Stereochemistry and Molecular Recognition in "Two Dimensions"

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Introduction

"Molecular recognition" has become one of the most evocative buzz terms in the chemistry of the late 1980s, with enzymes as the model of perfection for catalytic efficiency and specificity. A number of clever "enzyme mimetic" systems such as crown ethers,[1] cryptands,[2] cyclodextrins,[3] and convergent cleft molecules[4] have been designed as artificial receptor sites to bind appropriate substrate molecules or ions. The demonstrated success of these studies has ushered in a new era of supermolecular chemistry aimed toward the design of organized molecular assemblies as artificial receptors to capture substrates by the use of intermolecular forces. Of these, hydrogen bonding, stacking interactions, and ion–dipole or dipole–dipole forces are the most powerful. In an era during which the control of covalent bond formation has established the ability to synthesize virtually any molecule of molecular weight under 1000 that obeys the rules of valence, it is not surprising that the new frontiers for development are expanding toward the manipulation of *intermolecular forces*, a field where nature clearly still does it best.

In contrast to the design of molecular receptor units where the dimensions and orientation of the receptor site depend on the shape of the host molecule, the surfaces of solids provide an extended framework of rigid sites whose geometry is fixed. However, until recently there have been so few tools for characterizing solid surfaces that the detailed mechanisms for their operation have been as mysterious as the behavior of enzymes.

One outstanding exception to the difficulties of studying interfacial systems is the investigation of monolayers at the air/water interface. As their name implies, monolayers are films one molecule thick which are spread at an interface. Their unsurpassed advantage for the study of intermolecular forces is that it is possible to actually manipulate the orientation and degree of organization of molecules in a monolayer assembly and to control directly the approach of molecules to each other by variation of the surface area.[5,6]

The Langmuir Film Balance. The elegant tool by which monolayers may be studied, and also manipulated at the air/water interface, was developed by Irving Langmuir and his colleague Kathleen Blodgett at General Electric Laboratories during the 1920s and 1930s (Figure 1). The film balance, or Langmuir trough, is an oblong tray, usually about 2 ft long and 8 in. wide, which is filled with superpure water and divided into two sections by a fixed barrier placed about one-third of the length of the tank from one end.[7] Another barrier, which may be moved either manually or by a screw-drive arrangement, is used to vary the surface area of the larger section of the trough. A suitable means for measuring the difference in surface tension between the two areas separated by the fixed barrier completes the required elements of the Langmuir film balance.

Appropriate molecules for study as monolayers are natural or synthetic surfactants (lipids). Such amphipathic compounds have a highly polar functionality (carboxylate, amino, or hydroxyl) as a head group, attached to a fatty chain of 10 carbons or more. If a very dilute solution of surfactant molecules is dropped on the surface of pure water, and the solvent evaporates or dissolves, the surface-active molecules are restricted to the interface with their polar head groups bound to the aqueous subphase and their fatty tails assuming various orientations relative to the surface plane, depending upon the available area per molecule.

Unlike molecules with shorter chain lengths which may dissolve in the aqueous subphase, surfactant molecules are constrained to stay at the interface, or aggregate to form microcrystals. If the area per molecule is large (over 1000 Å^2/molecule), a "gaseous" monolayer is usually formed, in which most of the molecules float freely and independently on the surface, with their chains spending most of the time on the interface, moving at random with no long-range order or organization. If the surface area is reduced, there is inadequate space to accommodate all of the hydro-

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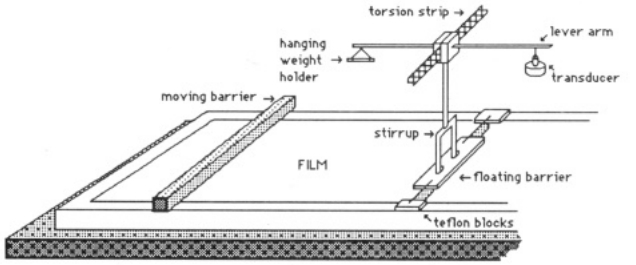

Figure 1. Schematic representation of the Langmuir film balance for the measurement of pressure–area monolayer film properties.

carbon chains on the surface, and they are forced into various standing positions. This state of the monolayer is often called a *two-dimensional liquid*. Finally, when the area is reduced to about 20 Å^2/molecule, the normal cross section of a hydrocarbon chain in a crystal, lateral compression has reached its limit and a completely ordered monolayer has been produced with the head groups at the interface and the fatty chains packed vertically to it. Further compression will result in collapse of the monolayer in which sections are dislodged and forced on top of each other, similar to a sheet of ice that has been broken by compression so that some sections slide up over others to form a multilayer.

The important point in the above discussion is that the orientation of the hydrocarbon chains with respect to the surface, and to each other, may be varied by moving the surface barrier and can be monitored as a function of the surface pressure (which in turn is directly proportional to surface tension if the monolayer is insoluble in the subphase).

Micelles may be considered as sections of liquid monolayer that have been rolled up into small aggregate units and dispersed through the aqueous subphase. The crucial difference between the study of micelles and of monolayers is the ability to control the orientation in the latter, and to monitor the degree and type of packing through the relation of surface area to surface pressure. In general, the micellar state is much more floppy and has considerably less long-range order than is the case for liquid or solid monolayers.

The film balance may be regarded as a two-dimensional piston, and the most commonly studied property is the Π/A isotherm. The analogy to a PV isotherm is so apt that in the "gaseous monolayer regime" the two-dimensional analogue of the ideal gas law pertains: $\Pi A = nRT$. It is therefore reasonable to relate discontinuities in Π/A isotherms as the film is compressed to phase changes like those that take place in three-dimensional condensed matter as one passes from a gas to a liquid to a solid. Figure 2 presents a typical surface pressure (Π) vs area (A) isotherm and also depicts the inferred orientations of molecules with respect to the surface. The natural question that follows is, What is the true nature of the changes in molecular orientation and packing as we pass from random arrangements in the gaseous state to the highly ordered "two-dimensional crystalline state", assuming throughout that the polar head group is constrained to lie in the liquid surface?

An interesting example of the manual manipulation of molecules on a water surface is shown by Figure 3, which compares the isotherms for dipalmitoylphosphatidylcholine (a ubiquitous phospholipid in cell membranes) with a similar compound bearing a hydroxyl group at the 12-position. The enormous difference in the Π/A isotherms is readily attributed to the fact that at large molecular areas this molecule has two head groups: the usual choline system and the 12-hydroxyl group, which anchors part of the chain to the surface. Upon compression, extra work must be invested to pull the hydroxyl group out of the surface to bring the chain to the standing position. The area enclosed between the two isotherms is a quantitative measure of the extra free energy required to pull the molecule from the inchworm arrangement with the hydroxyl group in the surface to the vertical arrangement.[8]

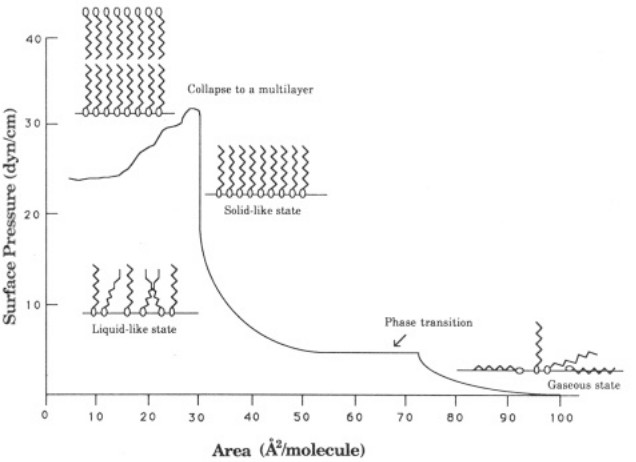

Figure 2. Idealized surface pressure (Π) versus area (A) isotherm detailing the inferred molecular orientation and aggregation states during a compression cycle.

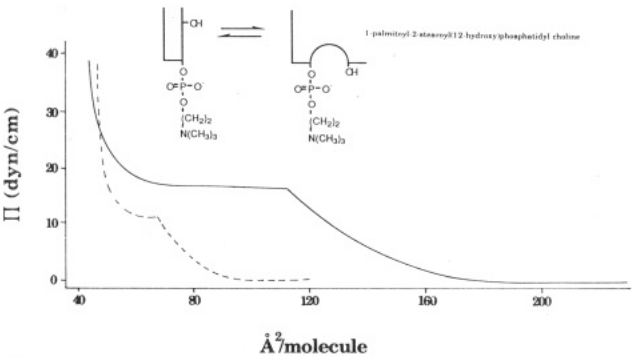

Figure 3. Surface pressure–area isotherm for the compression cycle of dipalmitoylphosphatidylcholine (– – –) and 1-palmitoyl-2-(12-hydroxystearoyl)phosphatidylcholine (—) on a pure water subphase at 25 °C.

Chiral Monolayers. The most powerful tool in chemistry for the study and manipulation of molecular shapes and symmetry properties is stereochemistry. Our involvement in monolayer research began about a dozen years ago with the realization that there had never been a systematic investigation of the effect of stereochemistry on molecular aggregation in monolayers. In the light of the above introduction, it should be clear that the study of chiral surfactants as monolayers should provide a unique opportunity to investigate molecular recognition under the ideal circumstances where the interaction of enantiomers to form racemic or diastereomeric mixtures can be examined over a wide

(8) (a) Dr. Lynn Collins Gold, unpublished results, Duke University. (b) See also: Tachibana, T.; Hori, K. *J. Colloid Interface Sci.* **1977**, *61*, 398.

range of *controlled aggregation* states as the surface pressure on a chiral monolayer is varied. This Account reports some of the most striking examples of stereoselective behavior in monolayers from our laboratory. We have reviewed earlier examples from other laboratories.[9] For more recent experimental and theoretical reports, see ref 10–17.

With virtually no precedent to go on, we were faced with two fundamental problems. The first was an appropriate choice of chiral surfactants that might express maximum stereoselectivity; the second was the design of a sufficiently sensitive film balance to detect chiral recognition effects in case they turned out to be extremely subtle. Symmetry requirements of packing chiral molecules absolutely require that there *must* be differences between pure enantiomers and their racemic mixtures or between different diastereomeric combinations. However, that does not mean that they are readily detectable by experiment, and it is well-known that in the liquid phase such stereochemical effects are usually too small to detect.

The instrumental problem was solved by Dr. Barbara Kinzig, who designed a Langmuir balance capable of detecting film pressures as small as 0.005 dyn/cm on the floating barrier.[18] In practice, chiral recognition in Π/A isotherms has turned out to be readily detectable for most compounds with much less sensitive equipment than this. The choice of compounds was solved initially by preparing the stearoyl derivatives of amino acid methyl esters. Subsequently a variety of other types of chiral systems have been studied. Both enantiomers of most common amino acids are readily available in large quantity and at modest cost. A fatty acid side chain is easily attached. Accordingly, a series of stearoyl amino acid methyl esters was produced.

The rules of stereochemistry provide an added value from the use of chiral surfactants by providing protection against one of the perennial problems of monolayer chemistry—the production of artifacts due to the intrusion of impurities into the tiny quantities of material in the monolayer film. Both enantiomers of all of our surfactants were made and were purified until they produced exactly identical physical and chemical properties. This is an absolute test for impurities and in several cases demonstrated how difficult it is to avoid errors from this source.[19]

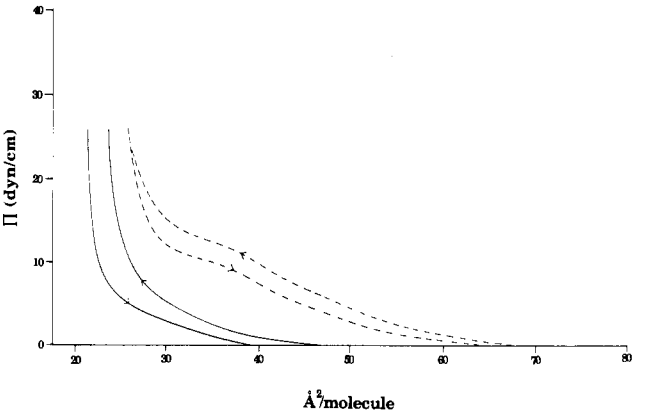

Figure 4. Surface pressure–area isotherm for the compression–expansion cycle of diastereomeric monolayers of stearoylalanine methyl esters mixed with stearoylserine methyl esters on a pure water subphase at 35 °C. (– – –) 1:1 *R*:*S*′ or *S*:*R*′; (—) 1:1 *R*:*R*′ or *S*:*S*′ film.

Typical results for mixing stearoyl amino acid methyl esters are provided by Figures 4 and 5. The former portrays the diastereomeric interaction between the enantiomers of stearoylalanine methyl ester and the corresponding serine compound on an aqueous subphase at 35 °C. The four combinations of enantiomers of each compound show clearly a large diastereomeric difference, which, interestingly enough, is scarcely apparent at 25 °C. Obviously, in contrast to mixtures of chiral liquids, large diastereomeric interactions reminiscent of those in the crystalline state can be expressed in monolayers and they may be highly sensitive to temperature.

Figure 5 deals with the more subtle question of how the surface properties of pure enantiomers compare with those of their racemic mixtures. Large differences are seen between the compression isotherms for (*R*)- or (*S*)-stearoylserine methyl ester (SSME) and their racemic mixture, which is considerably more expanded in the sense that there is a greater molecular area on the surface at every pressure.[20]

What Is the Time Scale for Relaxation in Monolayers?

Figure 5 introduces another interesting question, that of the dynamics of relaxation in the monolayer state. Curve A represents the classic compression isotherm for stearic acid, which is typical of many of the simple straight-chain carboxylic acids. Over the time scale for the experiment, say a half-hour, the compression–expansion behavior is reversible. Looking to curves B for (*R*)- or (*S*)-SSME, a considerable difference is observed between the compression curve and that for expansion, implying at once that the relaxation behavior in these monolayers takes place on a relatively slow time scale. An even greater hysteresis effect is seen for racemic SSME.

We have pursued the interesting question of relaxation processes with two techniques. A dynamic surface tension film balance, developed by Eric Johnson from a commercially available model, was used to compare the hysteresis phenomenon for a variety of enantiomeric surfactants. This device compresses and expands

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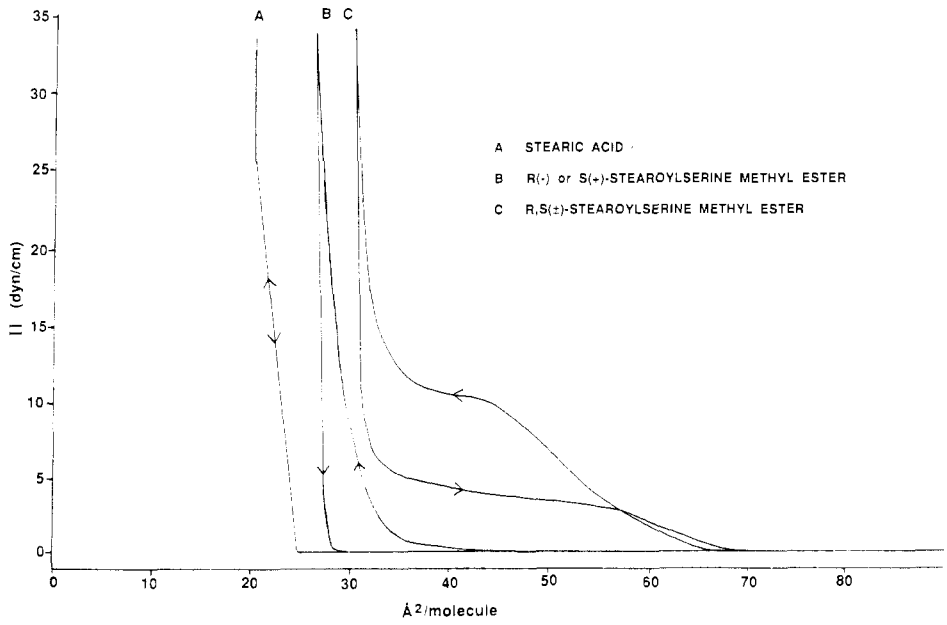


Figure 5. Surface pressure–area isotherms for the compression–expansion cycle of (A) stearic acid, (B) (*R*)-(−)- or (*S*)-(+)-stearoylserine methyl ester, and (C) (*RS*)-(±)-stearoylserine methyl ester on a pure water subphase at 25 °C and compressed at 29.8 Å²/molecule/min.

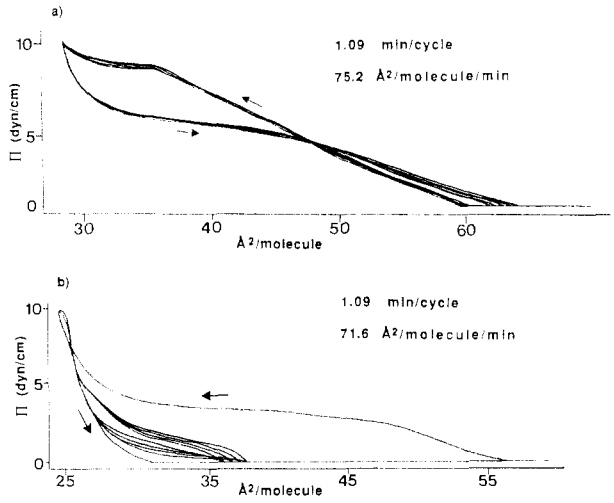


Figure 6. Compression–expansion hysteresis loops for monolayers of (a) racemic and (b) enantiomeric SSME doped with 17% palmitic acid.

monolayers on a regular cycle with a small Langmuir film balance system. Figure 6 compares the hysteresis curves for the monolayers of enantiomers of SSME with the racemic system. (These films have been doped with fatty acid to increase their stability.) Again the racemic material is considerably more expanded and springy than the enantiomeric, which appears to undergo a faster reorganization upon compression and respreads much more slowly than the mechanical cycling rate.

Surface viscosity is another relevant rheological property which may be measured by several devices.[21] In our laboratory we have chosen to measure the rate of flow of the film through a narrow slit (the two-dimensional analogue of a capillary) using a modified Verger film balance equipped with a feedback control system which provides for constant surface pressure as the monolayer flows isobarically through a canal of carefully controlled dimensions. Table I provides a

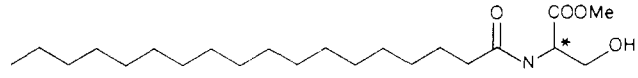
(21) (a) Langmuir, I.; Schaefer, V. J. *J. Am. Chem. Soc.* **1937**, *59*, 2400. (b) Joly, M. *Kolloid-Z.* **1939**, *89*, 26. (c) Jaffe, J.; Lootz, J. M. *J. Polym. Sci.* **1958**, *29*, 381.

Table I
Surface Shear Viscosities of Stearoylserine Methyl Ester Monolayers at 30, 35, and 40 °C

temp, °C	viscosity (surface), msp			
	Π = 2.5 dyn/cm		Π = 5.0 dyn/cm	
	RS-(±)	*R*-(−) or *S*-(+)	*RS*-(±)	*R*-(−) or *S*-(+)
20,25	condensed films, no surface flow			
30	0.553 ± 0.026	2.00 ± 1.11[a]	0.573 ± 0.042	no flow
35	0.472 ± 0.026	0.504 ± 0.038	0.535 ± 0.040	0.666 ± 0.109[a]
40	0.419 ± 0.047	0.393 ± 0.036	0.507 ± 0.039	0.493 ± 0.020

[a] Indicates measurable non-Newtonian flow.

Table II
Chiral Discrimination in *N*-Stearoylserine Methyl Ester



property	enantiomeric	racemic
melting point	89.8–90.5	93.5–94.2
ESP at 25 °C	0	2.5 ± 0.3 dyn/cm
film type	"consensed"	"expanded"
surface viscosity	higher	lower

summary of surface viscosities between enantiomeric and racemic SSME at several temperatures.

What Is the Nature of the Surface Phases? Table II summarizes the qualitative evidence for chiral recognition in the surface properties of stearoylserine methyl ester as a monolayer film at 25 °C in contrast to the melting points of the enantiomers and the racemic mixture. The equilibrium spreading pressure (ESP) is the film pressure generated by a crystal of pure surfactant on the surface of pure water at equilibrium. This experiment may be regarded as the two-dimensional analogue of sublimation and indicates clearly the significant film pressure generated by the racemic crystals compared to the immeasurably small surface pressure from the less expandable enantiomers. The lift-off areas (defined as the first point on the Π/A isotherm where a monolayer shows detectable resistance to compression) for the two modifications of SSME are readily observable from the isotherms in Figure 5. This area is important since it may describe the point at

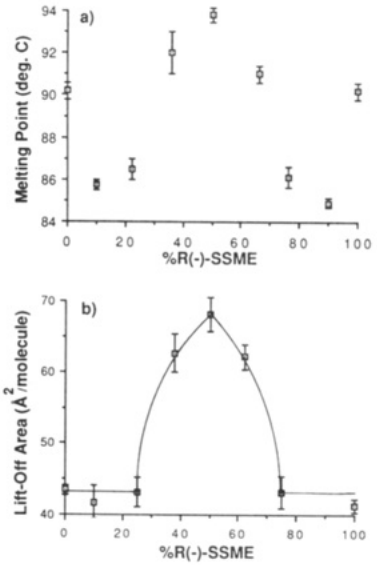


Figure 7. (a) Melting point versus composition diagram for stearoylserine methyl ester crystals. (b) Lift-off area versus composition diagram for mixed monolayers of (*R*)- and (*S*)-stearoylserine methyl ester at 25 °C.

which the molecules pack stereoselectively in a condensed phase and, thus, may reflect stereoselective interaction. The surface viscosity and hysteresis areas for enantiomeric material all support a greater degree of surface cohesion for the enantiomers. Finally, comparison of crystal melting points with the rest of the properties indicates a definite difference between the lattice forces in the three-dimensional crystalline system.

As might be expected intuitively, chiral discrimination appears to be expressed primarily in the more condensed surface states—those approaching "two-dimensional crystals". What can we say about the actual nature of the condensed surface phases?

The melting point vs composition diagram[20] for SSME (Figure 7a) indicates clearly that the interactions between enantiomers are dependent on composition, where the racemic crystal appears to be a true racemate, or racemic compound.[22] The differences in packing in monolayers cast from pure enantiomers and their mixtures may be determined qualitatively in a similar manner. When the "lift-off" area of the Π/A isotherm is plotted vs film composition, a quasi-phase diagram is obtained (Figure 7b) which indicates a dependence of lateral packing on enantiomeric purity. When compared with the monolayer shear viscosities at 25 °C (Table I), this diagram suggests that the tightly packed, solid-like homochiral SSME films become more highly "fluid" with successive incorporation of the antipode, with the most highly expanded, fluid-like state occurring at the racemic composition.

Differences in the associations between enantiomers in homochiral and heterochiral monolayers may be visualized directly by microscopy. Figure 8 compares photomicrographs of racemic and enantiomeric films of SSME examined by the elegant epifluorescent method of McConnell and co-workers.[17a,b] This technique employs mixtures of SSME with a fluorescent surfactant probe and video-enhanced microscope images.

(22) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill Book Company, Inc.: New York, 1962; pp 43–47.

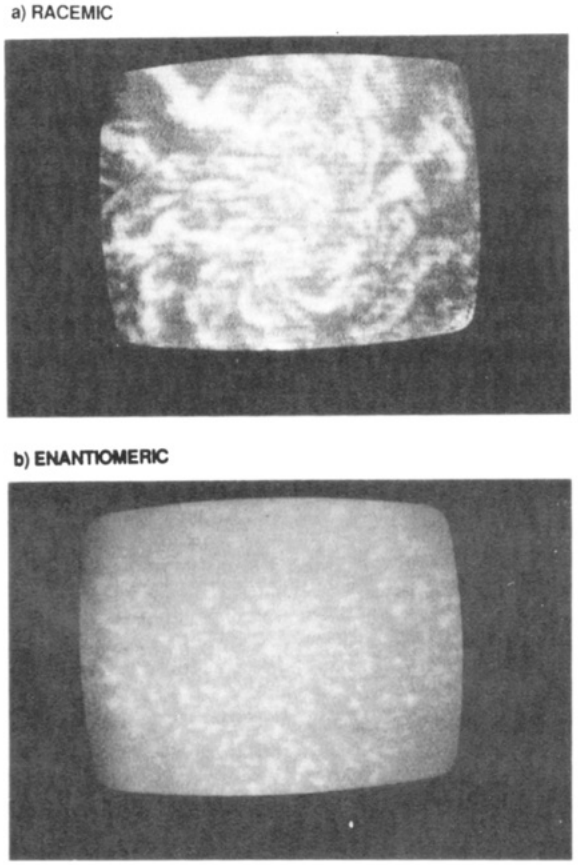


Figure 8. In situ epifluorescence micrographs of (a) racemic and (b) enantiomeric SSME monolayers at the air/water interface. Lighter domains are fluorescing probe *L*-NBD-PC; darker domains are SSME. Total magnification during experiment is 5000×.

Magnified 5000 times, the enantiomeric film presents a much more condensed appearance than the loose swirling "Mother Earth" appearance of the racemic mixture. Striking figures have been generated by monolayers of phospholipids with epifluorescent visualization.[17]

Finally, we have examined Langmuir–Blodgett (L–B) films transferred to solid substrates.[20] Transmission electron micrographs on carbon film coated EM grids yielded images of multilayer assemblies indicative of collapsed domains. Figure 9 compares scanning tunneling micrographs for films transferred to graphite under identical conditions. These highly reproducible images demonstrate more clearly the much greater long-range order in the collapsed enantiomeric films than in the racemic ones. In addition, they suggest that the mechanism of tunneling in the STM experiment itself is dependent on the degree of association between chiral surfactants in these collapsed domains. Although the mechanism of tunneling through these collapsed domains is still unclear, Kuhn has demonstrated that tunneling through surfactant films is possible.[23]

In summary, all of the above evidence implies a much greater overall degree of order and close packing in the enantiomeric films of SSME and that the racemic films

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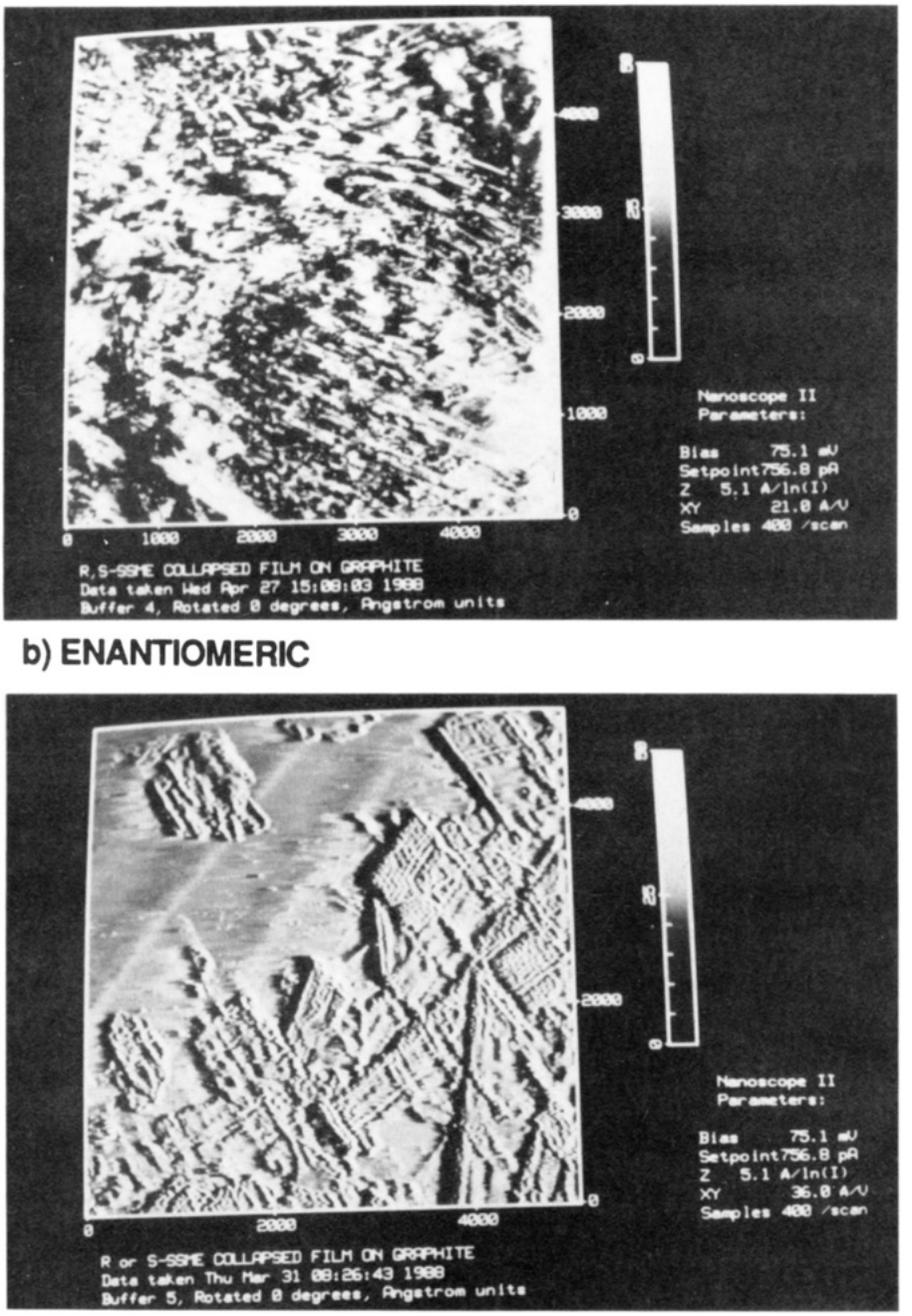

Figure 9. Scanning tunneling electron micrographs of L–B films of collapsed domains in (a) racemic and (b) enantiomeric SSME films pulled onto pyrolytic graphite monochromators. x and y axes are in angstroms.

are probably formed from random combinations of the two enantiomers in the monolayer. It is a reasonable speculation that racemate formation involves hydrogen bonding through the serine hydroxyl groups; however, there is no obvious reason why films of the pure enantiomers should not be held together through the same means.

After a decade of research, we have studied a wide variety of chiral surfactants. All of them, with the exception of the phosphatidylcholines, exhibit stereoselectivity in all of their monolayer properties.[24] It is a mystery why these phospholipids, which are such ubiquitous components of cell membranes, should show so little chiral discrimination in their intermolecular interactions, which should in principle be reflected by their physical monolayer properties.

Opposition of Inter- and Intramolecular Forces. If two fatty acid chains are attached to each other by a linking group, diastereomeric two-chain systems are generated, with the stereochemistry at the point of linkage being either meso or *d,l*. Conformational analysis of dialkyl ketones shows that the most stable conformation is that achieved when the epimeric hydrogen atoms on the carbons attached to the keto group are nearly eclipsed. If one applies this fact to a series of meso and *d,l* diacids held together by a carbonyl

(24) (a) Arnett, E. M.; Gold, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 636. (b) Arnett, E. M.; Gold, J. M.; Harvey, N. G.; Johnson, E. A.; Whitesell, L. G. In *New Applications of Phospholipid Bilayers, Thin Films and Vesicles*; Plenum Press: New York, in press.

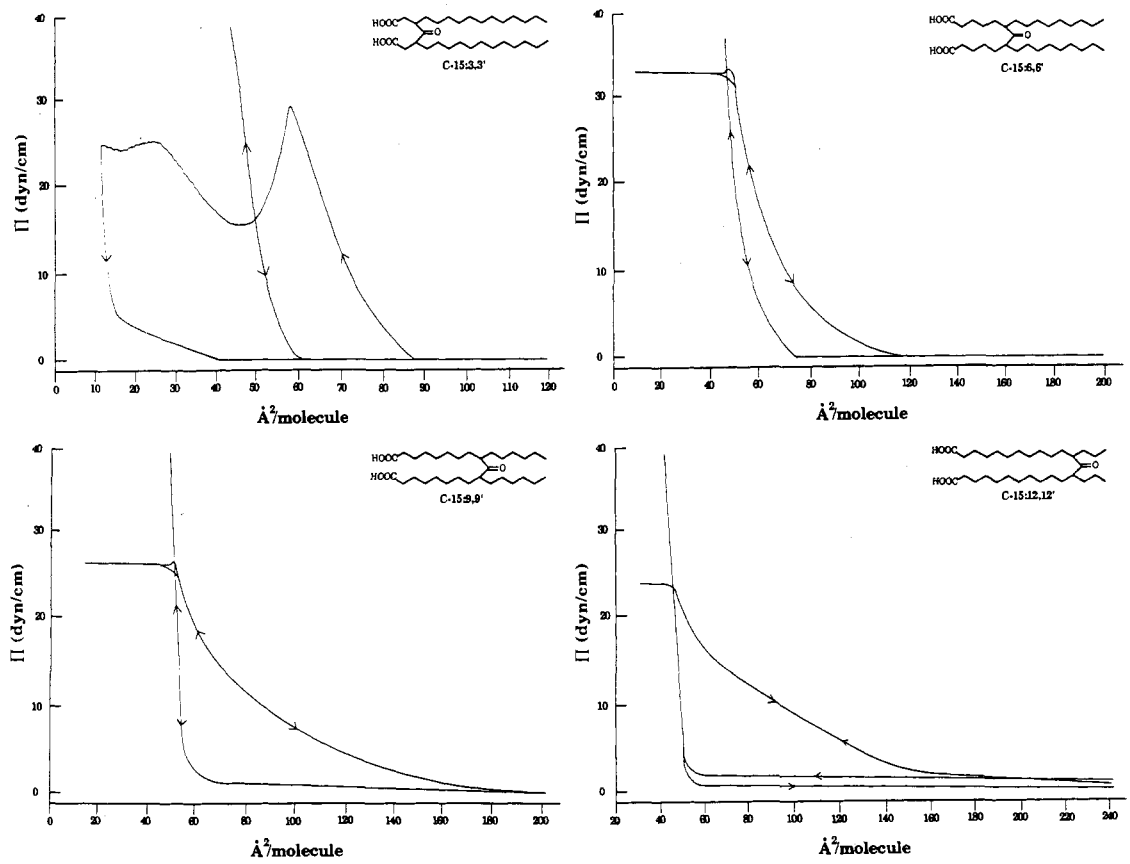

Figure 10. Surface pressure–area isotherms for the compression–expansion cycle of *d,l* and meso keto diacids linked at the 3,3′-, 6,6′-, 9,9′-, and 12,12′-positions on a pure water subphase at 25 °C.

group, with the added requirement that the two chains will be side by side with the two carboxylate groups in the water surface, it may be readily shown by molecular mechanics that the *d,l* systems in this conformation are less stable than the meso by 1.5 kcal/mol. Dr. Ned Porter's group has substantiated this analysis by determining the meso-*d,l* equilibrium constant for epimerization in hydrophobically enforced micellar and bilayer media.[25] The question then arises as to how this difference in intramolecular conformation manifests itself when films of meso and *d,l* diacids are compressed in monolayers.

To test this question, Porter's group has constructed a series of diastereomeric diacids of different chain lengths and with the carbonyl bridge at various positions along the chains. Figure 10 compares the Π/A isotherms for the meso and *d,l* diacids with 15 carbons in each acid chain linked at the 3,3′-, 6,6′-, 9,9′-, and 12,12′-positions. Comparison of these sets shows some points of striking similarity. The meso diacids all show an isotherm pattern that is similar to that which might be expected for two stearic acid molecules held side by side. For the *d,l* diacids there is a variety of isotherm patterns, all of which indicate the investment of an energy term that is lacking in their meso diastereomers. It is reasonable that this is the repulsive energy term that is developed when the two fatty acid chains of the *d,l* compound are brought into a position of colinearity with the carboxylate groups side by side in the surface, as would be required by compressing them to a condensed monolayer.

The difference in behavior can be visualized readily as shown in Figure 11 by using a pair of scissors or hedge clippers as a model for the diacids. The meso ketone diacids have their lowest energy conformation with the hydrogens eclipsed at the bridge and the chains bearing the carboxylate groups side by side in the ideal arrangement for a "good amphiphile". At large surface areas these molecules lie on the surface in the conformation of a closed pair of scissors. As the film is compressed, the two chains are forced side by side out of the surface and are finally packed in the same way as would be expected for a pair of stearic acids joined together. The similarity between the isotherms for all four of the meso keto diacids indicates that the point of juncture between the chains has relatively little effect on their compression.[26]

In marked contrast, the isotherms for the *d,l* keto acids all show a large extra degree of expansion at every pressure, and this varies with the position of the carbonyl bridge and is reminiscent of the behavior of the 12-hydroxy phospholipid in Figure 3. The high degree of expansion for these compounds and the large areas under their compression curves imply that extra work is required to force them to a condensed film with all molecules brought to a position perpendicular to the surface plane. In the case of the 12-hydroxy compound, the extra work was required to detach the hydroxyl group from the water surface.[8b] In the case of the *d,l*

(25) (a) Porter, N. A.; Ok, D.; Adams, C. M.; Huff, J. B. *J. Am. Chem. Soc.* **1986**, *108*, 5025. (b) Porter, N. A.; Ok, D.; Huff, J. B.; Adams, C. M.; McPhail, A. T.; Kim, K. *J. Am. Chem. Soc.* **1988**, *110*, 1896.

(26) (a) Harvey, N.; Rose, P. L.; Porter, N. A.; Huff, J. B.; Arnett, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 4395. (b) Arnett, E. M.; Harvey, N. G.; Rose, P. L. *Langmuir* **1988**, *4*, 1049.

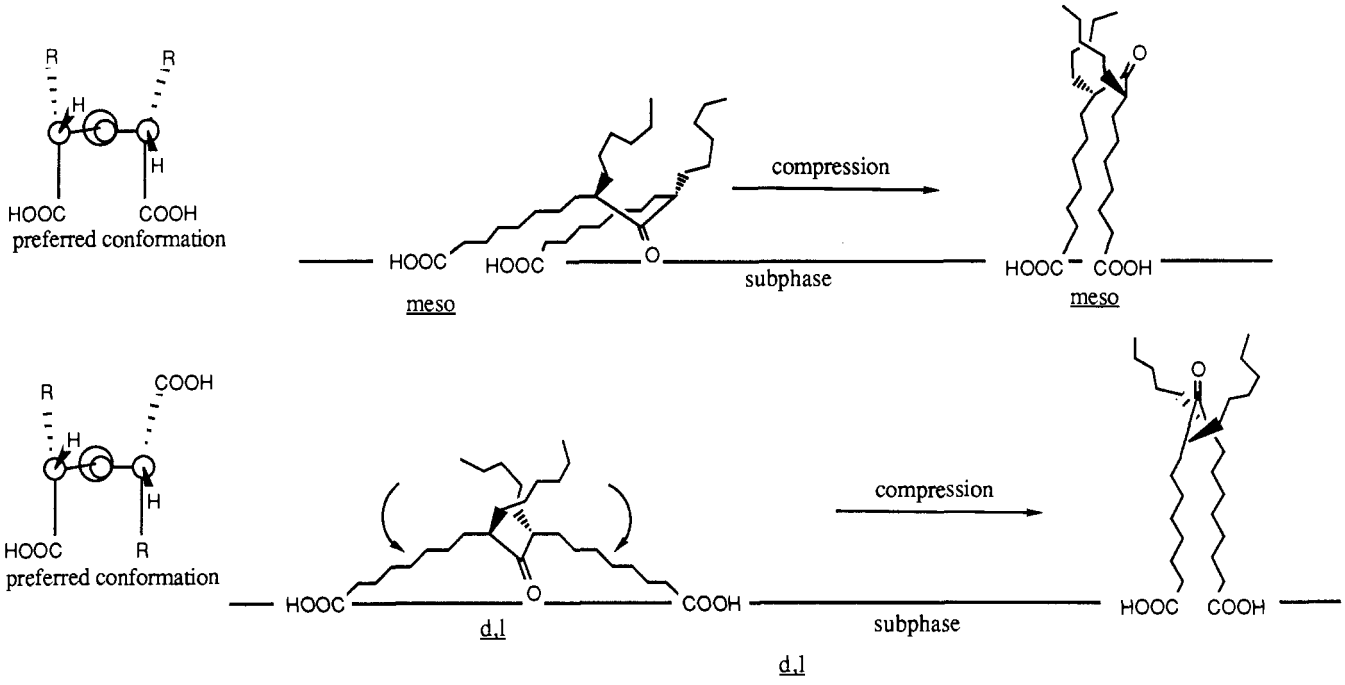

Figure 11. Preferred lowest energy conformations of *d,l* and meso diastereomers and the effect of configurational stereochemistry on the mechanism of film compression.

keto diacids, extra effort is required to overcome the stereochemically directed intramolecular conformation and to force the two chains together into a higher energy configuration of coalignment before or during the detachment of the chains from the surface. The "hedge clippers" lie wide open on the surface and must be forced to the closed arrangement as the chains are brought to a standing position. This is reflected also in a greater free energy of activation to viscous flow for the *d,l* isomer as opposed to its meso cognate.[26a] We have also shown that diastereomeric recognition between meso and *d,l* isomers is reflected in their excess free energies of mixing.[26b]

Directions for Future Studies. The work described here demonstrates the potential of monolayer techniques as applied to chiral films as a means for examining and manipulating the interplay between *intra*molecular and *inter*molecular forces in a state of matter that lies partway between the liquid and crystalline states. The methodologies of stereochemistry allow the comparison of isomers that differ only in shape or symmetry properties, while monolayer techniques allow one to observe the response of molecules whose conformations and packing can be varied continuously by variation of surface pressure. A much wider variation of surfactant structure will be required if we are to understand the nature of the interactions and packing in the most condensed states, where chiral recognition is expressed most completely. Structural techniques such as X-ray scattering, FTIR, and scanning tunneling microscopy should help provide insight into this question.

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