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A Greener Pathway to Enantiopurity: Mechanochemical Deracemization through Abrasive Grinding.

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Abstract: We report the first case of mechanochemical deracemization by using liquid-assisted abrasive grinding. The target molecule is a precursor of Paclbutrazol, an important fungicide and plant growth inhibitor. Using mechanochemical deracemization, we are even able to transform a 10% ee scalemic mixture of this latter in an enantioenriched product of 97% ee in a couple of hours. This is substantially shorter compared to solution-based deracemization methodologies. The present paper thus introduces an efficient and greener process to enantiopure material.

Introduction

Homochirality is an intrinsic property of life.^[1] Biological systems are therefore often sensitive to stereochemistry,^[2] with the two enantiomers of an active compound potentially presenting significant differences in pharmacological properties.^[3]

In 2005^[4], Viedma reported the total conversion of a racemic mixture into a homochiral solid by continuous stirring and attrition of the racemic crystal suspension in equilibrium with a saturated solution. This process relies on a complex interplay between solution racemization and crystal ripening which amplifies imbalances between the different enantiomeric crystal populations. Latter coined "Viedma Ripening" (VR, hereafter) or more generally "deracemization by abrasive grinding", the process permits to reach a total enantiomeric conversion of the solid state.^[5] It is however limited to conglomerate forming compounds^[6] (both enantiomers crystallize in different crystals), which are furthermore characterized by rapid racemization in solution (usually involving the use of a racemizing agent).^[7] VR has been successfully applied to deracemize a multitude of racemic mixtures, including inorganic compounds, as well as small organic molecules^[8,9], and several variants of this technique have been since developed.^[10-12]

Plant growth inhibitors are widely used in the field of agro-chemistry. One such inhibitor, paclbutrazol (PBZ), also known as (2R,3R; 2S,3S)-1-(4-chloro-phenyl) 4,4-dimethyl-2-(1,2,4-triazol-1-yl)-pentan-3-ol^[13] is sold as a racemic mixture, even though both enantiomers have distinct biological properties.^[14] Whereas the (2R, 3R) enantiomer is mainly responsible for the antifungal activity, the (2S, 3S) enantiomer has regulation and inhibiting properties.^[15]

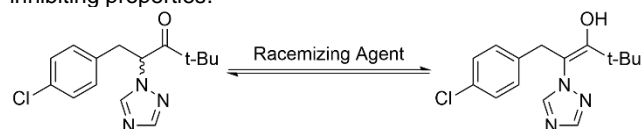


Figure 1. Keto-enol equilibrium of compound 1.

PBZ can be synthesized from 1-(4-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)pentan-3-one (Compound 1

hereafter), which crystallizes as a conglomerate and which can undergo rapid solution racemization via a keto-enol equilibrium^[7] (Figure 1). Compound 1 has been successfully deracemized with different processes (Temperature Cycle Induced Deracemization, TCID hereafter, or VR).^[16-18] A typical VR procedure of 1 has been performed and the results shown in Figure 2 are in agreement with published results^[18]: the process is characterized by a long induction period (> 4 days), long overall process time (± 10 days), and shows an autocatalytic behavior which is characteristic of solution-based VR process.^[9] Beside the long process times, solution-based deracemization processes require substantial amounts of solvent, often organic ones, to allow the racemization.

To tackle both issues, we aimed at transposing the deracemization process to a concentrated environment. To do so, we focused on the emerging field of mechanochemistry, considering its recent successes in performing organic reactions in a solvent-free manner.^[19-21] Furthermore, Ikekawa and Haykawa^[22] showed how racemization can successfully be achieved mechanochemically working on L-Leucine.

We here successfully introduce an almost solvent-free mechanochemical VR process, showing a significant reduction of the process time. Deracemization of compound 1 is achieved using high energy milling and a mere catalytic amount of solvent (Liquid Assisted Grinding, LAG). This is the first reported full "solid-state deracemization" based on the VR methodology paving the way for the development of 'greener' deracemization methodologies.

Results and Discussions

In an initial set of exploratory trials, we started from the racemate using sodium hydroxide (NaOH) as racemizing agent similar to the solution-based VR procedure.^[18] Water-LAG was performed with a mixer-mill equipped with zirconium oxide vessels. These latter were charged with 100mg of racemate ($ee=0\%$), 0.033g of NaOH (2.5 eq) and 10 μ L of water. We venture the hypothesis that the small amount of water would allow the creation of a sufficient amount of amorphous phase in which racemization could occur. The solubility of CITAK in water is too low to dissolve a significant amount of product under these conditions.^[16] The powder obtained at the end of the experiment is crystalline and shows the same solid phase as the initial powder (Figure S6). For two of the six experiments (Table S8) the ee shifted from 0% up to 60%, showing for the first time the feasibility of a "solvent-free" mechanochemical deracemization process. Similarly to solution-based VR processes, the sign of the chiral end state is random.^[23] The 4 processes not showing substantial deracemization likely remained in an induction period similar to the induction period observed for solution-based processes (as

observed in Figure 2). Remarkably, those process leading to 60% ee do so in an incredibly short process time of 6h30 to 9h.

In the solvent-based approach induction times are attributed to the lack of an initial crystal population imbalance when starting with a racemate. To circumvent this, the process can be started introducing an initial ee, placing the system in the exponential part of the kinetic curve. We took a similar intake for further experiments, starting with an initial 10% ee in an attempt to monitor the deracemization kinetics. As the jars are sealed during the milling, sampling implies stopping the milling operation. As shown elsewhere this induces changes to the outcome.^[24] To gain information on the process kinetics, and as homogeneous sampling during milling was not feasible with our set-up, the experiment was repeated numerous times, for an overall of 42 experiments, varying the process time for each sample (Table S9). Interestingly, the data seem to indicate that even starting with an initial ee of 10% there is still an induction time of about 30 minutes (MM-10-1 to MM-10-8). This is in contrast to solution-based VR processes which start from an initial population imbalance and do no longer show such an induction period. This induction period seems to be typical to the mechanochemical process and we believe that it is due to the necessity for the creation of a racemization media, which is here expected to be an amorphous or disordered phase containing the compound of interest, the small amount of water and some dissolved base. Such activation periods are commonly encountered in mechanochemical reaction processes.^[25–29]

Following this initial induction, deracemization rapidly sets in, as shown by samples MM-1-9 to MM-1-42. After a mere 3h reaction time, ees varying from 77 to 97% are obtained, highlighting the tremendous kinetic advantage of mechanochemical deracemization with respect to solution-based deracemization (as a comparison, classical VR has been done by starting with 10% ee and full deracemization stills take about 13h, see SI, table S7). Mechanochemical deracemization also shows strong variation between experiments having identical reaction times. This cannot only be explained by the above-mentioned stochastic induction time as even after 180 min (end of the process), this variation remains. This can in part be explained by the ratio of amorphous vs crystalline phase. This former is the medium in which rapid racemization occurs and which therefore contains a near-racemic composition. For the analysis of our samples both amorphous and crystalline phase are recovered.ⁱ As the ratio of amorphous vs crystalline phase is expected to vary from one experiment to the other, so is the overall ee. For future process optimization, parameters impacting the amount of amorphous vs. crystalline phase will need to be carefully controlled, to achieve the highest ee possible.

Figure 3 graphically illustrates the data points of Table S9, with each data point belonging to a different autocatalytic kinetic curve typically found for any Viedma Ripening experiment. For solution-based experiments these curves also vary substantially even when starting from identical conditions.^[30–32] As a guide to the eye, some such curves are sketched to highlight the origin of the strong variation observed in mechanochemical deracemization experiments. These curves are not obtained experimentally. To obtain these curves *in situ* follow-up of the ee during milling is required, but to the best of our knowledge no such technical set-up is currently available.

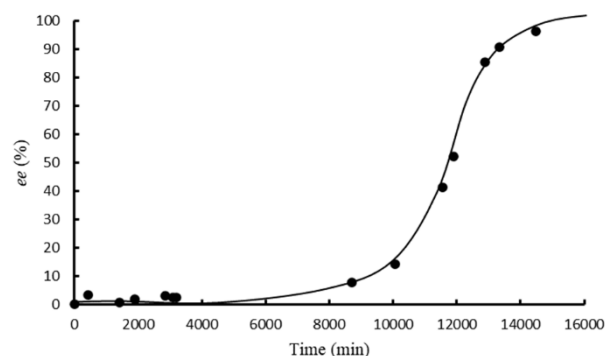


Figure 2. Deracemization of compound (±)-1 using classic Viedma Ripening in a TCID process.

Interestingly, the spread in Figure 3, does show (i) a deracemization kinetics following the autocatalytic behavior, also encountered during the solution-based VR processes (ii) deracemization to be achieved in time-spans incredibly quicker compared to the solution-based processes. The blue double arrow in Figure 3 represents the shortest induction time possible for the reaction to set in and could correspond to the time needed to create an amorphous phase in which racemization occurs. As this induction period would represent the necessary time to obtain a racemizing media, it is likely impacted by mechanochemical conditions such as the amount of water, number of grinding beads, amount of beads vs material.^[33,34] Changing the milling conditions would probably change the length of this arrow. The red double arrow represents the underlying stochastic variability in induction times. The inherent experimental variability in Viedma Ripening induction times was already highlighted by Blackmond et al., who stipulated that even under identical starting conditions, not all crystal-breaking events for any given crystal size occur in a similar manner.^[23] Finally, the purple double arrow represents the spread in final ee likely due to the proportion of amorphous vs crystalline phase at the end of the experiment. In an ideal set-up, this spread should be kept as narrow as possible with an average value close to 100% ee. In a solution-based process, the racemic mixture remaining in solution at the end of the process is removed by filtration, whereas in a mechanochemical process separation of the amorphous from crystalline phase cannot be performed, explaining the overall 80% ee measured at the end of the process. To achieve the highest enantiopurity possible, the amount of amorphous material present during the final stages of the grinding process should therefore be reduced as much as possible (eg. reducing the grinding intensity at the end of the process, reducing the temperature at the end of the process, ...).^[34]

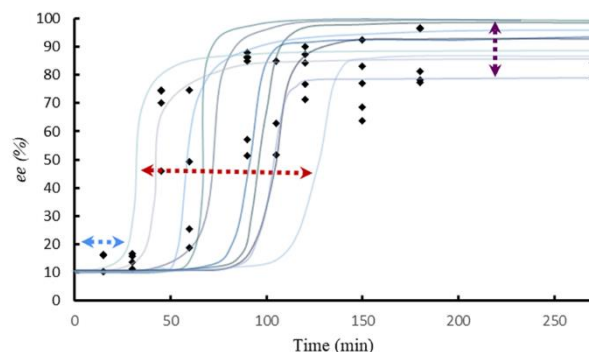


Figure 3. Deracemization kinetics of compound 1 under high energy milling conditions.

Conclusion

ⁱ This corresponds to recovering the racemic solution together with the enantiopure solid in a classical suspension-based VR process.

In this paper, we introduce a greener pathway to enantiopurity, being the first to enable VR mechanochemically. Even though a full mechanistic understanding is not yet achieved, results indicate that high energy milling yields enantioenriched material in a process much faster than the classic solution-based processes. Although some characteristics of the solution-based process (autocatalytic kinetics, induction time to population imbalance) are also encountered here, our data suggests careful control of amorphous vs crystalline phase is going to be key to truly understanding and optimizing these processes.

Materials and methods

CITAK has been synthesized by following the method of Guillot *et al.*^[35] substituting the p-fluorobenzyl chloride by chlorobenzyl chloride.

Solution-based Viedma Ripening were performed by following the procedure of C.Rougeot *et al.*^[18] changing the amount of base when necessary.

Milling experiments were all conducted with a Mixer Mill MM400 equipped with two 10mL-jars. They are composed of ZrO₂ as well as the 10mm diameter bead used to assure the milling. In all experiments, 100mg of CITAK is ground with around 2.5eq of NaOH and 10μL of water. One part of the milled powder is analyzed by XRPD and ¹H NMR. The maximum of the ground material is removed and washed with a sufficient amount of water to remove any trace of base before chPLC analyses.

Part of chPLC analyses were performed on a Waters Alliance 2695 System with a photo array detector (Waters 2998) at 220nm. Samples were measured using a 1mL flow of 98/2 Isohexane/EtOH, on a Chiralpak IC 5μm 250x4.6mm column from Daicel. Retention time are found at 22.2min and 23.2min for R and S respectively. Alternatively analyses were performed on Ultimate 3000 system, with a UV detection at 220nm. Samples were measured using a 1mL flow of 80/20 Heptane/IPA, on a Chiralcel OD-H 5μm 250x4.6mm column from Daicel. The retention time are found at 7.4 and 9.2min for the R and the S enantiomer respectively.

Acknowledgements

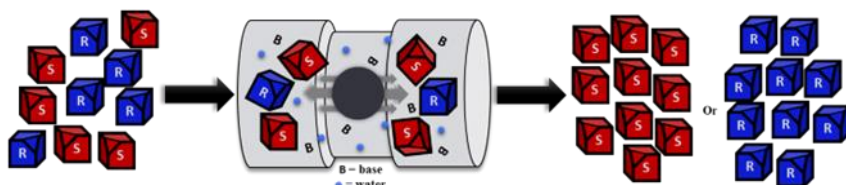
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Enantiopurity is of crucial importance for compounds of biological interest. Over the last decade, various solution-based deracemization technologies have been introduced, transforming a racemic mixture into an enantiopure compound. Here we thrust deracemization into the era of Green Chemistry, being the first to enable deracemization mechanochemically, with as a bonus deracemization occurring over a matter of hours instead of days as observed for the solution-based processes.

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