Oscillating Crystallization in Solution between (+)- and (−)-5-Ethyl-5-methylhydantoin under the Influence of Stirring

Claire Gervais, Stéphane Beilles, Pascal Cardinaël, Samuel Petit, and Gérard Coquerel*

Unité de Croissance Cristalline et de Modélisation Moléculaire (UC²M²), UPRES EA 2659, IRCOF, Université de Rouen, rue Lucien Tesnière, F-76 821 Mont Saint-Aignan Cedex, France

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Although the title compound crystallizes as a stable conglomerate without any detectable solid solution, particles in the shape of single crystals grown from the racemic aqueous solution without stirring contain almost no enantiomeric excess. From stereoselective dissolution experiments carried out in a solution saturated with a single enantiomer, it is shown that the formation of these particles results from the epitaxial association of macroscopic homochiral lamellar fragments parallel to the {101} faces. This alternated 2D nucleation and growth process is shown to constitute an oscillating crystallization mechanism controlled by diffusion only. This is confirmed by the implementation of a gentle stirring of the mother liquor during the crystallization which led to crystals having a high enantiomeric excess. Molecular modeling investigations indicate that the epitaxial region can be described at a molecular level. The structure of two racemic compounds could be generated from this epitaxial zone.

1. Introduction

Preferential crystallization is an efficient and cheap method for the large scale enantiomeric resolution of chiral compounds but requires that the racemic mixture crystallizes as a stable conglomerate (physical mixture of crystals containing only R or S molecules) without any detectable solid solution.[1] Furthermore, it has been shown that the existence of an unstable racemic compound (in which each particle contains equal proportions of the two enantiomers) can in some cases limit the performances of preferential crystallization.[2]

Although only 5−10% of the racemic mixtures exist as conglomerates, the family of 5-alkyl-5-arylhydantoins exhibits a much higher frequency of conglomerates[3] and several of these derivatives could be resolved in our laboratory during the last years.[4,5] By contrast, only one member was found to crystallize as a conglomerate in the series of 5-alkyl-5-alkylhydantoin derivatives, namely, 5-ethyl-5-methylhydantoin (12Hyd hereafter). This compound is of particular interest, because of its biological activity[6] and the possibility to obtain optically pure isovaline by means of ring opening.[7] Nevertheless, its resolution by means of preferential nucleation[8] and crystallization[9] appeared to be not easy. Indeed, poor yields and enantiomeric excesses were obtained during preferential crystallization attempts carried out in water, and the use of a wetting agent was shown to be necessary because of wettability difficulties. To explain these results, a comparative crystal growth study between the racemic mixture and the pure enantiomer was undertaken and allowed to identify the influence on crystal habit of several parameters such as enantiomeric purity, supersaturation and presence of a wetting agent.[9] This study also revealed that large particles in the shape of single crystals obtained from unstirred racemic solutions under smooth conditions of supersaturation contain almost no enantiomeric excess, indicating that these particles probably result from a "polyepitaxy" phenomenon. Similar situations have been previously encountered with hexahelicene[10] and a triazolyl ketone.[11] In the same area, Potter et al.[12] have described the spontaneous oscillating crystallization of (+) and (−) enantiomers of a bicyclic lactam during preferential crystallization attempts. This phenomenon was explained by the high α values in the system (α = solubility of the racemic mixture/solubility of one enantiomer) and by the formation of "twins" (actually epitaxy) between the crystals of the two enantiomers. It was also demonstrated from seeding experiments that crystals of one enantiomer could grow on the surface of the other, which induced that apparent single crystals were almost racemic despite the existence of a stable conglomerate. Nevertheless, no crystal growth study nor structural determination was undertaken in order to describe accurately the epitaxy mechanism. More recently, Berfeld et al.[13] noticed that many α-amino acid salts crystallize as conglomerates, with the frequent occurrence of lamellar epitaxy.[14] They presented an interesting description of such polyepitaxy where crystals are composed of an alternation of homochiral lamellae of opposite handedness. Furthermore, they described the possible prevention of lamellar epitaxy by adding a chiral tailor-made inhibitor that impedes the nucleation of a particular enantiomer and allows only the crystals of the opposite configuration to appear (see also ref 4).

In our previous paper devoted to 12Hyd,[9] crystal structure determination and molecular modeling allowed us to formulate some hypotheses regarding the insertion mechanism of counter enantiomer molecules or ribbons. The present paper gives new insights on these continuing investigations because the experimental part of this work is devoted to selective dissolution experiments of large particles grown with or without stirring under gentle conditions, with the aim of identifying more accurately the factor(s) responsible for the insertion of both enantiomers in the same crystal lattice. Molecular modeling is used to describe the epitaxial zone between homochiral fragments and to envisage the existence of racemic compounds. The associated discussion focuses on the major roles played by diffusion and supersaturation, as well as the possible analogy with the so-called "lamellar eutectic" phenomenon occurring in alloys.

* To whom correspondence should be addressed. gerard.coquerel@univ-rouen.fr. Fax: +33(0)2-35-52-29-27.

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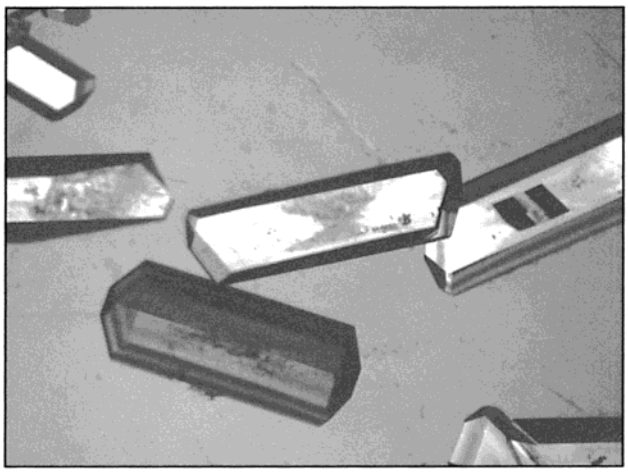

Figure 1. Photograph of representative crystals of 12Hyd obtained in water at 4 °C from the racemic mixture ($\beta_{init} = 1.2$).

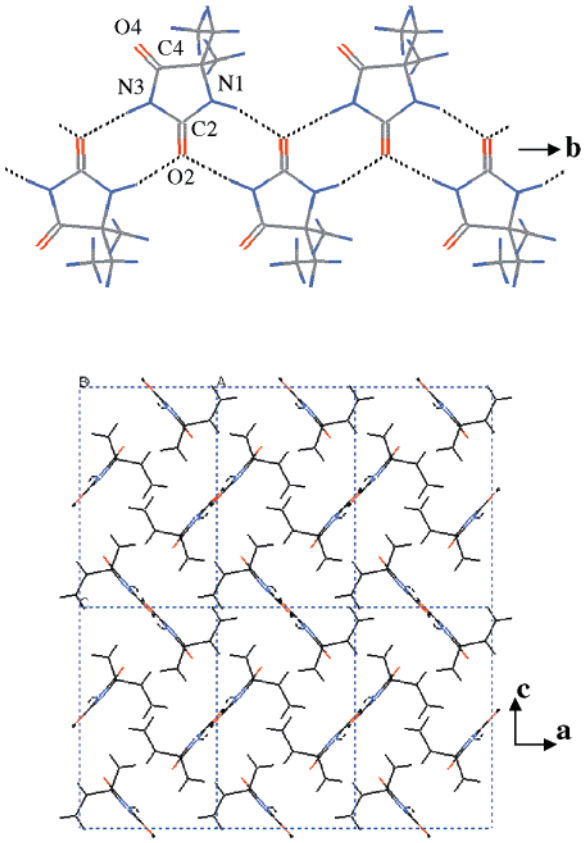

Figure 2. Crystal structure of 12Hyd: molecular ribbons running along the *b* axis (upper) and projection along the *b* axis showing the stacking of molecular ribbons (lower).

2. Crystal Growth, Structural Analysis, and Morphological Study

Large crystals of 12Hyd were grown within a few days from the racemic mixture in water at 4 °C (solubility, 3.8% w/w), with initial dimensionless supersaturation equal to $\beta = 1.2$ and without evaporation. When not otherwise mentioned, no stirring was applied, and the final size of most crystals was in the range of 0.2−0.8 cm along the main axis (Figure 1).

The structural determination of 12Hyd (pure enantiomer) has been reported previously[9] and has revealed that this compound crystallizes in the space group $P2_12_12_1$ with the following unit cell dimensions: $a = 7.980(2)$ Å, $b = 7.219(2)$ Å, and $c = 12.818(3)$ Å. The main structural feature is the presence of infinite chains of hydrogen bonded molecules parallel to the *b* axis (Figure 2, upper). These strong molecular ribbons (two H bonds per molecule involving N1, O2, and N3 atoms) are held together by means of van der Waals contacts (Figure 2, lower).

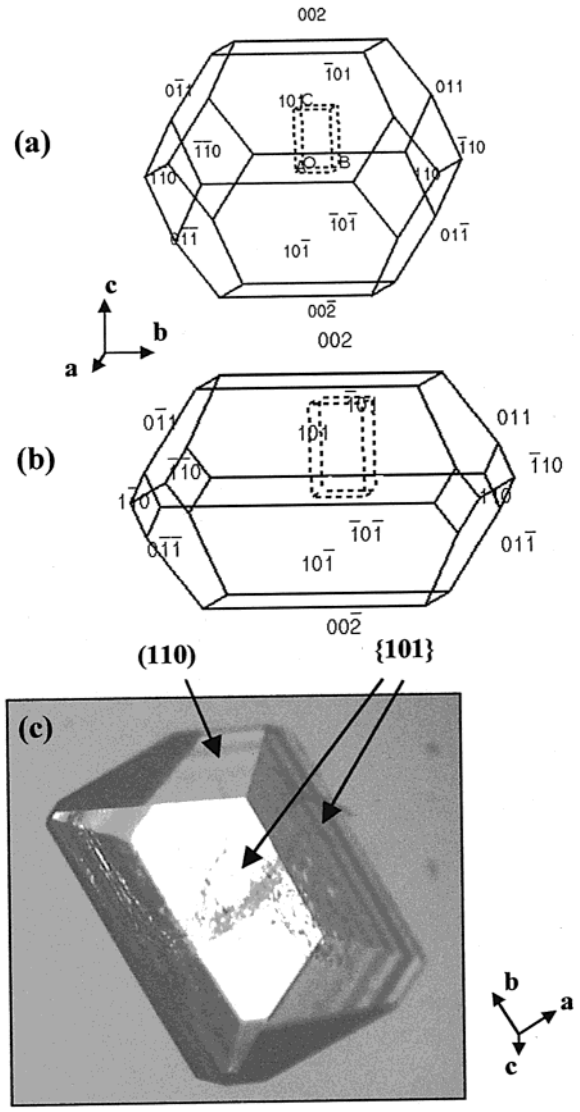

Figure 3. Predicted morphology for 12Hyd obtained with the BFDH model (a) or with the attachment energy model (b) and photograph of the experimental morphology obtained at $\beta = 1.2$ from a solution of pure enantiomer (c).

On the basis of structural data, the Miller indices (*hkl*) of the most developed faces were determined from morphological predictions, using either the geometric Bravais−Friedel−Donnay−Harker (BFDH) model or the attachment energy model.[15] All calculations were performed with the Cerius[2] software (MSI). Whatever the selected model, force field, and atomic charge set, the predicted morphology is similar to that presented in Figure 3 parts a and b, with the most developed faces being {101} and {002}, i.e., faces parallel to the *b* direction. Compared to geometric calculations (BFDH), morphology simulations carried out with the attachment energy model lead to crystal habits more elongated along the *b* axis, which is consistent with the presence of strong molecular ribbons running along this direction. The (*hkl*) indices of the existing faces were assigned on the basis of comparisons between calculated and representative experimental habits (Figure 3), as well as from angle measurements between faces or edges. The

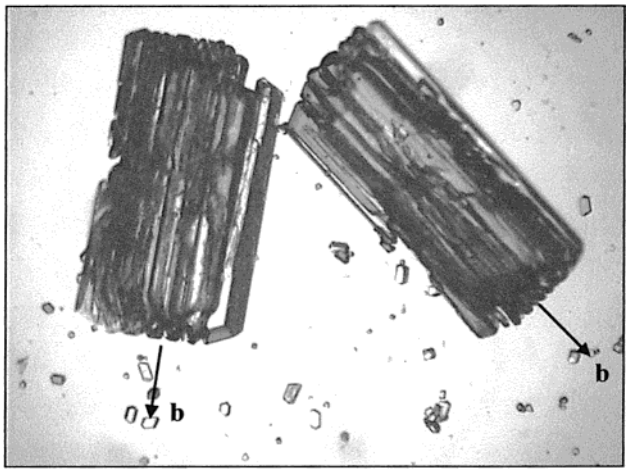

Figure 4. Photograph of 12Hyd crystals after partial dissolution in a solution saturated with a single enantiomer.

most developed faces on experimental habits are {101} and {110} faces, and the differences between experimental habits of crystals grown under low supersaturation from a solution of pure enantiomer and predicted morphologies are probably due to solvation effects.

3. Selective Dissolution of Crystals

Although 12Hyd crystallizes as a conglomerate, it has been established from chiral gas chromatography analyses that particles in the shape of single crystals grown at 4 °C in aqueous solution without stirring from the racemic mixture exhibit almost no enantiomeric excess.[9] This paradoxical situation was further investigated by means of partial dissolution of these particles in a solution saturated with a single enantiomer, according to the methodology proposed by Toyokura et al.[16] Because the solubility of the racemic mixture is approximately twice that of the pure enantiomer (quasiideal behavior, i.e., the solubility of one enantiomer is not altered by the presence of the other), the experimental procedure consisted of preparing a slightly undersaturated solution with one enantiomer (solubility, 1.8% w/w at 4 °C). A crystal grown from the racemic mixture was then immersed in this solution, and its selective dissolution (fragments containing only the R enantiomer should be preferentially dissolved in a solution saturated with the S enantiomer) was observed by optical microscopy. Similar dissolution experiments were also achieved in pure water for comparative purposes.

These experiments revealed that "single crystals" are actually made of lamellar fragments parallel to the *b* direction, as can be seen from Figure 4. Several of these fragments were isolated, and their analysis by chiral gas chromatography indicated enantiomeric excesses superior to 90%, which confirms the selective dissolution of one enantiomer only. Furthermore, dissolution of similar particles in pure water appeared to occur in a roughly isotropic way.

Further partial dissolution experiments were carried out with the initial particle being orientated along the *b* direction. These experiments led us to identify two types of regions (Figure 5): The "central" region of the crystal is composed of ill-defined fragments (often in the shape of tubes) running along the *b* axis. This part of the initial "crystal" results from the first stages of growth and was therefore grown under relatively high supersaturation. The "peripheral" region, which results from the latest growth stages, is composed of lamellar domains parallel to {101} faces.

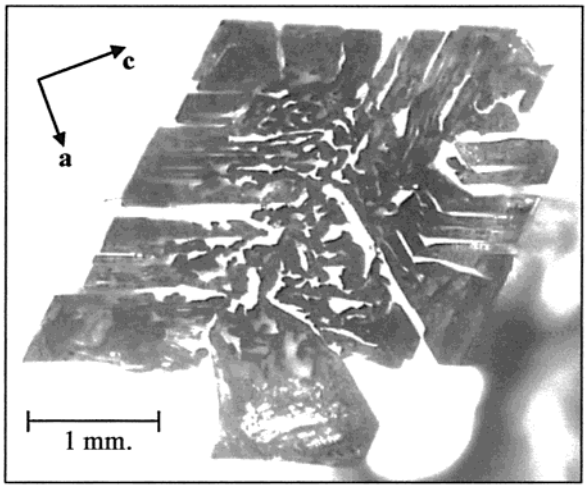

Figure 5. Photograph of a 12Hyd crystal orientated along the *b* direction, after partial dissolution in a solution saturated with a single enantiomer.

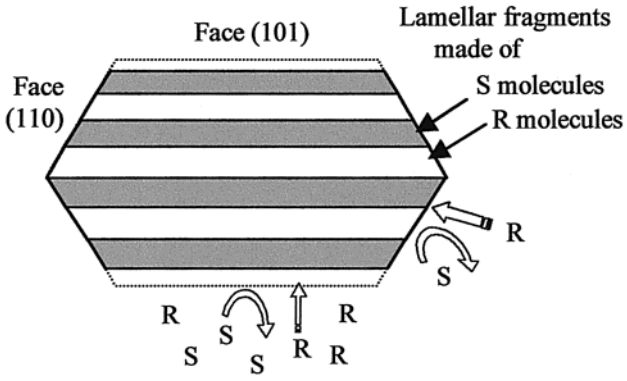

Figure 6. Schematic representation of the growth mechanism leading to a lamellar R−S multiepitaxy along the (101) growth directions.

4. Multiepitaxy Phenomenon during the Growth of 12Hyd from an Unstirred Racemic Aqueous Solution

As shown above, crystals of 12Hyd grown in the absence of stirring from an aqueous racemic solution are actually composed of the stacking of tubular or lamellar fragments of high enantiomeric purity. Under the smoothest growth conditions (i.e., close to the thermodynamic equilibrium), the growth of {101} faces proceeds via the alternated formation of homochiral lamellar fragments, with a mean thickness of 0.1−0.3 mm. for each fragment (Figure 6). This growth mechanism leading to enantiomerically pure fragments (or subcrystals) is represented in Figure 7a and is probably induced by the absence of stirring. It can be described as follows: During the growth of a (101) face under smooth conditions, only one enantiomer (for instance R molecules) is inserted on the growing surface, leading to an enantiomerically pure fragment. In absence of stirring, the proportion of solvated R molecules in the vicinity of the solid−solution interface decreases with reference to the counter enantiomer (S molecules). Therefore, the relative local supersaturation for the S enantiomer increases continuously, up to a limit value. When this local critical supersaturation is reached, the heterogeneous secondary bidimensional nucleation of an S fragment occurs and initiates the growth of a new lamellar fragment, made of S molecules. Therefore, the formation of crystals can be described as an oscillating process where the frequency of 2D nucleation and growth of a new homochiral fragment is determined by continuous variations of the local supersaturation for each enantiomer.

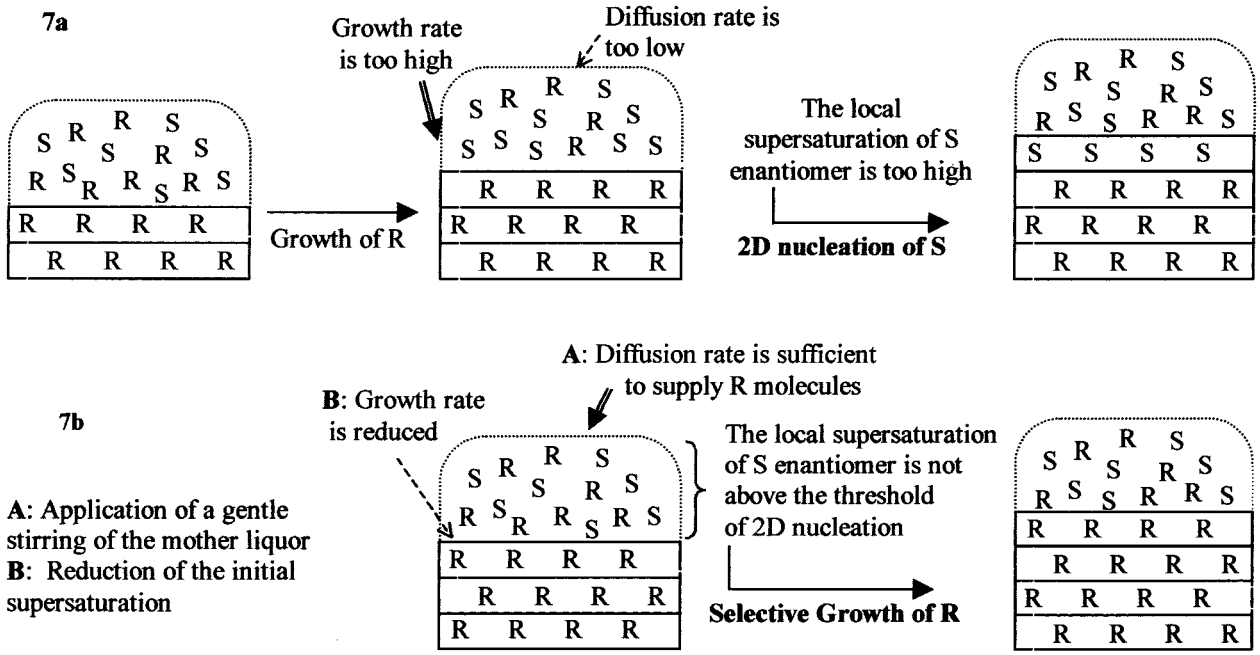

Figure 7. Influence of the diffusion and of the growth rate at the solid-solution interface during the growth of a crystal from a racemic solution. (a) Case of lamellar epitaxy occurring without stirring. (b) Application of a sufficient stirring (A) and/or a lower supersaturation (B) to prevent lamellar epitaxy.

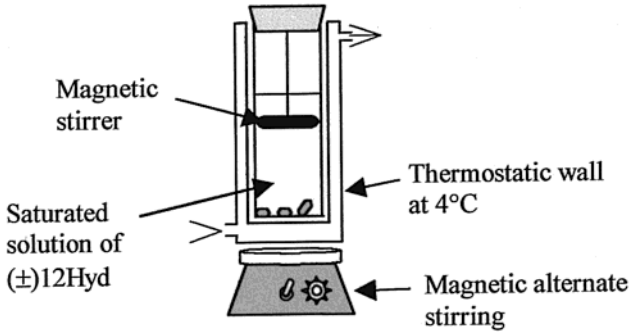

Figure 8. Experimental device used to grow crystals under gentle stirring at 4 °C (about 30 alternate movements per minute).

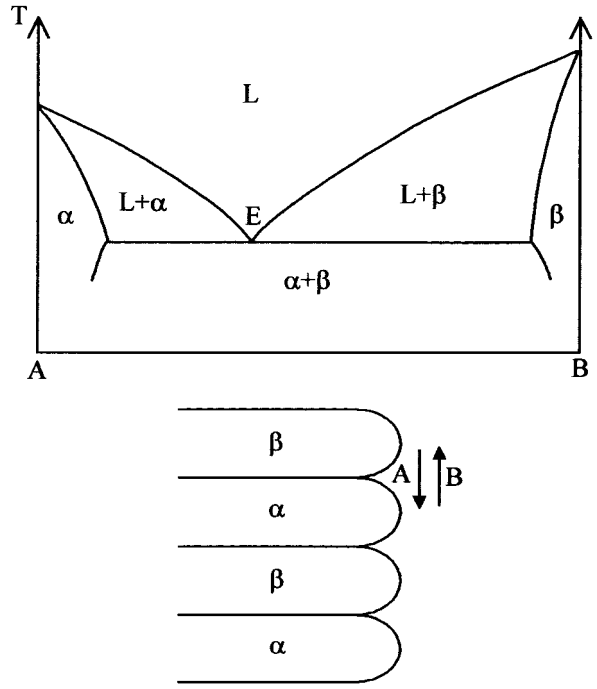

Figure 9. Crystallization of an alloy starting from a mixture of eutectic composition E(L → α + β). The two crystallized phases adopt frequently a structure in lamellae to reduce the distance of diffusion.

In contrast with this growth mechanism of {101} faces, both enantiomers can be simultaneously adsorbed during the growth of {110} faces, concluding that local fluctuations of concentration for each enantiomer are less important. In the regions corresponding to the interface between neighboring homochiral fragments, the insertion of counter enantiomer molecules within a H-bonded ribbon is likely to occur and should generate important crystal defects, because of the disruption of the H-bond network existing along the *b* direction (Figure 2). These larger proportions of crystal defects formed during the growth of {110} faces could also be responsible for the frequent appearance, observed under polarized light, of hourglass figures through {101} faces[9] (see Figure 1). This hypothesis is in agreement with the work of Davey et al.[11] which noticed the presence of hourglass figures on crystals of a triazolyl ketone grown from a racemic solution. Furthermore, they have established that crystals of high enantiomeric purity usually did not exhibit such hourglass figures.

The alternated growth mechanism described above is consistent with the results observed during the selective dissolution experiments and allows us to account for the absence of enantiomeric excess in particles in the shape of single crystals. Owing to this mechanism, the inversion frequency and, therefore, the thickness of the lamellar fragments are controlled by diffusion only. Therefore, a way to confirm our interpretations is to perform growth experiments of 12Hyd under gentle stirring, which should modify significantly the diffusion phenomenon and lead to lamellar fragments of larger thickness. Actually, particles containing large enantiomeric excesses should be obtained if diffusion is made sufficient. Using the experimental setup described in Figure 8, crystals of sufficient size for subsequent chiral gas chromatography analyses were prepared and were shown to contain enantiomeric excesses in the range of 75−85%. These data provide an unambiguous confirmation of the predominant role played by diffusion during our growth experiments because the multiepitaxy phenomenon is strongly affected

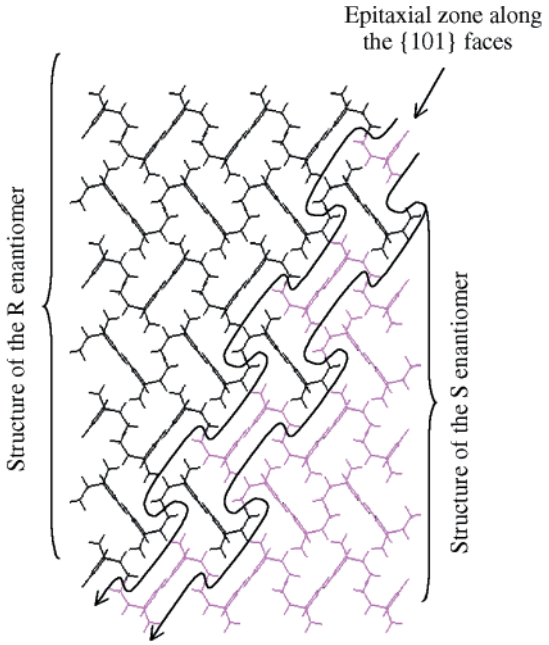

Figure 10. Modeling of the epitaxial zone along {101} faces between the two enantiomers of 12Hyd.

by gentle stirring. Berfeld et al.[13] noticed that the higher the degree of supersaturation of the solution in which the crystals were grown the closer the crystal composition to that of a racemic compound. This can be explained as follows: if the growth rate (which increases with the degree of supersaturation) is too high, the number of molecules adsorbed on the surface is higher than the number of molecules the diffusion can supply. Thus, the counter enantiomer in excess starts to grow, and a new lamella of opposite handedness appears (Figure 7a). From these two observations (i.e., the higher the diffusion or the lower the supersaturation, the higher the enantiomeric excess), it seems that polyepitaxy can be (at least) reduced by stirring the solution in order to increase the diffusion rate and/or by applying a lower initial supersaturation in order to decrease the growth rate (Figure 7b).

This oscillating crystallization mechanism leading to the formation of lamellar epitaxy can be compared to that occurring during the crystallization of a metallic alloy from a mixture of eutectic composition[17] (Figure 9). As the α phase rich in A crystallizes, an excess of B appears and diffuses a short distance laterally where it is incorporated in the β phase rich in B. Similarly, the A atoms "rejected" ahead of the β phase diffuse to the tips of the adjacent lamellae. Such a structure made of lamellae (defined as "lamellar eutectics") is preferentially adopted in order to reduce the distance of diffusion.

Although a racemic mixture of an organic compound in solution also constitutes a eutectic mixture, the occurrence of lamellar structures has been rarely described. This can be explained, on the one hand, by the high diffusion rates usually existing in solution, which are sufficient to supply the vicinity of the interface with molecules of both enantiomers. On the other hand, the interface between two lamellae is structurally more complex in organic structures than in alloys because assembling molecules as a periodic packing is obviously more difficult than packing atoms. Therefore, the creation of an energetically stable interface (in order to prevent a high excess of energy) is often impossible in the case of organic structures. In the opposite, the occurrence of oscillating crystallization for 12Hyd indicates that an intermediate structure, corresponding to the interface between adjacent lamellar fragments should have a lattice energy close to that of the conglomerate.

5. Relationship between Conglomerate and Racemic Compound: Molecular Modeling Study

Attempts to simulate at a molecular scale the structure of the interface between homochiral domains were performed using the Cerius[2] molecular modeling software (MSI). The packings of the two enantiomers were cleaved along the (101) faces, and the interface could be built (Figure 10).

The above discussion has established that, during oscillating crystallization, the higher the diffusion rate the larger the width of homochiral fragments and the lower the frequency of formation of epitaxial slices. Therefore, assuming that diffusion could be decreased in such a way that homochiral fragments

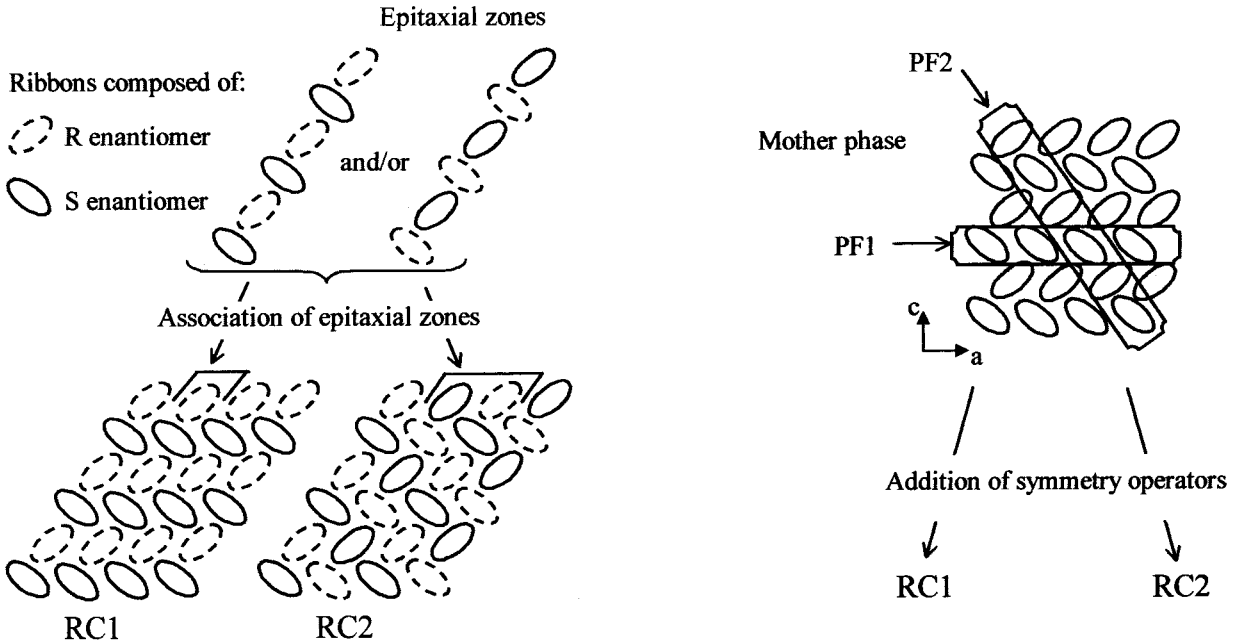

Figure 11. Schematic representation of the two ways used to generate two racemic compounds RC1 and RC2: regeneration of the epitaxy zones (left) or selection of two periodic fragments (PF1 and PF2) and addition of symmetry operators (right).

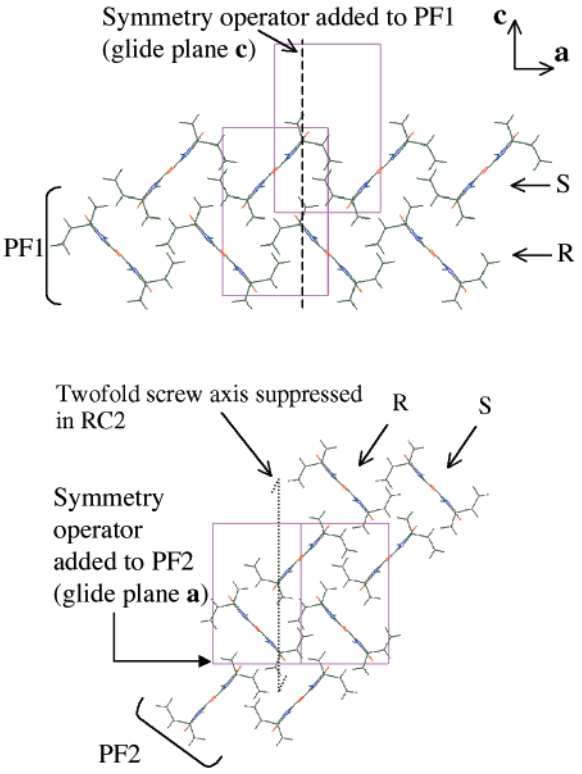

Figure 12. Construction of RC1 (upper) and RC2 (lower) starting from PF1 and PF2, respectively, and adding one symmetry operator.

disappear completely, we could obtain particles made of two-dimensional slices with a racemic composition, namely, a racemic compound. Two possibilities can be contemplated for the association of racemic slices, leading to two distinct hypothetical structures (RC1 and RC2) for the racemic compound, as shown in Figure 11 (left).

A more rational way to elaborate crystal structures with a racemic composition is to apply the methodology elaborated in our laboratory for the research of new derived structures[18] (Figure 11, right). This predictive model uses data extracted from a known crystal structure and proceeds by means of a two-step procedure. The first one consists of selecting a mono- or two-dimensional periodic fragment (PF) from the mother structure, and the second one generates a three-dimensional lattice consistent with one of the 230 space groups by adding symmetry operators.

In the case of 12Hyd, two distinct periodic fragments (PF1 and PF2) of high energetic stability can be selected in order to build the hypothetical racemic compounds (RC1 and RC2, respectively) schemed in Figure 11. PF1 and PF2 contain the H-bonded molecular ribbons running along the *b* direction (Figure 2, upper) associated with a translation along the *a* axis (PF1) and a translation along the [101] direction (PF2). It is worth mentioning that identical periodic fragments are present in the structure of the 5-methyl-5-methyl hydantoin.[19] Furthermore, these bidimensional slices, including the entire H-bond network, contain the major part of the energetic stability of the derived structures. The RC1 structure is generated by adding to PF1 a glide plane parallel to the *c* axis at $x = {}^1/_4$ (Figure 12, upper). The space group of RC1 is then $Pc2_1n$ (standard setting $Pna2_1$). The symmetry operator added to PF2 is a glide plane parallel to the *a* axis at $y = 0$ (Figure 12, lower). The 2-fold screw axis existing between two neighboring ribbons in PF2 is not consistent with one of the three translations of the generated crystal packing and is therefore suppressed in the final structure. Consequently, the space group of the RC2 structure is $P2_1/c$

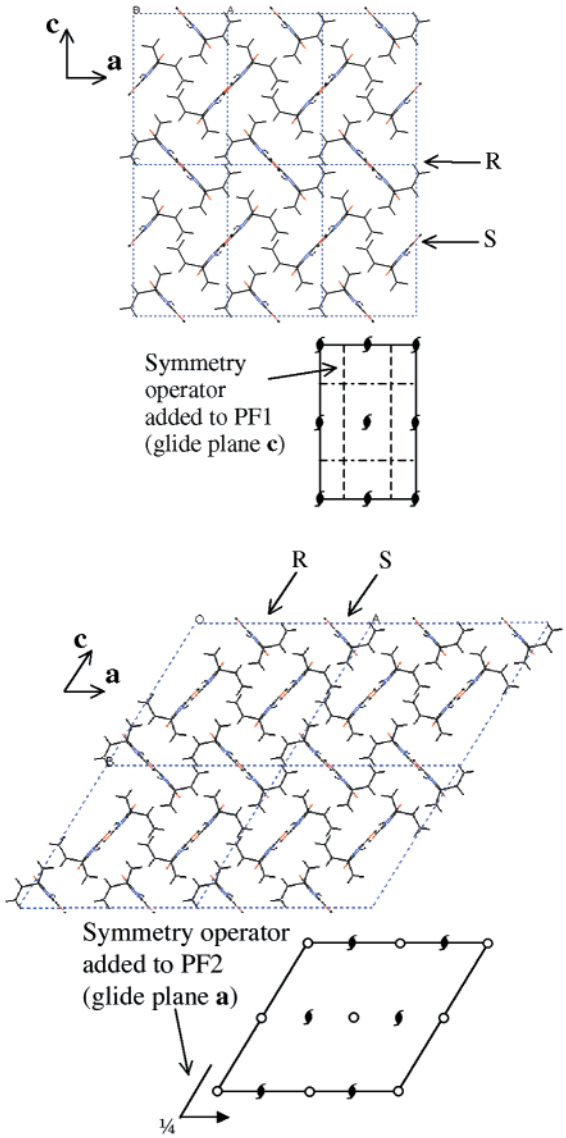

Figure 13. Hypothetical crystal structures of RC1 (upper) and RC2 (lower) of 12Hyd, derived from PF1 and PF2 of the conglomerate, respectively.

with $Z' = 2$ (two independent ribbons in PF2). The two derived crystal structures of racemic compound are presented in Figure 13, with the associated space groups.

The relative energetic stability of the derived structures was estimated by means of molecular mechanics calculations and compared with that of the conglomerate. Lattice energies of the three structures were calculated and minimized using the open force field module of the Cerius[2] software (force field Dreiding 2.21,[20] with charges derived from the charge equilibration algorithm[21]). The final values of lattice energies are −100.5 kcal/mol for the enantiomer and −98.0 kcal/mol for both racemic compounds. These results confirm the higher stability of the conglomerate, although the difference between these values is small. This is consistent with the fact that only a few van der Waals contacts are modified by the construction of the racemic compounds. These structural and energetic similarities between the three structures allow us to assume that the two racemic compounds should be easily obtained experimentally. Moreover, the 2D fragments constituting these compounds are encountered in the epitaxial zone described in Figure 10. Nevertheless, the strong analogies between the crystallographic parameters and packing features of the structures induce that

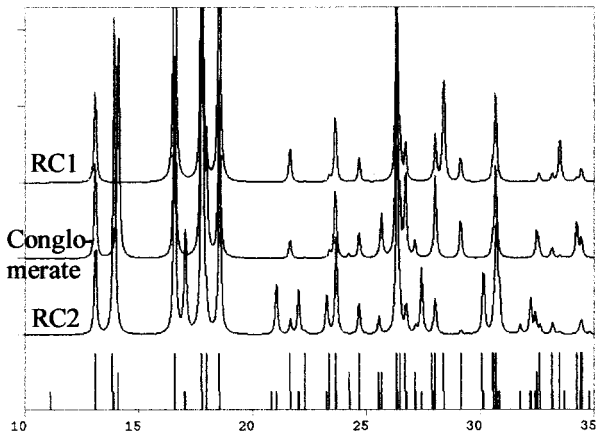

Figure 14. Superimposition of calculated X-ray powder diffraction patterns for the conglomerate and for the generated racemic compounds.

only a few differences can be noticed between the calculated X-ray powder diffraction patterns (Figure 14). These differences are the extinction of some peaks for RC1 and the appearance of a few supplementary peaks of low intensity for RC2, with reference to the conglomerate. X-ray diffraction is therefore not suitable for the detection of these racemic compounds or for that of epitaxial zones, because of the too low proportion of these zones, compared to the quantity of matter contained in homochiral fragments. Besides, other physical methods such as X-ray topography[22] could constitute valuable tools for the characterization of these zones, and topography techniques using neutron sources could possibly be used in order to measure the thickness of the lamellar fragments.[23]

6. Conclusion

The careful analysis of the enantioselective dissolution of 12Hyd particles in the shape of single crystals grown from an aqueous racemic mixture without stirring indicates that these particles are actually made of lamellar homochiral fragments parallel to {101} faces. This information leads us to describe the formation of these particles by means of an oscillating nucleation and growth process of enantiomerically pure crystals, with an inversion frequency controlled by diffusion and similar to those observed with lamellar eutectics in metallurgy. The use of smooth stirring conditions, by inducing a significant change in the diffusion mode, allowed us to confirm this mechanism and provided particles of significant enantiomeric excess. The multiepitaxy phenomenon occurring during the growth of 12Hyd in the above conditions was further investigated by simulating, at the molecular level, the epitaxial zone and by constructing two hypothetical structures for the racemic compound.

The procedure applied here for the construction of racemic compound structures derived from the structure of one enantiomer can be used for other similar situations. For instance, the predictive model has been used to investigate the multiepitaxy phenomenon occurring during the growth in a racemic solution of hexahelicene[10] (space group $P2_12_12_1$). A racemic compound (space group $Pna2_1$) has been generated from the mother phase and could describe exactly the epitaxial zone occurring along the [100] direction. This methodology could therefore constitute an interesting new approach for the understanding of structural relationships between the structure of enantiomers crystallizing as conglomerates and the structure of racemic compounds.

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(14) The term lamellar twinning is employed to describe this particular epitaxy between two enantiomers. In *Acta Crystallogr.* **1995**, *B51*, 619, J. D. Dunitz re-stated that "racemate and conglomerate crystals are to be classed as *polymorphs* when the rate of interconversion of the enantiomers in the melt or in solution is fast, but as three *different compounds* when the interconversion is slow". Therefore, in the context of the references cited and in this study, the term lamellar twinning is inappropriate and has to be replaced by lamellar epitaxy. The authors wish also to express that this rigorous use of the term "epitaxy" is designed to avoid any confusion with pure enantiomer that can indeed be twinned.

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