Angewandte Chemie

DOI: 10.1002/anie.200801846

Homochirality

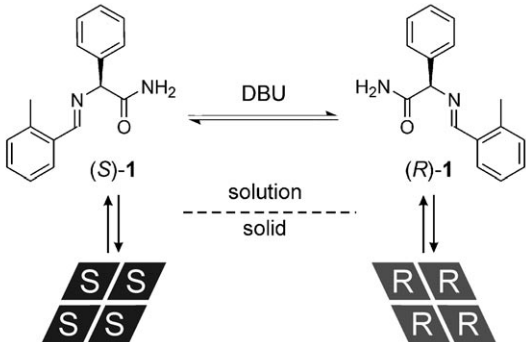
Complete Deracemization by Attrition-Enhanced Ostwald Ripening Elucidated**

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

Direct resolution by crystallization of racemic mixtures, induced by seeding or by adding tailor-made additives, constitutes an attractive alternative to separation using diastereomeric salts.[1–4] Unfortunately, the yield in a single resolution step is low and the overall yield limited to 50 % of each enantiomer. Combination of a direct resolution with racemization in the solution permits a total enantiomeric transformation.[5–14] Complete resolution in a single operation would be of great practical use but examples have been limited. Recently, Viedma has demonstrated the total resolution of an intrinsically achiral molecule, $NaClO_3$, by means of abrasive grinding.[15,16]

Inspired by Viedma,[15] proof of principle was given with a solid phase of a *chiral* amino acid derivative in contact with a solution in which racemization occurs; this evolved smoothly to a single chiral solid end state on abrasive grinding.[17] This was demonstrated for the conglomerate *N*-(2-*m*ethylbenzylidene)-phenylglycine amide (**1**) (Scheme 1). Starting the process with a mixture slightly enriched in one enantiomer in the solid phase, the solid phase is completely converted into the major enantiomer through the solution-phase racemization reaction. Within a few weeks either solid enantiomer can be obtained quantitatively with *ee* > 99.9 %.

Monte Carlo simulations led to a model that showed that two processes are responsible for the deracemization: continuous attrition of crystals and Ostwald ripening, which leads to growth of large crystals at the cost of smaller ones.[18–20] Here we explore the parameters of this deracemization process as derived from theory by varying the experimental conditions. The insight obtained also allows definition of suitable conditions to increase the deracemization rate drastically.



Scheme 1. Equilibria involved in the attrition-enhanced crystallization/dissolution for compound **1**.

The Monte Carlo simulation model is expressed in terms of the experimental parameters. In the model three parameters are crucial. First, the rate at which molecules racemize in solution is described by the racemization efficiency χ. Second, the continuous ablation of crystals is determined by an attrition probability ζ, and, third, the growth of larger crystals at the cost of smaller proceeds according to the Ostwald ripening probability κ. The simulation results confirmed the experimentally observed exponential behavior typical for asymmetric autocatalysis of the time evolution of the enantiomeric excess *ee* in the solid state according to Equation (1)[20] for not too small values of the initial enantiomeric excess *ee*(0).[21]

$$ee(t) = ee(0)\exp(kt) \qquad (1)$$

The deracemization rate constant *k* (see Supporting Information) can be expressed in terms of the three parameters [Eq. (2)], where the proportionality parameter ν_0 is an event frequency and b_{solid} the amount of solid material.[22]

$$k = \frac{\nu_0}{b_{\text{solid}}}\chi\kappa\zeta \qquad (2)$$

The racemization efficiency via the solution, χ, depends on the amount of the racemization catalyst, b_{rc}. Assuming a linear relationship we can write $\chi = \alpha_{\chi,\text{solv}} b_{\text{rc}}$, where the proportionality constant $\alpha_{\chi,\text{solv}}$ depends on the solvent used. The Ostwald ripening probability κ is determined by the

---

[*] W. L. Noorduin, 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: bernard.kaptein@dsm.com

A. Millemaggi, Dr. B. Kaptein
Innovative Synthesis & Catalysis, DSM Pharmaceutical Products
PO Box 18, 6160 MD Geleen (The Netherlands)
Fax: (+31) 46-476-7604
E-mail: r.m.kellogg@syncom.nl

M. Leeman, Prof. Dr. R. M. Kellogg
Syncom BV, Kadijk 3, 9747 AT Groningen (The Netherlands)
Fax: (+31) 50-575-399
E-mail: e.vlieg@science.ru.nl

[**] We acknowledge Prof. D. G. Blackmond for the stimulating discussions. The SNN agency (Cooperation Northern Netherlands) and the European Fund for Regional Development (EFRO) are acknowledged for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801846.

solute exchange frequency between the solution and the crystallites, which in turn depends on the surface free energy of the crystallites in the solution. Nielsen and Söhnel have shown that a logarithmic relation exists between the surface free energy and the solubility.[23] Using this relation, κ can be shown to be proportional to the solubility b_{solute}, according to $\kappa = \alpha_{\text{Ost}} b_{\text{solute}}$ (see Supporting Information). The attrition probability ζ is not further specified in experimental terms, as this depends on complicated parameters like the stirring speed, the grinding agents used and the crystal hardness.[24] Combination of all the relations leads to Equation (3) for the deracemization rate constant k:

$$k = \frac{\nu_0}{b_{\text{solid}}} \alpha_{\chi,\text{solv}} \, b_{\text{rc}} \, \alpha_{\text{Ost}} \, b_{\text{solute}} \, \zeta \qquad (3)$$

Using this equation we have studied the dependencies of the deracemization rate experimentally (see Experimental Section). Deracemization experiments were performed for various molalities b_{rc} of the base DBU (1,5-diazabicyclo-[5.4.0]undec-5-ene) using MeCN as a solvent (Figure 1 a).[25]

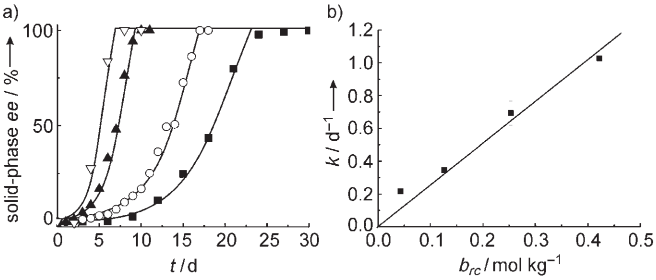


Figure 1. a) Evolution of the solid-phase *ee* in MeCN for different amounts of DBU: 0.42 (▽), 0.25 (▲), 0.13 (○) and 0.04 mol kg^{-1} (■) (lines are guide to the eye). b) Rate constant k obtained from the data in (a) according to Equation (1).

Fitting Equation (1) to the data shows that the rate constant k increases linearly with increasing b_{rc} (Figure 1 b).

Figure 2 shows the dependence of the deracemization rate on the amount of solid material, b_{solid}, in MeCN with all other parameters fixed. As expected, k is inversely proportional to b_{solid}.

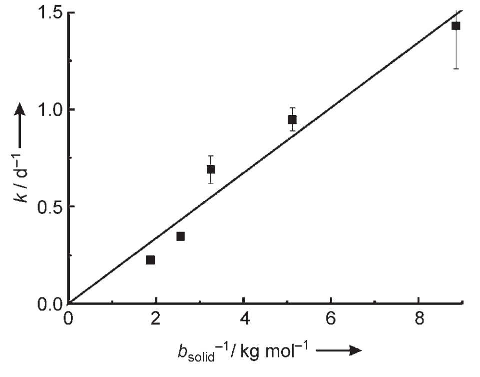


Figure 2. The deracemization constant k as a function of the amount of solid, b_{solid}^{-1}, in MeCN (35 g) with 0.13 mol kg^{-1} DBU, 10 g of glass beads and stirring at 1250 rpm.

To study the effect of the solvent, toluene was used as a low solubility solvent (0.4 wt %) and tetrahydrofuran (THF) as a good solvent (6.8 wt %), as compared to acetonitrile (MeCN) (2.2 wt %, all at 25 °C). In toluene, after 30 days the enantiomeric excess in the solid phase was merely 10 % (Figure 3). As expected, for the solvents with a higher solubility, MeCN and THF, the deracemization is faster and complete chiral purity is reached after 21–24 days.

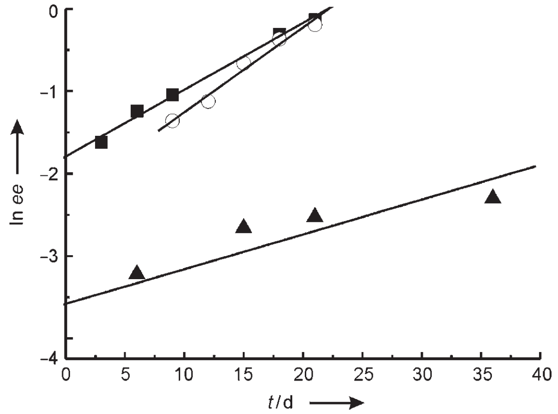


Figure 3. Evolution of ln *ee* in the solid phase for the deracemization experiments in THF (■), MeCN (○), and toluene (▲).

The measured solubilities b_{solute}, the solvent dependent racemization parameters $\alpha_{\chi,\text{solv}}$, the amount of solid material b_{solid}, and the normalized deracemization rate constant k_{theo}, calculated using Equation (3), are given in Table 1; ζ is kept constant. The decreasing trend in the experimental rate constants for the three solvents is also found for the theoretical values. These results show that for practical applications the efficiency increases on use of a good solvent but that the solution racemization rate must be considered as well. On comparison of MeCN and THF, the latter has the higher solubility but the former has a higher racemization rate constant (Supporting Information) resulting in the highest deracemization rate in MeCN.

Table 1: Comparison of the theoretical deracemization rate k_{theo} and the experimentally observed deracemization rate k_{exp}.

	b_{solute}	b_{solid}	b_{rc}	$\alpha_{\chi,\text{solv}}$ [a,b]	k_{theo} [a,c]	k_{exp} [a,d]
MeCN	0.088	0.387	0.0573	1.00	1.00	1.00
THF	0.287	0.390	0.0409	0.23	0.53	0.77
Toluene	0.018	0.204	0.0177	0.31	0.04	0.16

[a] Normalized for MeCN. [b] The solution racemization rates were determined in saturated solutions for the three different solvents without any solid present (Supporting Information). [c] Calculated using Equation (3). [d] Determined from the data in Figure 3.

All experiments described thus far were performed at constant stirring rates and amounts of glass beads. This results in an approximately constant crystal size distribution (CSD)

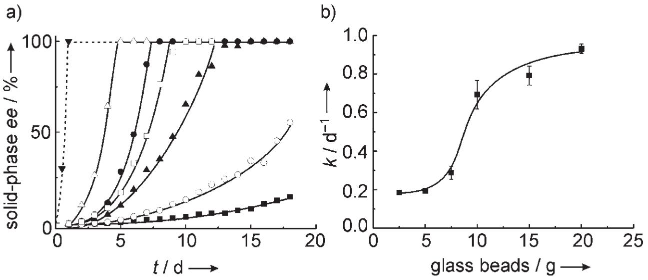


Figure 4. a) Evolution of *ee* as a function of the amount of glass beads in grams: 2.5 (■), 5.0 (○), 7.5 (▲), 10.0 (□), 15.0 (●), 20.0 g (△), for a constant amount of DBU (0.25 mol kg^{-1}), 4 g of **1** in MeCN (35 g), and stirring at 1250 rpm (left). Additionally the deracemization was performed under these conditions with 15.0 g glass beads using an ultrasonic bath (▼). b) Rate constant *k* as a function of the amount of glass beads obtained from the results in (a) according to Equation (1) for a constant amount of DBU (0.25 mol kg^{-1}) in MeCN. The lines are a guide to the eye.

during the process. The computer simulations, however, predict that the deracemization process can be enhanced by applying intense attrition conditions leading to a CSD of smaller crystals.[20] Therefore, the influence of the attrition on the deracemization time was explored by varying the amount of glass beads. As expected, the deracemization time decreases for increasing amounts of glass beads as the crystals are ground to smaller sizes (Figure 4).[26] The shape of the curve shows that the relation between the amount of glass beads and *k* in Equation (3) is rather complicated. Note that even in the absence of glass beads, the magnetic stirrer will cause attrition of crystals. To intensify the grinding even more, we repeated the experiment with 15 g glass beads (see Figure 4), now using a thermostated standard ultrasonic bath instead of magnetic stirring. These experiments led to an approximately five times higher rate with $k = 3.9\,\mathrm{d}^{-1}$, reducing the deracemization time to a single day (Figure 4). As predicted from Equation (1) a further decrease in the deracemization time can be realized by starting with a solid state that is already enriched, instead of beginning with almost racemic material.[27]

These results offer a detailed understanding of the processes involved in attrition-enhanced Ostwald ripening leading to an enantiomerically pure solid phase. Attrition-enhanced Ostwald ripening is a valuable new technique to achieve single step conversion rapidly with virtually 100 % yield of the solid phase.[28]

Experimental Section

Solution-solid mixtures of **1** (4 g) were magnetically stirred (1250 rpm) at ambient temperature in a given solvent (36 g) in the presence of 2.5 mm glass beads (10 g). After establishing solution–solid equilibrium (24 h), solution-phase racemization was initiated by adding 200 mg DBU (ca. 0.04 mol kg^{-1}). Samples of the solid were collected over time and the enantiomeric purity was measured using two independent chiral HPLC methods.[17]

Received: April 21, 2008
Published online: July 11, 2008

Keywords: amino acids · asymmetric amplification · chiral resolution · chirality · grinding

[1] H. Murakami, *Top. Curr. Chem.* **2007**, *269*, 273.
[2] J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolution*, Krieger, Florida, **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] a) E. Havinga, *Chem. Weekbl.* **1941**, *38*, 642; b) E. Havinga, *Biochim. Biophys. Acta* **1954**, *13*, 171.
[6] D. H. R. Barton, G. W. Kirby, *J. Chem. Soc.* **1962**, 806.
[7] R. E. Pincock, R. R. Perkins, A. S. Ma, K. R. Wilson, *Science* **1971**, *174*, 1018.
[8] J. Van Mil, L. Addadi, M. Lahav, *Tetrahedron* **1987**, *43*, 1281.
[9] 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.
[10] D. K. Kondepudi, R. J. Kaufman, N. Singh, *Science* **1990**, *250*, 975.
[11] B. Kaptein, T. R. Vries, J. W. Nieuwenhuijzen, R. M. Kellogg, R. F. P. Grimbergen, Q. B. Broxterman, *Handbook of Chiral Chemicals*, CRC, Taylor & Francis, New York, **2006**, pp. 97 – 116.
[12] R. Yoshioka, *Top. Curr. Chem.* **2007**, *269*, 83.
[13] K. M. J. Brands, A. J. Davies, *Chem. Rev.* **2006**, *106*, 2711.
[14] D. A. Chaplin, N. B. Johnson, J. M. Paul, G. A. Potter, *Tetrahedron Lett.* **1998**, *39*, 6777.
[15] C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504.
[16] See also P. S. M. Cheung, J. Gagnon, J. Surprenant, Y. Tao, H. Xu, L. A. Cuccia, *Chem. Commun.* **2008**, 987.
[17] 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.
[18] C. Viedma, *Astrobiology* **2007**, *7*, 312.
[19] J. H. E. Cartwright, O. Piro, I. Tuval, *Phys. Rev. Lett.* **2007**, *98*, 165501.
[20] 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.
[21] The simulations show that in the case of instantaneous racemization in the solution the deracemization process becomes stochastic. Here, we limit the discussion to relatively low racemization efficiencies ($\chi \leq 0.1$, Supporting Information) and nonzero values for *ee*(0), for which the process becomes deterministic.
[22] Throughout the paper we express amounts in terms of molalities (mol per kg solvent).
[23] A. E. Nielsen, O. Söhnel, *J. Cryst. Growth* **1971**, *11*, 233.
[24] H. Briesen, *Powder Technol.* **2007**, *178*, 87 – 98.
[25] The linearity of the relationship between the solution racemization time and the DBU concentration was also checked (Supporting Information).
[26] The computer simulations show a minimum in the deracemization time as a function of the attrition probability ζ, which was found at high attrition rates, for which the CSD is dominated by the minimal crystal size that can be obtained by attrition (Supporting Information).
[27] Starting with $ee(t{=}0) \neq 0$ also suppresses stochastic behavior at low *ee* values.[20]
[28] As expected from Equation (3), scaling up of all parameters in the experiment has no influence on the deracemization rate. This was verified by performing experiments at a five times larger scale (ca. 20 g (*R*,*S*)-**1**, 0.25 mol kg^{-1} DBU, 50 g glass beads, 175 g MeCN). The enantiopure end state was again reached in 7 days (cf. Figure 1).