Efficient Havinga–Kondepudi resolution of conglomerate amino acid derivatives by slow cooling and abrasive grinding†

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The complete resolution of the conglomerate racemates of two amino acid derivatives susceptible to racemization in solution was achieved by slow crystallization from a supersaturated solution accompanied by cooling and abrasive grinding.

Nearly 70 years ago, Havinga demonstrated that the chiral quaternary ammonium salt 1, which racemizes in solution and crystallizes as enantiopure crystals of opposite handedness, i.e. as a conglomerate, deposited large single crystals of high enantiomeric purity on slow undisturbed crystallization from a supersaturated stagnant solution. The process is illustrated schematically in Scheme 1 and explained in the caption.

Over the years many other examples of “racemizing conglomerates” which are chiral by conformation or configuration have been crystallized into the enantiomerically pure form.

Kondepudi, in 1990, carefully analyzed an analogous process based on NaClO3, a conglomerate when crystalline. Although intrinsically achiral, NaClO3 crystallizes in the chiral space group P212121 and thus forms enantiomorphous crystals. However, instead of crystallization from stagnant or gently agitated solution (Scheme 1), in this case efficient stirring resulted in the formation of an enantiomerically pure solid phase of random absolute configuration. The proposed mechanism of this resolution is depicted and explained in Scheme 2. Kondepudi found that if the solution is not stirred, the supersaturation is not consumed efficiently and primary nucleation of the other enantiomer will be observed, resulting in both enantiomeric crystals rather than a stochastic choice for a single chiral solid phase.

We describe here, application of these principles to the crystallization of the imine of 2-methylbenzaldehyde and phenylglycine amide (2) from solution (Scheme 3). (R)-Phenylglycine amide is an important chiral building block used in the enzymatic synthesis of semi-synthetic β-lactam antibiotics.

Scheme 1 Deracemization of allylethylmethylanilinium iodide (1) by slow crystallization from chloroform as performed by Havinga. An undersaturated solution (situation I) is cooled or evaporated to a point where both enantiomers are slightly supersaturated (situation II). The absolute configuration of the first crystal formed on primary nucleation is determined randomly and is arbitrarily illustrated for the (S)-enantiomer (situation III). This (S)-crystal consumes the supersaturation of the (S)-enantiomer in the surrounding liquid and as a result of racemisation in solution also the supersaturation of the (R)-enantiomer (situation IV).
the temperature reached 20 °C. A magnetic stirrer, with or without the addition of glass beads, was then used to stir the solution (situation II). In situation III, the temperature was raised to 70 °C and then cooled to 20 °C at a rate of 0.5 °C min⁻¹. This process was repeated until a supersaturated solution of NaClO₃ was obtained by further evaporation of the solvent (situation IV). The supersaturation of the undesired enantiomer cannot be consumed fast enough by the grinding action of the stirrer. More intense grinding by the addition of the glass beads leads to higher ee's as expected by the mechanism where a greater crystal surface can consume the supersaturation of the unwanted enantiomer more readily.

![Scheme 2](Image 82x594 to 250x725)

**Scheme 2** Kondepudi deracemization of achiral NaClO₃ by evaporation and grinding. Starting with situation I where the NaClO₃ is completely dissolved, the solvent is slowly allowed to evaporate to produce a supersaturated solution of NaClO₃ (situation II). In situation III, by primary nucleation one enantiopure crystal of random handedness has formed (the (S)-enantiomer in this example). In contrast to the Havinga resolution, this first crystal is ground down by a magnetic stirrer, producing multiple crystals of the same handedness with a larger combined surface than the single crystal. Larger crystal surface leads to faster consumption of the supersaturation by secondary nucleation. Higher yields can be obtained by further evaporation of the solvent (situation IV).

![Scheme 3](Image 139x384 to 193x450)

**Scheme 3** Racemizable conglomerate amino acid derivative 2.

![Scheme 4](Image 378x542 to 480x592)

**Scheme 4** Racemizable conglomerate 3 and alanine 4.

Far from equilibrium conditions. The isothermal process is efficient but, despite many improvements, still time consuming.

We have developed an optional deracemization procedure based on combination of the Havinga and Kondepudi deracemization. This is applicable to 2 and other conglomerates. Controlled cooling and abrasive grinding were combined during the crystallization of conglomerate 2 under racemizing conditions starting from a homogenous solution. This approach led to complete conversion to enantiomerically pure material without seeding in a rapid and easy to perform process readily carried out on a multigram scale. Racemization in solution was again catalyzed by DBU.

The following process is representative. A clear, homogenous solution of 6.0 g racemic 2 in MeCN in the presence of 30 mol% DBU at 70 °C was cooled with temperature programming to 20 °C. Throughout the experiment, the mixture was vigorously stirred by a magnetic stirrer, with or without the addition of glass beads. Once the temperature reached 20 °C, the solids were collected immediately. These were washed and the ee determined by chiral HPLC. The results of these experiments are given in Table 1. The average yield of 2 was 76% in these experiments.

An optimal result (entry 2, with glass beads) can be obtained within 50 min. As expected, the cooling rate is of great importance to the success of the resolution. If cooling is too fast, apparently the supersaturation of the undesired enantiomer cannot be consumed fast enough by the grinding action of the stirrer. More intense grinding by the addition of the glass beads leads to higher ee's as expected by the mechanism where a greater crystal surface can consume the supersaturation of the unwanted enantiomer more readily.

![Table 1](Image 103x747 to 193x910)

**Table 1** Deracemization of 2 by crystallization and secondary nucleation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cooling rate °C min⁻¹</th>
<th>Stirrer ee (%)</th>
<th>Glass beads ee (%)</th>
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<td>25</td>
<td>85</td>
</tr>
<tr>
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<td>99</td>
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<tr>
<td>4</td>
<td>0.05</td>
<td>&gt;99</td>
<td>&gt;99</td>
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Notes and references


