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GENERATION AND AMPLIFICATION OF OPTICAL ACTIVITY BY CRYSTALLIZATION: THE SYSTEM NICKEL ∝-AMINO CAPROLACTAM/LYSINE.

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ABSTRACT

A number of possible model systems for the spontaneous generation and amplification of net chirality in chemical systems by the process of crystallization are presented. In one of these a chiral resolved product (S') [or (R')] generated from crystals of a multimolecular complex $\{S_n\}$ or $\{R_n\}$, forms by ligand exchange diastereomeric complexes $(S_{n-1}\ S')$ and $(R_{n-1}\ S')$ which act as growth inhibitors of the parent conglomerate crystals, but at different extents. The Nickel complex of ∝-amino caprolactam (ACL) grown in ethanol, in basic conditions, has been investigated as an appropriate system for such a model. Kinetic, structural and morphological studies shed light on the mechanism of the asymmetric induction and demonstrated the feasibility of a complete cycle of generation and amplification of net chirality in this chemical system or others of the same type.

INTRODUCTION

The generation and amplification of net chirality in organic compounds, starting from achiral or racemic materials and in the absence of external chiral agents has raised and continues to raise both theoretical and experimental interest as a viable possibility to the origin of optical activity in the prebiotic world.[1]

It has been shown mathematically that any small fluctuation in the concentration of the two enantiomeric components of a racemic mixture may be transformed into a large excess of one of the two, in systems where a chemical substance acts as a catalyst for its own production and as an inhibitor for the formation of its enantiomer.[2-4]

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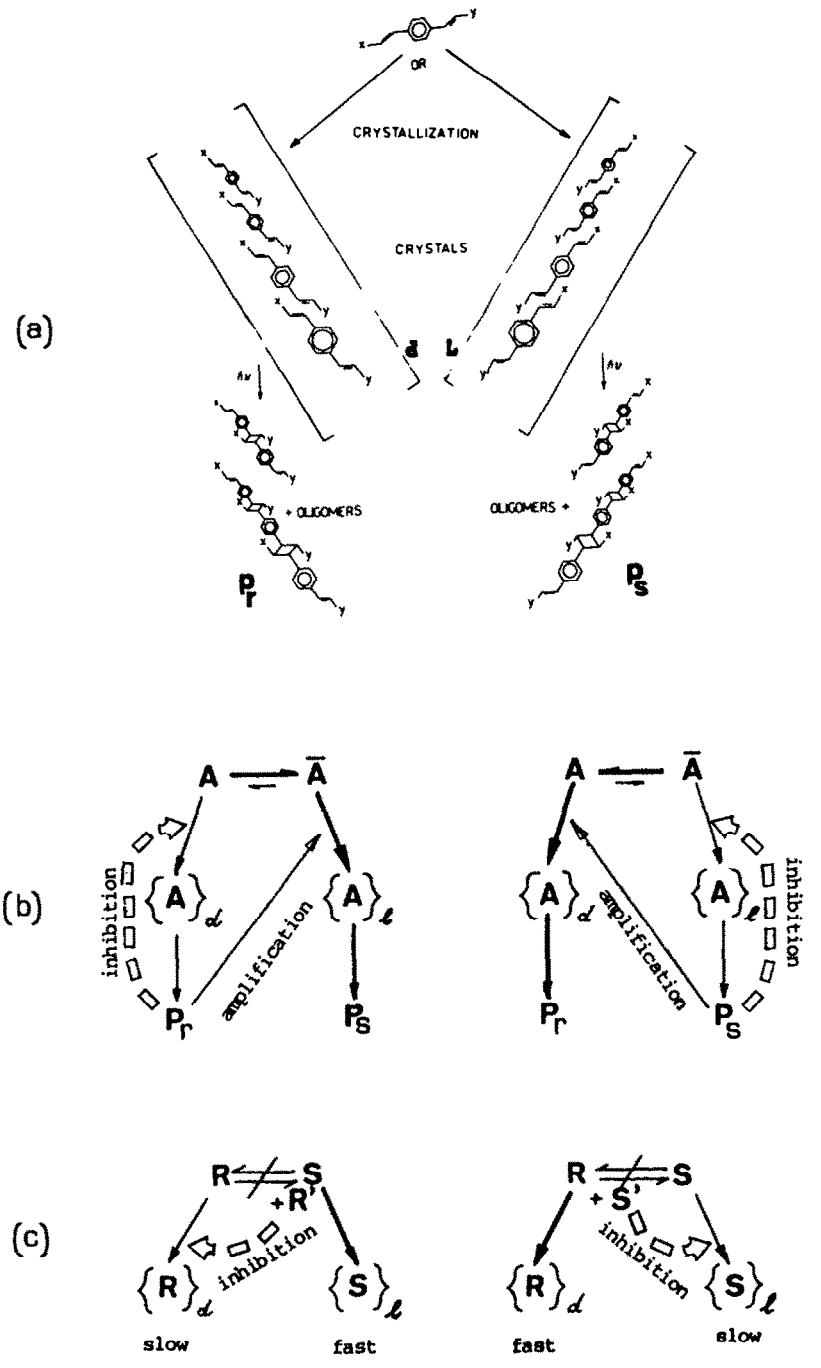
Crystallization of compounds that are achiral or racemic in solution but display chiral structures in the solid phase would appear to be an ideal experimental set for such a model. It has indeed been shown in a number of systems in the past, since the classical experiment of Havinga,[5] that direct amplification of chirality can be induced by crystallization starting from seeds of arbitrary absolute configuration.[6-7] Green and Heller have proposed a model involving a feedback mechanism, in which chiral products generated by topochemical reaction in the first chiral crystal are exploited as inducing agents in solution for further directed crystallization.[8] Preferential crystallization of the opposite enantiomorphous phase was observed in this instance, but in the absence of a mechanistic interpretation, this example remained as an isolated curiosity.

Modeling of Systems

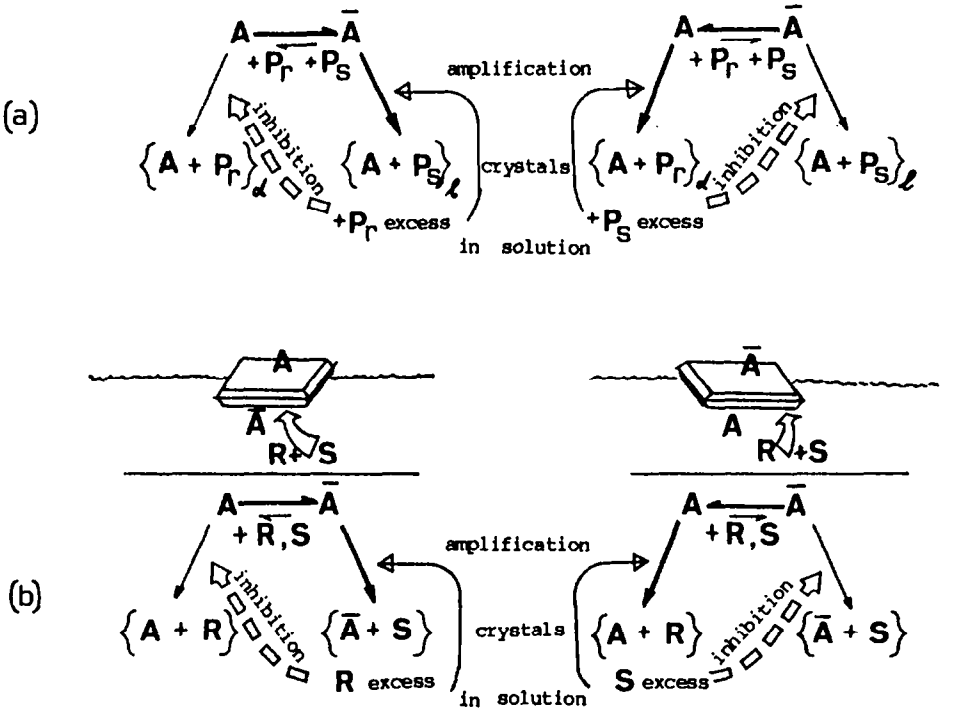
We have tried in the past years to systematically design various systems which lead to generation and amplification of optical activity by crystallization. We considered first systems as in Scheme 1a: various unsymmetrically substituted but achiral or racemic phenylene diacrylates were crystallized under controlled conditions to yield chiral crystals of one handedness only. A subsequent topochemically controlled solid state photopolymerization resulted in enantiomerically pure dimers, trimers and oligomers which are closely related stereochemically to the arrangement of two, three or n-monomer molecules in the parent crystals.[9] The influence of the presence of these products on a fresh crystallization of the monomer was then systematically studied. It was seen that a product Pr, generated in a crystal of chirality say d, induced without exception a large excess of crystals of chirality *l*.[10] The stereochemical similarity between product and parent crystal allowed us in this instance to understand the mechanisms of the process. It was found that the chiral additive Pr is selectively adsorbed at the surface of the growing crystals (and crystal nuclei) of chirality d (and vice-versa Ps at *l*). Pr cannot be adsorbed as well at the surface of *l* crystals because of its opposite absolute configuration. Once adsorbed the additive causes an obstacle to the further regular attachment of monomer molecules. Growth of the crystal is thus kinetically unfavoured with respect to that of the unaffected enantiomorphic phase and the whole equilibrium A ----> Ā is shifted towards the faster growing phase (Scheme 1b). This effect (which we named the "rule of reversal") was proven to be valid in a general way, and the mechanism was applied to resolution of conglomerates[11] (Scheme 1c) as well as to the solution of a number of other different problems in the field of stereochemistry,[12] crystal dissolution,[13] material sciences etc.[14,15]



Scheme 1

Concerning the generated optical activity, it is clear in the light of the demonstrated mechanism that the reversal of absolute configuration is an inherent property of the system, and that amplification by these means can only assume an oscillating pattern.

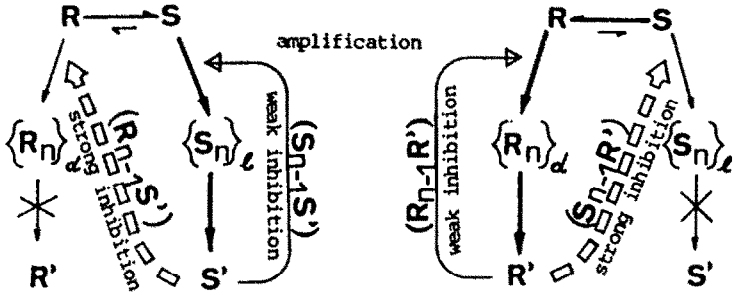
One can, however, envisage conditions in which the same systems could give rise to direct amplification. We have shown that the parent crystals $\{A\}_d$ and $\{\bar{A}\}$ selectively occlude during growth small amounts of the inhibitors Pr and Ps respectively. A random crystallization of the parent material in a multicrystalline mixture would, after reaction, result in the production of both Pr and Ps in equal amounts. Crystallization of A and $\bar{A}$ would then continue in the presence of racemic products in solution. If a fluctuation induces preferential crystallization of say $\{A\}_d$ at time t, selective occlusion of Pr in these crystals would generate an excess of Ps in solution (Scheme 2a). This excess selectively inhibits growth of $\{\bar{A}\}_\ell$, thus triggering amplification by further crystallization of $\{A\}_d$. An analog of this system is an achiral molecule crystallizing in a centrosymmetric crystal which displays enantiotopic faces (Scheme 2b). The crystal grows in contact with a solution which contains a racemic additive. Each enantiomer of the racemic mixture can be stereoselectively adsorbed at, and eventually occluded through, only one of the enantiotopic faces of the crystal (A or $\bar{A}$). If only one of these latter faces is exposed to solution, as in the case of crystals growing at an interface, then the system of the centrosymmetric crystal + the orientation at the interface is formally equivalent to that of a conglomerate A ----> $\bar{A}$. The first growing crystal of arbitrary orientation,



Scheme 2

say A, will generate by selective adsorption of one enantiomer, say (R), a small excess of (S) enantiomer in solution. This excess subsequently catalyses further crystallization of the compound in the A orientation, thus triggering amplification. This pattern has been shown to be operative in the case of ∝-glycine crystals crystallizing at the air interface of a solution containing mixtures of racemic amino acids.[16,17]

In a third possible approach, the additive (R) or a derivative of it, generated in d crystals, selectively inhibits the growth of ℓ crystals. This can be achieved either by a reaction that leads to inversion of configuration of the additive, or by the formation of diastereomeric complexes (Scheme 3). If the crystallizing species are $\{S_n\}_\ell$ and $\{R_n\}_d$ with $n \neq 1$ and S' or R' is the chiral product, then the two diastereomeric species (S_{n-1} S') and (R_{n-1} S') can both conceivably act as additives, and kinetically affect crystal growth of $\{S_n\}$ and $\{R_n\}$, but to different extents. One is therefore using the identical part of the complex, S_{n-1}, as a "carrier" for the additive of opposite absolute configuration. Here we wish to report a system in which chirality is generated and amplified following this last model.



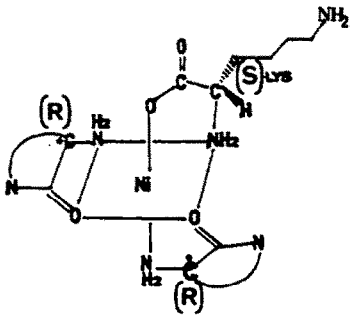
Scheme 3

The System Ni ∝-amino caprolactam lysine

Experiments conducted by Sifniades et al.[18] on crystallization of the Nickel complex of ∝-amino caprolactam indicated that this might be a suitable system to test the model illustrated in Scheme 3. This compound has been extensively investigated because of its industrial importance as a precursor of lysine. Racemization of ∝-amino caprolactam (ACL) was found to be catalyzed by Nickel II cations in solution in the presence of base ethoxide. Under racemizing conditions a supersaturated solution of $Ni(ACL)_3$ can be almost

quantitatively converted to one enantiomer by crystallization in the presence of seeds of the appropriate (R) or (S) complex. Even though many possible diastereoisomers of the complex may exist in solution, only the conglomerate of $\{Ni[(R)ACL]_3Cl_2EtOH\}$ and $\{Ni[(S)ACL]_3Cl_2EtOH\}$ crystallizes under these conditions. Thus due to the coupling of fast racemization to fast ligand exchange a continuous process of resolution can be triggered by seeding. Decomposition of the complex after separation and redissolution of the crystals, followed by hydrolysis of the resulting lactam under acidic conditions provide then an efficient route to preparation of enantiomerically pure lysine. Although seeding leads to efficient amplification of chirality, it does not, however, provide a sufficient "memory effect", because small changes in temperature and supersaturation under metastable conditions can lead either to spontaneous precipitation of the opposite enantiomer or to dissolution of the seeds.

It was observed that crystallization of racemic $Ni(ACL)_3$ in the presence of small amounts of resolved lysine resulted in an excess of the complex of the same absolute configuration as the lysine added.[19] If indeed the conditions of Scheme 3 are operating, the complete cycle of generation and amplification of net chirality would be represented as follows (Scheme 4): the first crystal separating from a super-saturated solution containing $NiCl_2$ and (R,S) ACL is by chance, of absolute configuration say (S). By hydrolysis, (S) lysine is produced, which in turn kinetically favours the crystallization of new $[(S)ACL]_3.NiCl_2$ by virtue of the different inhibiting effects of the diastereoisomeric complexes $Ni[(R)ACL]_2$ $[(S)lys]$ Cl_2 (1) and $Ni[(S)ACL]_2$ $[(S)lys]Cl_2$ (2) on the crystals of $\{Ni[(R)ACL]_3.Cl_2.EtOH\}$ and $\{Ni[(S)ACL]_3.Cl_2.EtOH\}$ respectively.



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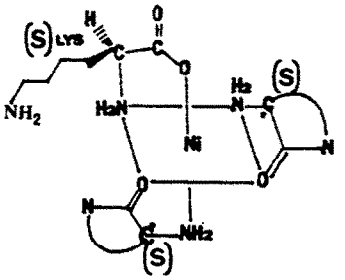

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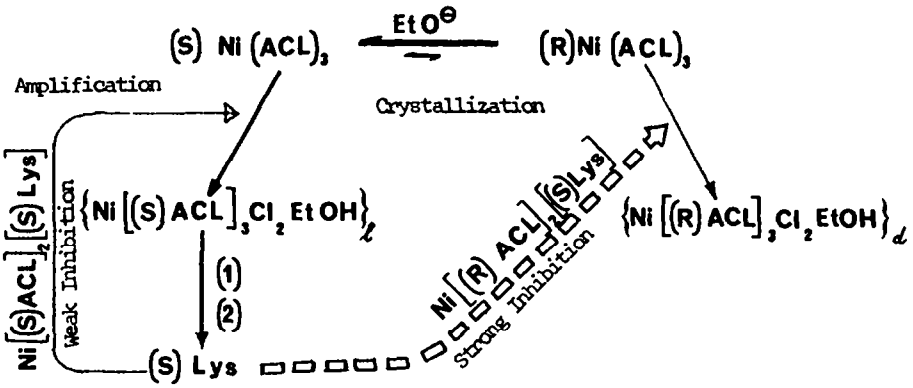
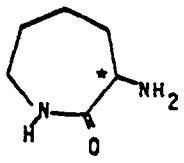


(1) Dissolution

(2) Hydrolysis in acidic conditions.



ACL

Scheme 4

RESULTS

A large number of crystallizations of racemic $Ni(ACL)_3.Cl_2$ were performed under conditions that allow racemization of caprolactam to take place in the complex, and with various amounts (R) or (S)-lysine present in solution. In contrast to caprolactam, neither lysine nor the other amino acids used in this study undergo racemization under these same conditions. The crystallization was initiated by addition of a small amount of racemic conglomerate crystals as seeds, and the enantiomeric purity of the precipitate was analyzed by optical polarimetry. Some representive results are summarized in Table 1 and Fig.1

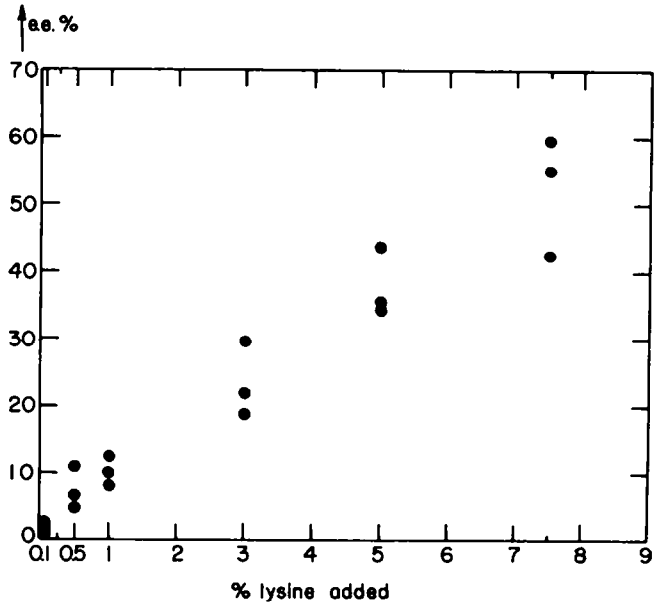


Figure 1
Dependence of the enantiomeric excess of crystalline {Ni(ACL) $_3$.Cl$_2$.EtOH} on the amount (wt/wt of complex) of added lysine

Table 1

Some typical results of crystallization (after 16 hrs) of racemic {Ni(ACL) $_3$.Cl$_2$.EtOH} complex in the presence of resolved lysine

Lys Added	% Lys (wt/wt of complex)	Seeds racemic (mg)	Amount[a] cryst (mg)	$[\alpha]_D$[a] (°)	e.e. (%)
S	7.5	1	37.3	-13.9	59.7
S	7.5	1	57.0	-12.6	54.1
S	5.0	1	26.6	- 9.2	39.5
S	5.0	1	51.6	-10.8	46.4
S	3.0	1	45.5	- 5.0	21.8
S	5.0	-	5.8	- 9.2	39.3
S	5.0	-	5.1	-11.1	47.2
R	5.0	1	72.4	+12.6	54.1
R	5.0	1	61.9	+11.9	51.1

(a) Starting from 400 mg ACL in solution (2 ml).
(b) Not corrected for seeds added. The $[\alpha]_D$ of the pure (R) complex is +23.30 (c=4, 1N HCl).

As can be seen from the Table and from Fig.1 the e.e. increases with increasing amount of additive up to a maximum of 60% e.e. for 7.5% lysine added. From the graph (Fig.1) it is

and assuming the linear behaviour will hold for higher concentrations, an amount of ~12% (wt/wt) of lysine should bring the process to near 100% e.e. However, 7.5% is the maximum that could be dissolved under the conditions of the experiment. Addition of (S)-lysine results after crystallization in the presence of racemic seeds in an excess of the (S)-complex, while (R)-lysine yields the (R)-complex in larger amounts. Without seeds crystallization takes place much more slowly but chiral induction of the same order of magnitude is nevertheless obtained. Seeding, however, plays an important role in the process and a chiral seed takes preference even over the lysine added.

The effect is not limited to lysine. A large number of the amino acids that were tested for their inductive power on the (ACL)-complex showed chiral induction in the same direction albeit in most cases to a much lesser extent than lysine. Only ornithine yields an e.e. of the same order of magnitude as lysine (Table 2).

Table 2

Effect of various additives (5% wt/wt of complex) on the crystallization of racemic $\{Ni(ACL)_3.Cl_2.EtOH\}$ in the presence of racemic seeds (1 mg.)

Additive	Cryst. time(hrs)	Amount[a] Cryst.(mg)	$[\alpha]_D(^o)$[a]	e.e. (%)
(S)-ornithine	16	42.0	-12.0	51.3
	12	38.1	-11.4	48.9
	12	39.8	- 9.8	42.1
(R)-ornithine	16	66.0	+11.9	51.1
	16	57.6	+10.6	45.5
	12	51.3	+11.2	48.1
(S)-norvaline	4	48.9	- 3.1	13.3
	4	68.6	- 4.3	18.5
	4	42.9	- 3.6	15.5
	4	51.3	- 3.4	14.6
(S)-norleucine	3	41.2	- 2.0	8.6
	4	43.6	- 2.6	11.2
	4	49.1	- 1.9	8.2
	4	44.0	- 1.5	6.4
N-methyl-(S)-Lys.	4	25.1	- 4.6	19.7
	4	20.9	- 3.3	14.2
	4	28.6	- 3.9	16.7
(S)-alanine	4	31.1	- 3.7	15.9
	4	28.6	- 2.9	12.5
	4	24.3	- 3.4	14.6
	4	29.2	- 3.1	13.3
R-alanine	4	29.6	+ 3.1	13.3
	4	31.3	+ 3.9	16.7
	4	37.6	+ 2.8	12.0
	4	26.3	+ 3.4	14.6
(S)-threonine	5	48.9	- 1.4	6.0
	5	41.3	- 1.9	8.2
	5	41.8	- 2.1	9.0
	5	39.6	- 1.6	6.9

(a) See note, a,b in Table 1

A series of experiments were performed in order to ascertain whether the additives are acting at the crystallization stage and whether the mechanism is indeed the one postulated in Scheme 3.

Selective Additive Adsorption.

In previous studies with conglomerate systems following the "rule of reversal", the additive (R') selectively inhibits the growth of {R} crystals by adsorption and subsequent inhibition.[11] On these systems (R') was found occluded in small amounts into the {R} crystals exclusively, while the opposite enantiomer (S') was not.

Single crystals of ACL complex of chirality (R) or (S) grown in the presence of (R,S) lysine in solution, were dissolved and analysed by HPLC under conditions of chiral separation.[27] Both enantiomers of lysine were found occluded into the same single crystals in approximately the same amounts (Fig.2). This indicates that both additives interact with each chiral crystal of the complex, and that resolution is not due to differential adsorption of the two diastereoisomers 1 and 2 onto the conglomerate crystals.

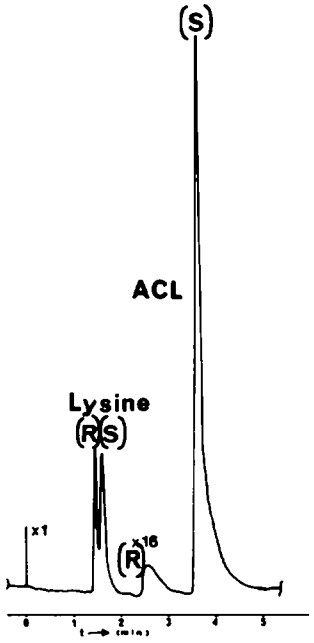


Figure 2
HPLC chromatogram of (R) and (S) lysine occluded into a single crystal of $Ni[(S)ACL]_3.Cl_2.EtOH$. The small amount of (R) ACL present is due to racemization.

Growth rate

The amount of crystallized resolved complex $Ni[(S)ACL]_3.Cl_2.EtOH$ was measured as a function of time after seeding under non racemizing conditions, in the absence of additive as well as in the presence of (R) or (S) lysine (5% wt/wt). The resulting curves are reported in Fig.3. Both (R) and (S)lysine retard the growth of the (S) complex, but (R)lysine retards it to a larger extent than the (S) enantiomer. Thus, although both enantiomers of lysine are adsorbed onto the crystals in the same amounts, (R) lysine is a much more effective inhibitor.

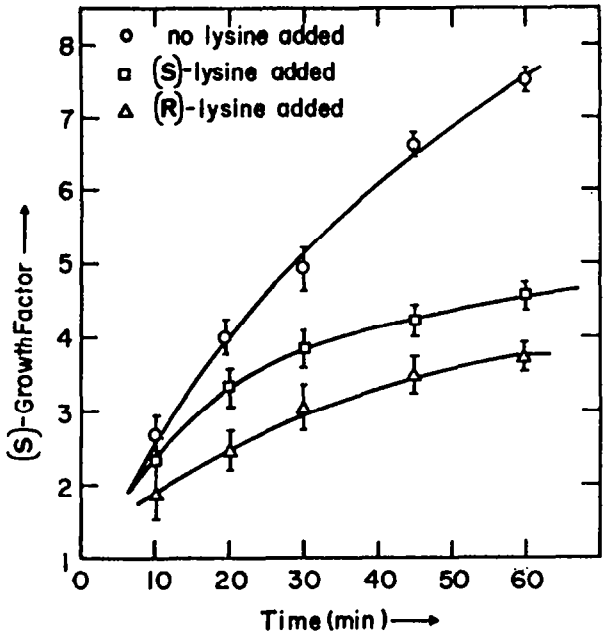


Figure 3
Relative growth rate (in arbitrary units) of crystalline $Ni[(S)ACL]_3.Cl_2.EtOH$ from pure solution and with added (R) or (S)lysine

Etching.

It has been observed in previous studies that a selective inhibitor of nucleation and growth is a selective etchant of the same crystals upon dissolution.[13] This means that in conglomerate systems, where (R') inhibits the growth of {R} crystals, partial dissolution of {R} in the presence of (R') in solution induces formation of etch-pits on the surface of the crystals. Dissolution of {R} in the presence of (S') does not affect the smoothness of the surfaces, as for dissolution in the absence of additive.

Single crystals of $Ni[(S)ACL]_3.Cl_2.EtOH$ complex were submitted to partial dissolution in undersaturated solutions in the presence of (R) or (S)lysine. Etching was observed with

both additives, while dissolution in a pure ACL solution resulted in smooth surfaces (Fig.4). In agreement with the adsorption experiments, these results indicate that both enantiomers of lysine (or diastereoisomers 1 and 2) interact with the corresponding chiral complex crystals.

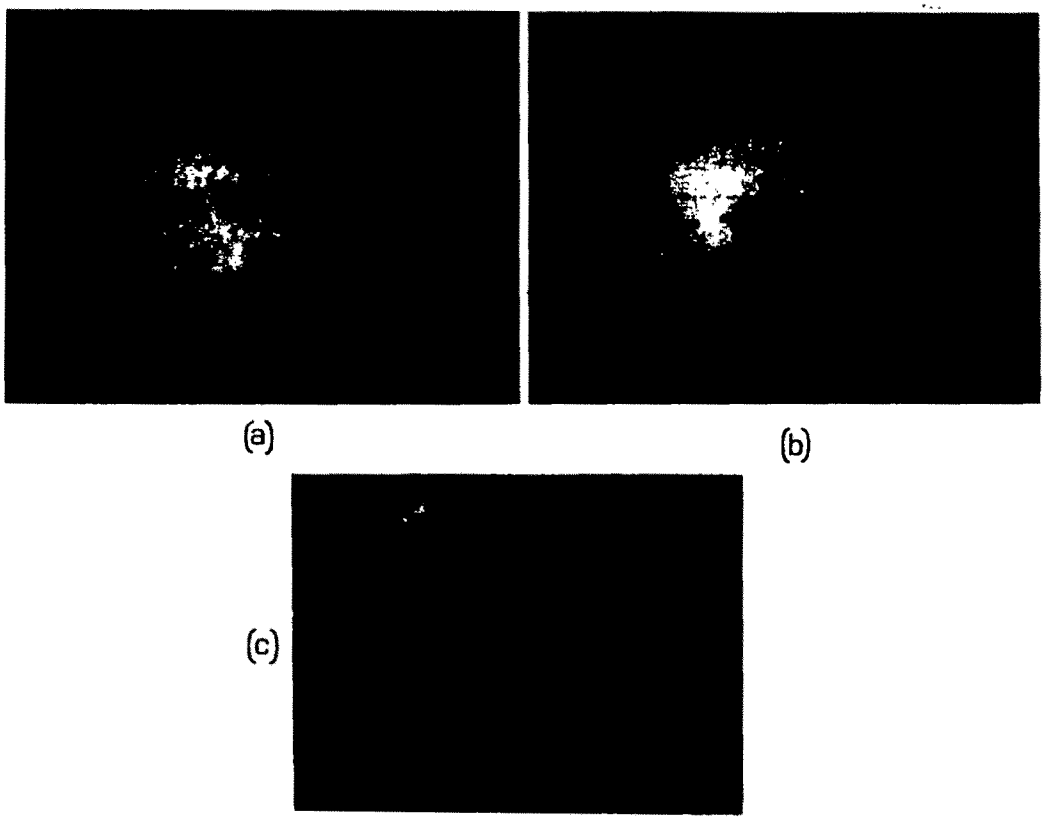


Figure 4
Optical micrograph (x280) of the (001) face of (S)ACL Nickel complex single crystals after dissolution in the presence of (a) (S)lysine; (b) (R)lysine; (c) no additive.

Circular Dichroism

Circular dichroism measurements were performed on the (S) complex in solution in the absence and in the presence of (R) or (S) lysine. The spectrum of the pure (S) complex shows two Cotton effects at λ=356nm $[\vartheta]$=155°mole^{-1} decm^2 and λ=602nm, $[\vartheta]$=147°mole^{-1} decm^2. Addition of either (R) or (S) lysine results in the same slight decrease in both peaks (17%). This effect is due neither to free lysine nor to contributions of a nickel complex of lysine. Both these compounds would have led to opposite effect with the addition of the two opposite enantiomers. The results indicate that a mixed complex is formed, but with no stereoselectivitiy.

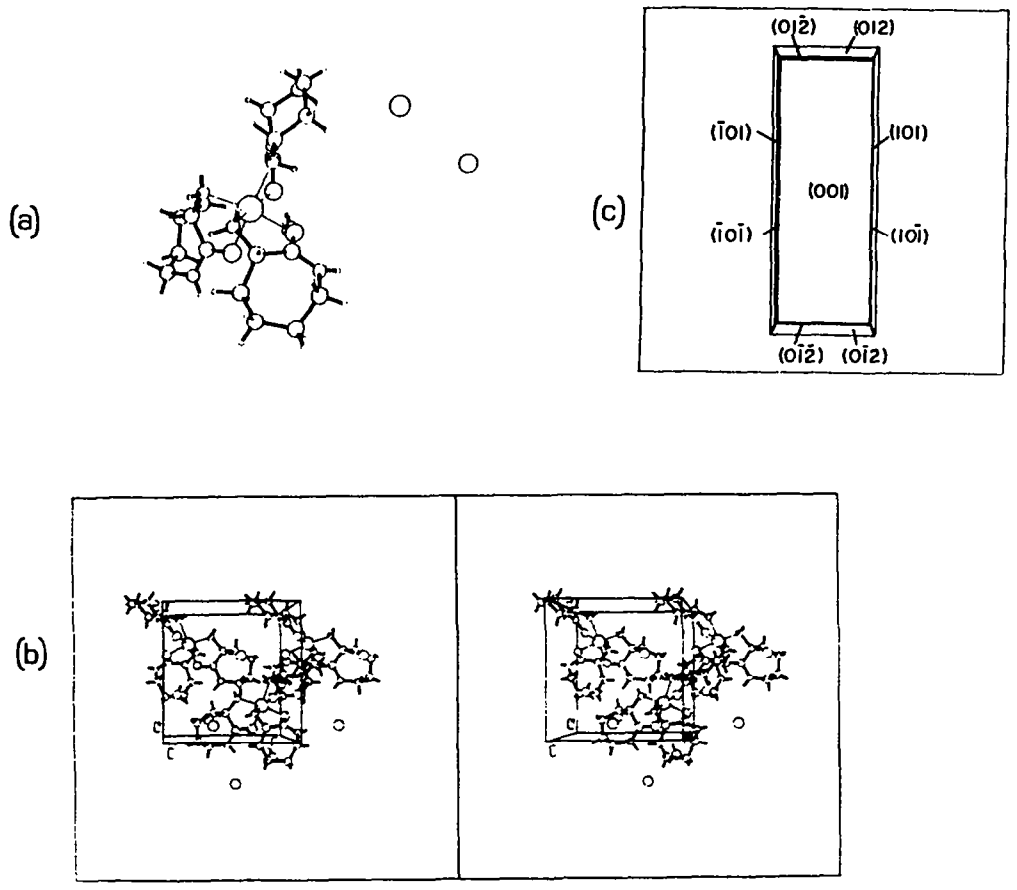


Figure 5
(a) Molecular structure of (S) Ni[(S)ACL]$_3$.Cl$_2$.EtOH;
(b) Packing arrangement viewed along c.
(c) Crystal morphology of the complex, pure and grown in the presence of (R) or (S)lysine.

Crystal Structure and Crystal Morphology

The crystal structure of the complex was solved[20]. Ni[(S)ACL]$_3$ Cl$_2$EtOH crystallizes in space-group $P2_12_12_1$ with cell constants a=9.760Å; b=9.801Å; c=29.221Å; (z=4), as thin (001) plates elongated in b. The structure of one complex molecule and the packing arrangement are given in Figs.5a,b. From a steric point of view it would indeed seem that within one single complex moiety, both (R) or (S) lysine can substitute one ACL molecule without apparent difference in the intermolecular interactions. The side chain of the two enantiomers of lysine in the diastereomeric complexes 1 and 2 would, however, emerge in different directions, thus creating different intermolecular contacts. This can conceivably result in different inhibiting effects.

We have used changes in the morphology of crystals grown in the presence of additives as a tool to pinpoint specific interactions of additives with the different crystal faces and subsequent inhibiting effects in the various growth directions.[21] In the present case no changes in morphology were observed between pure {R} or {S} complex crystals, and crystals of complex grown in the presence of either (R) or (S) lysine (Fig.5c). It is, however, conceivable from an examination of the packing arrangement that, if lysine can replace ACL at any positions in the complex, due to the high symmetry of the structure, growth will be affected in all directions rather than preferentially in one. The overall morphology would thus not be modified, although the overall rate of growth is decreased.

DISCUSSION

It has been shown that crystallization of the nickel complex of (R,S) -amino-caprolactam in the presence of small amounts of resolved lysine (or other amino acids) leads to precipitation in large excess of the enantiomer of the same absolute configuration as that of the additive. The crystallization is performed in the presence of base, which induces racemization of caprolactam, but not of the resolved additive. Since hydrolysis of -amino caprolactam yields lysine, a cycle of generation and amplification of optical activity can be envisaged, in the absence of initial chiral induction. (Scheme 4).

We have presented a mechanistic interpretation of the effect, which takes into account the differential inhibiting effect of diastereomeric mixed complexes 1 and 2 on enantiomeric substrate crystals. This mechanism stems from our knowledge on the effect of inhibition on crystal nucleation and growth and is supported by a number of independent experiments.

Circular dichroism measurements show that when lysine is introduced in the solution containing the chiral complex, ligand exchange takes place to some extent, but the same effect is observed with the additions of either enantiomer of lysine. Mixed complexes of the type 1 and 2 are thus formed in the same amounts, indicating that the overall induction upon crystallization cannot be due to pure solution effects. The two diastereoisomers on the other hand can be adsorbed at the surface of growing conglomerate crystals and interfere with their growth. Analysis of the lysine content of ACL complex crystals indeed shows that both enantiomers of lysine can be adsorbed and eventually occluded without enantioselectivity into the same crystal. Etching experiments confirm that the same type of interactions exists upon dissolution. Growth of the (S) complex in the presence of (R) or (S) lysine shows, however, that (R) lysine is a much stronger inhibitor than (S). On the basis of our previous knowledge on the mechanism of adsorption-inhibition it is reasonable

to expect that not pure lysine, but rather the mixed complexes are adsorbed onto the growing crystals since in these last a large part of the molecule is identical to that of the substrate forming the crystal. This explains also why many resolved amino acids cause induction in the same direction, but with a different magnitude. The adsorption of the diastereomeric species seems practically not to be affected by the nature of the side chain, but the magnitude of their inhibitory effect does mainly depend on this factor. Ornithine, which is very similar in molecular structure to lysine, also yields a similar induction. We expected to be able to measure this difference in inhibiting effect from the modifications in crystal morphology which result from anisotropic adsorption of the additive onto the crystal. Here no morphological changes were observed. Cases of this kind have already been observed, especially when the additive can be adsorbed from more than one direction and the symmetry of the crystal and of the molecule is high.

In this system we have overcome the "rule of reversal", which leads to an oscillating amplification pattern, by using diastereomeric inhibitors. Under these conditions it is however very difficult to predict "a priori" which one of the two diastereoisomers will be a stronger inhibitor, and therefore in which direction the amplification will proceed. In fact, an experiment reported by Harada,[22] on the optical resolution of (R,S) aspartic acid in the presence of resolved amino acids (alanine, glutamic acid, proline) and copper (II) ion, is in all likelihood an example of this mechanism, involving two diastereomeric additives, where the chirality is reversed. The crystallization of the copper complex of aspartic acid in the presence of (S)-alanine results in nearly pure (R)-aspartic acid complex crystals. It was shown by ORD-measurements[23] that no stereoselective ligand exchange takes place, and the suggestion was made that the chiral additive selectively inhibits the crystal growth of one of the two enantiomeric complexes. However, considering the above results, a reasonable explanation involves the formation of two diastereomeric complexes, (R)Asp-Cu-(S)Ala and (S)Asp-Cu-(S)Ala which affect differently the growth rate of $[(S)Asp]_2.Cu$ and $[(R)Asp]_2.Cu$. In this case, however, the two complexes are recognized already at the adsorption stage, since we have measured a ratio of 3/1 (R)Ala to (S)Ala inside polycrystalline samples of $[(R)Asp]_2.Cu$ grown in the presence of racemic alanine.[11]

The understanding of the mechanism of inhibition in crystal growth and nucleation by engineered additives paved the way to the practical realization of the models proposed in Schemes 2 and 3. Recent studies by Richarson *et al*[25] and our group, have in fact shown that spontaneous generation of net chirality by crystallization is not confined to chiral crystals only but is extendable to centrosymmetric ones displaying chiral enantiotopic surfaces. Thus crystals of α-glycine act as substrates for complete separation into

enantiomers of racemic α-amino acid additives.[17] The same is true for crystals of the dipeptide glycyl-glycine grown in the presence of racemic glycyl-leucine.[26] Asymmetric synthesis of chiral mixed dimers of guest cinnamic acid with host cinnamide was obtained inside the centrosymmetric crystals of the host.[12] The occlusion process lowers at the same time the symmetry of the host crystals, transforming them into chiral enantiomeric ones. The possibility of finding crystals acting as appropriate substrates for spontaneous generation and amplification of optical activity is thus greatly increased, even in the field of minerals, (e.g. gypsum).

The multiplicity and relative simplicity of the examples in different systems, emerging from these systematic studies, lead to the conclusion that crystallization is indeed a viable and efficient process for the realization of theoretical models of "chiral symmetry breaking in non equilibrium systems".[27,29].

EXPERIMENTAL

Materials

Nickel chloride was obtained from BDH in the hexahydrate form and dried at 120°C for 24 hrs to release the crystal water. Solutions were prepared by refluxing for 8 hrs in absolute ethanol. Absolute ethanol was obtained from Frutarom Ltd., (Haifa) and distilled over magnesium ethoide prior to use. α-amino-ε-caprolactam was synthesized from lysine following published procedures.[18] Lysine and ornithine were obtained from Sigma Chem. Corp. and used as received. The various other amino acids were from Fluka AG.

Analytical Methods

Optical rotations were performed on a Perkin Elmer 141 Polarimeter, (c=4, 1N HCl). CD-spectra were recorded on a JASCO 500-C instrument, in 10 mm cells ($c=8.2\times10^{-2}$). HPLC was performed on chiral columns by methods described in Ref.[28].

Resolution of (R,S)ACL Nickel Complex by Crystallization in the Presence of Various Amino Acid Additives

A solution of 115.4mg $NiCl_2$ (0.89 mmol) in 2.0 ml ethanol was added to a solution of 399.4 mg (R,S)ACL (3.12 mmol) in 2.0 ml ethanol containing the appropriate amount of amino acid and, if necessary, a calculated amount of lithium ethanolate to assure that the amino acid additives be in the form of free base. The resulting deep-blue solution was evaporated to exactly 2.0 ml by boiling, after which 1.0 mg racemic seeds (as powder) was added and the solution left to crystallize at 60°C in a shakerbath for different periods of time, specified in Tables 1 and 2. The obtained crystals were dried in vacuum and their rotation measured.

Effect of the Amount of Lysine on the Induction Process

Samples were prepared as above with respectively 7.5, 5.0, 3.0, 1,0, 0.5 and 0.1% of (S) lysine. After crystallization at 60°C in a shakerbath the crystals were filtered and dried and their rotation measured.

Crystal Structure and Morphology

Single crystals were grown from an ethanol solution containing 200 mg/ml complex, by slow cooling. The affected crystals were obtained by adding 10 mg/ml of (R) or (S)lysine and the equivalent amount of LiOEt. Crystal morphology, including the determination of crystal faces and of their areas, was performed on a Siemens diffractometer. The crystal structure was determined on a Nonius CAD-4 diffractometer.[20]

Dissolution experiments

Single crystals of the pure (S)-complex were dissolved in an undersaturated solution containing (S) complex (180 mg/ml) and 5% w/w of (R) or (S)lysine, for a period of 3 minutes. The partially dissolved crystals were dried and examined on an optical microscope (x 280).

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REFERENCES

1. Mac Dermott, A.J. Nature, 1986, 323, 16.

2. Franck, F.C., Biochim. Biophys. Acta 1953, 11, 459.

3. Seelig, F.F., J. Theor. Biol. 1971, 31, 355.

4. Decker, P., J. Mol. Evol. 1974, 49, 4.

5. Havinga, E., Chem. Weekbl. 1941, 38, 642; Biochim. Biophys. Acta, 1954, 13, 171.

6. Pincock, R.E. and Wilson, R.R., J. Amer. Chem. Soc. 1975, 97, 1474.

7. Newman, A.C.D. and Powell, H.M., J. Chem. Soc. 1952, 3747.

8. Green, B.S. and Heller, L., Science, 1974, 185, 525.

9. Addadi, L. and Lahav, M., J. Amer Chem. Soc. 1978, 100, 2838;
Addadi, L., van Mil, J. and Lahav, M., J. Amer. Chem. Soc., 1982, 104, 3422.

10. van Mil, J., Addadi, L., Gati, E. and Lahav, M., J. Amer. Chem. Soc. 1982, 104, 3429.

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

12. Addadi, L., Berkovitch-Yellin, Z., Weissbuch, I., Lahav, M. and Leiserowitz, L. in "Topics in Stereochemistry" Eliel, E.L., Wilen, S.H., Allinger, N.L. Eds., J. Wiley & Sons, 1986, 16, 1.

13. Shimon, L.J.W., Lahav, M. and Leiserowitz, L., J. Amer. Chem. Soc. 1985, 107, 3375.

14. Addadi, L., Berkovitch-Yellin, Z., Weissbuch, I., van Mil, J., Shimon, L.J.W., Lahav, M., and Leiserowitz, L., Angew. Chem. Int. Ed. Engl. 1985, 24, 466.

15. Weissbuch, I., Shimon, L.J.W., Landau E., Popovitz-Biro, R., Berkovitch-Yellin, Z., Addadi, L., Lahav, M. and Leiserowitz, L., Pure & Appl. Chem. 1986, 58, 947.

16. Weissbuch, I., Addadi, L., Berkovitch-Yellin, Z., Gati, E., Lahav, M. and Leiserowitz, L., Nature (London) 1984, 310, 16.

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

18. Sifniades, S., Boyle, W.J. Jr., and van Peppen, J.F., J. Amer. Chem. Soc. 1976, 98, 3738; Boyle, W.J., Sifniades, S. and van Peppen, J.F., J. Org. Chem. 1979, 44, 4841.

19. Sifniades, S., Lahav, M. and Boyle, W.J. Jr., U.S. Patent No.4,259,239; Addadi, L., van Mil, J., Weissbuch, I., Berkovitch-Yellin, Z., Leiserowitz, L. and Lahav, M., Chemica Scripta 1985, 25, 91.

20. The crystal structure was determined by H.C. Chang. All data concerning this structure will be separately sent to the Cambridge files.

21. Berkovitch-Yellin, Z., van Mil, J. Addadi, L., Idelson, M., Lahav, M. and Leiserowitz, L., J. Amer. Chem. Soc. 1985, 107, 3111.

22. Harada, K. and Tso, W., Bull. Chem. Soc. Jap. 1971, 45, 2859.

23. Harada, K. and Iwasaki, T., Chem. Lett. 1972, 1057.

24. In our hands, single crystals large enough for analysis could not be grown.

25. Chenchaiah, P.C., Holland, H.L. and Richarson, M.F., J. Chem. Soc. Chem. Comm. 1982, 436.

26. Weissbuch, I., Berkovitch-Yellin, Z., Leiserowitz, L. and Lahav, M., Isr. J. Chem. 1985, 25, 362.

27. Kondepudi, D.K. and Nelson, G.W., Phys. Rev. Lett. 1983, 50, 1023.

28. Weinstein, S., Engel, M.H. and Hare, P.E., Anal. Biochem., 1982, 121, 370.

29. For recent asymmetric syntheses in chiral crystals see Evans, S.V., Garcia-Garibay, M. Omkaram, N., Scheffer, J.R., Trotter, J., and Wireko, F. J. Am. Chem. Soc. 1986, 108, 5648.