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Clément Pinètre, François-xavier Gendron, Reiko Kuroda, Ryusei Oketani, Christian Aupetit, et al.. Use of Conglomerate Mixed Crystals to Deracemize a Stable Racemic-Compound-Forming System. Chemistry - A European Journal, 2023, 29 (27), 10.1002/chem.202300441 . hal-04235961v2

HAL Id: hal-04235961

<https://hal.science/hal-04235961v2>

Submitted on 10 Oct 2023

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Use of conglomerate mixed crystals to deracemize a stable racemic compound forming system

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Deracemization extended to racemic compound forming systems is demonstrated. We present here the first results of an alternative for the resolution of systems that exhibit a stable racemic compound but also a closely related conglomerate forming system. If the couples of enantiomers forming the racemic compound and the enantiomers of the stable conglomerate can syncrystallize in mirror related partial solid solutions, it is possible to deracemize the racemic mixture of mixed crystals to access to a single handedness. The evidence of that possibility is given on three examples by using Temperature Cycling Induced Deracemization.

1. Introduction

Since 2005, the seminal paper of Cristobal Viedma,¹ an intense research activity has been taking place in the domain of deracemization. By coupling racemization, and crystallization of a conglomerate in the same pot, numerous examples show that it is possible to direct the complete symmetry breaking towards 100% of the desired enantiomer.^{2–5} Unfortunately, the two conditions: (i) full discrimination in the solid state (ii) fast racemization in solution appear to be difficult to fulfil at the same time. They represent severe limitations for the scope of application of this method as only circa 5% of known chiral systems crystallize as conglomerates whereas 95% crystallize as racemic compounds.⁶ Hopefully, reaching chiral discrimination in the solid state for racemic compound forming systems remain possible. Several examples of conglomerate cocrystals, salts or solvates and their resulting chiral resolution are reported in the literature.^{7–9} Moreover, enantiomeric systems can also present a partial miscibility in the solid state either for a conglomerate or a racemic compound. In the case of conglomerates, it prevents a total chiral discrimination and limits the effectiveness of chiral resolution methods by crystallization up to the extreme composition of the partial solid solution in equilibrium. By contrast, it can be beneficial for racemic compound forming system as showed by the intriguing phenomenon of

preferential enrichment.^{10,11} The structural aspects of solid solutions in enantiomeric system were reviewed by Brandel *et al.*¹² and Rekis *et al.*¹³ Solid solutions between resolving agents of the same handedness also improves the Pasteurian resolution. This improvement is known as: Dutch resolution.¹⁴ This work aims at identifying a new approach to reach chiral discrimination in the solid state for racemic compound forming systems by using the occurrence of solid solution between enantiomers of two chiral molecules.¹⁵ To do so, the miscibility in the solid state between enantiomers of two chemically related chiral molecules; one crystallizing as a conglomerate and the other crystallizing as a racemic compound; was investigated. Thus, the phase equilibria investigated between the two racemic compositions is a binary isoplethal section of a quaternary system. This section is thermodynamically described by the classical isothermal tetrahedral representation (Figure 1a) or by what we called the “extended binary” representation assuming that no diagonal equilibrium occurs (Figure 1b).¹⁶ Three model compounds were studied. Two of them are racemic compound (Figure 2 oMe-TAK; o,pCl-TAK) which belong to family of a conglomerate forming compounds: Triazole Ketone (TAK) derivatives. Their respective chemically related conglomerate (Figure 2 pMe-TAK; pCl-TAK) were successfully deracemized by temperature cycling induced deracemization (TCID).^{17,18} The last model compound is an atropisomer crystallizing as a racemic compound (Figure 2 p-Cl).¹⁹ The activation energy to switch from one configuration to the other is too high in the solid state.

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

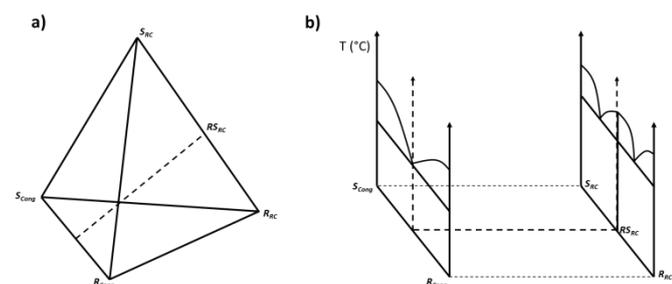


Figure 1. (a) Tetrahedral and (b) extended binary representations of the studied systems. Racemic isopleth section is represented in dotted line.

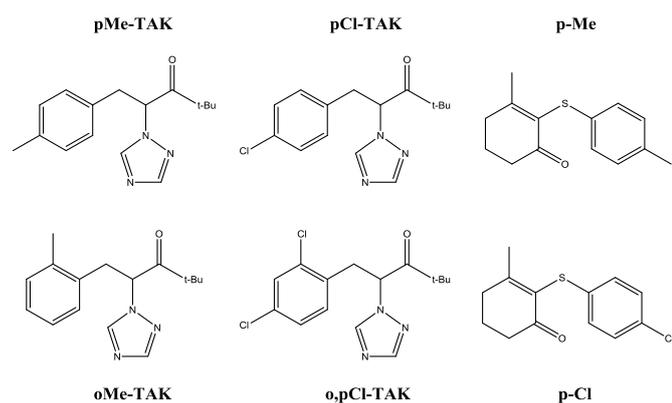


Figure 2. Racemic compound forming systems (bottom) and their chemically related conglomerate forming system (top).

By contrast, the sulfur bond rotation is no more limited in the liquid state leading to a spontaneous and instantaneous racemization in the liquid state. Therefore, its chemically related conglomerate (Figure 2 p-Me) is a good candidate for deracemization. The occurrence of partial solid solution on the three systems (i) pMe-TAK / oMe-TAK (ii) pCl-TAK / o,pCl-TAK (iii) p-Me / p-Cl was highlighted by the experimental determination of their racemic binary isopleth section. We show that enantiomers of the racemic compound forming system can fit into the conglomerate structure and thus, form mixed crystals which can be deracemized.

2. Results & discussions

2.1. Racemic binary isopleth sections

2.1.1. pCl-TAK / o,pCl-TAK

The racemic binary isopleth section of the system pCl-TAK / o,pCl-TAK was constructed by plotting the thermal data in the whole compositions range (Figure 3). This phase diagram shows that o,p-CITAK is miscible in the solid state with p-CITAK within a small composition range (*i.e.* less than 5%mol).

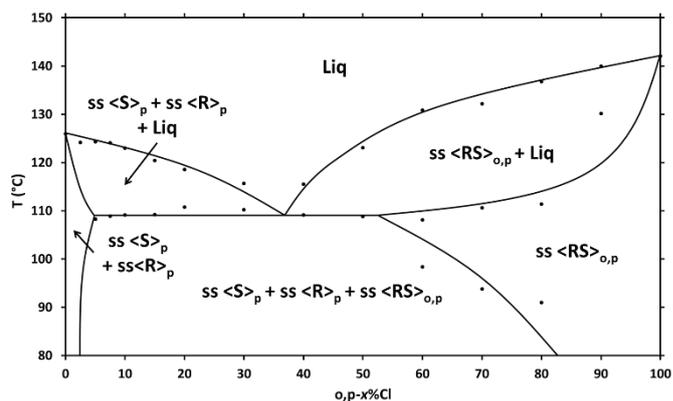


Figure 3. Racemic binary isopleth section o,pCl-TAK (o,p) / pCl-TAK (p). Bolded lines are for equilibria supported by the thermal data (guides for the eyes).

By contrast, the miscibility of p-CITAK in o,p-CITAK, which is strongly temperature dependent, is much larger. One can note that the same behavior is obtained by high energy milling.

2.1.2. pMe-TAK / oMe-TAK

A second racemic binary isopleth section has been investigated: the system oMe-TAK / pMe-TAK. DSC measurements on the whole compositions range all presented two distinct phenomena (i) an endothermic invariant around 61 °C (ii) an endothermic signal varying between the melting point of pure components with a minimum around o-70%Me. In this case, the widths of partial solid solutions were determined by plotting the enthalpy of the eutectic invariant of each composition to draw the Tammann graph. According to the Tammann graph, this system must be a eutectic invariant with a eutectic point at *circa* o-76%Me and partial solid solution domains below o-9%Me and above o-96%Me (Figure 4).

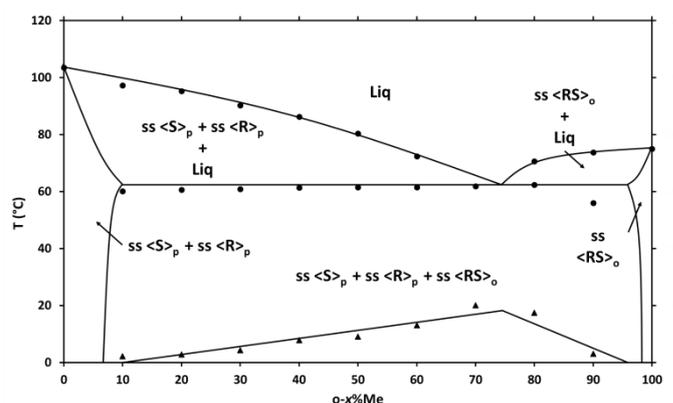


Figure 4. Racemic binary isopleth section oMe-TAK (o) / pMe-TAK (p). Bolded lines are for equilibria supported by the Tammann plot (\blacktriangle) and the thermal data (guides for the eyes).

Interestingly, the solid solution on the conglomerate side can be extended up to *circa* o-30%Me by using high energy milling. However, this metastable forced extension of the solid solution domain cannot be used under deracemization conditions.

2.1.3. p-Me / p-Cl

According to the DSC measurement of each composition and their corresponding crystallographic data, a racemic isopleth section can be drawn as in Figure 5. The equilibrium observed corresponds to partial solid solutions on each side with a eutectic invariant at *circa* 50°C between p-60%Cl and p-74%Cl compositions. The eutectic composition cannot be determined accurately but it may be approximated at *circa* 67% p-Cl composition.

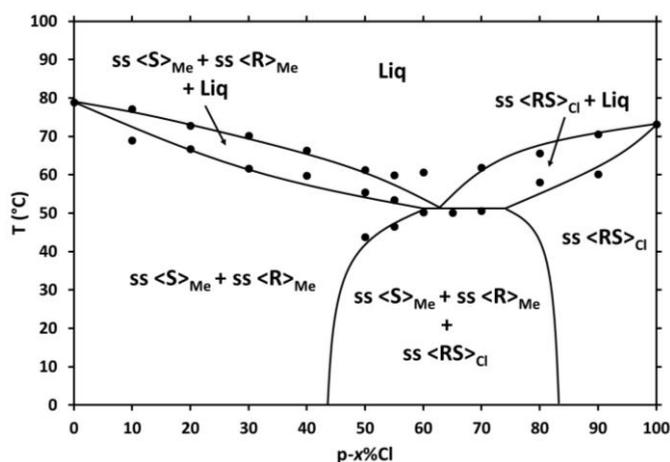


Figure 5. Racemic binary isopleth section p-Cl (Cl) / p-Me (Me). Bolded lines are for equilibria supported by the thermal data (guides for the eyes).

2. Deracemization

2.1. TAK derivatives

Successful deracemization by temperature cycling (TCID) of pCl-TAK and pMe-TAK was already reported in the literature.^{17,18} For both systems (pMe-TAK/oMe-TAK and pCl-TAK/o,pCl-TAK), a narrow domain of partial miscibility in the solid state could be highlighted. TCID experiment in those domains was performed using the same protocol as that reported by Suwannasang *et al.*

2.1.1 Solubility

The addition of the solvent adds one more dimension to the deracemized system. Therefore, compositions above the maximum miscibility were used to ensure the crystallization of the solid solution at its maximum composition. Thus, the solubilities of o,p-5%Cl and o-50%Me in various Methanol/Water mixtures were determined and summarized in Table 1.

Table 1. Solubilities of o,p-5%Cl and o-50%Me respectively in MeOH/H₂O 85/15 (v/v) and 65/35 (v/v).

	o,p-5%Cl		o-50%Me	
T (°C)	20	30	20	30
Solubility (wt%)	4.66	5.15	9.43	12.11

2.1.2 Chiral resolution

First, TCID experiment on o,p-5%Cl was carried out to give the proof-of-concept that the deracemization of a stable racemic compound through conglomerate mixed crystals was possible. The increase in enantiomeric excess of pCl-TAK is followed by a similar increase in enantiomeric excess of o,pCl-TAK and a mixture of enantiopure p-CITAK and o,p-CITAK is obtained after 100 h of TCID (Figure 6a). One can note the slight decrease at *circa* 120 h that must be due to the several sampling that may have disturbed the system during the TCID experiment. Actually, the final solid obtained was not composed of o,p-5%Cl. According to the calibration curve, the deracemized solid is an enantiopure o,p-2,5%Cl which is likely to be the stable limit of miscibility of o,pCl-TAK in pCl-TAK.

Second, TCID experiment on o-50%Me was performed to conclude on a possible domino effect wherein more materials could be involved in the deracemization matrix and thus exceed the stable limit of solid solution. As for the previous one, the increase in enantiomeric excess of pMe-TAK is followed by a similar increase in enantiomeric excess of oMe-TAK and a mixture of enantiopure p-MeTAK and o-MeTAK is obtained after 80 h of TCID (Figure 6b). According to the calibration curve, the deracemized solid is an enantiopure o-8,5%Cl which is close to the stable limit of solid solution at the racemic composition highlighted by the experimental determination of its racemic binary isopleth section. There is no domino effect observed.

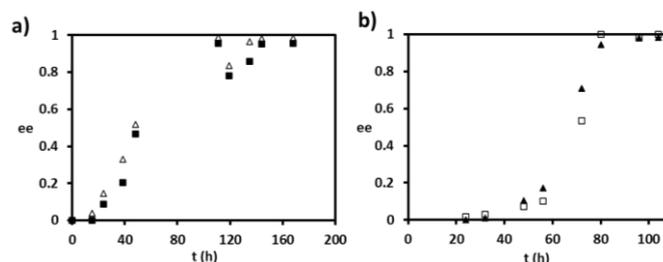


Figure 6. Evolution of the enantiomeric excess versus time of a) o,p-5%Cl (Δ : pCl-TAK; \blacksquare : o,pCl-TAK) and b) o-50%Me (\blacktriangle : pMe-TAK; \square : oMe-TAK)

2.2. p-Me / p-Cl

The system p-Me / p-Cl presents the larger domain of solid solution of this study. Therefore, it is the more favourable system for this deracemization method.

2.2.1. Solubility

In this case, the deracemized composition was selected to be in the stable domain of the partial solid solution (*i.e.* p-45%Cl at 20°C). The solubility of p-40%Cl in MTBE was determined and summarized in Table 2.

Table 2. Solubilities of p-40%Cl in MTBE

T (°C)	15	20
Solubility (wt%)	9.34	10.97

2.2.2 Chiral resolution

The spontaneous and instantaneous racemization in solvated media makes this system suitable for deracemization. However, the monitoring of the enantiomeric excess cannot be achieved in solvated media (e.g. HPLC, polarimetry). The efficiency of this experiment was determined within two different analysis (i) Vibrational Circular Dichroism (VCD) to ensure the complete symmetry breaking (ii) HPLC analysis to quantify the composition of the deracemized mixture. VCD experiments were performed in the solid state using KBr pellets of powdered materials.²⁰ VCD spectrum of the deracemized mixture is identical to the VCD spectrum of the deracemized pure p-Me (Figure 7). Thus, we can confirm that the complete symmetry breaking toward a pure enantiomer has been achieved. The titration of the deracemized solid shows that a mixture of *circa* p-25%Cl was deracemized during the TCID experiment.

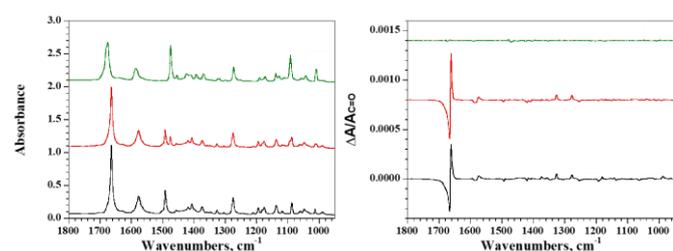


Figure 7. IR spectra (left) and VCD spectra (right) of deracemized p-Me (black), deracemized p-40%Cl (red) and p-Cl samples (green).

Table 3 Titration of deracemized p-40%Cl.

ID	Concentration (mg.mL ⁻¹)	%wt
p-Me	15.0	75.1
p-Cl	4.98	24.9

Conclusions

This work gives a proof-of-concept for the deracemization extended to stable racemic compounds using a deracemizable conglomerate host. More precisely, it is possible to direct the complete symmetry breaking toward a single handedness for a racemic compound forming system by using a solid solution with a chemically related racemizable conglomerate. Among the three successful examples, we could deracemized up to 25%wt of the racemic compound inside the conglomerate matrix. The effectiveness of this deracemization method does not seem to exceed the stable limit of solid solution. Indeed, a clear example of a forced extension of the solid solution domain under high energy milling has been characterized but, operative deracemization conditions cannot use this metastable equilibrium.

The effect demonstrated in this work renew the interest in the prediction of large domains of solid solutions for chemically related enantiomers easy to racemize. For non-racemizable enantiomers it is likely that preferential crystallization can be achieved.

Author Contributions

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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