Oscillating Crystallisation of a Chiral Compounds in quasi-racemic solution; Evidence of a Multiepitaxy Crystal Growth Mechanism and Influence of Stirring

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Preferential crystallization is a cheap and efficient process for the preparative resolution (separation) of chiral drug substances or key intermediates[1]. Nevertheless, the implementation of this type of process requires that the racemic mixture crystallizes as a conglomerate (i.e., a physical mixture of crystals containing only one enantiomer), which can be established from the binary phase diagram between the two enantiomers[2].

This condition is fulfilled in the case of 5-ethyl-5-methylhydantoin (12Hyd hereafter), which is used for its antibacterial and antifungal activity[3], and as an intermediate for the synthesis of isovaline[4]. Nevertheless, applying preferential crystallization to (±)12Hyd in water was shown to be uneasy and led to poor yields[5], although no metastable racemic compound was detected[6].

A systematic crystal growth study, combined with stereoselective dissolution experiments have revealed that particles in the shape of single crystals are actually made of the association of homochiral lamellar fragments[5]. Therefore, the growth mechanism actually involves the alternated bidimensional nucleation and growth of macroscopic homochiral domains, leading to a “lamellar polyepitaxy” phenomenon, which is responsible for the absence of enantiomeric excess in apparent single crystals, and also for the formation of hourglass figures through specific crystal faces.

These aspects could be rationalized by using a “crystal engineering” approach based on structural and molecular modelling data. In particular, the interface between neighbouring lamellar fragments and the possible existence of a racemic compound could be investigated by using a model developed in our laboratory, devoted to the prediction of derived crystal structures[7]. Furthermore, it could also be established that the alternated 2D nucleation and growth process of (±)12Hyd constitutes an oscillating crystallization mechanism controlled by diffusion only. This was experimentally confirmed by the implementation of a gentle stirring of the mother liquor during the crystallization, which led to crystals exhibiting high enantiomeric excess[8].

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