**Deracemisation via temperature cycles: the effect of the initial and operating conditions**

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**Highlights**

* Effect of the initial and operating conditions on the deracemisation process.
* Qualitative comparison between experiments and PBE model.
* Experimental variability due to small variations of the experimental conditions.

**1. Introduction**

Solid-state deracemisation via temperature cycles is among the techniques used to attain chiral purity. By applying periodic temperature variations to a suspension of a conglomerate forming compound in the presence of a racemisation reaction occurring in solution, only one pure enantiomer is obtained1.

Previous contributions have shown that by starting the process with asymmetric initial conditions, i.e. an excess of one enantiomer, this one will be isolated at the end of the process1. However, a thorough investigation of the conditions affecting the deracemisation outcome has been performed only for a similar isothermal deracemisation process2. In this work, we combine results obtained by performing experiments and by running simulations to investigate the effect of the initial and operating conditions on the process outcome. Particularly, we analyse how the initial enantiomeric excess (*ee0*), the parameters describing the initial particle size distribution (PSD), and their combination affect the attained handedness and the deracemisation time, when performing temperature cycles. We also evaluate some additional parameters, such as the suspension density, to better explain the variability of the outcome observed in some deracemisation experiments.

Finally, we vary several operating conditions, especially the temperature profile, to investigate their effect on the process in terms of time and productivity.

**2. Methods**

The simulations of the process are performed with a PBE-based model, previously presented3. The experiments are carried out using chiral model compounds and a base as racemising agent. The temperature profile is monitored with thermocouples and the evolution of the enantiomeric excess over time with chiral HPLC4.

**3. Results and discussion**

In the case of experiments as well as of simulations, when the process started with the same PSD for both enantiomers and an initial excess of the desired one, the deracemisation proceeded towards this handedness (Fig. 1) 4,3. In the absence of *ee0*, the asymmetry in the initial conditions can be introduced by differentiating the PSD of the two enantiomeric populations. These differences would determine the outcome of the deracemisation process.

We also combined the parameters describing the PSD and the *ee0*, looking at how they compete for the initial asymmetry. For example, when the process started with an excess of the D-enantiomer, we obtained the L-enantiomer, if the mean size of its population was large enough to counterbalance the *ee0*.

The described sensitivity to the initial conditions, is used to better analyse the variations among experiments repeated at the same nominal conditions. Taken an experimental parameter, we exploited the process model to test the variation of the deracemisation outcome as a function of small realistic deviations from the nominal value of this parameter. We, hence, qualitatively compared experimental and simulation results and we verified the agreement among the trends, when small variations are introduced.

By investigating different operating conditions, i.e. the cooling rate and the temperature range, we have verified how the process time shortens when the cooling rate increases. Thanks to the combination of experimental and simulation results, we could verify the presence of optimal conditions.

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**Figure 1.** Effect of the initial enantiomeric excess. Evolution of the enantiomeric excess over time, obtained by running simulations at *ee0* = 0.2, 0.4, 0.6, 0.8 (a) and experiments at *ee0* = 7, 18, 32 % (b).

**4. Conclusions**

We have shown, experimentally and by running simulations, that the outcome of the deracemisation via temperature cycles is strongly influenced by the initial conditions, i.e. enantiomeric excess and particle size distribution. By further analysing the initial conditions, we have shown how the high sensitivity of the process to these parameters explains the variability observed during experiments. Finally, we investigated several operating conditions, and we identified the ones favourable for the process.

**References**

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