J Therm Anal Calorim (2011) 103:125–129
DOI 10.1007/s10973-010-1035-y

Racemizable systems crystallizing as conglomerate and spontaneous symmetry breaking

S. Gonella · G. Levilain · G. Coquerel

Received: 30 June 2010 / Accepted: 1 September 2010 / Published online: 8 October 2010
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Abstract Heterogeneous equilibria are reviewed in binary and ternary systems of enantiomers without and with in situ racemization. The twofold symmetry between the two chiral components is also found in the phase diagrams except for stable conglomerate forming systems associated with a fast in situ racemization in the liquid phase. In this particular case, a gentle attrition speeds up the irreversible evolution of the system towards a spontaneous symmetry breaking, i.e., a single crystallized enantiomer in equilibrium with its racemic solution. This final evolution is predicted to reach the limit of miscibility in the solid state for conglomerate forming system with partial solid solution and in situ racemization.

Keywords Phase diagrams · Enantiomers · Racemization · Attrition · Spontaneous symmetry breaking

Introduction

Nonsuperimposable mirror image phases are called chiral phases. As far as the phase rule is concerned, these chemical entities offer a degenerated situation which necessitates a special treatment. As early as 1977 Scott [1] proposed a revised version of the Gibbs phase rule to take into consideration the twofold symmetry between the two nonracemizable components.

When the two enantiomers undergo a fast racemization in the liquid state the system can be considered as a unary system with two dynamical conformations in the liquid phase [2]. Nevertheless, in the solid state the two configurations can be 'freezed' (*R* and *S* hereafter). The same applies with mineral systems such as quartz or sodium chlorate for which chirality simply exists in the solid state. In case of asymmetric molecules, the two configurations are in equal number if the crystal lattice of the solid contains at last one inverted symmetry operation; the solid phase is called a racemic compound. By contrast, if the space group of the crystal lattice belongs to the Sohnke series (65 chiral space group) and $Z' = 1$, every single crystal contains a unique configuration. For this latter case, a racemic mixture is made of a 50–50 composition in *R* and *S* crystals; this has been defined as a conglomerate.

Recent results [3] have shown that for racemizable systems crystallizing as conglomerates (i.e. eutectic mixtures), a gentle attrition is able to induce a shift in the enantiomeric excess of the solid (defined by the following relation: e.e. $= (R - S)/(R + S)$) so that a single chirality *R* either or *S* is ultimately obtained as a steady state. The nature of the solid *R* or *S* depends on the initial conditions. The initial amount of *R* and *S* but also the crystal size distribution of the two solids *R* and *S* are the key parameters to predict the evolution of the system towards pure *R* either or pure *S*.

This communication aims at clarifying the different situations ranging from nonracemizable enantiomers to racemizable enantiomers with or without abrasive effects.

Discussion

Nonracemizable enantiomers

Figure 1a–m depicts the most common cases of heterogeneous equilibria between nonracemizable enantiomers.

It was presented at JEEP2010 Montpellier, France.

S. Gonella · G. Levilain · G. Coquerel (✉)
UC2M2, EA3233, Université de Rouen, rue Tesnière,
76821 Mont Saint Aignan Cedex, France
e-mail: gerard.coquerel@univ-rouen.fr

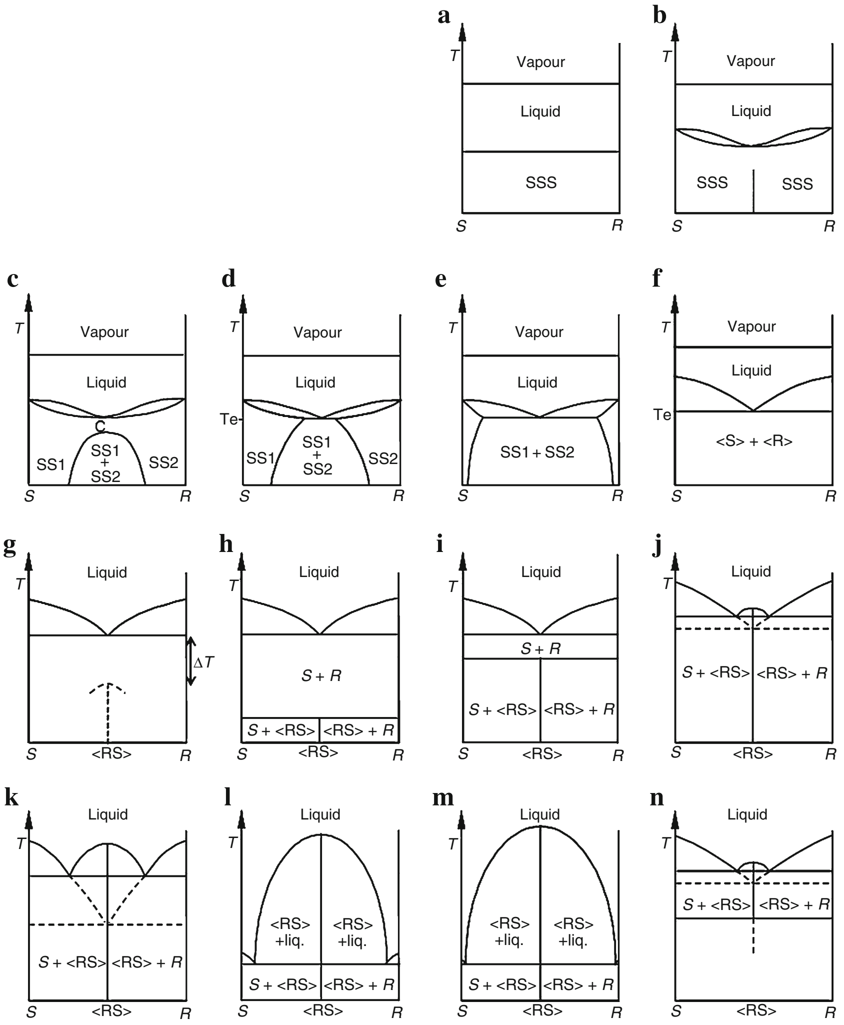


Fig. 1 *T* versus composition binary phase diagrams between nonracemizable enantiomers

Polymorphism has been omitted from this discussion for clarity [4]. Moreover, a full chemical stability is being assumed here, it means that for any thermal investigation the point representative of the system will move vertically in the phase diagrams.

Figure 1a depicts the simplest case where chirality has no impact on solid–liquid heterogeneous equilibria. This might happen for chiral molecules whose stereogenic centres are not accessible to the first neighbouring molecules (SSS stands for solid solution by means of substitution).

Figure 1b shows weak interactions in the solid state which have a small impact on solid–liquid equilibria. The vertical dotted line represents the possibility of superstructure (ordered crystal structure). Indeed, for the exact composition $x = 0.5$ additional inversion symmetry can appear.

Figure 1c–f represents the evolution towards a better discrimination at the solid state. Ideally, Fig. 1f represents the so called conglomerate which is the ultimate chiral discrimination in the solid state [5]. It is usually accepted that 5–10% of the racemic mixtures (composed of 50% of *S* and 50% of *R*) lead to conglomerate forming systems [6]. Actually this is nothing more than a eutectic without partial solid solution. Nevertheless it is of particular importance since it allows a quantitative enantiomeric enrichment (e.e. >99% can be obtained with almost 100% yield) and in roughly half of the cases a quantitative separation of the two enantiomers can be performed by preferential crystallization (i.e. no resolving agent is necessary to separate the enantiomers) [7].

In Fig. 1g, a metastable stoichiometric (1-1) compound is represented. The Δ*T* between the metastable melting points of the racemic compound and the eutectic invariant gives a rough estimation of the energetic advantage of the conglomerate over the racemic compound. Fast precipitation can, in accordance with the Ostwald rule of stage, lead to the crystallization of the metastable intermediate compound which, upon annealing, irreversibly transforms into the eutectic mixture [8, 9].

Figure 1h–m shows the emergence of a stable racemic compound with increasing thermal stability. Figure 1h, i displays peritectoid invariants (unfortunately often confused with simple polymorphism) that separate the domain of stability of the intermediate compound at 'low temperature' from the 'high temperature' domain where the conglomerate is stable [4]. From Fig. 1j–m, the thermal stability of the racemic compound versus the conglomerate increases. It is sometime possible to observe such a difference in the melting point than the eutectic composition is beyond 99% e.e.

Figure 1n shows the opposite situation as that depicted in Fig. 1h, i. The racemic compound is stable at high temperature and the conglomerate is stable at low temperature. The frontier between these domains corresponds to a eutectoid invariant [10].

Regardless their domains of stability, the racemic compound forming systems represent 95–90% of the chiral organic molecules. This strong packing preference probably comes from the possibility of centre of symmetry and glide planes in the organic crystal structures (the two first 'preferred' symmetry elements after translation). These additional symmetry elements (forbidden for a pure enantiomeric crystal lattice) are also supposed to lead to a better density (Wallach 'rule') [11].

Racemizable enantiomers

The existence of in situ racemization in the liquid phase has an important impact on the phase diagrams of enantiomeric pairs. Indeed, it allows the composition to evolve during the process without adding any species. New phase diagrams should be used to understand and design processes involving the crystallization of racemizable enantiomers.

The molecule displayed in Fig. 2a, which leads to a racemic compound forming system, gives a spontaneous racemization in the molten state, such as shown in Fig. 2b. Any mixture different from e.e. = 1 (i.e. the pure enantiomers) instantaneously racemizes in the liquid state as soon as the sample is heated even for few seconds above the eutectic temperature. By contrast, in the solid state any deviation from the racemic composition remains unchanged over very long period of time (undetectable over the years). The thermal treatment up to fusion leads to the irreversible evolution towards the racemic composition and thus to the crystallization of the (1-1) intermediate compound. Any subsequent heating/cooling will correspond to vertical movements at $x = 0.5$ of the representative point in the binary system. Thus, the system behaves like a unary system after the first fusion. A borderline case is obtained with e.e. = 1. In principle, if the component is absolutely a pure enantiomer, it might be possible to reach a temperature situated between T_e and T_f (temperature of fusion of the ultra pure enantiomer). Nevertheless a minute amount of impurities will be enough to return to the complete racemization.

In ternary systems, from the usual situation without racemization depicted on Fig. 3a, the only accessible states with in situ racemization are represented on Fig. 3b. Any composition will evolve towards the racemic line due to the fast racemization in the liquid phase. As a consequence, the systems behaves like a binary system; the final state will be composed of a mixture of the racemic compound and a racemic liquid (the proportion of both phases will be determined by the solubility).

In case of in situ racemizable conglomerate forming system, recent results have demonstrated an irreversible evolution towards a single chirality in the solid state. As illustrated in Fig. 4a, b, the application of a gentle grinding speeds up the attainment of the thermodynamic equilibrium by several magnitudes of order. The first observation due to Viedma [12] on sodium chlorate has been rapidly extended to organic systems [13, 14] proving the general aspect of the two opposite phenomena: (i) racemization in the liquid phase (this is suppose to be fast in comparison to the crystallization kinetics); (ii) deracemization in the solid state. At the end of the evolution, crystals of a single enantiomer are in equilibrium with a racemic solution [15].

This new route to access to pure enantiomer has been already applied via direct crystallization from the melt [16]. In that case the binary phase diagram, represented by Fig. 1f without racemization, should be described by Fig. 5. As long as the system remains below the eutectic temperature, the e.e. of the solid remains unchanged. However, at the eutectic temperature, two different 'equilibrium' states, excluding each other, must coexist: a racemic liquid and a solid of a single chirality (either *R* or *S*). If the temperature of the system exceeds for few seconds the eutectic temperature, the system, composed of a single liquid phase, will reach the racemic section. The crystallization of the melt under smooth grinding leads to the crystallization of a single enantiomer, indicating that

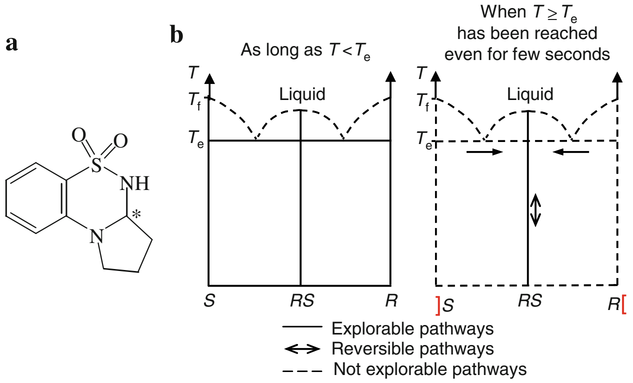


Fig. 2 **a** Example of a chiral molecule that racemizes instantaneously at fusion, **b** pseudo-binary diagrams for molecule displayed in **a**

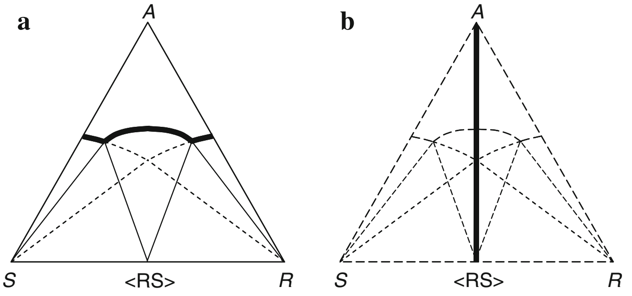


Fig. 3 **a** Isothermal section without racemization, **b** isothermal section with racemization. *Dash* areas are not accessible

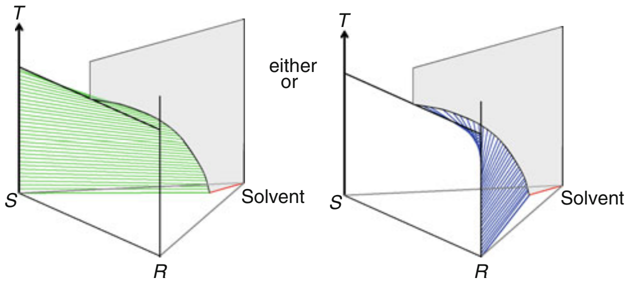


Fig. 6 Degenerated ternary system of conglomerate undergoing a fast racemization in the liquid state only

below the eutectic temperature the system should be composed of a single enantiopure solid under mechanical equilibrium.

By analogy, polythermic systems in thermodynamic equilibrium (which implies: thermal, mechanical, chemical and energetic equilibria) can only be represented by Fig. 6. The corresponding isotherms are respectively displayed in Figs. 7. One should keep in mind that the e.e. of the final solid is still governed by the energetic equilibria. In case of partial solid solution, we can predict that the e.e. of the final solid should correspond to the limit of the miscibility in the solid state (Fig. 8).

The mechanism(s) by which the complete deracemization occurs in the solid state has (have) raised some controversies. The Ostwald ripening is the common accepted explanation, but more works have to be undertaken to spot the nature of the driving force(s) [17] and other agonist phenomena (agglomeration, Gibbs–Thomson effect, etc.) that could participate to the irreversible evolution.

Fig. 4 **a** Illustration of the effect of a smooth grinding on a conglomerate of racemizable components. **b** Example of a chiral molecule that racemizes instantaneously, in basic medium, in the liquide state only

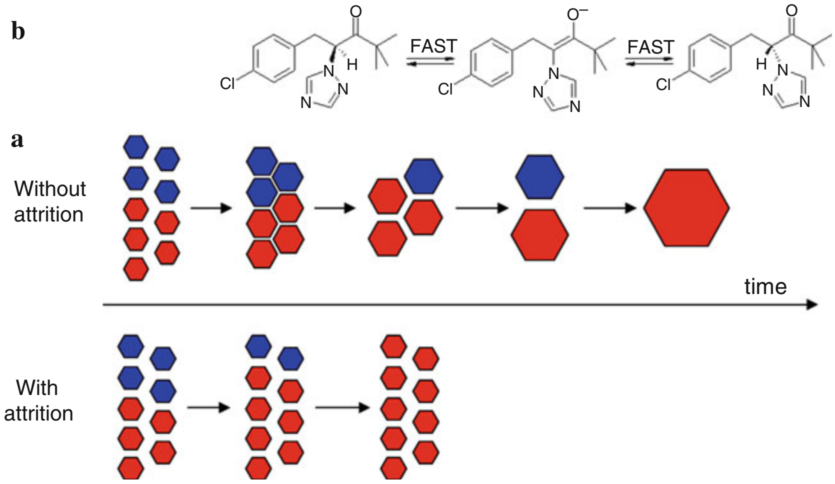
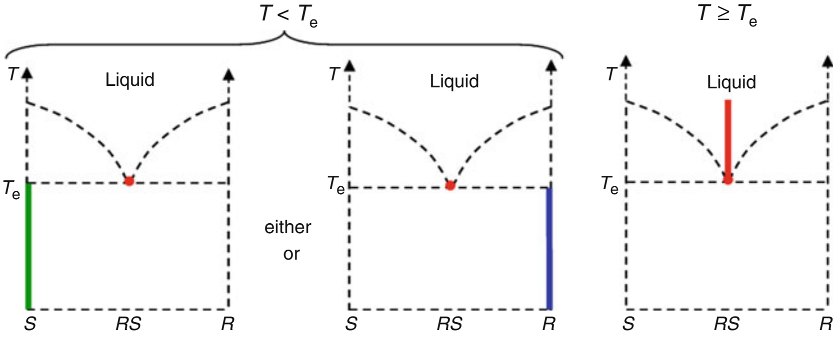


Fig. 5 Degenerated binary diagrams of a conglomerate forming system undergoing a fast racemization. *Dash* areas are not accessible



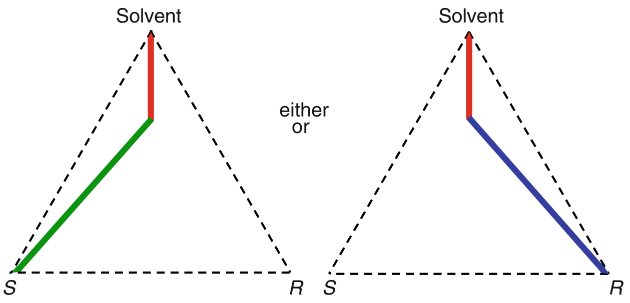


Fig. 7 Isotherms of Fig. 6. *Dash* areas are not accessible

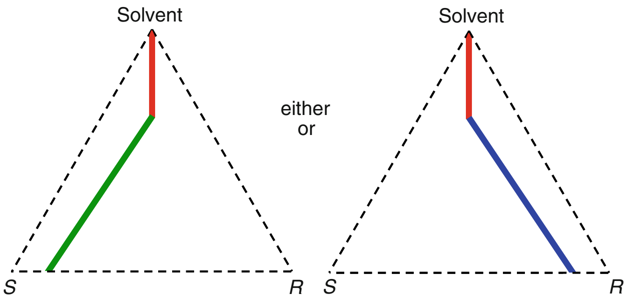


Fig. 8 Isotherms of a conglomerate with partial solid solution and racemization in the liquid state (racemization in situ of case depicted in Fig. 1e). *Dash* areas are not accessible

Conclusions

The degenerated situation resulting from the mirror image components lead to symmetrical phase diagrams as long as the couple of enantiomers is not in situ racemizable and does not crystallize as a stable conglomerate. In the latter case with a solvent, the symmetry breaking catalyzed by a smooth attrition leads to two possible mirror image 'ternary' systems constituted by the conoids of the single components and the plane of the racemic liquid. Nevertheless, for conglomerate forming system with partial solid solution and in situ racemization, we predict that the final e.e. of the solid phase will be limited by the miscibility in the solid state.

More efforts are necessary to fully understand the mechanism(s) prevailing during deracemization by means of attrition.

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