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DESIGN OF STEREOSPECIFIC INHIBITORS FOR CRYSTAL DISSOLUTION

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Abstract: A new class of monomeric and polymeric crystal dissolution inhibitors has been prepared taking into consideration the packing arrangements and the morphologies of organic crystals. The efficiency of these inhibitors has been demonstrated by comparative morphological studies of α-glycine and by the kinetic resolution of the racemic conglomerates of his·HCl·H_2O, threonine, glu·HCl, and 2,4-sec-phenethyl-3,5-dinitrobenzoate

INTRODUCTION

In previous studies we described a general method for the design of stereospecific inhibitors of crystal growth[1,2]. We found that the most efficient inhibitors are molecules which may be considered as composed of two segments, one identical to that of the substrate molecule, and the other different from, and generally larger than, its counterpart in the substrate. We could infer from the change in crystal morphology during growth, and from the mode of occlusion of the inhibitor inside the crystal,

that the inhibitor is adsorbed mainly at those faces at which the altered part of the adsorbate emerges from the crystal face. Once adsorbed, the additive inhibits the regular deposition of further layers of substrate molecules, slowing down the growth perpendicular to that face, and leading to a concomitant increase in its surface area, relative to those of unaffected faces.

Growth and dissolution of crystals are considered, at conditions close to equilibrium, as reciprocal processes that can be interchanged by altering the degree of saturation of the solution[3]. In practice these processes are kinetically controlled and thus it is suggestive that inhibitors of growth should be useful in modifying crystal dissolution as well. Here we will report dissolution morphological and kinetic studies on various organic crystals, using both low molecular weight and soluble polymeric reagents as inhibitors. Indeed, experiments along these lines of thought led previously to a general method of stereospecific etching of preselected faces of crystals[4,5]. Any process of crystal etching takes place at the initial stages of dissolution.

As model systems we studied the relative rate of dissolution of the enantiotopic {010} faces of centrosymmetric crystals of glycine from enantiotopic faces, and the kinetic resolution of racemic mixtures of crystalline conglomerates such as histidine hydrochloride monohydrate, glutamic acid hydrochloride, threonine and sec-phenethyl-3,5-dinitrobenzoate.

RESULTS

Dissolution of {010} plates of α-glycine

Glycine crystallizes from pure aqueous solution in its α-crystal form (space group $P2_1/n$), exhibiting a bipyramidal habit. Small concentrations of racemic α-amino acid additives cause these crystals to grow as {010} plates. Systematic morphological studies have demonstrated that (R)-α-amino acids bind enantioselectively to the chiral (010) face of glycine, whereas the (S)-α-amino acids bind to the (0$\bar{1}$0) face[6].

Fig.1 summarizes results on the effect of varied amounts of α-amino acids on the dissolution of glycine plate-like crystals. As little as 5% of racemic alanine already influences dissolution. An increase in the concentration of this additive in solution to 50% reduces

the rate of dissolution of the glycine plates to less than one third of its original value. The effect of racemic phenylalanine was more pronounced; 5% of the latter is a more effective inhibitor than 5% alanine and an increase in the concentration of the phenylalanine to 10% in solution reduces the dissolution rate substantially below that in the presence of 50% (R,S)-alanine. Similar results were obtained with 5% (R,S)-lysine or with 3% N^{ε}-2,4-dinitrophenyl-(R,S)-lysine. These observed differences in dissolution rate of the glycine plates in the presence of additives of increasing size is a clear indication of the role of the size and structure of the α-amino acid residue in hindering crystal dissolution. The efficiency of these inhibitors was raised by at least an order of magnitude by anchoring the amino acids to a polymer such as poly-(N^{ε}-methacrylolyl-(S)-lysine) ((S)-PMAL)[7]. Of this polymer, 1-3% were found to be sufficient, under the given experimental conditions, to completely inhibit the dissolution of the {010} plates of glycine. In this case it is reasonable to assume that the grafted α-amino acids bind cooperatively and non-reversibly onto the {010} faces of glycine.

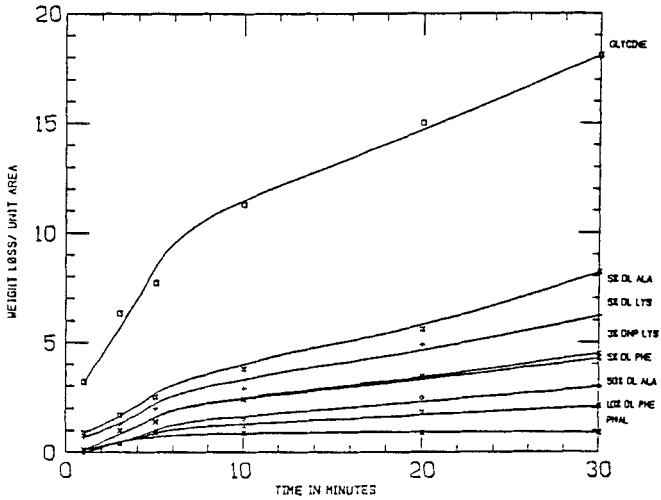

FIGURE 1: Dissolution of α-glycine plates in the presence of various α-amino acids expressed as loss per unit area/time. All experiments were performed on batches of twenty crystals at 20°C in solutions of 200mg glycine/ml H_2O.

Dissolution of α-glycine at its {110} faces

When α-glycine is grown from aqueous solution in the absence of additives the resulting bipyramidal crystals are delineated by {110} and {011} faces (Fig.2a). The question arose as to how such a crystal would dissolve in the presence of α-amino acid additives, which are known to adsorb on the {010} faces.

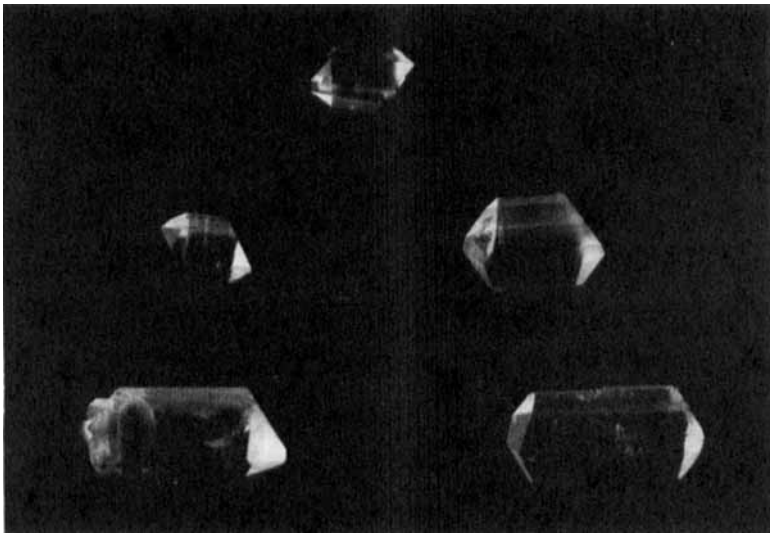

FIGURE 2a: Crystals of bipyramidal α-glycine delineated by {011} and {110} faces.

When single bipyramidal crystals of α-glycine were dissolved in an undersaturated solution of glycine the crystals dissolved in a symmetric manner from all faces. On the other hand, when the crystals were dissolved in an undersaturated glycine solution containing 10-20% of a chiral resolved α-amino acid (such as (R)-alanine) they dissolved anisotropically: the +b half of the crystal dissolved much faster than the opposite half yielding first a "basket-like" shape and subsequently into a "canoe-like" shape, with the development of an (010) face

at the more dissolved side (Fig.2b). The partially dissolved crystal is delineated by well preserved (011) and (01$\bar{1}$) faces while the (0$\bar{1}$1) and (0$\bar{1}\bar{1}$) faces appear more rounded. By symmetry, dissolution in the presence of an (S)-α-amino acid yielded the enantiomorphous crystal shapes. At first sight, these results appear paradoxical, in view of our knowledge that (R) amino acids are adsorbed at the (010) face and should therefore inhibit dissolution in the +b direction; however, further examination of the mechanism enabled rationalization of the experimental observations. Careful inspection of the faces newly formed on dissolution reveals etch figures thereon in the form of parallelepipeds.

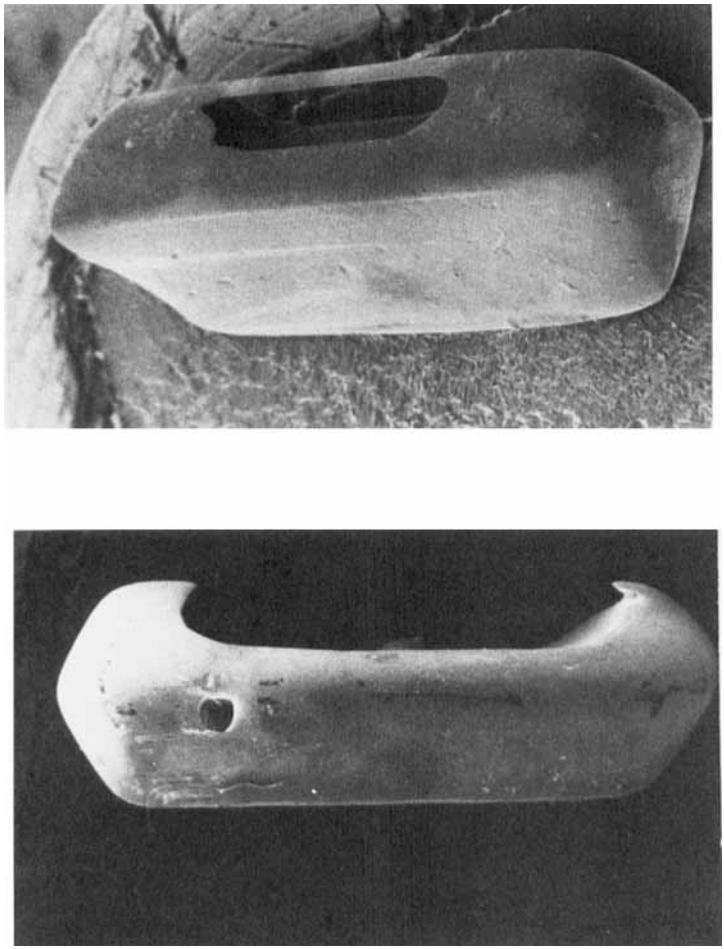

FIGURE 2b: Crystals of α-glycine after partial dissolution in the presence of R-alanine, and exhibiting a "basket" or "canoe-like" shape.

In previous studies we demonstrated that etch-pits of such chiral shape form only on the (010) face[4,5]. Further scanning electron microscope studies of bipyramidal crystals at early stages of dissolution, in the presence of, say, (R)-α-amino acids, indicated formation of well-defined steps, exhibiting an (010) surface, running parallel to the c-axis on the (110) and ($\bar{1}$10) faces (Fig.2c). These results may be interpreted as follows: dissolution of the (110) and ($\bar{1}$10) faces will proceed unhindered by additive but a poisoning of the (010) surface of the steps on these faces will occur resulting in preferential dissolution along the a-direction. As the steps move in that direction, the (010) surface which forms is stabilized by the additive in solution, increasing progressively its surface area. Conversely, any (0$\bar{1}$0) face of the adjoining steps which may form will dissolve without inhibition. This leads to the anisotropic dissolution of the +b half, as shown in Fig.2c. Dissolution at the -b half proceeds isotropically as the (R)-additive is not adsorbed at the (0$\bar{1}$0) surfaces, thus precluding step formation.

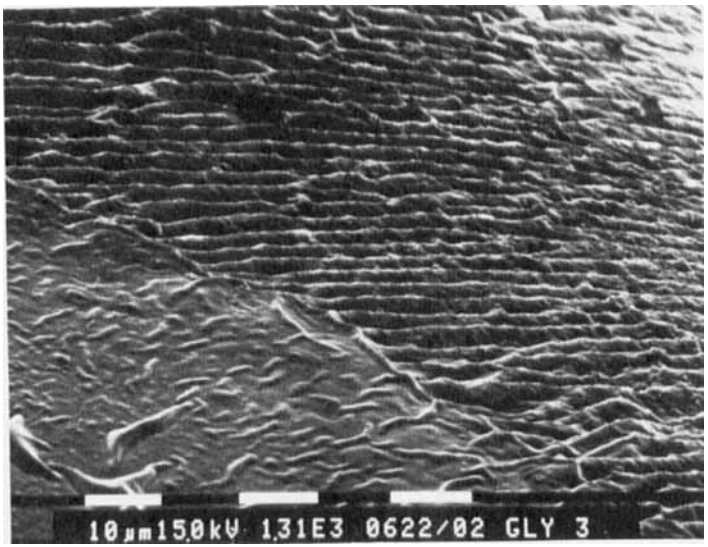

FIGURE 2c: Scanning electron micrograph of an (110) face of α-glycine with steps running parallel to the c-axis and exhibiting an (010) surface.

Additionally, the stereoselective adsorption of the (R) additive at the (011) and (01$\bar{1}$) faces, as opposed to (0$\bar{1}$1) and (0$\bar{1}\bar{1}$), leads to the retention of those faces at the +b half. In many single crystals holes were formed at early stages of the dissolution process. Subsequently, the crystal started to dissolve in the three directions, a, c and +b, leading to the canoe-like shape. The formation of this shape indicates that preferential

dissolution takes place along a, as compared to c. By symmetry, when S-α-amino acids were used, the crystals dissolved preferentially from the -b side, displaying similar shapes. On the other hand, dissolution in the presence of racemic α-amino acid solutions results in symmetric poisoning of both the (010) and (0$\bar{1}$0) steps at the (110) surface. The overall dissolution of the crystal then remains isotropic without formation of the "basket" or "canoe" like crystalline morphologies.

POLYMERIC REAGENTS FOR STEREOSELECTIVE DISSOLUTION OF CONGLOMERATES

(R,S)-Histidine Monohydrochloride Monohydrate

When racemic histidine hydrochloride is crystallized above 45°C from aqueous solution it precipitates in the form of a conglomerate of enantiomorphous crystals of (R) and (S)-histidine monohydrochloride monohydrate[8a,b]. We have reported elsewhere[9] that poly-(p-acrylamido-(S)-phenylalanine) (PA-Phe) interacts enantioselectively with the {111} faces of the (S) enantiomorph of His·HCl·H_2O thereby inhibiting its growth and leading to kinetic resolution of the conglomerate by crystalliza-

tion. We assume that upon dissolution of the conglomerate in the presence of the (S)-polymer the latter will also enantioselectively bind to the same faces of the (S) crystals and consequently delay their dissolution. On the other hand, the polymer will not adsorb onto the {111} or any other faces of the (R) enantiomorphs resulting in kinetic resolution of the conglomerate by dissolution. Some representative results of such experiments are summarized in Table 1. Increasingly efficient resolution is obtained with increasing amounts of polymer in solution (Fig.3.).

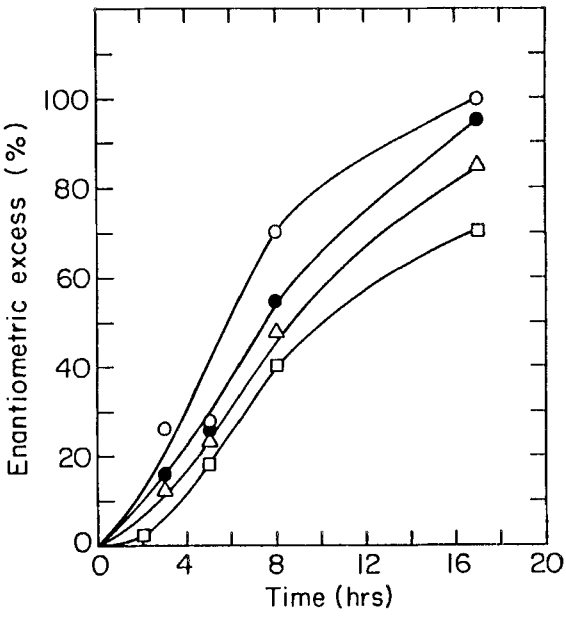

FIGURE 3: Dissolution rate of (R,S)-His·HCl·H_2O in the presence of different amounts of poly-(p-acrylamido-(S)-phenylalanine). □ 10mg polymer/3 ml; △ 30mg/3ml;●50mg/3ml;○ 70mg/3ml.

Conversely, dissolution of this conglomerate in the presence of poly-(N^{ε}-methacryloyl-S-lysine), PMAL, delays the overall rate of dissolution but no kinetic resolution could be achieved. This implies that the imidazole ring of the histidine substrate can be replaced by a phenyl of the PA-Phe but not by the lysine methylinic groups of

PMAL. The results in the presence of PMAL indicate non-stereospecific interaction and are in agreement with the experiment performed with non-chiral polyacrylic acid.

Additional experimental information on the mode of binding of the polymer at the various surfaces of the crystals could be obtained by dissolution of the two enantiomorphous crystals in the presence of fluorescently labeled polymer (1% dansyl moieties bound to the side chain of α-amino groups), and inspection of the partially dissolved crystals under fluorescent light. When (S)-His·HCl·H_2O was dissolved in the presence of (S) polymer, the crystals fluoresce stronger from the {111} faces indicating preferential adsorption at these surfaces. On the other hand, when a crystal of (S)-His·HCl·H_2O was dissolved in the presence of fluorescent (R) polymer, all crystal faces were weakly fluorescent implying a non specific interaction of the polymer with all faces.

Table 1: Typical dissolution data[a] of (R,S)-His.HCl.H_2O crystals (0.17 g) in an aqueous solution (3 ml) in which had been dissolved (R,S)-His.HCl.H_2O (0.68g) and the appropriate polymer (50 mg).

Type of polymer (config.)	Time (hrs)	Amount of crystals left mg (%)	enantiomeric excess % (config.)
(S)-PA-Phe*	2	115(68)	26 (S)
"	3	90(53)	50 (S)
"	5	81(48)	60 (S)
"	8	65(38)	93 (S)
"	16	62(36)	100 (S)
(R)-PA-Phe	2	112(66)	25 (R)
"	3	91(53)	52 (R)
"	5	84(49)	63 (R)
"	8	62(36)	91 (R)
"	16	60(35)	100 (R)
(S)-PMAL**	2	105(61)	0
"	16	44(26)	0
Polyacrylic acid (MW-2000)	2	95(56)	0
" " "	16	39(23)	0
Blank (no polymer)	2	93(55)	0
	16	42(25)	0

* PA-Phe = Poly-(p-acrylamido-phenylalanine)

** PMAL = Poly-(N^{ε}-methacryloyl-lysine)

[a] All the experiments in the Tables 1-4 were performed by agitation at 25°C.

Glutamic Acid Hydrochloride, Threonine, and sec-Phenethyl-3,5-dinitrobenzoate

Similar studies of enantiomeric enrichment upon dissolution were carried out with the conglomerate racemic mixtures of (R,S)-glutamic acid·HCl, (R,S)-threonine and (R,S)-sec-phenethyl-3,5-dinitrobenzoate[5], in the presence of the appropriate polymers previously used for kinetic resolution by crystallization[7]. Glu·HCl crystallizes in space group $P2_12_12_1$ in the form of {001} plates. Kinetic resolution of (R,S)-Glu·HCl was achieved by dissolution in the presence of poly-(N^{ε}-methacryloyl-(S)-lysine) (Table 2). This polymer is stereoselectively adsorbed at the {001} faces of the (S) enantiomorph through the α-amino acid side-chain of (S) lysine. The stereoselective effect was further confirmed by separate dissolution of the (R) and (S)-Glu·HCl crystals in the presence of the (S) polymer (Table 2).

Resolution of (R,S) threonine by crystallization of the conglomerate had been successfully performed in the presence of poly-(N^{ε}-methacryloyl-(R) or (S)-lysine). Attempts to obtain enantiomeric enrichment of this racemic mixture by dissolution in the presence of the same polymer were however unsuccessful.

Table 2: Dissolution experiments of Glu·HCl [(R,S), (R) or (S)] in the presence and absence of PMAL.

Substrate dissolved	Type of polymer	Time (hrs)	Amount of crystals left mg (%)	enantiomeric excess % (config.)
(R,S)-Glu.HCl[a]	(S)-PMAL	3	120(60)	2 (S)
"	"	5	35(17)	44 (S)
"	"	7.5	20(10)	100 (S)
"	No polymer	3	60(30)	0
"	"	5	30(15)	0
(S)-Glu.HCl[b]	(S)-PMAL	3	55(55)	
"	"	5	22(22)	
(R)-Glu.HCl[b]	"	3	51(51)	
"	"	5	9(9)	
(S)-Glu.HCl[b]	No polymer	3	27(27)	
"	"	5	5(5)	

[a] Crystals (200 mg) were dissolved in an aqueous solution (3 ml) containing (R,S)-Glu.HCl (1.34 g) and PMAL (30 mg).

[b] Crystals (100 mg) were dissolved in an aqueous solution (3 ml) containing Glu.HCl (R or S) (0.75 g) and PMAL (30 mg).

Previous studies had shown that crystals of threonine prepared by direct crystallization of the racemate in aqueous solution have a pronounced tendency to form microtwins[10]. This may well be the reason for our inability to resolve this material by dissolution.

In order to verify that possibility, artificial racemic mixtures were prepared by mixing equal amounts of crystals of (R) and (S)-threonine grown separately. Such mixtures were then submitted to dissolution in the presence of the (S) polymer (Table 3). In contrast to the results obtained with the directly crystallized racemic mixture, preferential enrichment in (S)-threonine crystals was observed (Table 3). In all the above systems, under the same experimental conditions, no resolutions whatsoever could be achieved by use of the monomeric inhibitors.

Table 3: Typical dissolution data of an artificial mixture of (R) (60 mg) and (S) (60 mg) threonine in aqueous solution (3 ml) containing (R,S)-threonine (0.48 g) and polymer (40 mg)

Type of polymer (config.)	Time (hrs)	Amount of crystals left mg (%)	enantiomeric excess % (config.)
(S)-PMAL	2	73(60)	14 (S)
"	3	49(41)	34 (S)
"	4	37(31)	55 (S)
"	5	31(26)	74 (S)
"	7	28(23)	81 (S)
Blank (no polymer)	2	36(30)	0
"	7	12(10)	0

Analogously, kinetic resolution of (R,S)-sec-phenethyl-3,5-dinitrobenzoate, which is a molecular crystal and does not possess ionic bonds, was achieved by the partial dissolution of the conglomerate mixture in the presence of poly-(N-acryloyl-(p-amino-benzoyl)-(S)-sec-phenethyl-amide) (Table 4).

Table 4: Typical dissolution experiments of sec-phenethyl-3,5-dinitrobenzoate (PDNB) [(R,S), or (S)] in the presence and absence of poly-[N-acryloyl-(p-aminobenzoyl) (S)-sec-phenethyl-amide].

Substrate dissolved	Polymer config.	Time (hrs)	Amount of crystals left mg (%)	enantiomeric excess % (config.)
(R,S)-PDNB[a]	S	3	105(55)	10 (S)
"	S	4	54(28)	50 (S)
"	S	5	37(19)	83 (S)
"	No polymer	3	66(34)	0
(S)-PDNB[b]	S	3	55(55)	
"	S	5	40(40)	
"	No polymer	5	24(240	

[a] Crystals (190 mg) were dissolved in a solution of toluene:DMF (0.5:1 ml) containing (R,S)-PDNB (0.6 g) and (S)-polymer (40 mg).

[b] Crystals of (S)-PDNB (100 mg) were dissolved in a solution of toluene:DMF (0.5:1 ml) containing (S)-PDNB (0.35 g) and (S)-polymer (40 mg).

CONCLUSIONS

In the past we have demonstrated that one may utilize the structural information contained in the packing arrangement of crystals and their morphologies for the design of stereospecific inhibitors of crystal growth.[1,2] Here we present an extension of these studies by demonstrating that a stereoselective crystal growth inhibitor acts as crystal dissolution inhibitor as well. Both low molecular weight and polymeric additives have been tested and there is a pronounced difference between the two classes, the polymers being always much more effective. The low molecular weight inhibitors presumably reside only temporarily at the given surfaces of the crystal and are in dynamic exchange with the solution close to these surfaces. They therefore provide part of the effective solute concentration which these faces feel. Consequently, the degree of saturation for the various faces is different, dependent upon the stereospecific additive interactions. On the other hand, the polymers adsorb stereospecifically at the appropriate faces by a number of the side groups grafted on the chain. Owing to strong cooperative effects, one may

expect that once a few groups have bound to the surface of the dissolving crystal, it will become very difficult or even impossible for the polymer to be detached from the crystal surface. Coverage of these faces will block their overall dissolution.

In the present study we have used predominantly atactic polymers prepared by radical polymerization of the corresponding vinyl monomers. Improvement of the fit between the surface of the crystal and the arrangement of the grafted groups by increasing the tacticity of the polymers should increase the efficiency of these dissolution inhibitors.

Finally we point out that although the efficiency in the enrichment in each step is not quantitative, there exists a possibility of exploiting these polymeric growth and dissolution inhibitors in a cycle of consecutive enrichment processes, for total separation of enantiomers. A conglomerate mixture dissolved in the presence of say (R) polymer will yield a solution enriched in (S) enantiomer. Crystallization of this mother liquor will yield crystal mixtures even more enriched in (S), because of the presence of the R

inhibitor in solution. This cycle can be repeated with addition of racemate at each step, and thus result in more efficient resolutions.

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REFERENCES

1. Addadi,L., Berkovitch-Yellin, Z., Weissbuch, I., van Mil, J., Shimon, L.J.W., Lahav, M., and Leiserowitz, L., Angew. Chem. 24, 466 (1985).

2. Addadi, L., Berkovitch-Yellin, Z., Weissbuch, I., Lahav, M., and Leiserowitz, L. Topics in Stereochemistry 16, 1-85 (1986).

3. Buckley H.E. "Crystal Growth", John Wiley and Sons:New York (1951)

4. Shimon, L.J.W., Lahav, M., and Leiserowitz, L. J. Am. Chem. Soc., 107, 3375 (1985).

5. Shimon L.J.W., Lahav, M. and Leiserowitz L. Nouveau Journal de Chimie, 10, 723 (1986).

6. Weissbuch I., Addadi, L., Berkovitch-Yellin Z., Gati E., Weinstein S., Lahav, M. and Leiserowitz L. J. Am. Chem. Soc., 105 6615 (1983).

7. Zbaida D., Weissbuch I., Shavit-Gati E., Addadi L., Leiserowitz L. and Lahav, M. Reactive Polymers, 6, 241 (1987).

8. (a) Dushinsky R. Chem. Ind., 53, 10 (1934).
(b) Collet, A., Brienne, M.J., Jacques, J. Chem. Rev. 80, 215 (1980).
(c) Brienne, M.J., Collet, A. and Jacques, J. Synthesis, 704, (1983).

9. Weissbuch I., Zbaida D., Addadi, L., Leiserowitz L., and Lahav, M. J. Amer. Chem. Soc., 109, 1869 (1987).

10. Addadi, L., Weinstein S., Gati E., Weissbuch I. and Lahav, M. J. Amer. Chem. Soc. 104 4610 (1982).