function relations, Kirkwood derived an equation for the order variable s :

$$s = -iJ_1(i\alpha s)/J_0(i\alpha s) \quad (17)$$

where $i = (-1)^{1/2}$ and J_0 and J_1 are Bessel functions of the first kind. When $\alpha < 2$ the only solution of (17) is $s = 0$, but for $\alpha > 2$ there are nonzero solutions. It is envisaged that as the area a per monolayer molecule decreases the lattice constant also decreases and the interaction parameter ω_0 increases. When the parameter α , which is proportional to ω_0 , passes through the value 2, long-range orientational order, represented by a positive s value, sets in and the transition occurs. Kirkwood writes $\omega_0 = \epsilon(a) - T\eta(a)$, where the energy term ϵ and the entropy term η are dependent only on the area a per molecule. By feeding in experimental values of change of transition area with temperature, he then gives values of the discontinuities in heat of spreading and specific heat. These are compared with experimental values and give agreement at least as to order of magnitude.

However, molecular field theories like the one just outlined are now regarded as inaccurate in the immediate neighborhood of transition points. If they are effective for a particular model, it is in giving a qualitative picture of the general phase behavior. The assumption of a regular lattice of molecules is hardly appropriate for a fluid which is a long way from maximum density, and indeed Kirkwood gives no method of constructing surface pressure/area isotherms for his model. The positional disorder inherent in a fluid can only be represented in a lattice model by allowing vacant sites and relating the lattice constants to the distance of nearest approach (see, for instance, Runnels¹¹⁴ and Bell¹¹⁵). It would not, in fact, be difficult, at the same zero-order mean field level of approximation, to modify Kirkwood's model to a lattice fluid. If ρ denotes the number of molecules per lattice site, then eq 14 would be replaced by

$$f_c = kT \left\{ \rho \ln \rho + (1 - \rho) \ln (1 - \rho) + \rho \int_0^{2\pi} g(\phi) \ln g(\phi) d\phi \right\} - \frac{1}{4}\omega_0 z \rho^2 \int_0^{2\pi} \int_0^{2\pi} g(\phi) \cos 2(\phi - \phi') g(\phi') d\phi d\phi' \quad (18)$$

The number density ρ would appear as an additional factor in the parameter α in the minimization eq 13 and,

if ω_0 is now regarded as independent of density, isotherms could be constructed. Unfortunately certain developments in the modern theory of cooperative phenomena make a theory of a two-dimensional assembly based on the interaction 11 of doubtful value. Section VII deals with other lattice-gas models.

Define for each chain a unit vector S which makes an angle 2ϕ with the reference line. Then the interaction Hamiltonian eq 1 can be written as

$$-\frac{1}{2}\omega_0 S \cdot S', |S| = |S'| = 1 \quad (19)$$

and we thus have a two-dimensional classical Heisenberg or D -vector model. Stanley¹²⁰ classifies models of this general type by two numbers, D , the dimension of the vector, and d , the dimension of the space, and in this notation Kirkwood's monolayer model has $d = D = 2$. (His corresponding three-dimensional model has $d = D = 3$. Review articles on classical Heisenberg models do not mention this work.) For $d = 2$, this model is one of a class for which Mermin and Wagner¹¹⁶ showed that long-range orientational order cannot exist for any $T > 0$. Hence the mean-field theory is erroneous in predicting the transition in s . Stanley,¹²⁰ however, points out, using magnetic language, that series expansions give some evidence for a susceptibility divergence at a nonzero temperature and postulates a "quasi-ordered phase" below this temperature. It is not inconceivable that the liquid-condensed state is such a phase, but unfortunately little seems to be known about the microscopic or thermodynamic properties of a quasi-ordered phase. Alternatively it might be suggested that these mathematical difficulties reflect the physical fact that expression 11 is too smooth to represent a steric interaction energy.

We now consider an approach to cooperative phenomena in monolayers (and bilayers) due to Nagle^{5,14,117} which is based on the fact that a carbon chain can "disorder" from the all-trans conformation in which the carbon atoms are coplanar into various isomeric forms. This occurs by relative rotation of the carbon-carbon bonds from the "trans" angle to one of the "gauche" angles, each such rotation taking an energy of about 0.5 kcal/mol or 250*k*/(molecule deg). Other conformations cost too much energy to be considered. In such isomers the carbon atoms are no longer coplanar, the chain is "bent", and the minimum monolayer area occupied by the molecule is greater than when the chain is in the all-trans conformation. This is sometimes called the "excluded volume" or "steric interaction" effect, but these terms could equally well be applied to orientational disordering of all-trans chains, which Nagle does not consider. We shall refer to such states as "isomeric" or "extended", noting that the extension in question is parallel to the interfacial plane. Clearly if one chain in a fairly closely packed group of chains is isomerized, the positions of the other chains will be disordered and free volume created. Thus other molecules of the group can isomerize with a smaller entropy change and the effect is cooperative.

In Nagle's model A,¹¹⁷ which he uses for a theory of monolayers,¹⁴ the carbon chain is of infinite length and the links lie on the edges of a triangular lattice in a plane normal to the interface. The all-trans configuration is represented by all links of the chain lying on a vertical line while in the isomers some links lie on

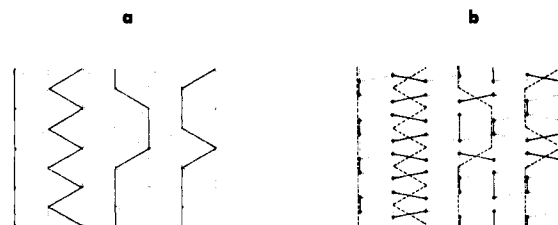


Figure 13. (a) Nagle's model A, all-trans conformation (vertical line) and three isomers. (b) The dimer state corresponding to the chains shown in (a). (Both figures reproduced from *J. Chem. Phys.*, 1973, 58, 252, by permission. Copyright 1973, American Institute of Physics.)

edges at 60° or 120° to the vertical. The isomerization leads to unoccupied edges and vertices (see Figure 13a). Density variables ρ_x and ρ_y are introduced which are respectively proportional to the number of nonvertical links and unoccupied edges. Nagle¹⁴ regards the horizontal length per chain as a monolayer "area" A and the area per link in the vertical plane as a "volume" V . Then

$$A = (1 - 2\rho_y - \rho_x)^{-1}, \quad V = \rho^{-1} v (1 - 2\rho_y)^{-1} \quad (20)$$

where ρ is the number of links per lattice edge. The enthalpy per chain link is

$$H = 2\epsilon\rho_x V - \alpha V^{-b} + \pi A \quad (21)$$

where ϵ is the energy per "gauche" link, α is a van der Waals energy, b is a coefficient usually put equal to $3/2$, and π is surface pressure per chain link. Nagle obtains the thermodynamic properties of this model by relating it to an exactly solvable dimer model. This is done by showing that any chain configuration on the triangular lattice is equivalent to a complete dimer occupation of a related lattice, which is topologically identical with a plane square lattice. (See Figure 13b.) The nonvertical chain links become horizontal dimers while the vertical links and the empty edges respectively become vertical dimers lying on alternate vertical lines of edges in the new lattice. The partition function of the dimer model is obtained by a method due to Kastelyn.¹¹⁸

To obtain exact results for a microscopic model, however simplified, of chain-link interactions is a considerable achievement. However it must be recognized that the theory is unrealistic in important respects, many of which are noted by Nagle himself. For critical phenomena at temperatures greater than absolute zero the system space must have at least two infinite dimensions ($d \geq 2$), where in practice "infinite" means a very large multiple of the intermolecular spacing. Thus phase transitions, either first order or continuous, can occur in monolayers because their area involves two "infinite" dimensions. Nagle replaces the monolayer area by a line and provides the second infinite dimension needed for critical behavior by making the chains of indefinite length. In experimental monolayer systems the chains consist of a small finite number of links, and transition properties are strongly dependent on the length of the chain.^{23,119,121} Again, in this model the all-trans chain has no orientational degree of freedom, although experimental close-packed systems of all-trans chains in bilayers are orientationally disordered below T_m .¹²² It seems reasonable to assume that disorientation as well as isomeric bond rotation must play a part in the progressive chain disordering which accompanies

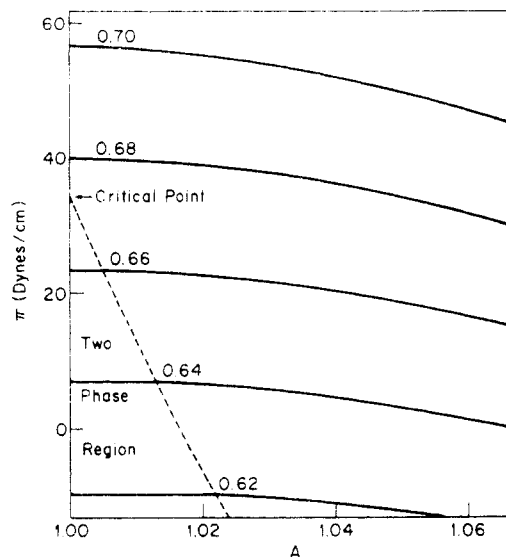


Figure 14. π/A isotherms derived from Nagle's model A; parameter values $a = 1.84$ kcal, $b = 3/2$. (Reproduced from *J. Chem. Phys.*, 1975, 63, 1255. Copyright 1975, American Institute of Physics.)

increase in monolayer area.

Below a critical temperature T_c the surface-pressure/area isotherms derived from Nagle's model display a first-order transition from a fluid state to the state of closest packing ($A = 1$)¹⁴ (see Figure 14). Consequently the critical point lies on the $A = 1$ axis. Above T_c each isotherm intersects the $A = 1$ axis at a finite pressure. Nagle⁵ attributes the discrepancy between the density discontinuities resulting from his theory and the continuous liquid-expanded/liquid-condensed transitions observed experimentally in many monolayer systems to irreversibility. This is said to be due to either kinetic or boundary effects. As regards the former, Cadenhead¹ states that the positive slope on the high-density side of the continuous transition is "reproducible over a wide range of compressional velocities, although there does appear to be a small... hysteresis associated with it". He remarks that "even very slow film compressional velocities do not eliminate the positive slope of the transition suggesting that the transition is not first-order". Nagle suggests that influence of the boundary is especially important because of strong excluded volume effects. However, though it is possible that correlation lengths for steric effects are higher in amphipathic monolayers than in a "classical" fluid, steric or "hard-core" interactions are extremely important for all condensed systems. Gas/liquid transitions with a density discontinuity occur at a lower pressure on the same isotherms as continuous liquid-expanded/liquid-condensed transitions or without the latter on lower temperature isotherms. Furthermore, as the temperature increases so does the isotherm slope on the high-density side of the continuous transition. It is difficult to see why boundary or any other irreversibility effects should change some first-order transitions to higher ones but not others or why they should increase in magnitude with increasing temperature. Again, experiments with lipids at both the air/water¹¹⁹ and oil/water^{23,121} interfaces show that increasing chain length has a similar effect on the isotherms as decreasing temperature, which would mean, if we follow Nagle, that the boundary steric effects decrease with

chain length. This seems unlikely. A better way to correlate the results of Nagle's model with experimental observations might be to claim that the former represents a long-chain limit, although it must be remembered that Nagle's theory is the long-chain limit of a one-dimensional model.

For the values of the energy parameters which Nagle considered most likely ($\epsilon = 0.5$ kcal/mol, $\alpha = 1.84$ kcal/mol), most of the transition range lies on the negative side of the surface pressure axis. However he argues⁵ that, for comparison with monolayers, pressures calculated from the theory should be increased by the difference between the surface tensions of water and that of a hydrocarbon fluid, that is $70 - 20 = 50$ dyn/cm. The basis of this contention is that when the monolayer area is increased there is an equal decrease in clean water surface and, from the upper side of the monolayer, a corresponding increase in effective hydrocarbon/air surface. However, any water effect is due to a difference in the surface free energies of the water under the monolayer and clean water, respectively. This difference is not likely to equal the total surface tension of water and, furthermore, it must decrease with the monolayer density. The hydrocarbon effect should be taken care of if the chain interactions are correctly treated. Even if it were argued that a surface tension term should be added to correct for the infinite chain assumption, then this term also should decrease as the chain density decreases. Hence to simply translate the calculated isotherms upward by a constant amount of 50 dyn/cm is questionable.

In his 1976 paper⁵ Nagle incorporates various additions to his basic model, including head-group interactions and soft-core repulsive interactions which are treated on a mean-field basis. He argues that head-group effects are responsible for observed differences between the DPPE and DPPC lipid molecule systems. A claim is made that an unrealistic feature of the theoretical results (that every isotherm reaches the $A = 1$ axis at a finite pressure and then continues as a vertical line of this axis) would disappear if the lattice spacing decreased with increasing π . However, the lattice spacing is simply the carbon-carbon distance in the chain,¹¹⁷ and it seems unlikely that this would change appreciably. Introduction of "soft" repulsive terms does modify the phase diagram⁵ and shifts the critical point from $A = 1$, although each isotherm still ends with a vertical line on the $A = 1$ axis. Nagle⁵ emphasises the role of the glycerol groups on phospholipid molecules in the "soft" repulsion effect. Although these groups will be important for the detailed properties of phospholipid monolayers, qualitatively similar phase diagrams are obtained for monolayers of molecules like myristic acid which consist of a simple head group and a single chain. "Hard-core" interactions with a potential rising abruptly from zero to infinity are in any case an idealization of the physical situation.

Quite a large number of authors (Scott,¹²³ Priest,¹²⁴ Jacobs et al.,¹²⁵ Marcelja,¹²⁶ and Marsh¹²⁷) have considered models in which, as in Nagle's, the primary effects are chain isomerism and van der Waals attraction. Various types of approximation have been used, but phase transitions obtained are invariably first order. Usually the main interest of the author is in comparison with experimental bilayer properties. Scott¹²³ develops a model for finite chains with each chain segment oc-

cupying a "cell". The cells are arranged in a square pattern, and all-trans conformations correspond to segments occupying vertical sets of cells. The possible conformations of each chain are considered in detail, and the number of ways in which a given conformer can be added to the assembly in the presence of a given fraction of the various types is approximated by randomized factors of the "Flory-Huggins" type. Scott states that the horizontal layers of cells are two-dimensional but the randomized factors do not seem to reflect this, though in the interest of brevity the theory is only presented in detail for a three-segment chain. There are no transitions in the absence of a van der Waals interaction term. This is used in a mean-field approximated form with (in Nagle's notation) $b = 3/2$ and leads to van der Waals loops in the isotherms which represent first-order transitions. Isotherms are shown for a five-segment chain with 10 possible conformations and a nine-segment double chain with 14 possible conformations. Scott (like Marcelja¹²⁶) explains the discrepancy between the theoretical first-order transitions and the continuous transitions observed in experimental monolayers by the presence of impurities in the latter. Similar remarks can be made to those given previously about the boundary effect hypothesis. In particular it would be necessary to assume that impurity levels are systematically greater or their effect more marked in lower chain length monolayers. In earlier work Scott¹²⁸ considered a model where the molecules have several rotational states and can be displaced from cell centers to interstitial sites and which displays successive first-order transitions.

Priest¹²⁴ reinterprets the exactly solvable model of Nagle and uses it as the basis of a Landau or mean-field treatment of a two-dimensional system with finite chains. The theory of Jacobs et al.¹²⁵ is of interest in that their model system is a continuous one. The head groups are hard disks on a two-dimensional plane and molecular dynamics calculations are used for the coefficients in truncated series expansions for the partition function and pressure of a hard disk fluid. The expansion parameter is $\alpha = (a - a_0)/a_0$ where a is the area per molecule and a_0 its value at closest packing. The steric effects due to the lateral extension of a chain after isomeric bond rotation are treated by a method motivated by scaled particle theory. The increase Δa in chain area is taken to be proportional to the distance of the first gauche bond from the head group, and for each isomer a term $P\Delta a$ is added to the energy, where P is equal to the pressure in the hard-disk system. A term corresponding to the energy of the trans-gauche rotations is also included. Marcelja¹²⁶ used a self-consistent mean-field method in which each chain takes up various configurations in a mean field. The latter describes the dispersive or van der Waals interactions of the chain with its neighbors and depends on an order parameter which is proportional to the average over all chains of a function of the bond angles. The area occupied by an isomeric chain of length L is assumed to be $a_0 L_0/L$ where a_0 and L_0 are the area and chain length, respectively, in the all-trans close-packed state. March¹²⁷ assumes that any given chain's proximity to other chains permits only a limited number of bond-type sequences. With this restriction the statistics of a single chain are treated accurately by a matrix method. The van der Waals energy term is calculated by

regarding the head groups as arranged on a plane triangular lattice and adding interactions up to third neighbors.

Kimura and Nakono¹²⁹ developed a theory of chain disordering which they applied to the melting of n -alkane crystals as well as to bilayer behavior. Unlike the authors just discussed, they incorporated chain orientational effects as well as bond rotation isomerism into their model. The chain-pair Hamiltonian assumed is (with slightly simplified notation)

$$-C\sigma\sigma'P_2(\cos\phi) \quad (22)$$

Here C is a function of the interchain distance, σ and σ' are factors depending respectively on the configurations of the two chains, P_2 is the Lagrange polynomial of order two, and ϕ is the angle between the long axes of the molecules. The mean-field formulation used is based on an orientational order parameter and another order parameter representing the average vertical extension of the chains. Experimental and theoretical values for transition temperatures and entropies of transition are compared for first-order phase changes in n -alkanes and lipid bilayers.

Scott and Cheng^{130a} have developed Scott's monolayer model¹²³ (discussed above) by incorporating head-group effects. The head-group and surface-water interactions are treated by a cell-lattice model similar to that used by Scott¹²³ for chain interactions. These authors regard the chains and head groups as quasi-independent, and the surface-pressure/area isotherm for the monolayer is obtained by adding the pressure of the chain assembly to an entropic term which represents the change in water surface tension due to the presence of the head groups in the surface layer. In this theory the head-group term is a continuous function of the area per molecule while the chain term has the horizontal segment parallel to the area axis which corresponds to the first-order phase change in Scott's previous theory.¹²³ This horizontal portion results from applying the Maxwell construction to the van der Waals loop in the chain pressure. Hence the sum of the two terms has a nonzero slope everywhere, and each first-order transition in the previous theory is replaced by a pair of slope discontinuities at densities corresponding to the end points of the horizontal segment. The discontinuity at the lower density is regarded as corresponding to the liquid-expanded/liquid-condensed transition while the other one occurs at too high a surface pressure to be seen on the diagrams. However it should be noted that if, as would seem more reasonable, the Maxwell construction were applied *after* the summing of the chain pressure and the head-group term, quite different results would be obtained. Depending on the relative magnitudes and slopes of the two terms, either the original first-order phase change would be shifted or it would disappear without giving rise to slope discontinuities.

Nagle and Scott^{130b} have discussed membrane permeability from both thermodynamic and model considerations. Permeability depends on the availability of "holes" in the membrane and thus on the size of fluctuations in monolayer area per molecule if the membrane bilayer is regarded as two "back to back" monolayers. Since the mean square area fluctuation is proportional to the lateral isothermal compressibility K_T , these authors take the permeability itself to be

proportional to K_T . They derive plots of K_T from both Nagle's statistical mechanical theory^{14,117} and Scott's,¹²³

Albrecht et al.^{130c} envisage a phase diagram for phospholipid monolayers at the air/water interface which is far more complex than the usual picture presented in Figure 1. They present experimental data including isotherms (which seem to be of the standard type), isobars, lateral compressibilities, expansion coefficients, and heats of transition. Four phases are postulated which in order of increasing density are (I) fluid, (II) anisotropic fluid (ordered in the sense that the lateral projections of the chains tend to parallelism), (III) crystalline with tilted chains, and (IV) crystalline nontilted. The "main" II-III transition, which corresponds to the experimental liquid condensed-liquid expanded transition, is first order at lower temperatures but changes to second order at a tricritical point. Besides the "main" and the liquid-vapor transition there are second order I-II and III-IV transitions. These authors base the first-order nature of the II-III transition on the hysteresis observed with L- α -dipalmitoyllecithin isobars. However they state that the II-III transition portion M_1M_2 of an isotherm in the surface pressure-area plane is "straight but not horizontal". This is not compatible with a first-order transition because if M_1 and M_2 correspond to conjugate phases they must be at the same pressure, and hence M_1M_2 must be horizontal. As they make a similar remark about the corresponding portion $M_1'M_2'$ of an isobar in the temperature-area plane, there must be some doubt about their interpretation of the nature of the transition. Albrecht et al. discuss the transitions in their phase diagram in terms of a Landau-type mean field theory. They regard the monolayer states as characterized by a density ρ and a "stretching vector" J , which is ρ multiplied by the mean vector distance between adjacent carbons in a chain. Their order variables for the "main" transition are $\rho_{III}-\rho_{II}$ and $\phi_{III}-\phi_{II}$ where ϕ is the angle between J and the normal to the surface.

VII. Lattice Gas Models and Their Applications to Monolayers

The lattice gas was introduced in 1952 by Yang and Lee to describe the phenomenon of condensation. The statistical theory of lattice fluids is a very well developed subject, the fundamentals of which are outlined in many texts on statistical thermodynamics. We will give here some essential definitions, and in doing so we will also introduce the concept of a diluted monomer-polymer model. Dilution with a neutral component enables a description to be given of the expansion and compression of a monolayer.

Exact treatments of lattice fluids are only possible for one-dimensional systems. We will now consider a lattice of N_s sites in one dimension and assume cyclic boundary conditions. We refer the reader to several publications for rigorous discussion of the methods of lattice statistics. For M molecules occupying N_s sites, the canonical partition function is given by

$$Q(M, T, N_s) = \sum_{\substack{\text{all} \\ \text{config-} \\ \text{urations}}} \exp(-\beta E_c) \quad (23)$$

where E_c is the configurational interaction energy. Bell

and Dunne¹³¹ studied a one-dimensional lattice fluid of length L by working with the constant pressure partition function $\Omega(M, T, p)$ obtained as the Laplace transform of $Q(M, T, N)$, where p is the one-dimensional pressure corresponding to the experimental surface pressure. Thus we have

$$\Omega(M, T, p) = \sum_L \sum_{\substack{\text{config-} \\ \text{urations}}} \exp(-\beta(E_c + pL)) \quad (24)$$

For an assembly of several species on a ring (cyclic boundary conditions) a configuration $(\alpha, \beta, \gamma, \delta \dots \omega, \alpha)$ contributes a term to the constant pressure partition function which can be written as a product of M factors:

$$A_{\alpha\beta}A_{\beta\gamma}A_{\gamma\delta} \dots A_{\omega\alpha} \quad (25)$$

The elements $A_{\mu\nu}$ involve energy and pressure terms. The essence of the matrix method is that the required partition function $\Omega(T, M, p)$ can be derived as a power of the largest eigenvalue of a square matrix A . Hence for large M ,

$$\Omega(T, M, p) = \text{trace } A = \lambda_1^M + \lambda_2^M + \lambda_3^M \dots \sim \lambda_{\max}^M \quad (26)$$

Here $\lambda_1, \lambda_2, \lambda_3$ are the eigenvalues of the matrix A and λ_{\max} is the largest of these. The required partition function having been evaluated, macroscopic thermodynamic quantities may be obtained according to the usual principles of statistical thermodynamics.

Lattice-gas systems have been studied by approximate methods and by formally exact methods such as the series expansion approach of Gaunt and Fisher¹³² and the exact finite method (EFM) of Runnels¹³³ with applications by Runnels and Combs,¹³⁴ Runnels, Combs, and Salvant,¹³⁵ Casey and Runnels,¹³⁶ Runnels, Salvant, and Streiffer,¹³⁷ and Runnels, Craig, and Streiffer.¹³⁸ The heart of the EFM is the matrix approach to the grand ensemble partition function which will now be outlined.

Consider M molecules on a two-dimensional lattice of L rows with each row containing N_s sites. Let Ψ_i be the possible state or arrangement of a ring of N_s sites with $1 \leq i \leq d(n)$ where $d(n)$ is the total number of arrangements possible for a ring of N_s sites. Thus the states Ψ_i take into account horizontal interactions. Vertical interactions are specified by a matrix with elements ϵ_{ij} , where $\epsilon_{ij} = 1$ if row i is compatible with Ψ_j on row 2 and otherwise $\epsilon_{ij} = 0$. To include the activity $Z = \exp(\mu/kT)$, one defines the matrix elements

$$P_{ij} = \epsilon_{ij} Z^{(m_i + m_j)/2} \quad (27)$$

where m_i is the number of molecules in Ψ_i ($0 \leq m_i \leq 1/2 N_s$). The essence of the matrix method is that

$$\sum_{i,j} Z^{1/2 m_i} (P^{L-1})_{ij} Z^{1/2 m_j} = \sum_M \Omega(N_s, M) Z^M = \Xi(N_s, Z) \quad (28)$$

where $\Omega(N_s, M)$ is the number of arrangements of M molecules on N_s sites (canonical partition function) and Ξ is the grand partition function which contains all thermodynamic information through

$$\Xi = \exp(pN_s/kT) \quad (29)$$

where p is the pressure in units of energy, and

$$N_s \rho = \langle M \rangle = Z \frac{\partial \ln \Xi}{\partial Z} \quad (30)$$

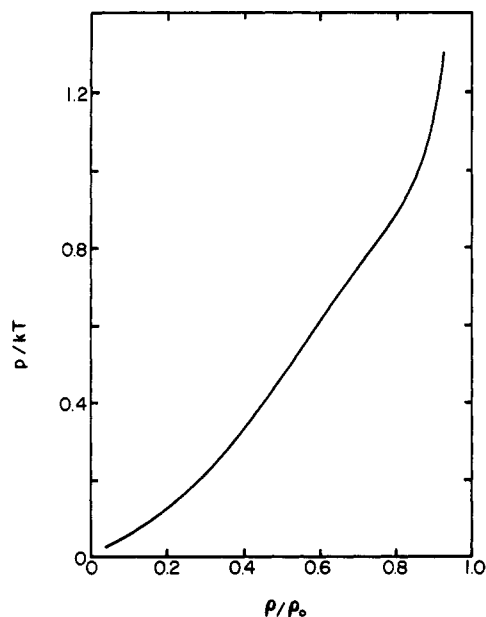


Figure 15. Equation of state for the square lattice gas of lattice width 14 (adapted from *J. Chem. Phys.*, 1966, 45, 2482, by permission).

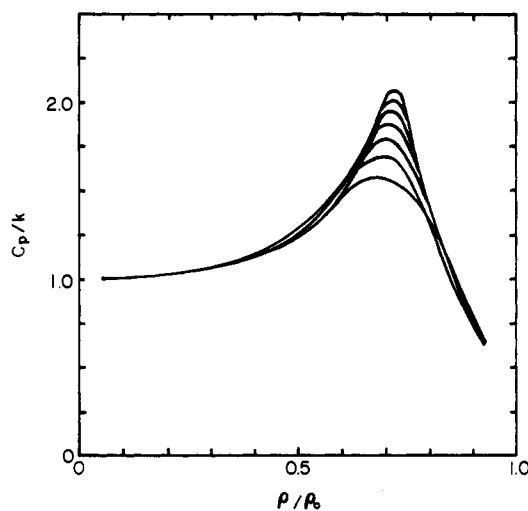


Figure 16. Compressibility of the square lattice gas for even values of lattice width from 6 to 18 (adapted from *J. Chem. Phys.*, 1966, 45, 2483, by permission).

(ρ is the dimensionless number density) augmented by the universal relationships of thermodynamics. The utility of the matrix formulation is the asymptotic relationship

$$\ln \Xi \rightarrow L \ln [\lambda_1(N_s; Z)], L \rightarrow \infty \quad (31)$$

where $\lambda_1(N_s; Z)$ is the largest eigenvalue of P as defined by equation 27. One then sets up P for various lattice widths, determines the largest eigenvalue of P (the Kramers-Wannier transfer matrix), calculates the required thermodynamic properties, and then extrapolates to infinite lattice width. Thus the square lattice, the triangular lattice, and the honeycomb lattice have been studied over the entire density range.

The equation of state for the square lattice gas with $N_s = 14$ is given in Figure 15, and the constant-pressure specific heats for even values of N_s from 6 to 18 are given in Figure 16. The equation of state for the triangular lattice is given in Figure 17, and the heat capacities are given in Figure 18. The transition is obvious in these plots, and extrapolations indicate that

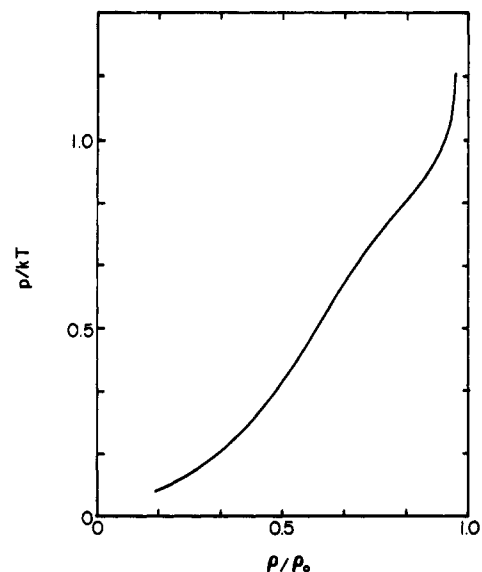


Figure 17. Equation of state for the triangular lattice gas of lattice width 12 (adapted from *J. Chem. Phys.*, 1966, 45, 2483, by permission).

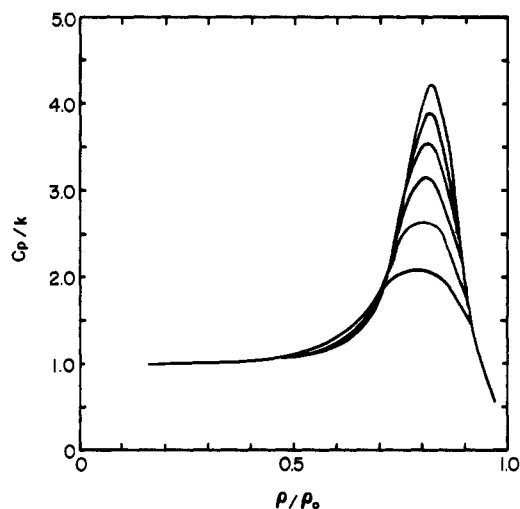


Figure 18. Compressibility of the triangular lattice gas for lattice widths of 6, 9, 12, 15, 18, 21 (adapted from *J. Chem. Phys.*, 1966, 45, 2483, by permission).

they are indeed continuous rather than first order. The transition is more pronounced in the triangular lattice (a close-packed lattice) with the transition in the triangular system occurring at a relative density of 0.742 and at 0.837 for the square lattice. The honeycomb-lattice gas behavior is more like the square lattice than the triangular lattice with a continuous transition occurring at a relative density of 0.845. Upon reflection, such models are excellent for monolayers of rigid asymmetric molecules.

Casey and Runnels¹³⁶ investigated the effect of non-spherical molecular shape on the thermodynamic properties of a dense system of molecules. Their model was a one-dimensional lattice with each site occupied by a square which was allowed to rotate about its center with the only interaction being the (infinitely) hard-core potential. The canonical ensemble partition function is

$$Q(N, L, T) = \Lambda^{-N} \int_{-\pi/4}^{\pi/4} \dots \int_{-\pi/4}^{\pi/4} \exp(-\epsilon/kT) d\phi_1 \dots d\phi_N \quad (32)$$

where $\Lambda = h/(2\pi I kT)^{1/2}$ and I is the moment of inertia with $\epsilon = \infty$ if any molecules overlap. The square edge is set equal to 1 and the lattice separation is $a = L/N$, where L is the length of the system and N is the number of molecules. They study various forms for the orientation-dependent part of the interaction, from none to harmonic to delta function (or lattice model). The lattice model gives rise to a particular sort of first-order phase transition which they discuss in depth due to its unusual nature. They comment that rotational contributions are seen to be quite significant to the total pressure and thermal properties and that they expect the rotational contributions to be most dramatic under conditions which render molecular rotation neither very unlikely nor very easy. It is most interesting that such observations also hold for monomer models. Bell and Salt¹³⁹ also considered a one-dimensional system of orientable molecules, their motive being to obtain an exactly solvable system which would show some of the anomalous properties of water. Each molecule was allowed two orientations: one with one lattice site occupied and the other occupying two sites. The interaction energies favored the "dimer" state, thus creating the low-energy open structure characteristic of water which is stable at low pressures and temperatures. As in the standard lattice fluid, the density depends on the number of vacant sites. They used a matrix method similar to that discussed above except that the constant pressure partition function was replaced by the grand partition function. For appropriate parameter values the isobars below a characteristic pressure displayed a density maximum and the other waterlike property of a compressibility minimum is also forecast. By use of an "open-ended" linear lattice rather than a ring, boundary properties were investigated. This paper foreshadowed some of the work discussed later in this section and in the next in which two-site occupation represents laterally extended chain states. It is of particular interest in relation to the bipolar monolayers which have anomalous thermal properties similar to those of water (see section VIII). Lavis¹⁴⁰ applied a method similar to the EFM to a two-dimensional waterlike model on the triangular lattice. In this model each molecule has three "bonding arms" at angles of 120° to each other, and hydrogen bonding is simulated in two dimensions to create a low-energy open structure in which one-third of the sites are unoccupied (Bell and Lavis¹⁴¹). Lavis again found anomalous properties and also discussed the relevance of his results to phase changes as well as boundary behavior.

Runnels, Salvant, and Streiffer¹³⁷ studied a lattice model consisting of symmetric molecules with infinite repulsion at the first-neighbor distance and finite interaction (attractive or repulsive) at the second-neighbor distance. They observed at all temperatures studied a single first-order phase transition for attractive interactions at sufficiently low temperatures. The addition of the attractive interactions did not lead to a liquidlike phase but rather the transition is representative of a solid-gas transition since the model precludes clustering of three molecules with all interactions attractive and thus leads to a third virial coefficient which remains unrealistically positive at all temperatures.

Runnels, Craig, and Streiffer¹³⁸ have also studied the preceding arrangement for a triangular lattice gas. The molecules have hard cores which exclude other mole-

cules from the first- and second-neighbor positions. For third-neighbor distances, an interaction term (attractive or repulsive) is also included. A first-order phase transition is observed at all temperatures with an attractive third-neighbor term, with the transition being more intense at the lower temperatures. Again, no liquidlike phase is observed.

In the hope of obtaining separate "melting" and vapor/liquid transitions, Kaye and Burley¹⁴² investigated a plane-square-lattice model with first-neighbor exclusion and a much longer range attractive interaction than in the models discussed above. This extends up to ninth-neighbor distance. They used a high-order Kikuchi method of approach to the problem and solved the resulting equations by numerical methods (COFE). Isotherms are obtained which display both a first-order vapor/liquid transition and, at higher density, a slope discontinuity which represents a transition to a long-range ordered state in which one of the two equivalent sublattices is preferentially occupied. At lower temperatures the two transitions degenerate into a single first-order transition while at higher temperatures only the continuous transition remains. The phase behavior is thus similar to that of a lipid monolayer at the air/water interface, and this resemblance is discussed by the authors at the end of their paper. However, it is found in lattice fluid models that a transition which is continuous when the hard core is represented by first-neighbor exclusion becomes a first-order melting transition when the exclusion is extended to second or further neighbors (Runnels¹⁴⁴). Kaye and Burley¹⁴² regard the first-neighbor exclusion as constituting molecular "roughness" corresponding to Kirkwood's orientation interaction between close-packed molecules. This is not easy to understand since their model contains no mechanism for molecular orientation. Nevertheless, their results are significant since they show that air/water interface monolayer behavior can result from the combination of an attractive interaction with a mechanism (in this case first-neighbor exclusion) giving rise to long-range ordering. This theme is taken up in the work of Bell, Mingins, and Taylor¹¹⁸ (BMT).

The BMT theory was developed to describe second-order phase changes at both the air/water and the oil/water interfaces. It is supposed that the amphipathic molecules can be in one of two possible orientational states, labeled 1 and 2, respectively. The 11 and 22 pairs have an interaction energy $-(\epsilon + J)$ while unlike 12 pairs have an interaction energy $-\epsilon + J$ ($J > 0$). BMT use a first-order statistical approximation in which the number of configurations on a lattice with coordination number Z for a given set of species numbers $\{N_i\}$ and pair numbers $\{N_{ij}\}$ is given by

$$g = \left(\frac{N_1! N_2! N_h!}{N!} \right)^{Z-1} \frac{(\frac{1}{2}ZN)!}{N_{11}! N_{22}! N_h! (\frac{1}{2}N_{12})! (\frac{1}{2}N_{1h})! (\frac{1}{2}N_{2h})!} \quad (33)$$

The configurational free energy is given as

$$F_c = (N_{12} - N_{11} - N_{22})J - (N_{12} + N_{11} + N_{22})\epsilon - kT \ln g \quad (34)$$

Two ordering parameters S and U are defined where

$$S = (N_2/N_1)^{1/Z} = (N_{22}/N_{11})^{1/[2(Z-1)]} \quad (35)$$

The last relation results from minimization with respect to N_2 for a given number of molecules $N_1 + N_2$, while

$$U^2 = N_{hh}/N_{11} \quad (36)$$

Two Boltzmann factors η and ξ are defined by

$$\begin{aligned} \eta &= \exp(-2J/kT), \\ \xi &= \exp(-\frac{1}{2}(\epsilon + J)/kT) \end{aligned} \quad (37)$$

BMT show that the equilibrium relations for the system may be expressed in the form

$$\begin{aligned} N_{12} &= 2\eta S^{Z-1}N_{11}, & N_{1h} &= 2\xi UN_{11}, \\ N_{2h} &= 2\xi S^{Z-1}UN_{11} \end{aligned} \quad (38)$$

which may be solved both in the ordered and disordered phases. The surface pressure π and configurational chemical potential μ_c are given by

$$\pi = \frac{ZkT}{2a_0} \ln \left[\frac{U + \xi(1 + S^{Z-1})}{U} \right] + \frac{kT}{a_0} (\frac{1}{2}Z - 1) \ln(1 - \rho) \quad (39)$$

$$\mu_c = kT \left[(Z - 1) \ln \frac{(1 - \rho)(1 + S^Z)}{\rho} - Z \ln(U/\xi) \right] \quad (40)$$

As the surface density of a monolayer of amphipathic molecules decreases from a value corresponding to close packing, three main mechanisms of disordering can be identified; these are (i) disorientation, where the associated energy may include head group as well as chain terms; (ii) chain bending (isomerism) leading to lateral extension; (iii) the creation of free area, which in lattice fluid terms means an increase in the number of vacant sites or "holes". In the work of Nagle and the authors who have used similar models to his, discussed in section VI, mechanisms ii and iii are taken into account but mechanism i is disregarded. On the other hand BMT have based their theory on (i) and (iii) but have disregarded (ii). This neglect is, of course, a defect in their theory. Again, their treatment of relative orientation, which is based on the simplest possible model (i.e., that of Ising), must represent a drastic simplification of the interaction of amphipathic molecules. However, in spite of the crudity of the BMT model, results indicate that it may represent some of the essential physical factors in the situation.

BMT calculated the theoretical surface-pressure/area isotherms given in Figure 19 to correspond with the experimental isotherms for a phospholipid at the interface between oil (*n*-heptane) and a weak aqueous salt solution which are shown in Figure 20. For each theoretical isotherm the values of ϵ and J were adjusted to make the transition point coincide with the experimental one for that temperature. The values of ϵ are repulsive (i.e., negative in BMT's convention), which can be explained physically by the immersion of the hydrocarbon chains in a hydrocarbon medium neutralizing the usual attractive dispersion forces. The magnitude of ϵ in each instance is considerably greater than that of J and, together with the sign of ϵ , this

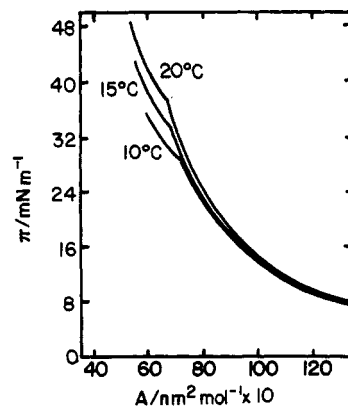


Figure 19. Theoretical surface pressure against A isotherms for di-C₁₆-lecithin at the *n*-heptane/water interface. (Reproduced from *J. Chem. Soc., Faraday Trans. 2*, 1978, 74, 223, by permission. Copyright 1978, The Chemical Society.)

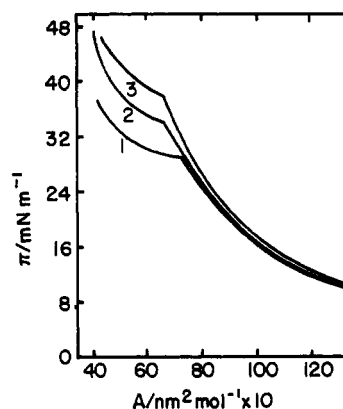


Figure 20. Surface pressure against A isotherms for di-C₁₆-lecithin monolayers at the *n*-heptane/aqueous NaCl interface. Concentration of NaCl = 0.01 mol dm⁻³. Monolayers are spread from *n*-heptane + ethanol mixtures. (1) 10 °C, (2) 15 °C, (3) 20 °C. (Reproduced from *J. Chem. Soc., Faraday Trans. 2*, 1978, 74, 223, with permission. Copyright 1978, The Chemical Society.)

explains why liquid-vapor transitions are absent from the theoretical isotherms, just as they are experimentally. The variation in ϵ and J is large in relation to the small temperature interval, suggesting that these parameters should be regarded as free energies. The theoretical isotherms have greater slopes than the observed ones, which may be due to the absence of laterally extended states in the model.

BMT showed that with positive (attractive) values of ϵ , phase behavior qualitatively similar to that of monolayers at the air/water interface, with liquid/vapor transitions in addition to the continuous ones, is obtained. Dunne and Combs¹⁰⁶ have recently considered this correspondence in greater detail with reference to comparatively simple molecules such as myristic acid. Figure 21 shows π/A curves calculated, using BMT theory with $Z = 3$ and $a_0 = 17.72 \text{ \AA}^2$, for some simple aliphatic carboxylic acids assuming an interaction energy of 0.418 kJ/mol per pair of methylene groups for molecules in like orientational states and zero otherwise (i.e., $\epsilon = J$). It is also assumed that the first four methylene groups in each chain are in some way screened from each other and are hence noninteracting. This may be a substrate effect. Dunne and Combs compared the predictions of the lattice model with approximate intermolecular force calculations for CH₃(CH₂)₁₁CO₂H pairs, using the PCILO method. The

size of the molecules places a limitation on the ability to calculate intermolecular forces between pairs of long lipid chains. Hence they proceeded by making an approximate energy decomposition. It was supposed that the interaction energy is decomposable into the sum of the interactions between (a) two long paraffin chains and (b) two short fatty acid molecules without appreciable error. Figure 11 (intermolecular forces section) shows the potential-energy curves calculated according to such a scheme for $\text{CH}_3(\text{CH}_2)_{12}\text{CO}_2\text{H}$ molecules. These figures compare favorably with those giving the best results for the BMT model.

In the BMT theory the continuous liquid-expanded/liquid-condensed transitions are regarded as due to the onset of orientational ordering. Dunne and Bell¹⁴³ also regard these transitions as primarily orientational but attempt to incorporate the chain-flexibility effect neglected by BMT into the theory in a simple way. Since the isomers formed by bond rotation are laterally extended, Dunne and Bell assume an additional dimer state in which a molecule occupies a nearest-neighbor pair of sites. Relative to the "monomer" state each molecule in the dimer state requires an additional free energy

$$-(u_0 + \alpha kT) \quad (41)$$

$-u_0$ being an energy term and αk an entropy. For monopolar molecules $u_0 < 0$ due to the energy required for trans-gauche rotation and $\alpha > 0$ due to the multiplicity of possible isomers. If the numbers of molecules in orientational states 1 and 2 are denoted by N_1 and N_2 , the number in the extended state by N_d , and the number of holes by N_h , then

$$N_1 + N_2 + N_d = M \quad (42)$$

$$N_1 + N_2 + 2N_d + N_h = N_s \quad (43)$$

where M and N_s denote the numbers of molecules and lattice sites, respectively. Since the model is rather more complicated than BMT a zero-order (Flory-Huggins) statistical approximation was used in which the number of lattice arrangements for given species numbers is

$$\Omega = \left(\frac{Z}{\lambda N_s} \right)^{N_d} \frac{N_s!}{N_d! N_1! N_2! N_h!} \quad (44)$$

where λ is a symmetry factor. The free energy can now be written as

$$F_c = -kT(\ln \Omega + N_d \alpha) - N_d u_0 + E_c \quad (45)$$

where E_c is the configurational energy. The latter is calculated by using randomization assumptions and, as well as the BMT parameters, depends on interaction energies ϵ_{dd} and ϵ_{md} for nearest-neighbor pairs consisting respectively of segments of two different dimers and a monomer and a dimer segment. For given M and N_s it is necessary to minimize F_c with respect to internal parameters to obtain the equilibrium state. Dunne and Bell chose the ordering parameters

$$\begin{aligned} s &= (N_1 + N_2)/M, \\ \sigma &= (N_1 - N_2)/(N_1 + N_2) \end{aligned} \quad (46)$$

but this is not a unique choice. The pressure and configurational chemical potential are now given by

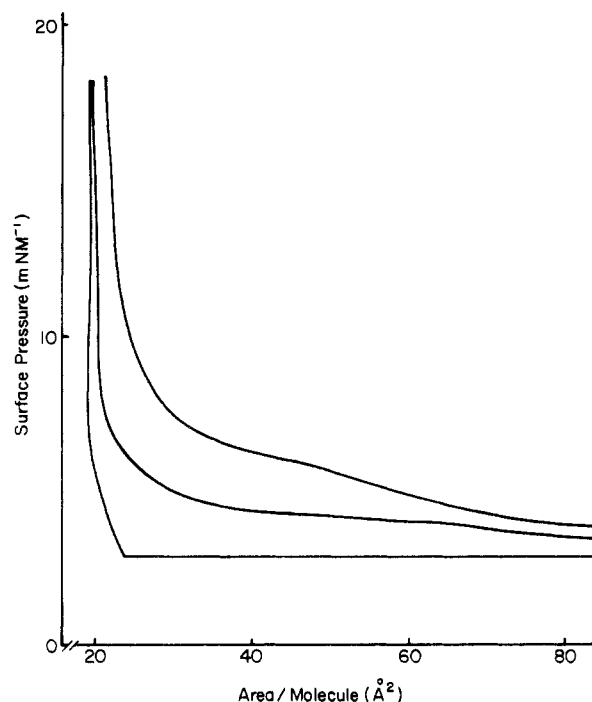


Figure 21. Theoretical surface pressure/area curves for monolayers of $\text{CH}_3(\text{CH}_2)_{12}\text{CO}_2\text{H}$, $\text{HC}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$, and $\text{CH}_3(\text{CH}_2)_{16}\text{CO}_2\text{H}$, bottom to top, on a water substrate at 298 K, pH 2, using the Bell-Mingins-Taylor model.

$$\pi a_0 = -(\partial F_c / \partial N_s)_M, \quad \mu_c = (\partial F_c / \partial M)_{N_s} \quad (47)$$

Like the assumptions behind the original BMT theory, the "dimer" representation of the isomeric states is undoubtedly a crude approximation. However it does incorporate into the model, even if in a highly "course-grained" manner, another important physical effect which is certainly operative in real monolayers. The resulting orientable monomer-dimer hole model can be used to discuss the behavior of a wide variety of monolayers. Dunne and Bell considered it in relation to a series of hydroxyhexadecanoic acid isomers, but since these represent a progression from monopolar to bipolar structure they are discussed in the next section. Dunne, Bell, and Combs¹⁰⁷ have used the model to calculate theoretical π/A curves for some simple long-chain carboxylic acids. They assumed that 1-1 or 2-2 pairs interact with an attractive energy of 0.375 kJ/mol per active methyl group, that 1-2 pairs have effectively zero interaction energy, and that ϵ_{md} and ϵ_{dd} are likewise zero. They took $Z = 3$ and α_0 was put equal to 24 \AA^2 . The best results were obtained by assuming that the "dimers" were asymmetrical ($\lambda = 1$) and correspond to one trans-gauche rotation with $-u_0$ equal to 2.3 kJ/mol. The entropy term α is thus equal to $\ln L$ where L is the number of links in the chain. To reproduce the chain length dependence it is essential, as in the corresponding work on the BMT model, to assume that the first four methylene groups are "screened", by immersion or some other mechanism, and make no contribution to the interaction energy. Figure 22 shows isotherms calculated for myristic acid ($\text{C}_{13}\text{H}_{22}\text{CO}_2\text{H}$). The transition points fall roughly within the observed pressure/area range, but the vapor pressures are too high. The latter seems to be a characteristic defect either of the model or the method of approximation used. Figure 23 shows isotherms for various chain

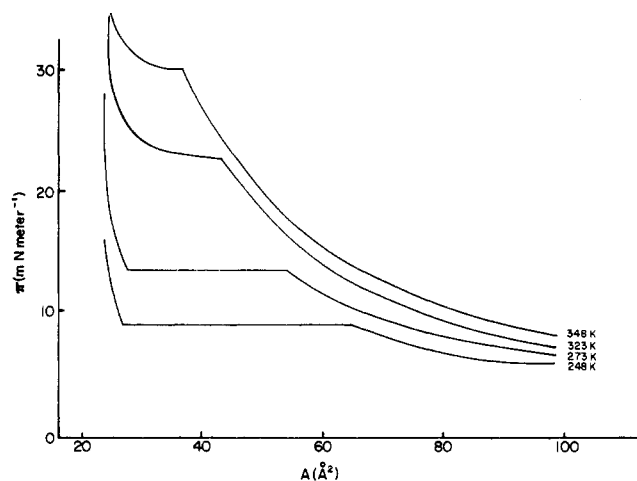


Figure 22. Theoretical π/A diagrams for myristic acid spread on 0.01 N HCl at various temperatures.

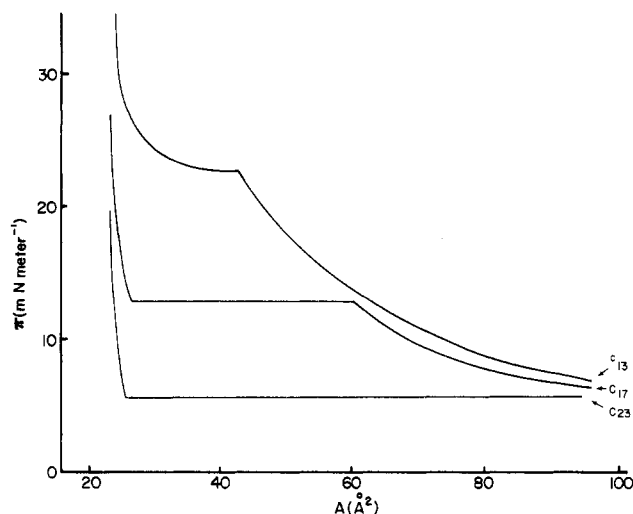


Figure 23. Theoretical π/A diagrams for various chain length aliphatic carboxylic acids spread on 0.01 N HCl.

lengths calculated at 323 K and gives at least the right qualitative dependence. Note that if the interaction energy has the postulated dependence on the number of chain links, then the relevant Boltzmann factor will depend on a quantity

$$(\text{constant} + L\delta)/T, \quad \delta = \text{constant} \quad (48)$$

and hence an *increase* in chain length will have a similar effect to a *decrease* in temperature.

A puzzling feature of the work reported above is that order of magnitude agreement with experiment is obtained by putting $z = 3$ (plane honeycomb lattice) rather than $z = 6$ (plane triangular lattice), although experimental results for bilayers indicate $z = 6$. This may reflect the fact that the liquid condensed-liquid expanded transitions in fatty acid monolayers occur at areas up to twice as great as the minimum area (see Figure 3). On the other hand, the observed bilayers are close packed.

We may mention some work (Dunne and Bell, unpublished) on mixed monolayers treated within a mean field approximation. Pairs of molecules of a two-component mixture were considered and were treated as in the BMT model with favorable like orientational states and unfavorable unlike orientational states. Details of the models are to appear in full elsewhere. Figure 24

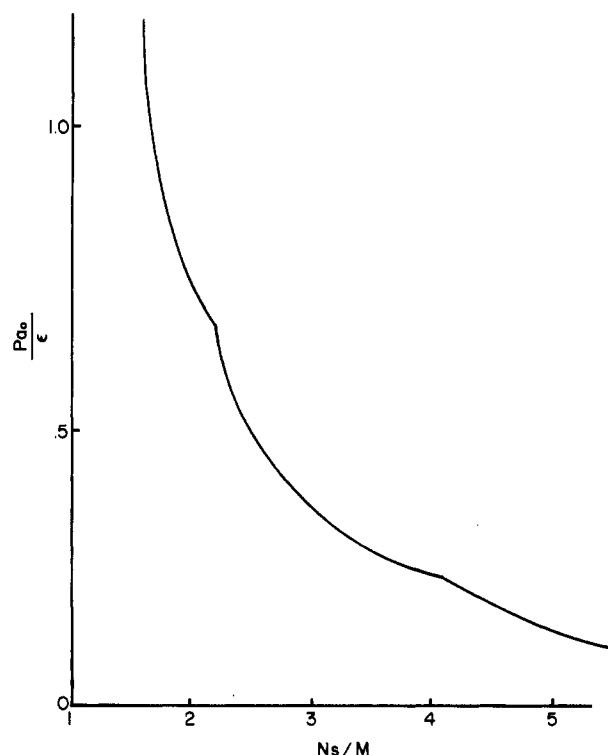


Figure 24. Theoretical isotherm of reduced surface pressure against the reduced area per molecule (Dunne and Bell, unpublished).

shows a π/A curve which exhibits two kink points and which resembles the dual transitions found for monolayers of mixtures of phospholipids at the heptane/water interface. Clearly much has to be done to improve the statistical treatment of such mixtures, but the qualitative results seem promising.

Several papers have recently appeared on two-dimensional lattice-fluid models with molecules each occupying p sites ($p > 1$) on a plane square lattice. Since the p -mers are regarded as rigid the molecules have two distinguishable orientations on the lattice. Boehme and Martire^{143a} postulate in addition an erect state with the molecule occupying one site only and assume an interaction energy w for each nearest-neighbor pair of lattice sites occupied by segments of different molecules. They give a randomized expression for the assembly interaction energy but point out certain inconsistencies. There is also an adsorption energy ϵ' per occupied lattice site, and a free energy is constructed using a configuration number formula due to Di Marzio.^{143b} Adsorption isotherms and surface pressure-area isotherms, some of which have a plateau form, are obtained and first-order transitions appear for some parameter values. Boehme and Martire remark that "the prediction of equilibrium phase separation for adsorbed rigid rods with attractive interactions is the most significant feature of the present work".

Firpo et al.^{143c} use a simplified version of the above model to discuss monolayer properties. In their theory there is no erect state, and all molecules occupy p sites on the plane square lattice. They use a van der Waals type interaction energy

$$p(p+1)\epsilon M^2/N_s \quad (48a)$$

which assumes the correct value $(p+1)M\epsilon$ when the lattice is completely occupied by p -mers and thus pM

$= N_s$. To obtain the free energy this expression is used in conjunction with the formula, due to Di Marzio,^{144b}

$$\frac{[N_s - (p - 1)N_1]![N_s - (p - 1)N_2]!}{N_h!N_1!N_2!N_s!} \quad (48b)$$

for the configuration number. Here N_1 and N_2 respectively are the numbers of p -mers in the two orientational states. Firpo et al. are interested in transitions from the low-density state where $N_1 = N_2$ to orientationally ordered states with $N_1 \neq N_2$ and they identify these with the experimental liquid condensed-liquid expanded transitions. Since the interaction energy is independent of the ratio N_1/N_2 , it assumes a constant value at closest packing. In these circumstances it is known¹¹⁸ that for the close-packed dimer ($p = 2$) case there is no transition, and it is therefore unlikely that transitions occur when the dimers are diluted with holes. The results of Firpo et al. are in agreement with this, but they do find orientational transitions at closest packing for $p = 3$ and in diluted systems for $p = 4$. In the latter case, transitions from orientationally ordered states occur as the monolayer density is decreased and are first-order at lower temperatures but second-order above a tricritical point. Vapor-liquid transitions occur at lower densities, and the authors note that the corresponding critical indices agree well with those found experimentally by Kim and Cannel.^{8,9} This, however, is not surprising since any mean-field or closed-form approximation gives "classical" values¹⁷ for the indexes and the results of Kim and Cannel are close to the latter. For $p = 5$ the orientational and vapor-liquid transitions degenerate into a single first-order transition. For low monolayer densities the approach of Firpo et al. is in agreement with that of Pethica et al.^{143d} who deduce by comparison of experimental and theoretical second virial coefficients that the carbon chains are extended along the water surface at high dilutions. However from monolayer area data alone this can hardly be the case at high densities, and the omission of an erect state is an unrealistic feature of the theory of Firpo et al. Again, it is unlikely that any orientational transition is entirely steric in nature since both dispersion and head-group dipolar interactions are orientation dependent. Also, in spite of the views of Albrecht et al. (see section VI), we are not convinced that there is sufficient experimental evidence for the existence of a tricritical point.

D'León and Moreau^{143e} use the same model as Firpo et al. and expression 48b for the coordination number. However, instead of (48a), they use a special case of the formula of Boehme and Martire for the interaction energy. It can be verified that in the close-packed state this depends on the ratio N_1/N_2 , which is contrary to these authors' basic assumption that the interaction energy is proportional to the mean number of "common sides" (nearest-neighbor segment-segment pairs). D'Leon and Moreau are chiefly interested in the correspondence between the theoretical values of the critical indices for the vapor-liquid transition and the experimental results of Kim and Cannel.^{8,9} Our comment about Firpo et al. in this context also applies here.

A very recent study by Kaye¹⁴⁴ is based on a model which resembles that of Firpo et al., but there are some important differences in Kaye's treatment. He considers only the case $p = 2$ (dimers) and assumes dif-

ferent energies of interaction between segments of parallel and perpendicular pairs of molecules, the values being such as to promote parallel alignment. Also he uses a more accurate statistical method of a high-order cluster variation (Kikuchi) type. Continuous orientational transitions, leading to slope discontinuities in the surface pressure-area isotherms, are found. For appropriate parameter values there are also vapor-liquid transitions in the lower temperature range. Kaye considers that his theory is preferable to that of BMT since it provides a "natural basis" for orientationally dependent interactions. Certainly an asymmetrical cross section seems justified for phospholipid molecules, even with erect chains, but this hardly applies to the simpler fatty acids which have very similar monolayer phase properties. There is no orientational transition for dimers unless the appropriate assumptions are made about the interaction energies, and this seems no less "arbitrary" than BMT's Ising interaction. The ratio of vapor pressure to continuous transition pressure is much lower in Kaye's results than in BMT's, which is a considerable improvement. On the other hand the surface pressure and its slope approach finite values in the close-packing limit in Kaye's case, and this does not correspond to experiment, where the slope magnitudes become very large at high densities unless film collapse occurs. All the "orientable p -mer" theories described use the plane square lattice, and it would be interesting to have corresponding results for a triangular lattice, where there would be three distinguishable orientations instead of two.

VIII. Monolayers of Bipolar Molecules and Thermal Anomalies

A "bipolar" molecule is defined as an amphipathic molecule with a polar head group and a second polar group attached to the carbon chain and separated by several links from the head group. Cadenhead and Müller-Landau¹⁴⁵ have observed a number of remarkable thermal anomalies with monolayers of one type of bipolar molecule, that is, long-chain fatty acids or their derivatives with a nitroxide spin-label.

There appear to be three main kinds of thermally anomalous behavior.¹⁴⁶ The first kind is typified by stearic acid 12-nitroxide where, over a range of about 10–50 °C, the normal order of surface-pressure/area isotherms is inverted with each isotherm lying above those corresponding to higher temperatures. Each isotherm has a "plateau" form with a range of reduced slope at areas below about 80 Å²/molecule, the plateau being more pronounced at lower temperatures. In the second kind of behavior, displayed by methyl palmitate 8-nitroxide, isotherm inversion also occurs but the "plateau" form is absent. Each isotherm is convex to the surface-pressure/area axes till a sudden break, apparently caused by film collapse, occurs at an area of about 50 Å². The third kind of behavior, typified by methyl stearate 5-nitroxide, is even more remarkable. Isotherms from 20 to 47 °C are effectively coincident, except in a very small range below 40 Å²/molecule where isotherm inversion occurs. The coincident isotherms are convex to the surface-pressure/area axes. Liquid-expanded/liquid-condensed transitions appear to be absent in the spin-labeled systems, but there are

examples of bipolar monolayers where these transitions occur in conjunction with some degree of isotherm inversion.^{147,148} This situation will be considered later in this section.

In the spin-labeled systems the first and second kinds of behavior referred to above imply that negative thermal expansion occurs over the quite large region of phase space spanned by the inverted isotherms. This negative thermal expansion is attributed by Cadenhead and Müller-Landau^{145,146} to the ability of the nitroxide group to bond to the water, thus putting the molecule into an extended conformation in which it occupies a larger area of the water surface than when bonded to it by the head group alone. Since the water-nitroxide bond is weaker than the water-head group bond, the proportion of molecules in the extended conformation decreases with temperature sufficiently fast to counteract the normal positive thermal expansion. In this interpretation the "driving force" is one molecule in nature from the point of view of the monolayer assembly, but the anomalous behavior is cooperative since it depends on steric effects in a mixture of monolayer molecules with effectively different sizes.

It is well-known that negative thermal expansion occurs in water, though over a relatively smaller region of phase space than in the spin-labeled monolayers. A number of statistical studies have been based on the idea that the anomalous thermal behavior depends on the existence of a lowest energy configuration which occupies more space than configurations of higher energy. A distinct energy gap between the open structure and higher energy structures appears to be necessary to produce the required results (see Bell and Sallouta,¹⁴⁹ Bell and Salt,¹⁵⁰ Lavis and Christau,¹⁵¹ and Southern and Lavis,¹⁵² where references to earlier work are given). In the work reviewed below the same point of view is taken with respect to monolayers, although the physical mechanism underlying the open structure is different from that in water. In bipolar monolayers this mechanism involves the creation of an extended molecular state by double bonding to the substrate whereas in water it is due to intermolecular tetrahedrally directed hydrogen bonds. Incidentally, hydrogen bonding is thought to be responsible for anomalous behavior in monolayers of a rather different chemical type, that is, monodecyl- and hexadecylurea.¹⁵³

Bell and Dunne¹⁹ investigated a one-dimensional model with erect and extended molecular states as well as holes employing the constant pressure partition function defined in eq 24 of the previous section, with p standing for a one-dimensional "surface" pressure. Exact results were derived from the matrix formalism described in the previous section and isotherm inversion is found for suitable parameter values. Subsequently these authors²⁴ considered a similar model which, like the monolayer itself, is two dimensional, and we shall look at this in greater detail.

Bell and Dunne²⁴ suppose that, on the N_s sites of a two-dimensional lattice of coordination number Z , there are N_h vacant sites or "holes", N_m molecules in the upright or "monomer" state occupying one site each, and N_d in the extended or "dimer state", each occupying a nearest-neighbor pair of sites. The dimer state represents molecules which are doubly bound to the substrate. If the number of monolayer molecules is denoted by M , we then have the relations

$$N_m + N_h = M, \quad 2N_d + N_m + N_h = N_s \quad (49)$$

The number density, ρ , and the fraction of sites, ρ_d , occupied by dimers are then given by

$$\rho = M/N_s, \quad \rho_d = 2N_d/N_s \quad (50)$$

The free energy of the dimer state relative to the monomer state is given by eq 41 of the previous section. Since the term $-u_0$ now incorporates the energy of bonding of the second polar (spin-label) group, we take u_0 as positive. It is found that for the region of negative thermal expansion in surface-pressure/area space to be comparable to that observed experimentally it is necessary to take the entropy term α as negative. This is reasonable since the additional bonding to the substrate in the extended (dimer) state must involve a loss of configurational freedom relative to the singly bound (monomer) state.

Bell and Dunne²⁴ first assumed that there are no intermolecular energies so that the behavior of the model depends only on molecular interaction with the substrate and steric effects. Use can then be made of the accurate series expansion methods of Nagle¹⁵⁴ and Gaunt¹⁵⁵ for a lattice incompletely occupied by dimers, suitably modified for the presence of monomers as well as holes. Asterisks are used for quantities connected with the dimer-hole system, and $S^*(N_d, N_s)$ denotes the entropy of N_d dimers on N_s lattice sites. The configurational Helmholtz free energy of the monomer-dimer-hole model can then be expressed as

$$F_c = -N_d(u_0 + \alpha kT) - TS^*(N_d, N_s) \quad (51)$$

$$+ kT[N_h \ln N_h + N_m \ln N_m - (N_s - 2N_d) \ln (N_s - 2N_d)] \quad (52)$$

The last term derives from the entropy of mixing of N_m monomers and N_h holes on the $N_s - 2N_d$ available sites. The fraction of molecules in the extended (dimer) state is determined by the equilibrium relation

$$(\partial F_c / \partial N_d)_{M, N_s} = 0 \quad (53)$$

The surface pressure is obtained from the relation

$$\pi a_0 = - \left(\frac{\partial F_c}{\partial N_s} \right)_M = \pi^*(N_d, N_s) a_0 + kT \ln \frac{1 - \rho_d}{1 - \frac{1}{2}\rho_d - \rho} \quad (54)$$

where a_0 is the area per lattice site, which is assumed constant. The series are expressed in terms of a quantity x which is defined in terms of the chemical potential $\mu^*(\rho_d, T)$ of the dimer-hole system by

$$\exp[\mu^*/(kT)] = x/[1 - (z - 1)x]^2 \quad (55)$$

For the triangular ($z \approx 6$) lattice, Gaunt¹⁵⁵ derives the series

$$\pi^* a_0 = -kT[\ln(1 - 5x) + 2 \ln(1 + 2x)] + kT[-2x^3 + 3x^4 + \dots] \quad (56)$$

where powers of x up to the 10th are given. The logarithmic terms on the right-hand side represent the Bethe method result and the power series correction to it. Gaunt¹⁵⁵ gives similar expressions for the quadratic ($z = 4$) lattice and three-dimensional lattices. Bell and Dunne²⁴ first assumed a value for x from which μ^* and $\pi^* a_0$ immediately follow by eq 55 and 56. The value of ρ_d is then given by the relation

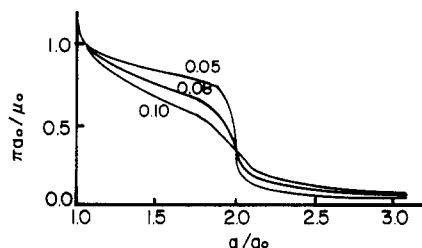


Figure 25. Series method isotherms of reduced surface pressure, $\pi a_0/u_0$, against area, a/a_0 . The curves are labeled with the value kT/u_0 . The entropy constant $\alpha = -4$ (reproduced from *J. Phys. C: Solid State Phys.*, 1979, 12, 4137, by permission).

$$\rho_d = 2a_0(d\pi^*/d\mu^*) = 2a_0(d\pi^*/dx)/(d\mu^*/dx) \quad (57)$$

The corresponding values of ρ and πa_0 then follow from eq 53 and 54. Each value of ρ_d corresponds to two values of ρ and πa_0 . This occurs because, as ρ increases from very small values, ρ_d first increases with ρ and then decreases again as closest packing is approached.

Sets of isotherms calculated using the triangular lattice with $\alpha = -4$ for three ranges of reduced temperature kT/u_0 are displayed in Figures 25–27. Figure 25 shows plateau-shaped isotherms with strong temperature inversion at areas below a crossover point at about $a = 2a_0$. Since for large areas the behavior of a monolayer approaches that of an ideal two-dimensional gas, such a crossover must occur experimentally, but it cannot be seen on the diagrams of Cadenhead and Müller-Landau¹⁴⁶ except possibly for stearic acid 16-nitroxide. Evidently the Bell–Dunne model gives ratios of “crossover pressure” to “plateau pressure” which are considerably larger than the experimental values. With this reservation, Figure 25 corresponds to the first kind of anomalous behavior referred to at the beginning of this section. Figure 26, calculated for a higher range of reduced temperature kT/a_0 , again shows isotherm inversion below a crossover point, but the plateau shape is absent and there is thus a similar correspondence to the second kind of anomalous behavior. In Figure 27, calculated for a still higher range of reduced temperature, the isotherms are nearly coincident and thus correspond to the third kind of anomalous behavior. The reason for this third type of behavior is now reasonably clear, at least in this model. Suppose that $(\partial\rho/\partial T)_\pi$ is negative at a given surface pressure and temperature. Then by raising the temperature sufficiently at the given pressure, the system must revert to “normal” behavior with $(\partial\rho/\partial T)_\pi$ positive. Hence for a certain temperature $(\partial\rho/\partial T)_\pi = 0$, and if this temperature does not vary much over a range of pressure, isotherms will be nearly coincident in its neighborhood.

Bell and Dunne²⁴ thus confirm that the “flipping” hypothesis of Cadenhead and Müller-Landau^{145,146} can account for the various kinds of anomalous behavior in monolayers of nitroxide spin-labeled molecules. Since these phenomena are all observed in about the same real temperature range, the theory requires that the variation in behavior depend on variations in the energy difference, u_0 , of the singly and doubly bound states. Denoting the number of chain links between the two polar groups by n , it may be that for double bonding to the substrate at small n values the two polar groups and the intervening CH_2 groups are forced into conformations which are less favorable energetically than those available at larger n . Cadenhead and Müller-

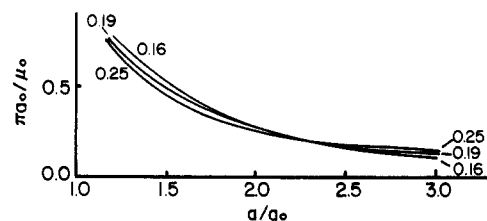


Figure 26. As for Figure 25 but with isotherms in a higher temperature range (reproduced from *J. Phys. C: Solid State Phys.*, 1979, 12, 4137, by permission).

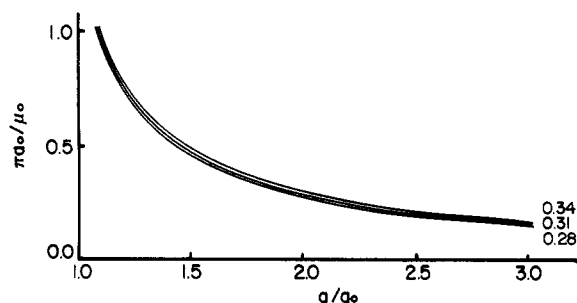


Figure 27. As for Figure 25 but for a still higher temperature range (reproduced from *J. Phys. C: Solid State Phys.*, 1979, 12, 4137, by permission).

Landau¹⁴⁶ consider that, as n decreases, steric hindrance becomes more important and that, for the 5-nitroxide compounds, immersion of the two polar groups involves the immersion of the CH_2 groups between them. The Bell–Dunne model is limited by the fixed 1:2 area size ratio between molecules in the singly and doubly bound states. However, the resulting value $a/a_0 = 2$ at the isotherm plateau edge (see Figure 25) does appear to correspond reasonably well with experiment. Cadenhead and Müller-Landau emphasize the variability, due to the flexibility of the carbon chain, of the distance between the two polar groups in the doubly bound state especially at large n . These authors even regard this size variability as responsible for the absence of liquid-expanded/liquid-condensed transitions in spin-labeled monolayers, although Bell and Dunne,²⁴ in conformity with their other work, attribute this absence to the disordering effect of the bulky spin-labels in the singly bound state. Change in the value of n should affect the entropy difference between the two states, but Bell and Dunne use the same value for the entropy term α in all the calculations presented in Figures 25–27 here. However these authors state that other calculations show that while a fairly large value of α is necessary, the value of kT/u_0 at which anomalous properties disappear is not very sensitive to changes in α .

The absence of lateral interactions between the monolayer molecules is an unrealistic feature of the foregoing theory, but it would be difficult to introduce such interactions into the modified series method. Hence Bell and Dunne²⁴ also use a Flory–Huggins-type formalism, which is similar to that presented in the previous section, except that states 1 and 2 are combined into a single monomer state. Several comparisons were made between isotherms calculated by the series and Flory–Huggins methods, respectively, for the same parameter values; one of these is shown in Figure 28. It appears that using the Flory–Huggins approximation instead of the more accurate method does not change the shape of the isotherm substantially. It is found that, with attractive energies of interaction $\epsilon = \epsilon_{\text{md}} = u_0/10$,

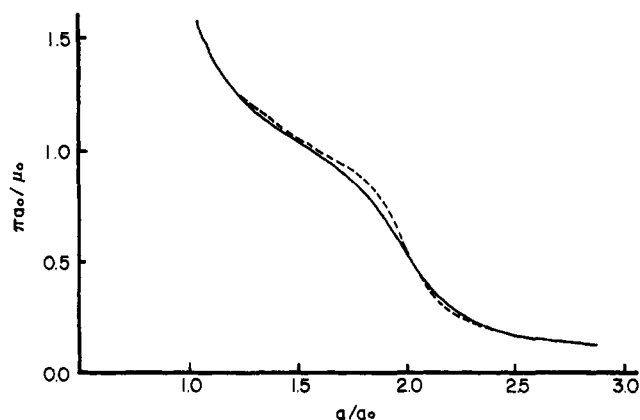


Figure 28. Comparison between series method (broken curve) and Flory-Huggins method (full curve) isotherms of reduced surface pressure against reduced area: quadratic lattice, $\alpha = 0$, $kT/u_0 = 0.15$ (reproduced from *J. Phys. C: Solid State Phys.*, 1979, 12, 4137, by permission).

$\epsilon_{dd} = u_0/20$, a very similar sequence of behavior types to those shown in Figures 1-3 is found. The changeover to normal behavior occurs at a somewhat lower value of kT/u_0 than is given by the series method.

Kellner and Cadenhead¹⁴⁸ obtained experimental surface-pressure/area isotherms for the 2, 3, 9, and 16 isomers of hydroxyhexadecanoic acid (HHA). The additional polar group in these compounds is simply an OH radical, and liquid-condensed/liquid-expanded transitions were observed for all isomers. These authors considered that in 2- and 3-HHA the two polar groups are too close together for one to be immersed without the other and that these compounds are effectively monopolar. This is borne out by their isotherms, which have the standard form for monopolar compounds at the air/water interface with those for 3-HHA considerably more expanded than for 2-HHA. The situation for 9-HHA is completely different. The liquid-expanded/liquid-condensed transitions occur in a higher area range: on the low-density side of the transitions there is noticeable isotherm inversion while on the high density side the isotherms are much flatter. The isotherms for 16-HHA are of a similar form to those for 9-HHA, but there seems to be no inversion and the nearly vertical "condensed" regions are absent. Kellner and Cadenhead regard 9- and 16-HHA as doubly bound to the substrate at high monolayer areas, with the weaker hydroxyl bonds broken near the transition point. Another example of monolayers of bipolar molecules displaying isotherm inversion in conjunction with liquid-expanded/liquid-condensed transition is provided by estradiol diacetate. Cadenhead and Phillips¹⁴⁷ found that at 23 °C the fairly flat part of the isotherm below the transition point occurs at a pressure of about 6 dyn/cm while at 7.5 °C the corresponding portion of the isotherm occurs at about 8 dyn/cm. In contrast to 9-HHA, isotherm inversion thus takes place on the high-density side of the transition point.

Dunne and Bell¹⁴³ used the orientable monomer-dimer-hole model with the Flory-Huggins formalism, as briefly described in section VII, to account for the types of behavior observed with the HHA isomers. For the effectively monopolar compounds the dimer state represents the "bent" configurations (bond-rotational isomers) and $u_0 < 0$. Isotherms displaying continuous transitions and first-order vapor-liquid transitions are

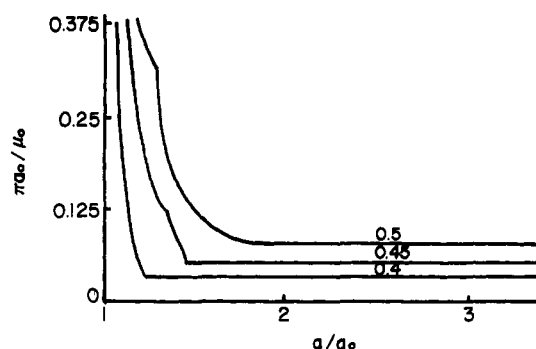


Figure 29. Reduced pressure vs. reduced area isotherms for effectively monopolar case. Curves are labeled with the values of kT/μ_0 . Parameter values are $\alpha = 0$, $J = 7\mu_0/40$, $\epsilon_{mm} = \mu_0/2$. (Reproduced from *J. Chem. Soc., Faraday Trans. 2*, 1980, 76, 431-440, by permission. Copyright 1980, The Royal Society of Chemistry.)

shown in Figure 29. Although their assignment of energy parameter ratios ($\epsilon = \epsilon_{mm} = \epsilon_{dd} = 20J/7$) and their value $\alpha = 0$ differ from those of Dunne, Bell, and Combs,¹⁰⁷ Figure 29 resembles the set of isotherms derived by the latter for a monopolar monolayer in general form. For the bipolar HHA isomers Dunne and Bell¹⁴³ regarded the dimer state as representing double bonding to the substrate and accordingly put $u_0 > 0$ and $\alpha < 0$. In fact, for bipolar monolayers with transition points their model is a combination of BMT with their own previous model for the spin-labeled monolayers. A valid criticism is that, since molecules in the singly bound state retain their chain flexibility, a consistent theory should provide *two* extended states, one to represent bent configurations of singly bound molecules and the other to represent doubly bound molecules, with appropriate values of u_0 and α in each case. However, it could be argued that, since the singly bound state is most probable at high monolayer densities, the chief physical consequence of chain flexibility in the bipolar monolayers is the possibility of double binding. Also, two extended states would considerably increase the difficulty of dealing with the model.

Figures 30 and 31 show sets of isotherms obtained by Dunne and Bell using the approach just described for the bipolar case. In Figure 30 the parameter values used were $\epsilon = \epsilon_{md} = \epsilon_{dd} = J = 3u_0/10$, $\alpha = -2$, while in Figure 31 the relative values of the attractive pair interactions ϵ , ϵ_{md} , and ϵ_{dd} are doubled. Figure 31 displays a type of isotherm inversion very similar to that found experimentally for 9-HHA while isotherm inversion is absent in Figure 30, as it is experimentally for 16-HHA. This indicates that the behavior of monolayers of bipolar molecules is rather sensitive to the details of intermolecular interactions. Cadenhead and Kellner¹⁴⁸ think that, due to the position of the second polar group, there are repulsive dipole interactions in certain singly bound configurations of 16-HHA which are absent in 9-HHA. They attribute the film collapse of 16-HHA before the condensed state is reached to the destabilizing effect of these interactions. This tends to agree with the model result that 9-HHA-type behavior occurs with larger attractive interactions, although the model is too coarse grained to incorporate the varieties of configuration sketched by Cadenhead and Kellner. However the observed 9-HHA isotherms seem in fact to be a little more expanded than the 16-HHA iso-

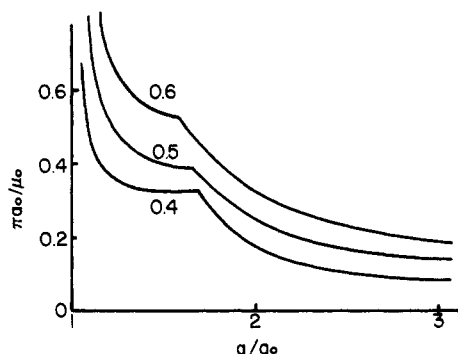


Figure 30. Surface pressure vs. reduced area isotherms labeled with the values of kT/u_0 . Parameter values are $\alpha = -2$, $J = \epsilon_{mm} = 3u_0/10$. (Reproduced from *J. Chem. Soc., Faraday Trans. 2*, 1980, 76, 431-440, by permission. Copyright 1980, The Royal Society of Chemistry.)

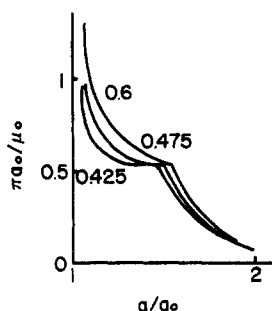


Figure 31. As for Figure 30, with parameter values $\alpha = -2$, $J = 3u_0/10$, $\epsilon_{mm} = 3u_0/5$. (Reproduced from *J. Chem. Soc., Faraday Trans. 2*, 1980, 76, 431-440, by permission.)

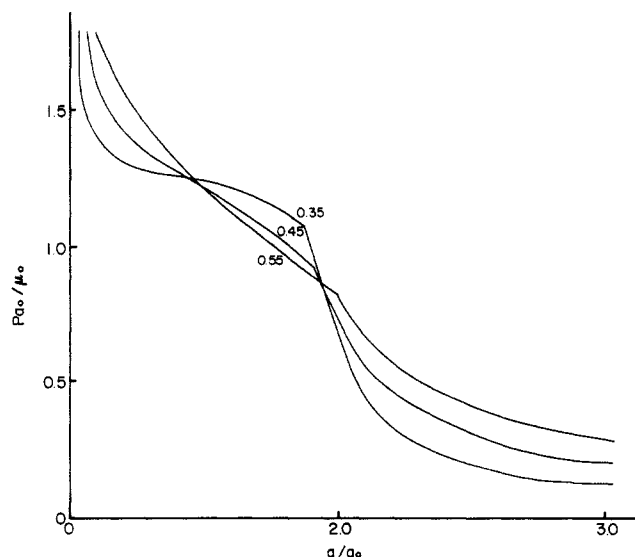


Figure 32. As for Figure 30, with the kT/u_0 values indicated on the curves. (Reproduced from *J. Chem. Soc., Faraday Trans. 2*, 1980, 76, 431-440, by permission.)

therms. Finally, we show in Figure 32 a set of isotherms from unpublished work of Dunne and Bell which show the feature observed in estradiol diacetate monolayer¹⁴⁷ of isotherm inversion in the liquid-condensed state, although the experimental isotherms in this region are flatter than the theoretical ones. The parameters used were $J = u_0$, $\epsilon = -9u_0/10$, $\epsilon_{md} = 0$, $\epsilon_{dd} = u_0/5$, $\alpha = -1$. The repulsive nature of the overall monomer-monomer interaction is puzzling here and more study of this case is needed.

Dubault et al.¹⁵⁷ present sets of experimental isotherms for some bipolar long-chain unsaturated esters, the polar heads being situated at the opposite ends of

the chain. In the case of A_{12} both liquid-expanded/liquid-condensed transitions and isotherm inversion are shown. For B_{12} and B_{16} there is isotherm inversion at high areas, but in the lower area region the isotherms appear to have van der Waals loops. These authors also present a theory based on the Ising model in which the singly and doubly bound states are represented by the two species of Ising dipole. There are no vacant sites, and the size difference between the two states is neglected in the entropy factor which has the usual Ising form. A constant pressure partition function is constructed, and in the pressure term a molecule in the doubly bound state is regarded as occupying an area r times as large as that of a singly bound molecule. The model is shown to be equivalent to an Ising model in a "field" which includes a term proportional to the pressure. Hence, below the Ising critical temperature there is a first-order transition at a pressure which depends on the difference between the intramolecular free energies in the two states.

IX. Influence of the Double Layer

A lipid bilayer has a surface charge density which, in an aqueous solution, will attract ions of the opposite charge and repel ions of the same charge. The result of this Coulombic interaction is the establishment of a diffuse electrical double layer.¹⁵⁸ The presence of this double layer has an important effect on the thermodynamics of phase transitions. The earliest model of the double layer was given by Helmholtz in 1879. His model was essentially that of a simple parallel-plate capacitor with a layer of ions at the solid surface and a rigid layer of oppositely charged ions in the solution. The potential difference across such a layer is given by eq 58, where d_{\pm} is the distance between the rigid layers,

$$\begin{array}{c}
 + \quad - \\
 + \quad - \\
 + \quad - \\
 + \quad - \\
 + \quad - \\
 + \quad - \\
 + \quad - \\
 \hline
 \text{fixed}
 \end{array}
 \quad
 V = \frac{d_{\pm}}{\epsilon_0 \epsilon} \frac{Q}{A}
 \quad (58)$$

ϵ is the dielectric constant of the medium, and Q/A is the surface charge density. This model is inadequate because thermal motions of the molecules in solution will not allow such a rigid arrangement of charges at the surface.

The first to allow for a diffuse double layer was Goüy¹⁵⁹ who proposed that the thermal movement of the molecules in solution gave rise to a mobile charge arrangement near the surface (eq 59). Chapman¹⁶⁰

$$\begin{array}{c}
 + \quad - \quad + \\
 + \quad - \quad + \\
 + \quad - \quad + \\
 + \quad - \quad + \\
 + \quad - \quad + \\
 + \quad - \quad + \\
 + \quad - \quad + \\
 \hline
 \text{mobile}
 \end{array}
 \quad (59)$$

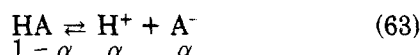
applied this model and the Poisson-Boltzmann equation in a paper on electrocapillarity, so this model is referred to as the Goüy-Chapman model. This model assumed point charges for the ions and a plane surface of uniform charge density and thus led to an unrealistic

transition of dipalmitoyl lipid membranes and showed that the chemical nature and charge of the lipid head group can modify the transition temperature considerably. They also noted a distinct difference in the effects of Ca^{2+} and Mg^{2+} which is not completely understood.

Chapman, Urbina, and Keough¹⁷¹ also used differential scanning calorimetry to study some simple model biomembranes and their phase transitions. They also observed the raising of the transition temperature by divalent cations as only part of their broad study of factors affecting biomembrane phase transitions.

Studies on the stability of monolayers at fluid–fluid interfaces have been studied by Lamsweerde-Gallez, Bisch, and Sanfeld.¹⁷² They show that discrete interactions between dipoles perpendicular to the interface induce a coupling between longitudinal and normal modes of deformation. The negative electrical contribution to the interfacial tension from the repulsion between dipoles is three times larger for mutually parallel dipoles than when they are oriented normally to the interface. However the destabilizing effects of dipoles on surface tension are weaker than those of ions. They thus predict that the destabilization of membranes should be favored by the presence of charged lipids.

Goddard¹⁷³ has presented a review of applications of electrical double layer treatments to charged monolayers. For an ionizable material at the interface



the degree of dissociation has been given by Payens¹⁷⁴ as

$$(1 - \alpha)/\alpha = [\text{H}^+]_b \exp[-(e\Psi_0 - \Delta G_0)/kT] \quad (64)$$

where $[\text{H}^+]_b$ is the hydrogen ion concentration in the bulk, ΔG_0 is the standard free energy of ionization of the acid, and Ψ_0 is the electrical potential at the interface, usually given by the Gouy–Chapman equation for flat plates at 20 °C:

$$\Psi_0 = (2kT/e) \sinh^{-1} (134\alpha/(Am^{1/2})) \quad (65)$$

where m is the concentration of uni-univalent electrolytes in solution and A is the area/molecule for the monolayer of degree of dissociation α . Charging the monolayer results in a change of the free energy of the double layer

$$\Delta F = -\kappa\epsilon k^2 T^2 / (\pi e^2) \cosh [(e\Psi_0/2kT) - 1] \quad (66)$$

which results in a positive contribution to the surface pressure as given by Davis¹⁷⁵ for 20 °C:

$$\Delta\pi = 6.1m^{1/2}[\cosh \sinh^{-1} (134\alpha/A m^{1/2}) - 1] \quad (67)$$

Shulman and Hughes¹⁷⁶ have shown that ΔV -pH curves for a fatty acid resemble a titration curve where ΔV is given by the following for a partially ionized monolayer:

$$\Delta V = (12\pi/A)[(1 - \alpha)\mu_1 + 2\mu_2] + \Psi_0 \quad (68)$$

where μ_1 and μ_2 are the surface moments of the unionized and ionized forms of the monolayer. Several approaches may now be taken for comparing with experiment. From eq 67, measured $\Delta\pi$ as a function of m will yield α to be compared with other calculations of α . An experimental ΔV vs. pH plot can also be used

to determine degree of dissociation as a function of $[\text{H}^+]_b$. Bagg¹⁷⁷ et al. have reported on the composition of spread fatty acid monolayers on solutions containing only monovalent counterions. They obtained values of the extent of ionization of stearic acid and behenic acid as a function of pH, in good agreement with the Gouy–Chapman model. Plots of surface pressure vs. A show a marked dependency upon pH, with a flat portion appearing for some at various pH values. Anderson and Pethica¹⁷⁸ observed a plateau region from pH ~ 2.5 to 8 in a ΔV -pH plot of distearoylphosphatidylcholine, PC, a zwitterion comprising a medium strength acid group and a strong base group. There is an upswing below pH 2.5 consistent with deionization of phosphate groups and a downswing at pH 8 which was difficult to explain. They speculated on the possibility of a reorientation of the head group above pH 8. At pH 10 the monolayer was observed to develop considerable instability.

The treatment of the role of the solvent in double-layer properties is far from complete. The review by Conway⁹⁴ mentioned in another segment of this review covers a number of aspects of this topic, so we will only make a few comments. There are two extremes of models for liquid water. One is the continuum model of Lennard-Jones and Pople^{179,180} and the other is the cluster treatment by Frank and Wen¹⁸¹ and the "significant structure" model of Marchi and Eyring.¹⁸² The successful molecular dynamics calculations¹⁸³ seem to support the type of model used by Pople,¹⁸⁰ even though this model has not received the attention of the cluster models.

X. Implications for Membrane Science

Living cells have outer walls called membranes which play a vital role in cell function. It is the cell membrane which must initially respond to the interaction of the cell with other molecules in the outside environment. It is pertinent to briefly summarize here some current views on biological membrane structure to enable this work to be put in a proper perspective. There exists a very extensive literature in this field, and hence what follows is unavoidably incomplete.

A biological membrane is a complex integrated system of lipids, proteins, and carbohydrates, and consequently its properties are highly dependent upon the precise molecular arrangement. The chemical composition of many membranes has been determined, and typically contain a high proportion of lipids and proteins. The earliest notable model of a biological membrane was that of Gorter and Grendel,¹⁸⁴ which was followed by that of Davson and Danielli.¹⁸⁵ The Davson–Danielli model has had outstanding success, but the modern view of membrane structure is contained in the fluid mosaic model of Singer and Nicholson.¹⁸⁶ In the Singer–Nicholson model, the membrane is assumed to consist of a lipid bilayer containing a variety of proteins where some proteins in certain membranes may penetrate right through the membrane. The experimental support for this type of structure is now strong. In particular, the beautiful work of Henderson and Unwin¹⁸⁷ on the structure of the purple membrane of *Halobacterium halobium* is a notable example which strongly supports the Singer–Ni-

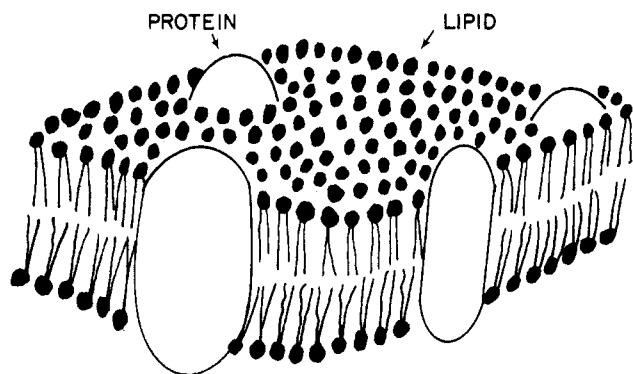


Figure 33. A sketch of the Singer-Nicholson membrane model.

cholson model. Figure 33 shows a sketch of a single Nicholson-type membrane with proteins "floating" in a "sea of lipid". The bilayer structure of the membrane is of fundamental importance. It should be noted that no particular spatial distribution of proteins in the membrane should be inferred from this figure. The existence of "phase transitions" in cell membranes is well-documented. Early experiments were concerned with the cell membranes of *Mycoplasma laidlawii*,¹⁸⁸ *Micrococcus lysodeikticus*,¹⁸⁹ and *Escherichia coli*.¹⁹⁰ These transitions were initially interpreted as a "fluidizing" of the membrane lipid hydrocarbon chains.¹⁹¹ Such an interpretation is perhaps vague, but is supported and has been reinterpreted by recent theoretical work. The transitions are such that hydrocarbon chains are in the "fluid" phase at the normal growth temperature of the organism. This phase has been called the "liquid-crystal phase". The precise physiological significance of such phase transitions is still an open question. Phase transitions resembling those found in cell membranes have also been observed in phospholipid bilayers.¹⁹² The work on bilayers is clearly of closer connection to that on real membranes than monolayer work, yet many people have chosen to regard a bilayer membrane as a pair of weakly interacting monolayers.

The main experimental techniques used in such studies are infrared spectroscopy, X-ray diffraction, differential thermal analysis, dilatometry, electron spin resonance, nuclear magnetic resonance, fluorescence, and light scattering. While it is not feasible to interpret the fine details of all the data provided by such investigations in a single scheme, it is possible, by using a modified monomer-dimer model, to account for the overall molecular trends. One starting point for such a discussion is the order-disorder model put forward by Ranck et al.,¹⁹³ the monolayer data of Chapman and Williams,¹⁹² and the specific heat data of Hinz and Sturtevant.¹⁹⁴

The model which we adopt is that partly suggested by the X-ray diffraction studies as in Figure 34. Here we regard a bilayer as two weakly interacting monolayers. Two conformations dominate. In Figure 35, the black dots represent the polar head groups, the wiggles the hydrocarbon chains in the α conformation, and the straight chains in the β conformation. The polar head groups have large electric dipole moments due to their zwitterionic character which we suppose lie perpendicular to the chain axis. It is known that the cross-sectional area per chain in the α conformation is roughly twice that in the β conformation.¹⁹⁵ Hence, if we localize

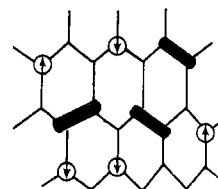


Figure 34. Projection of a monolayer of lipids viewed from above onto a two-dimensional hexagonal lattice.

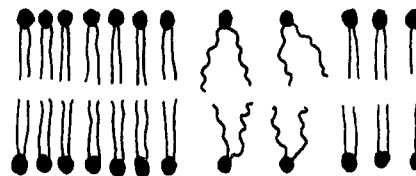


Figure 35. Sketch of a bilayer arrangement showing two conformations.

lipid molecules on the sites of a two-dimensional hexagonal lattice of sites, then an orientable monomer-dimer model is appropriate, as shown in Figure 34. The circled arrows (monomers and dimers) represent molecules in β and α conformations, respectively; the arrow signifies the orientation of the electric dipole of the polar head group where for simplicity only two orientations are considered. The vacant vertices are holes, thereby allowing the system to expand. The model is evidently a crude description of reality, especially since chain tilting is not considered explicitly but does take into account the essential conclusions of the X-ray diffraction work.

It is evident from our previous discussion that a monomer-dimer model of this type may be parameterized to reproduce the monolayer behavior of L- α -dipalmitoyllecithin monolayers for which heat capacity data are also available for the corresponding bilayer system. It is now possible to qualitatively understand the heat capacity data for sonicated vesicles^{196,197} which show two transitions. Tredgold¹⁹⁸ has discussed this point in some detail. In accordance with the double transitions which may occur in the π/A behavior (gaseous \rightarrow liquid expanded, liquid expanded \rightarrow liquid condensed), it is reasonable to suppose that the two peaks in the specific heat of sonicated vesicles represent the analogous process in the bilayer systems. A detailed analysis of this suggestion is in progress.

There are clearly several factors affecting the transition in pure lipid systems and chemical inferences to be drawn from the model. We have made the following inferences:

(1) Since the interaction parameters are likely to depend on the nature of the polar head groups and the chain length, then both such factors should affect the transition temperatures.

(2) If the polar head groups are hydrated, then any solvation changes will affect the head group interactions and thus lead to increased or decreased transition temperatures. It is reasonable to suppose that water molecules screen zwitterionic polar head groups, and thus one expects more highly hydrated lipids to have lower transition temperatures.

(3) Increased lateral pressure on a bilayer (viewed as two weakly interacting monolayers) would lead to increased transition temperatures. This is observed experimentally.¹⁹⁹

(4) The effect of increasing lipid chain length is complicated by at least two competing factors. It may be supposed that longer lipid chains have stronger interactions than short lipid chains and the increased interaction has the effect of ordering the membrane. However, this trend is opposed at high temperatures by the tendency of the chains to kink into the possible rotational isomers, thereby disordering the system. The increased entropy possible for assemblies of longer chains is the physical basis for such an effect.

We will now give a brief discussion of the description which the model allows of a monolayer stretching or contracting under mechanical stress. Such an expansion and contraction model has been discussed several times²⁰⁰⁻²⁰² in relation to the continuous compression and expansion loops which occur in lung membranes during respiration. It will be assumed that a dipalmitoyllecithin monolayer resembles a lung membrane and that the temperature is 38 °C.

At high surface areas when the lung is expanded, practically all molecules are in the α conformations, but with a small fraction remaining in the $\beta \uparrow$ and \downarrow conformations. The populations of the \uparrow and \downarrow states are equal. The membrane is thus disordered, and highly fluid and can have a large number of vacant sites or holes. This may be important for biological transport processes. As compression of the lung occurs, a critical area is approached where a phase transition occurs. At this point the fraction of molecules in all the various possible conformations changes discontinuously. The fraction of lipids in α conformations drops sharply, and the onset of an alignment process occurs in which one orientation of molecules in the β conformation becomes favored. The discontinuous nature of the transition is due entirely to the possibility of the two-state alignment of molecules in the β conformations. The upshot of this is that a small change in surface area near the critical surface area may cause a large fraction of molecules to undergo conformational transitions. This feature may be important in the respiration process.

XI. Outlook and Promising Lines for Further Work

(1) Since a biological membrane is composed of mixtures of different molecules, experimental and theoretical work on mixed monolayers and mixed bilayers of these molecules should be pursued further. In particular, work should be concentrated on lipid-lipid and lipid-protein π/A behavior in mixed monolayers and heat capacity data in the corresponding bilayer systems.

(2) Work should be undertaken to clarify the role of the electrical charge distribution on the head group and the relation of head-group orientation to the measured potential difference across the monolayer.

(3) Experimental work should be pursued on the dynamics of molecular motion occurring around the biomembrane phase transitions using perhaps magnetic resonance and dielectric relaxation spectroscopy. Particularly, do the present theories adequately describe the two phase transitions which bound physiological temperature?

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