Chiral Resolution

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Attrition-Enhanced Deracemization of an Amino Acid Derivative That Forms an Epitaxial Racemic Conglomerate**

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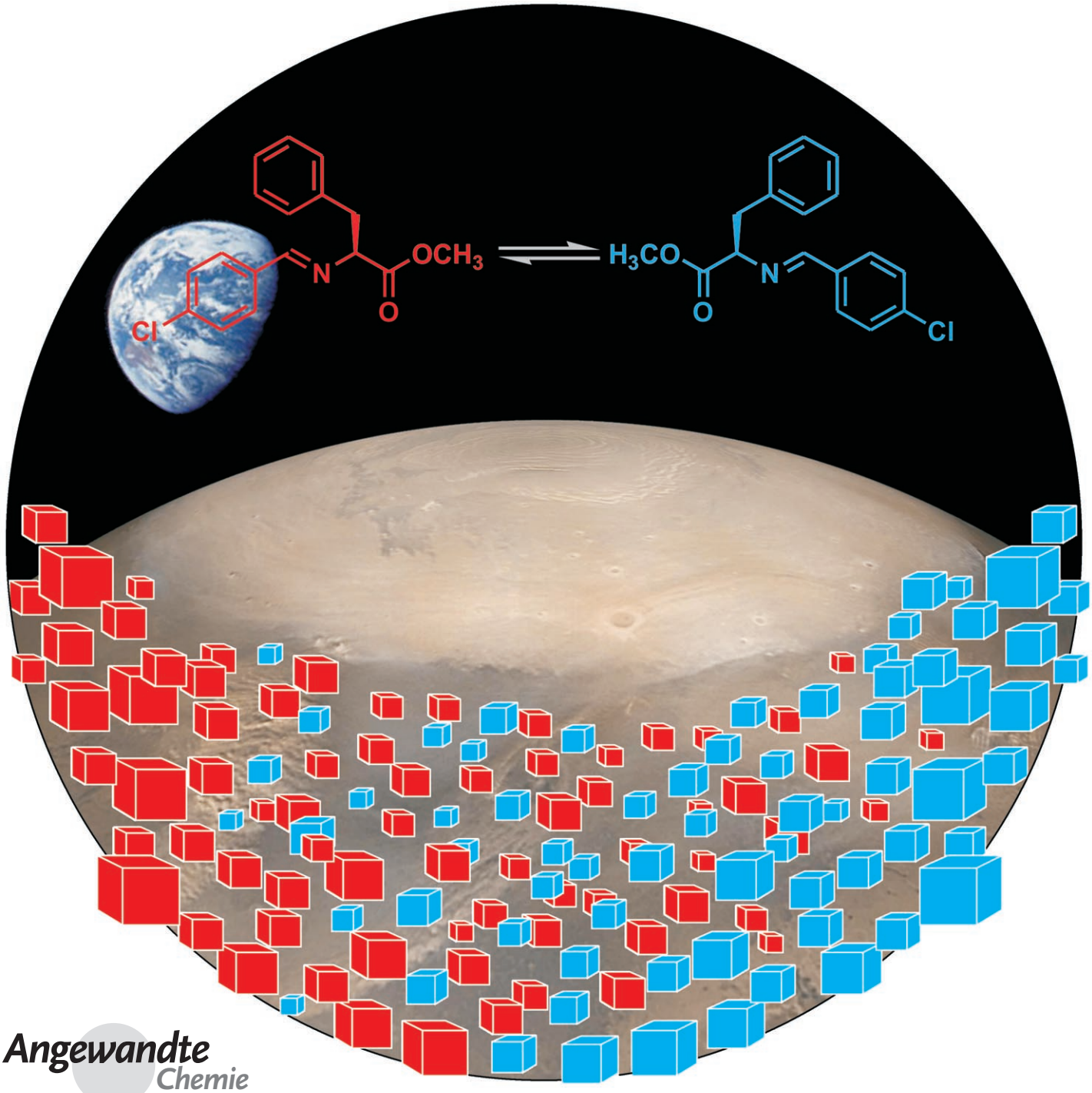
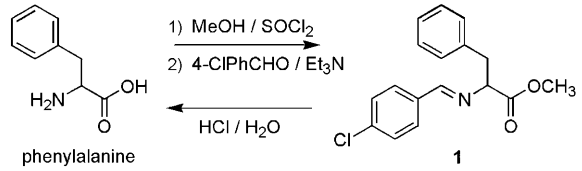


Unraveling the origins of single chirality as found in nature is a fundamental scientific goal. Moreover, such understanding has practical ramifications for the preparation of enantiomerically pure compounds, including pharmaceutical components. Separate *R* and *S* solid phases (known as racemic conglomerates) were the starting point for obtaining enantiomerically pure compounds from racemic mixtures when Pasteur manually sorted the mirror-image crystals of a tartrate salt.[1] In the direct resolution of conglomerates, enantiomers of the desired handedness can be obtained more efficiently by preferential crystallization through enantioselective seeding or by using enantiomerically pure tailor-made additives.[2–5] Although applied on an industrial scale nowadays, the yields in a single operation are limited and often this type of resolution is hampered by mutual epitaxial growth of the enantiomers.[6] In the latter case, enantioselective seeding is of no use.

From this perspective, the recently reported attrition-enhanced complete deracemization of $NaClO_3$ and other achiral salts is of interest, as it occurs under near-equilibrium conditions.[7,8] On application of this abrasive grinding technique to the solid phase of a nearly racemic nonproteogenic amino acid derivative in contact with a saturated solution, in which racemization takes place, the solid phase evolved smoothly to a single chiral end state.[9,10] An explanation for this deracemization process was given in terms of attrition-enhanced Ostwald ripening: the dissolution of small crystals in favor of larger ones.[11–13] Herein, we demonstrate for a conglomerate derivative of the natural amino acid phenylalanine that attrition-enhanced total resolution is possible for a system that exhibits the complication of enantiomeric epitaxial growth. Furthermore, we provide support for the role of Ostwald ripening in this process.

The compound *N*-(4-chlorobenzylidene)phenylalanine methyl ester (**1**), which was synthesized as indicated in Scheme 1, was chosen as the starting material for attrition-enhanced deracemization, as it crystallizes as a conglomerate.[14] Owing to the presence of a relatively acidic hydrogen atom at the α carbon atom of **1**, this compound undergoes ready racemization in solution under basic conditions (pK_a=19.0).[15]



Scheme 1. Synthesis of **1** from phenylalanine.

X-ray crystal-structure determination of single crystals grown from a solution of (*S*)-**1** in isopropyl alcohol revealed that this compound crystallizes in the space group $P2_12_12_1$ (Figure 1; see the Supporting Information). The presence of

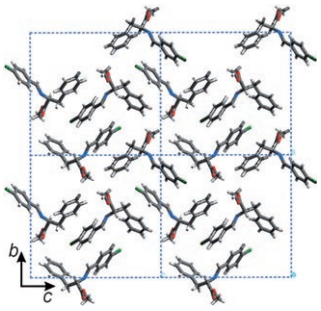


Figure 1. Crystal structure of (*S*)-**1** viewed along the *a* axis.

the relatively heavy chloride atom enabled the assignment of the *S* absolute configuration by anomalous dispersion.[16] Crystals grown from both racemic and enantiomerically pure solutions of **1** were analyzed by X-ray powder diffraction. The two patterns were identical and showed good resemblance to those calculated from the single-crystal structure. However, the analysis by HPLC on a chiral phase of individual crystals grown from the racemic solution revealed these crystals to be almost racemic. This result is inconsistent with expectations for a conglomerate.[17]

We investigated this paradoxical situation further by partial dissolution of the crystals grown from the racemic mixture in a saturated enantiomerically pure solution.[6j,18] The enantioselective dissolution of fragments of the crystal was observed by optical microscopy (Figure 2), which indicated that the crystals are composed of domains of single chirality. A crystal that consists of many domains of chirality, both left- and right-handed, will thus be nearly racemic.

By polarization microscopy and X-ray diffraction, we found that these domains were all well ordered as match-shaped crystallites stacked parallel to the crystallographic [100] direction. The morphology of the resulting mutual epitaxial conglomerate is made up of {100} top faces and {011}

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Supporting information for this article, including experimental details of the synthesis, X-ray crystal-structure analysis, and deracemization of **1**, are given in the supporting information is available on the WWW under http://dx.doi.org/10.1002/anie.200802468.

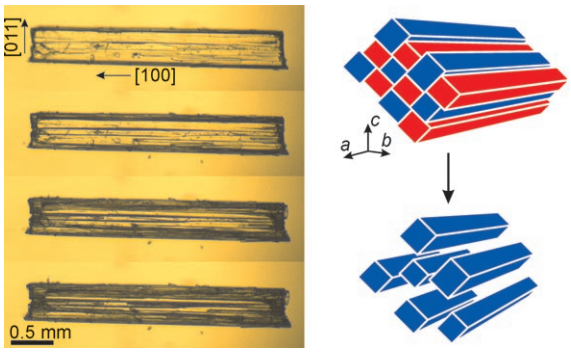
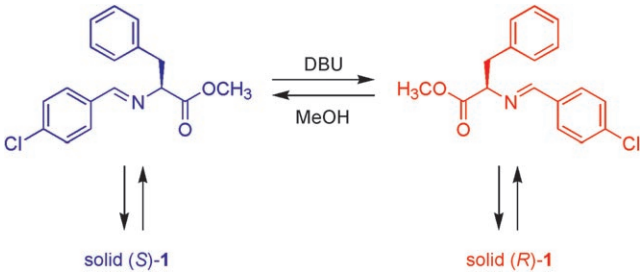


Figure 2. Left: Optical microscopy images showing the partial dissolution of (*RS*)-**1** in a saturated solution of (*S*)-**1** in isopropyl alcohol (time interval between images: 10 min). Right: Schematic representation of the enantioselective dissolution; the enantiomorphs of (*R*)- and (*S*)-**1** are colored red and blue, respectively.

side faces in terms of the crystallographic axes of the individual domains. As the enantiomers crystallize epitaxially on one another, standard resolution by preferential crystallization is not possible.

Intrigued by this challenge, we tried to deracemize these epitaxial conglomerate crystals to give a single chiral solid phase by using the recently developed method of attrition-enhanced Ostwald ripening (Scheme 2).[7,9,10] For these near-equilibrium deracemization experiments, nearly racemic



Scheme 2. Chemical and physical equilibria in the process of attrition-enhanced crystallization/dissolution of **1**. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

mixtures of **1** (3.2 g) were suspended in MeOH (10.0 g) and ground by magnetic stirring (600 rpm) in the presence of glass beads (6.0 g) at ambient temperature. Once the equilibrium between the solution and solid states had been established, the racemization in solution was initiated by the addition of the base DBU (10 mol % with respect to **1**).[19] Samples of the solid were collected over time, and the *ee* value was measured by HPLC. We found that even a slight initial enantiomeric imbalance of 0.35 % *ee* in **1** was sufficient to direct deracemization within 4–5 days to provide the enantiomer initially in excess in enantiomerically pure form in the solid state (Figure 3; see the Supporting Information for the opposite enantiomer). The evolution of the *ee* value of **1** in the solid state with time follows the exponential behavior typical for this process (Figure 3, right), despite the epitaxial behavior.[10,13] Although the rate of racemization of **1** in the solution phase is relatively low ($t_{1/2} \approx 8$ min), the high solubility of

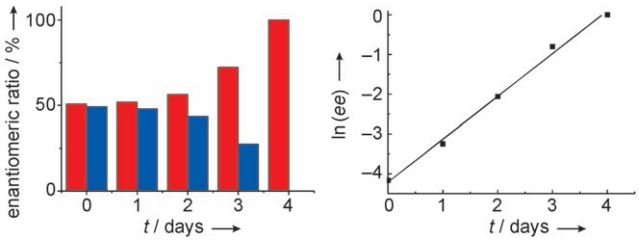


Figure 3. Typical change in the enantiomeric composition of the solid phase during grinding (left; (*R*)-**1**: red bars, (*S*)-**1**: blue bars); this evolution corresponds to an exponential increase in the enantiomeric excess of (*R*)-**1** (right). The initial *ee* value in the solid phase before dissolution is 0.35 %; the *ee* value increases slightly upon dissolution.

racemic **1** of approximately 20 wt % results in a relatively high deracemization rate.[10]

To obtain more insight into the role of Ostwald ripening in the deracemization process, we studied the effect of the initial crystal-size distribution on deracemization. Two enantiomerically pure solution–solid mixtures were prepared and subjected to racemizing conditions. One mixture was ground by glass beads to give many small crystals, whereas the other mixture, which contained the opposite enantiomer, was stirred only gently in the absence of glass beads, so that the crystals remained relatively large. The latter mixture was added to the former, and deracemization was monitored with respect to time. Even mixtures with an initial excess of the enantiomer present as small crystals evolved rapidly to a single chiral solid phase of the enantiomer initially present as large crystals (Figure 4; see the Supporting Information for deracemization to give the opposite enantiomer). These results clearly demonstrate the Ostwald ripening character of this process, whereby large crystals grow at the expense of smaller crystals.

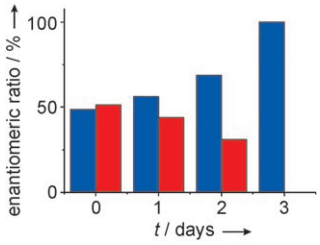


Figure 4. Evolution of the solid-phase enantiomeric ratio of **1**, initially composed of an abundance of small crystals of (*R*)-**1** and a minor population of large crystals of (*S*)-**1**. The small crystals dissolve rapidly and nurture the larger (*S*)-**1** crystals until complete deracemization has occurred.

The crystal packing of **1** is mainly determined by weak van der Waals and dipole forces, as the molecule is not able to form any hydrogen bonds. These rather isotropic weak forces should make the crystallization process sensitive to epitaxial 2D nucleation of the opposite enantiomer. Gervais et al. explained the alternating formation of the two chiral domains by oscillating local supersaturation in the solution.[6j] During the growth of one specific domain, the supersaturation of the corresponding enantiomer decreases, and, therefore, the

nucleation of the other enantiomer becomes more likely. Once that domain starts growing, this process repeats itself. The local differences in supersaturation that cause this alternating 2D nucleation could be circumvented by gentle stirring of the mixture to give crystals with a significant enantiomeric excess.[6j] Although in our near-equilibrium experiments primary nucleation is a rare and probably negligible process, epitaxial heterochiral nucleation, albeit slow, can not be excluded. Vigorous stirring and solution-phase racemization, however, remove local differences in supersaturation between the two enantiomers.[20,21] Additionally, the continued fragmentation of the crystals is more likely to occur at the domain boundaries and thus separate the enantiomorphous phases.

The mutual epitaxial growth of enantiomers in conglomerate crystals has been reported frequently.[6] Herein, we have described the use of attrition-enhanced deracemization to resolve the solid phase in liquid–solid mixtures of **1**. Under near-equilibrium conditions, a mixture of enantiomers in the form of epitaxial racemic conglomerate crystals was converted completely into a single chiral solid phase of the desired handedness. The observation that a population of small crystals, initially in enantiomeric excess, nurtures the population of large crystals of the opposite handedness supports the fundamental role of Ostwald ripening in this process. In conclusion, this method of attrition-enhanced Ostwald ripening offers an attractive alternative in situations in which the formation of epitaxial racemic conglomerates hampers resolution by preferential crystallization.

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[1] L. Pasteur, *C. R. Hebd. Seance Acad. Sci. Paris* **1848**, 26, 535.
[2] J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolution*, Krieger, Malabar, **1994**.
[3] L. Addadi, Z. Berkovitch-Yellin, N. Domb, E. Gati, M. Lahav, L. Leiserowitz, *Nature* **1982**, *296*, 21.
[4] L. Addadi, S. Weinstein, E. Gati, I. Weissbuch, M. Lahav, *J. Am. Chem. Soc.* **1982**, *104*, 4610.
[5] G. Coquerel, *Top. Curr. Chem.* **2007**, *269*, 1.
[6] a) S. Furberg, O. Hassel, *Acta Chem. Scand.* **1950**, *4*, 1020; b) B. S. Green, M. Knossow, *Science* **1981**, *214*, 795; c) I. Weissbuch, D. Zbaida, L. Addadi, L. Leiserowith, M. Lahav, *J. Am. Chem. Soc.* **1987**, *109*, 1869; d) R. J. Davey, S. N. Black, L. J. Williams, D. M. McEwan, D. E. Sadler, *J. Cryst. Growth* **1990**, *102*, 97; e) G. A. Potter, C. Garcia, R. McCagau, B. Adger, A. Collet, *Angew. Chem.* **1996**, *108*, 1780; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1666; f) M. Berfeld, D. Zbaida, L. Leiserowitz, M. Lahav, *Adv. Mater.* **1999**, *11*, 328; g) D. Zbiada, M. Lahav, K. Drauz, G. Knaup, M. Kottenhahn, *Tetrahedron* **2000**, *56*, 6645; h) R. G. Kostyanovsky, K. A. Lyssenko, A. N. Kravchenko, O. V. Lebedev, G. K. Kadorkina, V. R. Kostyanovsky, *Mendeleev Commun.* **2001**, *11*, 134; i) S. Beilles, P. Cardinael, E. Ndzié, S. Petit, G. Coquerel, *Chem. Eng. Sci.* **2001**, *56*, 2281; j) C. Gervais, S. Beilles, P. Cardinael, S. Petit, G. Coquerel, *J. Phys. Chem. B* **2002**, *106*, 646; k) V. Yu. Torbeev, K. A. Lyssenko, O. N. Kharybin, M. Yu. Antipin, R. G. Kostyanovsky, *J. Phys. Chem. B* **2003**, *107*, 13523; l) P. A. Levkin, V. Yu. Torbeev, D. A. Lenev, R. G. Kostyanovsky *Top. Stereochem.* **2006**, *25*, 81; m) J. Th. H. van Eupen, W. W. J. Elffrink, R. Keltjens, P. Bennema, R. de Gelder, J. M. M. Smits, E. R. H. van Eck, A. P. M. Kentgens, M. A. Deij, H. Meekes, E. Vlieg, *Cryst. Growth Des.* **2008**, *8*, 71.
[7] C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504.
[8] P. S. M. Cheung, J. Gagnon, J. Surprenant, Y. Tao, H. Xu, L. A. Cuccia, *Chem. Commun.* **2008**, 987.
[9] 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.
[10] W. L. Noorduin, H. Meekes, W. J. P. van Enckevort, A. Millemaggi, M. Leeman, B. Kaptein, R. M. Kellogg, E. Vlieg, *Angew. Chem.* **2008**, DOI: 10.1002/anie.200801846; *Angew. Chem. Int. Ed.* **2008**, DOI: 10.1002/ange.200801846.
[11] C. Viedma, *Astrobiology* **2007**, *7*, 312.
[12] J. H. E. Cartwright, O. Piro, I. Tuval, *Phys. Rev. Lett.* **2007**, *98*, 165501.
[13] 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.
[14] Y. Takahashi, K. Arai, Y. Obara, H. Matsumoto (Nissan Chem. Industr., Ltd. Japan, **1986**), JP 61103852 (*Chem. Abstr.* **1986**, *105*, 43327).
[15] K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013.
[16] J. M. Bijvoet, A. F. Peerdeman, A. J. van Bommel, *Nature* **1951**, *168*, 271.
[17] Similar observations were made for crystals grown from MeOH.
[18] K. Toyokura, K. Mizukawa, M. Kurotani in *CGOM3, ACS Conference Proceedings Series* (Eds.: A. S. Myerson, D. A. Green, P. Meenan), Washington DC, **1996**, 72.
[19] It is essential to use new glassware, beads, and stirring bars for each experiment to avoid chiral contamination; see also ref. [9] and: a) D. W. Armstrong, J. P. Kullman, X. Chen, M. Rowe, *Chirality* **2001**, *13*, 153; b) M. Lahav, I. Weissbuch, E. Shavit, C. Reiner, G. J. Nicholson, V. Schurig, *Origin Life Evol. Biosph.* **2006**, *36*, 151; c) C. Viedma, *Cryst. Growth Des.* **2007**, *7*, 553; d) S. Osuna-Esteban, M.-P. Zorzano, C. Menor-Salván, M. Ruiz-Bermejo, S. Veintemillas-Verdaguer, *Phys. Rev. Lett.* **2008**, *100*, 146102.
[20] This effect might explain the successful crystallization-induced enantiomeric transformation of **1** and of 1-(4-chlorophenyl)-4,4-dimethyl-2-(lH-1,2,4-triazol-l-yl)pentan-3-one from solution. In the absence of solution-phase racemization, these compounds form epitaxial racemic conglomerates.[14,6d,21]
[21] S. N. Black, L. J. Williams, R. J. Davey, F. Moffatt, R. V. H. Jones, D. M. McEwan, D. E. Sadler, *Tetrahedron* **1989**, *45*, 2677.

