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Chiral Resolution

Enantiopure Isoindolinones through Viedma Ripening

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Abstract: Here we demonstrate that deracemization of isoindolinones using Viedma ripening is possible starting from a racemic mixture of conglomerate crystals. Crystals of the enantiopure isoindolinones lose their chiral identity upon dissolution even without the need for a catalyst. This enabled complete deracemization of the reported isoindolinones without a catalyst.

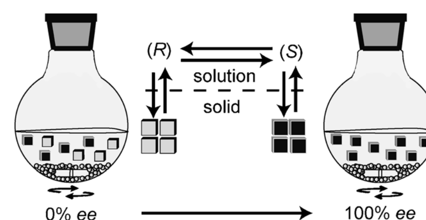

Figure 1. Stirring in the presence of glass beads of a racemic mixture of conglomerate crystals which can racemize in solution results in complete deracemization of the solid state (Viedma ripening).

The single-handedness of biomolecules, such as amino acids and sugars, is an important feature of our biochemical system. Due to this intrinsic property, two enantiomers of the same compound generally will interact very differently with the human body. Chiral pharmaceutical drugs must therefore be registered and acquired in the correct enantiopure form. A common industrial approach to isolate the desired enantiomer of a drug proceeds by separating enantiomers (i.e. resolution), which is usually facilitated through crystallization of a diastereomeric salt.[1] Techniques based on crystallization are appealing as these are cheap, simple, and widely applicable. Resolution of a racemate in the absence of racemization gives the required enantiomer in only 50% maximum yield, but methods are available by which complete deracemization can be realized.[2]

One of the examples of such a deracemization process is Viedma ripening in which a single chiral solid end state can be generated from an initial slurry of racemic conglomerate crystals.[3] Noorduin et al.[4] extended Viedma ripening to deracemize intrinsically chiral molecules (Figure 1), which enabled the possibility to deracemize pharmaceutically relevant chiral compounds such as key intermediates for the synthesis of both Naproxen[5] as well as Clopidogrel (Plavix),[6] of which the latter compound was deracemized on a larger scale.[7]

Isoindolinones are another class of interesting compounds that display potent biological activities and are therefore used as core structures for many pharmaceutical drugs.[8] Recently it was reported by Yagishita et al. that 3-hydroxy-3-phenylisoindolin-1-ones **1**–**3** (Figure 2) crystallize as conglomerate crystals and can also rapidly racemize in solution using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst through an intramolecular equilibrium reaction via an achiral intermediate.[9] This enabled access to all three isoindolinones in high yield and high enantiomeric excess (*ee*) through preferential crystallization from solution (i.e. total spontaneous resolution).[9] The conglomerate behavior of these compounds should also allow the deracemization of an initial racemic solid state through Viedma ripening (Figure 1), which is a fundamentally different approach to reach an enantiopure end state as compared to total spontaneous resolution. However, the reported isoindolinones **1**–**3** surprisingly failed to deracemize through Viedma ripening despite an applied initial solid state *ee*.[9] These results were not investigated further and a recent overview reported that these isoindolinones are one of the

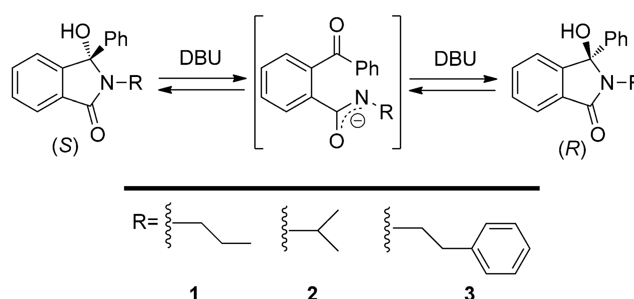

Figure 2. Compounds **1**–**3** crystallize as conglomerate crystals and are able to quickly racemize in solution via an achiral intermediate using DBU as a catalyst.

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rare examples of compounds that cannot be deracemized by using Viedma ripening.[10]

Here we show that by optimizing the Viedma ripening conditions based on previous findings[11] and by avoiding racemization during the analysis of the *ee*, Viedma ripening is possible for these compounds. We also found that the isoindolinones racemize in ethanol, allowing Viedma ripening without the need for a catalyst. Our working method resembles the previous Viedma ripening attempt by Yagishita et al.,[9] but was optimized in three ways:

First, the amount of glass beads was increased, as the Yagishita attempts involved Viedma ripening experiments with a rather small amount of glass beads. The continuous fragmentation of the crystals is an important prerequisite for Viedma ripening to be successful and the rate of deracemization is strongly coupled to the number of glass beads.[11a]

Second, a solvent should be used in which the crystals are allowed to partially dissolve and racemize with a high rate (i.e. a high solubility increases the deracemization rate).[11a] Yagishita et al. used *n*-hexane in which the isoindolinones are only poorly soluble (see the Supporting Information).

The third and most important step that was improved involved sample preparation and analysis. Determination of the *ee* was performed through chiral-HPLC analysis after dissolving the crystals in the HPLC solvent, which is ethanol. However, we found that isoindolinones **1**–**3** racemize in ethanol, even in a stagnant solution in the absence of a racemization catalyst (Figure 3 a). During the time it takes to perform an HPLC analysis, the *ee* will therefore decrease. As Figure 3 shows, the longer the delay, the smaller the measured *ee*. Extrapolating this to time zero, we indeed find that the *ee* after a deracemization experiment is 100 % within the accuracy of the experiment (Figure 3 b). The racemization rate increases from **1**–**3**–**2** which is in the same order as the racemization rate with a catalyst.[9] The rate of racemization in an ethanol solution becomes slower if acetic acid is present (see the Supporting Information).

Putting these three points into practice, Viedma ripening was carried out to deracemize isoindolines **1**–**3** in toluene at ambient temperature with DBU (20 mol %) as a racemization catalyst. All the three isoindolinones were successfully deracemized, even when starting without any measurable initial enantiomeric excess (0 % *ee*, Figure 4). Complete deracemization was also successfully conducted on a larger 1-gram scale (see the Supporting Information).

The ease with which these isoindolinones racemize in ethanol prompted us to investigate the possibility of Viedma ripening in the absence of a racemization catalyst. In ethanol, compounds **1** and **2** were both successfully deracemized without a catalyst (Figure 5 a). The time to reach a critical value for the solid state to set off the deracemization process (i.e. induction time) was significantly longer as compared to that with the experiments with a catalyst (Figure 4). However, once the *ee* of the solid state was sufficiently high, deracemization proceeded fast. The end state was measured to be 100 % *ee* or sometimes lower (Figure 4 and 5 a), which is the result of racemization in solution during analysis (Figure 3 b).

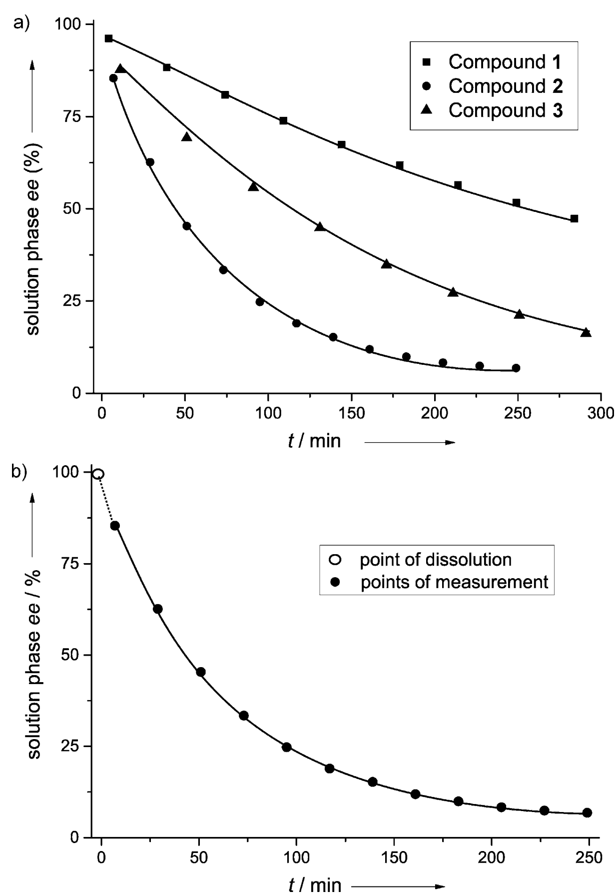

Figure 3. a) Racemization rate of all three isoindolinones in ethanol in the absence of a racemization catalyst. b) Solution phase *ee* of compound **2** in ethanol in the absence of a racemization catalyst as a function of time in a stagnant solution. The time between sample preparation ($t=0$ min) and the first measurement ($t=7$ min) is sufficient to decrease the *ee* from about 100 % (not measured) to 85 %. The lines are a guide to the eye.

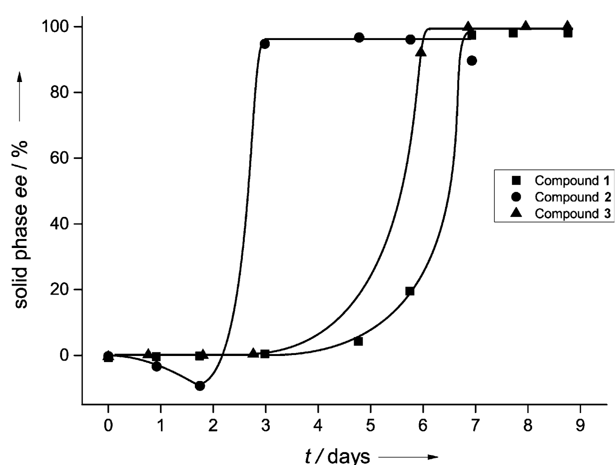

Figure 4. Solid phase *ee* of compounds **1**–**3** versus time during Viedma ripening in toluene using DBU as a racemization catalyst. The lines are a guide to the eye.

Deracemization of (*rac*)-**3** could not be realized within 45 days without a catalyst. The poor solubility in combination

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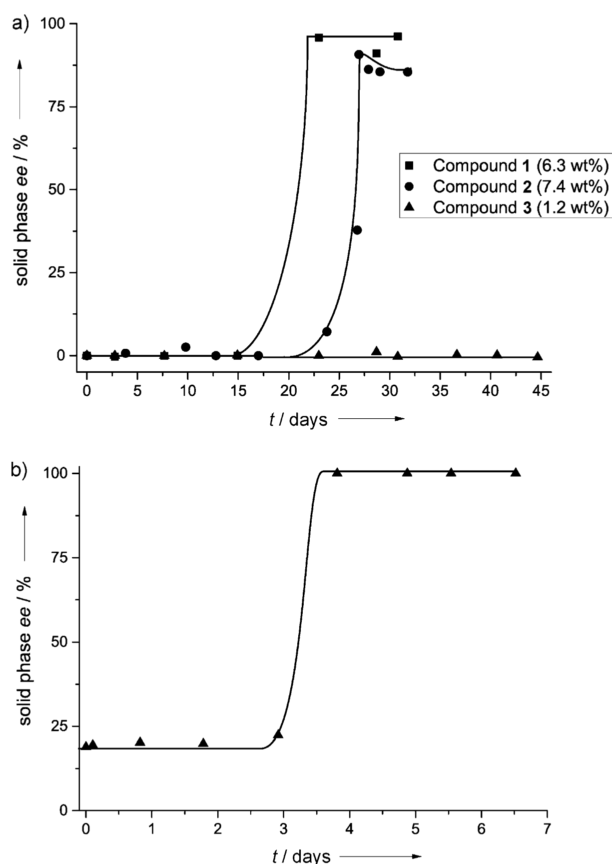

Figure 5. a) Viedma ripening experiments of compounds **1**–**3** in ethanol in the absence of a racemization catalyst. The solubility in ethanol is shown between brackets. b) Viedma ripening experiment in which an initial applied *ee* of compound **3** ultimately evolves into an enantiopure end state. The lines are a guide to the eye.

with the slow racemization rate of compound **3** in ethanol possibly prevents the system from overcoming the critical value to set off Viedma ripening. Deracemization of compound **3** could however be realized with an initial offset of 20% *ee* (Figure 5 b). Remarkably, a significant induction time was still required before deracemization started which could be attributed to the poor solubility of **3** in combination with a slow racemization rate.

The absolute configuration of isoindolinones **1**–**3** was determined by single-crystal X-ray diffraction (see the Supporting Information) to show that in total, complete deracemization proceeded three times toward (*R*)-**1** and seven times toward (*S*)-**1**.

In conclusion, deracemization of isoindolinones **1**–**3** using Viedma ripening is possible by 1) applying a sufficient amount of glass beads for the attrition to be strong enough, 2) using a suitable solvent to ensure a high enough solubility, and 3) by carefully preparing and measuring the samples avoiding racemization as well as possible during these steps. Taking these three aspects into account, all three isoindolinones **1**–**3** evolved to a single chiral solid state within 10 days using DBU as a racemization catalyst. Even without an initial *ee*, an enantiopure end state was still obtained, also on a gram scale. Samples should be measured immediately after dissolution since in an ethanol solution these isoindolinones can racemize without a catalyst. This uncatalyzed racemization behavior led us to demonstrate that compounds **1**–**3** can also be deracemized by Viedma ripening in the absence of a base. It remains, however, important to be aware of the fact that these isoindolinones are able to racemize upon dissolution when further functionalization is required.

Experimental Section

Viedma ripening procedure with catalyst: Isoindolinone **1**, **2**, or **3** (1.1 mmol) was suspended in toluene (9.2 mL) in a round-bottom flask (50 mL) equipped with an octahedral stirring bar. Glass beads (16 g) and DBU (45 μL, 0.2 mmol) were added and the suspension was magnetically stirred at 650 rpm at room temperature to reach an enantiopure solid end state.

Viedma ripening procedure without catalyst: Similar to the procedure with catalyst, but with a larger amount of isoindolinone **1**, **2**, or **3** (2.6 mmol) in ethanol (without DBU). This experiment was similarly carried out with isoindolinone **2** (1.1 mmol) in toluene which did not lead to deracemization, even after 35 days.

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Keywords: asymmetric amplification · chiral resolution · chirality · grinding · heterocycles

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