

## Response to “Comments on a Possible Transition to Solid-Phase Homochirality”

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**Abstract:** As part of an ongoing discussion comparing models for the evolution of homochirality, we address the preceding Correspondence by Ribó and co-workers. We demonstrate that our previous Concept article did *not* include errors concerning solubility behavior and we address the challenge of

representing equilibrium phase behavior for systems of racemizing enantiomers. In addition we re-emphasize the

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point that the homochiral state is *not* inherently more stable than the heterochiral state and we show that concerning this point the Ribó treatise misinterprets the Frank model for the evolution of homochirality.

### Introduction

The mystery of asymmetry in living systems holds as much fascination for scientists today as it did when the importance of molecular single chirality to life on earth was first recognized. Over the past two decades three distinct models for the evolution of homochirality involving physical phase behavior have been reported. Kondepudi's “Eve crystal” model<sup>[1]</sup> provided a far-from-equilibrium scenario, while our own eutectic model is based on thermodynamic control of asymmetric amplification.<sup>[2,3]</sup> And in the middle is perhaps the most compelling concept of all: Viedma's model<sup>[4]</sup> involving an interplay between kinetics and thermodynamics, which we have termed the “chiral amnesia” model.<sup>[5]</sup>

Viedma's model has raised considerable interest, engendering two *Concept* articles and this correspondence as well as a report in the popular science literature.<sup>[5–7]</sup> Indeed, at first sight, the results appear to be inexplicable to many scientists, and I can say that I have spent many an enjoyable hour pondering and discussing its rationalization and its potential impact (see Acknowledgments). The simple action of adding glass beads to a stirred system of racemic enantiomorphs moves this thermodynamically stable system away from equilibrium and allows it to establish a new stable ho-

mochiral state. It seems like magic. And we recognize that the aura of magic and mystery has long been a cue for scientists to seek rational explanations for observed phenomena. That is just what this discussion is about.

I will address here the key points in the vigorous treatise by Prof. Ribó, divided, as in his discussion, into two main topics. His first point focuses on our disagreements having to do with general aspects of equilibrium phase behavior, including application of the phase rule and construction of phase diagrams. His second point critiques our discussion of the model Viedma developed to rationalize his results, and in this case Prof. Ribó goes so far as to state boldly that this model represents a “thermodynamic impossibility”.<sup>[6b]</sup>

### Phase Behavior

Undertaking to understand and describe the relationships between species and phases in multicomponent, multiphase systems has never been a simple or an unambiguous task; witness the stimulating discussions in the literature at the turn of the 20th century,<sup>[8–10]</sup> just decades after Gibbs' seminal work. We must remember that the Gibbs phase rule and phase diagrams represent mathematical constructs to help us make sense of physical systems under equilibrium conditions. The differences between Prof. Ribó's discourse and my own do not arise from “errors” in my discussion or in my application of the phase rule but result simply from the different connections we each make between the mathematical identities of “components” and their identities based on chemical/physical properties.

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**Number of components:** Laidler<sup>[11]</sup> defines the number of “components” in a system for the purposes of the phase rule as “the smallest number of independent chemical constituents needed to fix the composition of every phase in the system.” Laidler also noted that if a chemical reaction can take place between two components, they are related by an equilibrium condition and they are no longer independent. In this sense Prof. Ribó is completely correct in counting racemizing enantiomers in solution as one component. But where does this definition leave us in our attempt to describe the physical and chemical behavior of the system? There are clear differences in the behavior of the two systems depicted in parts a) and b) of Figure 1, which shows the solution-solid equilibrium for an achiral system such as NaClO<sub>3</sub> and for a system of racemizing enantiomers, respectively.

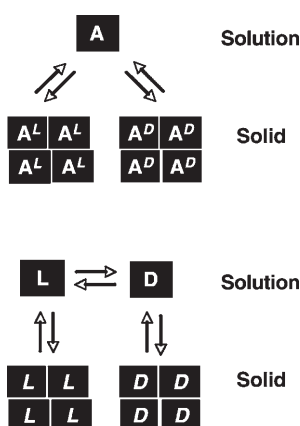


Figure 1. Illustration of solid-liquid equilibrium for systems forming chiral solids. a) achiral material that forms two enantiomorphous solids; b) chiral compound forming a conglomerate (separate crystals of the two enantiomers).

Let us carry out a thought experiment where we isolate one crystal from the D solid phase and one crystal from the L solid phase in Figure 1 a, and the same from the system in Figure 1 b. Assuming we can deconstruct these crystals into their molecular level constituents, we may ask the following questions:

- Does each component (constituent) rotate polarized light in a manner opposite to the molecules of its enantiomorphous crystal?
- Do the molecules of one component react or interact with chiral additives differently than do the molecules that make up its enantiomorphous crystal?
- Are the molecules of one component unable to contribute to the growth of crystals of the opposite type?

We can immediately see that the answer to these questions is “no” for NaClO<sub>3</sub> (Figure 1 a) and “yes” for racemizing enantiomers (Figure 1 b). The conundrum is that *mathematically* the systems behave as one component in both cases, but in the case of enantiomers we continue to require

two species to describe fully the chemical and physical behavior of the system at equilibrium. The definition of “components” for the purposes of the phase rule says that a stable system of enantiomers under racemizing conditions is identical whether the solid state is racemic, enantiopure, or anywhere in between, but we know that this description is of little use to us when we wish to describe the chemical behavior of the system.

**Meyerhoffer double solubility rule:** Solubility is another property for which the mathematical definition of “components” fails to provide an accurate description of the observed behavior for a racemizing system of enantiomers at equilibrium. A theoretical treatment can show that the double solubility rule<sup>[12]</sup> does indeed hold for enantiomers under racemizing conditions; here we beg to differ with Prof. Ribó and state again that in this particular respect the behavior of racemizing enantiomers is *not* analogous to the NaClO<sub>3</sub> system.

Consider the following simple illustration in Figure 2 of two constant concentration reservoirs A' and B', involved in equilibrium reactions producing A and B, respectively. Con-

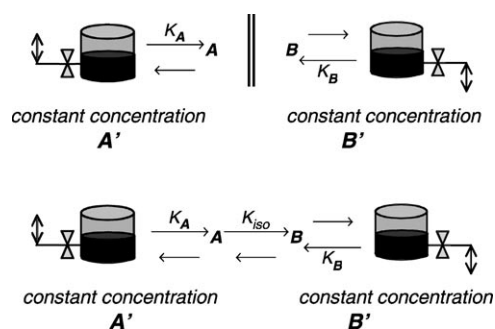


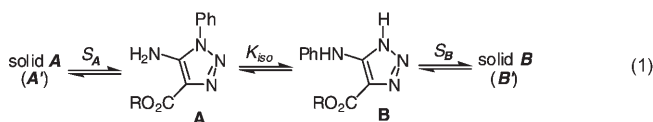
Figure 2. System showing coupled and uncoupled equilibria; a) system in which reaction between A and B is blocked; b) flow through system.

centration in the reservoirs in Figure 2 is depicted by the volume of the vessels, with an inlet/outlet valve attached that allows flow to maintain a constant level. Each reaction exhibits its own characteristic thermodynamic equilibrium constant,  $K_A$  and  $K_B$ , at fixed conditions of temperature and pressure (Figure 2 a). Let's turn to a case where a reversible reaction can occur between A and B (Figure 2 b). This simulates a biological system, as metabolite control in a living cell is generally maintained through changes in flux in the metabolic pathway, while the absolute metabolite concentrations most often remain fixed. Imagine the system in Figure 2 a at equilibrium, with the barrier between A and B then suddenly lifted, as shown in Figure 2 b. Now we have added the equilibrium relation dictated by  $K_{iso}$  between A and B. What happens as the system strives to maintain the concentrations dictated by  $K_A$ ,  $K_B$ , and  $K_{iso}$ ?

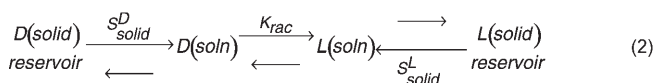
What we find is that mass will flow either in the direction of A to B or vice versa, depending on the magnitude of  $K_{iso}$ . This in turn will trigger flow to or from each reservoir as the

system attempts to re-establish the equilibria according to  $K_A$  and  $K_B$ . Except for the case of an initial set of conditions where the reservoir concentrations are perfectly balanced with the three equilibrium constants, a steady state flow will continue, and this system will never achieve equilibrium.

Figure 2b provides an analogy to solid-solution phase equilibria for isomerizing systems, where the reservoirs represent solid phases, employing solubility relations rather than chemical equilibria to describe the relationships between the solid reservoirs and solution isomers (solubilities  $S_A$  and  $S_B$  instead of  $K_A$  and  $K_B$ ). This situation was treated nearly a century ago by Dimroth<sup>[9]</sup> for systems that couple chemical equilibria with solid-solution equilibria, and it is applied today in crystallization-induced enantiomeric and diastereomeric transformations.<sup>[13]</sup> Dimroth treated the case of equilibrating isomers under heterogeneous conditions for systems such as the isomerization of triazole derivatives as in Equation (1), where in contrast to enantiomeric systems the isomers clearly may have different solubilities ( $S_A \neq S_B$ ) and chemical properties ( $K_{iso} \neq 1$ ). Depending on the relative values of  $S_A$ ,  $S_B$  and  $K_{iso}$  in such a case, mass will flow either from solid **B'** to **A'** or in the reverse direction, as the system attempts to establish equilibrium.



“Dimroth’s principle”<sup>[14]</sup> applied to our example reveals that in the special case of racemizing enantiomers and conglomerate solids as in Equation (2), the “perfect balance” between chemical and physical equilibria exists ( $S^{\text{D solid}} = S^{\text{L solid}}$  and  $K_{rac} = 1$ ) such that the system in Figure 2 equilibrates to the same solution concentration of **D + L (A + B)** whether the barrier to racemization is in effect or not. The equilibrium concentrations of **D** and **L** are additive and identical both in the absence and in the presence of solution racemization.



*Thus fundamental thermodynamic principles dictate that the Meyerhoffer double solubility rule holds both in the presence and in the absence of a fast solution-phase equilibrium between the enantiomers.*

**Equilibrium phase diagram for racemizing enantiomers:** This discussion settles the question of the Meyerhoffer double solubility rule, but it leaves us with the problem of how to represent the equilibrium behavior of racemizing enantiomers on a phase diagram. Both Prof. Ribó and I agree that the standard ternary phase diagram will not suffice.

However, because phase diagrams represent such an excellent tool for the compilation and description of equilibrium compositions, it makes sense to look for a way to extend the tool to the challenging case of racemizing enantiomers. What we have described above tells us that certain regions of the standard ternary phase diagram of Figure 3a become

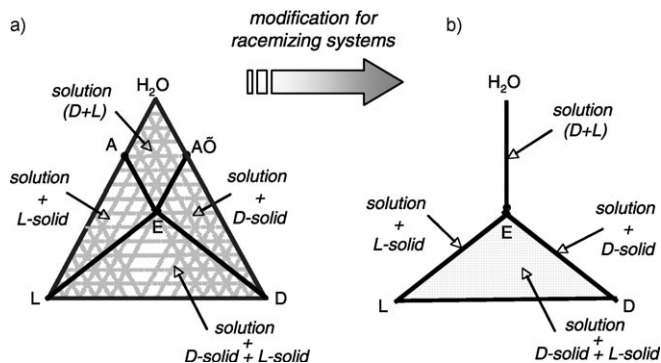


Figure 3. a) Standard ternary phase diagram of a conglomerate system for the case of non-racemizing enantiomers; b) proposed modified ternary phase diagram for the case of racemizing enantiomers with “forbidden” regions removed.

“forbidden” to a system of racemizing enantiomers. Figure 3b proposes a modification in a conglomerate system of **D** and **L** solids in which forbidden regions have been removed.<sup>[15]</sup> The enantiomers may exist as an equilibrium mixture in the solid phase in any relative proportion but only as a racemic mixture in the solution phase. The enantiopure solution concentrations of **L** and **D**, given by points **A** and **A'** respectively in Figure 3a, are meaningless for racemizing enantiomers, but the eutectic point **E** in Figure 3b remains at a racemic composition with twice the solubility exhibited at **A** and **A'** in Figure 3a in the absence of racemization.

The diagram in Figure 3b offers a solution to the dilemma of the phase diagram that remains true to the mathematical definition of “components” as demanded by Prof. Ribó, without compromising important distinguishing information about the separate enantiomers in a racemizing system under equilibrium conditions, as we have discussed here and in <sup>[5]</sup>.

## The Viedma Model<sup>1</sup>

Prof. Ribó disputes the explanation for the results given in Viedma’s work<sup>[4,7]</sup> and paraphrased in my Concept article.<sup>[5]</sup> He also disputes our statement that the homochiral state is not more stable than the heterochiral state.

**Gibbs–Thomson rule and Ostwald ripening:** Viedma’s rationalization of his results is described briefly here and sum-

<sup>1</sup> Prof. Ribó calls this the “Blackmond–Viedma model”; however, since the experimental results and the full rationalization have been provided by Prof. Viedma, it is correct to refer to it as the “Viedma model”.

marized schematically in Figure 4. When a system consisting of a racemic mixture of the two solid enantiomorphs of  $\text{NaClO}_3$  is stirred in the presence of glass beads, a dynamic

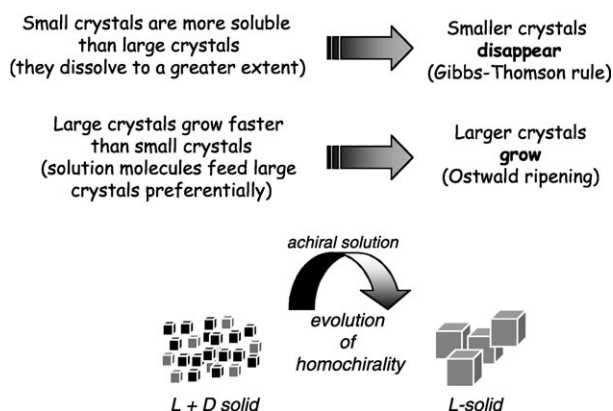


Figure 4. Description of the Viedma model for the evolution of solid-phase homochirality based on his experiments with  $\text{NaClO}_3$ .

process of dissolution and growth of the two solid enantiomorphs is induced by the mechanical energy imparted to the system by attrition. According to the Gibbs–Thomson rule, smaller crystals produced by attrition dissolve faster than larger ones, resulting in an increased local solution concentration of  $\text{NaClO}_3$ . This is what Prof. Ribó calls “the undisputed starting point”<sup>[6b]</sup> for the discussion, and it is here that our views begin to diverge.

The Viedma model states that this increased solution concentration itself provides an increased driving force for crystal growth via Ostwald ripening, which favors large crystals regardless of their handedness. The net result is that small crystals disappear and large crystals grow larger. A small imbalance in the handedness of large compared to small crystals, which may develop stochastically, coupled with the achirality of the solution phase, allows depopulation of one solid chiral state (the one randomly favored by the small crystals) towards the other (the one randomly favored by the larger crystals). Paradoxically, the “chiral amnesia” induced when crystals dissolve provides the driving force for the evolution of solid-phase homochirality.<sup>[4,5,7]</sup>

Prof. Ribó disputes that “the very existence of the redissolution/recrystallization steps alone explains the transition towards homochirality.”<sup>[6b]</sup> He argues that these processes are simply the behavior we expect even in the absence of attrition energy applied to the system; why does this not lead inexorably to homochirality in the stagnant or slightly stirred experiments?

This question has been addressed by Viedma,<sup>[4b]</sup> and it involves another divergence from Prof. Ribó’s thinking. The model considers the state of single chirality to be a kinetic “trap” accessible because of the input of energy into the system in the attrition process. Homochirality could indeed result from a stagnant or slightly stirred state if a means of scaling the energy barrier is available (Figure 5).

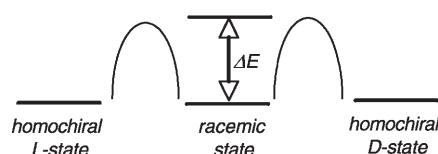


Figure 5. Depiction of the energy barriers between homochiral and heterochiral states.

**Cluster formation:** Prof. Ribó complains that I neglected to discuss his arguments concerning the formation of chiral clusters in my Concept article;<sup>[5]</sup> this is indeed a valid complaint. I did not discuss these concepts because the model given above provides a splendid rationalization of Viedma’s results without the need to invoke any “extra” phenomena that, given the absence of experimental evidence for these phenomena, might find Occam looking askance. We briefly address these points here.

Prof. Ribó believes that under these attrition conditions the dissolution of small crystals causes sufficient supersaturation to bring about the formation of chiral clusters as a step towards primary nucleation. By this logic such cluster formation should occur equally in systems of  $D + L$  crystals or homochiral crystals when each is stirred with glass beads. Prof. Ribó will certainly not argue against the fact the  $D$  homochiral state and the  $L$  homochiral state are equally stable. The random formation of chiral clusters from the achiral solution ought therefore to produce a system that cycles continuously between the two equally stable homochiral states. This behavior is not observed experimentally. Continued attrition of the system in one homochiral state does not move the system to the other homochiral state. This suggests that the system is “kinetically locked” into one homochiral state because the conditions are not met for chiral recognition between aggregating species to occur.

We are left with a situation in which there exists clear evidence *against* the role of primary nucleation or cluster formation and nanoscale chiral recognition, and there exists clear evidence *for* the combined effects predicted by the Gibbs–Thomson rule and Ostwald ripening. If this assessment represents a “denial of the significance of chiral recognition in the implied process”,<sup>[6b]</sup> then I am guilty as charged.

**Homochiral and heterochiral stability:** The final points made in Prof. Ribó’s discussion concern the relative stability of homochiral versus heterochiral interactions. He begins the discussion with a rather mischievous syllogism: “the Blackmond–Viedma model does not accept that the homochiral state... is a more stable state than the heterochiral state. Consequently, the Blackmond–Viedma model predicts that a less stable state can be achieved by the simple repetition of the recycling process.”<sup>[6b]</sup>

Stating that a model does not predict that a *more* stable state does *not* imply that it predicts a *less* stable state. As we wrote clearly in our text, we believe these are *equally* stable states.

Prof. Ribó goes on to comment: “Let us now suppose that our opinion of the Blackmond–Viedma model is incorrect, and that this model does in fact allow the existence of a thermodynamic reason for the transition towards homochirality.”<sup>[6b]</sup>

The supposition is correct: their opinion of the Viedma model is indeed *incorrect*, as can be seen from this excerpt from the Conclusions of my Concept article, in which thermodynamic reasoning is clearly invoked:

“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.**”<sup>[5]</sup>

Further weaknesses in the Ribó arguments are evident in their discussion of the Frank model. Ribó et al. state that “the Frank scheme assumes a chemical behavior in which homochiral interactions are more favored than heterochiral ones, so that we could extrapolate that it assumes that the racemic state is less favored than the homochiral one when a cyclic nonlinear dynamic network is available.”<sup>[6b]</sup>

This is a clear misinterpretation of Frank’s seminal work.<sup>[16]</sup> The Frank scheme does *not* require that homochiral interactions are more favored than heterochiral ones, nor that a racemic state is less favored than a homochiral one. His paper did not treat specific chemistry or specific chemical reactions.

Frank stated his model simply as the following: “A simple and sufficient life model for the present purpose is a chemical substance which is a catalyst for its own production and an anti-catalyst for the production of its optical antimer.” (ref. [16], p. 459).

The question of stability of homochiral versus heterochiral interactions is not specifically addressed in Frank’s statement. As it turns out, there are a number of mathematically distinct mechanisms that can fulfil the criteria stated by Frank, including cases where homochiral interactions are **more** stable, **equally** stable, and **less** stable than heterochiral interactions.

Indeed, the very first case treated by Frank stands at odds with Prof. Ribó’s statement. This case was termed “specific mutual antagonism” and described mathematically as Equations 1 and 2 on p. 459, in reference [16], reproduced here as Equations (3):

$$\frac{dn_1}{dt} = (k_1 - k_2 \cdot n_2) \cdot n_1 \quad (3a)$$

$$\frac{dn_2}{dt} = (k_1 - k_2 \cdot n_1) \cdot n_2 \quad (3b)$$

In chemistry terms, these Equations correspond to a system where  $n_1$  and  $n_2$  are the concentrations of enantiomeric autocatalysts each for its own production. Interaction between the enantiomers is represented by the second term on the right side of each equation. In this model, homochiral

interactions ( $n_1 \cdot n_1$ ) are *forbidden*, and it is *solely* heterochiral interactions ( $n_1 \cdot n_2$ ) that account for amplification of the concentration of the major enantiomer. It is in fact correct to say that the first example treated by Frank was a case where heterochiral interactions are *more* stable than homochiral interactions, rather than the converse as stated by Ribó et al.<sup>[6b]</sup>

In collaboration with Dr John M Brown at Oxford, we have published our own experimental data and modelling of the Soai autocatalytic reaction<sup>[17]</sup> showing that the system follows a different case of the Frank model, where homochiral and heterochiral dimers are formed with **equal** stability, and enantiomeric enrichment is achieved because the heterochiral dimer species is kinetically inert as a catalyst.<sup>[18]</sup>

Thus it is incorrect to invoke the Frank model to support the claim that homochiral interactions are more stable than heterochiral interactions. More important, however, is the fact that this question is immaterial in a discussion of the behavior of conglomerates.<sup>[5]</sup> The relative stability of a racemic state (say, 500 D and 500 L particles) compared to a homochiral state (say, 1000 L particles) is not a matter of relative homochiral versus heterochiral stability. Heterochiral interactions do not occur *at all* in conglomerates, whether we have a system consisting entirely of D crystals, entirely of L crystals, or a mixture, in any proportion, of D + L crystals. The more pertinent question is: if the homochiral state is generally more stable, as proclaimed by Prof. Ribó, why do conglomerates represent the minority, while the vast majority of compounds known to man prefer to crystallize as racemic compounds, a form in which heterochiral interactions are clearly more stable?

## Conclusion

The conundrum posed by the phase rule for construction of equilibrium phase diagrams in the case of racemizing enantiomers has been discussed, and a compromise has been offered that allows both the mathematical and the physical/chemical characteristics of the system to be described. We re-emphasize the key feature of the Viedma model for the emergence of solid-phase homochirality in the NaClO<sub>3</sub> system: a combination of kinetic and thermodynamic processes moves the system inexorably towards a single solid chiral state by flow of mass through the achiral solution phase. The possibility that chiral recognition on the nano-scale may play a role in the evolution of solid-phase homochirality under some as yet undefined conditions cannot be ruled out. However, there is neither experimental evidence for such interactions nor a need to invoke them to produce a lucid explanation of Viedma’s compelling results.

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- [1] a) D. K. Kondepudi, *Science* **1990**, *250*, 975; b) D. K. Kondepudi, J. Laudadio, K. Asakura, *J. Am. Chem. Soc.* **1999**, *121*, 1448; c) D. K. Kondepudi, K. Asakura, *Acc. Chem. Res.* **2001**, *34*, 946.
- [2] a) M. Klusmann, H. Iwamura, S. P. Mathew, D. H. Wells Jr., U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621–623; b) M. Klusmann, A. J. P. White, A. Armstrong, D. G. Blackmond, *Angew. Chemie Int. Ed.* **2006**, *47*, 7985–7989.
- [3] a) We recently showed that observations of enantioenrichment via sublimation are rationalized by the eutectic model of Ref. [2]: M. Klusmann, D. G. Blackmond, *Chem. Commun.* **2007**, 3990–3996; see also: b) R. H. Perry, C. Wu, M. Neffliu, R. G. Cooks, *Chem. Commun.* **2007**, 1071–1073; c) S. P. Fletcher, R. B. C. Jagt, B. Feringa, *Chem. Commun.* **2007**, 2578–2580.
- [4] a) C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504; b) C. Viedma, *Astrobiology* **2007**, *7*, 312.
- [5] D. G. Blackmond, *Chem. Eur. J.* **2007**, *13*, 3290.
- [6] a) J. Crusats, S. Veintemillas-Verdaguer, J. M. Ribó, *Chem. Eur. J.* **2006**, *12*, 7576; b) J. Crusats, S. Veintemillas-Verdaguer, J. M. Ribó, *Chem. Eur. J.* **2007**, *13*, DOI: 10.1002/chem.200700538; preceding Correspondence.
- [7] *Physics Today*, April **2005**, pp. 21–22.
- [8] a) J. H. van't Hoff, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 4252; b) H. W. B. Roozeboom, *Zeitschrift fuer Physikalische Chemie Stoichiometrie und Verwandtschaftslehre* **1899**, *28*, 494–517.
- [9] O. Dimroth, *Justus Liebigs Ann. Chem.* **1910**, *377*, 127–163.
- [10] J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolution*, Krieger Publishing Company, Florida, **1991** (earlier edition: Wiley, New York, **1981**), and references therein.
- [11] K. J. Laidler, Meiser, Sanctuary, *Physical Chemistry*, 4th ed, Houghton Mifflin, Boston, **2003**, pp. 225–226.
- [12] W. Meyerhoffer, *Ber.* **1904**, *37*, 2604–2610.
- [13] a) K. J. Brands, A. J. Davies, *Chem. Rev.*, **2006**, *106*, 2711–2733; b) R. Yoshihoka, *Topics Curr Chem.* **2007**, *269*, 83–132.
- [14] N. A. Hassan, E. Bayer, J. C. Jochims, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3747–3757.
- [15] I am grateful for stimulating discussions with Prof. R. M. Kellogg, Dr. B. Kaptein, Prof. E. Vlieg, Dr. H. Meekes, and W. Noorduyn, in developing the modified phase diagram of Figure 4b.
- [16] F. C. Frank, *Biochim. Biophys. Acta* **1953**, *11*, 459.
- [17] K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767.
- [18] 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. Klusmann, *AIChE J.* **2007**, *53*, 2.

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