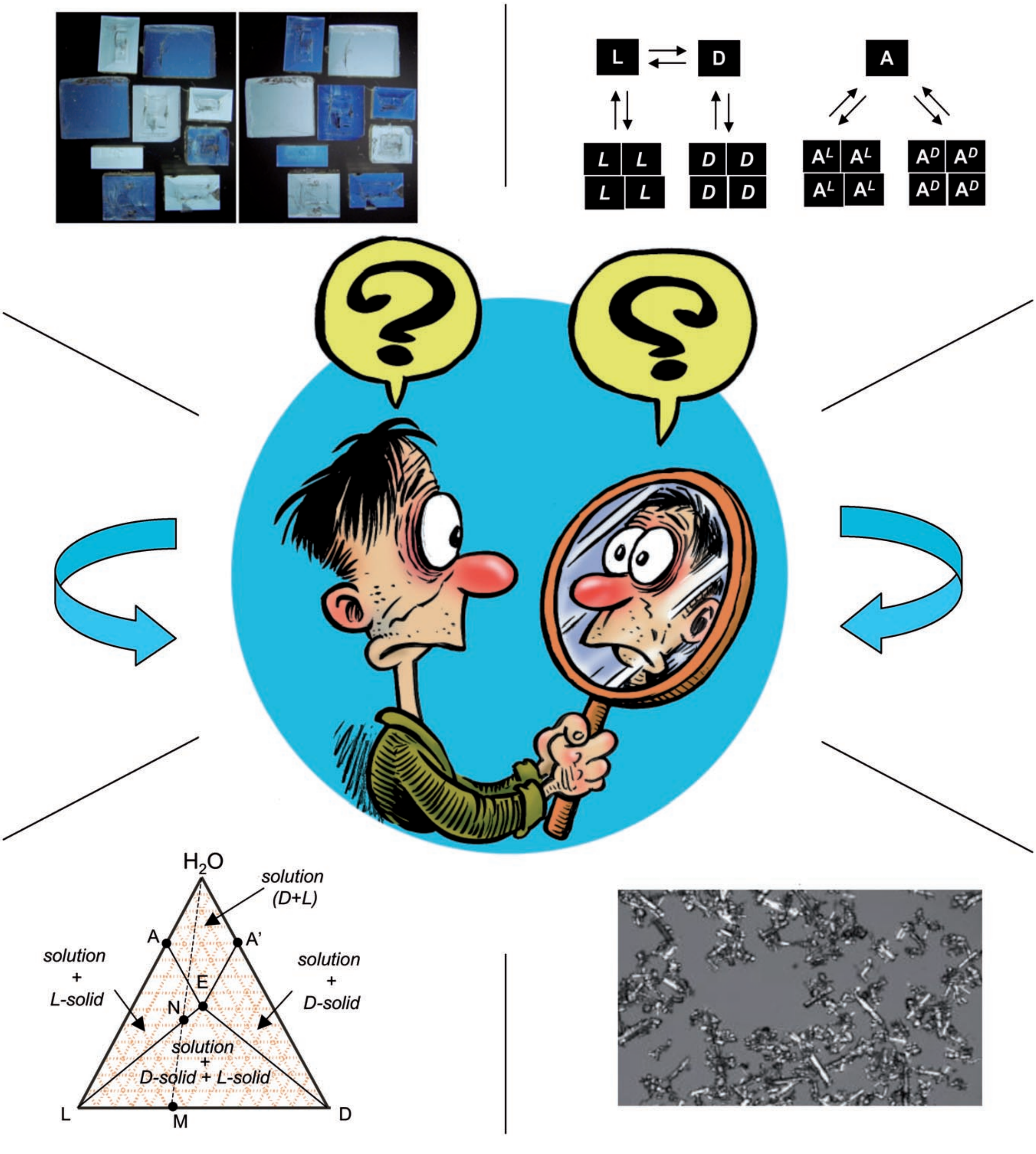
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200601463



"Chiral Amnesia" as a Driving Force for Solid-Phase Homochirality

“Chiral Amnesia” as a Driving Force for Solid-Phase Homochirality

Donna G. Blackmond*[a]

Abstract: The formation of a single homochiral solid phase from crystallization of achiral compounds has recently been under discussion. We show that the state of single solid-phase homochirality does not represent a more stable thermodynamic state than that of a racemate consisting of two separate homochiral solids. We introduce the term “chiral amnesia” as a more appropriate molecular-level description than “chiral recognition” to describe the driving force for establishing solid-phase homochirality in the case of achiral molecules that form chiral solids as well as in the case of rapidly racemizing enantiomers.

Keywords: chiral resolution • chirality • crystal growth • crystallization • eutectic • phase rule

Introduction

The origin of life remains one of the most tantalizing unanswered scientific questions of our time. Biological processes are characterized by molecular recognition, making an understanding the evolution of molecular homochirality an important part of this question.[1] A rationalization of how our present-day world of left-handed amino acids and right-handed sugars came about must provide for two features: a) a means of chiral symmetry breaking; and b) a means of amplifying the resulting imbalance of enantiomers.[2] Experimental results involving both autocatalytic chemical reactions[3,4] and analogous physical processes occurring in crystallizations[5] have provided proof of concept for “far-from-equilibrium” models for the evolution of single chirality in solution and in the solid phase.

Recent discussions probing the nature of the driving forces for achieving homochirality have suggested that reversibility in both chemical and physical processes may play an important role.[6–11] Here we would like to offer a different perspective on the development of homochirality through physical processes in the crystallization of enantiomeric molecules or the formation of enantiomorphic solids from achiral molecules. Using the Gibbs phase rule, we show that a system of rapidly racemizing chiral compounds forming separate homochiral solid phases (e.g., racemic conglomerates) is not strictly analogous to a system of achiral molecules that forms chiral solid phases. We propose that the evolution of homochirality is driven by a feature of these systems that we might term “chiral amnesia”, rather than chiral recognition, under reversible crystallization/dissolution conditions.

Enantiomorphic Solids Derived from Achiral Molecules

It has been known for over 100 years that certain achiral molecules such as $NaClO_3$ crystallize as chiral solids. Work from the early 1900s noted that these crystallizations often resulted in the formation of two separate chiral solid phases.[12,13] Kondepudi’s[5] striking finding that complete homochirality could be achieved in this system under some conditions was rationalized by proposing that formation of a first “Eve” crystal, randomly of either chiral form, may then be broken by shear from stirring into thousands of “daughter” crystals of the same chiral form. If nucleation takes place on these daughter crystals faster than random primary nucleation of a new crystal, formation of a solid of single chirality may be induced. Most recently, however, experimental results from Viedma[7] necessitated a modification to this model. Viedma showed that under some conditions, a single enantiomorphic solid could result from the starting point of equal portions of the two chiral solids; thus one chiral solid is converted completely to the other in this pro-

---

[a] Prof. D. G. Blackmond
Department of Chemistry and
Department of Chemical Engineering and Chemical Technology
Imperial College, London SW7 2AZ (UK)
Fax: (+44) 20-7594-5804
E-mail: d.blackmond@imperial.ac.uk

cess. In such a case all crystals clearly do not originate from the same primary crystal. Viedma reasoned that the continual abrasion of the crystals by stirring with small glass beads resulted in a repetitive dissolution/crystallization cycle. The evolution of homochirality was rationalized by the stochastic breaking of symmetry followed by this autocatalytic, nonlinear recycling crystallization process. They suggested that evolution towards single chirality is an inexorable consequence of some physical processes.

Crusats et al.[11] speculated that these ideas might be extended to describe systems of rapidly racemizing chiral compounds, which they see as analogous to achiral systems such as $NaClO_3$. To compare these systems, we first turn to a brief discusssion of the Gibbs phase rule.

The Gibbs Phase Rule

The phase rule [Eq. (1)] dictates the number of "degrees of freedom", F, in a given system of C components and P phases at equilibrium. This parameter F tells us how many variables we need to specify to describe the state of a system. For example, solid sucrose in equilibrium with liquid water is a system of two components and two phases, giving $F=2$. The two degrees of freedom are the temperature and pressure of the system. This means that if we hold temperature and pressure constant, the solution phase composition must be fixed.[14]

$$F = C + 2 - P \tag{1}$$

At the turn of the 20th century, when scientists began to apply recently developed concepts in equilibrium thermodynamics to problems in liquid-solid systems, the enantiomorphic crystallization of achiral molecules, such as $NaClO_3$, posed a puzzle that was voiced by van't Hoff.[12] Considering a solid–liquid two-component system such as $NaClO_3/H_2O$, we should find a total of three phases, consisting of the two enantiomorphic solid phases (A^L and A^D in Figure 1 a)[15] and the solution phase containing the achiral compound (A in Figure 1 a). The phase rule applied to this system would then give $F=2+2-3$, or one degree of freedom (univariant). This would suggest that we cannot choose both temperature and pressure in this system under solid–liquid equilibrium. But we know from experimental evidence that this is not the case.

Van't Hoff solved the conundrum by asserting that in the $NaClO_3$ case, the two enantiomorphic solid phases may in fact be considered to be identical, thus making $P=2$ and $F=2$, analogous to our sucrose example. Crusats et al.[11] see a contradiction here, since the nonequivalence of enantiomorphic crystals of chiral compounds is a fact that has been recognized since Pasteur first separated the enantiomorphous crystals of the conglomerate sodium ammonium tartrate.[16] This line of argument is misleading, however, because as we will show, an achiral system crystallizing as two enantiomorphic solid phases as shown in Figure 1 a is *not* completely analogous to the system of rapidly racemizing enantiomers that is shown in Figure 1 b.

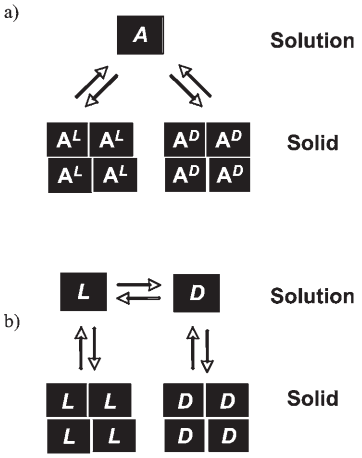


Figure 1. Illustration of solid–liquid equilibrium for systems forming chiral solids. a) Achiral material that forms two enantiomorphic solids.[16] b) Chiral compound forming a conglomerate (separate crystals of the two enantiomers).

How do the two types of systems shown in Figure 1 differ, and how does the phase rule help us understand these differences? One key to answering this question lies in comparing solution concentrations at equilibrium for the two systems shown in Figure 1. Viedma was able to produce randomly one homochiral solid phase (either A^D or A^L) in the $NaClO_3$ system starting from an equilibrium mixture of equal amounts of the two solids, meaning that only one of the two solids A^D or A^L was present at the end of the experiment. The solution phase in such a homochiral case will exhibit the characteristic solubility of $[A]^{sat}$ at the temperature and pressure of the experiment. Under conditions where both A^D and A^L solids are present, the solution still exhibits this same concentration of $[A]^{sat}$. However, for the system of enantiomers shown in Figure 1 b, a saturated solution in equilibrium with both D and L solid phases exhibits roughly *double* the solubility of the solution in a system containing either the D or the L solid alone. This is because each solution phase enantiomer communicates exclusively with its own solid phase to establish its own solid–liquid equilibrium, much in the way each separate type of liquid in an ideal mixture of liquids exhibits its own vapor pressure, independent of the others. This property is known as "Meyerhoffer's double solubility rule"[17] and has been recognized for more than a century as a characteristic of chiral compounds forming conglomerates. Thus, in contrast to the $NaClO_3$ system, where a *single* component in solution is simultaneously in communication with *two* separate solid phases, a system with a chiral compound maintains separate identities for each enantiomer in solution, and each enantiomer communicates separately with its own solid.

It is this communication *via the liquid phase* that is critical for rationalizing the phase behavior both in systems of achiral compounds forming two enantiomorphic solid phases as well as for chiral compounds forming conglomerates. To bring this back to the phase rule, what this solubility behavior tells us is that the achiral system possesses one less independent phase relationship than does the chiral system. The fact that the two separate solid phases are each in equilibrium with the *same* liquid phase for the achiral system makes the liquid composition independent of whether the solid phase is A^D or A^L or a combination of both. This effectively reconciles van't Hoff's problem with the phase rule for the achiral system, and it explains what he meant when he spoke of the enantiomorphic solid phases being "thermodynamically identical".

Extension to Chiral Compounds

The solubility comparison above makes it clear, however, that this characteristic of enantiomorphic solid phases that are derived from achiral compounds does *not* apply to chiral solid phases that are formed from enantiomers, even in systems where the enantiomers racemize rapidly. To show the implications of this fact, let's consider what happens when we apply the phase rule to the case of rapidly racemizing enantiomers.

A hypothetical system of rapidly racemizing enantiomers that has achieved homochirality in the solid phase is depicted in Figure 2a. In such a case, there are two separate phases and three components, and the phase rule gives $F=3$. Once we have specified temperature and pressure, we still have one more variable to specify before the system's state is determined. In the case of a chiral compound that forms a conglomerate but does *not* racemize, this situation corresponds to a non-racemic system where the minor enantiomer D is not present in sufficiently high concentration to establish its own solid phase. The overall composition of this non-racemizing system is found in the region (solution + L-solid) in the phase diagram in Figure 2b. Under solid-liquid equilibrium, the solution *ee* for this system is found at a point somewhere along the line EA, showing that the system can depart from the racemic value of its eutectic at E. The phase rule tells us that this solution *ee* value depends on the overall quantities of D and L in the system (our third degree of freedom). The solution will be saturated in component L, but not necessarily in component D, and the solution *ee* is not known until we specify the total amount of D in the system. For example, if the system's composition is found at point Q, and if the system has an overall D/L composition at point P, then the solution phase composition is given by point R.[16]

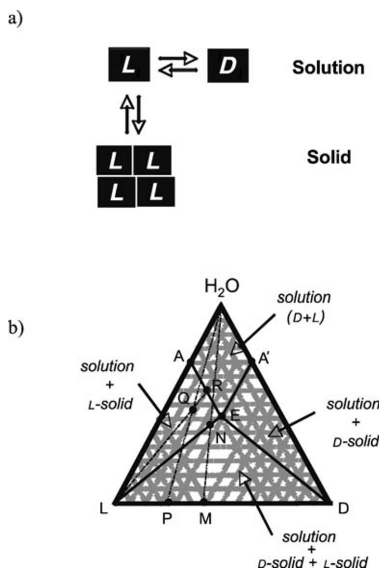


Figure 2. a) Example of rapidly racemizing enantiomers of a conglomerate that forms one single homochiral solid phase. b) Phase diagram for a conglomerate showing regions for a single solid phase and for two solid phases.

What happens in this case if we allow the enantiomers to racemize rapidly as shown in Figure 2a? When we apply the phase rule to this case, we begin to see the problem we have created: if the enantiomers are racemizing rapidly, the solution *must* be racemic! Thus the solution composition is fixed at E and is *not* found somewhere along the line EA. We seem to have lost the degree of freedom granted to us by the phase rule. How can we reconcile this contradiction? Simply put, the phase rule and this phase diagram tell us that a system of rapidly racemizing enantiomers that contains only one homochiral solid is at equilibrium *only* under the condition where the total amount of the minor enantiomer is exactly equal to its solubility at that temperature and pressure, so that its solution concentration matches that of the major enantiomer, which is at its saturation value. In this case the overall system composition does not lie in the region (solution + L-solid) but will be fixed somewhere along the line EL, and, as expected, the solution is racemic (point E). For example, a racemizing system with a total D/L composition of point M will have its overall system composition at point N.

To date, the routine, random production of a single homochiral solid from an initially racemic (unseeded) system of enantiomers has not been realized experimentally, although large excesses of one enantiomorphic solid phase compared to the other have been obtained in rapidly racemizing chiral conglomerate systems such as binaphthyl.[18] An unseeded initially racemic system of rapidly racemizing enantiomers with two chiral solid phases as shown in Figure 1b that experiences a perturbation causing it to deviate from an overall racemic composition will be driven to re-equilibrate by keeping both enantiomorphic solid phases replenished (the region marked (solution + D-solid + L-solid), in the absence of continued dynamic surface effects such as the repeated grinding/abrasion processes described by Viedma. Thus the phase rule demonstrates that spontaneous enantiomorphic purity is a special case but is *not* a thermodynamically more stable state in a system of rapidly racemizing enantiomers, as was suggested by Crusats et al.[11]

Chiral Recognition?

Another important difference must be emphasized here between an achiral compound forming two enantiomorphic solid phases and a system of enantiomers forming a conglomerate of separate D and L crystals. Crusats et al.[11] state that a system of either achiral or enantiomeric molecules must evolve towards solid-phase homochirality if homochiral interactions between molecules are more stable than heterochiral interactions. In the achiral system, chirality is not established at the molecular level. The solid-phase destiny of any achiral solution phase molecule of $NaClO_3$ is not decided until the molecule interacts with one or the other of the two chiral solid phases; it feeds either solid independently. The concept of homochiral versus heterochiral interactions is thus not applicable for the process through which an achiral solution phase molecule becomes part of a chiral crystal. The driving force for solid phase homochirality comes about as the molecules in one chiral solid continually redissolve, thereby losing their chiral identity and gaining a "second chance" at choosing their solid-phase chiral destiny.

By contrast, in the crystallization of chiral molecules, the destiny of a solution phase enantiomer is already imposed before interaction with the solid takes place. Homochiral interactions are clearly more stable than heterochiral interactions in enantiomeric systems that form conglomerates, but homochiral D–D and homochiral L–L homochiral interactions are equally stable;[19] a collection of homochiral crystals is not thermodynamically favored over a racemic conglomerate comprising equal parts D–D and L–L crystals. Thus the greater stability of homochiral versus heterochiral interactions is a necessary but not a sufficient condition for establishing solid-phase homochirality by such recycling processes. An enantiomer's "second chance" at choosing its solid-phase chiral destiny by dissolution/recrystallization processes is provided by the solution-phase racemization process, where considerations of homochiral versus heterochiral stability have no relevance.

Indeed, it might be stated that rather than invoking "chiral recognition toward the nano level" as discussed in reference [11], instead we may attribute the driving force for solid-phase homochirality to a kind of "chiral amnesia": molecules get a second chance at determining their solid-phase chiral destiny when they *forget* their solid-phase history, either by re-dissolving to form achiral molecules in the $NaClO_3$ case, or by re-dissolving and undergoing racemization in the case of enantiomers.

Conclusion

The Gibbs phase rule description of a solid–liquid system consisting of an achiral compound forming two enantiomorphic solid phases is shown to be *not* strictly analogous to that of rapidly racemizing enantiomers that crystallize as separate D–D and L–L solids. The puzzle concerning adherence to the phase rule for the former system is resolved by recognizing that it is the communication between the two solid phases through their common liquid phase that allows the two enantiomorphic phases to be considered as equivalent for achiral molecules. Movement between two chiral solids via the solution phase is also the key to establishing solid-phase homochirality in the case of rapidly racemizing enantiomers. The phase rule also demonstrates that homochirality in the solid phase in this case does *not* represent a more stable thermodynamic state and that the relative stability of homochiral versus heterochiral interactions is not the key to solid phase homochirality. Homochirality in enantiomers forming conglomerates is therefore not to be expected as a consequence of thermodynamic equilibrium but might be approached due to the interplay between a kinetic departure from equilibrium in dynamic crystallization/dissolution processes and the system's attempts to re-establish equilibrium.

Note added in proof: While this paper was in press, the author became aware of a Hypothesis paper submitted to Astrobiology, now in press (DOI: 10.1089/ast), by C. Viedma, describing and interpreting his model of reference [7] in more detail, including the following statement: "Paradoxically, the molecular racemization in solution can be considered as the driving force that guaranties chiral purity in the solid state from a previously solid racemic medium." This is an independent and simultaneous introduction of the concept of "chiral amnesia" that we describe in this paper.

Acknowledgements

Stimulating discussions with Dr. M. Klussmann, Prof. J. S. Bradley, Prof. R. M. Kellogg, Dr. B. Kaptein, Prof. E. Vlieg, Prof. C. Viedma, Dr. C. J. Welch, and Prof. A. Armstrong are gratefully acknowledged.

---

[1] J. Podlech, *Cell. Mol. Life Sci.* **2001**, *58*, 44.
[2] F. C. Frank, *Biochim. Biophys. Acta* **1953**, *11*, 459.
[3] K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767.
[4] a) D. G. Blackmond, C. R. McMillan, S. Ramdeehul, A. Schorm, J. M. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103; b) D. G. Blackmond, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5732; c) D. G. Blackmond, M. Klussmann, *AIChE J.* **2007**, *53*, 2.
[5] D. L. Kondepudi, *Science* **1990**, *250*, 975.
[6] R. Plasson, H. Bersini, A. Commeyras, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 16733.
[7] C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504.
[8] Y. Saito, H. Hyuga, *J. Phys. Soc. Jpn.* **2004**, *73*, 33.
[9] M. Uwaha, *J. Phys. Soc. Jpn.* **2004**, *73*, 2601.
[10] I. Gridnev, *Chem. Lett.* **2006**, *35*, 148.
[11] J. Crusats, S. Veintemillas-Verdaguer, J. M. Ribo, *Chem. Eur. J.* **2006**, *12*, 7776.
[12] J. H. van't Hoff, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 4252.
[13] a) A. Byk, *Z. Phys. Chem.* **1903**, *45*, 465; b) R. Wegscheider, *Z. Phys. Chem.* **1903**, *45*, 697.

[14] The analysis throughout this discussion defines the system as including liquid and solid phases and excludes the vapor phase. If we define the system in our sucrose/H_2O example as a closed vessel including the vapor phase, the phase rule gives $F=2+2-3=1$, meaning that if we specify temperature, then pressure in the vapor

phase is fixed. It is conventional practice to draw system boundaries excluding the vapor phase when considering liquid-solid equilibria (see K. J. Laidler, J. H. Meissner, B. C. Sanctuary, *Physical Chemistry*, 4th ed., Houghton Mifflin Company, Boston, p. 223).

[15] We use the terminology A^D and A^L to describe the two chiral solid phases formed from an achiral material A. Although strictly the assignment of D and L is reserved for handedness in sugars and amino acids, much of the literature in crystallization, including references [1] and [2], adopts this nomenclature.

[16] J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolution*, Krieger Publishing Company, Florida, **1991** (earlier edition: Wiley, New York, **1981**).

[17] W. Meyerhoffer, *Ber.* **1904**, *37*, 2604–2610.

[18] a) R. E. Pincock, R. R. Perkins, A. S. Ma, K. R. Wilson, *Science* **1971**, *174*, 1081; b) D. K. Kondepudi, J. Laudadio, K. Asakura, *J. Am. Chem. Soc.* **1999**, *121*, 1448.

[19] Homochiral and heterochiral interactions were discussed in reference [11] in terms of the Frank model for absolute asymmetric synthesis (see reference [2]). The authors state that the Frank autocatalytic model includes the assumption that the heterochiral state is more stable than the homochiral state. Such an assumption is not in fact necessary in the Frank model to obtain amplification of *ee*. Indeed, experimental kinetic studies of the Soai autocatalytic reaction have been shown to follow the Frank model in the case where heterochiral and homochiral dimers are formed with equal stability. Asymmetric amplification of product *ee* is not dependent on differing stability of homochiral and heterochiral interactions. See reference [4] for a detailed explanation.