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A Cyclic Continuous Process for Converting Conglomerates into Optically Pure Enantiomers by Crystallization and Dissolution with the Assistance of 'Tailor-made' Polymers

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Abstract—An industrially feasible kinetic process for the conversion of D,L racemic mixtures that crystallize in the form of conglomerates into optically pure materials was elaborated. The method takes into consideration the presence of a single-enantiomer polymer that causes crystals that match it in chirality to lag far behind their enantiomers both in growth and in dissolution. This phase lag is exploited in a repeated cycle of growth and dissolution to collect crystals of one kind after partial growth and of the other before complete dissolution. Three major steps are involved: (a) Kinetically controlled crystallization of a racemic conglomerate in the presence of chiral polymers at temperature T_1, modeled on the basis of the structure and morphology of the 3D crystals. The polymer inhibits the precipitation of the undesired enantiomorph, collecting the desired one by filtration; (b) Preferential dissolution of added racemic mixture of crystals of the substrate in the mother liquor enriched with the undesired enantiomer and the chiral polymer at temperature T_2. This step takes advantage of concentration-gradients of the two enantiomers in the filtrate and the enatioselective dissolution induced by the chiral polymer; (c) The separation by filtration followed by racemization of the undesired enantiomer for additional cycles of resolution. The process is illustrated for the conversion of D,L methionine·HCl that crystallizes in the form of a conglomerate that displays twinning of enantiomorphous lamellae into the corresponding L or D Met·HCl in kilograms scale.

Introduction

In recent years, remarkable progress has been made in the preparation of optically pure materials either via asymmetric synthesis or via the resolution of racemates, in particular by applying chromatographic and enzymatic methodologies.[1] The method of resolution by kinetic crystallization is the oldest one, yet, it is seldom applied for the preparation of chiral compounds at the industrial scale. Efficient processes should comprise the separation of the desired enantiomer by kinetic crystallization, the recovery of the opposite enantiomer and its efficient racemization for further resolutions. Major intrinsic difficulties in the present approach rest on the need to elaborate specific conditions for each single system. One of the most common ways to improve the resolution step in the kinetic crystallization is via enantioselective seeding. This method, however, is not general and suffers from deficiencies particularly in systems displaying crystal twinning or posses low energy barrier for crystal nucleation. For that reason it happens quite frequently that the two enantiomers crystallize simultaneously even in the presence of the desired seed-crystals.[2–6]

Our group has introduced recently an efficient method for the enantioselective inhibition of the early stages of crystal nucleation and crystal growth.[7–9] Here we propose a continuous cyclic enantioselective crystallization/dissolution process that does not require the isolation of the polymer from the solution. This method is based upon a working hypothesis stating that within supersaturated solutions either one finds nano-size clusters that assume a structure that resemble the corresponding 3D mature crystals, or such clusters are formed during the crystallization process.[10–14] Following this logic we anticipate that in supersaturated solutions of racemic mixtures chiral and racemic clusters with a structure akin to these of the corresponding 3D enantiomorphs and racemic compounds are present or are formed and play the role of embryonic nuclei at the onset of crystallization. Furthermore, on the basis of this hypothesis we modeled chiral polymers, based on the packing and morphology of the 3D crystals, that interact enantioselectively with the surfaces of particular chiral clusters and avoid their transformations into crystals. If appropriately designed these polymers will not interact with the nuclei of the other enantiomoph and thus crystals of the latter will precipitate almost unperturbed. Thus, for example, the addition of a D polymer will inhibit the precipitation of the D enantiomorph. The filtration of the L enantiomorph after crystallization will result in a mother liquor enriched with the D enantiomer and the D polymer.

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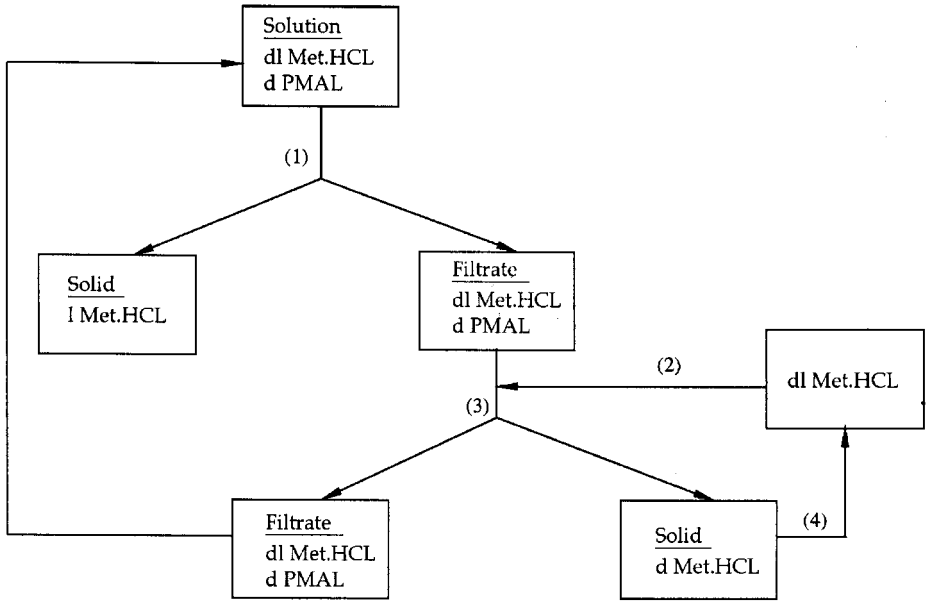

Scheme 1. A cyclic continuous process for the conversion of D,L Met·HCl into L Met·HCl: (1) Crystallization/filtration at T=13–4°C. (2) Addition of solid D,L Met·HCl to the enriched filtrate with D Met·HCl. at T=19.2°C. (3) Enantioselective dissolution of L Met·HCl in the presence of D PMAL, followed by filtration of D Met·HCl. (4) Racemization of D Met·HCl in acetic acid in the presence of salicylaldehyde.

The isolation of the D enantiomer can be achieved by enantioselective dissolution of a fresh powder of the racemic mixture of the substrate to the above filtrate. In that step we take advantage of two effects; the concentration gradients of the two enantiomers in the filtrate, and the enantioselective inhibiting dissolution properties of the chiral polymer. Solid powder of a DL racemic mixture is added to the filtrate enriched with the D enantiomer at a temperature at which it is supersaturated for the D and undersaturated for the L enantiomer. This results in a preferential dissolution of the L crystals till a solution of a racemic composition is formed. The remaining crystals of the D enantiomorph are collected by filtration.

Previously we have shown that chiral polymers that operate as enantioselective inhibitors of crystal growth and crystal nucleation are also enantioselective inhibitors of crystal dissolution.[15] Therefore, the presence of this chiral polymer in solution will assist the enantioselective dissolution of the L enantiomorph. The D enantiomorph is collected by filtration leaving a racemic solution, which still contains the chiral polymer. The solution is ready for a second cycle of crystallization of the L enantiomer. The different steps can be summarized as follows:

(a) The enantioselective crystallization of the e.g. L enantiomer in the presence of the D polymer at a temperature T_1;
(b) The filtration of the crystals of the L enantiomorph;

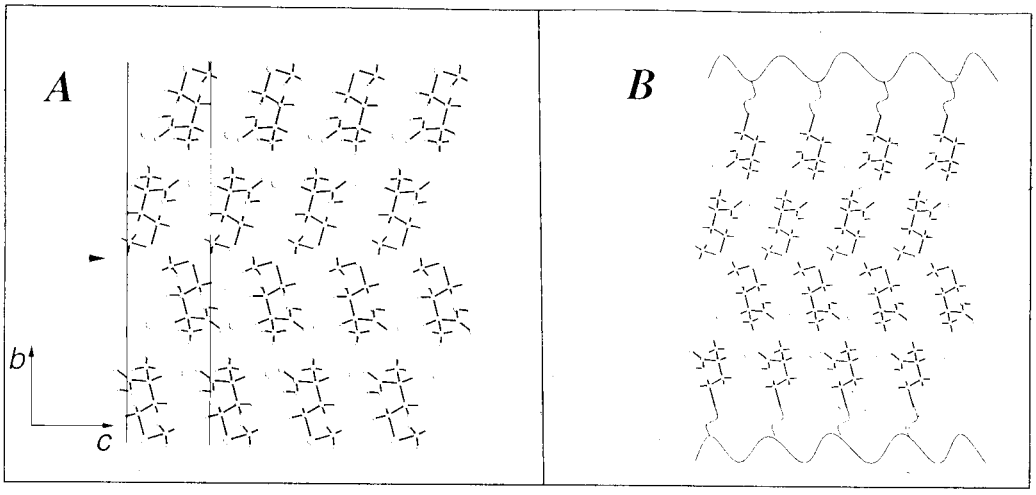

Figure 1. (A) Packing arrangement of Met·HCl·H_2O. Space group $P2_12_12_1$, (a=7.09 Å, b=24.64 Å, c=5.30 Å), viewed along the a-axis, the dashed arrow indicates the hydrophobic surfaces between bi-layers, where the lamellar twinning is taking place. (B) Schematic representation of the enantioselective interactions of poly-(N^{ϵ}-acryloyl L lysine) (L PAL) or poly-(N^{ϵ}-methacryloyl L lysine) (L PMAL) with structured clusters or crystals during growth or dissolution of L Met·HCl·H_2O.

(c) Raising the temperature of the filtrate that comprises an excess of the D enantiomer and the chiral polymer to a temperature T_2, and adding powder of crystals of the racemate to the solution at this temperature; this results in an enantioselective dissolution of the L enantiomoph. Crystals of D enantiomoph are filtered, whereas the filtrate of a racemic composition and the chiral polymer are cooled to T_1 and resubmitted again to an additional cycle of resolution. The method has been successfully applied for the resolution and the conversion of several racemic amino acids to either one of the enantiomers. The method is illustrated here for the conversion of D,L Met into the L Met (see Scheme 1). The latter is a commercially important amino acid since it is widely used as a food additive, a component of parenteral nutrition and as starting material for pharmaceutical synthesis.

Results and Discussion

Racemic methionine hydrochloride (Met·HCl) crystallizes from HCl solutions in the chiral space group $P2_12_12_1$. Single crystals of Met·HCl·H_2O assume a bar-like morphology with well expressed {010} faces.[6] The X-ray powder diffraction patterns of the resolved and the racemic crystals are identical implying that the racemate undergo spontaneous resolution. However, an analysis of single crystals by gas chromatography on chiral support indicates that the compositions of each of these crystals are almost racemic. The packing arrangement of the crystal is shown in Fig. 1A. Cutting a single crystal perpendicular to the plane of the hydrogen-bonded layers yield sectors of a composition identical to the enantiometric excess of the whole parent crystal, i.e. racemic or slightly enantiomerically enriched. On the other hand cleaving the crystals in directions parallel to the plane of the bi-layer demonstrates that the latter assume a composition of an enantiomeric excess varying from 40–60%. This implies that the single crystals are composed from homo-chiral domains of a micron thickness. Since diffraction takes place from each sector separately, it is not always easy by simple X-ray diffraction study to detect the presence of these hetero-chiral lamellae.

Chiral polymers for kinetic resolution

Previous studies had demonstrated that efficient inhibitors for crystal nucleation, growth and crystal dissolution for a given crystal are molecules composed from two segments, one identical to that of the substrate molecule, and the other different from, and generally larger than its counterpart in the substrate. These molecules are recognized by the growing surfaces of the crystal or by the crystalline clusters and inhibit their growth (Fig. 1B). Similarly these same molecules interact with the dissolving faces of crystals and delay the rate of their dissolution. Guided by these principles we prepared a polymeric inhibitor for growth and dissolution of methionine, by grafting the D or L lysine via the ϵ-amino group to acrylic or methacrylic acids. These monomers were polymerized to the corresponding D or L PAL or D or L PMAL, respectively.[14]

Isolation of the 'inhibited' enantiomer from the mother solution

In the end of the preferential crystallization in the presence of enantioselective polymer (1–3% by weight of the D,L racemic mixture), the desired enantiomer e.g. L obtained in high chemical and optical yields is separated by filtration. The filtrate being enriched with the D enantiomer, contains also the initial concentration of the polymer that has not been adsorbed on the surfaces of the L crystals.

The efforts were directed towards the recovery of the D enantiomer by applying a process that does not require the removal of the polymer from the solution. The filtrate was warmed to a temperature, where the L enantiomer is at the state of undersaturation while the D enantiomer is close to saturation. Powder of racemic mixture is added to the mother solution, in about twice the amount of the L enantiomer isolated by filtration in the first cycle of crystallization. During stirring of this heterogeneous suspension the L enantiomer dissolves, while the D remains as a powder. Crystals of D Met·HCl·H_2O can be successfully obtained in high chemical and optical yields. This leaves the composition of the filtrate similar to that of the starting supersaturated solution of the D,L racemic mixture containing the initial amount of the chiral polymer. Therefore, this solution can be subjected to an additional cycle of resolution.

We have found that the formed suspension by the addition of powder D,L substrate to the mother solution reaches equilibrium after ~12 h of stirring depending upon the temperature. Optimal resolution is achieved after prolonged stirring at a temperature at which the amount of the collected crystals of the 'inhibited' enantiomer, is equal to the amount of the 'uninhibited' one which crystallized in the first cycle. The overall process is illustrated here especially for the conversion of D,L methionine·HCl·H_2O to either one of the enantiomers.

The undesired enantiomer in its hydrochloride form was racemized in acetic acid in the presence of salicyl aldehyde according to the method of Yamada et al.[16]

Conclusions

In the present manuscript we describe a continuous cyclic process for converting racemic conglomerates, into the chiral resolved D or L enantiomers which is illustrated for the resolution of Met·HCl·H_2O. The method takes advantage of unique properties of polymers modeled on the basis of the crystal structure of the substrate. The process is illustrated for the large scale resolution of Met, however, it has been successfully applied for the resolution of other amino acids crystallizing in form racemic mixtures[17] such as Glu·HCl, Thr, Asn·H_2O, Leu·HCl, Isoleu·HCl, Cys·HCl. Some of these systems display lamella-twinning and therefore are not amenable to resolution by seeding alone. Furthermore, it was also applied for the resolution Val·HCl and His·H_2O·HCl that crystallize in the form of racemic compound thermodynamically close to the optical isomer.[6]

Table 1. Continuous separation of L and D Met·HCl·H_2O over the first 20 cycles

Cycle no.	L Met·HCl·H_2O recovered (g)	D Met·HCl·H_2O recovered (g)
1	6.69	5.41
2	5.50	5
3	5.76	4.91
4	5.31	4.30
5	5.19	4.40
6	4.80	4.18
7	4.57	4.18
8	3.61	3.58
9	4.35	3.63
10	3.72	3.29
11	3.55	3.32
12	3.43	3.2
13	2.29	2.7
14	2.96	2.68
15	2.66	2.55
16	2.18	2.26
17	2.04	1.9
18	2.3	2.1
19	2.02	1.8
20	1.8	1.6

In principle this process is continuous since a fresh D,L substrate and minute amount of the polymer can be added to the crystallization pot together with the racemized fraction provided the original volume and the concentration of the substrate are kept constant.

This resolution technique might have also some advantages over the enzymatic processes for the resolution of the amino acids, e.g. selective enzymatic hydrolysis of *N*-acetyl-L amino acids using acylase I which suffer from several drawbacks. The acylase process is limited by the substrate specificity of the enzymes and requires a derivatization of the amino acids, while the present method can be done directly with the amino acids. Furthermore, the present process is not limited to amino acids but can be generally applied to all chiral compounds which crystallize as conglomerates.

A major deficiency of the present method is, however, that it is not applicable for the resolution of racemates that form racemic compounds that are thermodynamically much more stable than the corresponding conglomerates. On the other hand this process should be applicable for the resolution of diastereoisomeric materials including racemates that are not amenable to enzymatic reactions.

Experimental

The continuous resolution of methionine hydrochloride from hydrochloric aq. solution is described below. The whole cycle contain the crystallization of L Met·HCl·H_2O, recovery of D Met·HCl·H_2O and further cycles of continuos isolation of both enantiomers separately. It was found out that the best chiral polymer is poly-(N^{ϵ}-methacryloyl-L or D lysine) (L PMAL or D PMAL) with molecular weight range of 10,000–2,000,000 (by G.P.C) whose synthesis was described elsewhere.[14]

Resolution of D,L-methionine hydrochloride (D,L Met·HCl·H_2O)

Crystallization of L Met·HCl·H_2O. D,L Methionine (feed grade, 45 g, equivalent to 55.87 g of D,L Met·HCl·H_2O) was dissolved by heating and stirring in 105 ml of aqueous concentrated 32% (wt/wt) hydrochloric acid and the solution was cooled to room temperature. 0.9 g, of poly-(N^{ϵ}-methacryloyl-D lysine) (D PMAL) was dissolved in 7.5 ml of water at room temperature and the resulting solution was added to the methionine hydrochloride solution. The HCl concentration in the resulting solution was about 22% (wt/wt). The combined clear solution was seeded with L methionine hydrochloride seed crystals (3 mg) and placed in a thermostat-cooling bath. The starting temperature of crystallization was 13°C which was decreased to 6°C at a rate of 0.5°C per hour for the first 2 h, and 1°C every further hour, down to 6°C. The solution was then left at that temperature for 1 h. Mechanical stirring was started after 3–4 h from the beginning of the crystallization and continued regularly till the end of the crystallization process. (Alternatively, the stirring can start at the beginning of the crystallization without affecting the end result.) The precipitated small needle-like crystals were filtered through a sintered glass filter (No. 1) and dried. 6.69 g (23.9%) of L Met·HCl·H_2O were obtained consisting of 97% L and 3% D (by chiral G.C. Hewlett–Packard 5890 on chirosil.Val. column). A sample of the product was washed with 37% (wt/wt) hydrochloric acid to obtain crystals consisting of 98.74% L and 1.26% D Met·HCl·H_2O.

Recovery of the D Met·HCl·H_2O. 13.4 g of solid powdered D,L Met·HCl·H_2O were added to the mother liquor obtained in step (a) above, and the resulting slurry was stirred at 19.2°C for 12 h. The precipitate was then filtered off to obtain 7.13 g of a mixture composed of 1.72 g of D,L Met·HCl·H_2O and 5.41 g of D Met·HCl·H_2O. It follows that 11.68 g of D,L Met·HCl·H_2O were introduced into the mother liquor, resulting in a new solution comprising 27.28 g of L Met·HCl·H_2O and 28.16 g of D Met·HCl.H_2O and having a L/D ratio of 49.2/50.8% which can be subjected to a repeated crystallization of the L Met·HCl·H_2O as described in step (a).

Continuous isolation of L Met·HCl·H_2O and D Met·HCl·H_2O

The obtained mother liquor was crystallized as described before to afford 5.5 g of L Met·HCl·H_2O composed of 96% L and 4% D (by chiral G.C.).

To the mother liquor obtained above there were added 12.5 g of solid powdered D,L Met·HCl·H_2O and the resulting suspension was stirred for 8 h at 19.2°C and then filtered to obtain 5.5 g of a solid mixture composed of 0.5 g of D,L Met·HCl·H_2O and 5 g of D Met·HCl·H_2O. Therefore, 12 g of D,L Met·HCl·H_2O were introduced into the solution.

The above procedure was repeated for 18 more cycles and the L Met·HCl·H_2O and D Met·HCl·H_2O were collected separately. In general, the amounts of solid powdered D,L Met·HCl·H_2O added in each cycle to the mother liquor obtained after the filtration of the crystallized L

Met·HCl·H_2O, ranged between 2 to 2.7 times the amount of the L Met·HCl·H_2O recovered in the preceding step. Some losses of the viscous D,L Met·HCl·H_2O containing solution have been observed in each cycle, which explains the gradually decreasing amount of L and D Met·HCl·H_2O collected. The results of the first 20 cycles are summarized in Table 1.

The following polymers and their abbreviations have been used for the resolution of the following systems:

L or D PAL, Poly-(N^{ϵ}-acryloyl L or D lysine);
L or D PMAL, Poly-(N^{ϵ}-methacryloyl-L or D lysine).

Resolution of racemic Met·HCl·H_2O in kilogram scale

D,L Met. 7.2 kg. (feed grade) in 16.8 l HCl 32% (equal to 8.9 kg. D,L Met·HCl·H_2O). D PMAL 144 g in 1.2 l HCl. Total volume 25 l. 5 g of L Met·HCl was used as seed crystals. Crystallization started at 13 to 6.5°C for 8 h and stirred with a mechanical stirrer. 1.1 kg of L Met·HCl·H_2O (22%chemical yield) was obtained without washing, composed of 97.04% L and 2.96% D. 100 g were washed with HCl to yield a product with 98.74% L and 1.26% D (G.C. analysis).

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