J.Mol.Evol.6,99-115 (1975)

Crystallization and Solid-State Reaction as a Route to Asymmetric Synthesis from Achiral Starting Materials*

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Received January 13, 1975; March 3, 1975

Summary. Many molecules which are achiral can crystallize in chiral (enantiomorphic) crystals and, under suitable conditions, crystals of only one chirality may be obtained. The formation of right- or left-handed crystals in excess is equally probable. Lattice-controlled (topochemical) photochemical or thermal solid-state reactions may then afford stable, optically active products. In the presence of the chiral products, achiral reactants may preferentially produce crystals of one chirality, leading to a feedback mechanism for the generation and amplification of optical activity. Amplification of optical activity can also be achieved by solid-state reactions. The optical synthesis of biologically relevant compounds by such routes may be envisaged.

Key words: Origin of Optical Activity - Chiral Crystals - Abiotic Asymmetric Synthesis - Enantiomorphic

INTRODUCTION

The interest in reactions in organized systems and the recognition that many biological reactions occur in highly organized media make a study of reactions in crystals, where the order is amenable to exact definition by the methods of X-ray crystallography, particularly important. In recent years attention has focused, in particular, on the reactivity of molecules comprising chiral crystals and this work is especially relevant to the topic "Generation and Amplification of Asymmetry".

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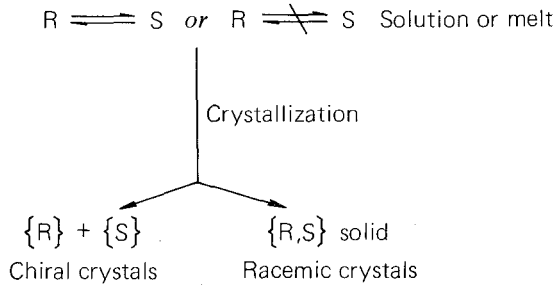
*Presented at the "International Symposium on Generation and Amplification of Asymmetry in Chemical Systems", Jülich, September 24-26 (1973).

The origins of optical activity in the molecules of living matter have puzzled and intrigued scientists since shortly after the phenomenon was first recognized. In this paper we describe several experimental approaches, based on the chirality of crystals, which have, in the absence of any outside dissymmetric agents, yielded stable, optically active products with significant enantiomer excess, from achiral starting materials. It is then shown that, in principle, the reactions can be autocatalytic: once generated, an optically active product can amplify the production of more of that enantiomer. Finally, one can conceive of pathways whereby chiral polymers as well as chiral, biologically significant materials can be produced by chemical reactions in the solid.

CHIRAL CRYSTALS

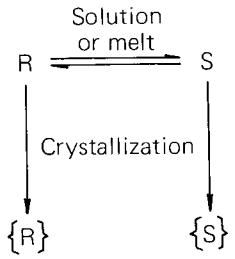
Crystals can, in general, be classified on the basis of their space groups[1] into two classes: 1. *chiral* (sometimes called enantiomorphic, optically active, conglomeric, or dissymmetric) *crystals* and 2. *racemic* (or achiral) *crystals*. (Scheme 1). The crystals of the former, chiral crystal class contain only symmetry elements (rotation and translation) which do not interconvert right- and left-handed objects and any single crystal of a substance crystallizing in this class must contain only molecules[2] of one (either right- *or* left-) handedness. Crystals of the latter class contain amongst their symmetry elements at least one (mirror or glide plane, center of inversion) which interconverts right- and left-handed objects; any single crystal contains either symmetrically achiral molecules or an equal number of symmetry-related right- and left-hand molecules.

The process of crystallization of a racemic mixture may then be pictured as in Scheme 1.



Scheme 1[3]

It is important to note that when the enantiomeric forms (R,S) are rapidly interconvertable with respect to the rate of crystallization, the number of right- and left-handed crystals (for a substance which undergoes spontaneous resolution) will not, in general, be the same because of seeding effects, and, under suitable conditions of crystallization, the entire, racemic, sample can be converted to a crystalline sample of *one* homogenous chirality. That is, if R and S can equilibrate in the phase from which the crystals separate, the entire sample can eventually exist as {R} (or, with equal probability, as {S}) crystals.



Although racemic crystals predominate, the number of chiral crystals is quite large (Collet et al., 1972) in a variety of chemical systems - including organic, inorganic, clathrate inclusion and organometallic compounds and complexes. A sampling of substances whose time-averaged molecules lack any elements of chirality (are achiral in solution) but which form chiral, optically active, crystals is given in Table 1.

The crystallization process may be considered as an elementary reaction since the variety of conformations which are present in dispersed phases are transformed, in general,

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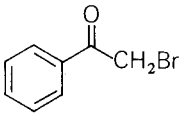
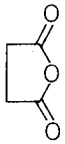
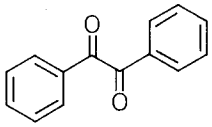
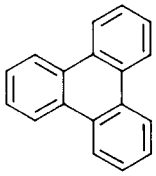
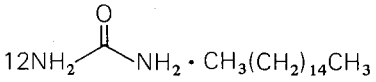
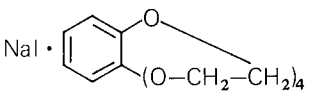
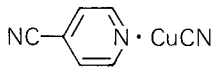
[1] The symmetry notation for a crystalline sample is denoted by its space group, and for a given specimen this can generally be assigned in a straight-forward manner after several single-crystal X-ray photographs.

[2] These may sometimes be more correctly considered as enantiomeric molecular conformations, and in some cases, perhaps only as enantiomeric environments.

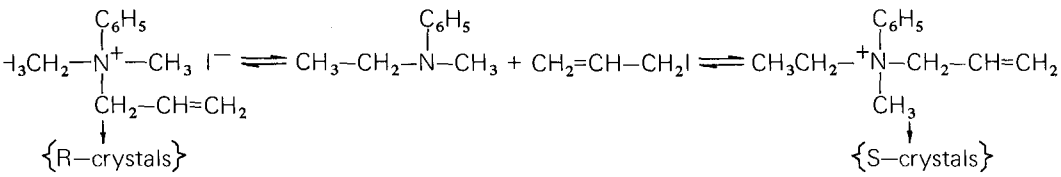
[3] Another possibility should also be recognized. Crystallization in the form of "racemic solid solutions" can occur, whereby molecules of opposite chirality crystallize with disorder and occupy the same, chiral *or* racemic, crystal sites (Eliel, 1962). Several such systems are presently being studied in this laboratory (Lahav et al., 1974; Addadi et al., 1974).

Table 1. Some substances which afford chiral crystals

Compound	Space group	Reference
	$P2_12_12_1$	Gupta and Prasud,1971
	$P2_12_12_1$	Shahat,1953
	$P3_121$	Brown and Sadanaga, 1965
$CH_3-C\equiv C-COOH$	$P2_1$	Benghiat and Leiserowitz, 1972
	$P2_12_12_1$	Klug,1950
SiO_2 (quartz)	$P3_{1,2}21$;$P6_{2,4}21$	Wei,1935
OsO_4	I 2	Zalkin and Templeton, 1953
$NaClO_3$	$P2_13$	Huber,1940
	$C6_12$	Smith,1952
	$P2_12_12_1$	Bush and Truter, 1970
CH_3CH_2-Li	$P2_122$	Brown and Rogers, 1957
	$P2_12_12_1$	Cromer and Larson, 1972

to a single homogenous conformation (Cohen & Green, 1973); in some cases there are changes in configuration or even in functional groups. When a racemic substance affords enantiomeric crystals in different amounts, an absolute asymmetric synthesis can be considered to have occurred. Some of the first such experiments involved sodium chlorate (Landolt,

1896; Kipping & Pope, 1898). A beautiful demonstration of the conversion of a racemic mixture to an enantiomerically homogenous sample by means of racemization in solution and crystallization in a chiral crystal structure was first reported by Havinga (1941, 1954) who found that chloroform solutions of methylethylallylanilinium iodide may deposit crystals which give a stable, measurable optical rotation when dissolved in water, but which give no rotation when dissolved in organic solvents. Evaporation of the latter solutions can regenerate optically active, (+) or (-), salt. Thus the chiral molecules racemize rapidly in organic solvents from which chiral crystals can grow. This equilibration of enantiomers proceeds via the conformationally labile amine and allyl iodide (Scheme 2).[4]



Scheme 2

More recently Pincock et al. (1971) have studied this phenomenon in 1,1'-binaphthyl where crystallization, proceeding at temperatures where enantiomer equilibration is possible, affords an excess of one of the enantiomeric crystals. At temperatures where the rate of racemization is not rapid, solutions of these crystals give optical rotations which are easily measured. The same phenomenon is observed in some of the clathrate inclusion compounds of the interesting molecule, tri-o-thymotide (Newman & Powell, 1952).

REACTIONS INVOLVING CHIRAL CRYSTALS

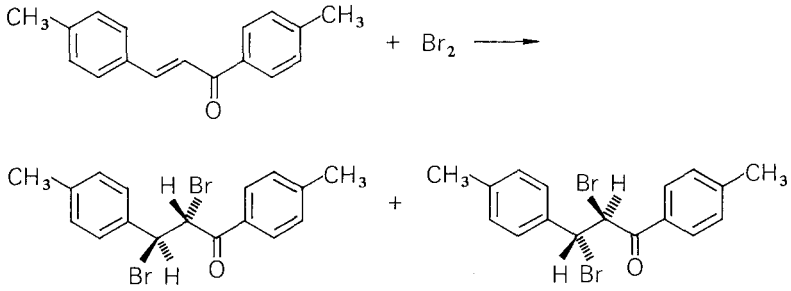
It was apparently Ostromisslensky who first suggested, in 1908, that reactions involving chiral crystals may lead to optically active products. This suggestion and the experiments designed later to test it considered the use of chiral crystalline surfaces as catalytic sites for asymmetric synthesis. It is perhaps not surprising that unambiguously positive results have been difficult to obtain through the action, for example, of optically active quartz (Amariglio & Amariglio, 1971); here the reactant molecules are confor-

[4]All absolute configurations are assigned arbitrarily in this paper.

mationally mobile and it may be difficult to achieve the required specific interactions on the surface which would lead to differentiation between the enantiomeric conformations or the prochiral faces. It has been reported very recently, however, that powdered enantiomeric quartz crystals show a small but significant preference for the absorption of the corresponding enantiomers of alanine (Bonner et al., 1974).

On the basis of lattice-control over solid-state chemical reactions (topochemistry; Cohen & Schmidt, 1964)it is expected that reactions wherein the reactant itself has a chiral crystal structure would be more promising. Indeed this approach has been suggested (Morawetz, 1966) and attempted in several laboratories (Miller; Wudl et al., 1967; Bender, 1969).

The first successful asymmetric synthesis in which the chirality of the crystal provided the sole dissymmetric influence was reported in 1969 (Penzien & Schmidt). Reaction of bromine vapor with powdered single crystals of 4,4'-dimethylchalcone (space group $P2_12_12_1$) yielded one of the enantiomeric erythro dibromides (Hadjoudis et al., 1972) in *ca.* 6% excess over the other (Scheme 3). Some crystals afforded (+)-dibromide and others (-)-dibromide, as expected if there is no *external* chiral influence. More recently it



Scheme 3[5]

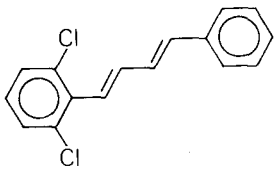
has been found that the optical yield can be increased to ca.20% by the careful growth of large crystals, by powdering them to a fine mesh, and by avoiding the presence of large concentrations of bromine vapor (Green & Heller, 1974b).

Other halogens, such as chlorine and iodine monochloride, also react with chiral single crystals of 4,4'-dimethyl chalcone to afford optically active dihalides (Green & Heller, 1974b). However these reactions are more complex than the bromine addition since both erythro and threo products are

[5] See footnote, p.103

obtained, the latter presumably arising from *cis* addition to the double bond. Since the solution reaction gives trans-addition almost exclusively, i.e., leads to the erythro product, this indicates additional control of the crystalline medium over the course of the reaction.

Other chiral, crystalline olefinic materials which undergo halogen addition to yield optically active products include the substituted butadiene, *3*, which affords primarily tetrabromo products (Green & Heller, 1974b).



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A chiral crystal structure is necessary but not sufficient for obtaining optically active products (Rabinovich & Shaked, 1974). Experiments in our laboratory with chiral single crystals of p-methoxy-chalcone, a number of vinyl sulfones, several thienyl olefins, etc. failed to afford optically active dihalides. Further research is required to explain whether factors such as dislocations or disorder, or mode of dissipation of the heat of reaction, are responsible for these observations.

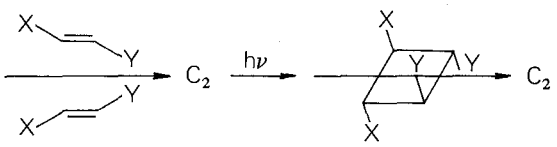
Many of the molecules which form clathrate inclusion compounds (Hagan, 1962; Powell, 1964; Fetterly, 1964) crystallize in chiral crystal structures even though both the host and guest are, in solution, time-averaged achiral molecules. Transformation of an included prochiral molecule to a product containing a chiral center should yield, if the reaction proceeds with an element of control by the chiral environment of the clathrate, a non-racemic product.

PHOTOCHEMICAL REACTIONS IN CHIRAL CRYSTALS

The photochemistry of the solid-state, and especially of 2+2 photocyclodimerization, has been studied in great detail (Schmidt, 1971). The stereochemistry of the observed photoproducts is strictly controlled by the crystalline arrangements of the reactant olefins and such reactions may be particularly suitable for asymmetric synthesis in those cases where the monomers have chiral crystal structures. A detailed analysis of the chemical and crystallographic requirements for the conversion of reactant molecules, related

in the monomer crystal by space symmetry elements of the first kind (translation, rotation, screw), to chiral molecules, has recently been made and at least three processes appear to be feasible (Green et al., 1975). Of particular interest is the prediction that reactions proceeding with quantitative optical yields should readily be realized. The following three approaches were considered to be promising:

i) Molecules crystallizing in a chiral crystal structure with an olefinic (center to center) separation of ca.4 Å and related to one another by a two-fold axis parallel to the olefinic bonds will, on irradiation, afford chiral cyclobutane derivatives having point group C_2.



Although this mode of packing might lead to high optical yields, our experience has been that such intermolecular arrangements are quite rare for olefinic systems. (See, however, Frank & Paul (1973) and refs. therein).

ii) Molecules with two, non-identical, potentially reactive sites can adopt packing arrangements which are commonly observed and which, in chiral crystals, should lead to optically active products. One requires a system with an intermolecular juxtaposition such that the non-equivalent double bonds are properly aligned for cycloaddition, but the equivalent double bonds are too far apart to react. A system which has these properties is provided by *4* where a disordered solid solution of the racemate affords chiral crystals (i.e., the *sec*-butyl group sites in a crystal of one handedness contain both antipodes). Irradiation of a crystal of *4* leads to chiral cyclobutanes. The optical yields of the dimers and polymers from such systems are presently being determined. For monomer samples of one crystalline handedness, the optical yield is expected to be quantitative. (Addadi et al., 1975) (Fig.1).

iii) A mixed crystal approach was used in the first successful solid-state photochemical asymmetric synthesis (Elgavi et al., 1973). Here the translational symmetry of the chiral monomer lattice was destroyed by incorporating a guest molecule in this lattice, and this in turn destroyed the mirror symmetry of the photodimer. The host material was 1-(2,6-dichlorophenyl)-4-phenyl- *trans,trans*-1,3-butadiene *3* (space group $P2_12_12_1$) which has a short 4 Å translation axis so that, on irradiation, the strongly overlapped neighboring molecules react to yield the mirror-symmetric dimer *5*

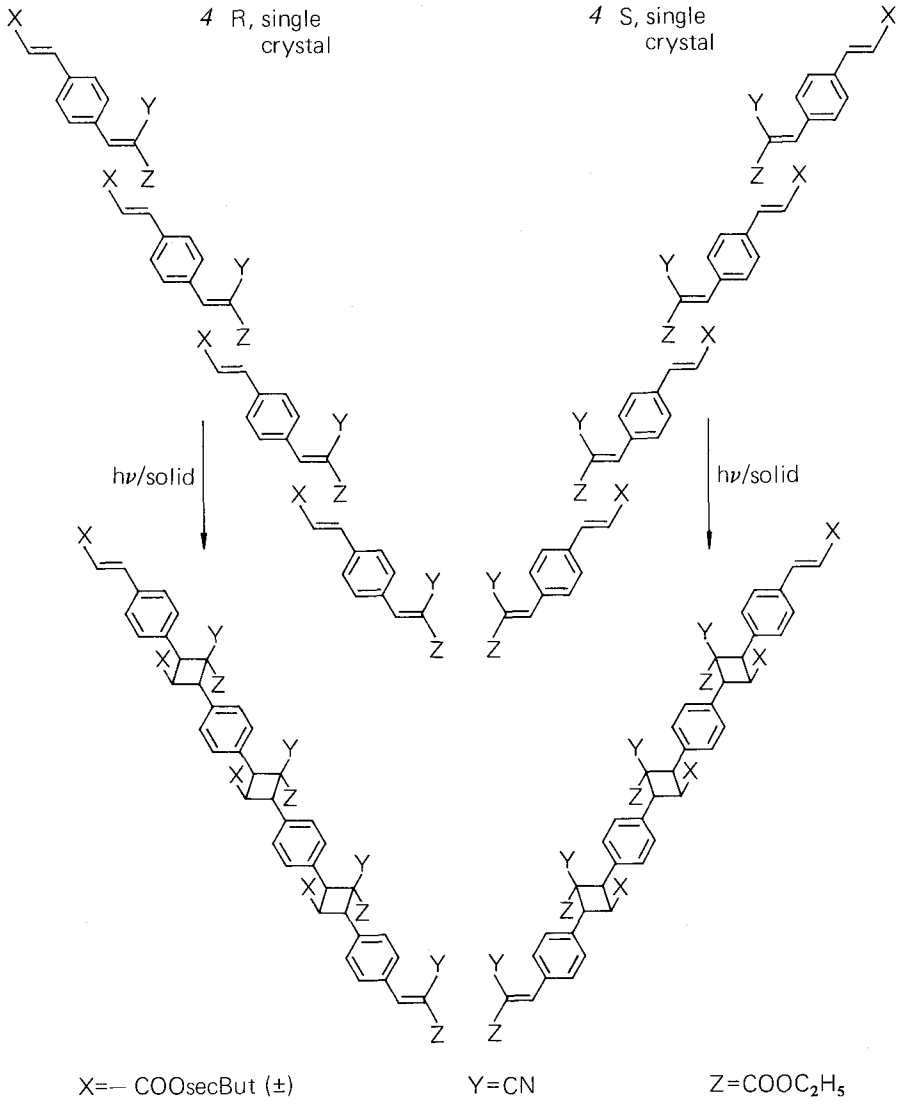
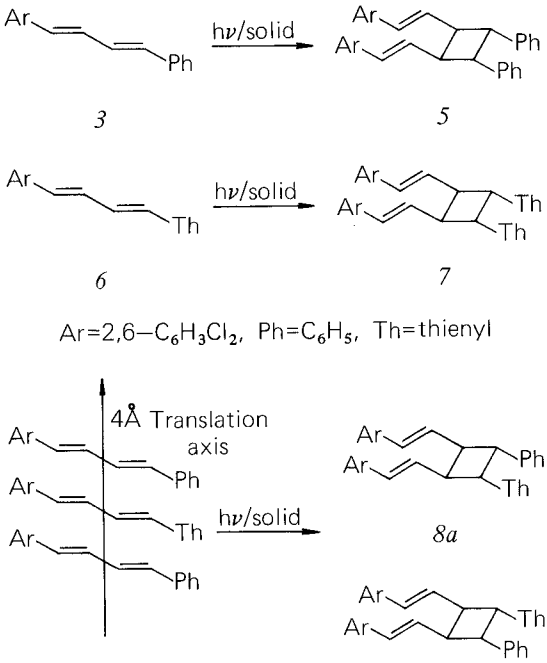


Fig.1. Schematic representation of the stack structures and polymerization reactions in the enantiomeric, R and S, crystals of *4*

(Cohen et al., 1972; Rabinovich & Shakked, 1975). The thiophene analog, *6*, is isomorphous with *3* and yields the corresponding photodimer *7*. (Scheme 4).

The absorption spectra of *3* and *6* are sufficiently different that mixed crystals containing a small amount of *6* can be irradiated at long wavelengths such that only *6* absorbs the light. The thiophene compound *6* is distributed homogeneously through *3* so there are few adjacent pairs of *6*; the phenyl compound *3* does not absorb and thus the enantiomers of the mixed dimer *8* are the main product of the



Scheme 4

reaction. When the irradiation was performed on single mixed crystals containing 85% *3* and 15% *6*, the mixed dimer *8* was consistently found to be optically active, and, as with the chalcone (*1*) discussed above, some crystals afforded (+)-*8* and others (-)-*8* ensuring that the asymmetry had not arisen through extraneous sources.

The majority of the thiophene molecules *6* are sandwiched in between two phenyl molecules *3* and on excitation can react either "upwards" or "downwards" in the molecular stack (Scheme 4). The ratio of enantiomers *8a* and *8b* was found to be ca. 85:15, i.e., an optical yield of ca. 70% (Elgavi, 1974).

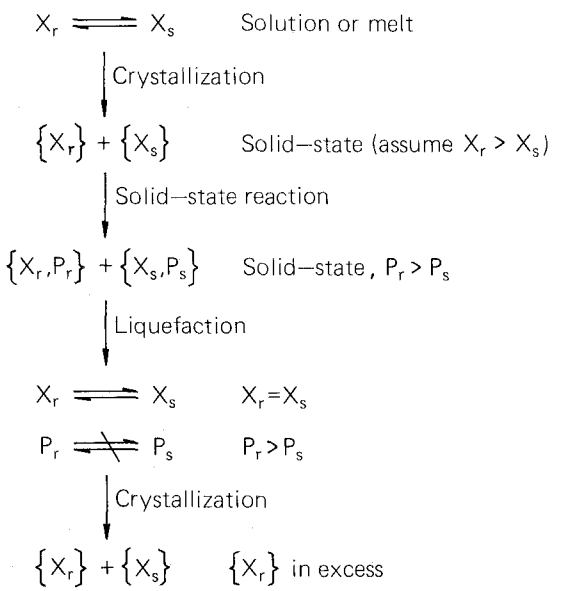
The above discussion has dealt with one topochemically controlled photoreaction, namely, photodimerization, but the principles are undoubtedly applicable to other systems undergoing solid-rate reactions. Indeed, it can be anticipated that a topochemically controlled solid-state reaction, whether photochemical or thermal, of any prochiral molecule in a chiral crystal structure yielding a chiral product, will afford an asymmetric synthesis. For each specific example, it remains to establish the optical yield and, more importantly, the factors which influence this yield; in the experiments performed thus far these factors have not generally been clearly identified.

The examples above suffice to clearly demonstrate that thermal and photochemical asymmetric reactions can proceed in crystals which arise from achiral solutions *without any outside dissymmetric influence.* The chirality is an intrinsic property of the molecules themselves, namely, the chiral crystal structures which they adopt. The reactions are experimentally simple, afford relatively high optical yields, and are observed in polycrystalline samples as well as in single crystals. Indeed, it was found in both the dimethyl chalcone bromination and in the mixed photodimerization that polycrystalline samples prepared without any intent to favor one crystal chirality inevitably yielded optically active products. Thus, the widely-held view that "outside of organisms, all syntheses of dissymmetric molecules produce equal numbers of optical antipodes unless deliberate means are employed to bias the result by the use of asymmetric reagents or forces" (Wald, 1957), is not valid. (See also Pincock & Wilson, 1973)

The main argument for the absence of outside chiral influences is that in the cases studied the formation of both dextrorotary and levorotary crystals are essentially equal. It has been shown that the presence of dissymmetric agents can direct the chirality of the crystals grown from melts of 1,1'-binaphthyl (Pincock et al., 1971) and this leads one to consider the possible effects of the presence of an optically active solid-state reaction product during crystallization on the chirality of the crystalline reactant. In the case of dimethylchalcone, *1*, it was indeed found that the product *2* shows a striking control over the chirality of crystallization of *1*. Solutions of dimethylchalcone (i) containing no additive, (ii) containing 4 mole percent (+)-dibromide *2*, (iii) containing 4 mole percent (-)-dibromide *2*, and (iv) containing 5 mole percent racemic (±)-*2* were allowed to evaporate. The polycrystalline material resulting from samples (i) and (iv) gave, on exposure to bromine vapor, either (+)-*2* or (-)-*2* in excess. However, samples (ii) afforded, on bromination, only (-)-dibromide *2*, and samples (iii) yielded only (+)-dibromide *2*. Even when the optical purity of the added dibromide was relatively low (17%) so that the ratio of optically pure *2* to dimethylchalcone *1* was only ca. 1:150 in the solutions before crystallization, the samples uniformly contained crystals of the same chirality in excess (Green & Heller, 1974a). The chiral products resulting from addition of chlorine or iodine monochloride to *1* and the products from bromine addition to *3* also direct, respectively, the chirality of the crystals of the reactant (Green & Heller, 1974b).

These results lead one to consider the following scheme (Scheme 5) for the genesis of optically active compounds from achiral starting materials in the absence of any dissymmetric influences, and the subsequent action of the chiral product to direct the chirality of the crystalline reactant during the next and all following crystallizations.

Consider a solution or melt containing a reactant, X, which rapidly interconverts between enantiomeric states X_r and X_s and is thus optically inactive. If X crystallizes in a chiral structure, the resulting crystals will, as discussed above, generally contain unequal amounts of right-handed crystalline material $\{X_r\}$ (we use the brackets { } to indicate a crystalline phase) and left-handed crystalline material $\{X_s\}$, it being completely a matter of chance which enantiomer is in excess. Suppose that the sample thus produced now undergoes reaction to yield a product, P, with an asymmetric center. The reaction of $\{X_r\}$ and of $\{X_s\}$ will proceed at the same rate but since they are not present in equal amounts (assume that $\{X_r\}$ happens to exceed $\{X_s\}$) then the amount of product enantiomer P_r will exceed P_s (the reactions being $X_r \rightarrow P_r$ and $X_s \rightarrow P_s$). If this sample now dissolves or melts, the unreacted X enantiomers will quickly interconvert, the concentration of X_r and X_s becoming equal, but the product P does not racemize under these conditions and P_r remains in excess over P_s. Now if P_r has the property of inducing X to crystallize in the chirality which leads to more P_r, namely $\{X_r\}$, the system can reproduce simply by going through cycles of solidification, solid-state reaction, and liquefaction.



Scheme 5

One of the criticisms leveled against the concept of involvement of chiral crystals in the origin of optical activity is that although an excess of one enantiomer may arise in one locality, its mirror-image will be produced elsewhere leading to an inevitable overall racemic product. It can be seen from the scheme outlined above that this need not be true. If one region produces an excess of one enantiomer and another region produces the second enantiomer this can continue until the two areas come into contact and begin to mix. The larger area, or the region with a greater enantiomer excess, can now control the chirality of future crystallization in both areas.

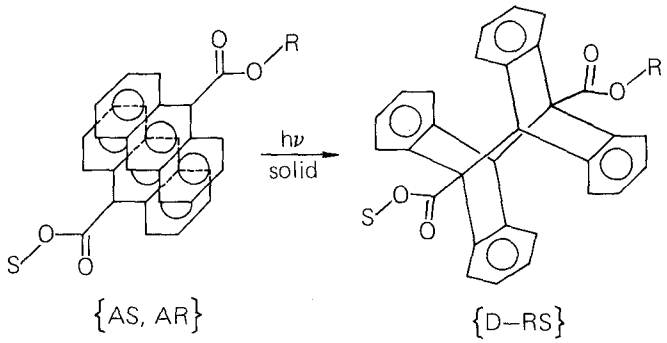
The mechanism whereby P participates in determining the chirality in which Y crystallizes has not been investigated. It is possible that a small concentration of P molecules are actually incorporated into {X}. The effect of impurities on the stabilities of crystal phases is well known, leading in some cases to separation of a phase which is metastable for the pure host material (e.g. Hung et al., 1972).

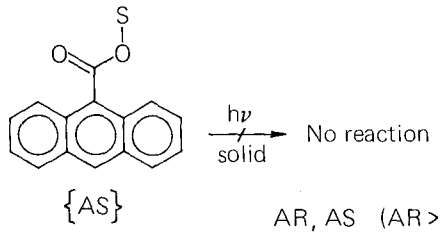
AMPLIFICATION OF OPTICAL ACTIVITY VIA TOPOCHEMICAL REACTIONS

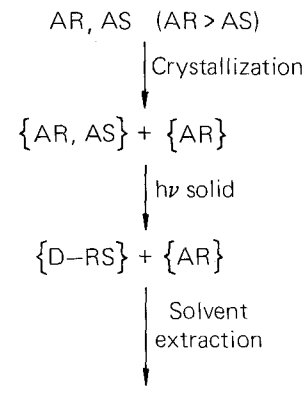
It was shown above that symmetrical molecules crystallizing in chiral crystals can yield dissymmetric products. Once a sample containing unequal populations of enantiomer molecules has been produced ($R \neq S$) by such a process, the crystallization of this sample will (assuming that the racemic material does *not* spontaneously resolve) give two distinctly different kinds of crystals, racemic and chiral. These crystals may differ not only in their physical properties but also in their chemical properties and these differences may be utilized for further enantiomeric enrichment.

An example of enantiomer enrichment as a result of the solubility differences between {R} (or {S}) and {R,S} crystals has been given by Morowitz (1969). The chemical reactivity difference between chiral and racemic crystals have recently been exploited for the amplification of optical activity via solid-state photodimerization of partially resolved samples of 9-anthroic acid derivatives (Scheme 6).

In the racemic crystal {AR,AS} the enantiomeric molecules are related by a center of inversion and yield, on irradiation in the solid, the sparingly soluble meso-dimer {D-RS}. However, the crystalline monomer {AR} (or {AS}) is light stable and can be readily extracted after the irradiation. The chirality could thus be amplified from an initial 10% enantiomer excess to greater than 95% (Gati et al.).







Scheme 6

BIOLOGICALLY RELEVANT MOLECULES

A considerable number of solid-state reactions or reactions on crystal surfaces have been studied recently as models of prebiotic chemistry and the number of biologically significant molecules thus produced, already quite impressive, will undoubtedly increase even more as a result of future experiments (Fuller et al., 1972; Paecht-Horowitz et al., 1970; Verlander & Orgel, 1974; Hubbard et al., 1973). Indeed, the thesis has been put forward that crystals could have served as possible genetic "ancestors" (Cairns-Smith, 1972).

We are presently considering pathways involving plausible prebiotic molecules which may have crystallized in chiral structures and then reacted to afford biologically relevant optically active products. For example glycine is generally a major product in model prebiotic amino acid synthesis. It is noteworthy that two of the three known crystalline modi-

fications of glycine are chiral, space groups $P2_1$ and $P3_1$ ($P3_2$) (Iitaka, 1960). An alkylation reaction whereby one of the methylene hydrogens (which become nonequivalent in the crystal) is preferentially replaced, would produce an α-amino acid with one enantiomer in excess.[6] Other symmetrical molecules of biological interest, which afford chiral crystals include hippuric acid (Harrison et al., 1972), diglycine hydrochloride and diglycine hydrobromide (Buerger et al., 1957), γ-aminobutyric acid hydrochloride (Tomita, 1971), γ-amino-crotonic acid hydrobromide (Tomita, 1971) and succinic anhydride (Shahat, 1953). The reactions of enantiomeric single crystals containing molecularly chiral acids have been found to proceed at appreciably different rates with enantiomeric amines (Lin et al., 1974) and the use of enantiomeric single crystals containing molecularly achiral species should also discriminate between chiral reagents. The possible role of chiral crystals, including chiral clathrate inclusion compounds such as urea, in the origins of optical activity have been discussed by Lemmon (1973). Finally, sugar derivatives are produced from formaldehyde on a variety of crystalline surfaces (Cairns-Smith et al., 1972). It would be of interest to investigate whether any chiral minerals can catalyze the formation of optically active sugar alcohols.

If the optically active compounds of life evolved prior to life by processes based on chiral crystals then it is to be expected that the choice of handedness in life as we know it (L-amino-acids, D-sugars, etc.) was simply a matter of chance, which crystal "won in the fight" (Wald, 1957). However, perhaps the "natural" dissymmetric forces on earth, e.g. spinning magnetic field, could have influenced the chirality of crystallization. The experiments of this type which have been attempted proved unsuccessful, but some very interesting effects such as changing crystal chirality by means of an external electric field (Newnham & Cross, 1974) have been demonstrated and it would be intriguing to uncover other cases where external physical forces direct crystallization chirality. Perhaps some of the unexplained biases in chirality of crystallization (Rogacheva et al., 1971; Harada, 1970) will eventually be explained on this basis.

Acknowledgement. We are grateful to Professor M.D. Cohen for valuable discussions and for his critical comments and suggestions.

[6]Alkylation reactions on glycyl peptides has been demonstrated in solution (Sperling & Elad, 1971).

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