CRYSTAL GROWTH & DESIGN

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Article

Simultaneous High-Purity Enantiomeric Resolution of Conglomerates Using Magnetic Substrates

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Cite This: *Cryst. Growth Des.* 2021, 21, 2925−2931

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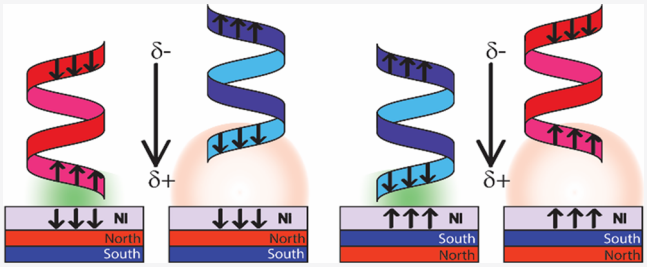
ABSTRACT: Applying magnetic substrates, magnetized perpendicular to the surface, we were able to crystallize from racemic solution pure conglomerates of several molecules. The resolution is based on the spin-dependent charge reorganization (SDCR) effect. By having two surfaces with opposite magnetization, it was possible to simultaneously crystallize on each surface a different enantiomer. The method does not require any seeding or chemical modification and is generally employable to any conglomerate. A system is presented for performing the separation, while the racemic mixture flows between the two magnetic surfaces.



INTRODUCTION

Crystallization is the most commonly used technique for the separation and purification of enantiopure molecules from a racemic mixture, whether it is by formation of a diastereomer by addition of a resolution agent[1] or by spontaneous resolution in the case of conglomerates.[2−4] Industrially, it has a great importance as most of the active pharmaceutical ingredients have in their preparation at least one crystallization step.[5−7] Since many enantiomeric drugs have different biological effects for the two enantiomers,[8−10] regulatory bodies are aiming for the development and commercialization of enantiopure active molecules rather than their racemic form,[11,12] giving even more importance to the development of efficient resolution techniques. Tassinari et al.[13] demonstrated that the preferential crystallization of a conglomerate could be directed toward one enantiomer or the other using a magnetized surface as the crystallization substrate. The mechanism at the base of this effect lies in the intrinsic property of chiral molecules to become transiently spin-polarized upon charge polarization. Namely, even if all the electrons in the molecules are paired and the total spin is zero, upon charge polarization and the formation of an induced dipole, the two electric poles are also spin-polarized so that one pole has a charge with spin polarization opposite to that on the other pole. Which spin polarization is associated with which pole is defined by the handedness of the chiral molecule.[14] This spin-dependent charge reorganization (SDCR) effect is related to the chiral-induced spin selectivity (CISS) phenomenon reported almost two decades ago.[15,16] As a result of the SDCR effect, there is a (partially) unpaired electron that is on the electric pole near the surface. The ferromagnetic surface itself is also spin-polarized due to it being immersed in a magnetic field: the electrons' spin population at the Fermi level, once degenerate, is now split between a majority spin and a minority spin due to the interaction with the magnetic field. Which spin has lower energy depends on the orientation of the magnetic field. The spin-polarized molecule interacts via spin-dependent exchange interaction with the spins of the magnetized surface. The magnitude of this interaction depends on the relative orientations of the spin in the molecule and the spin in the ferromagnetic substrate.[17] In a way, the presence of a magnetized surface plays the same role of a crystal seed of one enantiomer, driving the separation process known as kinetic entrainment, where the crystallization of the selected enantiomer is kinetically favored to allow for the separation of enantiopure products.[18] Note however that the same magnetic surface can be used to separate many different chiral materials.

The ability to use the SDCR for separation of enantiomers by crystallization with no need for seeding was demonstrated qualitatively using a ferromagnetic substrate positioned horizontally in a solution containing the racemic mixture.[13] This configuration suffered from contamination due to the random crystallization in the solution. Here, we present a quantitative result on the enantioseparation of several compounds in a new configuration. This method is general and allows one to obtain a highly pure material in a single separation stage.

Received: January 26, 2021
Revised: April 11, 2021
Published: April 21, 2021

https://doi.org/10.1021/acs.cgd.1c00093
Cryst. Growth Des. 2021, 21, 2925−2931

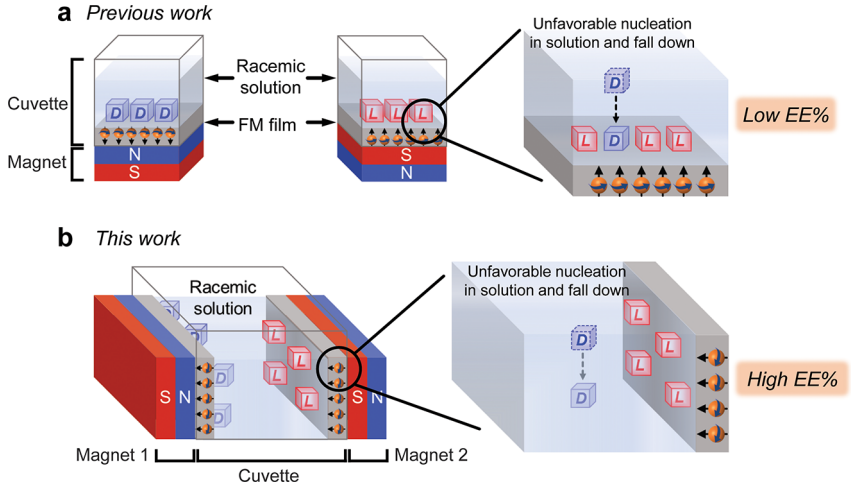


Figure 1. (a) Schematic of the experimental setup used in the previous study. (b) Schematic of the setup used in the crystallization experiments, having the FM substrates in a vertical configuration. The north pole is defined as the pole at which the magnetic field lines are going into the surface of the magnet.

METHODS AND RESULTS

Figure 1 shows the schematic of the setup used for the crystallization experiments. Ferromagnetic nickel substrates were prepared by evaporating a 10 nm titanium layer on Si(100) wafers, followed by a 20 nm layer of nickel and, finally, a 7 nm layer of gold. The thin gold capping layer is reducing the oxidation of the ferromagnetic layer in air and in solution so that it preserves the magnetic and spin transport properties for long operating conditions. The crystallization process was carried out in plastic cuvettes of 5 × 10 × 30 mm, having a total volume of 1.5 mL. Two permanent neodymium magnets (each having a 0.45 T field strength) were placed outside the two opposite long walls of the container, oriented such that the magnetic interaction between the two is attractive. During crystallization, two ferromagnetic substrates were held vertically against the long walls of the cuvette so that both substrates remain parallel to each other, with the metallic surface pointing toward the inside of the cuvette. This gives rise to opposite spin polarizations of the two ferromagnetic (FM) substrates, according to the direction of the magnetic field. The distance between the two substrates in the setup was 4 mm.

Figure 2 presents the crystallization results for three different amino acids: glutamic acid, threonine, and asparagine. The enantiomeric excess of crystalization reaches numbers that are close to 100%, with crystalization yields between 10 and 20%. We now address each amino acid separately.

Glutamic Acid Crystallization. Glutamic acid crystallization was carried out from a supersaturated racemic solution of the amino acid in 5 M HCl (1.02 g/mL Glu·H_2O), which was gradually cooled down from 80 °C to 33 °C over a time period of 2 h and then left for 36 h at constant temperature. The crystals grown on the ferromagnetic substrates were collected and characterized (Figure 2a), while the ones that were formed in solution and precipitated at the bottom of the cuvette were not considered. The crystals at the bottom of the cuvette, considered as a whole, do not have a preferential enantiomeric excess and show a random, very weak enantiomeric excess, as expected for crystals growing from a racemic conglomerate solution. The CD spectra of the collected crystals, shown in Figure 3a, were measured by dissolving all the crystals collected from each ferromagnetic surface in water. The CD spectra show that an enantiospecific crystallization takes place on the surface of the ferromagnetic substrates and that the enantiospecificity depends on the magnetic field applied on the substrate. The substrates polarized by the north-pole magnet show a preferential growth of L-isomer crystals, whereas the south-pole polarized surfaces show the growth of the D-isomer.

Enantiomeric excess (EE) of the crystals has been determined using CD spectroscopy, comparing the CD signal with respect to a

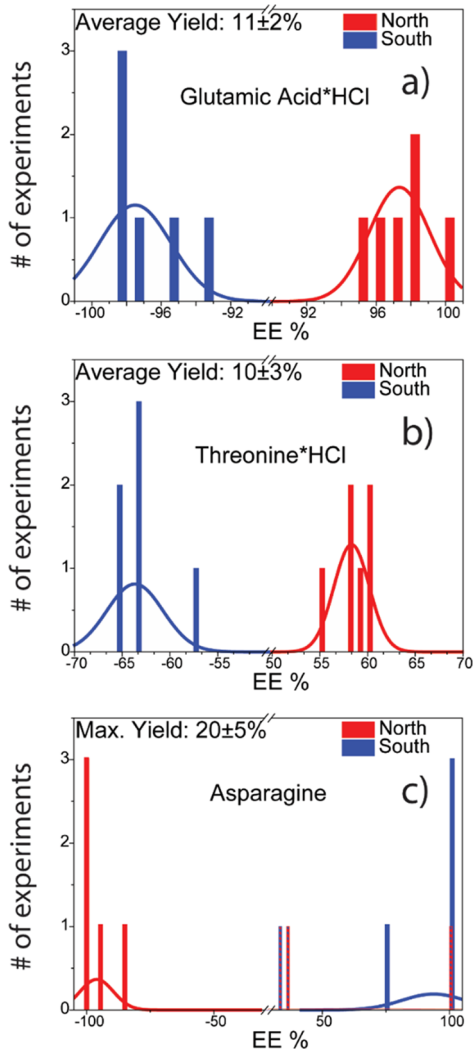


Figure 2. Statistics of the crystallization experiments for (a) glutamic acid·HCl, (b) threonine·HCl, and (c) asparagine. A positive EE value indicates a majority of the L-enantiomer, while a negative EE value indicates a majority of the D-enantiomer.

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Cryst. Growth Des. 2021, 21, 2925−2931

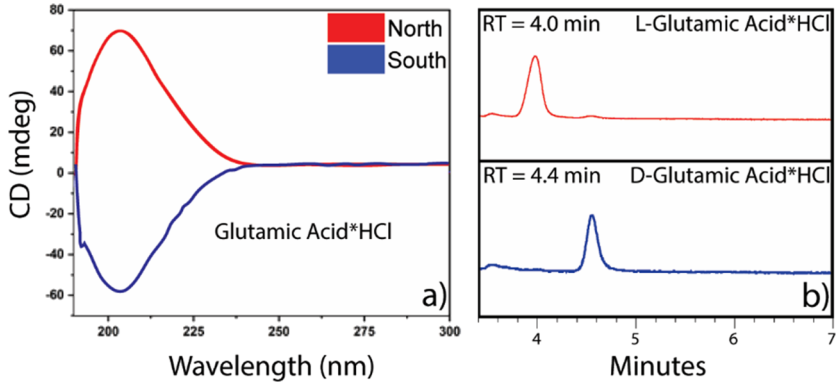

Figure 3. (a) CD spectra of crystals of glutamic acid·HCl grown on ferromagnetic surfaces magnetized respectively with north and south magnet poles close to the back of the surface. (b) HPLC chromatograms of crystals collected from the magnetized surfaces polarized by the north-pole and south-pole magnets, respectively.

calibration curve obtained from the pure isomer (see SI Figure 1a) and with chiral HPLC (Figure 3b) (Astec CHIROBIOTIC T 250 × 4.6 mm; 5 μm column; eluent, MeOH/H_2O/formic acid (70/30/0.02); flow, 1 mL/min; 25 °C; 10 μL injection volume; detector, 205 nm). The EE% of the L-enantiomer obtained by this process is 97 ± 2% and that of the D-enantiomer is 97 ± 2%. The results show that it is possible to separate simultaneously enantiomers with very high purity from the racemic mixture and that the EE% of the obtained crystals is greatly improved compared to the results obtained in the horizontal configuration, where the EE% reached was around 8%. Figure 2a shows the data for each repetition of the experiment, with the EE% of crystals collected from the surfaces of FM substrates. The average yield obtained by applying this method is around 11 ± 2% (calculated from the amount of starting material) for a single step of crystallization.

Threonine Crystallization. Threonine is reported to form a conglomerate upon crystallization from water, but the process was found to not be very straightforward. There are difficulties to get a selective crystallization on magnetic surfaces from its racemic mixture, as also described in ref 2. In the present study, threonine crystallization was carried out starting from a supersaturated racemic mixture in 2 M HCl solution (600 mg/mL Thr), with gradual cooling from 80 °C to 28 °C over a time period of 1.5 h and then left for 36 h at constant temperature. The CD spectra (Figure 4) of the crystals collected from the surfaces show that the crystals grown at the north-pole polarized substrates have an enantiomeric excess of L-threonine·HCl, while crystals grown at the south-pole polarized substrates have D-threonine·HCl excess.

The purity of the crystals obtained by applying this method was around 64 ± 3% EE for D-threonine·HCl and 58 ± 2% for L-threonine·HCl, as shown in Figure 2b, determined by CD spectroscopy only (see the calibration curve of the pure isomer in SI Figure 1b). The average yield obtained by applying this method to threonine is around 10 ± 3% (calculated from the amount of starting material) for a single step of crystallization.

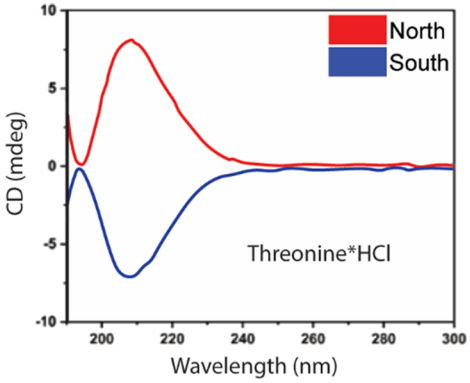

Figure 4. CD spectra of crystals of threonine·HCl grown on ferromagnetic surfaces magnetized respectively with north and south magnet poles close to the back of the surface.

Asparagine Crystallization. Asparagine crystallization was carried out from a supersaturated racemic solution of the amino acid in water (190 mg/mL Asn), which was heated at 95 °C, left to cool down to room temperature, and then left to crystallize for 12 h. The enantiopurity of the crystals collected from the surfaces was measured with CD spectroscopy (Figure 5a) and chiral HPLC (same analytic method used for the glutamic acid; Figure 5b). The crystals grown on the north-pole polarized substrates were D-asparagine, while the crystals grown on the south-pole polarized substrates were L-asparagine (Figure 2c). The enantiopurity of the crystals was around 94 ± 12% for D-asparagine crystals and 96 ± 6% for L-asparagine crystals, which is a considerable improvement compared to the 47% EE% obtained in the horizontal configuration. The maximum yield of the crystallization was 20 ± 5%. It is important to note though that these data are calculated, considering only the successful crystallizations: we have to report that in one repetition, the selectivity of the crystallization was exactly reversed, while in another, the selectivity was extremely low, obtaining only a 30% enantioselectivity.

Imeglimin Hydrochloride Crystallization. Imeglimin is reported to form conglomerates when crystallized as hydrochloride salt.[19] The resolution of the racemic imeglimin hydrochloride salt was carried out by crystallization on magnetic substrates from methanol (325 mg/mL Imeglimin).

The solution was gradually cooled down from 30 °C to 6 °C over a time period of 2 h and left to crystallize for 20 h at this temperature. CD spectroscopy of the collected crystals confirms opposite enantiomeric excess at the opposite magnetized substrates (Figure 6a). Chiral HPLC measurements (Astec CHIROBIOTIC T 250 × 4.6 mm; 5 μm column; eluent, MeOH/ATFA/TEA (100/0.1/0.1); flow, 1 mL/min; 25 °C; 10 μL injection volume; detector, 245 nm) showed EE up to 22 ± 3% for the R-isomer at the south-pole polarized substrate and up to 27 ± 3% EE for the S-isomer at the north-pole polarized one (Figure 6b).

■ DISCUSSION

The crystallization experiments performed showed that a one-batch simultaneous resolution of a conglomerate couple is obtainable by utilizing magnetized surfaces as substrates for the crystallization. This phenomenon is general, and the same system was used for all the materials studied. However, since the interaction strength of chiral molecules with the ferromagnetic substrate (see Figure 7 for the scheme of the mechanism) depends on the molecular properties, the system should be tuned for efficient separations to be achieved. The

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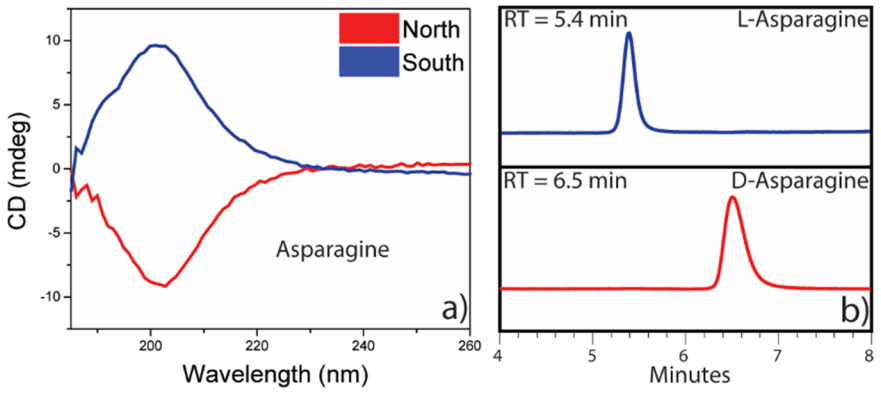

Figure 5. (a) CD spectra of crystals of asparagine grown on ferromagnetic surfaces magnetized, respectively, with north and south magnet poles close to the back of the surface. (b) HPLC chromatograms of crystals collected from the magnetized surfaces polarized by the south-pole and north-pole magnets, respectively.

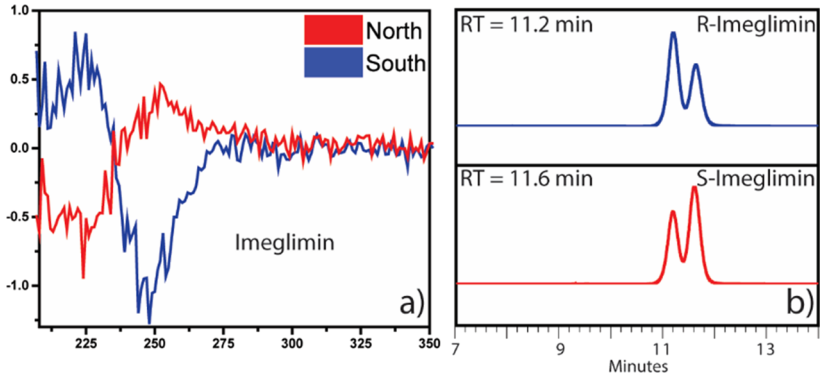

Figure 6. (a) CD spectra of the crystals of imeglimin·HCl grown on ferromagnetic surfaces magnetized respectively with north and south magnet poles close to the back of the surface. (b) HPLC chromatograms of crystals collected from the magnetized surfaces polarized by the south-pole and north-pole magnets, respectively.

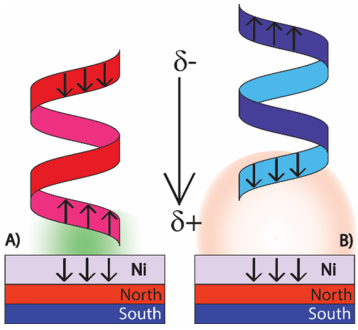

Figure 7. Scheme of the enantioselective mechanism. Upon interaction with the surface, the molecules (depicted as helixes in the scheme to represent the chiral structure) undergo a charge redistribution with the formation of a dipole moment, independent of the handedness of the molecule. Due to the SDCR effect, this dipole moment is spin-polarized, and the sign of the polarization depends on the handedness of the molecule. The spin-polarized molecules interact via exchange interaction with the spin-polarized surface, and depending on the handedness of the molecule, the interaction will be attractive or repulsive.

change in interaction relates to the strength of the CISS effect for a specific molecule and the electric dipole moment. Under a large enough external magnetic field, the electrons' spin states in the ferromagnetic material are split, with a majority of spins pointing in one direction. When a chiral molecule approaches the ferromagnetic surface, charge is reorganized in the molecule to form an induced dipole due to the dispersive forces. Because of the SDCR effect, this electron density reorganization is accompanied by spin polarization due to the chirality of the molecule. Each pole of the induced electric dipole is associated with spin polarization so that there is one orientation of spin polarization associated with the positive pole and the opposite orientation associated with the negative pole. Which orientation is associated with which pole depends on the handedness of the chiral molecule. The relative electronegativity of the molecule and the surface controls the attractive potential. One electric pole will be attracted to the surface more than the other. Hence, the spin-polarized pole interacts with the spin-polarized ferromagnetic substrate and the interaction is either more or less attractive depending on whether the spin on the pole and the spin on the surface are antiparallel (singlet-like state) or parallel (triple-like state). Since the orientation of the spin on the electric pole of the molecule depends on the specific enantiomer, clearly, this interaction is enantiospecific and allows one to separate the enantiomers by their adsorption rate on the surface. In a recent experiment, the interaction of two enantiomers with a ferromagnetic substrate was directly measured by AFM:[20] it was found that the difference in the interaction energy between the ferromagnetic substrate magnetized perpendicular to the surface and the two different enantiomers is of the order of 10 kJ/mole (0.1 eV).

This allows the surface to impart an asymmetric bias on the formation of the first crystal seeds. This mechanism, in which

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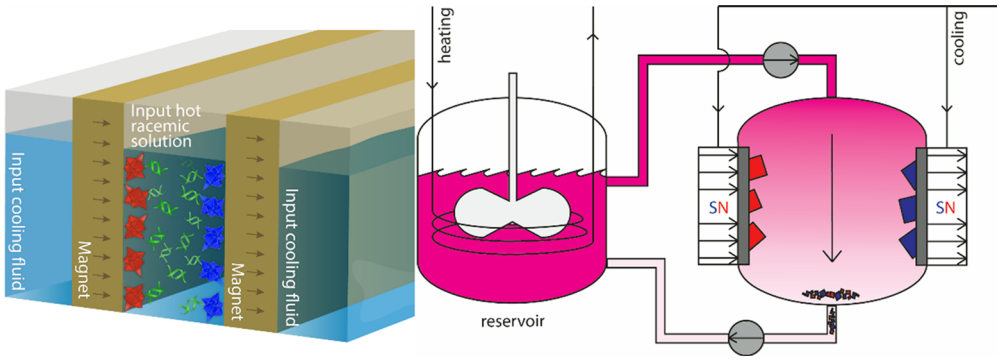

Figure 8. Design of the flow system to improve the crystallization yield of the ferromagnetic substrate-induced resolution.

the preferential crystallization stems from molecular interactions with the surface rather than the preferential adsorption of small chiral crystal seeds, is supported by experiments on the crystallization of sodium chlorate. Sodium chlorate is an achiral molecule that crystallizes in a chiral space group,[21] and therefore, for this system, there is no possibility for spin−spin interaction when the molecule is completely solvated. We did not observe any preferential crystallization for this system in our experiments with ferromagnetic surfaces and thus concluded that the asymmetric bias comes from the interaction of the dissolved chiral molecules with the ferromagnetic substrates, rather than the seeds formed in the initial phase of the crystallization process.

The most common procedure to enantioseparate a conglomerate couple is to use a kinetic resolution by seeding the racemic solution with small crystals of one of the two enantiomers, allowing the formation of one enantiopure crystal phase.[7,22] This procedure usually allows for a limited crystallization yield, usually below 10%,[23] since at higher crystallization yields, the solution becomes enriched with the opposite enantiomer that eventually starts to crystallize, lowering the enantiopurity of the obtained material. In principle, our method does not have this limit, since the crystallization of both enantiomers occurs simultaneously, thus leaving the enantiomeric ratio in the solution unchanged for the whole crystallization. In our experiments on glutamic acid, for example, we were able to obtain a maximum crystal yield of 14% in one step (7% of pure D-Glu and 7% of L-Glu, with an enantiopurity of >95%), which is nearly double to what is normally accessible with single-batch crystallizations based on kinetic resolution. Our yield is also limited by the fact that only the crystals that grew from the ferromagnetic surfaces and remained there are considered. Some of the crystals formed on the surface are falling down and are not considered in our analysis. Increasing the surface area of the ferromagnetic substrates should increase the number of crystals formed on the surfaces and thus lead to improved yields. Another appealing property of the presented method is that it does not require the seeding with enantiopure crystals, since the preferential crystallization is directed by the ferromagnetic substrates. While the attractiveness of this method might be lost when trying to apply it to large industrial productions, where the need for very large magnetic surfaces and the fact that the crystals are formed on a surface can make it unpractical, the simplicity and immediateness of it can actually make it quite interesting for small batches and laboratory-scale crystallizations.

A possible strategy to improve the crystallization yield is to switch from a static crystallization setup to a continuous flow system and to recycle the crystals that are not attached to the ferromagnetic substrates. By keeping the mother racemic solution at a higher temperature than the substrates, it is possible to promote the crystallization only on the ferromagnetic surfaces. At the same time, it is possible to remove the crystals not bound to the walls and feed them back to the reservoir (see Figure 8) to maximize the final crystallization yield. In this way, the crystals will grow only on the ferromagnetic surfaces with a very high EE%, and the final yield will depend on the substrate area available for crystallization. This concept is currently under study in our laboratory, and we expect to be able to substantially increase the final crystallization yield using this concept.

Among the molecules studied, the best results could be obtained with glutamic acid. Both high EE and a good crystallization yield could be obtained. The experiments performed on threonine on the other hand were less satisfactory. While the final crystallization yield was quite high, the EE was clearly inferior to the one observed for glutamic acid, attested in the 60% range. This unexpected behavior can be linked to the crystallization properties of threonine from racemic solutions. It was found in other reports that the enantiopure crystals can act as crystallization seeds also for the opposite enantiomer.[24] This means that after the formation of the first crystals, the process loses enantioselectivity, since the ferromagnetic surfaces cannot affect the selectivity of the crystal growth anymore. To circumvent this phenomenon, the crystallization time should be kept as short as possible, but this would limit the final yield of the process.

The results obtained with asparagine were not as reproducible as those with glutamic acid. While most of the experiments gave high EE and a yield of crystallization of 20%, one of the experiments performed showed a reversed preferential growth, with respect to the magnetic field, and another resulted in EE of only 30%. The reason for this instability is not clear and may result from contamination of the solution. However, if we focus the analysis only on the successful experiments, the results are encouraging. Former reported studies on the preferential crystallization of asparagine indicate less than 10% yield when performed in a single batch with seeding of the enantiopure crystals.[25]

The experiments on the resolution of racemic Imeglimin·HCl showed a rather poor enantiomeric excess. In the literature, there are very few reports on the crystallization behavior of Imeglimin·HCl. Levilain[26] reported very poor entrainment properties of the methanol solution of Imeglimin,

https://doi.org/10.1021/acs.cgd.1c00093
Cryst. Growth Des. 2021, 21, 2925−2931

where the maximum EE% reached in the solution was found to be around 4%, and the EE% of the crystals dramatically dropped after the first stages of crystallization. The ~20% EE observed here, albeit low, is thus perfectly in line with the previously reported results.

In summary, we presented the quantitatively analyzed ferromagnetic surface-induced crystallization of conglomerates. Although the results obtained are in low scale, upscaling does not require any technological transformation. The advantage of the method presented is that the method is general, no seeding is required, and both pure enantiomers are obtained simultaneously in a single stage.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd.1c00093.

Calibration curves for the CD quantification of the EE% of glutamic acid and threonine; non-aggregated data of the crystallization experiments for glutamic acid, threonine, and asparagine; description and results of the experiments on sodium chlorate (PDF)

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‖D.B. and Y.S. contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

We acknowledge the financial support from a BSF-NSF-CBET program grant #2018621.

Notes

The authors declare the following competing financial interest(s): FT, EC, RN and YP filed a patent on the magnetic separation of chiral compounds, US application No. 62/636,903.

■ ACKNOWLEDGMENTS

We thank Chiral Quest (Suzhou) Co. Ltd. for providing the Imeglimin·HCl used in the experiments.

■ REFERENCES

(1) Rouhi, A. M. Chiral business: Fine chemicals companies are jockeying for position to deliver the increasingly complicated chiral small molecules of the future. *Chem. Eng. News* **2003**, *81*, 45−61.

(2) Saigo, K. Resolution of Chiral Drugs and Drug Intermediates by Crystallization. In *Chirality in Drug Research*; Francotte, E., Lindner, W. Eds.; Wiley-VCH: Weinheim, 2006; pp. 127−154.

(3) Coquerel, G. Preferential Crystallization. In *Novel Optical Resolution Technologies*; Sakai, K., Hirayama, N., Tamura, R. Eds.; Springer: Berlin Heidelberg, 2006; pp. 1−51.

(4) Sakai, K.; Sakurai, R.; Nohira, H. New Resolution Technologies Controlled by Chiral Discrimination Mechanisms. In *Novel Optical Resolution Technologies*; Sakai, K., Hirayama, N., Tamura, R. Eds.; Springer: Berlin Heidelberg, 2006; pp. 199−231.

(5) Tung, H.-H.; Paul, E. L.; Midler, M.; McCarzuley, J. *Crystallization of Organic Compounds: An Industrial Perspective*; Wiley: Hoboken, N.J, 2009.

(6) Lewis, A.; Seckler, M.; Kramer, H. J. M.; Van Rosmalen, G. *Industrial Crystallization: Fundamentals and Applications*; Cambridge University Press: Cambridge, 2015; DOI: 10.1017/CBO9781107280427.

(7) Crosby, J. Chirality in Industry - An Overview. In *The Commercial Manufacture and Applications of Optically Active Compounds*; Collins, A. G. N., Crosby, J. Eds.; Wiley: Chichester, 1992; pp. 1−68.

(8) Hayes, S. T.; Assaf, G.; Checksfield, G.; Cheung, C.; Critcher, D.; Harris, L.; Howard, R.; Mathew, S.; Regius, C.; Scotney, G.; Scott, A. Commercial Synthesis of (*S*-*S*)-Reboxetine Succinate: A Journey To Find the Cheapest Commercial Chemistry for Manufacture. *Org. Process Res. Dev.* **2011**, *15*, 1305−1314.

(9) Graves, P. E.; Salhanick, H. A. Stereoselective Inhibition of Aromatase by Enantiomers of Aminoglutethimide. *Endocrinology* **1979**, *105*, 52−57.

(10) Muller, G. W.; Konnecke, W. E.; Smith, A. M.; Khetani, V. D. A Concise Two-Step Synthesis of Thalidomide. *Org. Process Res. Dev.* **1999**, *3*, 139−140.

(11) Food and Drug Administration. FDA's Policy Statement on the Development of New Stereoisomeric Drugs (Stereomeric Drug Policy). *Fed. Regist.* **1992**, *57*, FR22249.

(12) Committee for Proprietary Medical Products. *Working Parties on Quality, Safety and Efficacy of Medicinal Products. Note for Guidance: Investigation of Chiral Active Substances (III/3501/91)*; CPMP: Brussells, 1993.

(13) Tassinari, F.; Steidel, J.; Paltiel, S.; Fontanesi, C.; Lahav, M.; Paltiel, Y.; Naaman, R. Enantioseparation by Crystallization Using Magnetic Substrates. *Chem. Sci.* **2019**, *10*, 5246−5250.

(14) Naaman, R.; Paltiel, Y.; Waldeck, D. H. Chiral Molecules and the Spin Selectivity Effect. *J. Phys. Chem. Lett.* **2020**, *11*, 3660−3666.

(15) Naaman, R.; Paltiel, Y.; Waldeck, D. H. Chiral Induced Spin Selectivity Gives a New Twist on Spin-Control in Chemistry. *Acc. Chem. Res.* **2020**, *53*, 2659−2667.

(16) Ray, K.; Ananthavel, S. P.; Waldeck, D. H.; Naaman, R. Asymmetric Scattering of Polarized Electrons by Organized Organic Films of Chiral Molecules. *Science* **1999**, *283*, 814−816.

(17) Banerjee-Ghosh, K.; Ben Dor, O.; Tassinari, F.; Capua, E.; Yochelis, S.; Capua, A.; Yang, S.-H.; Parkin, S. S. P.; Sarkar, S.; Kronik, L.; Baczewski, L. T.; Naaman, R.; Paltiel, Y. Separation of Enantiomers by Their Enantiospecific Interaction with Achiral Magnetic Substrates. *Science* **2018**, *360*, 1331−1334.

(18) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolution*; Wiley: Krieger, Florida, 1994.

(19) Helmreich, M.; Niesert, C. P.; Cravo, D.; Coquerel, G.; Levilain, G.; Wacharine-Antar, S.; Cardinael, P. Process for Enantiomeric Separation of Racemic Dihydro-1,3,5 triazines via Preferential Crystallization. Poxel SAS, US 8742102B2, 2014.
(20) Ziv, A.; Saha, A.; Alpern, H.; Sukenik, N.; Baczewski, L. T.; Yochelis, S.; Reches, M.; Paltiel, Y. AFM-Based Spin-Exchange Microscopy Using Chiral Molecules. *Adv. Mater.* **2019**, *31*, 1904206.
(21) Abrahams, S. C.; Bernstein, J. L. Remeasurement of Optically Active $NaClO_3$ and $NaBrO_3$. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1977**, *33*, 3601−3604.
(22) Czapla, F.; Polenske, D.; Klukas, L.; Lorenz, H.; Seidel-Morgenstern, A. Cyclic Auto-Seeded Polythermal Preferential Crystallization—Effect of Impurity Accumulation. *Chem. Eng. Process.* **2010**, *49*, 22−28.
(23) Elsner, M. P.; Ziomek, G.; Seidel-Morgenstern, A. Efficient Separation of Enantiomers by Preferential Crystallization in two Coupled Vessels. *AIChE J.* **2009**, *55*, 640−649.
(24) Profir, V. M.; Matsuoka, M. Processes and Phenomena of Purity Decrease During the Optical Resolution of DL-threonine by Preferential Crystallization. *Colloids Surf., A* **2000**, *164*, 315−324.
(25) Petruševska-Seebach, K.; Seidel-Morgenstern, A.; Elsner, M. P. Preferential Crystallization of L-Asparagine in Water. *Cryst. Growth Des.* **2011**, *11*, 2149−2163.
(26) Levilain, G. Development and Improvement of Resolution Methods by Direct Crystallization. Ph.D. Thesis, University of Rouen, Rouen, France, 2010.

https://doi.org/10.1021/acs.cgd.1c00093
Cryst. Growth Des. 2021, 21, 2925−2931