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Role of Additives during Deracemization Using Temperature Cycling

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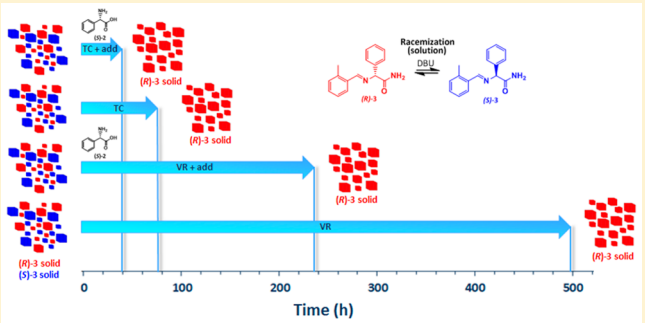
ABSTRACT: Temperature cycling, alongside Viedma ripening, has been established as a reliable method for deracemizing racemic mixtures of chiral compounds that crystallize as a conglomerate. Here we report that the speed of temperature cycling can be increased by using chiral additives. We also demonstrate that the chirality of the additive determines the final enantiomeric state of the solid phase. Viedma ripening experiments using equivalent conditions, with and without chiral additives, are always found to be slower.



1. INTRODUCTION

Strategies to create single chirality are an appealing topic in chemistry both from a fundamental and application point of view. Pharmaceutical companies for instance are increasingly driven to produce enantiopure compounds, aiming to lower the required amount of common drugs like ibuprofen, omeprazole, cetirizine, ofloxacin, and many more, which are still sold as racemates. Normally, synthesis of chiral compounds results in a racemic mixture of the two enantiomers. Because most physical and chemical properties are identical, their separation (a procedure called resolution) is not always straightforward and often requires several operations. Traditional approaches involving resolution techniques, e.g., diastereomeric resolution,[1] kinetic resolution,[2] all lead to a maximum yield of 50% in the absence of a racemization reaction.

A new alternative was introduced by the Viedma ripening process,[3−8] which involves grinding of the solid state of conglomerate-forming compounds, combined with a racemization reaction in solution. During this latter step, one of the two enantiomers is selectively converted into the desired one, reaching a final theoretical yield of 100% in the solid state. More recently, the groups of Flood and Coquerel,[9,10] as previously suggested by Viedma,[11] demonstrated that it is possible to obtain an analogous result by applying temperature cycles to the system, where the grinding is replaced by continuous heating/cooling sequences. Both methods show a sigmoidal increase in the enantiomeric excess (e.e.), with a generally faster deracemization rate in the case of temperature cycling. The speed of both processes can be influenced by several parameters, e.g., the size of the crystals, the initial e.e., the growth and dissolution rates of the enantiomers, the grinding speed in the case of Viedma ripening, and the selected cooling/heating cycles in the case of temperature cycling.[12−16] The reason why temperature cycling proceeds with a higher rate is not yet understood. At present, two models have been suggested to explain its mechanism. On the one hand, Uwaha et al. show that chiral cluster incorporation besides monomers could drive chiral amplification.[17] On the other hand, crystal growth rate dispersion, the difference in the growth rate distributions for the crystal populations of the two enantiomers, was proposed by Uchin et al. as the explanation.[16,18] Both these models can describe the autocatalytic behavior of the process, leading to sigmoidal deracemization curves.

Steendam et al. proved that by using chiral additives, the speed of Viedma ripening can be significantly increased.[19,20] The advantage of using an additive is not only displayed in terms of a higher deracemization rate but also allows one to choose the final configuration of the pure enantiomer.[19,20] The aim of this study is to determine if chiral additives can also enhance the speed of temperature cycling and to compare the overall speed with Viedma ripening.[19]

2. EXPERIMENTAL DETAILS

All the experiments were performed in 20 mL vials, sealed, and positioned inside a double-jacketed vessel connected to a Julabo thermostat that controlled the temperature cycles. The temperature profile chosen was as follows: the temperature was initially kept constant at 22 °C for 10 min, then increased to 40 °C in 15 min, kept at 40 °C for 10 min, and successively decreased back to 22 °C in 20 min, for a total cycle length of 55 min. This cycle was repeated continuously until deracemization was completed. In total, 0.8 g of racemic compound **3**, 10 mL of methanol, and the specific amount of chiral additives (**1** or **2**) were added 15−20 min before the DBU (40 μL), to ensure full homogenization. The time zero of each experiment corresponds to the time the DBU was added.

Viedma ripening experiments were performed at room temperature in 20 mL vials with 0.8 g of racemic compound **3**, 10 mL of methanol, 5 g of glass beads, and the specific amount of chiral additives (**1** or **2**, see Figure 1). DBU (40 μL) was added after 15−20 min of homogenization.

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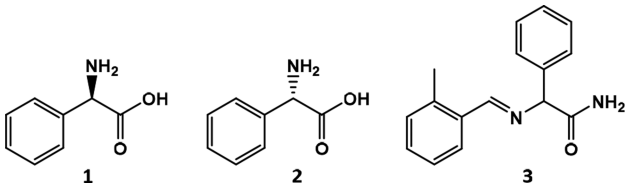

Figure 1. Additives (*R*)-phenylglycine (**1**), (*S*)-phenylglycine (**2**) and the chosen target compound *rac*-(2-methylbenzylidene)-phenylglycinamide (**3**).

Samples were taken by extracting 1 mL of suspension using a 5 mL syringe, vacuum filtered on a P4 glass filter, and washed with ethanol. The enantiomeric excess was measured using an Agilent chiral HPLC with a Chirobiotic T column and a 1 mL min^{-1} flow. Eluent: ethanol. Retention times were, respectively, 4.2 min (*S*) and 6.0 min (*R*).

3. RESULTS AND DISCUSSION

(*R*)- and (*S*)-phenylglycine, **1** and **2**, were chosen as the additives to promote the deracemization of **3**, an amino acid derivative and the first organic compound proven to deracemize using Viedma ripening.[4] We envisioned that it should also be possible to deracemize this molecule using temperature cycling in combination with chiral additives, as the basic requirements are the same as for the Viedma ripening process. The experiments were performed in methanol, and the base DBU was used as a catalyst to allow fast racemization. In a recent paper by Breveglieri et al., the same compound has been thoroughly investigated in a temperature cycling application, with a particular focus on how parameters like initial enantiomeric excess, operating temperature range, and cooling rate influence the deracemization pathway.[21] Here we concentrate on how additives can play a role in the process, keeping therefore the temperature cycle constant and starting all the experiments from an e.e. of 0%. The selected temperature profile was chosen to ensure that each experiment was completed in a relatively short time (i.e., between 15 and 50 h).

Starting with an e.e. of 0% and without any other bias, choosing the final end state of the deracemization is not possible.[3,4] For the present compound, however, all the experiments in the absence of additives led to only one single configuration, namely, the (*R*)-enantiomer. As was also reported by Steendam et al.,[19] this behavior can be attributed to the presence of chiral impurities, the nature of which is unknown. We will refer to these as (*S*)-impurities, assuming that their influence agrees with Lahav's rule of reversal,[22] according to which chiral tailor-made additives selectively hamper the nucleation or growth of the enantiomorphs with the same configuration, leading to crystals of the opposite handedness. In all the experiments we performed without additives, the deracemization was completed in about 2−3 days. When using additives, they take control over the process and the effect of the impurities is neutralized.[19] Amounts of the additive as small as 0.1% are capable of significantly speeding up the deracemization.

Figure 2 displays a series of experiments in which different concentrations of both configurations of additives were used in combination with temperature cycling. One might expect that the action of the additives is amplified by increasing their concentrations, but we find this is only true up to a maximum. As shown in the figure, an increase in the additive concentrations of up to a value of 2% results in a linear

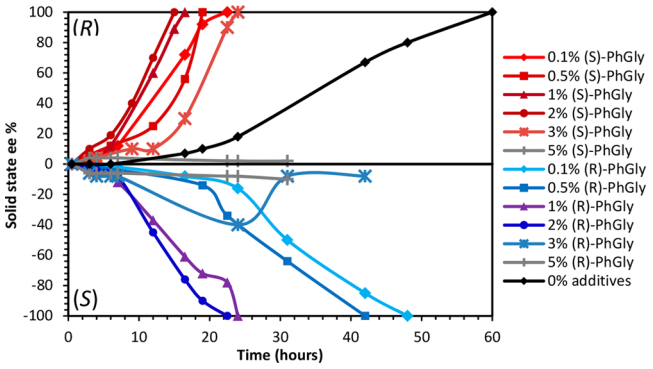

Figure 2. Deracemization experiments for various concentrations of additives (*R*) and (*S*)-phenylglycine.

upsurge in the deracemization rate. Higher amounts, however, have an opposite effect. Therefore, we conclude that a value of 2% is optimal for a fast deracemization given the chosen experimental conditions.

Interestingly, Figure 2 confirms that the (*S*)-impurities still play a role, as they collaborate with the (*S*)-phenylglycine to a faster deracemization toward the formation of the (*R*)-enantiomer. At the same time, they compete with the counter-additive (*R*)-phenylglycine, making the process in the direction of the (*S*)-enantiomer slower. The 0.1% (*R*)-phenylglycine, however, is already sufficient to lead to an (*S*) end state.

A too high concentration of additives (beyond 2% with the current working conditions) is not beneficial for the process anymore and has severe influence on the deracemization. The curve corresponding to a 3% additive concentration achieves deracemization toward the (*R*)-enantiomer but displays a curious effect for the (*S*)-enantiomer, in which the final e.e. returns to 0%. The 5% cases never achieve any significant e.e., regardless of the configuration of the additive involved. We see at least two possible explanations for this effect: (1) the high concentration of additives also affects the crystals of the other enantiomer or (2) the additives have an effect on the racemization rate. In order to test this, we performed racemization experiments for different additive concentrations. As shown in Figure 3, the additives indeed cause a significant decrease in the racemization rate and consequently also in the deracemization during temperature cycling. To corroborate

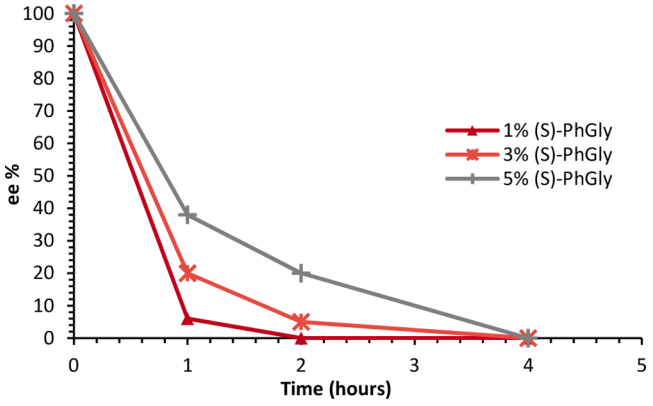

Figure 3. Racemization experiments in solution for 1%, 3% and 5% concentrations of the additive (*S*)-phenylglycine. The same trend is observed for (*R*)-phenylglycine.

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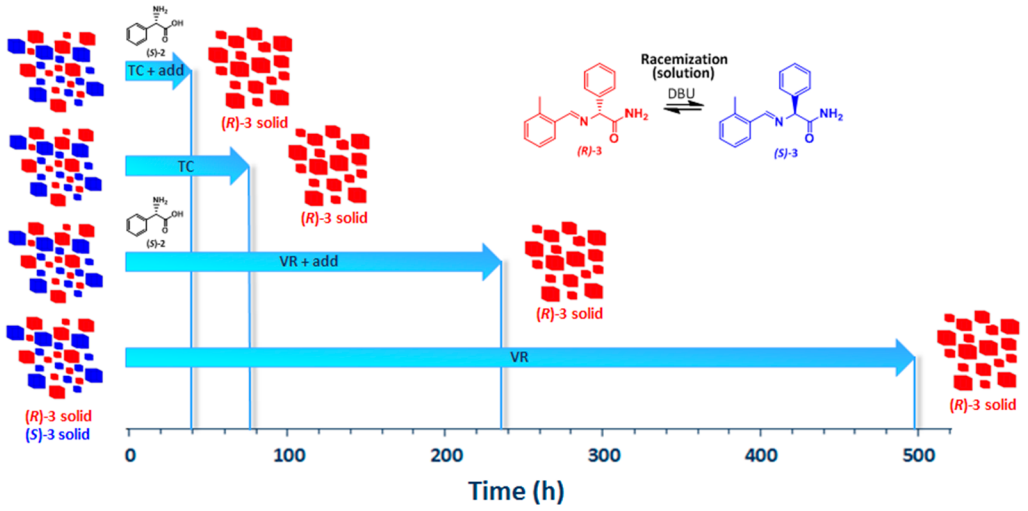

Figure 4. Evolution of the deracemization of compound **3** via temperature cycling (TC) and Viedma ripening (VR) without or with the use of enantiopure phenylglycine as an additive. Only the case of the additive (*S*)-phenylglycine is shown.

this, a few experiments with larger amounts of DBU have been performed showing that complete deracemization is indeed possible in the presence of high concentrations of additives, making the effect of additives on the racemization rate the most likely explanation for the observed behavior.

Having obtained these results, we can now make a valid comparison of the deracemization rates of the temperature cycling and Viedma ripening, with and without the use of chiral additives. Although Viedma ripening experiments were already performed by Steendam et al.,[19] in the current work a new set of experiments was carried out to ensure comparable experimental conditions to those used for the temperature cycling. An overview of the four deracemization conditions is presented in Figures 4 and 5. Temperature cycling, along the

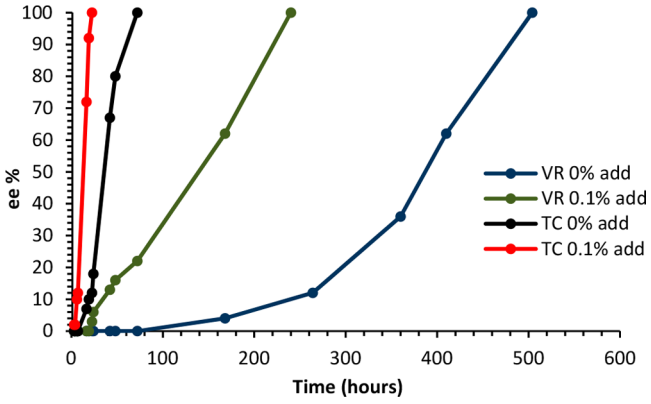

Figure 5. Comparison between the Viedma ripening (VR) and temperature cycling (TC) experiments with 0.1% (*S*)-phenylglycine and without chiral additives.

lines of Viedma ripening, shows an increase in the deracemization rate when chiral additives are used. A concentration of 0.1% allows Viedma ripening to reduce its deracemization time approximately by a factor of 2 (green line, Figure 5). It is remarkable that the same concentration of chiral additives allows temperature cycling to speed up its deracemization time also by a factor 2, reaching therefore completion still much faster (red line, Figure 5). Note that the presence of the (*S*)-impurities should to be taken into account, as the rate at 0% of additives for both Viedma ripening and temperature cycling would probably be slower in their absence.

Figure 5 reflects the situation of only one configuration of chiral additive at a specific concentration, a single temperature profile for temperature cycling and well-defined experimental parameters which were kept identical for each experiment. Although the deracemization times may slightly vary by changing one or more of these conditions, we expect the overall trend to remain the same. Therefore, this indicates that temperature cycling, in combination with chiral additives, has a tendency to proceed in a faster manner than Viedma ripening under comparable conditions. Furthermore, even though the effect of a chiral additive in the two deracemization processes has been compared here for only the present compound, we expect the results to be qualitatively similar for other compounds.

4. CONCLUSIONS

With this work we demonstrate that the speed of temperature cycling can be increased by using enantiopure phenylglycine, making this process the fastest out of the four deracemization routes investigated here, namely, Viedma ripening and temperature cycling with and without additives. Like for Viedma ripening, the choice of enantiomer for the additive determines the chiral outcome of the temperature cycling. In addition, while it is not clear which of the models best explains the temperature cycling mechanism without additives, in the present case the use of chiral additives induces a growth-inhibition process that corresponds to an extreme case of growth rate dispersion.[19,22] This may help to gain a deeper understanding of the mechanism behind temperature cycling.

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Notes

The authors declare no competing financial interest.

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