Radboud Repository

Radboud University Nijmegen

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/180467

Please be advised that this information was generated on 2020-11-30 and may be subject to change.

This is an open access article published under a Creative Commons Non-Commercial No Derivative Works (CC-BY-NC-ND) Attribution License, which permits copying and redistribution of the article, and creation of adaptations, all for non-commercial purposes.

CRYSTAL GROWTH & DESIGN

Article

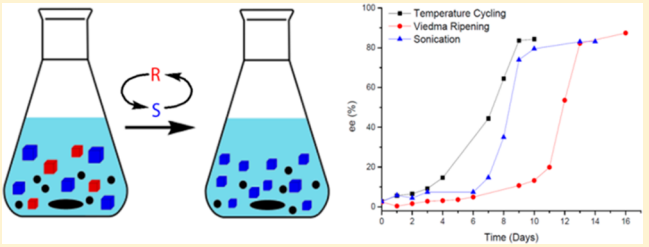
pubs.acs.org/crystal

Solid Phase Deracemization of an Atropisomer

Anthonius H. J. Engwerda,[†] Pim van Schayik,[†] Henjo Jagtenberg,[†] Hugo Meekes,*[,†] Floris P. J. T. Rutjes,[†] and Elias Vlieg[†]

[†]Institute for Molecules and Materials, Radboud University, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands

ABSTRACT: The scope of Viedma ripening and temperature cycling with respect to chiral molecules has remained mostly limited to molecules with a single stereogenic center, while racemization proceeds through inversion at that particular stereocenter. In this article we demonstrate for the first time that atropisomers, chiral rotamers that possess an axis of chirality, can be successfully deracemized in the solid phase by either applying temperature cycling or Viedma ripening.



INTRODUCTION

Single chirality is a key signature of living organisms and hence of utmost importance to the development of new drugs in the pharmaceutical industry. Obtaining molecules in an enantiopure way can however be troublesome, since straightforward synthesis typically yields a racemic mixture of both enantiomers. Viedma ripening is a process that converts a saturated slurry of crystals of a racemic conglomerate into an enantiopure end state by applying vigorous grinding. The first example of this process involved achiral sodium chlorate, which crystallizes in a chiral fashion.[1] Later studies have shown that this deracemization process can also be applied to intrinsically chiral molecules, such as amino acid derivatives,[2] as well as to the enantioselective synthesis of small molecules.[3,4] Most of these examples have focused on chiral molecules that exhibit an sp^3 hybridized carbon atom as a chiral center.[5] Notable exceptions include the work of the Hakansson group which involves a chiral transition state metal complex,[6] and one from our own group where the chiral center is a sulfur atom.[7] Other important classes of chiral compounds also exist, but have remained unexplored with regard to Viedma ripening.

One such class concerns atropisomers, nonplanar molecules that display chirality through the hindered rotation around a single bond, which in many cases can be overcome by raising the temperature. Atropisomers can be very stable, however, as is shown by the fact that quite a number of natural products exist as atropisomers, featuring only one of the two possible enantiomers.[8] In addition, atropismerism is a common feature in some drugs as well. An example is Telenzepine (**1**, Figure 1), an antisecretory drug of which the (+)-atropisomer is the most active form.[9] In addition, axially chiral molecules such as BINOL (**2**, 1,1-binaphthalene-2,2-diol) and BINAP (**3**, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene) are often used as ligands in transition metal based asymmetric synthesis.[10] Here, we report the deracemization of the atropisomer 4,6-dimethyl-1-(naphthalen-1-yl)pyrimidine-2(1*H*)-thione (**4**, Figure 2) using Viedma ripening or temperature cycling.

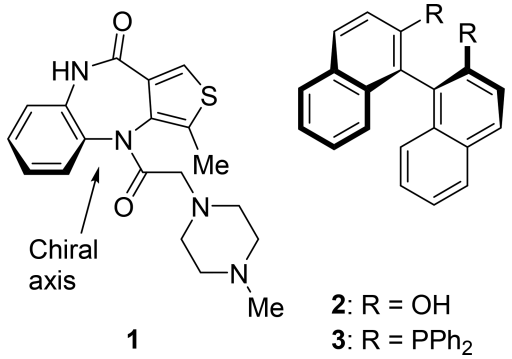


Figure 1. Telenzepine (**1**) is an example of an atropisomer drug, while BINOL (**2**) and BINAP (**3**) are chiral ligands often used in transition metal complexes.

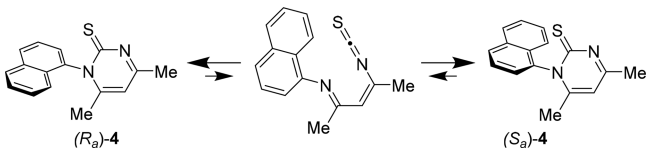


Figure 2. Atropisomer **4** crystallizes as a racemic conglomerate and spontaneously racemizes at elevated temperatures in apolar solvents.

RESULTS AND DISCUSSION

Compound **4** was selected since it crystallizes as a racemic conglomerate, which is a prerequisite for Viedma ripening. In addition, this compound racemizes swiftly in apolar solvents at elevated temperatures ($t_{1/2}$ = 4 min in xylene at 50 °C), whereas racemization at room temperature in polar solvents is negligible.[11] Racemization takes place relatively easily since it proceeds via a reversible ring-opening and closing-mecha-

Received: August 23, 2017
Revised: September 13, 2017
Published: September 13, 2017

 © 2017 American Chemical Society

DOI: 10.1021/acs.cgd.7b01180
Cryst. Growth Des. 2017, 17, 5583−5585

nism,[12] rather than via rotation around the chiral axis. Fujita and co-workers already showed that total spontaneous resolution can be achieved for this compound.[11,13] By slowly cooling a stirred, saturated solution of compound **4**, seeded with enantiopure crystals, they obtained an enantiomeric excess (*ee*) of up to 90%. A drawback of these experiments is that the deracemization was achieved only on small scale (50 mg). In addition, such total spontaneous resolution experiments need to be carried out in a carefully controlled manner, or crystallization of the unwanted enantiomer will take place. We investigate here whether alternative methods can be used to deracemize a racemic mixture of compound **4**. Viedma ripening is a technique that can be applied on a much larger scale.[14] In addition, it starts from a racemic suspension of crystals, making it a more robust method since unwanted crystallization of the other enantiomer is no problem.[15] As an alternative, we also investigated the possibility of deracemization using temperature cycling.[16]

Viedma Ripening Experiments. Viedma ripening experiments on compound **4** resulted in an *ee* of around 90% (see Experimental Section) with and without using a chiral bias. Deracemization typically took 15−20 days at 60 °C. We found that the outcome of the Viedma ripening experiments is stochastic. Out of a total of six experiments (starting from completely racemic conditions), three experiments yielded the (R_a)- and three the (S_a)-enantiomer. This is in contrast to previous examples of Viedma ripening, where often a bias was found for one chiral end state, caused by the presence of chiral impurities.[17] Apparently this system is very pure or insensitive toward a bias from impurities. When applying a small initial bias (by adding less than 1% enantiopure material), deracemization could be achieved in 15 days (Figure 3). During the filtration, the samples rapidly cooled down, resulting in additional crystallization of both enantiomers. This is most likely the reason the measured *ee* was 90%, while the actual value at the end of the deracemization should be (close to) 100%.

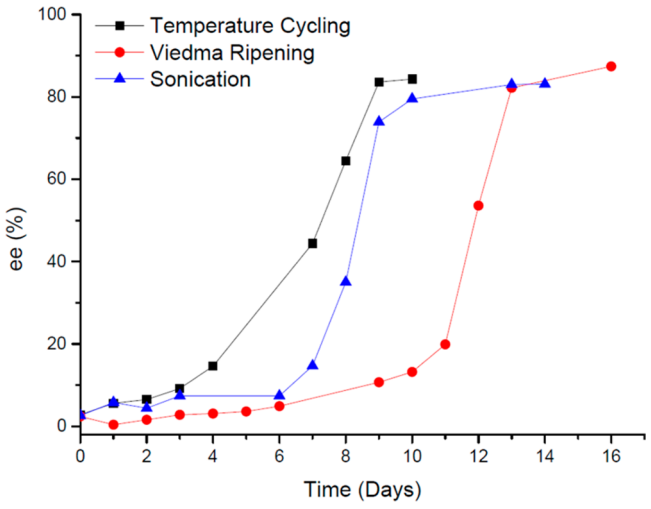


Figure 3. Deracemization curves of compound **4** using temperature cycling, Viedma ripening, and sonication. In these experiments, a small initial *ee* was created by adding less than 1% enantiopure material.

Sonication Experiments. In order to decrease the time required for deracemization, we evaluated different experimental configurations. Sonication of such a crystal suspension can also result in deracemization[18,19] and Noorduin et al. have shown that this can greatly enhance the deracemization speed.[18] By replacing the magnetic stirrer with a sonication bath, and starting from a small initial bias, deracemization could indeed be achieved (Figure 3). Since no experiments without an initial bias were performed, nothing can be said about the stochasticity of this process. The drastic decrease in deracemization time as described by Noorduin et al. was however not observed. Since racemization, solubility, and sonication energy[20] are not limiting factors here, this could possibly be due to a different hardness of the crystals, although no definite explanation can be given based on the current experiments.

Temperature Cycling Experiments. Recently, the groups of Flood and Coquerel described temperature cycling of a suspension of conglomerate forming crystals as an alternative method of deracemization.[16,21] In this process, the suspension is subjected to periodic heating−cooling cycles, resulting in solid phase deracemization.[22] By cycling the temperature between 65 and 55 °C (again with an initial bias), deracemization of **4** could also be achieved (Figure 3). The time required for deracemization under these conditions is not greatly different from that of the Viedma ripening experiments. Temperature cycling and Viedma ripening are however difficult to compare because of the different conditions (temperature, glass beads). In addition, the technique and temperature profile of the cycles have not been optimized for this specific system.[23]

CONCLUSION

In conclusion, we have successfully demonstrated the first example of the deracemization of an atropisomer using both Viedma ripening and temperature cycling at gram scale. Both methods enabled deracemization in 15−20 days at elevated temperatures.

EXPERIMENTAL SECTION

Synthesis of 4,6-Dimethyl-1-(naphthalen-1-yl)pyrimidine-2(1*H*)-thione (4). Ammonium thiocyanate (2.0 g, 26 mmol) was added to 100 mL acetone (100 mL), followed by the dropwise addition of benzoyl chloride (3.0 mL, 26 mmol). The resulting suspension was refluxed for 20 min and then allowed to cool to room temperature. Next, 1-naphthaleneamine (2.5 g, 17.5 mmol) was added and the mixture was refluxed for 1 h. The solution was poured into water (300 mL) and the resulting residue was filtered off. The precipitate was washed with water and added to 5% aqueous NaOH (100 mL). The suspension was heated to 80 °C for 30 min and then cooled to room temperature. 1 M aqueous HCl was added after which the pH was adjusted to 9 by adding aqueous saturated Na_2CO_3. The residue was filtered off, washed with water, and dried in air to yield 1-(naphthalen-1-yl)thiourea as a white powder in quantitative yield.

This product was added to ethanol (50 mL), followed by the addition of 2,4-pentadione (2.5 mL, 24 mmol). Next, 5 M aqueous HCl (20 mL) was added and the mixture was refluxed for 3 h. The mixture was added to ice-water containing NaOH (2.5 g). The product was extracted using DCM and dried with $MgSO_4$. The solvent was removed after which a thick red oil was formed. Upon addition of small quantities of acetone, product **4** precipitated as a yellow/orange powder in 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97−7.90 (m, 2H), 7.60−7.55 (m, 1H), 7.54−7.44 (m, 2H), 7.41−7.38 (m, 1H), 7.38−7.35 (m, 1H), 6.59 (s, 1H), 2.48 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 169.9, 158.3, 137.6, 134.6, 129.6, 128.8, 128.0, 127.8, 126.9, 125.8, 125.1, 121.2, 110.8, 25.0, 21.5.

Viedma Ripening Experiments. Compound **4** (800 mg), glass beads (5 g, Ø ca. 2 mm VWR international), an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm), and toluene (10 mL) were added to a round-bottom flask to which a condenser was

DOI: 10.1021/acs.cgd.7b01180
Cryst. Growth Des. 2017, 17, 5583−5585

attached. The vial was heated to 60 °C and stirred at 600 rpm. Samples were taken regularly.

Sonication Experiments. Compound **4** (800 mg), glass beads (5 g, Ø ca. 2 mm VWR international), and toluene (10 mL) were added to a round-bottom flask. The flask was sealed and placed inside a sonication bath (35 kHz, 320W) at 60 °C. Samples were taken regularly.

Temperature Cycling Experiments. Compound **4** (800 mg), an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm), and toluene (10 mL) were added to a round-bottom flask to which a condenser was attached. The temperature was cycled between 55 and 65 °C on a regular basis (5 min at 55 °C, 2 °C/min to 65 °C, 5 min at 65 °C, 1 °C/min to 55 °C), while the suspension was gently stirred. Samples were taken after 5 min at 65 °C.

Sampling. For sampling, 100 μL of the suspension was taken using a syringe. The crystals were filtered off on a P4 glass filter and air-dried.

Sample Analysis. Analysis of the samples taken during the experiment was performed using chiral HPLC, which gave good separation, but not the absolute configuration of the two peaks in the chromatogram. To determine the absolute configuration, X-ray diffraction was used to elucidate the structure of a single crystal. Designation of the HPLC peaks was done by sampling this single crystal, giving only a single peak.

The *ee* of the samples was determined using chiral HPLC (ADH column, 20% IPA in heptane, flow 1 mL min^{-1}, retention times: (S_a)-**4** 11.7 min, (R_a)-**4** 25.0 min).

AUTHOR INFORMATION

Corresponding Author

*E-mail: H.Meekes@science.ru.nl.

ORCID

Anthonius H. J. Engwerda: 0000-0001-9589-7129

Floris P. J. T. Rutjes: 0000-0003-1538-3852

Elias Vlieg: 0000-0002-1343-4102

Author Contributions

A.H.J.E., H.M., F.P.J.T.R., and E.V. designed the experiments and analyzed the data. A.H.J.E., P.v.S., and H.J. performed the experiments. A.H.J.E. wrote the manuscript with contributions from all other authors. All authors contributed to the discussions.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Viedma, C. *Phys. Rev. Lett.* **2005**, *94*, 4.

(2) Noorduin, W. L.; Izumi, T.; Millemaggi, A.; Leeman, M.; Meekes, H.; Van Enckevort, W. J. P.; Kellogg, R. M.; Kaptein, B.; Vlieg, E.; Blackmond, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 1158−1159.

(3) Steendam, R. R. E.; Verkade, J. M. M.; van Benthem, T. J. B.; Meekes, H.; van Enckevort, W. J. P.; Raap, J.; Rutjes, F. P. J. T.; Vlieg, E. *Nat. Commun.* **2014**, *5*, 5543.

(4) Kawasaki, T.; Takamatsu, N.; Aiba, S.; Tokunaga, Y. *Chem. Commun.* **2015**, *51*, 14377−14380.

(5) Sogutoglu, L. C.; Steendam, R. R. E.; Meekes, H.; Vlieg, E.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2015**, *44*, 6723−6732.

(6) Bjoremark, P. M.; Jonsson, J.; Hakansson, M. H. *Chem. - Eur. J.* **2015**, *21*, 10630−10633.

(7) Engwerda, A. H. J.; Koning, N.; Tinnemans, P.; Meekes, H.; Bickelhaupt, F. M.; Rutjes, F. P. J. T.; Vlieg, E. *Cryst. Growth Des.* **2017**, *17*, 4454−4457.

(8) Oki, M. *Top. Stereochem.* **1983**, *14*, 1−81.

(9) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398−6401.

(10) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155−3211.

(11) Sakamoto, M.; Yagishita, F.; Ando, M.; Sasahara, Y.; Kamataki, N.; Ohta, M.; Mino, T.; Kasashima, Y.; Fujita, T. *Org. Biomol. Chem.* **2010**, *8*, 5418−5422.

(12) Najahi, E.; Vanthuyne, N.; Nepveu, F.; Jean, M.; Alkorta, I.; Elguero, J.; Roussel, C. *J. Org. Chem.* **2013**, *78*, 12577−12584.

(13) Sakamoto, M.; Utsumi, N.; Ando, M.; Saeki, M.; Mino, T.; Fujita, T.; Katoh, A.; Nishio, T.; Kashima, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4360−4363.

(14) Noorduin, W. L.; van der Asdonk, P.; Bode, A. A. C.; Meekes, H.; van Enckevort, W. J. P.; Vlieg, E.; Kaptein, B.; van der Meijden, M. W.; Kellogg, R. M.; Deroover, G. *Org. Process Res. Dev.* **2010**, *14*, 908−911.

(15) Steendam, R. R. E.; van Benthem, T. J. B.; Huijs, E. M. E.; Meekes, H.; van Enckevort, W. J. P.; Raap, J.; Rutjes, F. P. J. T.; Vlieg, E. *Cryst. Growth Des.* **2015**, *15*, 3917−3921.

(16) Suwannasang, K.; Flood, A. E.; Rougeot, C.; Coquerel, G. *Cryst. Growth Des.* **2013**, *13*, 3498−3504.

(17) Steendam, R. R. E.; Harmsen, B.; Meekes, H.; van Enckevort, W. J. P.; Kaptein, B.; Kellogg, R. M.; Raap, J.; Rutjes, F. P. J. T.; Vlieg, E. *Cryst. Growth Des.* **2013**, *13*, 4776−4780.

(18) Noorduin, W. L.; Meekes, H.; van Enckevort, W. J. P.; Millemaggi, A.; Leeman, M.; Kaptein, B.; Kellogg, R. M.; Vlieg, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 6445−6447.

(19) Azeroual, S.; Surprenant, J.; Lazzara, T. D.; Kocun, M.; Tao, Y.; Cuccia, L. A.; Lehn, J. M. *Chem. Commun.* **2012**, *48*, 2292−2294.

(20) Rougeot, C.; Guillen, F.; Plaquevent, J. C.; Coquerel, G. *Cryst. Growth Des.* **2015**, *15*, 2151−2155.

(21) Suwannasang, K.; Coquerel, G.; Rougeot, C.; Flood, A. E. *Chem. Eng. Technol.* **2014**, *37*, 1329−1339.

(22) Viedma, C.; Cintas, P. *Chem. Commun.* **2011**, *47*, 12786−12788.

(23) Suwannasang, K.; Flood, A. E.; Coquerel, G. *Cryst. Growth Des.* **2016**, *16*, 6461−6467.

DOI: 10.1021/acs.cgd.7b01180
Cryst. Growth Des. 2017, 17, 5583−5585