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Performance Analysis and Model-Free Design of Deracemization via Temperature Cycles

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ABSTRACT: Solid-state deracemization via temperature cycles is a technique that has been shown to be effective to isolate the pure enantiomer of a conglomerate-forming compound. This process has a large number of operating parameters that can be adjusted according to system-specific properties. On the one hand, this feature makes the process flexible and prone to optimization. On the other hand, the design space is so large that experimental optimization of the process can become long and cumbersome. In this work, we achieve two results. First, we show that deracemization via temperature cycles works very effectively for two new experimental systems, namely, the chiral compounds 2-(benzylideneamino)-2-(2-chlorophenyl)acetamide (CPG) and 3,3-dimethyl-2-((naphthalen-2-ylmethylene)amino)butanenitrile (tLEU). Second, we propose a new approach for the design of an effective deracemization process via temperature cycles for a new compound. Therefore, in this work, we investigate the effect of different operating conditions, namely, the initial enantiomeric excess, the cooling rate, the temperature range, and the catalyst concentration, on the performance of deracemization via temperature cycles for the new compounds CPG and tLEU and for *N*-(2-methylbenzylidene)phenylglycine amide (NMPA), which was already studied in a previous paper. On the basis of these outcomes, we conclude by proposing a model-free screening strategy for the design of an effective deracemization process via temperature cycles for a new compound.

KEYWORDS: *deracemization via temperature cycles, resolution, racemization, process design, operating conditions*

1. INTRODUCTION

Separation and purification of the enantiomers of a chiral compound is a well-known challenge because they exhibit identical physical and chemical properties in an achiral environment. Solid-state deracemization processes are among the promising techniques under development for this purpose. These types of processes have the advantage of converting the undesired enantiomer into the desired one, thus enabling in principle a 100% yield. These methods allow deracemization of an enantiomerically enriched suspension of a conglomerate-forming compound with a single chiral and racemizable center in the presence of a catalyst that promotes the racemization of the enantiomers in solution. Deracemization occurs via dissolution of the crystals of the undesired enantiomer, racemization of the same, and growth of the crystals of the target enantiomer. In one approach, defined as attrition-enhanced deracemization or Viedma ripening, size-dependent solubility drives the whole process, since a grinding medium promotes the formation of crystal fragments that easily dissolve.[1−3] In another approach, periodic temperature variations between two temperature levels are carried out, and the process is driven by temperature-dependent solubility; this technique is defined as deracemization via temperature cycles.[4,5] In both cases, the desired enantiomer is collected as a solid product.

This work focuses on the design and implementation of the second method only, since it presents several advantages. First, deracemization via temperature cycles can be carried out in a standard thermostated stirred tank reactor without the addition of any grinding medium or unit. Second, the high flexibility of this method allows the operating conditions to be easily adapted to the system properties or the upstream and downstream processes as well as to effectively meet demanding process specifications.

To demonstrate the potential of the deracemization process via temperature cycles, in this work we implemented and studied this process for different compounds. In particular, we investigated the effect of the operating conditions on the process performance for different compounds as well as the criteria for choosing feasible operating conditions to apply to a new compound. The paper is structured as follows. First, we describe the experimental protocols followed to characterize the new model systems and to perform the deracemization process via temperature cycles. Second, we present the design of the deracemization experiments according to the solubility data of the model compounds. Third, we investigate the effect of some operating conditions on the deracemization of

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different model compounds, i.e., when the system properties differ. Finally, we discuss how to identify a favorable operating region in the parameter space for a new model compound on the basis of a small number of small-scale experiments and then draw some conclusions.

2. EXPERIMENTAL SECTION

2.1. Materials and Equipment.

The experiments presented in this work were performed with two different chemical systems. Both compounds are imine derivatives, which are already known to undergo successful attrition-enhanced deracemization.[3,6−8] They racemize in the presence of the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as racemizing agent. The solvents used were a mixture of 2-propanol (IPA) (95 wt %) in acetonitrile (ACN) for 2-(benzylideneamino)-2-(2-chlorophenyl)acetamide (CPG) (Figure 1 left), a precursor of the active pharmaceutical ingredient clopidogrel, and pure methanol for 3,3-dimethyl-2-((naphthalen-2-ylmethylene)amino)butanenitrile (tLEU) (Figure 1 right), which is readily convertible by hydrolysis to the amino acid *tert*-leucine. The compounds were synthesized according to procedures reported in the literature;[7,9] the racemizing agent and the solvents were purchased from Sigma-Aldrich.

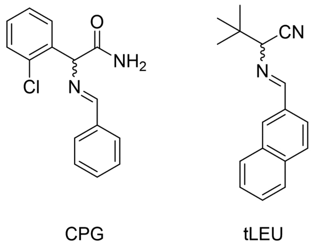


Figure 1. Molecular structures of the two compounds used in this work: 2-(benzylideneamino)-2-(2-chlorophenyl)acetamide (CPG) and 3,3-dimethyl-2-((naphthalen-2-ylmethylene)amino)butanenitrile (tLEU).

The experiments were performed in standard chromatographic vials (1.8 mL) undergoing temperature cycles in a customized version of a Technobis Crystal16 crystallization system.[10] The temperature in the device was regulated externally but measured inside each vial with thermocouples inserted in the suspension, which was stirred at 1250 rpm with rare-earth cylindrical PTFE stirring bars (8 mm × 3 mm).

The evolution of the deracemization process was monitored by collecting suspension samples by vacuum filtration with a Büchner funnel and a 0.5 μm MS PTFE membrane filter. The solid samples were washed with *tert*-butyl methyl ether (CPG) or ACN (tLEU), dried, and dissolved for HPLC analysis, conducted in a DIONEX UltiMate 3000 series HPLC system equipped with a quaternary pump and a DAD detector (Thermo Scientific, Reinach, Switzerland). The measurements for CPG were carried out at 213 nm on a CHIRALCEL OJ-H column (250 mm × 4.6 mm, 5 μm). As the mobile phase, a mixture of *n*-hexane and IPA (60:40 v/v) was used at a flow rate of 1 mL/min. The measured retention times were 7.2 and 9.6 min for (*S*)- and (*R*)-CPG, respectively. With regard to tLEU, the analytical determination was run on a CHIRALCEL IA column (250 mm × 25 mm, 20 μm) with a mixture of *n*-hexane and IPA (98:2 v/v) as the eluent at a flow rate of 0.7 mL/min. The retention times at 220 nm were 8.5 and 9.9 min for (*S*)- and (*R*)-tLEU, respectively. For both compounds, the enantiomeric excess was calculated using the HPLC peak areas for the two enantiomers.

2.2. Experimental Procedures for the Deracemization Experiments.

The deracemization experiments were carried out similarly to those reported previously for *N*-(2-methylbenzylidene)phenylglycine amide (NMPA),[11,12] as follows.

To obtain a solid mixture with the specified initial enantiomeric excess, we used the following methods. For CPG, we wet-ground a solid racemic mixture with a powder of the desired enantiomer and a few microliters of pure ACN, which then evaporated. For tLEU, we dissolved the racemic powder together with the desired amount of enantiopure compound in *tert*-butyl methyl ether. We crystallized the desired enriched homogeneous mixture by complete solvent evaporation under vacuum. The obtained crystals were wet-ground with a few drops of *tert*-butyl methyl ether to reduce their size and to further homogenize the composition.

The saturated solution at the minimum temperature was prepared by equilibrating a racemic suspension of the desired compound overnight in the presence of DBU. Finally, the vials were filled with the enriched mixture (32.5 mg) and the filtered saturated solution (1.3 g) to produce a suspension with a density of 2.5%, and the suspension was stirred at the minimum temperature of the chosen temperature profile for 10 min. Then the first sample was taken, and the temperature cycles were started. The final product was collected by vacuum filtration and washed with the corresponding solvent once an enantiomeric excess of at least 98% was reached.

The periodic temperature profile utilized in all of the experiments consisted of four steps: one heating ramp, one cooling ramp, and two isothermal steps in between at the maximum temperature ($T_{\max}$) and the minimum temperature ($T_{\min}$). For each experiment, the temperature values together with the other operating conditions (see Table 2) were chosen to enable comparison of the experiments. Each experiment under a given set of operating conditions was repeated three times (with the evolution of the enantiomeric excess reported with different symbols of the same color in the figures that follow) to assess the reproducibility of the result. For CPG, a fourth repetition was performed, and only three samples were taken during the entire process to verify that the standard sampling procedure did not affect the deracemization results. The evolution of the enantiomeric excess over time was monitored by sampling the suspension (7−9 μL) at the end of the isothermal step at low temperature and by HPLC analysis as described in section 2.1.

3. DERACEMIZATION EXPERIMENTS: RESULTS

In this work, we report the solid-state deracemization via temperature cycles applied to CPG and tLEU (this work) in comparison with the same process applied to NMPA as reported in previous papers.[11,12] Particularly, we focus on understanding the role of system-specific features resulting from different kinetics of the several phenomena involved and their different temperature dependences. Inspired by previous work on temperature cycles,[4,11−15] we verify the effects of the following key operating parameters: the initial enantiomeric excess, the cooling rate, the range of the temperature cycles, and the catalyst concentration. The values of the heating rate (1.30 °C/min), the suspension density at the minimum temperature (2.5 wt %), and the fraction of solid dissolved at the high temperature (30% of the total) are the same in all of the experiments, so as to obtain comparable experimental conditions. In order to keep the fraction dissolved constant and to operate at the same minimum temperature, the maximum temperature is selected on the basis of the solubility curve in such a way that

$$\Delta c = c^{*}(T_{\max}) - c^{*}(T_{\min}) \tag{1}$$

is the same for all of the compounds analyzed, where c^* is the gravimetric solubility at the desired temperature. To do that, we determine gravimetrically the solubility of each compound in the chosen solvent (Table 1) and compute the temperature intervals according to the solubility line (Figure 2) in a range upper-bounded by the compound thermal lability. Some measurements in the presence of DBU at different concentrations are also carried out to make sure that the solubility is not affected significantly by its presence, in the interest of this work. In the case of NMPA and CPG, we can perform experiments in the same temperature range because of the similarity of the solubility curves. Since the solubility line for tLEU is steeper, to dissolve the desired fraction of suspended solid we need a smaller ΔT, and thus, we apply a smaller temperature range. Therefore, for tLEU, we choose three different $T_{\min}$ values in order to look at the deracemization between 20 and 40 °C.

Table 1. Gravimetric Solubilities as Functions of Temperature for Racemic CPG and tLEU Measured in a Mixture of IPA in ACN (95 wt %) and in Methanol, Respectively, in the Presence of DBU (20 mM)[a]

	c^*[mg/g]	
T [°C]	CPG in IPA/ACN	tLEU in MeOH
20	7.00 ± 0.09	25.2 ± 0.3
25	8.0 ± 0.2	–
30	10.2 ± 0.2	37.8 ± 0.1
35	13.7 ± 0.2	52 ± 2
40	–	63.2 ± 0.3
45	24.3 ± 0.7	80 ± 4

[a] The results are reported as mean values of three samples with the corresponding standard deviations.

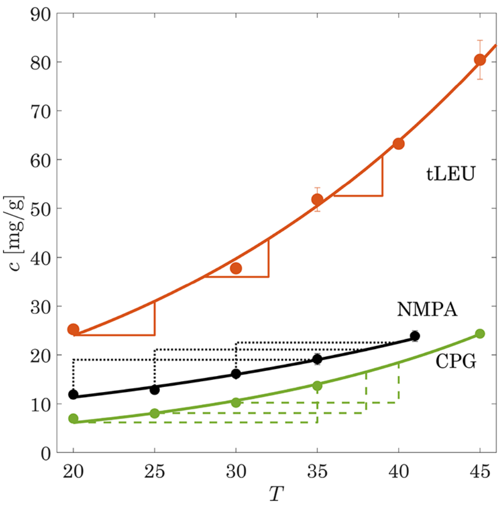


Figure 2. Solubilities of NMPA and CPG in ACN/IPA and tLEU in MeOH, indicated with black, green, and orange lines and markers, respectively. The experimental points (mean values of three repetitions with error bars) are fitted to the equation $c^* = a \exp(-b/T)$, where T is the absolute temperature ([K]). The coefficients values are $a = 3.127 \times 10^8$ mg/g and $b = 5208$ K for CPG and $a = 1.069 \times 10^8$ mg/g and $b = 4486$ K for tLEU. For NMPA, we refer to our previous work.[11] The dashed green, solid orange, and dotted black lines indicate the temperature ranges examined for CPG, tLEU, and NMPA, respectively.

Table 2 summarizes the experiments with CPG (c) and tLEU (t) and the corresponding operating conditions. For the experiments with NMPA, we refer to our previous papers, particularly to Table 2 in ref 11 and sections 2.2.2 and 5 in ref 12.

Table 2. Experiments Performed with CPG and tLEU[a]

expt	compd	ee_0	R_c [°C/min]	$T_{\min}$ [°C]	$T_{\max}$ [°C]	c_b [mM]	total time [h]	$n_{c,tot}$
c1	CPG	0.50	0.22	25	37	20	5.6	4.0
c2	CPG	0.36	0.22	25	37	20	9.3	6.7
c3	CPG	0.20	0.22	25	37	20	14.0	10.0
c4	CPG	0.20	0.43	25	37	20	12.7	13.3
c5	CPG	0.20	1.30	25	37	20	10.6	16.5
c6	CPG	0.20	1.30	20	35	20	11.1	15.5
c7	CPG	0.20	1.30	30	40	20	10.0	15.3
t3	tLEU	0.38	0.22	28	32	20	5.0	7.0
t4	tLEU	0.38	0.43	28	32	20	5.5	10.3
t5	tLEU	0.38	1.30	28	32	20	7.8	14.0
t6	tLEU	0.38	0.22	20	25	20	7.7	9.0
t7	tLEU	0.38	0.22	36	39	20	3.5	5.7
t8	tLEU	0.38	0.22	36	39	15	3.5	5.7
t9	tLEU	0.38	0.22	36	39	30	3.1	5.0

[a] The suspension density, heating rate, crystallizer volume, and fraction of suspended solid dissolved during each cycle were the same for all experiments (see the main text for their values). The operating parameters varied are reported: ee_0 is the initial enantiomeric excess, R_c is the cooling rate, $T_{\min}$ and $T_{\max}$ are the minimum and maximum temperatures in a cycle, respectively, and c_b is the DBU concentration. The total time and number of cycles, $n_{c,tot}$, are reported as mean values of the repetitions carried out under the same experimental conditions.

3.1. Initial Enantiomeric Excess.

Several contributions in the literature report about the effect of the initial enantiomeric excess, ee_0, on the solid-state deracemization.[14,16−18] In all cases, the deracemization process is reported to be accelerated with increasing ee_0, i.e., by increasing the content of the desired enantiomer in the initial enriched mixture. With large initial enantiomeric excess of the desired enantiomer, the initial asymmetry is more pronounced, and the amount of counter-enantiomer to convert is smaller. Hence, the enantiomeric excess evolves to enantiopurity faster than in the case of smaller values of ee_0.

The same behavior is observed in the case of CPG in Figure 3: deracemization is attained in about 4, 7, and 10 cycles with ee_0 equal to 0.50, 0.36, and 0.20 in experiments c1, c2, and c3, respectively. Therefore, the effect of the initial enantiomeric excess is confirmed also with CPG, and the choice of a high value of the initial enantiomeric excess is a generally applicable strategy to shorten the deracemization time and to select the desired handedness. This approach is also convenient in terms of productivity, as we presented in our previous computational and experimental works.[11,17] These results show how, when

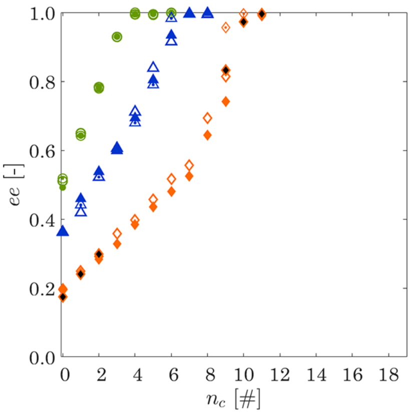


Figure 3. Evolution of the CPG *ee* as a function of the number of cycles, n_c, for increasing ee_0 in experiments c3 (0.20, orange symbols), c2 (0.36, blue symbols), and c1 (0.50, green symbols). Different symbols of the same color represent experimental repetitions under the same operating conditions. The black-filled symbols correspond to an additional repetition performed to verify that the sampling procedure does not affect the measurement of the process evolution.

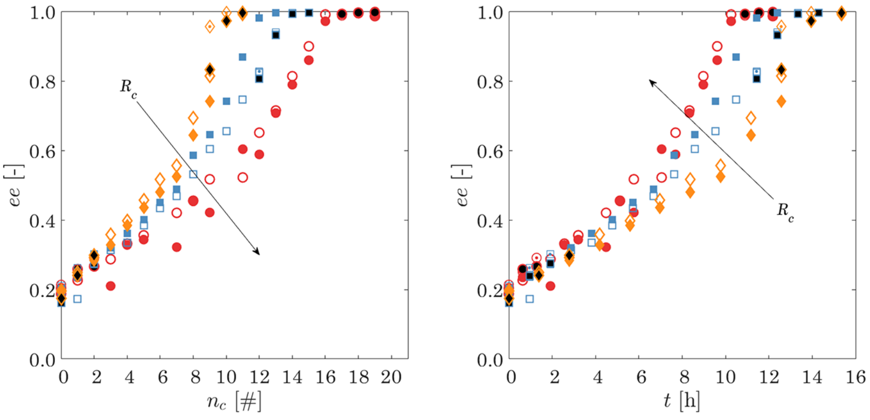
the ee_0 is large, the reduction of the number of cycles to achieve enantiopurity (i.e., the total process time) compensates for the product (pure enantiomer) invested to generate the desired initial enantiomeric excess, and high productivity is retained. It is worth noting that this amount of enantiopure material would not be wasted in the framework of an industrial process because it would be obtained from the product of the previous deracemization batch and would be recovered at the end of the current batch to be used in the next one.

3.2. Cooling Rate. Our previous work showed how the cooling rate affects the deracemization of NMPA.[11] The experimental trends confirmed by simulation results of our group[5] indicate that with increasing cooling rate the number of cycles to achieve deracemization increases. Meanwhile, the process time decreases with higher cooling rates, approaching a minimum given by the interplay between the changes in the number of cycles and the cycle duration (see Figure 5 in ref 5). The cooling rate value corresponding to this minimum is obviously system-dependent. Therefore, the experimental trends depend whether the cooling rate values explored for the specific system considered are to the right or the left of the minimum.

To investigate whether the deracemization of other compounds follows the same trends, we performed experiments with CPG and tLEU at cooling rates of 0.22, 0.43, and 1.30 °C/min in experiments c3, c4 and c5 and experiments t3, t4, and t5, respectively. Figures 4a and 5a show the evolution of the enantiomeric excess as a function of the number of cycles during these experiments for CPG and tLEU, respectively. In both cases, the number of cycles to achieve deracemization increases with the cooling rate: from about 10 to 13 and 16 cycles for CPG and from 7 to 10 and 14 cycles for tLEU. This trend suggests, as for NMPA, that at a low cooling rate the system stays close to equilibrium, since crystal growth quickly compensates for the supersaturation generated, and the racemization reaction keeps the solution composition close to racemic. On the contrary, for high cooling rates, the buildup of large supersaturation levels keeps the system far from equilibrium, thus promoting not only the growth and secondary nucleation of the desired enantiomer but also that of the counterenantiomer, hence leading to more cycles to achieve deracemization.

When we look at the deracemization time (Figures 4b and 5b), we observe that CPG follows the same trend as NMPA, i.e., the process time decreases with increasing cooling rate. This trend is due to the shortening of the cycle time in combination with the number of cycles to achieve enantiopurity, leading to a shorter absolute deracemization time. For example, in experiment c4 about 20 min is saved every cycle with respect to experiment c3 because of the shorter cooling ramp.

In the case of tLEU, when the cooling rate increases, the process time increases, similarly to the number of cycles. This result derives from the short cycle duration, due to the temperature range chosen, as a consequence of the steep solubility curve of tLEU (see section 3 and eq 1). The cycle time differs by only 10 and 5 min between experiments t3 and t4 and experiments t4 and t5, respectively. This small difference is not enough to compensate for the increase in the number of cycles in going from experiment t3 to t4 to t5



(a) (b)

Figure 4. Evolution of the CPG *ee* with (a) the number of cycles and (b) time at increasing cooling rate in going from experiment c3 (0.22 °C/min, orange markers) to c4 (0.43 °C/min, blue markers) to c5 (1.30 °C/min, red markers). Different symbols of the same color represent experimental repetitions under the same operating conditions. The black-filled symbols correspond to an additional repetition performed to verify that the sampling procedure does not affect the measurement of the process evolution.

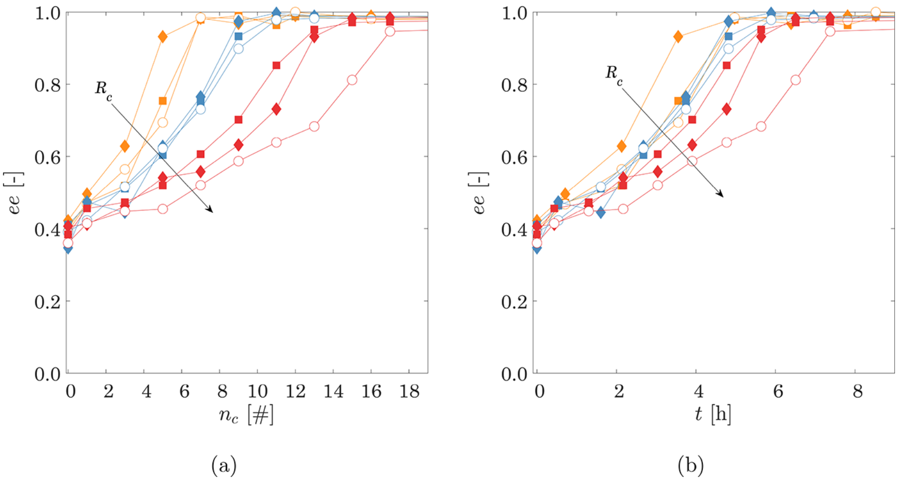


Figure 5. Evolution of the tLEU *ee* with (a) the number of cycles and (b) time at increasing cooling rate in going from experiment t3 (0.22 °C/min, orange symbols) to t4 (0.43 °C/min, blue symbols), to t5 (1.30 °C/min, red symbols). Different symbols of the same color represent experimental repetitions under the same operating conditions. The lines are guides to the eye.

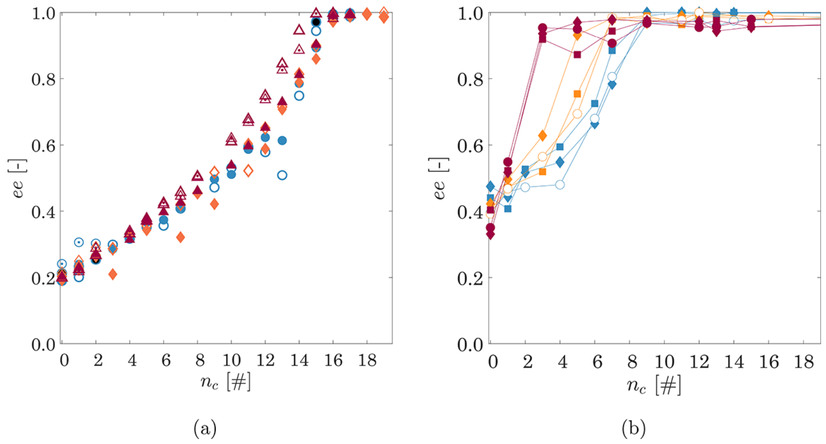


Figure 6. Evolution of the *ee* with the number of cycles for (a) CPG (experimental series c) and (b) tLEU (experimental series t) at increasing minimum temperature in going from experiment 6 (20 °C, blue symbols) to c5 and t3 (25 °C (c), 28 °C (t), orange symbols) to 7 (30 °C (c), 36 °C (t), red symbols). Different symbols of the same color represent experimental repetitions under the same operating conditions. The black-filled symbols correspond to an additional repetition performed to verify that the sampling procedure does not affect the measurement of the process evolution. The lines are guides to the eye.

and to invert the trend as a function of the cooling rate, in the same way as in the case of NMPA and CPG. Therefore, the difference in the behaviors of the three substances is related to the variation of the cycle duration among experiments as well as to system-specific kinetics.

3.3. Temperature Range.

A further effect investigated in this work is that of the operating temperature range. Operating in a temperature range that fulfils the condition stated by eq 1 but at higher temperature levels implies operating under similar thermodynamic conditions but different kinetic conditions, if the kinetics of the several phenomena involved are indeed significantly temperature-dependent. Moreover, because of nonlinearity of the solubility curve, for a given Δc the temperature difference ΔT becomes smaller when the temperature range shifts to higher values. The cycle duration decreases accordingly, and deracemization is accomplished in a shorter time. Such a benefit resulting from operating at higher temperature might be unattainable in a case where the compound exhibits thermal lability.

In our previous work, we found that higher temperature levels enhance the deracemization of NMPA as a result of the fast racemization, growth, and dissolution kinetics promoted at high temperature.[11]

Once again, we perform similar experiments with CPG and tLEU to identify the possible roles of different system kinetics. The choice of the temperature ranges follows the same principle as for the experiments with NMPA and is described at the beginning of this section, while the values for each experiment are reported in Table 2.

Experiments c5, c6, and c7 with CPG indicate that the kinetics of the phenomena responsible for the deracemization process do not vary to a great extent among the three experiments since the evolution of the enantiomeric excess overlaps in these cases and enantiopurity is attained in about 15 cycles (Figure 6a). This behavior suggests a weak temperature dependence of the CPG kinetic parameters, at least in the range investigated, which is suitable for the process (20−45 °C).

The outcome differs for the deracemization of tLEU, which presents the same trend as for NMPA: the number of cycles needed to obtain the desired enantiomer decreases from 9 to 7 to 6 as the temperature range shifts to higher values in going

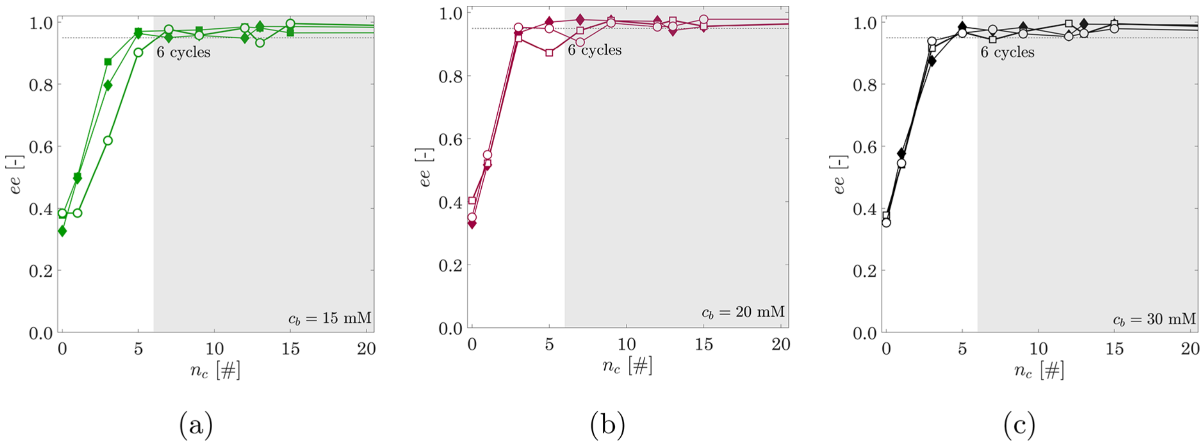


Figure 7. Evolution of the tLEU *ee* with the number of cycles for increasing DBU concentration, c_b: (a) experiment t8; (b) experiment t7; (c) experiment t9. The lines are guides to the eye.

from experiment t6 to t3 to t7 (Figure 6b). In this case, the kinetic parameters reveal a noticeable temperature dependence, which one can exploit in the design of a faster deracemization process for this compound.

This approach can be generalized and applied to any compound exhibiting a significant temperature dependence of its kinetic parameters. However, preliminary information on the effect of temperature on the diverse phenomena occurring during the process as well as the thermal stability of the species involved is relevant to understand whether this approach can indeed improve the overall process performance for a specific application.

3.4. DBU Concentration. The effect of the racemization kinetics can be investigated by varying the concentration of the catalyst responsible for the reaction, DBU, while all of the other operating conditions are kept constant. With this approach we previously showed that the deracemization rate of NMPA increases as the racemization rate increases.[12] We repeat similar experiments with tLEU as a model compound to verify whether this is always true.

The deracemization process runs for about six cycles to reach enantiopurity in experiments t8, t7, and t9, in which the concentration of DBU increases from 15 to 20 to 30 mM, respectively (Figure 7). The absence of substantial differences in the evolution of the enantiomeric excess indicates that the racemization reaction is not the rate-limiting phenomenon for tLEU. In fact, the racemization rate constant for tLEU is about 1 order of magnitude larger than that for NMPA,[9,12] suggesting that the racemization kinetics of tLEU is fast enough with respect to the growth kinetics that no benefit is gained by increasing the standard DBU concentration.

Thanks to the comparison with another compound, we have shown that the effect of the catalyst concentration depends on the specific system considered. According to the extent of this effect, the catalyst concentration can be either increased to accelerate the deracemization process or reduced to ensure a lower chance of product contamination with the catalyst itself or with byproducts of possible side reactions.

4. DISCUSSION AND CONCLUSIONS

Let us consider a new conglomerate-forming compound for which a suitable racemizing agent exists. Let us assume that we intend to deracemize it by implementing the temperature cycles process. Let us also assume that the solubility of the compound in the selected solvent is available or can be easily measured. The question that we would like to address is how to select the operating conditions of an experiment aimed at checking the feasibility. It should be noted that there are eight quantities to be assigned: (i) the initial enantiomeric excess, (ii) the suspension density at the minimum temperature, (iii) the fraction of solid dissolved during every cycle (proportional to Δc in eq 1), (iv) the duration of the isothermal steps, (v) the heating rate, (vi) the cooling rate, (vii) the minimum temperature, and (viii) the catalyst concentration. This is not a task that can in principle be tackled through either a model-based approach (which would require lengthy characterization of many different mechanisms; see ref 5 for details) or a model-free approach (which might require exploring too broad a design space).

In this paper we propose a model-free approach supported by the experience gained with the compounds discussed above. In particular, we describe how to effectively structure the screening experimental campaign by carrying out a few experiments around a benchmark case that is chosen as indicated in the following. The choice of the values specified below is suitable for this lab-scale investigation, which aims at understanding the features of the process rather then designing a highly productive industrial process. The values of some operating parameters might need to be adjusted depending on the specific equipment available and the objective of the study, particularly in the case of large-scale setups.

In the first step, the first five operating parameters are chosen once and for all on the basis of experience. They are not critical even when their choice is suboptimal:

(i) A high value of the initial enantiomeric excess ee_0, typically 40%, is chosen to speed up the individual experiments and the whole screening procedure.

(ii) The suspension density at the minimum temperature is chosen to be 2–3% for good processability (good suspension and easy sampling) and low compound utilization.

(iii) Accordingly, the fraction of solid dissolved during every cycle is chosen to be about 30% of the whole amount of suspended solid; this avoids reaching complete dissolution at high temperature and provides enough crystal surface for growth during cooling.

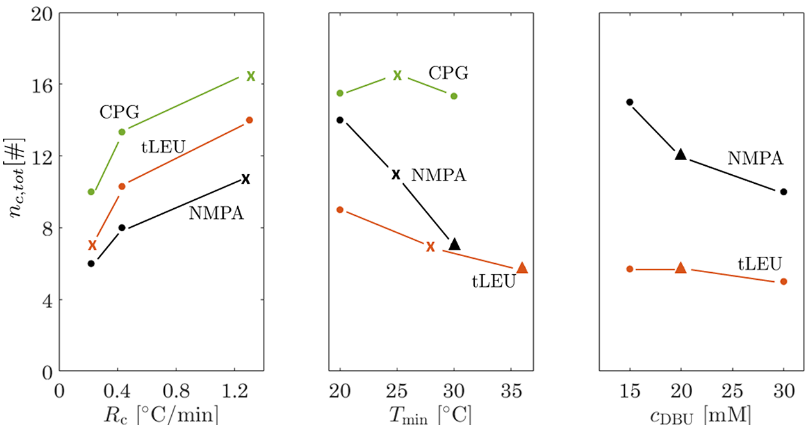


Figure 8. Effects of the cooling rate (left), the minimum temperature (middle), and the DBU concentration (right) on the total number of cycles, $n_{c,tot}$, to attain the deracemization of NMPA (black symbols), CPG (green symbols), and tLEU (orange symbols). The numbers of cycles are obtained mean values of three repetitions carried out under the same indicated experimental conditions. The reference cases are reported with cross symbols (and triangles for the study of the effect of c_b). The lines are guides to the eye.

(iv) The duration of the isothermal steps, usually 10 min, is chosen to let the suspension equilibrate at the new temperature without increasing the cycle time too much.

(v) Similarly, the heating rate is chosen to be around 1 °C/min to keep the cycle time short and also to ensure an effective and constant heating profile, depending on the equipment used.

In the second step, the value of the other three operating parameters in a reference experiment (× symbols in Figure 8) are selected, while keeping in mind that they are critical and a few experiments where their values are varied with respect to the reference case will be needed (see again Figure 8 for an example involving NMPA, CPG, and tLEU). The choice of the reference values is based on the following considerations:

(vi) The choice of the cooling rate is the outcome of a compromise between the willingness to keep the cycle time short and the need to avoid nucleation (if cooling is too fast and supersaturation is not depleted by growth fast enough): it is a difficult choice that might need a couple of trials (in the case of CPG and NMPA 1.30 °C/min was selected, while for tLEU 0.22 °C/min was preferred, since with a small ΔT the cycle time was already short enough).

(vii) The minimum temperature is selected close to ambient temperature (25 °C for NMPA and CPG, and 28 °C for tLEU) to facilitate the operations before, during, and after the experiments and to minimize compound degradation.

(viii) The catalyst concentration should preferably be low to limit product contamination and costs but high enough to enable a fast and reproducible process. This value is not easy to predict either, and in all of the cases above we selected a DBU concentration of 20 mM.

Once the reference case is defined and verified to be feasible (deracemization is indeed achieved), then the last three parameters can be varied in a reasonable range to understand how they affect the deracemization performance. This is illustrated in Figure 8 in terms of the number of cycles required for deracemization for the three compounds considered here (for NMPA and tLEU seven experiments are considered, while only five are considered for CPG). From the results obtained, one can draw conclusions about which operating parameter should be preferably tuned to improve the process performance the most and the extent to which the cooling rate has a major quantitative effect on the number of cycles (while the qualitative effect is clear). For example, in the case of NMPA the catalyst concentration has a stronger effect than the temperature level, while the latter is more effective than the former in the case of tLEU. Such empirical exploration of the design space of a complex process for a new compound allows for two things. First, it gives a first though very important impression of how effective temperature cycles are in deracemizing the new compound (compared to other compounds for which data already exist[4,13−15]). Second, it provides insight about how to further improve the deracemization performance by varying what and how in the design space of the process. It is worth underlining once more that deracemization via temperature cycles is a robust, simple, and versatile process that deserves to be considered for applications. This work has provided new experimental evidence of this plus an effective protocol to design such a process for a new chiral compound of interest.

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Notes

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