Chiral Resolution

DOI: 10.1002/anie.200806214

Complete Chiral Resolution Using Additive-Induced Crystal Size Bifurcation During Grinding**

Wim L. Noorduin, Pim van der Asdonk, Hugo Meekes, Willem J. P. van Enckevort, Bernard Kaptein, Michel Leeman, Richard M. Kellogg, and Elias Vlieg*

Chiral molecules that crystallize as separate solid phases, that is, racemic conglomerates, can in principle be resolved by manually sorting the crystals, as Louis Pasteur demonstrated for a tartrate salt.[1] Although enantioselective seeding of a clear supersaturated solution provides the desired enantiomer more readily, careful control of the experimental conditions is required to prevent nucleation of the opposite enantiomer.[2] This resolution process can be improved further by using enantiopure additives that hamper the crystallization of the unwanted enantiomer.[3]

Recently, abrasive grinding has been used to obtain a single chiral solid phase from an initially racemic mixture of conglomerate crystals in contact with a solution in which the molecules racemize or are achiral.[4] Although the execution of this process is remarkably simple, the requirement for an intrinsically chiral molecule that both crystallizes as a conglomerate and also racemizes in solution can be difficult to fulfill.

Herein we demonstrate for a racemic conglomerate of a derivative of the natural amino acid alanine that, even in the absence of racemization, a solid phase of single handedness can be isolated by applying abrasive grinding if the saturated solution contains a well-chosen chiral additive. This provides a robust route to enantiomerically pure materials without depending on the often unpredictable nucleation behavior of both solid phases and without having to apply (often severe) conditions for racemization.

Second harmonic generation and X-ray powder diffraction experiments recently revealed that the imine of 2-methylbenzaldehyde and alanine amide **1** (Figure 1) crystallizes as a racemic conglomerate.[4h,5] Single-crystal X-ray diffraction showed that the space group is $P2_12_12_1$. This crystal structure is suitable for the use of growth inhibitors, as the four symmetry-related and thus differently oriented molecules ensure that many crystal surface orientations have similar structures on opposite sides of the crystal.

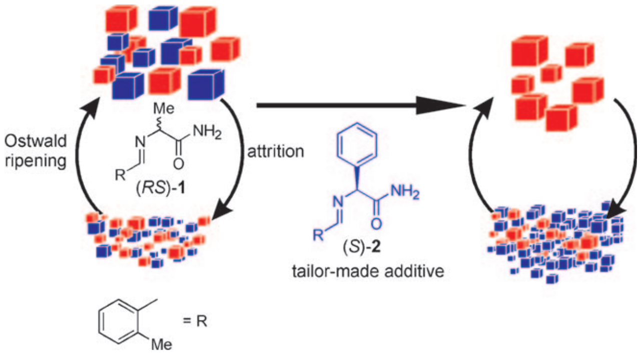

Figure 1. Dissolution and growth of racemic conglomerate crystals during continuous ablation of the crystals. Adding the enantiopure additive (*S*)-**2** stereoselectively hampers the growth of (*S*)-crystals (blue) of the same handedness. These crystals thus become smaller and the population of larger crystals becomes monopolized by the unhampered (*R*)-enantiomer (red). The two size populations shown separately are in reality completely mixed.

From the crystal structure (Figure 2), it follows that the α position occupied by the methyl group in **1** is a suitable

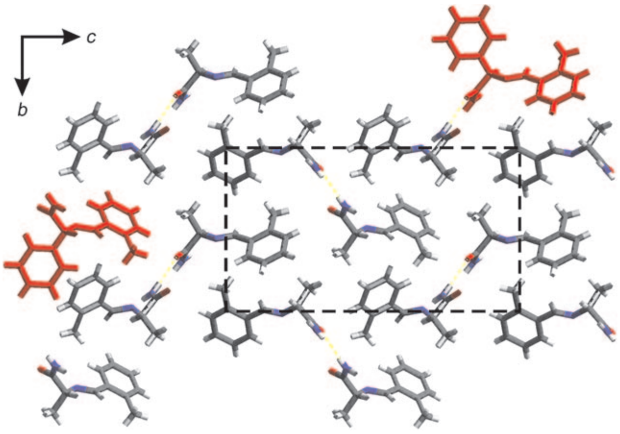

Figure 2. Crystal structure of **1** viewed along the [100] direction. The unit cell is indicated by the dashed lines. Two molecules of **1** have been replaced by tailor-made additive molecules **2** (in red) on two crystal surface orientations, indicating hampering of the growth as a result of the protruding phenyl groups at the α position. Atoms: C gray, O red, N blue, H white.

---

[*] W. L. Noorduin, P. van der Asdonk, Dr. H. Meekes,
Dr. W. J. P. van Enckevort, Prof. Dr. E. Vlieg
IMM Solid State Chemistry, Radboud University Nijmegen
Heyendaalseweg 135, 6525 AJ Nijmegen (The Netherlands)
Fax: (+31) 24-365-3067
E-mail: e.vlieg@science.ru.nl
Dr. B. Kaptein
Innovative Synthesis & Catalysis, DSM Pharmaceutical Products
PO Box 18, 6160 MD Geleen (The Netherlands)
M. Leeman, Prof. Dr. R. M. Kellogg
Syncom BV
Kadijk 3, 9747 AT Groningen (The Netherlands)

[**] J. M. M. Smits is acknowledged for performing the X-ray single-crystal determination. The SNN agency (Cooperation Northern Netherlands) and the European Fund for Regional Development (EFRO) are acknowledged for partial financial support of this work.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200806214.

position for the growth-inhibiting substituent of the tailor-made additive, as it is exposed on virtually all crystal surfaces. We chose a phenyl group as the substituent in a potential inhibitor, leading to compound **2**. Figure 1 depicts the process of grinding solution–solid mixtures of **1** using glass beads in the presence of the enantiopure additive **2**. Samples of the solid phase were collected using filtration, followed by a washing step to dissolve the smallest crystals. The enantiomeric excess (*ee*) of the collected solid phase evolves to the enantiopure state for the system containing the additive (Figure 3). Solution–solid mixtures ground in the presence of the additive (*R*)-**2** or (*S*)-**2** were inexorably enriched in the solid phase in (*S*)-**1** and (*R*)-**1**, respectively.[6,7] As expected, in the absence of the additive, the solid phase remained racemic (not shown).

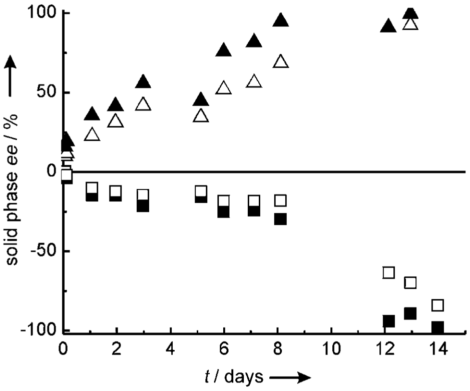

Figure 3. Evolution of the solid-phase enantiomeric excess during abrasive grinding of racemic **1** in the presence of 16.5 mol% enantiopure **2**. Positive *ee* values are assigned to (*S*)-**1**. Triangles: flasks containing (*R*)-**2**, squares: flasks containing (*S*)-**2**; open symbols: *ee* before washing, filled symbols: *ee* after washing.

During the ablation of the crystalline phase, small fragments dissolve, nurturing the growth of the larger crystals, a process called Ostwald ripening (Figure 1).[8] The continuous process of growth and ablation results in a steady-state for the crystal size distribution (CSD). If an additive stereoselectively hampers the growth, the CSD shifts towards smaller sizes for that enantiomer. The enantioselective hampering follows the "rule of reversal", that is, the additive (*R*)-**2** blocks (*R*)-**1**, resulting in a monopolization of large (*S*)-**1** crystals and vice versa.[3b] The effectiveness of the hampering depends, in addition to the additive itself, on its concentration in solution and the total crystal surface area to be blocked.

It should be noted that in the absence of the washing step, the enantioenrichment is less effective, although the yield in solids would be larger.[9] Not all small crystal fragments of the hampered enantiomer will pass the filter in that case, resulting in a smaller enantiomeric excess in the solid phase. Applying the washing step dissolves the small crystals, leaving the large crystals on the filter.

Crystallization in combination with tailor-made additives as a route to enantiopure materials has been used before.[3] Herein we have merged the use of tailor-made additives with the recently extensively studied technique of abrasive grinding.[4] In summary, we have demonstrated a chiral resolution technique based on additive induced asymmetric bifurcation in the crystal size distribution under near-equilibrium abrasive grinding conditions. In comparison with preferential crystallization, this resolution does not depend on the unpredictable nucleation behavior of the enantiomers. This easily applicable method may have profound implications for the screening and the separation of racemic conglomerates, even on an industrial scale, that do not racemize in solution. More generally, we foresee an increasing scope for near-equilibrium solid–liquid grinding as a versatile tool for solid-state chiral purification.

Experimental Section

Typically, (*RS*)-**1** (1.0 g), enantiopure **2** (16.5 mol%, 0.2 g), glass beads (2.5 mm, 8.0 g), and MeCN (20.0 g) were added to a 50 mL round bottom flask and stirred at 600 rpm using a magnetic bar. For sampling, circa 0.2 mL of the slurry was filtrated on a P3 glass filter and washed for 1–2 s with toluene (0.2 mL). Samples were analyzed using H NMR, XRPD, and HPLC (chiralcel AD-H column (250 × 4.6 mm), eluent *n*-hexane/2-propanol, 90/10 v/v%, flow 1 mL min^{-1}, retention times: (*S*)-**1** 7.5 min, (*R*)-**1** 8.2 min, (*R*)-**2** 13.6 min, (*S*)-**2** 15.2 min). For details on the CSD characterization, see the Supporting Information.

Received: December 19, 2008
Revised: February 6, 2009

Keywords: amino acids · chiral resolution · chirality · crystal engineering · grinding

---

[1] L. Pasteur, *C. R. Hebd. Seances Acad. Sci.* **1848**, *26*, 535.

[2] J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolution*, Krieger, Florida, **1994**.

[3] a) L. Addadi, Z. Berkovitch-Yellin, N. Domb, E. Gati, M. Lahav, L. Leiserowitz, *Nature* **1982**, *296*, 21; b) L. Addadi, S. Weinstein, E. Gati, I. Weissbuch, M. Lahav, *J. Am. Chem. Soc.* **1982**, *104*, 4610; c) I. Weissbuch, M. Lahav, L. Leiserowitz, *Cryst. Growth Des.* **2003**, *3*, 125.

[4] a) C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504; b) P. S. M. Cheung, J. Gagnon, J. Surprenant, Y. Tao, H. Xu, L. A. Cuccia, *Chem. Commun.* **2008**, 987; c) W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 1158; d) W. L. Noorduin, H. Meekes, W. J. P. van Enckevort, A. Millemaggi, M. Leeman, B. Kaptein, R. M. Kellogg, E. Vlieg, *Angew. Chem.* **2008**, *120*, 6545; *Angew. Chem. Int. Ed.* **2008**, *47*, 6445; e) B. Kaptein, W. L. Noorduin, H. Meekes, W. J. P. van Enckevort, R. M. Kellogg, E. Vlieg, *Angew. Chem.* **2008**, *120*, 7336; *Angew. Chem. Int. Ed.* **2008**, *47*, 7226; f) C. Viedma, J. E. Ortiz, T. de Torres, T. Izumi, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 15274; g) S. B. Tsogoeva, S. Wei, M. Freund, M. Mauksch, *Angew. Chem.* **2009**, *121*, 598; *Angew. Chem. Int. Ed.* **2009**, *48*, 590; h) M. Leeman, W. L. Noorduin, B. Kaptein, E. Vlieg, H. Meekes, W. van Enckevort, K. Zwaagstra, J. M. de Gooijer, K. Boer, R. M. Kellogg, submitted; i) C. Viedma, *Astrobiology* **2007**, *7*, 312; j) J. H. E. Cartwright, O. Piro, I. Tuval, *Phys. Rev. Lett.* **2007**, *98*, 165501; k) W. L. Noorduin, H. Meekes, A. A. C. Bode, W. J. P. van Enckevort, B.

Kaptein, R. M. Kellogg, E. Vlieg, *Cryst. Growth Des.* **2008**, *8*, 1675.

[5] G. Coquerel, *Top. Curr. Chem.* **2007**, *269*, 1.

[6] The filtrate is enriched in the hampered enantiomer, albeit to a lesser extent than the enrichment in the residue as it depends on the solubility.

[7] XRPD measurements showed no polymorphic transitions upon grinding, and HPLC showed no incorporation of **2** in crystals of **1**.

[8] W. Ostwald, *Lehrbuch der Allgemeinen Chemie*, *Vol. 2*, *Part 1*, Leipzig, Germany, **1896**.

[9] Under the present conditions, including the washing step, the yield of the resolution is approximately 40% based on the pure enantiomer.