

Asymmetric Synthesis via Reactions in Chiral Crystals[†]

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Received September 9, 1977 (Revised Manuscript Received October 23, 1978)

The possibility of utilizing the chirality of crystals to achieve asymmetric synthesis was considered as early as 1908,¹ but successful approaches awaited the better understanding of, and experience with, organic reactions which proceed in the crystalline state. Processes in which the crystalline lattice determines the course of reaction have been termed "topochemically controlled reactions".²

This approach not only comprises a novel route to asymmetric synthesis but also holds promise of affording quantitative optical yields in suitably designed systems.³ Moreover, optically active compounds can sometimes be generated from solutions of achiral starting materials by crystallization and subsequent solid-state reaction, in the absence of any outside dissymmetric influence.^{4,5} The latter studies, "absolute asymmetric syntheses", are relevant to philosophical questions concerning the generation and amplification of optically active compounds in biological systems.⁵ Furthermore, reactions in chiral crystals allow one to gain insight into subtle details of reaction mechanisms in both thermal and photochemical reactions and to probe features of the reaction coordinate which would not otherwise be accessible.

Asymmetric synthesis through reactions in chiral crystals involves two aspects: generating chiral crystals and performing topochemically controlled, solid-state reactions which yield chiral products.

The crystallization process itself may be considered as an elementary form of reaction, since molecules which may populate an infinite number of conformations in solution or in the melt are transformed to a finite number (generally one or two) of unique conformations in the solid. From the viewpoint of asymmetric synthesis, asymmetric induction is complete

after crystallization in a chiral structure; it remains only to trap this chirality in a configurationally stable entity by performing a solid-state reaction.

Chiral Crystals and Their Generation. There are 230 unique space groups which describe the modes in which equivalent (i.e., congruent and enantiomeric species) may be arranged in infinite lattices.⁶ These space groups may be divided into two categories, achiral and chiral, and their assignment can often be made by examination of several X-ray diffraction photographs without requirement for full structure determination. In suitable crystals,^{2d} the development of hemihedral faces allows one to visually distinguish between enantiomorphous crystals.⁷

A systematic solid-state approach to asymmetric synthesis demands the design of chiral crystal structures having certain intermolecular or intramolecular features. This problem, a part of the more general problem of crystal structure "engineering", has as yet no general solution. Thus, one's approach to achieving desired crystal structural types must be mainly heuristic.

In some special cases minimum energy calculations have provided crystallographic information.⁸ More

[†] Dedicated to Professor E. Havinga, a pioneer in optical activity from chiral crystals,¹⁶ on the occasion of his retirement.

(1) I. Ostromisslensky, *Chem. Ber.*, **41**, 3035 (1908). After many years of contradictory results concerning the preferential interaction of chiral crystals of quartz with enantiomeric molecules, it was recently demonstrated that *d*- or *l*-quartz crystals do selectively adsorb enantiomeric amino acid derivatives: W. A. Bonner, P. R. Kavasmeneck, F. S. Martin, and J. J. Flores, *Science*, **86**, 143 (1974); S. Furuyama, H. Kimura, M. Sawada, and T. Morimoto, *Chem. Lett.*, 381 (1978).

(2) (a) "G. M. J. Schmidt et al., Solid State Photochemistry", D. Ginsburg, Ed., Verlag Chemie, Weinheim, 1976; (b) G. M. J. Schmidt in "Reactivity of the Photoexcited Organic Molecule", Interscience, New York, 1967, p 227; (c) G. M. J. Schmidt, *Pure Appl. Chem.*, **27**, 647 (1971); (d) I. C. Paul and D. Y. Curtin, *Acc. Chem. Res.*, **6**, 217 (1973); (e) M. D. Cohen and B. S. Green, *Chem. Brit.*, **9**, 490 (1973); (f) J. M. Thomas, *Philos. Trans. R. Soc. London*, **277**, 251 (1974); (g) I. C. Paul and D. Y. Curtin, *Science*, **187**, 19 (1975); (h) M. D. Cohen, *Angew. Chem., Int. Ed. Engl.*, **14**, 386 (1975); (i) H. Morawetz in "Reactivity of Solids", J. Wood, O. Lindquist, C. Helgesson, and N. G. Vannerberg, Eds., Plenum Press, 1977, p 457; (j) R. Lamartine, G. Bertholon, M. F. Vincent-Falquet, and R. Perrin, *C. R. Hebd. Seances Acad. Sci.*, **279**, 367 (1974).

(3) (a) B. S. Green, M. Lahav, and G. M. J. Schmidt, *Liq. Cryst. Mol. Cryst.*, **29**, 187 (1975); (b) L. Addadi and M. Lahav, *J. Am. Chem. Soc.*, **100**, 2838 (1978).

(4) B. S. Green and L. Heller, *Science*, **185**, 525 (1974).

(5) B. S. Green and M. Lahav, *J. Mol. Evol.*, **6**, 99 (1975).

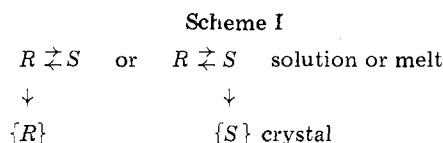
(6) For further discussion see M. J. Buerger, "Elementary Crystallography", Wiley, New York, 1956.

(7) For a summary of other methods for sorting chiral crystals, see: C. T. Lin, D. Y. Curtin, and I. C. Paul, *J. Am. Chem. Soc.*, **96**, 6199 (1974).

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useful, perhaps, to the chemist have been empirical and qualitative proposals. Kitaigorodsky pointed out that the close packing of organic molecules having arbitrary shape favors a limited number of space groups;⁹ it is noteworthy that of the eight most favored space groups, three are chiral.

Leiserowitz has considered the packing modes of carboxylic acids and of primary and secondary amides and has shown that the commonly observed centrosymmetric hydrogen-bonded dimer generally results in centrosymmetric, achiral crystals.¹⁰ If the acid or amide molecule contains a second hydrogen bonding function ($-\text{OH}$, $>\text{NH}$, $>\text{S}=\text{O}$, etc.), intermolecular interaction between the groups may occur, a spiral chain is generally adopted instead of centrosymmetric pairs, and the resulting structure is more likely to afford chiral crystals.¹¹

A possible correlation between molecular structure and crystal symmetry was sought by Jacques et al.¹² who reported that molecules having a twofold symmetry axis, C_2 , tend to crystallize in chiral structures. The probability of adopting a chiral structure may be even more pronounced with molecules having a threefold symmetry axis, C_3 .¹³

Since many clathrates (e.g., urea, tri-*o*-thymotide) form chiral crystals, the use of these materials may represent a widely applicable method for "engineering" chiral crystalline matrices with achiral guest molecules. Examples of their utilization will be discussed later. In this area of long-standing interest, it has proved feasible in several cases to successfully design novel clathrate hosts.¹⁴

The merging of quantitative methods and qualitative approaches may eventually provide enough insight into the factors which control crystal engineering to enable one to achieve systematically desired crystal structures from given chemical systems. At present the only certain, albeit trivial, entry into a chiral crystalline arrangement is the introduction of a stable chiral group.

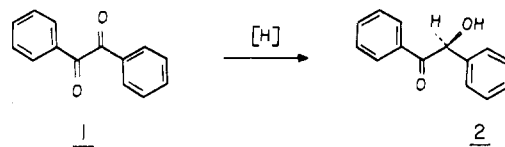
Chemical Transformations in Chiral Crystals. We shall consider first achiral or rapidly racemizing molecules which crystallize in chiral crystals. If configurational inversion is faster than the rate of crystallization, unequal amounts of enantiomorphous crystals may be produced with either enantiomorph in excess; the investigator does not, in general, control the crystal chirality.⁵ Moreover, under suitable conditions it is

possible to convert an entire sample to a single, enantiomeric crystal containing homochiral species¹⁵ (Scheme I). The latter point is important since the optical yield in reactions from such crystals depends on the homochirality of the sample.

In a second approach we deal with crystals of chiral, resolved molecules in which the crystal chirality is defined by the molecular chirality. Asymmetric syntheses in such systems can be carried out on a polycrystalline sample. The asymmetric induction here might depend both on the initial molecular chirality as well as on the chiral environment in the crystal; the effect of these two need not necessarily be in the same sense.

Heterogeneous Reactions. Although heterogeneous reactions of organic solids with gases and liquids are complex and not well understood, they have been used successfully for the performance of clean, stereospecific reactions.²⁰ A number of asymmetric syntheses using chiral crystals in heterogeneous reactions have been attempted, and we will describe some of them.

Benzil, **1**, crystallizes in a chiral space group. The diastereotopic faces of the two carbonyl groups (which were enantiotopic in the time-averaged, planar molecules of solution) suggest the possibility of a reaction upon chiral single crystals of **1** as a route to optically active benzoin, **2**. However, all attempts reported thus



far have yielded racemic **2**.²¹

Methanesulfinic acid, **3**, has been studied as another potential crystal structure for asymmetric synthesis.²² In solution the enantiomers rapidly interconvert via hydrogen exchange; in the crystal, however, the enantiomers are segregated into separate crystals.²³ Diazomethane reaction of a single crystal, which thus contains *R* or *S* molecules exclusively, conceivably might yield a nonracemic sample of methyl ester **4**. However, the isolated product was racemic, apparently because the crystal dissolved prior to reaction.

The first demonstration of a chiral synthesis based on a total asymmetric transformation was provided by the reaction of a chiral single crystal of 4,4'-di-

(8) D. Rabinovich and G. M. J. Schmidt, *Nature (London)*, **211**, 1391 (1966); D. E. Williams, *Acta Crystallogr., Sect. A*, **25**, 464 (1969); V. M. Coiro, P. Giacomello, and E. Giglio, *Acta Crystallogr., Sect. B*, **27**, 2112 (1971); A. Warshel, E. Huller, D. Rabinovich, and Z. Shakked, *J. Mol. Struct.*, **23**, 175 (1974); A. I. Kitaigorodsky, *Chem. Soc. Rev.*, **7**, 133 (1978).

(9) A. I. Kitaigorodsky, "Molecular Crystals and Molecules", Academic Press, New York, 1973, p. 33.

(10) L. Leiserowitz and G. M. J. Schmidt, *J. Chem. Soc. A*, 2372 (1969); L. Leiserowitz, *Acta Crystallogr., Sect. B*, **32**, 775 (1976).

(11) A. Collet and J. Jacques, *Bull. Soc. Chim. Fr.*, 3700 (1972); L. Leiserowitz and M. Weinstein, *Acta Crystallogr., Sect. B*, **31**, 1463 (1975).

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(13) B. S. Green, work in progress.

(14) D. D. MacNicol, J. J. McKendrick, and D. R. Wilson, *Chem. Soc. Rev.*, **7**, 65 (1978).

(15) Some interesting examples studied include methylethylphenyl-allylammonium iodide,¹⁶ tri-*o*-thymotide,¹⁷ and 1,1'-binaphthyl.¹⁸ Processes based on similar transformations have been used for the industrial preparation of enantiomerically pure amino acids.¹⁹

(16) E. Havinga, *Chem. Weekbl.*, **38**, 642 (1941); *Biochim. Biophys. Acta*, **13**, 171 (1954).

(17) A. C. D. Newman and H. M. Powell, *J. Chem. Soc.*, 3747 (1952).

(18) R. E. Pincock, R. R. Perkins, A. S. Ma, and R. R. Wilson, *Science*, **171**, 1018 (1971); R. E. Pincock and R. R. Wilson, *J. Am. Chem. Soc.*, **97**, 1474 (1975).

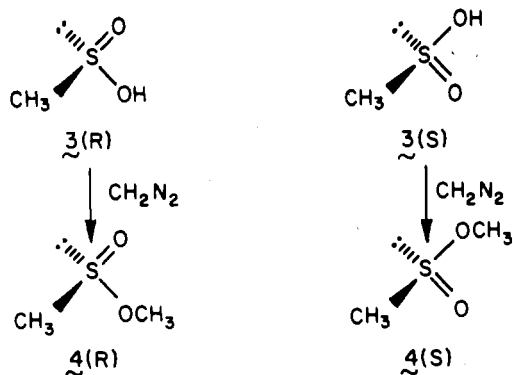
(19) P. H. Boyle, *Q. Rev. Chem. Soc.*, **25**, 323 (1971); S. Sifniades, W. J. Boyle Jr., and J. F. Van Peppen, *J. Am. Chem. Soc.*, **98**, 3738 (1976), and references cited therein.

(20) G. Friedman, M. Lahav, and G. M. J. Schmidt, *J. Chem. Soc., Perkin Trans. 2*, 428 (1974); G. Friedman, E. Gati, M. Lahav, D. Rabinovich, and Z. Shakked, *J. Chem. Soc., Chem. Commun.*, 491 (1975).

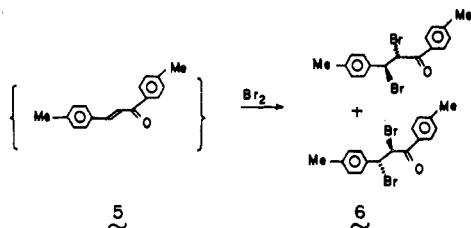
(21) See, for example, footnote 7 in D. Y. Curtin and A. R. Stein, *Can. J. Chem.*, **47**, 3637 (1969).

(22) F. Wudl, D. A. Lightner, and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 4099 (1967).

(23) K. Seff, E. G. Heidner, M. Meyers, and K. N. Trueblood, *Acta Crystallogr., Sect. B*, **25**, 350 (1969).



methylchalcone (**5**) with gaseous (or liquid) bromine.²⁴



The choice of this reaction was made from consideration of previous results in gas/solid reactivity and crystallographic studies on olefinic systems: 1,2-unsymmetrically substituted crystalline trans olefins react with bromine vapor to yield erythro dibromide via anti addition;²⁵ α,β -unsaturated ketones may adopt chiral crystal structures; and the chalcones may adopt heavily twisted conformations in the solid (i.e., the degree of deviation from the achiral planar conformation will be large).²⁶ It was subsequently shown that **5**, crystallizing in the chiral space group $P2_12_12_1$, is indeed highly deformed from planarity in the crystal.²⁷

Large single crystals of **5** are conveniently grown by slow evaporation from ethyl acetate solutions or by slow cooling of the melt, using the Bridgeman method.²⁸ When single-crystal specimens of **5** are powdered (to expose a large surface area) and treated with bromine vapor, dibromide **6** is formed with one enantiomer in excess. Optical yields ranging from 6% up to 25% have been obtained.^{24,29}

Recently, the absolute configuration of **5** in the crystal was established, with the anomalous dispersion of the oxygen being used as the heavy atom scatterer.³⁰ This made it possible to correlate the configuration of **5** in a given single crystal with that of **6** produced in excess during the gas/solid bromination of the same crystal. Figure 1 illustrates the enantiomeric conformation of **5**, which yields an excess of (-)-2(S),3(R)-dibromide (**6**).³¹

(24) K. Penzien and G. M. J. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **8**, 608 (1969).

(25) E. Hadjoudis, E. Kariv, and G. M. J. Schmidt, *J. Chem. Soc., Perkin Trans. 2*, 1056 (1972).

(26) D. Rabinovich and G. M. J. Schmidt, *J. Chem. Soc. B*, **6** (1970); D. Rabinovich, *ibid.*, **11** (1970).

(27) D. Rabinovich and Z. Shakked, *Acta Crystallogr., Sect. B*, **30**, 2829 (1974).

(28) J. N. Sherwood, "Purification of Organic and Inorganic Materials", M. Zief, Ed., Marcel Dekker, New York, 1969, p 157.

(29) B. S. Green and L. Heller, unpublished results.

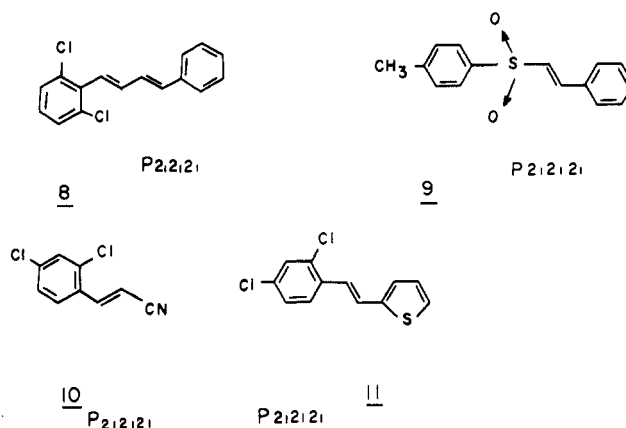
(30) D. Rabinovich and H. Hope, *Acta Crystallogr., Sect. A*, **31**, S128, (1975).

(31) B. S. Green, H. Hope, D. Rabinovich, Z. Shakked, and K. Swansen, submitted.

These results are consistent with a bromonium ion intermediate, formed preferentially from the side having the least steric hindrance by the ortho hydrogens and carboxyl oxygen (i.e., bromine attack upon the double bond from the left in Figure 1).

The above results have been primarily attributed to molecular chirality. We would therefore anticipate that for such gas/solid reactions the optical yield will depend on the deviation of molecular conformation from planarity. This is in part substantiated by the formation of racemic dibromide in the gas/solid bromine addition to single crystals of 4-methoxychalcone (**7**).³² Although the crystal is chiral, the molecules are less distorted from a planar conformation than are those of **5** (Figure 2). A recent systematic chemical and crystallographic study of bromine addition to racemic and resolved crystalline cinnamoyl- and (*o*-chlorocinnamoyl)alanines further supports the view that the molecular conformation is the dominant controlling factor in this reaction.³³

Other gas/solid reactions have been investigated as well. The addition of chlorine or iodine monochloride to **5** also yields optically active dihalides.²⁹ The addition of halogens to single chiral crystals of other olefins (**8**–**11**) have been studied in these laboratories. Diene



8 yields a mixture of optically active bromides, whereas no optical activity has been observed following the bromination of **9**–**11**. It remains to be established whether the specific rotations of the products are low, if twinning or disorder is present in the starting crystals, or if alternate reaction pathways, or destruction of the crystal lattice, precede the formation of new chiral centers. Although such reactions may provide routes for the synthesis of certain difficultly accessible, optically active compounds and allow one to better understand aspects of their overall mechanism, their complexity led us to consider in detail several photochemical solid-state reactions.

Photochemical Reactions. Many pericyclic solid-state photochemical reactions have been reported.^{2a-c,e,5} Since these reactions generally occur in the bulk, topochemical control may be preserved throughout the course of the reaction. (In some photochemical and thermal reactions topotaxy is observed; i.e., there is a defined relationship between axial directions in product and parent crystalline phases.)³⁴

(32) K. Penzien and G. M. J. Schmidt, unpublished results.

(33) S. Ariel, E. Gatti, M. Lahav, L. Leiserowitz, and L. Roitman, to be published.

(34) G. Wegner, *Chimia*, **475**, 28 (1974); K. Cheng and B. M. Foxman, *J. Am. Chem. Soc.*, **99**, 8102 (1977).

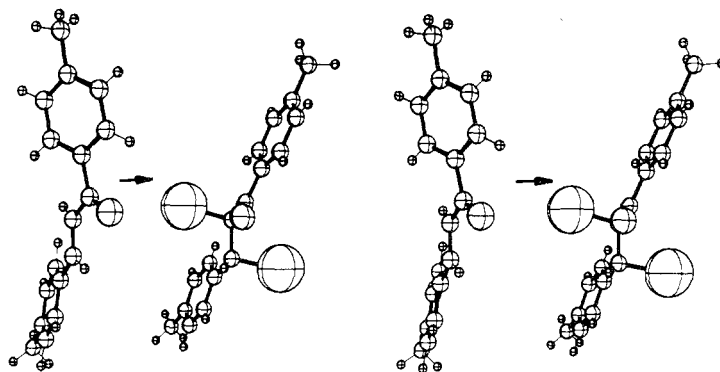


Figure 1. Stereoscopic view of the reaction, $5 \rightarrow (2S,3R)-6$. The reactant, 4,4'-dimethylchalcone (**5**), has the absolute configuration, established by X-ray crystallography,³⁰ of the enantiomer in a single chiral crystal which yields $(-)-2(S),3(R)$ -dibromide **6** as the predominant product.

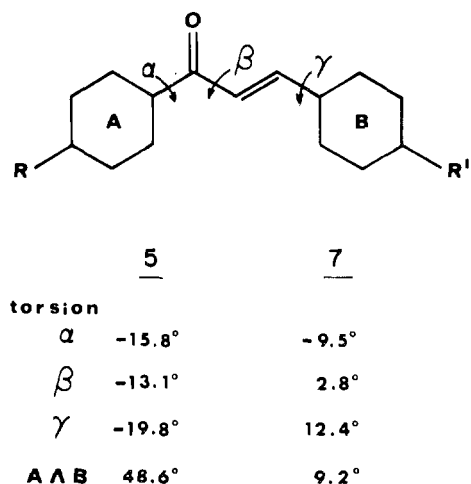


Figure 2. Dihedral angles between aromatic rings and the torsion angles in 4,4'-dimethylchalcone (**5**), $R = R' = \text{CH}_3$, and 4-methoxychalcone (**7**), $R = \text{H}$, $R' = \text{OCH}_3$.

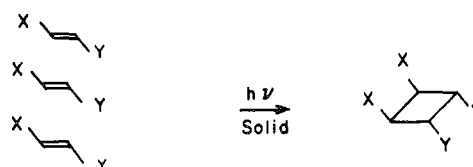
Reactions may be performed at low temperatures and the selective excitation of specific chromophores is possible. Several of these reactions lead to chiral products and are thus potential candidates for asymmetric synthesis.

The solid-state reaction par excellence is the $[2 + 2]$ photocyclodimerization of crystalline olefinic compounds to yield cyclobutanes. Reactivity in these systems demands suitable orientation of the two olefinic partners in the crystal lattice (good π -orbital overlap;³⁵ parallel double bonds separated by a distance of ca. 4.0 Å) which strictly controls the stereochemistry of the photoproducts. The possibilities of utilizing this reaction in asymmetric synthesis were considered in depth.^{3a} Two approaches appeared to be particularly feasible in consideration of the molecular packing modes of organic molecules; these are photodimerization in a single chiral mixed crystal and photodimerization of a diene having two chemically and crystallographically independent reactive groups. Both approaches have been realized.

In the first approach one starts with a chiral crystal structure comprising olefins, separated by a 4-Å translation distance, which on irradiation yield cyclobutane dimers of symmetry m (Scheme II). The central problem in this approach is to destroy the mirror symmetry of the product. This may be achieved

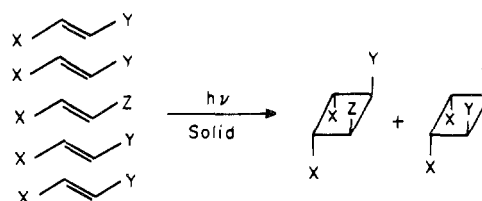
(35) Z. Berkovitch-Yellin, M. Lahav, and L. Leiserowitz, *J. Am. Chem. Soc.*, **96**, 918 (1974), and references therein.

Scheme II



β type

Scheme III



by introducing a suitable guest molecule in the host lattice. If there is appreciable miscibility between the two components (solid solution; mixed crystal), two enantiomeric heterodimers will be formed besides the two homodimers upon irradiation, and the suitability of the system for asymmetric synthesis of the mixed dimer may be considered (see Scheme III).

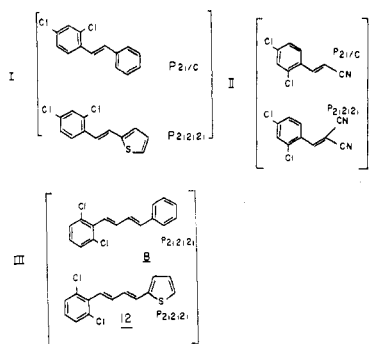
Several lines of research merged in the design of an experiment to test this approach. First, carboxylic acids and primary amides were avoided in view of their tendency to adopt centrosymmetric crystal structures.¹⁰ On the other hand, phenyl-substituted olefins (stilbenes, 1,4-diarylbutadienes) may adopt chiral structures, and hence the effort was directed toward molecules of this type. In order to achieve a 4-Å packing arrangement, the "dichloro rule" was used: aromatic and related molecules containing two chlorine substituents tend to crystallize in stack structures of the 4-Å type.³⁶ Thiophene and phenyl derivatives were favored as guest and host, respectively, since molecules with these substituents frequently form mixed crystals,^{37,38} and the feasibility of the selective excitation of the thiophene species in such mixed crystals had been established.³⁹

(36) B. S. Green and G. M. J. Schmidt, 23rd IUPAC Congress, Boston, 1971, Abstracts, p 94; B. S. Green, J. Leser, and G. M. J. Schmidt, to be published.

(37) J. D. Hung, M. Lahav, M. Luwisch, and G. M. J. Schmidt, *Isr. J. Chem.*, **10**, 585 (1972).

(38) A. Fredga, *Tetrahedron*, **8**, 126 (1960); A. Fredga, *Bull. Soc. Chim. Fr.*, 173 (1973), and references therein.

Mixed crystals of the systems I, II, and III were



possible candidates for this approach since at least one of the components in each pair crystallizes in a 4-Å chiral lattice, and all three systems yield mixed dimers upon irradiation. The butadiene system III was chosen in view of the isomorphous structures of the two components and the expectation of a heavily twisted ground-state structure, owing to the ortho chloro atoms. Crystalline samples of **8** or of **12** yield, on irradiation, a single achiral cyclobutane dimer (**13** and **14**, respectively) with symmetry *m*. When mixed crystals of **8** and **12** were irradiated, the reaction afforded the enantiomeric heterodimers **15a** and **15b** in addition to the (meso) homodimers **13** and **14** (Scheme IV).

In order to investigate the question of the chiral crystal influence on the enantiomeric distribution in **15**, it is important, as will be seen below, to selectively excite the thiophene butadienes, which absorb at longer wavelengths than the phenyl molecules. When small ratios of thiophene/phenyl are used, the selective thiophene excitation also effectively eliminates the formation of the achiral dimers **13** and **14**.

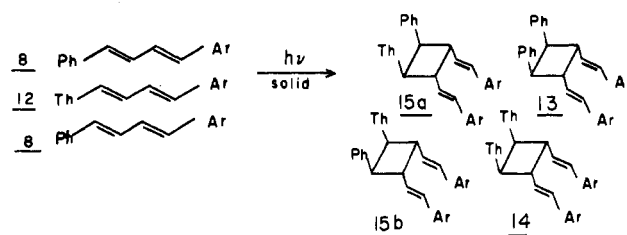
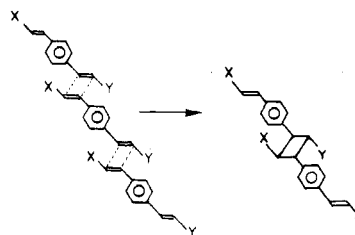
With use of a 400-nm cutoff filter, irradiation of mixed crystals containing 15% of **12** and 85% of **8** led to high yields of heterodimers; the filter minimized absorption by the phenyl compound, preventing formation of cyclobutane **13**, and the homogeneous distribution of the thiophene monomer in a large excess of **8** minimized the amount of homodimer **14**.

When large, homochiral single crystals were irradiated, optically active heterodimer was isolated.^{40,41} Some crystals afforded dextrorotatory and others levorotatory mixed dimer; the optical yield of this reaction was established as ca. 70%.⁴¹

Irradiation with shorter wavelength light, <350 nm, led to lower optical yields, as expected if the phenyl moieties absorb and show the same preferential direction of reaction within the 4-Å stack.

Figure 3 shows a guest molecule with its two nearest host molecules along the short 4-Å axis, as deduced by X-ray analysis of a crystal comprising **8** and **12** in a ratio 72:28.⁴² The optical yield in this reaction is seen to be a measure of the rate of reaction of the photoexcited thiophene **12** upward or downward. Although the translational symmetry in the ground-state crystal has been perturbed by the substitution of phenyl by a

Scheme IV

Scheme V^a

^a The enantiomeric dimer can only be formed in this enantiomorphic monomer crystal; the mirror image crystal will afford the second dimer enantiomer.

thienyl group, the degree of this perturbation, on the basis of the X-ray results (see Figure 3), is negligible. Along the 4-Å translation axis in the mixed crystal the intermolecular olefinic contacts between all pairs of molecules are almost identical. Thus, if there were no unimolecular deformation on excitation, one might anticipate that the photoexcitation of the thiophene compound would afford equal amounts of enantiomers **15a** and **15b**. However, we conclude that when the thiophene moiety is excited, it is deformed, and the difference in the interaction of photoexcited **12** with its two nearest neighbors leads to the formation of two diastereomeric transition states, giving rise to the observed asymmetric synthesis.

Knowing the configurations of the starting conformation in a crystal and of the dominant enantiomeric photoproduct which it yields, one could obtain information on the geometry of the excited-state species of **12** which is responsible for reaction. The absolute configuration of a mixed crystal has been determined;⁴² the absolute configuration of the pure enantiomer of the mixed dimer formed in excess from that crystal must yet be performed.

Recently a prediction of the enantiomeric configuration expected from a given chiral crystal of **8** and **12** was made on the basis of theoretical calculations which assume an excimer intermediate on the pathway to dimer.⁴³ (Excimer emission has been observed in crystals of **8**.⁴⁴) These calculations anticipate that molecules will adopt a more planar conformation on photoexcitation and predict that in the enantiomeric crystal shown in Figure 3 mixed dimer **15a** will be formed in excess. This prediction presently awaits experimental verification.

Our second approach requires that molecules having two nonidentical reactive sites pack in a chiral crystal in an offset stack such that the nonequivalent double bonds are in suitable overlap (parallel and center-to-center separation of ~4 Å) for efficient photocycloaddition to form only one of the two possible enan-

(39) M. D. Cohen, R. Cohen, M. Lahav, and P. L. Nie, *J. Chem. Soc., Perkin Trans. 2*, 1095 (1973).

(40) A. Elgavi, B. S. Green, and G. M. J. Schmidt, *J. Am. Chem. Soc.*, **95**, 2058 (1973).

(41) A. Elgavi and B. S. Green, to be published; A. Elgavi, Ph.D. Thesis, Weizmann Institute, 1973.

(42) D. Rabinovich and Z. Shakked, *Acta Crystallogr., Sect. B*, **31**, 819 (1975); D. Rabinovich and Z. Shakked, unpublished.

(43) A. Warshel and Z. Shakked, *J. Am. Chem. Soc.*, **97**, 5679 (1975).

(44) M. D. Cohen, A. Elgavi, B. S. Green, Z. Ludmer, and G. M. J. Schmidt, *J. Am. Chem. Soc.*, **94**, 6776 (1972).

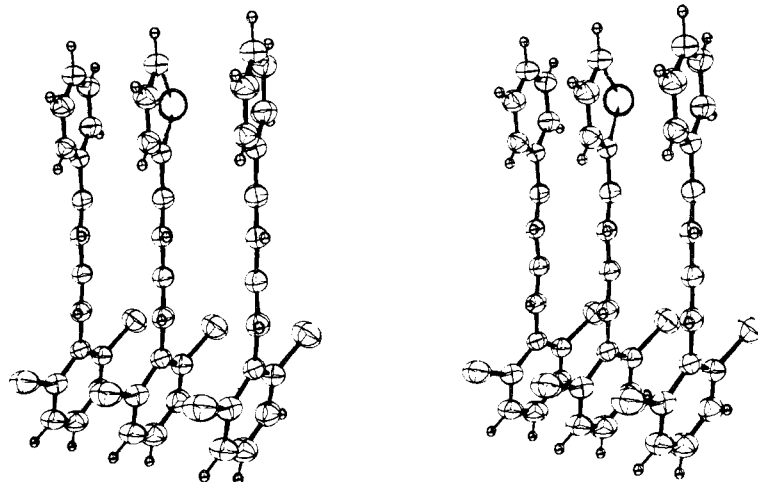
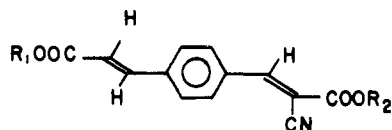


Figure 3. Stereoscopic view of the intermolecular overlap in mixed crystals containing 8 and 12. Irradiation of a single crystal yields optically active 15. In the crystal which was analyzed, the ratio of 8:12 was 72:28.⁴² The thiophene ring exhibits partial disorder; 40% of the molecules have the conformation shown while in the remaining 60% the thiophene ring is rotated by 180°.

tiomers. This is illustrated schematically in Scheme V.

A number of potential systems were examined, and finally the benzene-1,4-diacrylates (e.g., 16) were chosen



16 $R_1 = \text{sec-But}$; $R_2 = \text{Et}$

17 $R_1 = \text{sec-But}$; $R_2 = \text{Me}$

on the following grounds: symmetrically disubstituted compounds of this type are known to crystallize in structures which afford photopolymers;⁴⁵ a chiral *sec*-butyl group can be used to induce chiral crystal formation and can then be readily removed after product isolation; the *sec*-butyl group also effectively rules out the 4-Å-type packing (which would lead to reaction of equivalent double bonds) since bulky groups cannot generally be accommodated in this packing mode; and nonequivalence of the two double bonds is ensured by the nitrile function which also maintains the chirality of product after ester exchange.

The ethyl ester, (*R*)- or (*S*)-16, fulfilled all of the requirements outlined above.^{3,46} It crystallizes in the triclinic space group *P*1, where the sole symmetry element is translation, with the packing arrangement shown in Figure 4.^{47a} When crystalline samples of optically pure (*S*)-(+)-monomer were irradiated at 5 °C, dimer, trimer, and higher polycyclobutane oligomers were formed in optical yields approaching 100% as demonstrated by ¹³C and ¹H NMR measurements.^{3b} Irradiation of crystalline samples of the enantiomeric (*R*)-(-)-isomer of 16 afforded products having optical rotations of the same magnitude but of opposite sign.

In this reaction the photoproducts are determined by the crystalline arrangement of the molecules; optical induction is due to the crystal chirality and not to the

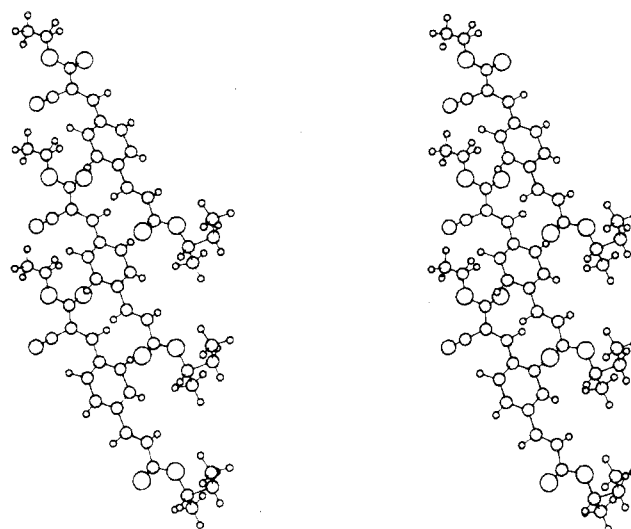


Figure 4. Stereoscopic view of the crystal packing of (*S*)-(+)-16, showing the stack along which [2 + 2] photocycloaddition takes place. From the known configuration of the *sec*-butyl group, the absolute configuration of the chiral cyclobutane products can be deduced. Adapted with permission from ref 3b.

local chiral influence of the *sec*-butyl group. This is shown by the different photobehavior of the analogous resolved methyl ester monomer, (*S*)-(+)-17. This material is dimorphic: form 1 is light stable; form 2 is photolabile and yields the chiral dimers 18 and 19.^{3b} Although the monomer crystal is chiral and a chiral dimer is formed, the irradiation product, after removal of the *sec*-butyl groups, is racemic. These results are explained by the fact that the reacting monomers are related by a pseudocenter of symmetry, as revealed by the crystallographic constants and the isomorphous structures of form 2 and racemic 17 (Figure 5);^{3b,47b} this allows the formation of both diastereomeric cyclobutanes, 18 and 19, in identical yields.

Racemic monomer 16 provides an interesting example of a racemate crystallizing in a single chiral crystal, with complete disorder of the *R* and *S* *sec*-butyl groups. (Disorder in racemic crystals containing *sec*-butyl groups is common.⁴⁸) Large crystals of the racemate

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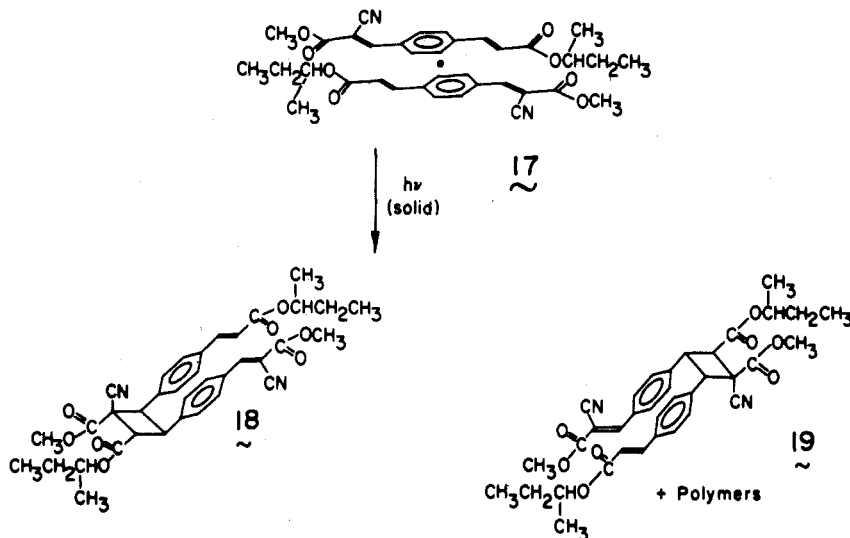


Figure 5. Schematic representation of racemic or enantiomeric 17 and its solid-state photodimeric products. Even when the *sec*-butyl groups have the same chirality, products 18 and 19 are obtained. Adapted with permission from ref 48.

were grown from the melt and irradiated. Dimers, trimers, and higher oligomers are formed and all display optical activity. The optical yields vary from experiment to experiment; the highest specific rotations thus far obtained are 30° for the dimer and 24° for the chloroform-soluble oligomer fraction.⁴⁹

Asymmetric Synthesis in Inclusion Complexes. A solid inclusion complex of resolved (+)-perhydrotriphenylene and *trans*-1,3-pentadiene was used in the first solid-state asymmetric synthesis. After exposure to γ -rays, an optically active pentadiene polymer was isolated even though the chiral agent interacts with the starting material only through van der Waals forces.⁵⁰ The optical yield of this reaction has not yet been reported. More recently the same synthesis has been performed in a chiral inclusion complex of deoxycholic acid.⁵¹ Many potential clathrate host species can be considered as matrices for asymmetric synthesis, and one can expect to see a variety of additional chiral transformations in these interesting systems.

Enantiomer Enrichment via a Solid-State Reaction. From the foregoing discussion it is clear that different packing arrangements in the crystal can be expected to lead to different solid-state reaction products. A chiral and a racemic modification of the same material should also display different reactivity. This difference was recently exploited for the enrichment of enantiomers in a series of chiral α -phenylethyl esters of 9-anthroic acids.

Racemic anthracene derivatives frequently crystallize in close-packed pairs in the crystal which display characteristic excimer emission and undergo rapid photodimerization. The pure enantiomeric crystals have a completely different packing, show characteristic monomer emission, and are light stable. Esterification of partially resolved 1-arylethanol with 9-anthroic acid

affords mixtures of racemic and chiral crystals. Upon irradiation, dimer is formed from the racemic crystal exclusively. Extraction with hexane separates the soluble unreacted chiral monomer from the insoluble meso dimer; the resulting optical purities can be higher than 95%.⁵²

Finally, we would like to call attention to an intriguing possibility. A solid-state reaction may provide an optically active product from a single *racemic* crystal. The principle is to cause reaction to occur exclusively on the upper (or lower) face of a suitable single crystal; one face should afford one enantiomer preferentially while the other should afford its antipode. Support for the feasibility of this kind of experiment is provided, perhaps, by differences in product distribution between reactions on different faces of a single crystal⁵³ and by the anisotropic effect,²⁶ observed in several gas/solid reactions with single crystals.

Conclusions

We have summarized the current status of organic transformations proceeding in chiral crystals. The future of this field is intimately connected with progress in the general area of organic solid-state chemistry as well as with deeper understanding of the molecular packing modes of crystals. As these disciplines broaden in scope and application, so will utilization of solid-state reactions for asymmetric synthesis. It is our feeling that in the same way that chiral groups play a role in the study of many organic and inorganic solution reactions, so too will chiral crystals allow one to obtain detailed information on solid-state reactions. This, in turn, will contribute information of synthetic value or mechanistic interest which could not be obtained in other phases.

We are grateful to M. D. Cohen for his comments on the manuscript. We thank him, L. Addadi, L. Leiserowitz, and Z. Shakked for stimulating discussions.

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