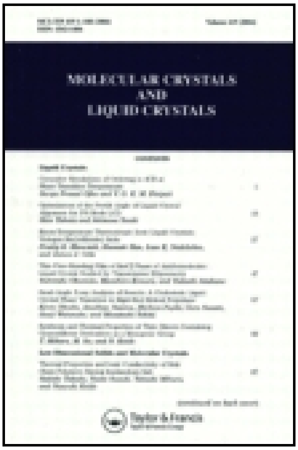

Molecular Crystals and Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl16

# Reactions in Chiral Crystals. Principles Governing Asymmetric Synthesis via Topochemically Controlled Solid-State Photo-Dimerization

Bernard S. Green [a], Meir Lahav [a] & G. M. J. Schmidt [a]

[a] Department of Structural Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Version of record first published: 21 Mar 2007.

To cite this article: Bernard S. Green, Meir Lahav & G. M. J. Schmidt (1975): Reactions in Chiral Crystals. Principles Governing Asymmetric Synthesis via Topochemically Controlled Solid-State Photo-Dimerization, Molecular Crystals and Liquid Crystals, 29:2, 187-200

To link to this article: http://dx.doi.org/10.1080/15421407508083200

*Mol. Cryst. Liq. Cryst.*, 1975, Vol. 29, pp. 187–200

Printed in Holland

# Reactions in Chiral Crystals. Principles Governing Asymmetric Synthesis via Topochemically Controlled Solid-State Photo-Dimerization

BERNARD S. GREEN, MEIR LAHAV and G. M. J. SCHMIDT†

*Department of Structural Chemistry, The Weizmann Institute of Science, Rehovot, Israel*

(*Received March 11, 1974; in final form May 21, 1974*)

The chemical and crystallographic requirements for utilizing solid-state photodimerization reactions in the medium of chiral single crystals to realize asymmetric syntheses have been considered. Asymmetric syntheses are possible from a variety of reactions in the monocomponent or two-component crystals which have been considered and in favorable cases quantitative optical yields are anticipated. These principles can be extended to other reactions including the formation of chiral cyclobutane photopolymers.

## 1. INTRODUCTION

In recent years there has been a growing interest in organic reactions which proceed in phases which are more highly ordered than are the media, dilute solution or gas phase, usually used by chemists. Thus, studies have been made of reactions at phase boundaries,[1] of included,[2] clathrated,[2] or complexed molecules,[3] in liquid crystals,[4] and in crystalline solids.[5] The chemistry of organic crystals is particularly amenable to systematic study since the powerful methods of X-ray crystallography can be exploited. One of the data which, in general, is readily available from a preliminary investigation of a crystal

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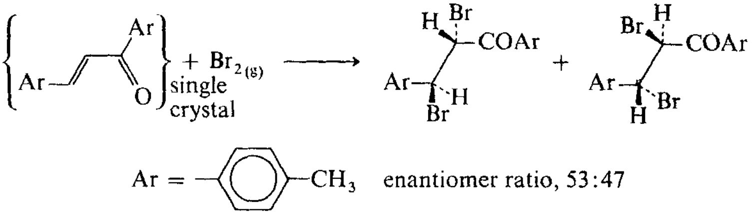
† Deceased July 12, 1971.

specimen is its space group, a description of the symmetry elements present in that crystal.

From the symmetry point of view crystals may be of two types: i) *racemic crystals* which contain symmetry elements, such as mirror planes, glide planes, or inversion centers, which interconvert right- and left-handed species, and ii) *chiral* (or *enantiomorphic* or *dissymmetric* or *optically active*) *crystals*, in which such symmetry elements are absent. Optically active compounds must crystallize in chiral structures; samples containing equal numbers of enantiomeric molecules can yield either racemic or chiral crystals, the latter case being known as *spontaneous resolution*. Of particular interest here is the observation that molecules which are achiral in solution (by virtue either of rapid interconversion of enantiomers or the presence of mirror-symmetric or centrosymmetric conformations) can also spontaneously resolve and afford chiral crystals. Many such examples are known, including representatives of a wide variety of molecular structure types.

It has long been recognised that the chemical transformation of a chiral crystalline specimen of one handedness containing achiral educts into an optically active reaction product would constitute a novel asymmetric synthesis[6] and several attempts along these lines have been recorded.[7] The first unambiguous success was obtained in the heterogeneous bromination of single crystals of 4,4′-dimethylchalcone (space group $P2_12_12_1$) with gaseous bromine, which afforded a 6% excess of one enantiomer.[8]

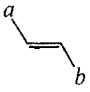


enantiomer ratio, 53:47

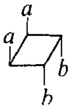
The only chiral influence utilized by this asymmetric synthesis is the enantiomorphic crystal structure of one of the reactants. It would seem advantageous to utilize a bimolecular reaction which proceeds with lattice control over both reactants.

Since extensive studies on solid state photodimerization reactions of olefinic and related systems[9] have shown that the space symmetry which relates two reactant molecules in the starting material uniquely dictates the point symmetry of the dimeric photoproduct, we have chosen to consider herein the chemical and crystallographic requirements for utilizing this reaction to accomplish asymmetric synthesis via chiral crystals. In addition to providing a novel approach to asymmetric synthesis, these studies may furnish a useful probe into reaction mechanisms as well as illuminate the role of order in reactions in non-crystalline systems.

We consider first the possible symmetry elements in chiral crystals which relate neighboring molecules of 1,2-disubstituted-*trans*-olefins, represented schematically by **1**, whose photocyclodimerization may, *a priori*, afford the four cyclobutane photoproducts **2**–**5**.† We next examine the possible consequences of irradiating a chiral, two-component, single crystal containing guest molecules **6** substitutionally distributed amongst host molecules **1** (mixed crystal, substitutional solid solution). The structures of the mixed dimers which may result from such mixed crystals are **7**–**10**. We then briefly extend our considerations to include dienes and other systems. For several of the single crystal photodimerization reactions considered herein optical yields approaching 100% may be anticipated.



**1**



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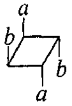

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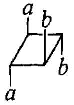
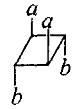
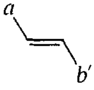


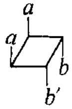
**4**



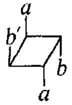
**5**



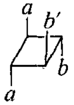
**6**



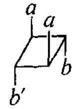
**7**



**8**



**9**



**10**

## 2. MONO-COMPONENT CRYSTALS CONTAINING OLEFINS WITH ONE REACTIVE DOUBLE BOND

In Table I are listed the possible space symmetry relationships of a pair of neighboring 1,2-disubstituted-*trans*-ethene molecules, **1**, as well as the point symmetries of the expected cyclobutane photoproducts, and the feasibility of asymmetric synthesis in a chiral crystalline assembly. Only those symmetry relationships which allow topochemical, lattice-controlled, photodimerization are listed, i.e., those which lead to intermolecular separations of 4.0 ± 0.3 Å between parallel double bonds.[9] Of these six cases only case 1, molecules related by translation, is commonly observed (more than 50 examples of $\alpha$, $\beta$-unsaturated acids, esters, nitriles, and ketones, stilbenes, butadienes, etc.)[9,10] but its photoproduct contains a mirror plane and is therefore not dissymmetric.

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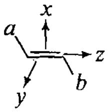
† The *trans* geometry of the monomer is maintained in the dimer in essentially all of the cases studied.[9]

TABLE I

Possible space symmetry relationships and topochemically-expected photodimers of **1** in chira crystals[a]



| Case | Space symmetry or pseudo-symmetry relating two adjacent molecules with parallel double bonds[b] | Point symmetry of the lattice-controlled photodimer expected or found | Optically active product possible |
|---|---|---|---|
| | Monocomponent single crystal | | |
| 1 | 1(translation along $y$)[c] | $m$ [structure **2**] | No |
| 2 | 211(two-fold axis parallel to $x$) | $mm$ [5] | No |
| 3 | 112(two-fold axis parallel to $z$) | 2 [4] | Yes[d] |
| 4 | $2_1 11$(two-fold screw axis parallel to $x$) | $mm$ [5] | No |
| 5 | $12_1 1$(two-fold screw axis parallel to $y$) | $\bar{1}$ [3] | No |
| 6 | $112_1$(two-fold screw axis parallel to $z$)[e] | 2 [4] | Yes[d] |
| | Two-component single crystal | | |
| 1′ | pseudo-translation along $y$ | 1(pseudo-$m$) [7] | Yes |
| 2′ | pseudo-two-fold axis parallel to $x$ | $m$(pseudo-$mm$) [10] | No[f] |
| 3′ | pseudo-two-fold axis parallel to $z$ | 1(pseudo-2) [9] | Yes[d] |
| 4′ | pseudo-two-fold screw axis parallel to $x$ | $m$(pseudo-$mm$) [10] | No[f] |
| 5′ | pseudo-two-fold screw axis parallel to $y$ | 1(pseudo-$\bar{1}$) [8] | Yes |
| 6′ | pseudo-two-fold screw axis parallel to $z$[e] | 1(pseudo-2) [9] | Yes[d] |

[a] Nomenclature and symbols follow the *International Tables for Crystallography*, Vol. I, The Kynoch Press, Birmingham, England, 1969.

[b] Axes are required to be approximately parallel to a molecular axis, as indicated, in order to allow the close packing and orbital overlap required for the cycloaddition reaction. Three- and higher-fold axes do not provide the parallel double bond requirement and have therefore not been included. Two-fold rotation axis parallel to $y$ (121) would not allow close, parallel double bonds.

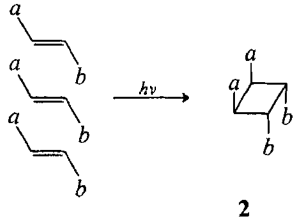
[c] This monomer packing type and resultant photodimer is often observed and is characterized by a short unit cell axis of 4.0 ± 0.3 Å in the monomer lattice.[9] A method for generating this packing type will be described shortly (B. S. Green, Y. Leser, and G. M. J. Schmidt, to be published).

[d] If the monomers crystallize only in pairs a 100% optical yield may be anticipated; if each monomer has two potentially reactive neighbors then either a racemate or an optically active product is possible.

[e] This case is only possible for very small molecules (e.g., $FCH{=}CH_2$) since a small displacement along $z$ is necessary for contact between the double bonds.

[f] If a guest molecule can be introduced, both ends of which differ from the host molecules, (i.e., a guest molecule $a'$  $b'$) then this case *can* be utilized to realize asymmetric synthesis.

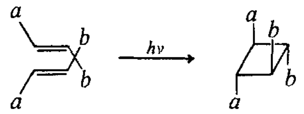
case **1**



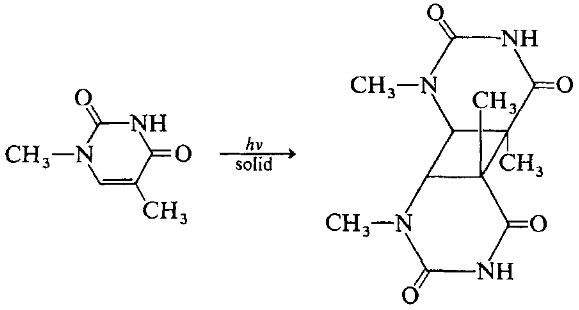
**2**

Case 3, molecules related by a two-fold axis, and case 6, molecules related by a two-fold screw axis (and cases 3′ and 6′, see below) can be expected to give a quantitative optical yield *if* the molecules pack in pairs, i.e., if each molecule has only one neighbor with which cyclodimerization is topochemically feasible. In these cases a given single crystal will contain only pre-**4** pairs while the enantiomeric crystals will contain only pairs enantiomeric to pre-**4**. Solid-state photodimerizations to cyclobutanes of symmetry 2 are not common, however an example is provided by 1-methylthymine **11**, which yields the dimer **12**.[11] The monomer **11** crystallizes in a racemic space group, $P2_1/c$.[12]

cases **3**, **6**
(pair-wise packing)



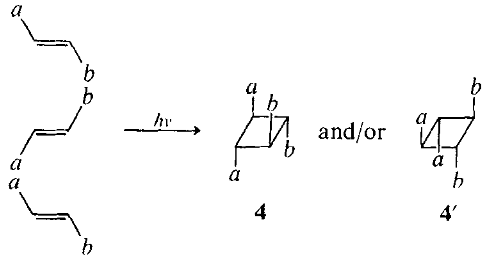
**4**



**11** **12**

If the molecular packing in cases 3 and 6 is not one of pairs but allows the formation of both enantiomers then an asymmetric synthesis is still possible from a reaction proceeding within a chiral single crystal but the optical yield will depend on the relative rates of reaction and cannot be predicted.

cases **3**, **6**
(packing in stacks)



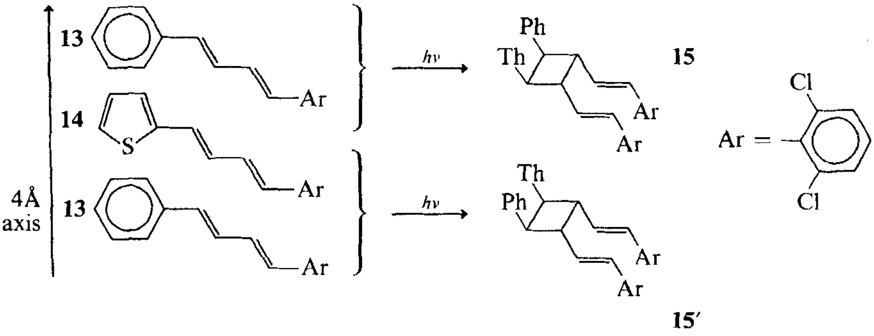
Molecules which are unrelated by any crystallographic symmetry elements but which can undergo lattice-controlled photoreaction to produce a chiral dimer can also be considered. For example, a stereospecific asymmetric synthesis, affording a single enantiomer, can be expected from photocycloaddition in a single crystal with space group $P_1$, if there are two molecules in the unit cell having contacts allowing the formation of a chiral dimer.

## 3. TWO-COMPONENT CRYSTALS CONTAINING OLEFINS WITH ONE REACTIVE DOUBLE BOND

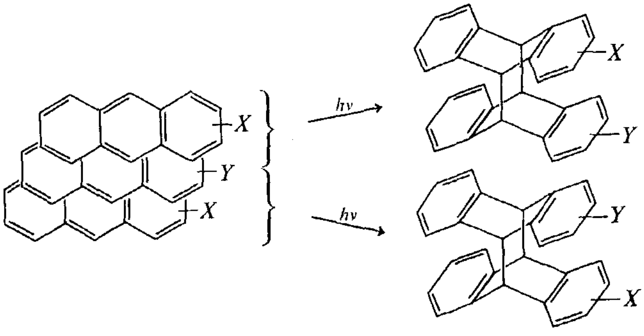
By including guest molecules in crystals of the space lattices considered above one destroys the space symmetry elements relating the molecules in the host crystal. However, by virtue of the structural similarity of guest and host, which enables a mixed single crystal to be formed, it is likely that a high degree of pseudo-symmetry will persist in the neighborhood of the guest molecules. The various possible pseudo-symmetry elements which can lead to mixed dimers are similar to the symmetry elements leading to homodimer in the one-component crystals and are indicated by corresponding primed numbers in Table I.

Case 1′ is especially intriguing because molecular features leading to this space symmetry and photoproduct formation have been extensively studied in monocomponent systems[9] and have recently been observed in two-component systems also.[13] Along the 4Å stack of **1**, present in excess, each molecule of **6** is sandwiched between two molecules of **1**. The contacts to these neighbors are non-equivalent, especially if the molecules are non-planar. Therefore, upon irradiation, two diastereomeric transition states of the mixed dimer may be formed with an appreciable difference in rate, so that the resulting asymmetric cyclobutane may contain one enantiomer in excess. Further, in suitable examples the difference in light absorption properties between **1** and **6** enables the selective excitation of one of the species,[14] **6**; this should lead to an additional, and perhaps more significant, change in intermolecular contacts, and thereby enhance the optical yield. If both compounds absorb, the situation is more complicated since each enantiomer of the mixed dimer can result from two excitation processes (excitation of the guest or of the host). In addition, energy transfer processes between guest and host can compete with cycloaddition. In cases of very efficient energy transfer from host to guest the results may be identical to those resulting from selective excitation of the guest.

Several examples of systems corresponding to case 1′ have been found to adopt chiral crystal structures and, indeed, in one example investigated recently, irradiation of single mixed-crystals containing olefins **13** and **14** afforded an optically active photoproduct, i.e., the enantiomers **15** and **15′** were formed in unequal amounts.[15]

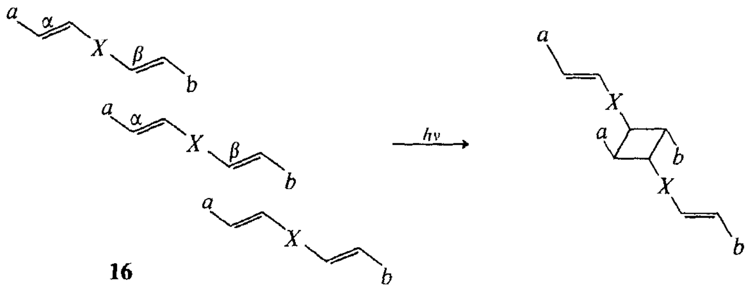


Chiral mixed crystals in which 4 + 4 photocycloaddition reactions can proceed are also accommodated within this category. Potential examples include substituted anthracenes, several of which afford chiral crystals.[16]



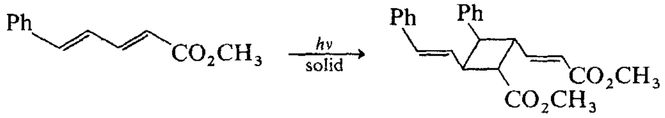
## 4. MONO-COMPONENT CRYSTALS CONTAINING MOLECULES WITH TWO REACTIVE DOUBLE BONDS

In Table I only photodimerization involving the same double bond of both monomer species has been considered. However, the photodimerization of molecules containing two or more non-equivalent olefinic groups can also lead to chiral cyclobutanes; in this case the symmetry requirements may be different. Consider, for example, a chiral crystal containing molecules with two potentially reactive double bonds, as in the diene **16**, where the molecules are related by translational symmetry but where the reacting double bonds are not related by any symmetry element. Let the distance between double bonds α and β of neighboring molecules be *ca.* 4Å while the equivalent double bonds may be appreciably farther apart. In the α + β ring closure it is always the "lower" face of β which reacts with the "upper" face of α, and the reaction should lead to only one enantiomeric product (100% optical yield).

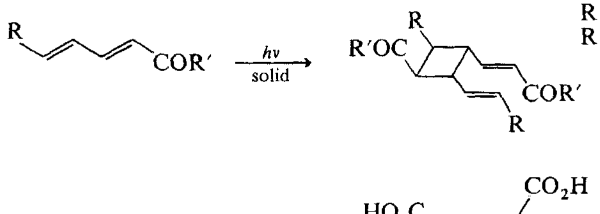


**16**

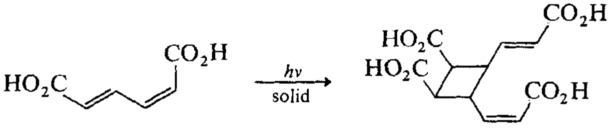
There are many examples in which symmetric (achiral) molecules containing two double bonds dimerize to give chiral products but none has yet been described which crystallizes in a chiral structure. Some of these examples are illustrated below.



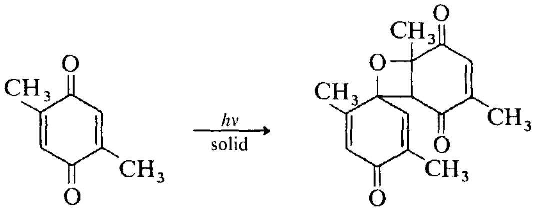
(Ref. 17)



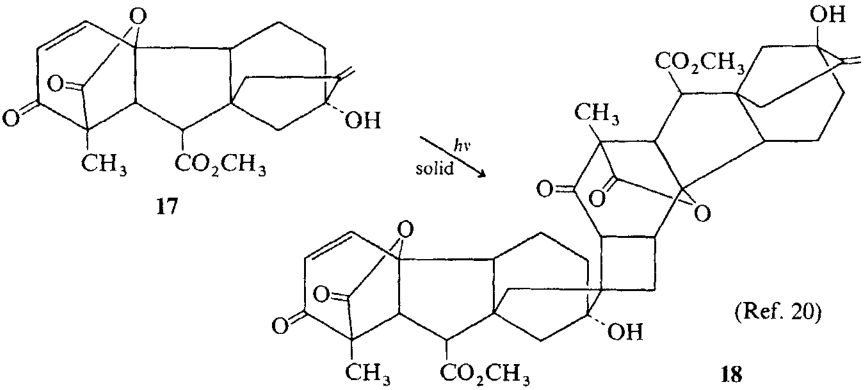
$R = CH_3$, $R' = OH$
$R = CH_3$, $R' = NH_2$
$R = Ph$, $R' = OH$
(Ref. 17)



(Ref. 18)



(Ref. 19)



17

(Ref. 20)

18

Since **17** is a chiral molecule the crystal structure of **17** is undoubtedly also chiral and therefore if a single contact is present leading to the cyclobutane dimer, we expect the newly formed chiral centers to be produced with enantiomeric stereospecificity.

Other solid-state 2 + 2, or 4 + 2,[21] photocycloadditions between chemically different double bonds ($C{=}C + C{\equiv}C$; $C{=}C + C{=}N$; etc.) can also be envisaged in this category. If a given double bond has only one nearby reactive partner then optically pure photoproducts can be anticipated from each single crystal. In cases where a given double bond can approach two reactive partners to afford the two enantiomers, respectively, then the optical yield will depend on the relative rate of reaction along the two pathways. One schematic example of a packing arrangement where two nonequivalent contacts are present, each giving one enantiomer, is illustrated by **19**, where contacts across *d* and *d′* are, in general, different since no crystallographic symmetry elements relate the upper and lower molecules. A chiral dimer, e.g. **20** would result if one contact, say *d*, were preferable.†

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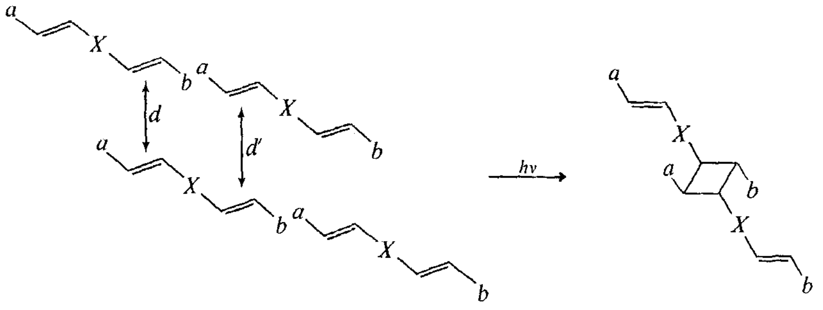
† Note, however, that if reaction were to continue along the chain, see next section, a polymer with cyclobutane units of alternating chirality, ... RSRS..., would be produced.

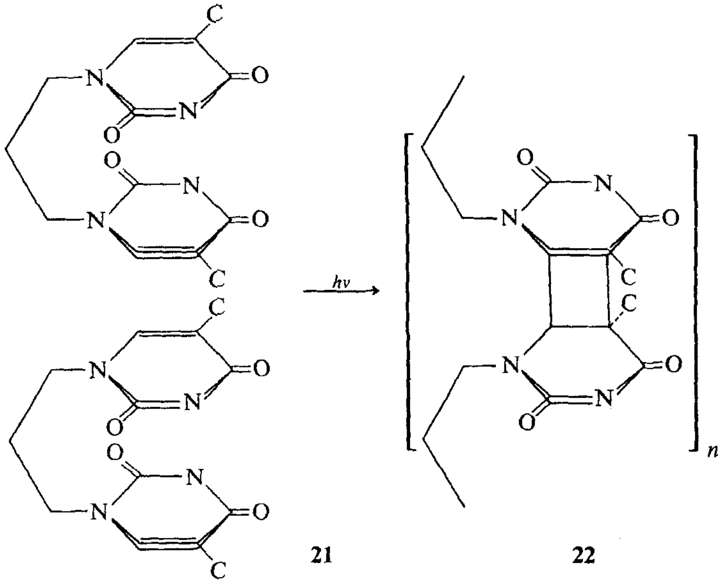


**19** **20**

## 5. PHOTOPOLYMERIZATION IN CHIRAL CRYSTALS

In the previous section we considered pairs of molecules and their photoreaction to produce dimers. However, since such molecules contain two potentially reactive sites it is also possible to consider packing arrangements where further reaction along a stack axis occurs to produce trimers, tetramers, etc., and, finally, high molecular weight polymers. Hasegawa and coworkers[22] have indeed shown that stereoregular, highly oriented cyclobutane polymers can be obtained by the irradiation of crystals comprising certain bis-olefinic monomers. Perhaps because the densities of the cyclobutane polymers are similar to those of the monomer crystals, the propagation steps of the polymerization are, in contrast to those of simple vinyl polymerizations, topochemically controlled.

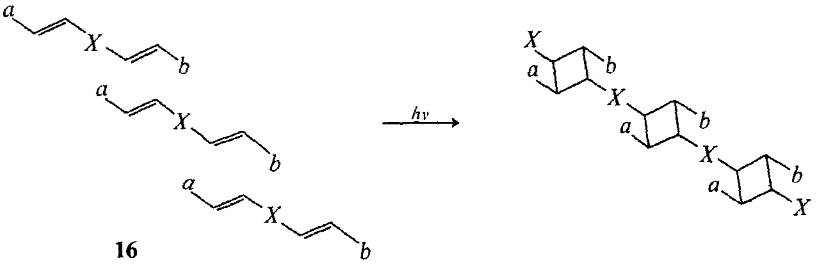
In the cases reported by Hasegawa[22] and by other workers[23] the symmetrical bis-olefins yield polymers with cyclobutane units containing centers of symmetry, and thus are optically inactive. Recently, however, Leonard[24] and Paul[25] and their co-workers have found that 1, 1′-trimethylenebisthymine, **21** yields, when irradiated in the crystal state, a lattice-controlled cyclobutane polymer, **22**, of which the cyclobutanes in the chain have two-fold symmetry axes and are chiral units. Each polymer chain should comprise, assuming no stacking faults, disorder, etc., only units of the same chirality, i.e., only . . . RRR . . . or only . . . SSS . . . , but there should be no mixed . . . RSRS . . . chains. Since 1, 1′-trimethylenebisthymine does not crystallize in a chiral space group[25] equal numbers of poly-R chains and poly-S chains should be formed, but these results encourage the search for similar packing modes in chiral crystals.



**21** **22**

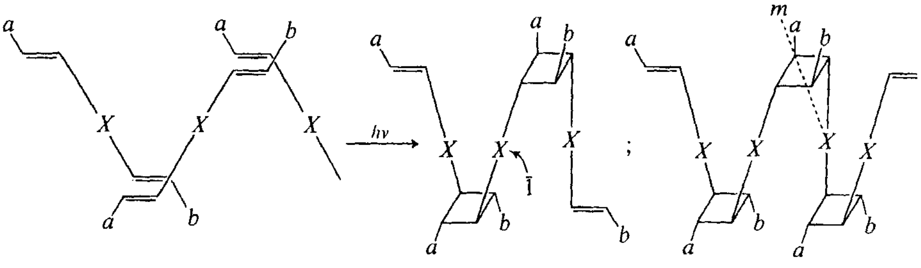
We now consider some of the packing arrangements of unsymmetrical bis-olefinic monomers whose single crystal photopolymers would be chiral. The requirements are short contacts between non-equivalent double bonds; these short contacts must continue along a translation axis; and, of course, the monomers must crystallize in chiral space groups.

The reaction of diene **16**, considered earlier as an example of photodimerization, also illustrates the formation of a photopolymer if cyclobutane formation is propagated along the translation axis. This case has been described earlier.[26]



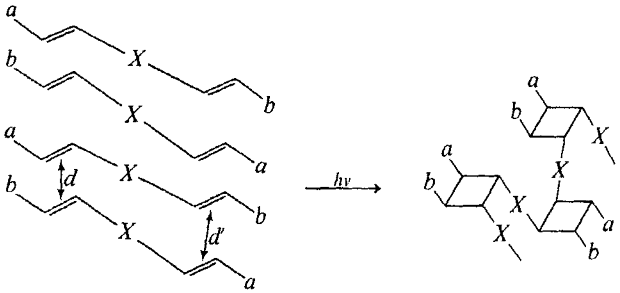
**16**

Dienes related by a two-fold screw axis parallel to the molecular axis can also yield a chiral oligomer, **23**, **24**, etc. As the chain length increases the polymer may become optically inactive as a result of the pseudo-center of inversion, $\bar{1}$, in the central *X* group of oligomers containing an odd number of monomer units, e.g., **23**, or due to the pseudo-mirror plane, *m*, in the central cyclobutane ring of oligomers having an even number of monomer units, e.g., **24** On the other hand, the optical activity may be retained in the solid photopolymer (not dissolved or melted) as a result of the conformation imposed by the monomer crystal lattice.



**23** **24**

A chiral crystal containing dienes related by a two-fold axis perpendicular to the molecular axis could afford a chiral polymer if the contacts and reactivities across *d* and *d′* as in **25** are sufficiently different. (This is formally similar to the case of Leonard[24] and Paul[25] discussed above).



**25**

## CONCLUDING REMARKS

The possibility of carrying out transformations via reactions in chiral crystals opens up lines of research which touch upon many aspects of chemical as well as biological studies. We have outlined various possibilities which can be anticipated for the photodimerization and photopolymerization of solid olefins. We consider, however, that many other solid-state photochemical as well as thermal reactions will also provide vehicles for asymmetric syntheses.

## Acknowledgement

We thank Prof. M. D. Cohen for his comments and assistance in preparing this manuscript. We are grateful to him and to Prof. F. L. Hirshfeld, Dr. L. Leiserowitz, Dr. D. Rabinovich, and Mrs. L. Addadi for helpful discussions.

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