Conclusions

It is apparent from this study that calculations at the RHF/4-31G + 3 × 3 CI and UHF/4-31G levels are insufficient to provide energetic predictions for the asynchronous portion of the energy surface. Limited configuration interaction is also inadequate. A minimum of seven occupied orbitals must be included in the CI in order to obtain reliable energies for this reaction. This and recent work by Davidson et al.[36,37] suggests that electron correlation may be more important than previously beleived for diradical-like structures.

In addition, it is evident that a low-lying two-step pathway exists for the addition of fulminic acid to acetylene via the extended diradical **2** and that it is energetically comparable with the one-step, concerted path. A second asynchronous pathway passing through the cyclo diradical transition state cannot be excluded, despite previous ab initio investigations of the symmetrical region of the potential energy surface. The present study suggests that a cyclo diradical transition state, if it exists, is destabilized by the lack of CI and would probably be missed in any search at the SCF level. As suggested by Harcourt[9] and Schaefer,[19] it is quite possible that no distinction exists between the cyclo diradical transition structure and the synchronous one.

For the particular case of the 1,3-dipolar cycloaddition of fulminic acid to acetylene, Huisgen's and Firestone's mechanisms (at least via the extended diradical) require comparable activation energies at our highest level of calculation, with the latter slightly favored by 3.6 kcal mol⁻¹. This energy difference is too small to rule out one mechanism or the other. Quite probably both mechanisms compete, depending on substituents and solvent effects, although the latter are known to be relatively unimportant. This conclusion cannot be extended to type I dipoles or Diels–Alder reactions, without similar quality calculations on specific examples of these reaction. Although any generalizations would be venturesome in the absence of other accurate calculations, our results suggest that Firestone's mechanism now merits serious attention for type II 1,3 dipoles.

(40) Beltrame, P.; Cattania, M. G.; Simonetta, M. *Z. Phys. Chem. (Frankfurt am Main)* **1974**, *91*, 225. Note that conjugative effects have been neglected in this estimate.

A van der Waals Model of Chiral Mixtures Using a Chiral Lennard-Jones Potential. Applications to the Pasteur Experiment and Phenomena in Chiral Solvents

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Abstract: Much of the understanding of the behavior of simple fluids stems from the combination of a simple Lennard-Jones potential and a subsequent van der Waals approach to the statistical thermodynamics of such fluids. In this paper, both are generalized to incorporate the effects of chirality as a basis for the discussion of the properties of chiral mixtures at the simplest level. In this way, the role of chirality in leading to characteristic thermodynamic effects may be rigorously defined. Although the model may be too simple to apply quantitatively in that chiral mixtures are frequently relatively complex in structure, it serves as a natural starting point for understanding and defining the role of chirality in thermodynamic phenomena in the solution phase. The model is applied to a number of solution phenomena, such as the possible role of solution configurations in spontaneous resolutions (the Pasteur experiment), and equilibrium shifts of labile racemates or differential enantiomeric solubilities in chiral solvents.

Introduction

In spite of the importance of chirality in many areas of chemistry, statistical-thermodynamic theories are generally concerned with achiral systems. The reason is, of course, a simple one. It is only natural to develop theories for simpler systems, gradually incorporating greater degrees of theoretical complexity in application to more complicated systems once the general behavior of the simpler systems has been understood. Thus an understanding of the interactions between, for example, inert gas atoms in terms of a Lennard-Jones potential leads to quantities such as excluded volume and well depths which may be used quantitatively for inert atom interactions and parametrically for more complex systems. The Lennard-Jones potential then serves as a basis for a range of statistical-mechanical approaches of different degrees of sophistication in linking the microscopic potential parameters to thermodynamic variables. The insensitivity of the usual Lennard-Jones potential to chirality means, however, that it cannot serve as a basis for discussing chiral phenomena.

In the case of chiral fluids, we are immediately confronted with seemingly insurmountable complications in an attempt to discuss the statistical-thermodynamic properties in a simple way. Firstly, a chiral molecule has, in general, a complex molecular structure which cannot be modeled in terms of a chiral atomic system (a contradiction in itself!). Secondly, the effects of chirality will only manifest through an interaction of two chiral systems, so that a statistical-thermodynamic treatment must be based at least on a binary mixture. (For example, the thermodynamics of a single component chiral system is identical with that of the reflected or inverted system if spatial parity is conserved, which seems to be the case at least on a chemical plane.) Thirdly, the interactions between chiral systems must be modeled in some way by a potential which is sensitive to chirality, but which will collapse into the usual forms in the achiral limit.

In this paper, therefore, we shall attempt the modest goal of understanding the effect of chirality at the simplest level by establishing an effectively chiral Lennard-Jones potential which

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constitutes the simplest representation of the interaction of a pair of chiral molecules. The simplifying features of a spherically averaged (and thus orientation-independent) potential with a minimum of parameters are retained. Although the relevance of the potential in application to real chiral systems may be disputed at a quantitative level, it serves as a basis for statistical-mechanical theories of various degrees of sophistication, as well as establishing the general behavior expected in chiral systems.

As an illustration of this, the potential is incorporated in a van der Waals approach to multicomponent chiral mixtures. The configurational free energy is explicitly derived in terms of the potential parameters and solution variables such as concentration. This is then used as a basis for discussing a number of chiral phenomena, such as the spontaneous resolution of inert racemates in an achiral solvent, the equilibrium shift associated with labile racemates in chiral solvents, and, finally, the differential solubilities of inert enantiomeric components in a chiral solvent. Again, the results should not be expected to give a quantitative description for real systems, although the potential for parametrization in the van der Waals scheme could alleviate some deficiences of the model.

The theoretical development of the interactions of chiral systems has followed two different approaches. The statistical-thermodynamic approach was initiated by Amaya in a series of papers[1-3] in which he exploited a statistical-mechanical lattice theory. The difficulties of Amaya's approach are inherent in his choice of intermolecular potential. Each molecule is represented by a series of "contact" points (or, alternatively, by four "atomic" centers, each with a characteristic interaction potential) disposed in a chiral manner, allowing certain orientations of the molecule within each lattice cell. Such a potential is directly geared to usage in the context of a lattice model and makes the final expressions difficult to parametrize. It is difficult to see how such a potential could be used in statistical-mechanical theories exploiting orientation-independent potentials. A number of authors have adopted an alternative approach of investigating the intermolecular potential in isolation, especially for orientationally uncorrelated systems, eliciting those contributions (discriminating terms) which are sensitive to the chirality of the species involed, for a given value of the intermolecular separation.[4-8] These have usually employed a more tractable multipolar formalism and explicitly ignored the short-range packing of effects. Incorporation of such potentials into a primitive lattice model was discussed by this author.[9] In this paper, the results of this alternative approach are used to determine the modifications required to generalize the Lennard-Jones potential to incorporate the effects of chirality.

The paper is conveniently structured into sections developing the chiral Lennard-Jones potential, followed by its incorporation into a van der Waals model of multicomponent chiral mixtures. The third section discusses the Pasteur experiment and proposes a solution model for spontaneous resolution. The van der Waals model is also applied in later sections to phenomena involving chiral solvents, namely, induced equilibrium shifts in labile racemates and differential enantiomeric solubilities.

The Chiral Lennard-Jones Potential

The main feature of the Lennard-Jones potential is its division into a hard (short-range repulsive) component and a soft (long-range dispersive) component. In the application to neutral chiral systems, the short-range repulsive terms arise from packing-type effects which by their very nature are usually sensitive to the

relative orientation of the two interacting molecules. However, sufficient orientations may be sampled in nondiastereoisomeric systems to allow the utilization of an effectively spherically averaged potential in which the repulsive terms are incorporated into an excluded-volume-type term.

Consider, for example, a ternary mixture of A', A'', S, where A', A'' are the enantiomeric forms of a chiral molecule A (i.e., A'' is the inverted or reflected form of A', and vice versa), and S is a particular enantiomer of another molecule. For the purposes of the following discussion, we shall consider only the interactions between the various A species, it being understood that similar considerations hold for the A–S interactions. The A'–A' and A'–A'' interactions will differ in their short-range component simply because there may be more closely packed configurations for one than for the other; i.e., one interaction will have a smaller distance of approach which will in turn manifest through the appropriate excluded volumes. However, the A'–A' and A''–A'' interactions (referred to as *like* interactions) will be identical by symmetry, as will the *unlike* A'–A'' and A''–A' interactions.

The short-range part of the potential may therefore be put in the form

$$c_{ij}(\eta)/r_{ij}^{12}$$

where c_{ij} is a positive constant and r_{ij}, the intermolecular separation. For simplicity, the i, j indexes label the molecules without specification of the chirality. The latter is incorporated into a *chirality index* η such that $\eta = 0$ for like interactions and $\eta = 1$ for unlike interactions. No further specification is necessary because all interactions are invariant to a change in the chirality of both species simultaneously, as mentioned above. In a way, the chiral molecule is being represented by a schizoid atom with an excluded volume which is a function of whether it is interacting with another "like" schizoid atom or an "unlike" one.

It may seem initially that the long-range or dispersive part of the potential cannot be restricted to the usual r^{-6} London term, which is insensitive (for a fixed intermolecular separation) to chirality. Although we shall see that this term plays an important role in discriminatory effects in an indirect way (through the combined effect with the $c_{ij}(\eta)$), it is possible to include another type of discriminatory effect at the outset by considering the extended rotationally averaged dispersive potential developed for molecules of arbitrary symmetry in which a series expansion in $1/r$ leads to a natural division into contributions which are explicitly either symmetric (nondiscriminating terms) or antisymmetric (discriminating terms) to inversion of the chirality of one of the interacting species, for a fixed value of the intermolecular separation. The full form of this potential has recently been derived[8] and will not be discussed in detail here.

Consideration will be restricted to purely electric interactions; electric–magnetic terms may be incorporated into the formalism if required. The leading symmetric term is the usual London dispersion term of the form

$$-a_{ij}/r_{ij}^6$$

which is independent of the chirality index. The leading electric antisymmetric term may be written in the form

$$-(-1)^\eta b_{ij}/r_{ij}^9$$

where b_{ij} is a chirality-independent parameter estimated by convention for like interactions. For self-interactions (i.e., those interactions between the A species alone), a_{ij} and b_{ij} are universally positive.

The combined potential may be written in terms of the three parameters as

$$\phi_{ij}(\eta) = -a_{ij}/r_{ij}^6 - (-1)^\eta b_{ij}/r_{ij}^9 + c_{ij}(\eta)/r_{ij}^{12}$$

To reduce this to the more familiar Lennard-Jones form, it is assumed that the b_{ij} term may be neglected in determining the excluded volume and the minimum of the potential. Defining the magnitude of the depth of the potential minimum as $\epsilon_{ij}(\eta)$, and

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(2) Amaya, K. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 1803.
(3) Amaya, K. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1794.
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(6) Craig, D. P.; Schipper, P. E. *Proc. R. Soc. London, Ser. A* **1975**, *342*, 19.
(7) Schipper, P. E. *Chem. Phys.* **1977**, *26*, 29.
(8) Schipper, P. E. *Aust. J. Chem.* **1982**, *35*, 1513.
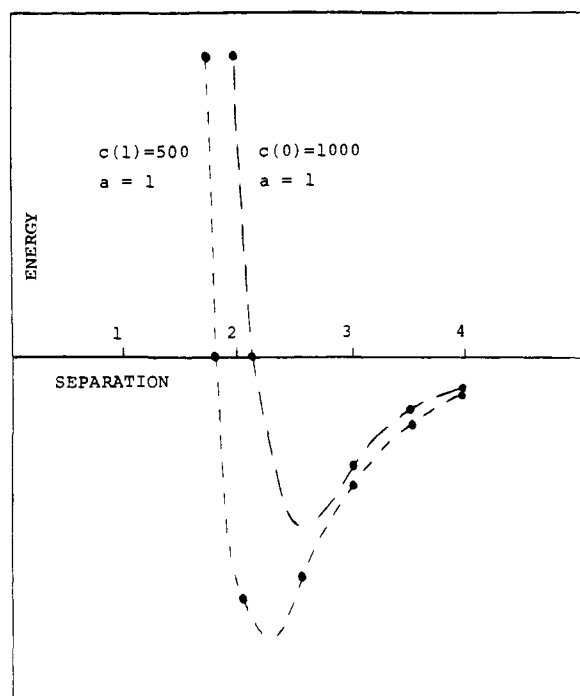(9) Schipper, P. E. *J. Am. Chem. Soc.* **1978**, *100*, 1079.

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Figure 1. A comparison of the Lennard-Jones potential for like and unlike interactions with $c(0) = 1000$, $c(1) = 500$.

the intermolecular separation when the potential vanishes as $\sigma_{ij}(\eta)$, it follows that the potential reduces to the form

$$\phi_{ij}(\eta) = -4\epsilon_{ij}(\eta)[\sigma_{ij}^6(\eta)/r_{ij}^6 - \sigma_{ij}^{12}(\eta)/r_{ij}^{12}] - (-1)^\eta b_{ij}/r_{ij}^9 \quad (1)$$

where

$$\epsilon_{ij}(\eta) = a_{ij}^2/4c_{ij}(\eta); \quad \sigma_{ij}^6(\eta) = c_{ij}(\eta)/a_{ij} \quad (2)$$

We shall refer to this potential in a general way as the 6-9*-12* potential, whith the asterisk indicating the terms which are functions of the chirality index.

There are two simpler forms of this potential which are still chiral, but correspond to particular physical situations in which a single type of discrimination is assumed to dominate. The first simply ignores the b_{ij} term completely, resulting in a 6-12* potential. It will lead, as is discussed in detail later, to a *packing* discrimination. The form of this potential is illustrated in Figure 1, with a_{ij} constant and for selected values of $c_{ij}(0)$ and $c_{ij}(1)$. Note that, although the a_{ij} is insensitive to η (for a fixed r_{ij}), the different values of $c_{ij}(0)$ and $c_{ij}(1)$ result in quite different potential curves. Thus a smaller value of c_{ij} leads to a slightly smaller distance of closest approach (σ_{ij}), but a considerably deeper minimum (ϵ_{ij}). The result of this is that, in spite of the constancy of a_{ij}, the total r^{-6} term is sampled at smaller r values, leading to a stronger dispersive interaction for the smaller c_{ij} value.

The second case may be referred to as a 6-9*-12 potential, in which $c_{ij}(0)$ is assumed equal to $c_{ij}(1)$. Any discrimination will arise purely from the b_{ij} term (*dispersive* discrimination) which is quite different in nature from the packing discrimination, persisting even for like and unlike interactions with the same r_{ij} value. The choice of the 6-9*-12*, 6-12*, or 6-9*-12 potential will thus depend on the particular system of interest.

A van der Waals Model for Chiral Mixtures

In this section, the van der Waals model of chiral mixtures is developed in a general way, and then the chiral potential developed in the previous section is explicitly incorporated. It is stressed that the chiral Lennard-Jones could be used as a basis for more sophisticated statistical-mechanical models, but the van der Waals approach affords the simplest theoretical link between the Lennard-Jones parameters and the thermodynamic variables of the chiral mixture.

We consider a solution of a chiral species A (enantiomeric forms A', A", respectively) in a solvent S which may or may not be chiral.

The total number of molecules of each type is denoted $N_{A'}$, $N_{A''}$, N_S respectively, with $N_A = N_{A'} + N_{A''}$, $N = N_A + N_S$. The concentrations may be reduced to dimensionless mole fractions defined as

$$c = N_A/N, \quad x = N_{A'}/N_A, \quad (1 - x) = N_{A''}/N_A, \quad (1 - c) = N_S/N$$

The free energy per particle is apportioned using a van der Waals approach[10] into an excluded volume contribution, a contribution from a pairwise potential which is integrated over volume ignoring density correlations, and an entropy contribution resulting from mixing the pure solutions into the more disordered racemate. The Helmholtz configurational free energy per molecule f_C may then be written as

$$f_C = h - Ts^m - Ts^e \quad (3)$$

where h is a purely energetic term, s^m the entropy of mixing term, and s^e the entropy term arising from excluded volume effects. We consider these three contributions in turn.

Entropy of Mixing Contributions. The contribution s^m is a direct measure of the disorder resulting from mixing the two enantiomers and then mixing the resultant system in the solvent S. It has the explicit form

$$s^m = -k[cx \ln x + c(1 - x) \ln (1 - x) + c \ln c + (1 - c) \ln (1 - c)] \quad (4)$$

The first two terms arise from mixing the enantiomers and the other two, from mixing with the solvent.

This entropy term plays an important role in chiral systems and results directly from the physical distinguishability of the enantiomers A' and A". It is a term which invariably favors the more disordered (racemic) configurations and the source of the chemical difficulty of obtaining optically pure (i.e., enantiomerically pure) forms of chiral compounds.

Excluded Volume Contributions. The entropy contribution s^e arises from excluded volume considerations. If V_{ij} is the averaged excluded volume per molecule in an ij mixture, and v is the volume per molecule in the final solution, then this entropy contribution may be approximated in two ways. Assuming a linear mixing rule, we have

$$s^e = k \ln [1 - (1 - c)\bar{v}_{SS} - cx\bar{v}_{A'A'} - c(1 - x)\bar{v}_{A''A''}] \quad (5)$$

A bilinear mixing rule leads, however, to the more complex form (where $\bar{v}_{ij} = v_{ij}/v$)

$$s^e = k \ln \{1 - (1 - c)^2\bar{v}_{SS} - 2c(1 - c)[x\bar{v}_{A'S} + (1 - x)\bar{v}_{A''S}] - c^2[x^2\bar{v}_{A'A'} + 2x(1 - x)\bar{v}_{A'A''} + (1 - x)^2\bar{v}_{A''A''}]\} \quad (6)$$

It has been argued that the linear form is more appropriate at higher concentrations,[11] and it is the form which we shall use in the work that follows. Note, however, that it is totally insensitive to chirality, as $\bar{v}_{A'A'} = \bar{v}_{A''A''}$, effectively eliminating x dependence. Although this is not the case for the bilinear form, the success of the linear form in binary mixtures suggests that discriminatory effects arising from the inequality of $\bar{v}_{A'A'}$ and $\bar{v}_{A'A''}$ in the bilinear form will not contribute appreciably to the final entropy.

Energetic Contributions. The energetic contribution is assumed to arise directly from the mutual pairwise interactions between A', A", S. The contribution h may be written in the form

$$h = \frac{1}{2}\{(1 - c)^2 E_{SS} + 2c(1 - c)[xE_{A'S} + (1 - x)E_{A''S}] + c^2[x^2 E_{A'A'} + (1 - x)^2 E_{A''A''} + 2x(1 - x)E_{A'A''}]\} \quad (7)$$

The derivation of this expression is illustrated by considering a particular contribution from the pair of molecules i,j interacting through the pairwise potential $\phi_{ij}(r_{ij})$, where r_{ij} is their separation in solution. The interaction of a particular i with the totality of j in solution follows from the integral

(10) Rowlinson, J. S. "Liquids and Liquid Mixtures"; Butterworths: London, 1969.

(11) Harrowell, P. R.; Nordholm, S. *Aust. J. Chem.* **1982**, *35*, 673.

$$e_{ij} = \int_{\sigma_{ij}}^{\infty} 4\pi r_{ij}^2 \phi_{ij}(r_{ij}) n_j(r_{ij}) \, dr_{ij}$$

where $n_j(r_{ij})$ is the number density of species j at r_{ij}, and σ_{ij} is the hard sphere radius. Use is then made of the continuum assumption

$$n_j(r_{ij}) = 0, \quad r_{ij} < \sigma_{ij}$$
$$= \rho_j, \quad r_{ij} > \sigma_{ij}$$

where

$$\rho_j = N_j/V = x_j/v$$

V is the total volume and v the volume per particle $(=V/N)$. The total energy due to this ij interaction per particle may be written as

$$e_{ij}^{\text{tot}} = (1 - \delta_{ij}/2) x_i x_j E_{ij}$$

where

$$E_{ij} = \frac{1}{v} \int_{\sigma_{ij}}^{\infty} 4\pi r_{ij}^2 \phi_{ij}(r_{ij}) \, dr_{ij} \qquad (8)$$

The factor $1/2$ is necessary for like interactions to avoid double counting.

In the expression for h, five distinct interaction terms appear: E_{SS} from solvent–solvent interactions, $E_{A'A'}$ $(=E_{A''A''}$ by symmetry) from like interactions of A, $E_{A'A''}$ $(=E_{A''A'})$ from unlike interactions, and finally $E_{SA'}$ and $E_{SA''}$ from the interaction of the solvent with the enantiomers of A. For an achiral solvent, the last two contributions are equal.

Of central importance to this work are the differences in the interactions of A′ and A″ with a given enantiomer of a chiral species. We therefore define the quantities

$$\Delta = E_{A'A'} - E_{A'A''} \qquad (9)$$

$$\Delta_S = E_{A'S} - E_{A''S} \qquad (10)$$

where Δ is the *self-discrimination energy of A* (the difference between the like and unlike interactions) and Δ_S is the *discrimination energy of A with S*. The latter will, of course, vanish if S is achiral. The energetic contribution to the free energy may then be written in the form

$$h = \frac{1}{2}\{(1 - c)^2 E_{SS} + 2c(1 - c) \times$$
$$[E_{A''S} + x\Delta_S] + c^2[2x^2\Delta - 2x\Delta + E_{A'A'}]\} \quad (11)$$

It remains finally to evaluate the E_{ij} (and hence the discrimination energies) in terms of of a suitably defined potential function.

At this stage, we return to the 6-9*-12* potential of eq 1. Substitution into the integral of eq 8 leads to energies explicitly expressed in terms of the chirality index η; i.e.,

$$E_{ij}(\eta) = -\frac{32\pi}{9v}\epsilon_{ij}(\eta)\sigma_{ij}^3(\eta) - \frac{2\pi}{3v}(-1)^\eta b_{ij}/\sigma_{ij}^6(\eta) \qquad (12)$$

and the discrimination energy may be calculated from eq 9 and 10 to give

$$\Delta_{ij} = E_{ij}(0) - E_{ij}(1) \simeq \Delta_{ij}^{\text{packing}} + \Delta_{ij}^{\text{disp}} \qquad (13)$$

where

$$\Delta_{ij}^{\text{packing}} = -\frac{32\pi}{9v}[\epsilon_{ij}(0)\sigma_{ij}^3(0) - \epsilon_{ij}(1)\sigma_{ij}^3(1)] \qquad (14)$$

$$\Delta_{ij}^{\text{disp}} = -\frac{4\pi}{3v} b_{ij}/\sigma_{ij}^6 \qquad (15)$$

and

$$\sigma_{ij} = [\sigma_{ij}(0) + \sigma_{ij}(1)]/2 \qquad (16)$$

The "packing" discrimination $\Delta_{ij}^{\text{packing}}$ arises ultimately from the η dependence of $c_{ij}(\eta)$. The smaller the value of c_{ij}, the closer i and j can approach before feeling the full force of the repulsive potential. The result is that the attractive a_{ij} term can be sampled at shorter distances, leading to a discrimination favoring the

interaction with the smaller excluded volumes. In eq 14 above, it is important to realize that a smaller σ_{ij} is coupled to an ϵ_{ij} factor which increases faster with a decrease in c_{ij} than the hard-sphere parameter; these two parameters are linked through the c_{ij} (eq 2) and cannot be varied independently.

The dispersive discrimination $\Delta_{ij}^{\text{disp}}$ has quite a different origin and persists even for equal separations in the like and unlike case. As discussed elsewhere,[8] it arises from the third-order dispersive interaction, which on rotational averaging survives only if both molecules are chiral. Some interpretation of dispersive interactions in second and third order should illustrate why this is so. Consider first the normal London (r^{-6}) term. This may be loosely interpreted as a linear fluctuation which leads to a transient dipole on one system which in turn interacts with a transient induced dipole on the other species. In a quantum framework, these linear fluctuations are resolved into a contribution from each discrete state as a transition moment coupling. Each such representation is achiral (a transition moment in the dipole approximation having an infinite number of reflection planes containing it), so that such contributions are insensitive to the molecular chirality. In third order (the r^{-6} being of second order in perturbation theory), the fluctuations are more of a helical nature, and thus of three-dimensional character. In quantum terms, the three moments coupling the ground and two excited states are involved, the moments being of necessity of such orientation so that their triple vector product is nonvanishing; i.e., no two of the moments can be coplanar. Such a product is required on each molecule, and is finite only for a chiral system. The overall interaction energy arising in third order will therefore change sign if the chirality of one of the systems is inverted. The quantum origin of dispersive interactions from correlation of electronic motion in the two systems leads to the second-order terms being invariably negative, and the third-order terms being invariably negative for like self-interactions.

With the free energy explicitly determined in terms of the potential parameters and solution variables, we now turn to the application of the van der Waals model to some particular problems. The fundamental expressions that are required are eq 3–5 and 11, it being understood that the discriminations have the form of eq 13.

Application to the Pasteur Experiment

The remainder of the paper will be concerned with the application of the model to three specific problems, as an illustration of the unique phenomena associated with chiral (as distinct from achiral) mixtures. A central assumption inherent in all the applications is that definite diastereoisomers (i.e., binary aggregates of the form A′A″, A′S, etc.) are not formed. A diastereoisomer effectively constitutes a single molecular species. Thus, even in isolation, the thermodynamics of a solution of, say, A′S diastereoisomers is quite different from that of a solution of A″S diastereoisomers. Such systems are beyond the scope of this paper. It is interesting to note, however, that historically discriminatory effects have generally been ascribed to diastereoisomeric differences. Although there are multitudinous systems where this may occur, there is increasing chemical evidence for discriminatory effects in dissociated systems. It is with the latter that we shall be exclusively concerned.

The first application is perhaps the most speculative, but illustrates how the model can provide a conceptual framework for understanding the most fundamental experiment in chirality: that of the first spontaneous resolution of an inert racemate into enantiomorphous crystals by Pasteur in 1848.[12] By hand-sorting the enantiomorphous crystals obtained from a solution of racemic sodium ammonium tartrate, Pasteur discovered the correlation of optical activity with the inherent chirality of microscopic structures. Although it is frequently stated in a somewhat humorous vein that Pasteur was fortunate to have lived in a relatively cool climate (the racemic crystals will precipitate out from the

(12) Natta, G.; Farina, M. "Stereochemistry"; Harper and Row: New York, 1972.

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solution if the temperature exceeds 27.2 °C), the temperature dependence of the result of the crystallization process has received little critical attention in the literature.

The simplest rationale for the Pasteur experiment (and, in particular, the existence of the transition temperature above which only racemic crystals are formed) is a simple thermodynamic one in which all details of the solution and the crystallization process are ignored. The results of the experiment are then assumed to be predetermined by the free-energy change associated with the reaction

$$\text{enantiomorphous crystals} \rightleftharpoons \text{racemic crystals} \qquad (17)$$
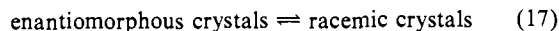
which has the form

$$\Delta G_{\text{solid}} = \Delta H_{\text{solid}} - T \Delta S_{\text{solid}}$$

ΔH_{solid} may be identified with the lattice energy or enthalpy difference and will be negative if the racemate has the lower lattice energy (a negative quantity); ΔS_{solid} will be invariably positive, the disorder being greater in the racemic crystal. It follows that for systems with $\Delta H_{\text{solid}} > 0$ (i.e., when the enantiomorphous crystals have the lower lattice energy), the greater stability of the enantiomorphs will lead to a positive ΔG_{solid} (and hence enantiomorphous crystallization) only if the temperature is below the critical value $T = \Delta H_{\text{solid}}/\Delta S_{\text{solid}}$. Above this temperature, ΔG_{solid} will be invariably negative and favor racemic crystallization. For $\Delta H_{\text{solid}} < 0$ (i.e., when the racemic crystals have the lower lattice energy), racemic crystallization should occur for all temperatures.

Experimental studies on enantiomorphous/racemic crystal systems fall into two essentially mutually exclusive categories: (I) those systems which exhibit spontaneous resolution from solution or the melt; (II) those systems for which thermodynamic studies indicate that the free-energy change ΔG_{solid} is approximately zero or negative. Of the 250 odd compounds which have been shown to spontaneously resolve,[13,14] the melting point of the enantiomorphous crystals T_e exceeds that of the racemic crystal T_r by at least 20 K. In only one isolated case does the racemic crystal have the higher melting point. The compounds of category II comprise those for which $T_e < T_r$ and those for which $T_e > T_r$, but the melting point difference is generally smaller than those of category I. If the melting point is taken as a measure of the magnitude of the (negative) lattice energy, then these results are consistent with the simple thermodynamic argument presented above. This would mean that only in the crystals of category I is ΔH_{solid} both positive and sufficiently large to lead to a high transition temperature. (It is interesting to note that this interpretation of the Pasteur experiment is essentially a diastereoisomeric one. The enantiomorphous and racemic crystals may, after all, be visualized as polystereoisomers $A'A'A'A' \ldots$ and $A'A''A'A'' \ldots$; this constitutes a simple generalization of the diastereoisomers discussed earlier.)

There are, however, some features of the Pasteur experiment which are not in accord with this simple solid-state thermodynamic argument. Pasteur himself noted that slow crystallization leads to resolution in the way described above (for category I compounds), but rapid crystallization of a solution made from mixing the enantiomorphs leads to racemic crystals. This suggests a partial kinetic or dynamic control, which must have its origin in the properties of the solution phase. Although such kinetic control cannot strictly be incorporated into the van der Waals model, it is possible to use a qualitative chemical argument in which we assume that the crystallization process may be interpreted in terms of a kinetic, transition-state model, the transition state being effectively a property of the solution phase.

Solution Model for the Pasteur Experiment. In the solution model to be developed here, it is argued that the result of the crystallization process is predetermined by the dominant solution configurations (transition states) just prior to the onset of crystallization. For example, consider the two "extreme" configura-
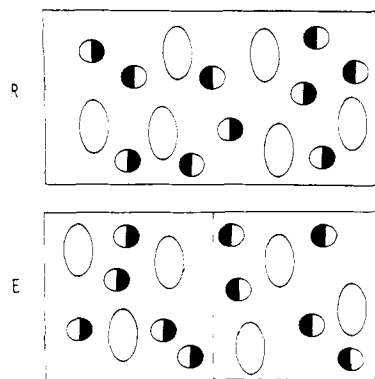

Figure 2. The racemic (R) and enantiomeric (E) configurations, the dashed line marking the phase separation. The small circles represent A molecules, with A' being shaded on the right-hand side. The large ellipses represent solvent molecules with unspecified chirality.

tions illustrated in Figure 2 in which configuration E is that in which A', A'' are separated into two distinct enantiomerically pure phases, and configuration R is that where the enantiomers are completely mixed (the miscible or racemic phase). In this context, the transition state represented by configuration E would lead, via a simple probability argument, to enantiomorphous crystallization, whereas transition state R would lead to racemic crystallization, irrespective of the energetics of the solid state. The determination of the result of the crystallization process then reduces to the determination of the most probable transition state or solution configurations, an archetypical statistical mechanical problem.

The van der Waals approach (in the form used here) is not geared to answering such questions directly, and a more satisfactory approach would be to incorporate the chiral Lennard-Jones potential into a more sophisticated statistical mechanical model which deals directly with density fluctuations or correlation lengths. Such approaches are beyond the scope of this paper. However, we shall approach the problem indirectly through a van der Waals approach for a ternary mixture of an inert racemate A', A'' dissolved in a solvent S, by determining the conditions under which there will be a tendency for the two inert enatiomers A', A'' to separate into different regions of space or, more correctly, in which two phases, one richer in one enantiomer and the other correspondingly richer in the other enantiomer, are favored. We shall refer to these as the A' and A'' phases, respectively, it being understood that both are still in solution with S.

The formalism adopted is that commonly used for binary mixtures XY in which X and Y are chemically different species.[10] It is then well known that if the XX, YY interactions are sufficiently stronger than the XY interactions, phase separation will occur if the temperature is sufficiently low to allow for the dominance of the energetic contributions to the free energy. Above the so-called critical temperature T_c, X and Y are completely miscible. If XY interactions are favored, the solution generally remains miscible at all temperatures, both entropic and energetic contributions favoring miscibility.

As A', A'' are distinguishable species, the same formalism may be used and leads to f_c being a function of x of the form of Figure 3, a number of isotherms being shown. Note that although the overall value of x in an inert solution will be unchanged, the van der Waals isotherms together with the usual Maxwell construction leads to two phases of concentrations x_1, x_2, such that the overall mole fraction of each enantiomer is unchanged. At temperatures below the critical temperature T_c, the solution *tends* to separate into two phases of mole fractions x_1, x_2, one richer in A' and the other correspondingly richer in A''. The optical or enantiomeric purity of the two phases increases the further the temperature is below the critical value.

The relatively small differences in A'A'', A'A' interactions in the solution phase would lead to an unlikelihood of macroscopic phase separation. However, the tendency toward phase separation may be reinterpreted in terms of spatial fluctuations of enan-

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(14) Collet, A.; Brienne, M.-J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1977**, 494.
(15) Leclercq, M.; Collet, A.; Jacques, J. *Tetrahedron* **1976**, *32*, 821.
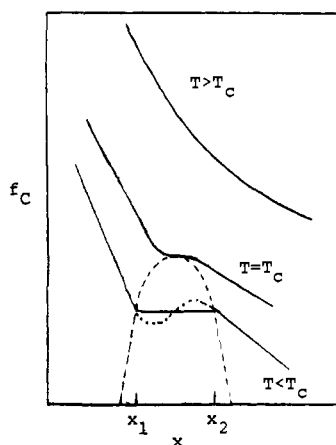
Figure 3. Free-energy mole fraction isotherms for an A', A'' mixture. x_1, x_2 are the mole fractions of A' in the two phases.

tiomerically pure regions, the fluctuations being larger as $(T_c - T)$ increases. Once the fluctuations are of sufficient size to encapsulate the nascent crytallites, the probability argument developed above would predict enantiomorphous crystallization. The critical temperature determined in the context of the van der Waals model therefore provides the qualitative link with the transition state or solution configuration picture.

The conditions determining the critical temperature are simply

$$\left.\frac{\partial^2 f_C}{\partial x^2}\right|_v = 0 \text{ and } \left.\frac{\partial^3 f_C}{\partial x^3}\right|_v = 0 \qquad (18)$$

which, using eq 3–5 and 11, reduce to

$$4c^2\Delta + kT_c c\left[\frac{1}{x} + \frac{1}{1-x}\right] = 0 \qquad (19)$$

and

$$kT_c c\left[-\frac{1}{x^2} + \frac{1}{(1-x)^2}\right] = 0 \qquad (20)$$

The second condition is satisfied only if $T_c = 0$ or $x = {}^1/_2$; i.e., the initial solution is racemic. This immediately suggests that nonracemic mixtures cannot lead to such critical phenomena. It would be indeed interesting to test whether this manifests experimentally or is the result of using an oversimplified approach to the problem. Substitution of $x = {}^1/_2$ for a racemic mixture into condition 19 leads directly to

$$T_c = -4c\Delta/k \qquad (21)$$

Thus T_c (i) is positive only if the self-discrimination energy is negative (i.e., like interactions are favored); (ii) is proportional to the overall mole fraction of A; (iii) is insensitive to whether the solvent is chiral or achiral.

The most important of these features is the necessity of a negative self-discrimination energy. This depends in turn on the signs and relative magnitudes of $\Delta_{AA}^{packing}$ and Δ_{AA}^{disc}. The packing discrimination may be positive or negative depending on whether $c_{AA}(\eta)$ is smaller for unlike or like interactions, respectively. Ideally, the relative magnitudes of c_{AA} should be determined through some independent experiment. This may be possible through excess volume of mixing experiments interpreted in terms of the van der Waals approach given here. Alternatively, one could argue that the dominant contributions to the rotationally averaged estimate of the excluded volumes arise from the orientations at which the packing energies are minimized; i.e. relate the packing discrimination to the difference in lattice energies of the enantiomeric and racemic crystals per molecular pair.

On the other hand, the dispersive discrimination is invariably negative for self-interactions, favoring like interactions. This could *in isolation* lead to the postulated critical phenomena and to spontaneous resolution as a universal phenomenon. It is unlikely,

however, that this discrimination is of sufficient magnitude to lead to the critical temperatures required for room-temperature resolutions. At the high concentrations required for the Pasteur experiment, there seems little doubt that the packing discrimination would be the dominant contribution.

The magnitude of the required discrimination energy may be determined as a "ball-park" estimate by noting that the transition temperature of the Pasteur experiment (300 K) must be less than T_c. With $c = {}^1/_2$, this leads to

$$|\Delta| > 0.6 \text{ kJ mol}^{-1} \qquad (22)$$

This is not unrealistic for solution interactions, suggesting there might be some credence to the solution mechanism for the Pasteur experiment. In addition, Pasteur's findings that rapid crystallization leads to racemic crystals even below the transition temperature may be interpreted in the solution picture as a "mechanical" disturbance of enantiomerically resolved configurations (or alternatively as an external kinetic factor in which the fluctuations or transition state are effectively altered by mechanical mixing).

In summary, both the solution and solid-state (i.e., the kinetic and thermodynamic) pictures are in accord with the experimental results concerning the energetics of the Pasteur experiment, provided the solution packing discriminations are proportional to the packing energy difference ($-\Delta H_{solid}$) of the solid phases. However, only the solution model can account for the kinetic aspects of the crystallization process, albeit in a rather primitive way. If the solution model is a more appropriate description, then the parametrization of the packing discriminations in terms of the lattice energies would seem to be justified from the agreement of the results with the solid-state energetics as discussed earlier.

The heats of mixing experiments of Amaya et al.[27,28] have shown that the difference in the heats of solution of enantiomorphous and racemic crystals in water is considerably larger than that for mixing two enantiomerically pure aqueous solutions to yield the racemic solution. This may be interpreted as an argument for thermodynamic control through the solid-state energetics. However, it is significant that the solution measurements apply to lower concentrations than those required for the onset of crystallization. The model presented in this paper for the Pasteur experiment may be considered as applying to the high concentration region, where the fluctuations may be interpreted as small pools of optically pure phases. It is interesting to note that a recent paper on ethanol–water mixtures indicates that the ethanol at high concentration exists as pools in a water matrix.[29]

Amaya's work does, however, point directly to an inherent weakness of our model. This is the fact that Δ is experimentally dependent on the concentration of the solute. The assumptions leading to eq 9 lead to a concentration-independent discrimination, so that we are forced to treat Δ parametrically with regard to concentration range of the experiment. However, for the near saturation conditions of the Pasteur experiment, Δ may be taken to be a constant proportional to the packing discrimination of the solids; for lower concentrations, the potential is likely to be more dispersive and considerably weaker. It would be interesting to determine this concentration dependence of Δ using Amaya's technique, but for a range of concentrations for the enantiomerically pure solutions.

Application to Phenomena in Chiral Solvents

In a seemingly unrelated series of experiments over a century later, Dwyer studied the interactions of chiral ions in aqueous solutions.[16-18] He found that the two enantiomers (say A', A'') of a chiral ion exhibited different thermodynamic and kinetic properties if another chiral ion, say B', was added to the solution. The related phenomena for uncharged organic systems had received considerable attention[19] and was invariably postulated to

(16) Dwyer, F. P.; Gyarfas, E. C.; O'Dwyer, M. F. *Nature (London)* **1951**, *167*, 1036.
(17) Davies, N. R.; Dwyer, F. P. *Trans. Faraday Soc.* **1953**, *49*, 180.
(18) Dwyer, F. P.; Gyarfas, E. C.; O'Dwyer, M. F. *J. Proc. R. Soc. N.S.W.* **1955**, *89*, 146.

arise through diastereoisomeric differences of A'B', A"B' as discussed earlier. (It is interesting to note that the "classical" interpretations of both Dwyer's and Pasteur's experiments contain the assumption that it is the energetics of the diastereoisomer formation that determines ultimately the result of the experiment.) The Dwyer experiments involved dissociated media, however, and the differences persisted even if A and B carried the same charge. Dwyer thus suggested that the results could be rationalized without recourse to diastereoisomer formation, and postulated that the ions A', A" have different activities in solution because of long-range interactions with B'. He referred to this as configurational activity and thus was the first to point out the importance of interactions in the solution or dissociated phase as capable of leading to measurable thermodynamic differences in the properties of the two enantiomers. This caused some controversy, which persists even in the more recent literature.[20-23]

Dwyer's experiments were largely in achiral solvents, with the chiral interactions coming from an added chiral ion B' (which in our formalism may be identified with S for convenience). These studies will not be discussed in detail here, as they have been reviewed in a number of recent papers.[9,24] More recent studies in chiral solvents have been reported by Bosnich and Watts.[25,26] These results will be briefly returned to later, but we now consider two particular phenomena studied by these authors in the context of the van der Waals approach.

Partial Resolution of Labile Racemates. Consider the case of the equilibrium of a mixture of kinetically labile A', A" in a solvent S. The lability of A leads to x being a real variable in the sense that the interconversion of A', A" can occur in the solution with the sole restraint that the overall concentration of A remains constant. The condition for equilibrium is obtained by minimizing the free energy; i.e.,

$$\left.\frac{\partial f_C}{\partial x}\right|_v = 0$$

Using eq 3–5 and 11, this condition reduces in the general case to

$$(1 - c)\Delta_S + c(4x - 2)\Delta = -kT \ln x/(1 - x)$$

If the solvent is achiral, $\Delta_S = 0$ and the equation has the solution $x = \frac{1}{2}$ corresponding to the racemate. For a chiral solvent, however, the discriminatory interactions of A', A" with S result in one of the species having a lower energy in the solvent than the other. Thus the equilibrium becomes a balance between the enthalpic drive toward the species with the lower energy and the entropic drive toward the racemate. Noting that $x = \frac{1}{2}$ if the solvent is achiral, we shall assume that the discriminatory interactions are sufficiently weak so that, in the chiral solvent, $x = \frac{1}{2} + \delta x$, where $\delta x \ll \frac{1}{2}$. Then the equation above reduces further to

$$\delta x = -(1 - c)\Delta_S/4(kT + c\Delta) \tag{23}$$

Before discussing this equation in a general way, we consider the simpler case where the mole fraction of A (c) is sufficiently small so that $|c\Delta| < kT$, when the equilibrium shift (relative to the pure racemate in an achiral solvent) reduces to

$$\delta x = -(1 - c)\Delta_S/4kT \tag{24}$$

Noting that $\delta x = \delta N_{A'}/N_A$ and $(1 - c) = N_S/N$, we have

$$\delta N_{A'} = -N_A N_S \Delta_S/4NkT \tag{25}$$

(19) Turner, E. E.; Harris, M. M. *Q. Rev. Chem. Soc.* **1948**, *1*, 299.
(20) Brasted, R. C.; Landis, V. J.; Kuhajek, E. J.; Nordquist, P.E.R.; Mayer, L. "Coordination Chemistry"; Plenum Press: New York, 1969; p 64.
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(25) Bosnich, B.; Watts, D. W. *J. Am. Chem. Soc.* **1968**, *90*, 6228.
(26) Bosnich, B.; Watts, D. W. *Inorg. Chem.* **1975**, *14*, 47.
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so that the change in the A' concentration is proportional to the product $N_A N_S$, a result in agreement with experiment[20] and the simple lattice model discussed elsewhere.[9] The equilibrium has an inverse dependence on temperature, also in agreement with experiment,[17,20] favoring the excess of the enantiomer with the lowest energy in the chiral solvent. (The experimental results mentioned above are for systems in an achiral solvent with an added chiral species S, but the distinction is minimal and the generalization trivial.)

Returning to the more general form of eq 23, it is interesting to note that the self-discrimination has a definite effect on the equilibrium shift, despite the fact that it cannot in itself shift the equilibrium. A positive self-discrimination energy (in which unlike interactions are favored) serves to increase the denominator and consequently decrease the shift. This may be understood physically by noting that the total number of pairwise unlike interactions is proportional to $x (1 - x)$, which is maximized of $x = \frac{1}{2}$, so that a decrease in the equilibrium shift is consistent with an increase in the number of unlike interactions. On the other hand, the number of like interactions is proportional to $x^2 + (1 - x)^2$, which is minimized at $x = \frac{1}{2}$. Thus a negative self-discrimination energy (favoring like interactions) serves to increase the equilibrium shift, favoring resolution. It is interesting to note that this has some similarity with the role of the self-discrimination energy in the Pasteur experiment. The equilibrium shift phenomenon for inorganic systems is known as the Pfeiffer effect.[21]

Solubilities in Chiral Solvents. We turn now to a comparison of the solubilities of the two enantiomers A', A" in a chiral solvent S. Two different systems, one with A' crystals in equilibrium with a solution of A' in S, and another with the analogous A", S system are compared. Consider first the A', S system. The equilibrium is established when the chemical potential of A' in the solution phase is equal to that of the enantiomorphous A' crystal. In the solution phase, the concentration variable is the mole fraction of A', which we denote by $c' = cx$. As there is no A" in this system, the free energy per particle is obtained from eq 3–5 and 11 by putting $x = 1$ and identifying the mole fraction c with c'. Then

$$f_C = \frac{1}{2}[(1 - c')^2 E_{SS} + 2c'(1 - c')E_{A'S} + c'^2 E_{A'A'}] + kT[c' \ln$$
$$c' + (1 - c') \ln (1 - c')] - kT \ln [1 - (1 - c')\bar{v}_{SS} - c'\bar{v}_{A'A'}]$$

The chemical potential of A' is then evaluated as

$$\mu_{A'}(c') = \frac{\partial f_C}{\partial c'} = -(1 - c')E_{SS} + (1 - 2c')E_{A'S} + c'E_{A'A'} +$$
$$kT \ln \frac{c'}{1 - c'} - kT\frac{\delta v_{SA'}}{(1 - \bar{v}_{SS} + c'\delta v_{SA'})} \tag{26}$$

with the notation

$$\delta v_{SA'} = \bar{v}_{SS} - \bar{v}_{A'A'}$$

The solubility of A' in the solvent S is then determined by the condition

$$\mu_{A'}(c') = \mu_A^0 \tag{27}$$

where μ_A^0 is the chemical potential of the enantiomorphous A' crystal.

The same analysis for the A", S system leads to an expression for $\mu_{A''}(c'')$ of the same form as eq 26 except that all primes are replaced by double primes, with c'' the mole fraction of A" in the solution phase. Noting that the enantiomorphous crystal A" has the same chemical potential as the A' crystal, it follows that

$$\mu_{A'}(c') = \mu_{A''}(c'') = \mu_A^0 \tag{28}$$

Thus eq 26 and the corresponding equation for A" combined with the condition of eq 28 provide a direct relationship between c' and c''. As we are interested in the difference in the solubilities of A' and A" in S, it is possible to cast eq 26 in a more convenient form prior to substitution into eq 28.

The mole fractions c', c'' may be replaced by the variables

$$c^0 = (c' + c'')/2$$

$$\delta c = (c' - c'')/2$$

Assuming that the difference in the solubilities of A' and A'' is significantly smaller than the overall solubility, i.e., $\delta c \ll c^0$, it is possible to approximate the chemical potential of A' at concentration c' by a truncated Taylor expansion about c^0, i.e., in terms of an incremental change $\delta c' = \delta c$ such that

$$\mu_{A'}(c') \simeq \mu_{A'}(c^0) + \left.\frac{\partial \mu_{A'}(c)}{\partial c}\right|_{c^0} \delta c \qquad (29)$$

Noting that for the A'' system the incremental change $\delta c'' = -\delta c$, the chemical potential of A'' at concentration c'' reduces to

$$\mu_{A''}(c'') \simeq \mu_{A''}(c^0) - \left.\frac{\partial \mu_{A''}(c)}{\partial c}\right|_{c^0} \delta c \qquad (30)$$

Trivial substitution into eq 28 gives an explicit expression for the solubility difference $(c' - c'') = 2\delta c$ in terms of c^0; viz.

$$\delta c = -[\mu_{A'}(c^0) - \mu_{A''}(c^0)]/\left[\left.\frac{\partial \mu_{A'}(c)}{\partial c}\right|_{c^0} + \left.\frac{\partial \mu_{A''}(c)}{\partial c}\right|_{c^0}\right] = -X/Y \qquad (31)$$

where

$$X = (1 - 2c^0)\Delta_S$$

$$Y = 2\left[E_{SS} + E_{A'A'} - 2E_{A'S} - \Delta_S + kT\left(\frac{1}{c^0} + \frac{1}{1 - c^0}\right) + kT\frac{(\delta v_{SA'})^2}{(1 - \bar{v}_{SS} + c^0 \delta v_{SA'})^2}\right]$$

Defining the energy terms $E_{AA} = E_{A'A'} = E_{A''A''}$ and $E_{AS} = (E_{A'S} + E_{A''S})/2$, and ignoring the invariably positive excluded volume terms, eq 31 reduces to the more compact form

$$(c' - c'') = 2\delta c =$$
$$[(2c^0 - 1)\Delta_S]/\left[\delta E_{SA} + kT\left(\frac{1}{c^0} + \frac{1}{1 - c^0}\right)\right] \qquad (32)$$

where $\delta E_{SA} = E_{SS} + E_{AA} - 2E_{AS}$.

We shall further restrict consideration to the physically reasonable case where the mole fraction of the solute is small compared with that of the solvent. Then $c^0 \ll 1$ and

$$\frac{(c' - c'')}{c^0} = 2\frac{\delta c}{c^0} \simeq \frac{(2c^0 - 1)\Delta_S}{(c^0 \delta E_{SA} + kT)} \qquad (33)$$

It is interesting to note that the denominator contains the entropic (kT) and energetic factors dominating the *overall* solubility. For example, the overall solubility increases as the temperature is increased and is favored by a positive δE_{SA} (for which AS interactions are favored over SS, AA interactions). These terms may be thought of as increasing the solubility *indiscriminately*, and thus effectively *reduce* the solubility *difference* through their insensitivity to the chirality of the systems. The numerator, however, is dominated by the $-\Delta_S$ term, leading to the physically

satisfying result that the energetically favored enantiomer will have the greater solubility.

Summary

A number of new features emerging from the theoretical results warrant mention. The first is the role of the self-discrimination energy. In the solution model for the Pasteur experiment, the critical phenomena are insensitive to the chirality of the solvent, and the phenomenon is controlled purely by the self-discrimination energy, with the spontaneous resolution being driven by a negative self-discrimination energy favoring like interactions. For labile racemates in achiral solvents, the self-discriminations cannot effect an equilibrium shift, but they can still act in setting up fluctuations of enantiomerically pure regions in the same way as for inert racemates in the Pasteur experiment, leading to a possibility of spontaneous resolution provided the crystallization kinetics are faster than the racemization rate. In chiral solvents, however, the equilibrium shift involves a delicate interplay between self- and solvent discriminations (Δ and Δ_S), with a negative self-discrimination serving to increase the equilibrium shift irrespective of which enantiomer is favored by the solvent discrimination. This immediately suggests an important practical exploitation which has not been previously recognized, in that the self-discrimination effectively *amplifies* the resolution (i.e., the equilibrium shift) of the labile racemate in a chiral solvent provided Δ is negative. The dispersive discrimination is always negative for self-interactions and will universally amplify the equilibrium shift. Packing discriminations can operate in either direction, as noted in the discussion of the Pasteur experiment. Another interesting feature is that, in principle, the ratio Δ_S/Δ may be determined through an extrapolation of δx to zero temperature for a fixed concentration c from eq 23. For enantiomeric solubilities in chiral solvents, however, only solute–solvent discriminations can lead to the differential solubilities.

Direct comparison with experiment support the general features of the model (such as temperature[17,20] and concentration dependence),[20] but the relative paucity of quantitative studies and the relative complexity of the systems studied make it difficult to unambiguously identify the source of the discriminations which can be estimated directly from the expressions derived in this section. The study by Bosnich and Watts of the equilibrium shift of a chiral complex in butanediol[26] indicates a direct role of packing discriminations, but the role of possible dispersive discriminations cannot be ruled out. In Dwyer's experiments, the S may be identified directly with the added solute, with the achiral solvent playing no role in the discriminatory effects, or, alternatively, the discrimination may arise from the packing differences of the *solvated* species, which would lead to a solvent dependence of the discrimination.[9] In all these experiments, the A species are relatively large, tris(bidentate) complexes.

There is now an extensive experimental literature on the thermodynamics of chiral mixtures, which has been admirably collected and discussed in a recent text.[30] It is hoped that the work of this paper will at least stimulate a broader theoretical interest.

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