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Authors

Hein, Jason E.
Cao, Blessing Huynh
van der Meijden, Maarten W.
[et al.](#)

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Resolution of Omeprazole Using Coupled Preferential Crystallization: Efficient Separation of a Nonracemizable Conglomerate Salt under Near-Equilibrium Conditions

Jason E. Hein,^{*,†} Blessing Huynh Cao,[†] Maarten W. van der Meijden,[‡] Michel Leeman,[‡] and Richard M. Kellogg^{*,‡}

[†]Chemistry and Chemical Biology, University of California, Merced, California 95343, United States

[‡]Syncom BV, Kadijk 3, 9747 AT Groningen, The Netherlands

S Supporting Information

ABSTRACT: A facile and efficient resolution of omeprazole as the monopotassium salt diethanol solvate using coupled preferential crystallization has been developed. This approach uses small perturbations in solution-phase concentration to control the competing process of selective crystal growth while suppressing unwanted primary nucleation. The result is a selective crystallization technique that replaces the traditional batch-type isolation with a continuous process amenable to scale, which provides easy access to enantiopure conglomerate crystals.

INTRODUCTION

Access to large quantities of enantiopure chemicals remains a major challenge for the fine chemical and pharmaceutical industries. The recently discovered method for the total resolution of racemizable conglomerates by attrition-enhanced grinding of suspensions provides a simple and efficient alternative to conventional asymmetric synthetic routes, diastereomeric resolution, or preferential crystallization procedures.^{1–3} These attrition-enhanced deracemization methods have attracted much interest with regard to the mechanism.^{4,5} Interest has not been limited to theory. Practical applications were quickly demonstrated. So far, attrition-enhanced deracemization has been applied in the synthesis of enantiopure esters of naproxen⁴ as well as the key chiral intermediate required in the preparation of clopidogrel (Plavix).^{6,7}

Attrition-enhanced deracemization is limited, however, to target molecules that are conglomerates and which can be racemized in solution in the presence of a stable crystalline phase. For those conglomerates that cannot be racemized—most in fact—resolution by preferential crystallization, also an approach free of any resolving agent, can often be applied to isolate the pure enantiomers.⁸ Preferential crystallization has been successfully employed to separate a wide variety of chiral molecules.⁹ However, application of this technique by nonexperts is rather challenging. Great care must be taken to control the crystallization conditions in order to ensure that the undesired enantiomer does not spontaneously nucleate. Generally, this requires detailed knowledge of the solubility phase diagram for the target system, including width of the metastable zone. In addition, this process typically is carried out in batch mode with limited yields, usually not more than 10%

per step, although the overall yield may approach the maximum of 50% per enantiomer.

To address these shortcomings, Coquerel et al. have developed the autoseeded polythermic-programmed preferential crystallization (AS3PC) method.⁹ Despite the improvement in productive efficiency, significant knowledge of the thermodynamic and kinetic parameters for all relevant solid–liquid equilibria must be acquired prior to attempting the operation.¹⁰ Preferential crystallization, although a powerful technique, remains a labor-intensive and exacting procedure reserved chiefly for specialists and experts.

A near-equilibrium, nonbatch method, recently introduced by our group, has been used to separate nonracemizable conglomerate crystals including threonine and sodium ammonium tartrate tetrahydrate (Pasteur's salt).¹¹ Two crystallization flasks containing suspensions of crystals both equilibrated at the same temperature (Figure 1a illustrated for the case of Pasteur's salt) are used. The racemic mixture is held in flask A and subjected to attrition, while crystals of the pure enantiomer are suspended in flask B, which is stirred gently. The liquid phases from the two flasks are circulated, using an effective filter to prevent transfer of any solids. Attrition in flask A breaks the larger crystals into smaller fragments, which are more soluble owing to the Gibbs–Thompson effect.^{12,13} The solution (Figure 1a, point 1), containing an equal concentration of both enantiomers, is delivered to flask B where larger, and less soluble, seed crystals grow. This leads to a drop in the solution-phase concentration of the seeded enantiomer (Figure 1a, point 2).

Over time this process leads to a net movement of the seeded enantiomer from flask A to B, resulting in two enantiopure crystal populations. The driving force for this near-equilibrium, essentially thermodynamically driven, process is provided by the solubility difference due to crystal size within the two flasks. This provides the small supersaturation necessary to facilitate deracemization. Note that the solution phase remains close to racemic. The general utility of our coupled preferential crystallization method is underscored by the successful resolution of sodium ammonium tartrate tetrahydrate. This famous conglomerate has been reported

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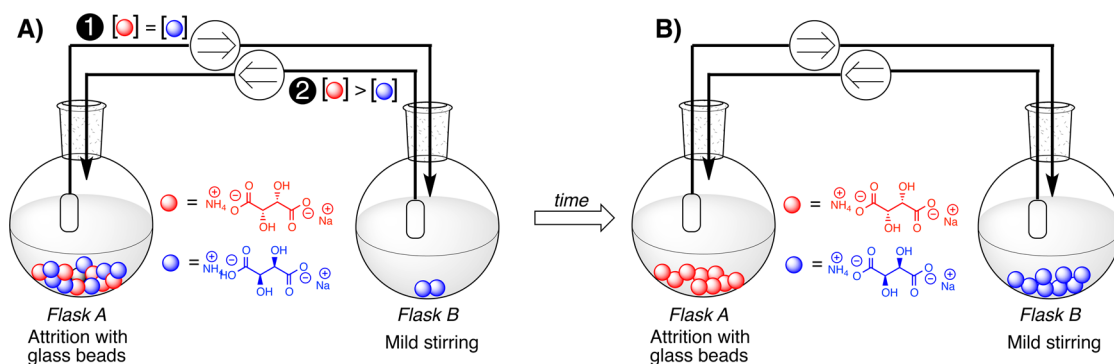


Figure 1. Schematic for coupled preferential crystallization using attrition.

not to be separable by classical preferential crystallization techniques although it can be resolved by the AS3PC method.¹⁴

More recently, Levilain et al.¹⁵ carried out a similar resolution using coupled preferential crystallization. A temperature difference between two flasks, rather than attrition, was used to accomplish a similar nonbatch enantioselective separation. In both the thermal¹⁵ and attrition-driven¹¹ examples, the near-equilibrium conditions of these processes ensured that unwanted primary nucleation of the nonseeded enantiomer did not occur. This process of coupled preferential crystallization represents an operationally far easier process than kinetically driven preferential crystallization techniques.¹⁶

Esomeprazole (Nexium, Figure 2, (S)-1), a proton pump inhibitor with international gross yearly sales in the billions, is

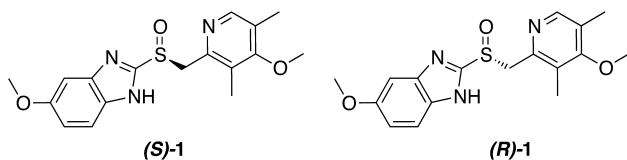


Figure 2. Enantiomers of omeprazole.

one of two nonracemizable enantiomers¹⁷ containing a single chiral sulfoxide center. Enantiopure (S)-1 is typically obtained by asymmetric oxidation of the precursor sulfide¹⁸ or via resolution of racemic mixtures by crystallization as a diastereomeric salt.^{19,20} Recently, Coquerel et al.²¹ developed a preferential crystallization approach for overall resolution of racemic 1 using the diethanol solvate of the monopotassium salt of 1 (Figure 3, (S)-2 and (R)-2), which is a conglomerate that crystallizes in the $P2_1$ space group. This challenging material must be handled with care, owing to a propensity towards decomposition¹⁷ and loss of solvate,²² and moreover, the crystals cannot readily withstand mechanical stress.²³ This major achievement by these authors was made possible by carefully elucidating the relevant phase diagrams to describe the requisite solid–liquid equilibria in this complex system.

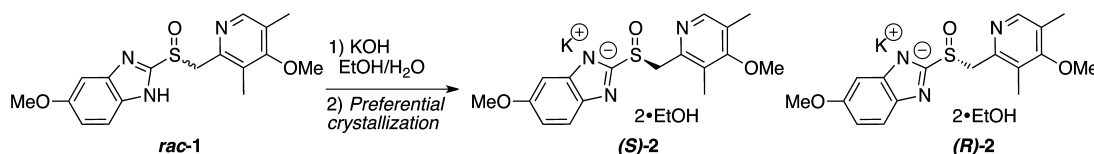


Figure 3. Crystallization of *rac*-1 as monopotassium salt/diethanol solvate.

DISCUSSION AND RESULTS

We wanted to adapt the selective crystallization of (S)-2 to our attrition-induced, nonbatch, preferential crystallization approach. Basic information on solubility and primary nucleation behavior are easily obtained using a Mettler ic10 ReactIR interfaced with Mettler EasyMax Synthesis Workstation.²³ This combination of equipment allows rapid and accurate determination of the solubility and crystallization behavior of the material, over a range of temperatures and solution compositions.^{24,25} Conglomerate 2 possesses a very wide metastable zone, potentially providing a very broad range wherein crystallization can be accomplished. However, attempts to carry out an attrition-induced deracemization working in the concentration range indicated in Figure 4 consistently failed. We attribute this to mechanical instability of crystals of 2.²³

In order to drive mass transfer, the necessary concentration gradient between the coupled vessels can also be achieved by holding one flask at an elevated temperature relative to that of the other.^{11,15} The magnitude of this temperature differential (Figure 5, $\Delta T = T_1 - T_2$) is critical to allow efficient resolution of the conglomerate solid. If ΔT is too large, primary nucleation of the undesired crystal antipode in flask B will result, whereas a low ΔT will result in an insufficient solubility gradient between the flasks, leading to very slow mass transfer.

To establish quickly an appropriate ΔT for the separation of *rac*-2, a series of separations was carried out. Flask A was charged with a racemic mixture of 2 (4.5 g), and (S)-2 (0.1 g) was added to flask B. The two flasks were then charged with a homogeneous solution of 2 in 5% water in ethanol (50 mL into each, $[rac-2] = 0.072$ M).²³ The internal temperature of the two suspensions was then independently set (Figure 5, $T_1 > T_2$), and the mixtures were stirred for 10 min to allow equilibration. The liquid phase was then circulated between the flasks at a rate of 0.5 mL/min. After 12 h the solid phase from both flasks was sampled, and the enantiomeric excess was measured. A temperature difference of 2–4 °C was found to be optimal; resolution failed when the temperature difference was increased to 10 °C.²³

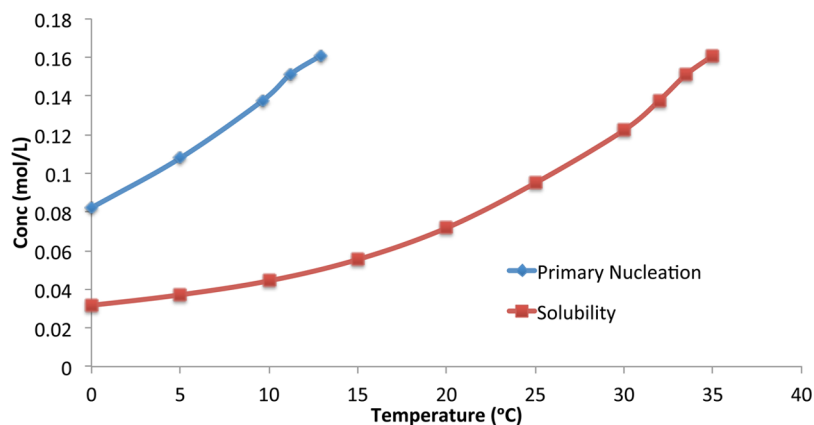


Figure 4. Solubility measurements of *rac*-2 in 5% water in EtOH.

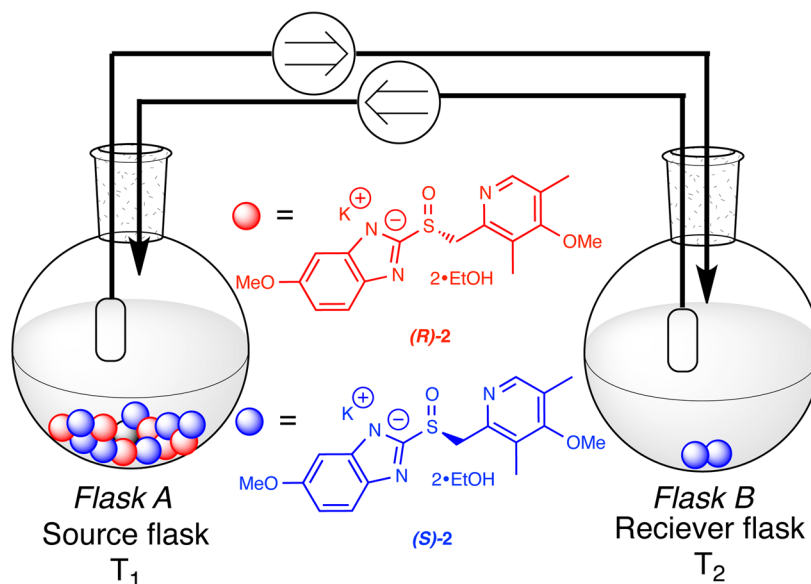


Figure 5. Coupled preferential crystallization using temperature bias; $T_1 = 25\text{ }^\circ\text{C}$, $T_2 = 21\text{ }^\circ\text{C}$.

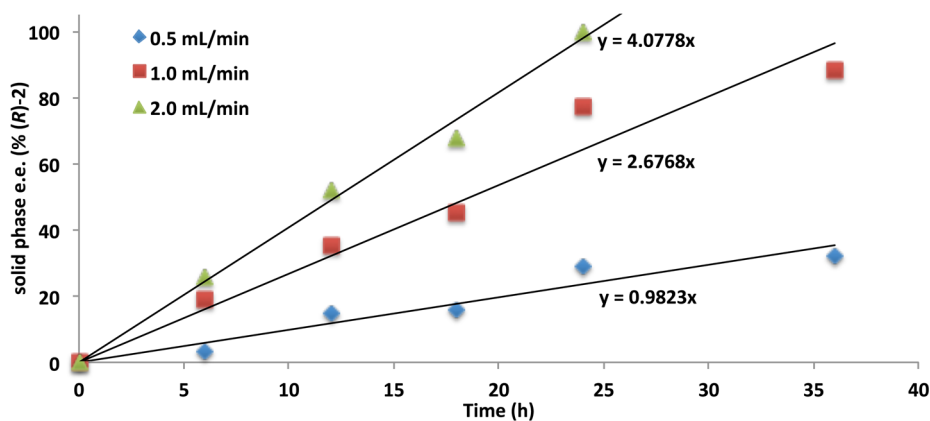


Figure 6. Change in solid-phase ee as a function of solution flow rate. (Ee is from solid phase in flask A source.)

The rate of liquid circulation also affects the efficiency of resolution. In a series of experiments, 4.5 g of *rac*-2 and 0.1 g of (*S*)-2 were added to flasks A and B with corresponding temperature differences of $T_1 = 25\text{ }^\circ\text{C}$ and $T_2 = 21\text{ }^\circ\text{C}$, respectively. The flasks were charged with a homogeneous saturated solution of 2 in 5% water in ethanol, and the liquid phase was circulated at different rates.

Solid-phase enantiomeric excess in flask A was measured at different time points (Figure 6). This revealed a constant rate of change. The speed of liquid circulation between flasks A and B appears to limit the rate of resolution. In our setup, flow rates higher than 2 mL/min were not possible due to mechanical failure as a result of clogging at the filters. However, more time-

efficient separation should be possible with appropriate modifications to the apparatus.

After both flasks had reached enantiopurity, crystals were recovered by filtration to give enantiopure (S)-2 and (R)-2 (Table 1). The average recovery of (S)-2 was ~87% based on

Table 1. Recovery and efficiency of resolution

| flow rate (mL/min) | flask A (g) ^{a,c} | flask B (g) ^{b,c} | efficiency (g L ⁻¹ h ⁻¹) |
|--------------------|----------------------------|----------------------------|---|
| 1 | 1.68 | 1.94 | 0.510 ^c |
| 2 | 1.48 | 2.01 | 0.838 |

^aMass of (R)-2. ^bMass of (S)-2. ^cEe's of recovered crystals were >98%

the initial charge of 4.5 g of rac-2. The mass discrepancy between recovered (R)-2 and (S)-2 was due to the temperature difference of the flasks. Monitoring the time to resolution for our small-scale apparatus allows us to also calculate an approximate maximum efficiency of 0.0838 g of (S)-2 per hour. Although this is comparatively lower than Coquerel's AS3PC approach,²¹ it should be noted that our continuous process required no manipulation of the solid phases once seeding and circulation had commenced. Moreover, scaling our process should be easily accomplished due to its procedural simplicity.

CONCLUSION

A clear practical advantage of a coupled preferential crystallization technique stems from near-equilibrium conditions maintained during the separation. The conglomerate enantiomers are crystallized continuously using only a small concentration gradient to drive mass transfer. As only a small supersaturation is created, the likelihood of primary nucleation of the unseeded enantiomer is minimal. In our previous work, we used crystallite size differences, created by exposing crystal populations to different mechanical attrition conditions to create the necessary concentration bias. Unfortunately, the crystals of 2 cannot withstand attrition. The use of a temperature gradient provides an alternative means of operation, whereby Gibbs–Thompson solubility effects dependent on crystal size and carefully controlled supersaturation to hinder primary nucleation are harnessed to power the resolution. Such an approach has the advantage of simplicity, economy, and nonbatch operation.

ASSOCIATED CONTENT

Supporting Information

Description of the coupled preferential crystallization apparatus; details of the solubility determinations and peripheral crystallization experiments; and details for the generation of the monopotassium salt/diethanol solvate. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jhein2@ucmerced.edu. Tel: 209-228-7920.

Notes

The authors declare no competing financial interest.

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