in the literature, but there are no unambiguous examples supporting the electron-transfer mechanism for the reaction of alkylcopper–Lewis acid reagents.

Finally, a possible theoretical rationale for our findings is as follows. The phenyl group, although larger than the methyl group, is a weak –I group. It therefore has an electronic preference for the outside position over the anti position, which contributes to stabilize 17(ii) over 17(i). This somewhat compensates for the repulsion between the phenyl group and the nucleophile. The latter steric effect is presumably still dominant; however, the preference for the anti position is reduced by the destabilizing electronic effect. The methyl group prefers the anti position to the outside position for both steric and electronic reasons and thus occupies the anti position in preference to the phenyl group.

It is natural to ask whether a similar argument might then apply to the reaction of the E isomers discussed earlier. Specifically, it could be argued that structure 16(i) (Figure 21, R = C4H9) is less stable than structure 16(iii) (R = C4H9), having the phenyl group inside and the methyl group anti. Indeed, the latter conformation is probably more favorable electronically. The steric preference for the anti position over the inside position, however, is very large, as can be seen in Table I. In 16(i), the value of φ is equal to −15° (see above, and Figure 21); for this value, the methyl group favors the anti position over the inside by about 3.9 kcal/mol. This preference for the less hindered position is probably too large to be overcome by the electronic effect which should favor 16(iii).

Summary and Conclusion

Ab initio calculations have been carried out to study the conjugate addition of alkylcopper reagents to chiral α,β-unsaturated carbonyl compounds. We have shown that there are certain similarities to the related nucleophilic additions to carbonyl groups, particularly with regard to the steric requirements of the addition to E isomers. On the other hand, the electronic characteristics are quite different; the substituent effects calculated in our study are more in line with the behavior expected for electrophilic reactions than with the findings of calculations on other nucleophilic additions.

Significant differences have been found between the modes of addition to E and Z isomers. In particular, the latter do not usually exhibit staggering of the C1 substituents with respect to the forming nucleophile–C2 bond, as the Felkin–Anh model would predict. This is a consequence of the steric encumbrance of the inside position as well as the possibility of coordination of the metal center by a suitable inside substituent.

Model transition states have been deduced from our calculations, and qualitative (and in some cases quantitative) agreement has been found between the calculated and observed stereoselectivity of the addition reactions to chiral α-alkoxy and α-phenyl α,β-unsaturated carbonyl compounds. The transition structures for addition to the E isomers prefer a conformation in which the two substituents prefer the anti and inside positions, respectively. In both cases, the hydrogen atom occupies the hindered outside position. When C1 bears an alkyl and an alkoxy group, the former takes the anti position and the latter the inside. When an alkyl and an aryl group are present, the former occupies the inside position and the latter the anti. In (Z)-4-alkoxy, α,β-unsaturated carbonyl compounds, the favored conformation in the transition state has the alkyl group outside and the alkoxy group inside, since this permits coordination of the oxygen to the copper center. Finally, in (Z)-4-aryl α,β-unsaturated carbonyl compounds, the preferred transition structure has the aryl group outside and the methyl group anti. We believe that these models provide a realistic description of the mode of addition of alkylcopper reagents as well as other alkylnitrogen compounds (including Grignard reagents) that undergo nucleophilic additions to the C=O bond of conjugated systems.

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Chiral Discrimination and Phase Transitions in Langmuir Monolayers

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Abstract: Chiral discrimination is investigated theoretically for chiral molecules that form an insoluble Langmuir monolayer at the water/air interface. For particular tripodal shaped molecules, we calculate the chiral discrimination for various types of intermolecular interactions: van der Waals, dipoles, charges, etc. The calculation, based on Boltzmann-weighted averaging of molecular or systems, predicts a preferred heterochiral behavior for van der Waals interactions and homochiral behavior for electrostatic ones. Other interactions are also discussed. To understand monolayer phase diagrams, we draw the analogy with sublimation experiments in bulk systems and propose a three-component thermodynamic model. The variable area per molecule and also the chiral discrimination parameter enter as important parameters in the model. Phase diagrams for conglomerates and racemic compounds are calculated in qualitative agreement with experiments. Possible connections and interpretation of existing experimental data are discussed, and some new experiments for chiral monolayers are proposed.

I. Introduction

Molecules with one or more chiral centers have been studied since the nineteenth century because of their tremendous importance in many biological and organic chemical processes as well as their applications as optically active materials. Although a vast amount of knowledge has been accumulated about chiral interactions, it is quite difficult to give an explanation to the origin of chiral discrimination and consequently predict whether a given chiral molecule interacts more favorably with its stereomeric twin.
or with its stereomeric mirror image. Experimentally, hundreds of natural and artificial chiral molecules have been studied. Crystalline structures of pure chiral substances called enantiomers and of 1:1 solid mixtures of the two different enantiomers—racemic compounds (racemates)—have been identified by using crystallography techniques. Phase diagrams of the melting-point temperature as function of enantiomeric composition are also known for many chiral systems and help in the identification of chiral discrimination on a macroscopic scale.

In addition, chiral molecules forming insoluble amphiphilic monolayers at the water/air interface have also been investigated. The motivation of studying such pseudo-two-dimensional systems is the following: (i) Many of the natural phospholipids, which are the building blocks of biological cell membranes, are chiral, and their chirality is known to be of importance to the interactions of the cell membrane with proteins and other substances passing through it. (ii) Chiral molecules have complicated crystalline structure as bulk solids. It is simpler to study chiral forces at the two-dimensional water/air interface because both the solid and liquid phases are highly incompressible.

Two important types of experiments exist for chiral monolayers: using epifluorescence microscopy, various groups have demonstrated the existence of microdomains with chiral domain boundaries in the range of few dozen micrometers. The chiral domain shapes are most probably due to a nonequilibrium growth process and are very different from the three-dimensional crystal shapes of chiral molecules having regular facettike boundaries in accord with their crystalline space group. Unfortunately, no systematic microscopy studies exist for monolayers of enantiomer mixtures as a function of enantiomeric composition.

The second type of monolayer experiments demonstrates the sensitivity of surface pressure-area isotherms to the specific stereochemistry. A chiral discrimination is found by comparing isotherms of pure enantiomeric amphiphiles with their enantiomer mixtures.

The aim of the present study is to propose a simple model for chiral discrimination and phase transitions in chiral monolayers. After briefly reviewing chiral discrimination and related phase diagrams for bulk, section II, and for chiral monolayers, section III, we calculate the chiral discrimination between two tripod-shape molecules in section IV. Some specific interactions are presented in section V. In section VI, we incorporate chiral interactions into a thermodynamic model for condensation and calculate the relevant monolayer phase diagrams. Finally, section VII contains further discussion of our results. Connection with experiments and some concluding remarks are given in section VIII.

II. Chiral Discrimination and Phase Diagrams of Enantiomer Mixtures

The crystallization of enantiomers and enantiomer mixtures is well documented for bulk three-dimensional systems. For an excellent review see ref 2. Melting-point phase diagrams exist for many enantiomer mixtures. The crystalline structure of different solid phases has been studied by conventional X-ray techniques. In addition, the difference between solid racemic

Figure 1. Melting temperature $T_m$ as a function of the enantiomer composition $x$, for (a) conglomerates, (b) racemic compound (racemates), (c) solid solutions. $T_A$ and $T_R$ are the melting points for pure and 1:1 enantiomer mixtures, respectively. $T_R$ is eutectic point. Two-phase regions between the liquid (liq), D solid (Sp), L solid (Sl), and the racemic solid (Sr) are indicated.

For congenomers, Figure 1a shows the melting temperature $T_m(x)$ as a function of $x$, the molar fraction of the two enantiomers D and L, called also the enantiomeric or racemic composition. $x = 0$ is pure D, and $x = 1$ is pure L. $T_m(x)$ varies between $T_A = T_m(x=0)$ and $T_R = T_m(x=1)$ for pure enantiomers and $T_R = T_m(x=0.5)$, with $T_A > T_m(x) > T_R$. For a given composition $x$, below the melting point $T_m(x)$ but above $T_R$, the liquid coexists with a pure enantiomeric solid: liquid + Sp for $x < 0.5$, and liquid + Sr for $x > 0.5$. The point $T = T_R, x = 0.5$ is an eutectic point. Since the homochiral interactions (HOC), D-D and L-L, are more favorable, for congenomers, than the heterochiral ones (HEC),


D-L, solidification is always accompanied by a full segregation of the two pure enantiomeric crystals, \( S_D \) and \( S_L \). Hence, for \( T < T_R \), the pure D crystal, \( S_D \), coexists with the pure L crystal, \( S_L \).

The second type of melting-point phase diagram is shown in Figure 1b and is characteristic of racemic compounds (racemates). For \( x = 0.5 \), the liquid solidifies at \( T = T_R \) as a racemic compound—a single crystal with no optical activity. \( T_R \) can be higher (as in Figure 1b) or lower than the pure melting temperature \( T_A \). At \( T = T_E \), there are two eutectic points symmetric with respect to \( x = 0.5 \). Above \( T_E \), the liquid coexists either with one of the pure solids: liquid + \( S_D \), liquid + \( S_L \), or with the racemate solid, liquid + \( S_R \). Below \( T_E \), there are two two-phase regions: \( S_R + S_D \) and \( S_R + S_L \). The tendency of the enantiomer mixture to form a racemic compound solid (at least in the vicinity of \( x = 0.5 \)) is an indication that the heterochiral interaction D-L is preferred over the homochiral interactions, D-D and L-L, in contrast with conglomerates.

The third type of racemic behavior is that of solid solutions, Figure 1c. The main difference between a solid solution and the two other cases discussed above is the existence of a racemic solid over the whole range of racemic compositions. If \( x > 0 \), with \( T_M(x=0.5) \) being higher (positive azetropic point), or equal to the pure \( T_M(x=0) \) (ideal solid solution). These three possibilities are shown in Figure 1c.

### III. Monolayer Isotherms and Chiral Discrimination

In 1982, Stewart and Arnett\(^{10}\) reviewed experimental works on phase behavior of chiral amphiphilic monolayers. Only a few experiments have been reported in the literature. The method most commonly used for detecting chiral discrimination is the measurement of the surface pressure vs the area per molecule while fixing the temperature (isotherms). This technique was invented by Langmuir\(^{9}\) and is widely used for monolayers of insoluble achiral amphiphiles at the water/air interface.\(^{10}\)

For relatively compressed monolayers having area/molecule in the range of a few dozen \( \text{Å}^2 \) and surface pressure in the range of few dyn/cm, a “kink” in the isotherm indicates a transition from an expanded to a more condensed phase of the monolayer. This is the so-called liquid expanded—liquid condensed transition. We note that the origin of the liquid expanded—liquid condensed transition is not well understood and a controversy still exists on whether this transition is a special liquid-to-liquid transition or just a liquid-to-solid one with poorly controlled environment.\(^{11}\)

Chiral discrimination manifests itself as a deviation of the enantiomer mixture isotherm from the pure enantiomeric one. In particular, the transition pressure (the pressure where the kink

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for the former play the role of the surface pressure and area/molecule for the latter. Thus, monolayer phase diagrams in the $\pi$-$\sigma$ plane should also look like Figure 2. In some of the experiments reviewed below, the whole surface pressure composition phase diagram was studied, and the identification of the chiral behavior of the monolayer, based on the analogy with sublimation, is possible. However, in several of the earlier studies only the pure and the 1:1 D + L isotherms have been obtained. With this partial information, we can identify a racemate (HEC) behavior for the cases where the 1:1 D + L transition pressure is lower than the enantiomeric pure one, Figure 4. Unfortunately, it is not possible to identify unambiguously the chiral behavior for the opposite case where the transition pressure for the 1:1 D + L isomers is higher than for the enantiomeric pure one, Figure 3, because both conglomerates and racemates can show this relation.

Zeelen has observed a liquid expanded–liquid condensed transition for N-stearoyltyrosine in its pure enantiomeric form and the lack of the transition in the 1:1 L + L racemic mixture. We can argue that the transition pressure, $\pi_L(D) = \pi_L(D) > \pi_L(L)$; thus, we expect a HEC (racemate) behavior as was explained above (cf. Figures 2b and 4).

More recently, Arnett et al. have found for a stearamide with one chiral center (N-(a-methylbenzyl)stearamide) spread on an acid subphase a chiral discrimination with $\pi_L(D+L) > \pi_L(L)$. Here, a definite identification of the chiral behavior requires the study of the full phase diagram, $\pi_L(x)$. Note that, in general, for racemates, any $\pi_L(D+L) > \pi_L(D)$ is possible, although $\pi_L(D+L) < \pi_L(D)$ for a strong HEC tendency.

A detailed study of a chiral lipid monolayer (N-myristoylalanine) has recently been published by Bouloussa and Dupeyrat. Pressure–area isotherms have been measured for several mole fractions of D/L and subsequently the transition pressure $\pi_L$ has been determined as a function of the D/L mole fraction x and the temperature T. From the phase diagram, the authors concluded that the monolayer behaves as a solid solution with a positive azetropic point (see our Figure 1c) with a HOF preference. Although we do not discuss solid solution behavior in monolayers, such a possibility exists. In bulk systems, a solid solution is an indication of a weak chiral discrimination. However, we believe that a conclusive determination of the phase behavior requires further investigation.

In a different experiment, Dvolaitzky and Guedeau have observed a HEC behavior using an amphiphile with two chiral centers in the polar head group (hexadecanol–thiophosphoryl-2-phenylglycinol). The $\pi_L(x)$ phase diagram has a minimum at $x = 0.5$ and is similar to the phase diagram of racemic compounds, our Figure 2b, in accord with their own conclusion of HEC behavior.

In summary, we would like to remark that the proposed analogy with sublimation can be useful. However, to achieve a better characterization of chiral monolayers, isotherm experiments have to be repeated over the whole range of enantiomeric composition as was done in a few studies. Just comparing the pure with the 1:1 enantiomer mixture isotherms can often be incomplete for determining the chiral behavior.

IV. Chiral Discrimination in Langmuir Monolayers: Theory

One of the simplest examples of a chiral molecule is a tetrahedral (asymmetric) carbon connected to four different groups: A, B, C, and D. It is easy to see that permutations of any pair of the four groups give a new molecular configuration that is the mirror image of the original molecule. In the past, theoretical studies have used a multipole expansion of the electromagnetic forces between two tetrahedral model molecules, and the dependence of the chiral discrimination on intermolecular distance and other parameters have been calculated.

For an insoluble Langmuir monolayer, the molecules are confined on the water/air interface. We propose the following simple model for a particular chiral amphiphile: one chiral center (e.g., a carbon or a phosphorous) connected to four different groups A, B, C, and D. Three of them, say A, B, and C, are restricted to lie on the water/air interface, while the fourth one, D, is a hydrophobic (aliphatic) chain pointing out of the water surface and into the air, as is shown on Figure 5. We coined the term tripod amphiphile for these chiral amphiphiles because they have three anchoring points on the water surface. Similar ideas about oriented triads have been used by Amaya to study certain chiral association in three dimensions.

Two possible stereomers can now be constructed with such tripod molecules. The groups A, B, and C can be arranged either counterclockwise or clockwise on the water surface, while the aliphatic chain D always points up into the air. These two molecular configurations form the two different enantiomers D and L, Figure 5.


\[(17)\] Craig, D. P. In ref 1, p 293.

\[(18)\] Schipper, P. E. In ref 1.


\[(20)\] (a) Schipper, D. P. Chem. Phys. 1977, 26, 29. (b) Ibid. 1979, 44, 261.


\[(22)\] In the model, tail–tail interactions are completely neglected. However, since the tail always points into the air, it forbids transformation of the D-tripodal base into the L one and vice versa.

Figure 7. One of the nine orientations used to calculate Z_{DD} and Z_{DL}.

The effective interaction between a pair of tripod chiral molecules is calculated by using the following assumptions: (a) We consider interactions only between groups that are spatially the closest and neglect longer range interactions. For example, we neglect cross interactions between farther neighbors shown in Figure 6b. In a more refined calculation, the effective intermolecular interaction will depend on all pairwise interactions between the various groups of each molecular. (b) A further simplification has to do with the relative orientation of neighbor molecules. We have chosen a possible, but certainly not unique, “back-to-back” arrangement of the tripod molecules, Figure 6a. The advantage of such an arrangement is that it can lead to a relatively closed packing of the monolayer with a hexagonal symmetry. Another possible arrangement not included in the present model is shown in Figure 6c. In our arrangement, Figure 6a, the three discrete 60° in-plane rotations of each molecule leaving the global orientation of the tripod base invariant are allowed. In a more realistic calculation, the second virial coefficient (or the pair partition function as explained below) should be calculated by properly averaging over the continuum range of all possible relative orientations.

Although these assumptions are somewhat restrictive, our simple model leads to chiral discrimination in several interesting cases and may be tested experimentally. The “effective” interaction between two molecules is calculated by averaging over the internal degrees of freedom—the relative orientation of one molecule with respect to the other—with the proper Boltzmann factor. Thus, the relevant quantity to calculate is the partition function of the degrees of freedom—the relative orientation of one molecule with respect to the other—with the proper Boltzmann factor. Thus, the relative orientation of neighbor molecules are connected to the fact that $V_{ij}$ in (4) depends only on the product of $\alpha_i$ and $\alpha_j$.

Though not able to prove analytically the inequality $\Delta < 0$, we have verified it numerically for several cases: (i) $\Delta = 0$ whenever two of the three $\alpha_i$'s are equal; (ii) high-temperature expansion up to third order in $1/T$ $\Delta \approx -\frac{f_0}{2}(M/k_B T)(\alpha_0 - \alpha)^2(\alpha_0 - \alpha)(\alpha_0 - \alpha) < 0$ (5)

(vi) $\Delta < 0$ if one of the $\alpha_i$'s is zero, e.g., $\alpha_A > \alpha_B = \alpha_C = 0$; (v) $\Delta < 0$ if one of the $\alpha_i$'s lies midway between the two others: $\alpha_A - \alpha_B = \alpha_B - \alpha_C$.

Details on the proof of (iii)–(v) are given in the Appendix.

3. Two van der Waals Groups and a Charged Group. Suppose that group A and B interact purely via van der Waals interactions and C is a charged group. Neglecting second-order terms in $f_{CC}$ = $u \approx 0$ and $f_{CB} = f_{BC} \approx v \ll 1$, we obtain

$\Delta = (f_{AB}^2 - f_{AB}f_{BB}) + (2v - u)(f_{AA} + f_{BB} - 2f_{AB})$ (7)

where

$$ f_{ij} = \exp\left(\frac{M}{k_B T}\alpha_{ij}\right) \quad \alpha_{ij} = \alpha_A \text{ or } \alpha_B $$

For $u \approx 0$, the second term in (7) can be neglected and

$\Delta \approx \exp\left(\frac{2M}{k_B T}\alpha_{AB}\right) \left(1 - \frac{M}{k_B T}(\alpha_A - \alpha_B)^2\right) < 0$ (8)

From (8), we see that this case is HEC.

4. Electrostatic Interactions. Two of the three groups are oppositely charged, e.g., B positive and C negative with $w = 1/f_{BB} \gg f_{CC}$.
Chiral Discrimination in Langmuir Monolayers

Figure 8. HOC ground-state arrangement for case 4 or section V.

Figure 9. HEC ground-state arrangement for case 5 or section V. Nearest-neighbor groups are always the same.

If the third group is apolar and interacts equivalently with B and C, then

$$\Delta = (w - f_{BB})(w + f_{BB} + 2u - 4v)$$

where $u = f_{AA}$ and $v = f_{AB} = f_{AC}$. HOC ($\Delta > 0$) occurs as soon as

$$w > f_{BB} \text{ and } w > 4v - 2u - f_{BB}$$

or

$$w < f_{BB} \text{ and } w < 4v - 2u - f_{BB}$$

However, condition 10' cannot occur since $w = f_{BC} \gg f_{BB}$ for B and C oppositely charged. Thus, only (10) is the condition for HOC.

As a first approximation we can set $f_{BB} = 0$ and write a simplified expression for the chiral discrimination parameter:

$$\Delta \approx w^2 + 2w(u - 2v)$$

As soon as $w > 2(2u - u)$, then $\Delta > 0$ (HOC).

Thus, for strong electrostatic attraction, $w \gg 1$, HOC is the preferred arrangement. The same conclusion holds if the opposite charges B and C are replaced by two opposite dipoles pointing in the direction perpendicular to the monolayer plane. For two oppositely charged and one neutral group, a most likely ground-state arrangement of our tripod molecules on a hexagonal lattice is shown on Figure 9. This is an HOC arrangement with opposite charge groups as nearest neighbors.

5. Strongly Preferred Like Groups. Intermolecular interactions strongly prefer the same groups as nearest neighbors: $f_{ij} > 0$ for $i = j$, and $f_{ij} = 0$ for $i \neq j$. For this case

$$\Delta = -(f_{AA} + f_{BB} + f_{CC} + f_{CC}f_{AA}) < 0$$

clearly, a HEC case. Moreover, the ground state ($T = 0$) can be obtained by arranging the D and L enantiomers on two interpenetrating triangular sublattices, Figure 9. The D sublattice has as its nearest neighbors only sites that belong to the L sublattice and vice versa. For this HEC arrangement (similar to an antiferromagnetic ground state on a hexagonal lattice) all interactions between like enantiomers are avoided.

Another possibility is having all three like interactions A, B, and C with the same weight, $f_i = u$, which differs from the weight of unlike groups, $f_{ij} = v$, $i \neq j$. This is also HEC (even for $u < v$, see case 6 below) since

$$\Delta = -3(u - v)^2 < 0 \quad \text{(HEC)}$$

6. Strongly Preferred Unlike Groups. The opposite case of 5 occurs when only different groups can be nearest neighbors: $f_{ij} = 0$ for $i = j$ and $f_{ij} > 0$ for $i \neq j$. Calling $u = f_{AB}, v = f_{BC},$ and $w = f_{CA} \Delta = u^2 + v^2 + w^2 - 2uv - 2uw$ (14)

For the physically realizable quarter, $u, v, w \geq 0$, the two cases HEC and HOC are possible depending on the values of $u, v,$ and $w$. The boundary, $\Delta = 0$, defines a cone of revolution in the three-dimensional parameter space ($u, v, w$), centered around the $u = v = w = (111)$ direction. The HEC ($\Delta < 0$) region lies inside the cone while the HOC region is outside.

7. One “Passive” Group. If one of the three groups A, B, and C is “indifferent”, e.g., $f_{AC} = w$ for any $i = A, B, \text{or } C$

$$\Delta = (f_{BC} - w)^2 - (f_{BB} - w)(f_{CC} - w)$$

then both HEC and HOC cases can be obtained. In particular, if $f_{BC}$ is larger than any of the other interactions, then $\Delta > 0$ (HOC).

VI. Phase Diagram for Chiral Monolayers: Theory

In section IV we averaged over the intermolecular interactions $V_0$ and obtained the chiral discrimination parameter $\Delta$. This single parameter indicates whether a pair of the same enantiomers D-D or L-L interacts more or less favorably than a pair of opposite enantiomers, D-L.

A thermodynamic model can now be constructed using this chiral discrimination as an important parameter. In general, three pair interactions exist for the two species; $E_{DD}$ and $E_{LL}$ are the interaction energies of the pair D-D and L-L, with $E_{DD} = E_{LL}$ because of the left-right symmetry, and $E_{DL} = E_{LD}$ is the interaction of the pair D-L.

The interactions $E_i$ between molecules as a whole should be distinguished from the previously introduced interactions, $V_0$, between the three molecular groups A, B, and C. By calculating the two-molecule partition function, we averaged over the various intermolecular group interactions $V_0$ with the proper Boltzmann factor and obtained the chiral discrimination parameter $\Delta$. For convenience, we introduce another (but equivalent) chiral discrimination parameter

$$J = \frac{1}{4}(E_{DL} - E_{DD}) = \frac{1}{4}k_BT \log \left(\frac{Z_{DD}}{Z_{DL}}\right)$$

instead of

$$\Delta = Z_{DD} - Z_{DL}$$

Both $\Delta$ and the new chiral discrimination parameter $J$ (eq 16) can be used interchangeably because $\Delta > 0$ if and only if $E_{DL} - E_{DD} > 0$ ($<0$); thus, both change sign simultaneously.

When a chiral enantiomer mixture is studied in a Langmuir trough, the area/molecule is controlled by the surface pressure $\Pi$. To allow a variable area/molecule, we use a lattice-gas model with three components: the two enantiomers, D and L, plus vacancies V as a third component. The “artificial” vacancies allow us to vary the area/molecule of the “real” molecules. The three-component model D + L + V can also be used to study sublimation of bulk three-dimensional systems where V is the vapor phase, mixtures of the two enantiomers with an achiral solvent V, or with some modifications even a D + L solution with a chiral solvent.

The three area fractions (two-dimensional volume fractions) of D, L, and S are $\Phi_D, \Phi_L$, and $\Phi_V$. The “real” area/molecule is proportional to $1/(\Phi_D + \Phi_L)$, since the three fractions add up to unity, $\Phi_D + \Phi_L + \Phi_V = 1$. In addition to the two interactions, $E_{DD} = E_{LL}$ and $E_{DL},$ between D and L, two other interactions describe the interactions with V: $E_{DV} = E_{LV}$ and $E_{VV}$.

The free energy of the three-component system is $F = E - TS_{\text{mix}}$, where $E$ is the internal energy and $S_{\text{mix}}$ is the entropy of mixing of the three components:

$$S_{\text{mix}} = -k_B \log \Phi_D + \Phi_L \log \Phi_V$$

(17)

$E = 1/2\Phi_D^2 E_{DD} + 1/2\Phi_L^2 E_{LL} + 1/2\Phi_D\Phi_LE_{DL} + 1/2\Phi_L^2 E_{VV} + \Phi_V E_{VV} + \Phi_D E_{DV} + \Phi_L E_{LV}$

(18)

Equation 18 includes the most general pairwise interactions between D, L, and V. From (17) and (18), $F = E - TS_{\text{mix}}$ is the free energy within mean-field approximation for the three-component system. In (18) there are four independent interactions $E_i$ and two independent area fractions (densities) $\Phi_i$. A similar expression for $F$ has been introduced by Schipper and Harrowell.

to compare solubilities of D and L enantiomers in a chiral solvent.

The following reduced densities are introduced for convenience:

$$\frac{Q}{D} = \Phi_D + \Phi_0 = 1 - \Phi_V$$

which is proportional to the monolayer coverage and

$$M = \Phi_D - \Phi_L$$

The densities $M$ and $Q$ are related to the experimentally controlled $D/L$ mole fraction: $x = (1 - M/Q)/2$.

The internal energy $E$ can be written as a function of $M$ and $Q$. Since linear terms in $E$ can be absorbed in the definition of the chemical potentials (see below), $E$ has the following quadratic form:

$$E = -kQ^2 - JM^2$$

with

$$K = -\frac{1}{2}(E_{DD} + E_{DL} + 2E_{Vv} - 4E_{DV})$$

$$J = \frac{1}{4}(E_{DL} - E_{DD})$$

The parameter $K$ measures the tendency of the system as a whole to condense, whereas $J$ is equal to the chiral discrimination (16); $J > 0$ is homochiral (HOC), $J < 0$ is heterochiral (HEC), and $J = 0$ if and only if $\Delta = 0$ (no chiral discrimination).

The convexity of the free energy $F$ as a function of $Q$ and $M$, (17)-(22), determines the phase behavior:

$$F(Q,M) = -kQ^2 - JM^2 - TS^{\text{mix}}$$

with

$$S^{\text{mix}} = -k_B[\frac{1}{2}(Q + M) \log (Q + M) + \frac{1}{2}(Q - M) \log (Q - M) + (1 - Q) \log (1 - Q) - Q \log 2]$$

Nonconvex regions of $F(Q,M)$ are multiphase regions. A common tangent construction indicates the extent of such multiphase regions. Alternatively, we look for coexistence of the minima of $G = F - DQ - HM$ (25) with respect to $Q$ and $M$, where $D$ and $H$ are the two conjugated fields (chemical potentials) to $Q$ and $M$, respectively. Notice that all linear terms omitted in (21) can be absorbed in the two fields $D$ and $H$.

The minima of $G$ satisfy the following equations:

$$\frac{\partial G}{\partial Q \mid M} = 0 \quad \frac{\partial G}{\partial M \mid Q} = 0$$

leading to

$$D(Q,M) = -2kQ + k_B T[\frac{1}{2} \log (Q^2 - M^2) - (1 - Q) - \log 2]$$

$$H(Q,M) = -2JM + \frac{1}{2}k_B T \log \frac{Q + M}{Q - M}$$

For given energy parameters $J$ and $K$ and a given temperature $T$, the two-order parameters $Q$ and $M$ depend on the two fields $D$ and $H$. In general, the transcendental equations (26) and (27) have to be solved numerically. Several minima of $G$ for a given $D$ and $H$ indicate multiphase regions. The value of the free energy at its minimum, $G^* = G_0$, can be obtained by substituting $D(Q,M)$ and $H(Q,M)$ from (26) and (27) into the general expression for $G$, (23)-(25):

$$G_0(Q,M) = KQ^2 + JM^2 + k_B T \log (1 - Q)$$

Using the relationship between the pressure $\Pi$ and the equilibrium free energy for lattice-gas models, the phase diagram can be calculated. Fixing the material-dependent energy parameters $J$ and $K$, one plots isotherms, i.e., the variation of the surface pressure $\Pi$ with the area/molecule or with $Q = \Phi_D + \Phi_L$, for fixed temperature. Two other useful plots are (i) $\Pi-x$ diagram for a fixed temperature and (ii) $\Pi-T$ diagram for a fixed $D/L$ mole fraction $x$.

It can be shown that our free-energy formulation for the $D + L + V$ chiral mixture, (26) and (27), is identical with the mean-field approximation of a general three-component liquid mixtures, extensively studied within the framework of Blume-Emery-Griffiths (BEG) spin-1 model. In the BEG model, a spin variable having three degrees of freedom ($S_i = -1, 0, 1$) for the three liquid components is assigned to each site of the lattice. For chiral monolayers, $S_i = +1, -1, 0$, is a site occupied by D, L, or an empty site (vacancy), respectively. The BEG model has the following Hamiltonian:

$$-\mathcal{H} = \sum_{\langle i,j \rangle} S_i S_j + \sum_{\langle i,j \rangle} S_i^2 S_j^2 + H \sum_{\langle i,j \rangle} S_i + D \sum_{\langle i,j \rangle} S_i^2$$

where the sum $(i,j)$ is over nearest-neighbor sites of the lattice and $D$, is a generalization of a lattice-gas model with $S_i = 0$, or used to study multi-component systems such as liquid–gas or binary liquid mixtures. Therefore, we make use of previously calculated phase diagrams for the BEM model (within mean field) for chiral mixtures.

In Figure 10, the $\Pi-x$ phase diagram is plotted schematically for the homochiral case (HOC), $J > 0$ and low temperatures, $0 < k_B T/J < 2.95, J/K \approx 0.3$. The exact phase diagram can be found in ref 27c. For this range of temperatures, the model gives essentially a conglomerate phase diagram as was explained in section III. The three phases, liquid (liq), D solid (SD), and L solid (SL) are separated by three two-phase regions: liq + SD, liq + SL, and SD + SL. This is very similar to the actual conglomerate phase diagram presented in Figure 2a.

The main difference between the calculated and experimental phase diagrams, Figures 10 and 2a, is the extent of the "pure" enantiomeric solid in Figure 10, namely, the existence of a solid solution in the vicinity of the pure enantiomers D and L. Such phase diagrams are characteristic of chiral mixtures called pseudocacereate. However, to understand it theoretically, we recall that the BEG model is appropriate for liquid mixtures or liquid–gas transitions. As for any lattice–gas model, it is less appropriate to describe solidification. Only for very low temperatures, the extent of the single solid phases shrinks to zero, and the phase diagram then looks exactly like that for a true conglomerate. Another complication occurs at higher tempera-

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(b) Ibid. 1975, 11, 2090-2100.
(c) Ibid. 1976, 11, 2101-2110.
(32) A general three-component mixture has also a cross Q-M term in the free energy. For enantiomer mixtures, such a term is always zero because of the left–right symmetry.
(33) See Chapter 2.4 in ref. 2.
Chiral Discrimination in Langmuir Monolayers

observed in solidification of enantiomer mixtures. Order parameters have to be allowed. Instead of the two order is not enough to complicated treatment is needed even on a mean-field level. It (23)-(29), for \( J < 0 \) and \( K > 0 \). Compare with sublimation of racemates, Figure 2b.

- For the heterochiral case (HEC), \( K > 0 \) and \( J > 0 \), a more complicated treatment is needed even on a mean-field level. It is not enough to look for the solution of (26)-(28) for \( J < 0 \). As for binary alloys (\( \alpha \)-brass), the two possible "antiferromagnetic" order parameters have to be allowed. Instead of the two order parameters \( M \) and \( Q \), we will have three: the coverage \( Q \) as before, but two enantiomeric compositions—one on sublattice \( A \), \( M_A = (S_A, \ldots) \), and the second on sublattice \( B \), \( M_B = (S_B) \). The detailed phase diagrams will be presented elsewhere. We expect them to show also a pseudoracemate behavior, where pure enantiomeric solids \( S_P \) and \( S_L \), as well as the racemate solid \( S_R \), extend over a finite range of racemic compositions. Otherwise, the expected phase behavior shown schematically in Figure 11 is quite similar to the actual racemic compound behavior, Figure 2b.

VII. Discussion

In section V, we discussed the chiral discrimination for several particular types of interactions. For simplicity, only two nearest-neighbor interactions have been taken into account, and a Boltzmann-weighted average has been performed on the nine "back-to-back" relative orientations of a pair of tripod molecules. In particular, we would like to note the difference between van der Waals (case 2) and electrostatic (case 4) interactions. For the former, a HEC behavior is predicted, whereas the latter is HOC. For most of the other cases, chiral discrimination depends more closely on the relative strength of the various \( V_{ij} \) interactions, and no general conclusion is possible.

Another chiral molecular arrangement worth mentioning is an asymmetric carbon connected to three different polar or charge groups and to an aliphatic tail. This proposed molecule is an amphiphile and has two stereomeric arrangements, \( D \) and \( L \). To the best of our knowledge such a chiral amphiphile has not been studied for its chiral discrimination. Theoretically, treating the case of three charges or dipolar groups is rather complicated (frustration effects), in contrast to tripods with only two opposite charges discussed in section V. Strong competition between electrostatic interactions can lead to complex crystalline order even for the two-dimensional monolayer geometry. Our simple model, which averages over all intermolecular interactions and predicts a single parameter—the chiral discrimination—is probably less suitable for this case.

In section VI, we presented a thermodynamical model that predicts qualitatively some of the features of a monolayer phase diagram. A three-component model is used to mimic the variable area per molecule of chiral amphiphilic monolayers. The molecular interaction parameters \( E \) depend crucially on the chiral discrimination. Generalizations of this model can describe solutions of enantiomer mixtures as well as sublimation of bulk enantiomer mixtures.

Most of the important features of conglomerate phase diagrams are reproduced theoretically, Figure 10, although the final extent of the "pure" \( D \) and \( L \) solids is an artifact (pseudoracemate behavior). For racemic compounds, the study of the phase diagram is more complex, but from preliminary studies we expect a qualitative agreement with experiments (Figures 2b and 11).

We also note that the mean-field approximation employed here does not predict correctly all the features of the two-dimensional critical behavior. Critical fluctuations should be included in future calculations. On the other hand, our mean-field phase diagrams can also be applied to explain three-dimensional sublimation or solutions of chiral mixtures.

VIII. Applications and Connection with Experiments

Is it possible to compare our predictions to available experimental data on chiral monolayers? Unfortunately, at present the answer is no. The main problem is that, in past experiments, chiral monolayers did not have the simple tripod structure. In some cases, the amphiphiles even have two chiral centers. Another important issue, even with one chiral center, is the need to attach to the chiral carbon three groups that will lie on the water/air interface.

Nevertheless, the various cases discussed earlier can be realized in experiments even if the affinity to the water/air interface is caused only by one or two groups, provided that the molecule behaves as an "effective" tripod, i.e., its molecular orientations include mainly rotation of the tripod backbone on the water surface. Our general consideration of the various types of molecular interactions, charges, dipoles, and van der Waals, can be tested, at least qualitatively, by designing new chiral tripods.

Another possible setup to test chiral discrimination in monolayers is the adsorption of a chiral monolayer on a graphite surface or the use of chiral molecules in graphite intercalation compounds.\(^{34}\) If a physisorption is carried out so that \( \alpha \)-brass always the same three of the four molecular groups lie on the graphite surface, chiral discrimination can play an important role.\(^{35}\) However, an additional complication of adsorption on solid surfaces such as graphite is the existence of preferred adsorption sites. The solid surface cannot be regarded only as a passive support. Rather, the interactions of the surface with the chiral molecules can influence the two-dimensional ordering of the monolayer.

Finally, we note that a promising future experiment, in our opinion, may be a simultaneous comparison between epifluorescence microscopy and a detailed monolayer isothermal investigation for the same material. As a first step, it will be even interesting to observe the chiral pattern formation (or the lack of it) as a function of enantiomeric composition for certain phospholipids where chiral domains have been seen for pure enantiomers and for some 1:1 D + L mixtures.\(^{47}\) Will a 1:1 D + L mixture show achiral domains or the two types of chiral domains side by side? The two are possible and depend on the chiral discrimination.

As a continuation, a comparison with the monolayer phase diagrams can follow and could greatly enhance our understanding of chiral discrimination in monolayers. We hope that the present study will motivate such experimental investigations. One possible difficulty to tackle is to find chiral amphiphiles that on one hand can be used in epifluorescence microscopy and on the other hand have a measurable variation in the transition pressure (bigger than a few dyn/cm) as the enantiomer composition is varied.

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Appendix

The proof of the inequalities used for van der Waals interactions, section V, is presented here.

(a) To show that \( \Delta < 0 \) in the low-temperature expansion (6), we recall that for any \( x \neq y \)

\[
\exp(x^2) + \exp(y^2) - 2 \exp(xy) > 2 \exp(\frac{1}{2}x^2 + \frac{1}{2}y^2) > 0
\]

(A1)

where the convexity of the exponential function is used in (A1); the HEC inequality in (6) immediately follows.

(b) For case iv of section V, one of the \( a_i \)’s is zero while the other two are positive. For example, \( a_A > a_B > a_C = 0 \). Using the expression for \( \Delta \) from (3) and (4) with

\[
x^2 = \frac{M}{k_B T} a_A^2, \quad y^2 = \frac{M}{k_B T} a_B^2
\]

we get\(^{(36)}\)

\[\Delta = e^{2\nu} - e^{2\nu x} + e^{\nu x} - e^{\nu y} = (e^{\nu y})^2 - (e^{\nu x})^2 \quad (A2)\]

since the function \( f(u) = \log(e^u - 1) \) is convex

\[f(u_A) + f(u_B) > 2f(\frac{1}{2}u_A + \frac{1}{2}u_B) \quad (A3)\]

Substituting \( u_A = 2 \log(x) \), \( u_B = 2 \log(y) \), we have from (A3)

\[\log(e^{\nu x} - 1) + \log(e^{\nu y} - 1) > 2 \log(e^{\nu y} - 1) \quad (A4)\]

Thus, \( \Delta < 0 \) in (A2).

\(^{(36)}\) De Gennes, P.-G., private communication.

Relative Ring-Current Effects Based on a New Model for Aromatic-Solvent-Induced Shift\(^1\)

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Abstract: A convenient method for measuring (relative to benzene) the above-plane ring-current effect of aromatic compounds is presented. The method is based on strictly linear relations \( \Delta_\omega = (a + b) [D_{\omega} \Delta_\omega] \) between the induced upfield shift \( \Delta_\omega \) of an (externally referenced) \(^1\)H NMR signal of a probe and the concentration \([D_{\omega}]\) of the aromatic D (solvent CCl\(_4\)). \( \Delta_\omega \) is the chemical shift relative to that of the solution where \([D_{\omega}] = 0\), and \( b \) is the necessary correction for the change in the susceptibility. A study of more than 30 compounds D (including the partial antiaromatic biphenylene) with 1-chloroisobutene as probe shows that its \( b \) values establish a relative scale of the above-plane ring-current effect. This relative scale generally displays a good agreement in a similar scale derived from diamagnetic exaltations. The probe behavior is explained by a simple model for ASIS (aromatic-solvent-induced shift) that divides ASIS into three components: upfield contributions from AUS effects (additional nonspecific shielding effects) and from complexation, counteracted by the downfield contribution through AUS effects on the customary internal reference. The AUS effect in its simplest mode depends linearly on the concentration \([D_{\omega}]\) of benzene (or other aromatic compounds). Prerequisites for the linear dependence are discussed.

Previous studies\(^2\) of solvent (or cosolvent or cosolute) dependence of \(^1\)H NMR chemical shifts \( \delta \) have usually compared chemical shifts of the solute at a more or less constant concentration. In some studies the chemical shifts \( \delta \) were extrapolated to zero solute concentration. To the best of our knowledge, however, a comparison of slopes of linear shift-concentration relations, obtained from constant solute concentration as a function of the much larger concentrations of a cosolvent or cosolute, have not yet been reported. Such linear relations over a large concentration range in high-precision experiments have seldom been observed before and never for a whole series of cosolvents or cosolutes. This paper reports now on such a unique behavior and on its relation to the so-called ring-current effect. An explanation of the observed linear relation is presented on the basis of a new model for ASIS, the

\(^1\) Dedicated to the memory of Professor Hans Musso.