

Comments on a Possible Transition to Solid-Phase Homochirality

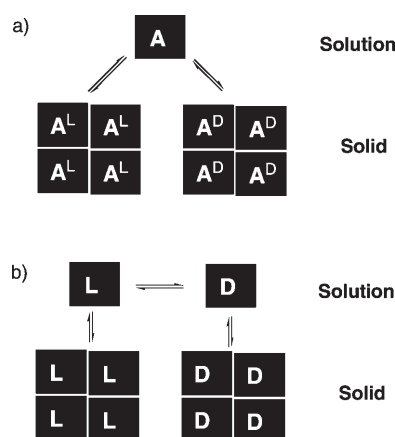
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Abstract: As a response to a Concept article published by D. G. Blackmond in this journal, which intended to offer alternative explanations to interpretations in a previous Concept article written by us, we show that errors concerning the solubility behavior of some enantiomorphs and concerning the application of the number of components in the Gibbs phase rule led the author toward the misunderstanding of our previous arguments and to non-valid conclusions.

Keywords: chiral resolution • crystal growth • phase rule • phase transitions

This Correspondence concerns D. G. Blackmond's Concept article, "Chiral Amnesia" as a Driving Force for Solid-Phase Homochirality,^[1a] which offered some different interpretations of the results of an experiment reported by C. Viedma^[2] on the transition of NaClO₃ crystals towards homochirality in a saturated solution by means of strong grinding, to those proposed by our group in our previously published Concept article, *Homochirality as a Consequence of Thermodynamic Equilibrium?*^[1b]

Blackmond's article tries to demonstrate that our application of the phase rule to the system consisting of a solution of an achiral compound (e.g. NaClO₃) in equilibrium with its enantiomorphous solid phases is misleading and cannot be extended to the similar system of a compound with fast racemization in solution, because both systems are "not completely analogous". For the sake of clarity, these two systems are reproduced in Scheme 1, using the same representation as that in Figure 1 in reference [1a]. In addition, Blackmond's Concept article tries to illustrate that our previous proposal to justify the Viedma experiment is incorrect and advances a new one, the central point of which lies in the "Chiral Amnesia" of the implied species during the recy-



Scheme 1.

cling process. Owing to the coincidence of this last interpretation model with that of a recent paper by C. Viedma,^[3] as explicitly recognized in a note added in proof in reference [1a], we will refer to it as the Blackmond–Viedma interpretation in this Correspondence.

We regret that in some parts of her article Blackmond misses to reproduce, or reproduces incorrectly, points of our argumentation. For example, in the section "Chiral recognition?", where our arguments concerning the formation of chiral clusters "before" achieving the critical size in the primary nucleation stage are not taken into account at all, or when in the discussion of the application of the Gibbs Phase Rule she states: "Crusats et al. see a contradiction here, since the nonequivalence of enantiomorphous crystals of chiral compounds is a fact that has been recognized since Pasteur first separated the enantiomorphous crystals of the conglomerate sodium ammonium tartrate. This line of argument is misled-

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ing.”. In fact what we actually wrote was “., the experimental evidence of the thermodynamic non-equivalence of enantiomorphous crystals became clear later (than the former citation corresponding to year 1903) with the study of their binary phase melting point diagrams” (see p. 7578 in reference [1b]). Note that here we are talking about “real” eutectic diagrams.

However, what we want to discuss in this letter are much more important aspects of Blackmond’s article. Our address is separated into two sections each concerning points raised in the Concept article by Blackmond. In the first section we address basic errors related to the application of the phase rule to the systems shown in Scheme 1, and in the second section we address the discussion of the Blackmond–Viedma model.

Basic errors related to the application of the Gibbs phase rule: Blackmond extensively explains that “Meyerhoffer’s double solubility” rule has to be applied in the case of a chiral compound when its L and D enantiomers are rapidly racemizing in solution (System b in Scheme 1): *for the system of enantiomers shown in Figure 1b [(Scheme 1b in this Correspondence)], 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.* The Meyerhoffer’s double solubility rule (assuming ideal gas and solution behavior) on the solubility of the racemic conglomerate compared to that of pure enantiomorphous crystals can only be applied to compounds yielding optically active solutions (i.e. non-racemizing). When racemization takes place, the vapor pressure change generated by the dissolution of a determinate amount of solid compound (regardless of whether it is a pure enantiomorph or a racemic conglomerate or a mixture of enantiomorphous crystals with any given *ee*) is always the same. Any chemist can advance that in the case of a system b) (see Scheme 1), the solubility of the pure enantiomorphous crystals is the same (assuming ideal behavior) as that of the racemic conglomerate (assuming that the racemization is very fast at that temperature). In summary, contrary to that stated by Blackmond, the solubility behavior of the systems a) and b) in Scheme 1 are analogous.

Blackmond’s error with respect to this point is reinforced in the discussion associated with Figure 2 in reference [1a]. Her argumentation to explain the behavior of a racemizing solution can only be followed by the reader if one accepts the misconception of the author regarding the solubility of these systems. Furthermore, a triangular phase diagram is used for this discussion. This can only lead to conceptual errors on the behavior of such systems (e.g. in the number of components as defined by the rule of phases). The triangular diagram corresponds by definition to a three-component system (solvent, D enantiomer, and L enantiomer, when racemization does not occur) and can be used, for example, for optically active tartrate salts and amino acids, but is meaningless for the racemizing system b) in Scheme 1.

Blackmond tries to demonstrate that our analogy between the two systems (the case of an achiral compound yielding enantiomorphous crystals and that of a fast racemizing chiral compound yielding enantiomorphous crystals) is incorrect on the basis that they are systems with two and three compounds, respectively. For example, this is clearly stated in respect to system b) (“*In such a case, there are ... three components and the phase rules gives.*”) and implicitly used in all the discussion. In this respect, we would like to cite the van’t Hoff article,^[4] also commented on by Blackmond, concerning the application of the phase rule. In this reference (part V, p. 4264), under the title “The Phase Rule and the active compounds”, van’t Hoff includes as analogous systems, and in the same group, the case of NaClO₃ and the case of a fast racemizing compound in solution,^[5] that is precisely the systems a) and b) in Scheme 1.

It should be noted that the key point of our Concept article lies in the application of the phase rule in the discussion as to whether two enantiomorphous phases are thermodynamically identical or not, and if under certain dynamical processes implying chiral recognition these phases can be considered to be thermodynamically different. Therefore, one can hardly start a scientific debate on this issue if one of the parties involved cannot accept that the proposed systems [a) and b) in Scheme 1] both correspond to a two-component system. In a more modern definition of the phase rule, when specifying the number of components from all the species in solution, their total number must be reduced by the number of chemical equilibrium equations implying transformations between them. It should be noted also that in the case of NaClO₃ [simplified as a) in Scheme 1] there are a lot of species in equilibrium in solution (ionic species, hydrated species, and molecular chiral clusters before reaching the critical crystallization size), therefore the similarity between the NaClO₃ system and a system b) is higher than that deduced from the comparison between the systems a) and b) in Scheme 1.

The Blackmond–Viedma model: the thermodynamic impossible?: In the Viedma experiment the strong perturbation generated by the grinding of the NaClO₃ crystals in a saturated solution generates very small crystals, the higher solubility of which leads to a new situation where the larger crystals are in a supersaturated solution. The consequence of this is that recycling can occur at a higher rate than in the case of stagnant or gently stirred solutions. This is an undisputed starting point. In our opinion, this allows the system to go again through primary nucleation steps, and also allows the recognition between chiral clusters, which are smaller than the critical crystallization size (see Scheme 1 in our Concept article, in which the recycling via achiral species is also included). In the Blackmond–Viedma model the very existence of the redissolution/recrystallization steps alone explains the transition towards homochirality. For example, Blackmond states; i) the molecules in the solution (NaClO₃) gain a “ ‘second chance’ at choosing their solid-phase chiral destiny”: ii) “*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.” In conclusion, according to Blackmond the growth of the crystals in the Viedma experiment is only performed by the incorporation of achiral molecules (NaClO_3). This is simply the expected behavior, as we have stated in our Concept article, in stagnant or gently stirred samples, that is in the common crystallization experience, but that cannot explain the Viedma experiment. Furthermore, the Blackmond-Viedma model does not accept that the homochiral state, in the systems a) and b) of Scheme 1 when they are strong perturbed, 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, and thus the amnesia of the implied species would eventually lead to one of the two enantiomorphous solid phases being filled preferentially, which is more than a surprising conclusion. 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. However, it is not correct to consider that the chiral recognition between the aggregating species plays a non-relevant role. In fact, chiral recognition plays the driving role in the construction of the clusters leading to the primary nucleation steps and in the direct growth of the solid phases with these chiral clusters. Note that the aggregation of two NaClO_3 molecules must already acquire a chiral shape to evolve towards the enantiomeric solid phase, and that four molecules of NaClO_3 in the unit cell,^[6] probably represents a size below the critical one to give a primary crystal (e.g. solution impurities, etc). This argument implying chiral clusters in the solution is central in our Concept article, in spite of it being not mentioned in Blackmond's Concept.

In our model the transition towards a homochiral set of crystals in such systems can be understood as a second-order phase transition. This would be achieved by the direct or indirect chiral recognition between the solid phases

through a Frank-like nonlinear kinetic scheme. In this respect, it is significant that recent reports relate Frank-like systems to critical phenomena.^[7,8] Note that the necessary *nonlinear* behavior in the breaking of the chiral symmetry or *ee* amplification, in the absence of chiral recognition, cannot take place by the recycling process alone.

We want to stress 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. This was indeed a provocative phrase in our Concept article, which we have proposed to the scientific community for discussion. However, although our proposal could be wrong, surely it is not so for the reasons outlined by Blackmond, as they are based on fundamental errors in the application of the phase rule, in the denial of the significance of chiral recognition in the implied processes, and in the proposal of a model that in our opinion corresponds to the thermodynamic impossible.

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[2] C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065604.
[3] C. Viedma, *Astrobiology*, **2007**, *7*, 312.
[4] J. H. van't Hoff, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 4252.
[5] “Aehnliches zeigt sich, wenn auch weniger deutlich, bei durch die Molekularstruktur activen Verbindungen, falls dieselben die Fähigkeit haben, ihre Activität spontan zu verlieren unter Bildung gleicher Mengen der entgegengesetzt activen ohne deren Verbindung zu einem Racemat.” This part of the van't Hoff article^[4] shows surprisingly clear concepts on the optical activity of organic compounds, taking into account the publication year (1902).
[6] See for example, S. C. Abrahams, J. L. Bernstein, *Acta Crystallogr. Sect. B* **1977**, *33*, 3601.
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