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Speeding up Viedma ripening†

Anthonius H. J. Engwerda,[a] Hugo Meekes,*[a] Bernard Kaptein,[b] Floris P. J. T. Rutjes[a] and Elias Vlieg[a]

Viedma ripening allows the conversion of a solid state racemate into a single enantiomer. Using the gradual conversion of a metastable racemic compound into the conglomerate, the speed of deracemization for two amino acid derivatives could be considerably increased from several days to a few hours.

Chirality is a key issue in the development of small molecule drugs in the pharmaceutical industry. Of the majority of chiral drugs, only one of the enantiomers displays the desired physiological effect, whereas the other enantiomer is inactive or in some cases even harmful.[1] Consequently, the number of chiral drugs which are being produced in the enantiopure form has increased significantly over the last few decades.[2] The synthesis of enantiomerically pure fine chemical products and pharmaceuticals often proceeds through the production of a racemic intermediate, which is then resolved into the two enantiomers through conventional techniques. One of the most widely used and robust techniques is chiral resolution through diastereomeric salt formation, requiring stoichiometric amounts of another chiral component.[3] Catalytic resolution approaches involve kinetic resolution using an enantioselective catalyst or an enzyme which preferentially reacts with one of the two enantiomers after which separation can take place.[4] Furthermore, dynamic kinetic resolution strategies can be applied (combining kinetic resolution with *in situ* racemization) leading to deracemization and formation of only one of the two enantiomers.[5] A recently developed deracemization method that can be applied without using chiral reagents is Viedma ripening.[6] In this process, vigorous grinding of a slurry of chiral crystals in a saturated solution is combined with racemization in solution, resulting in complete solid phase deracemization.[7] This approach has already been shown to be effective for chiral compounds such as amino acids[8,9] and their precursors[10] as well as derivatives,[11] isoindolinones[12] and also organometallic complexes.[13,14] In addition to a conceptual qualitative understanding of this phenomenon, elaborate mechanistic investigations on Viedma ripening have been performed.[15–18]

A crucial prerequisite for Viedma ripening is that the interconversion between the two enantiomers (racemization) takes place in solution. A second prerequisite is that the two enantiomers of the chiral compound crystallize as separate crystals *i.e.* as a racemic conglomerate. The majority of chiral compounds (~90%), however, crystallize as racemic compounds having both enantiomers in the same crystal. Most racemates will crystallize as either a racemic conglomerate, or a racemic compound, but for some compounds both crystal forms can appear.

Spix *et al.* investigated Viedma ripening of glutamic acid, which crystallizes as a (metastable) racemic conglomerate, that converts after several days of grinding into a (stable) racemic compound.[19] They observed that it was possible to achieve full deracemization as long as the process was halted before conversion into the racemic compound had taken place.

The opposite case, in which a conglomerate forming compound first crystallizes as a racemic compound, has, to the best of our knowledge, never been studied in combination with Viedma ripening. Here, we demonstrate that the presence of such a metastable racemic compound can still lead to complete deracemization using Viedma ripening. Surprisingly, we found that using such a compound can significantly reduce the time required for complete deracemization (Fig. 1).

Compounds **1** and **2** are both Schiff bases of phenylglycine amide (Fig. 2). Both compounds are closely related to **3**, the first organic molecule that was deracemized using Viedma ripening.[7] Compounds **1** and **2** undergo, like compound **3**, facile racemization in solution in the presence of catalytic amounts of DBU as a base. When subjected to Viedma ripening conditions, both compounds could be readily deracemized. This suggests that both compounds crystallize as racemic conglomerates, which is a prerequisite for Viedma ripening. To our surprise, however, different X-ray powder diffraction (XRPD) patterns were obtained

[a] *Institute for Molecules and Materials, Radboud University, Heyendaalseweg 135, 6525 AJ, Nijmegen, The Netherlands. E-mail: H.Meekes@science.ru.nl*
[b] *DSM Ahead R&D – Innovative Synthesis, PO Box 1066, 6160 BB Geleen, The Netherlands. E-mail: bernard.kaptein@dsm.com*

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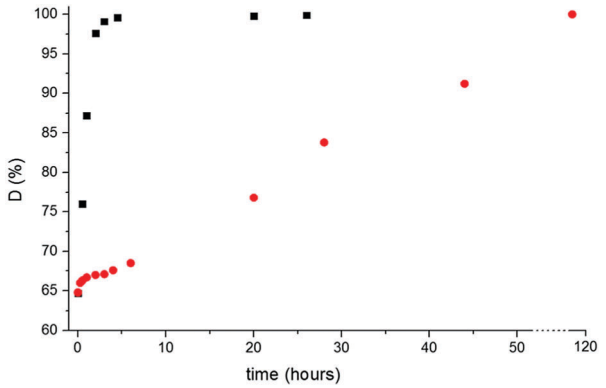

Fig. 1 Deracemization experiments of compound **1** in a standard Viedma ripening experiment starting from the conglomerate form (D + L, red circles) or using the gradual transformation of a metastable racemic compound (D + DL, black squares) into the conglomerate. Depicted percentages refer to the solid phase.

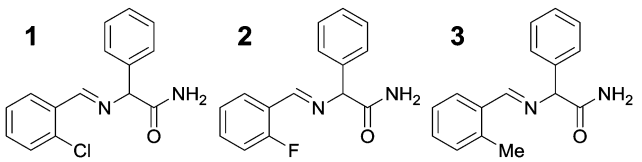

Fig. 2 Compounds **1** and **2** crystallize as a racemic compound, but convert into conglomerate crystals upon abrasive grinding. Viedma ripening on racemic conglomerate **3** has already been achieved by Noorduin *et al.*[7]

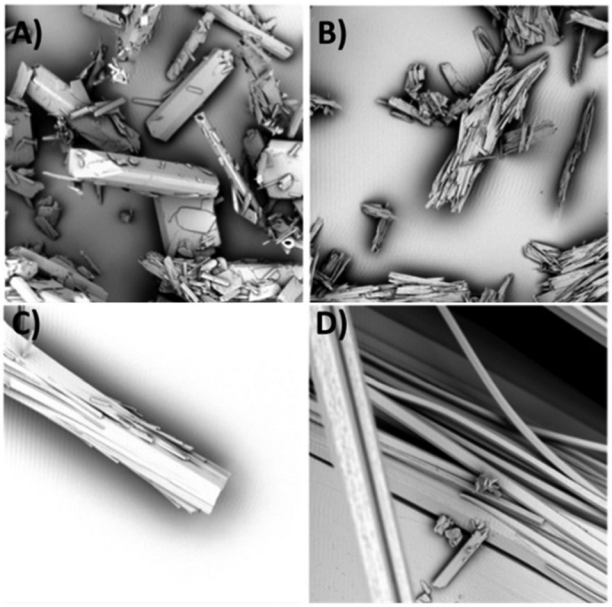

Fig. 3 Scanning electron microscope (SEM) images of the powder of D-**1** (A), DL-**1** (B) and DL-**1** crystals obtained after slow vapor diffusion of heptane into a saturated toluene solution of DL-**1** (C and D). Image sizes are approximately 400 × 400 μm for (A–C) and 50 × 50 μm for (D).

for crystals grown from enantiopure and racemic solutions, while for a conglomerate compound they should be identical. These patterns thus point towards a racemic compound.

Further experiments showed that both compounds indeed crystallize as racemic compounds (Appendix 1, ESI†). However, when a slurry of the racemic compound with some enantiopure seed crystals is subjected to several hours of abrasive grinding, or a single day of gentle stirring, XRPD patterns showed complete conversion into the conglomerate. It was therefore concluded that the racemic compound is in the metastable phase, whereas the conglomerate is the thermodynamically favoured product.

This phase behaviour is in line with Ostwald's rule of stages for polymorphic forms, stating that when a molecule can be present in multiple forms, the (kinetically) metastable form will appear first, followed by the thermodynamically stable form.[20]

Since compound **2** suffered from degradation (see the Experimental section), most further experiments were carried out using compound **1**.

The crystal structures of racemic and conglomerate compound **1** have already been determined by Leyssens *et al.*[21] They found that enantiopure **1** crystallizes as prisms, whereas its racemic form crystallizes as needles. A similar difference in morphology of the powders was visible in SEM images. The conglomerate crystals consisted of large blocks (Fig. 3A). In contrast, the racemic compound always crystallized as needles (Fig. 3B and C), which, in turn, consisted of a bundle of even thinner needles (Fig. 3D).

This crystallization behaviour turned out to have a large impact on the Viedma ripening experiments. In a typical Viedma ripening experiment, the slurry was vigorously ground for a certain time prior to addition of the racemization catalyst. This was done to ensure homogenization of the solid phase (this period is henceforth denoted as the homogenization time).[11,17] We observed that with decreasing homogenization times, the time required for deracemization of compounds **1** and **2** significantly decreased (Fig. 4 and Fig. S8, ESI†).

When the homogenization time was long (several hours), racemic compound crystals were completely converted into conglomerate crystals, even before the racemization catalyst was added. This in fact creates the starting conditions of a standard Viedma ripening experiment. Indeed, when performing a standard Viedma ripening experiment (by adding D- and L-crystals at the start), a similar long deracemization time was found. In other experiments, the homogenization time was too short to allow this (complete) conversion. The racemization catalyst (DBU) was in those cases added while the majority of the crystals were still present in the racemic compound form. During the experiment, racemic compound crystals will therefore keep on dissolving, thus providing a continuous feed of both D- and L-enantiomers for conglomerate crystallization. The presence of added D-seed crystals at the start of the experiment then becomes important.

The feed of D-enantiomers can be used for the growth of these D-seed crystals, through secondary nucleation. Grinding then ensures a constant increase in the number of crystals.

The feed of L-enantiomers cannot be directly incorporated into crystals, since no seed crystals of the L-enantiomer are present. Primary nucleation is therefore required for L-crystal formation. Moreover, due to the fast racemization in solution, the L-enantiomer is also (partially) converted into its counterpart,

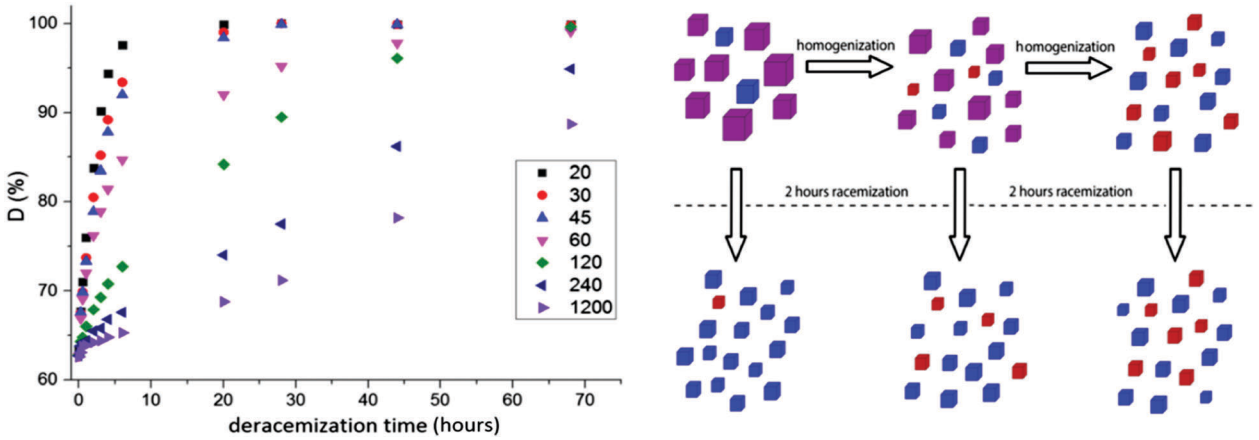

Fig. 4 Homogenization time dependent solid phase deracemization of **1** starting from the racemic compound (purple cubes, right picture) seeded with D crystals (blue cubes). Depicted homogenization times in the legend are in minutes. All experiments were started from a mixture of D + DL-crystals as described in the Deracemization experiments section.

allowing fast incorporation into the abundantly present D-crystals. The racemic compound crystals consequently serve as a gradual feed of building blocks for the conglomerate compound, similar to the *in situ* feed approach used by Noorduin *et al.* for naproxen.[22] The longer the homogenization time, the more the racemic compound is converted into the conglomerate. Consequently, more crystals of the minority enantiomer need to be converted in the Viedma ripening process and the deracemization rate decreases (Fig. 4). Fast deracemization can thus be achieved by keeping the homogenization time short. Interestingly, at very short homogenization times, the deracemization rate of compound **1** decreased again. This is further elaborated upon in Appendix 2 (ESI†).

The outcome of this fast deracemization could be simply directed towards the desired chirality by adding seeds of either the D- or L-enantiomer (Fig. 5). The deracemization rate was independent of the identity of the initial enantiomer in excess, as expected.

We demonstrated that Viedma ripening is possible starting from a metastable racemic compound. Moreover, deracemization of such a compound was much faster than in a normal Viedma ripening experiment. We found that the mechanism behind this process is a constant *in situ* feed of enantiomers, comparable to earlier work by Noorduin *et al.*[22] By optimizing the homogenization time, the time required for complete deracemization using the metastable racemic compound in combination with seed crystals could be reduced to three hours compared to two to five days for the conglomerate compound, *i.e.* a reduction by more than a factor of ten.

Deracemization experiments: all experiments were performed at room temperature. In a glass vial containing an oval PTFE-coated magnetic stirring bar (*L* 20 mm, ∅ 10 mm) a total of 1 g enantiopure Schiff-base (either 0.8 g DL and 0.2 g D, or 0.6 g D and 0.4 g L), 5.2 g glass beads (∅ *ca.* 2 mm VWR international) and 10 mL acetonitrile were added. The vial was closed and the resulting suspension was stirred at 700 rpm for the indicated time to ensure homogenization. After the homogenization

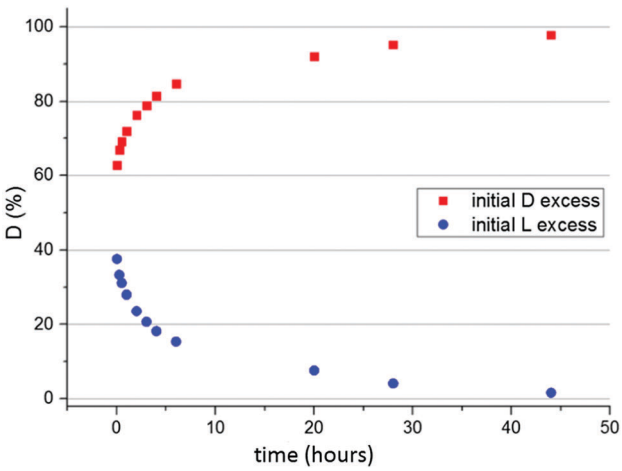

Fig. 5 Deracemization of compound **1** after a two hour homogenization time, starting with an initial excess of D (red) or L (blue) enantiomer.

time, 100 μL DBU was added to start the racemization process. For sampling, 0.3 mL of the suspension was taken using a syringe. The Schiff base was filtered off on a P4 glass filter and subsequently washed with 0.6 mL diisopropyl ether and air dried. The ee of the samples was determined using chiral HPLC (Chirobiotic T column, eluent ethanol, flow 1 mL min^{-1}, retention times: L-**1** 4.3 min, D-**1** 5.5 min, L-**2** 4.4 min, D-**2** 5.4 min).

We observed that compound **2** suffers from degradation after addition of the base (likely due to cyclization), resulting in a decrease of solid phase yield over time. No such decrease or side product formation was observed for compound **1**.

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