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.[1] 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[2] or configuration[3] have been crystallized into the enantiomerically pure form.

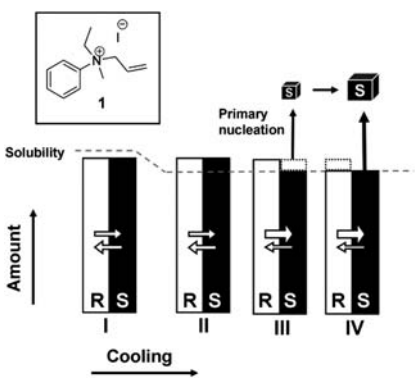
Kondepudi, in 1990, carefully analyzed an analogous process based on $NaClO_3$, a conglomerate when crystalline.[4] Although intrinsically achiral, $NaClO_3$ crystallizes in the chiral space group $P2_13$ and thus forms enantiomorphous crystals. However, instead of crystallization from stagnant or gently 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.[5]

Compound **2** was identified as a conglomerate from a series of 19 imines of various mono-substituted benzaldehydes and phenylglycine amide, using differential scanning calorimetry (DSC), Raman spectroscopy, X-ray powder diffraction (XRPD) and second harmonic generation (SHG).[6] The space group is $P2_12_12_1$ (see ESI†). In addition to the 2-methyl substituted compound **2**, also the corresponding 2-fluoro and 2-chloro derivatives showed conglomerate behavior but have not been examined further. Imine **2** was racemized by various organic bases. For example, racemisation with 10 mol% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol occurred with $t_{1/2} < 2$ min.[7a]

Consistent with expected behaviour of a conglomerate sensitive to racemization crystallisation with cooling of a 4 wt% solution of racemic **2** from toluene with 1 mol% DBU seeded with 5 mol% of ground (*R*) or (*S*)-crystals at the saturation temperature resulted in the formation of solid (*R*) or (*S*)-**2**, respectively, in 84 and 86% yield and enantiomeric excess (ee) > 98%. Corrected for rest solubility at room temperature and washing losses the crystallisation yield was almost quantitative.

Recently we also demonstrated that racemic **2** can be brought to enantiomeric purity under isothermal conditions by grinding of a saturated solution (in which racemization occurs) in contact with the solid crystals at ambient temperature.[7] In this case an explanation based on attrition induced Ostwald ripening was proposed.[8] Because this process operates under near equilibrium conditions in saturated solution it differs fundamentally from the kinetic crystallization by secondary nucleation from a seeded supersaturated solution under



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[1c] 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).

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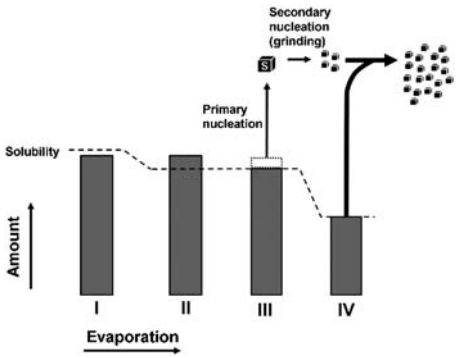
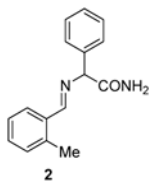


Scheme 2 Kondepudi deracemization of achiral $NaClO_3$ by evaporation and grinding. Starting with situation I where the $NaClO_3$ is completely dissolved, the solvent is slowly allowed to evaporate to produce a supersaturated solution of $NaClO_3$ (situation II). In situation III, by primary nucleation 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 Racemizable conglomerate amino acid derivative **2**.

far from equilibrium conditions. The isothermal process is efficient but, despite many improvements,[7b,c] 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.

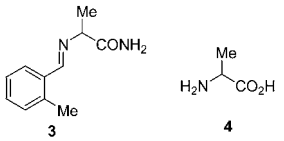
The following process is representative. A clear, homogenous solution of 6.0 g racemic **2** in MeCN in the presence of 30 mol% DBU at 70 °C was cooled with temperature programming to 20 °C. Throughout the experiment, the mixture was vigorously stirred by a magnetic stirrer, with or without the addition 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

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

Entry	Cooling rate °C min^{-1}	Stirrer[a] ee (%)[c]	Glass beads[b] ee (%)[c]
1	2.0	25	85
2	1.0	76	>99
3	0.5	83	99
4	0.05	>99	>99

[a] Magnetic stirring at 1250 rpm without glass beads. [b] Magnetic stirring at 1250 rpm with glass beads. [c] Enantiomeric excess.



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

expected by the mechanism where a greater crystal surface can consume the supersaturation of the unwanted enantiomer more readily.

Even at the highest cooling rate (entry 1, 2.0 °C min^{-1}) and stirring without glass beads, a significant ee of 25% was found. Note that by stirring the latter experiment at 20 °C for prolonged time, enantiopure material will be found because of attrition enhanced Ostwald ripening where particles with low volume are consumed by the growth of particles with a larger volume.[2,7,8]

Although one would expect a random outcome for the absolute configuration of the product, out of 12 experiments, 11 resulted in the (*R*)-enantiomer. In more than 200 isothermal grinding experiments carried out under isothermal Ostwald ripening conditions the (*R*)-enantiomer was always observed.[6] We have proposed that this is the result of an undetectable amount of a chiral impurity that blocks the growth and/or nucleation of (*S*)-enantiomer crystal by means of the rule of reversal.[9] The present procedure, which involves crystallization from supersaturated solution, appears to be slightly less sensitive to this effect.

Deracemization of another racemic conglomerate **3** (Scheme 4) was also successful when the same procedure as above was performed with a cooling rate of 0.05 °C min^{-1} and with the addition of glass beads for grinding. A single experiment was performed which delivered the (*R*)-enantiomer in >99% ee. The direction of this resolution could be steered by the addition of a closely structurally related compound, alanine (**4**). Addition of 4.6 mol% natural (*R*)-**4** to the above procedure gave optical pure (*S*)-**3** in the solid phase. Likewise, (*S*)-**4** delivered optical pure (*R*)-**3**, as would be expected from the rule of reversal.

Essentially the procedure described here has recently been used for deracemization of an intermediate in the synthesis of Clopidogrel.[10]

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