Influence of the Process on the Mechanisms and the Performances of the Preferential Crystallization: Example with (±)-5-(4-Bromophenyl)-5-methylhydantoin

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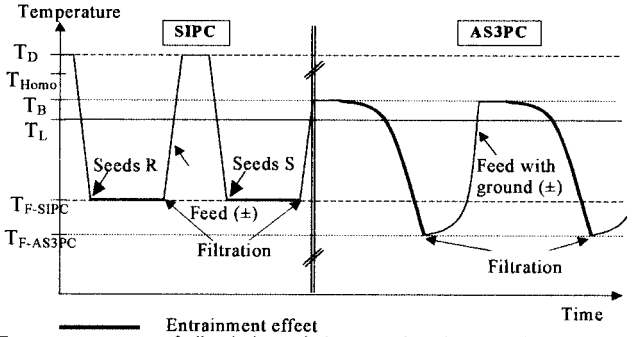
Resolution of the title compound is carried out at a two liter scale via two different processes of preferential crystallization (PC), the Auto Seeded Programmed Polythermic Preferential Crystallization (AS3PC) process and the classical Seeded Isothermal Preferential Crystallization (SIPC) process. The ratio, crystal growth rate/secondary nucleation rate, is strongly under the influence of the process. Consequently AS3PC process appears more efficient than SIPC process in terms of purity of the crops (optical purity), yield, easiness of scale up and downstream operations such as filterability.

The resolution of racemic mixtures still remains a challenge for the organist chemists. Literature reveals that the use of chiral resolving intermediates keeps on being the leading option.[1] Nevertheless, in case of racemic mixture crystallizing as a conglomerate, resolution via preferential crystallization (PC) (also called resolution by entrainment) is a valuable alternative. The main advantages of the PC over the conventional pasteurian method are that : a) the theoretical yield is quantitative since the mother liquor can be recycled, b) there is no need for chiral resolving agent, c) the two enantiomers are easily purified without loss of enantiomeric excess (ee) since they crystallize as a conglomerate.

By essence, in the course of the PC, one enantiomer must remain supersaturated while the second is selectively crystallizing; therefore this process is run far from thermodynamic equilibrium. The aim of this study is to investigate the influence of the process on the mechanisms and the performances of the PC. This is achieved by comparing the results obtained via the Auto Seeded Programmed Polythermic Preferential Crystallization (AS3PC) and via the conventional Seeded Isothermal Preferential Crystallization (SIPC). In the latter case, the following sequence of operations is alternatively repeated for each enantiomer (Figure 1): (i) The system composed of solvent, racemic mixture and M mass units of enantiomeric excess (e.g. *R*), is homogenized at T_D (> T_{HOMO}) and then cooled down to $T_{F\text{-}SIPC}$, without any spontaneous nucleation. (ii) Seeding is implemented with very pure nuclei of enantiomer (e.g. *R*). (iii) The selective secondary nucleation and crystal growth of the enantiomer *R* occur up to the inversion of the optical rotation of the mother liquor. (iv) The suspension is filtered and yields a 2 M mass of enantiomer *R*. (v) 2 M mass of (±) is thus added to the mother liquor to yield a system with M mass of ee with the enantiomer *S*. The process is simply continued by repeating this cycle of operations; this affords alternatively the *R* and *S* enantiomers.

The two main differences between AS3PC and SIPC procedures (cf. Figure 1) are that: (i) The starting point of the AS3PC process is not a homogenized solution at $T_D > T_{HOMO}$ but rather a suspension at T_B : $T_L < T_B < T_{HOMO}$ composed of crystals of the enantiomer in excess in thermodynamic equilibrium with their saturated solution. This preliminary operation (i.e. selective dissolution) is based on a precise adjustment of the temperature so that a biphasic system in thermodynamic equilibrium is obtained at T_B. If $T_B = 0.5 \times (T_L + T_{HOMO})$, about 50% of the initial enantiomeric excess (thus 25% of the expected crops) is present as initial seeds. Moreover, in favorable cases, T_B can be adjusted closer to T_L so that up to 45% of the total crops obtained at the end of the crystallization act as pure seeds in equilibrium at the beginning of the crystallization. (ii) From T_B to $T_{F\text{-}AS3PC}$, the above suspension is submitted to a set of appropriate: cooling program, stirring mode and stirring rate, so that the crystal growth is favored rather than a non controlled nucleation. An appropriate sieving is implemented on the racemic mixture added so that the crystals remaining undissolved at the end of the annealing (at T_B) are small enough to ensure a large surface of solid ready to grow. Thus, the supersaturation is kept under control by this well-fitted temperature versus time law, the large area of crystals and a smooth renewal of the mother liquor around the crystallites.

Because of the continuous control of the secondary nucleation and the crystal growth resulting in a smooth surface energy of the crystallites, the final temperature of the auto-seeded process $T_{F\text{-}AS3PC}$ can be adjusted below the temperature of the seeded isothermal process $T_{F\text{-}SIPC}$ allowing a larger yield.



T_L = temperature of dissolution of the racemic mixture only; T_{HOMO} = temperature of homogenization ; T_D and $T_{F\text{-}SIPC}$ = respectively, starting and end points of SIPC process, T_B and $T_{F\text{-}AS3PC}$ = respectively, starting and end points of AS3PC process.

Figure 1. Temperature versus time profiles for SIPC process (conventional) and AS3PC process (new and recommended).

The incidence of the process on the mechanisms prevailing during the stereoselective nucleation and crystal growth is demonstrated by using Focused Beam Reflectance Measurement (F.B.R.M.). F.B.R.M. technique is an in-line method which permits to monitor the evolution of particles in suspension by

measuring their chord lengths during the crystallization (0.8 – 1000 μm). The population of 3D particles is thus represented in a 1D space by means of a chord size distribution (CSD). We focused our interest on the smallest detectable chords (0.8–1.9 μm); on the one hand, a sudden increase of their counts means that nucleation rate has risen a short time before, on the other hand their decrease depicts a predominant crystal growth period.

This study has been carried out at two-liter scale on the title compound, (±)-5-(4-bromophenyl)-5-methylhydantoin, which crystallizes as a stable conglomerate and is a good chiral starting reagent for synthesis of non natural aminoacids.

At the beginning of each cooling of the AS3PC process, the crystals remaining after the selective dissolution are small enough to ensure a large surface ready for crystal growth, so that a constant decrease of the 0.8–1.9 μm chords is observed as depicted on Figure 2. Consistently, Figure 3 shows that the crude crops are constituted of well-shaped crystals easy to filtrate (3 min on a glass filter N°3; diameter 10 cm). In the SIPC process the driving force is created by a rapid cooling of the homogeneous solution from 85 °C down to the lowest possible temperature (22 °C) without any spontaneous nucleation. As shown on Figure 2, at 22 °C, the homogeneous solution, continuously stirred, undergoes a high secondary nucleation rate without any control, (3 min after the inoculation of the seeds ≈ 4.8×10^3 counts for 0.8–1.9 chords). It results in a large population of small particles (Figure 3) difficult to filtrate (30 min with same experimental set up as that for AS3PC).

Comparisons between yield and optical purity (O.P.) of the crude crops (Table 1) also give evidence of the interest of the auto seeding and smooth conditions in both secondary nucleation and crystal growth. Consistently, the crystallinity (assessed by the Full Width at Half the Maximum (FWHM) X-ray diffraction peak) of the crops obtained via SIPC process (FWHM = 0.317° /2θ scale λ(Kα)Cu for 18.97° diffraction peak) is significantly poorer than that via AS3PC process (FWHM = 0.185° /2θ scale λ(Kα)Cu).

Up to now, organic chemists have been more interested in running the PC for supply in pure enantiomers rather than analyzing the different mechanisms prevailing during the entrainment which thus, have been overlooked.

This study shows that, provided no unstable racemic compound limits the entrainment effect,[2] the process has a strong influence on both secondary nucleation and crystal growth rates. By enhancing the crystal growth at the expense of a non controlled nucleation, smooth conditions during the entrainment offer the possibility of a full control of the crystallization of one enantiomer and limit the spontaneous nucleation of its antipode. A better understanding of the mechanisms shows that a more rational approach of the stereoselectivity of both secondary nucleation and crystal growth can enhance significantly the interest in the PC. Moreover, the auto seeding and the continuous control of the crystallization give advantage in the scale up and are fully compatible with other variants proposed to improve the PC such as the replacing crystallization.[3]

Table 1. Comparative Results

Method	O.P./%	Crude crops/g
AS3PC[a]	96	42
SIPC[b]	44	62

[a] Average on 30 crystallizations. [b] Average on 4 crystallizations.

Initial conditions: mass of (±): 104.0 g, mass of solvent: 1640 g, mass of pure (–) enantiomer: 18 g, enantiomeric excess: 14.75%, racemic solution: 6.00%. T_L = 57 °C. Duration of the annealing at T_B : 30 min (determined by constant value of the rotary power of the mother liquor in equilibrium with the crystals of the enantiomer in excess), stirring rate: 250 rpm (maintained constant throughout the crystallization). T_B= 65°C; T_F= 20.5°C. Duration of the crystallization: 65 min. Cooling program: [60.5°C, 0 min], [22.9°C, 60 min], [20.5°C, 65 min].

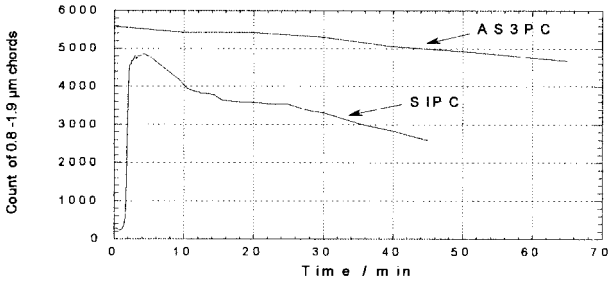


Figure 2. Evolution of the chords size distribution (0.8 μm–1.9 μm) versus time during implementation of AS3PC and SIPC processes.

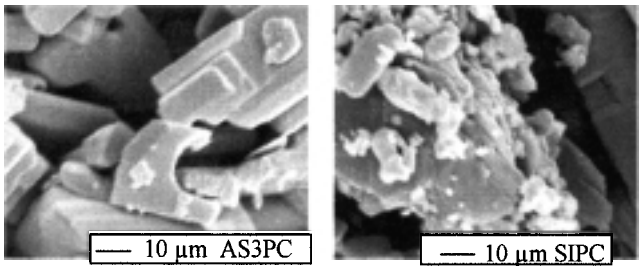


Figure 3. SEM photographs of crude crops obtained from SIPC and AS3PC processes.

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