TOPICS IN

STEREOCHEMISTRY

EDITORS

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To the 1987 Nobel Laureates in Chemistry
Donald J. Cram, Jean-Marie Lehn
and
Charles J. Pedersen

INTRODUCTION TO THE SERIES

It is patently impossible for any individual to read enough of the journal literature so as to be aware of all significant developments that may impinge on his or her work, particularly in an area such as stereochemistry, which knows no topical boundaries. Stereochemical investigations may have relevance to an understanding of a wide range of phenomena and findings irrespective of their provenance. Because stereochemistry is important in many areas of chemistry, comprehensive reviews of high quality play a special role in educating and alerting the chemical community to new stereochemical developments.

The above considerations were reason enough for initiating a series such as this. In addition to updating information found in such standard monographs as *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965; reprinted by American Chemical Society, 1981) as well as others published more recently, the series is intended also to deal in greater detail with some of the topics summarized in such texts. It is for this reason that we have selected the title *Topics in Stereochemistry* for this series.

The series is intended for the advanced student, the teacher, and the active researcher. A background of the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental importance aimed primarily at an audience of inorganic and organic chemists. Yet, many of these topics are concerned with basic principles of physical chemistry and some deal with stereochemical aspects of biochemistry as well.

It is our intention to produce future volumes at intervals of one to two years. The editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of editorial advisors who have been of great assistance by suggesting topics and authors for several chapters and by helping us avoid, in so far as possible, duplication of topics appearing in other, related monograph series. We are grateful to the editorial advisors for this assistance, but the editors and authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

E. L. ELIEL
S. H. WILEN

PREFACE

In the first chapter in this volume William A. Bonner surveys the fascinating research of scientists in several disciplines who have proposed hypotheses and carried out experiments aimed at understanding the origins of the chiral homogeneity of naturally occurring compounds. The stereochemical bias giving rise to so many enantiomerically pure compounds in nature is but one facet of the general question of the origin of life on earth. The range of experiments and techniques applied to the solution of this problem is very impressive. While there is not yet a definitive answer to the source of the enantiomeric bias, we believe that readers will be pleased to have the key facts and their interpretation as of 1987 presented and carefully reviewed by one of the principal participants in this multidisciplinary research effort.

The second chapter, by N. A. Porter and P. J. Krebs, deals with radical pair reactions. Both old and new stereochemical aspects of radical coupling are examined from the perspective of kinetics as well as that of coupling equilibria. In a short but far ranging analysis the authors describe the fate of radical pairs in solids and in other molecular aggregates (such as micelles) as well as in solution.

In the third chapter Henri Brunner examines enantioselective syntheses of organic compounds catalyzed by chiral transition metal compounds. In this survey Brunner has focused on quantitative results reported during the three-year period 1984–1986, during which a very large number of such syntheses have been reported. Much of the data presented is in the form of tables which are organized according to optically active catalyst ligands and reaction product structures. We believe that this collection of data will be of help to synthetic chemists, in particular, in the design of new stereoselective reactions.

The fourth and last chapter in this volume is a review of kinetic resolution by H. B. Kagan and J. C. Fiaud. This approach to optical activation, once considered limited to enzymatic reactions, has in recent years become a very practical way of preparing chiral compounds in nonracemic—even enantiomerically pure—form by purely chemical processes. This turn of events is in part due to recent developments leading to the very efficient kinetic resolution of compounds that can serve as starting materials and as intermediates in stereoselective syntheses of current interest. The seminal discovery by Barry Sharpless et al. (*J. Amer. Chem. Soc.*, **1981**, *103*, 6237) of asymmetric synthesis of optically active epoxides from allylic alcohols

coupled with kinetic resolution of the unreacted chiral allylic alcohol, in particular, dramatized the possibilities of kinetic resolution. Remarkably, kinetic resolution has also been applied to the optical activation of compounds on a commercial scale. Another and very significant reason for the increased application of kinetic resolution methods is a better understanding of the theory of such processes, which the authors have pioneered in their research and which they review in this chapter.

We are pleased to dedicate this volume to the 1987 Nobel Laureates in Chemistry, Dr. Charles J. Pedersen (DuPont), Professor Donald J. Cram (UCLA), and Professor Jean–Marie Lehn (Strasbourg and Collège de France, Paris); we are proud to have Professor Lehn as one of the members of our Editorial Advisory Board. The 1987 Nobel Prize was awarded "for development and use of molecules with structure–specific interactions of high selectivity"; stereochemical selectivity has clearly played an important part in the work recognized by the Nobel Prize. One aspect of the work leading to the award was featured in the preceding volume of *Topics in Stereochemistry*: J. F. Stoddart, "Chiral Crown Ethers," **1987,** *17,* 207.

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Origins of Chiral Homogeneity in Nature

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I. INTRODUCTION

Molecules that have the structural possibility of existing as either of two enantiomers, a "right-handed" form or a mirror-image "left-handed" form, are said to be chiral (from the Greek *cheir*, meaning hand). Chiral molecules are *optically active*, that is, they have the ability to rotate the direction of polarization of plane polarized light, one enantiomer being *dextrorotatory* [(+) rotation] and the other *levorotatory* [(−) rotation]. Organic molecules associated in nature with living matter are usually chiral and, accordingly, since the time of Pasteur the optical activity of such chiral molecules has been recognized as one of the principal hallmarks of life. It is thus not surprising that measurable optical activity has been suggested recently as a prime criterion for the recognition of life elsewhere in the universe (1, 2). It has also been discovered that life's crucial biomolecules are not only optically active, but that each has its own unique and constant sense of chirality, which is characterized further by essentially complete enantiomeric homogeneity. Thus, as is well known, we find that L-amino acids (or *S*) are the unique monomer subunits of protein polymers, that D-ribose (related by stereo-chemical conventions to D-glyceraldehyde) (or *R*) and 2-deoxy-D-ribose are the monomer units of the RNA and DNA nucleic acid polymers, and that D-glucose is the exclusive monomer unit of glycogen and of the plant poly-saccharide polymers, starch, and cellulose. The current biosphere is thus commonly characterized as being composed of L-amino acids and D-sugars. On the other hand, heterogeneity of chirality sense is tolerated and frequently observed among Nature's less consequential chiral molecules (e.g., certain terpenes) peripherally associated with living matter (3), and D-amino acids are found in rare instances involving proteins from bacterial cell walls and a few other sources (3, 4). Today it is generally accepted that enantiomeric hom-ogeneity of the monomers making up the critical biopolymers is not only essential for the existence of life, but that self-replicating living matter would be impossible without such absolute enantiomeric purity (5). Fundamental questions thus arise as to the ultimate origin of the unique chirality senses of our biosphere. When, where, and by what mechanism(s) did they arise, and how did they achieve their absolute chiral homogeneity? Such questions, which have intrigued scientists since the time of Pasteur, have recently received increasingly widespread attention. A number of review articles

addressing these questions has appeared in the past two decades, of which several are relatively comprehensive (3, 4, 6–9). Our intention in this chapter is to review critically the plethora of recent experimental, theoretical, and speculative publications pertaining to these questions, emphasizing the most recent literature to mid-1986.

II. BIOTIC THEORIES

Theories for the origin of a single chirality sense in Nature fall into two main categories, *biotic* and *abiotic*. Biotic theories presuppose that life on Earth originated at some advanced stage of chemical evolution from a primordial racemic environment, and that as living matter developed it somehow selected the utilization of today's L-amino acids and D-sugars as being the most efficient for continuous progression into higher forms. Such theories argue that the origin of chirality is an evolutionary process linked with the origin of life itself, and is an inevitable consequence of the evolution of living matter (10). In other words, chiral homogeneity developed as the molecular complexity of life itself developed, and the former was not a prerequisite of the latter. In 1957 Wald (11) suggested that the preferential incorporation of amino acids of one chirality into helical secondary structures of growing polypeptide chains might have been the original basis for chiral selection. Later theories postulate that D- and L-systems of organisms, unable to mate and frequently mutually antagonistic, arose on the racemic primitive Earth, and that eventually organisms of one chirality prevailed by the intervention of any one of a number of chance events. Such events include accidental changes in the environment favoring one system of organisms in their territorial competition (12), random mutations making one system inopera-tive (13), and random mutations allowing one system of organisms to develop a "killer enzyme" (e.g., a D-peptidase) which kills organisms of the enantiom-eric system (14). Recently it has been suggested (15) that all life developed from a common ancestor which already had its chirality selected by the chance intervention of environmental stresses or by "stylistic differences" favoring a particular chirality. It has been argued that the presence of the enzyme D-amino acid oxidase in certain contemporary organisms (11), as well as the rare occurrence of D-amino acids in the cell walls of certain bacteria (13) and antibiotics (14), support the concept that organisms of a competing D-system existed on the primitive Earth.

Biotic theories are fundamentally speculative and imprecise as to mechan-istic details, although a number are presented with elaborate mathematical analyses, which lend them notes of sophistication and authenticity. They are by nature not amenable to experimental verification, and are thus beyond

testing in any meaningful scientific sense. A fundamental criticism of the proposition that living matter predated chiral homogeneity on the primitive Earth was advanced by Avetisov and co-workers (5) in 1985. Recent elegant experiments (16) involving the template-directed (matrix) oligomerizations of nucleotides have shown that the formation of chirally pure polynucleotides is substantially dependent on the chiral purity of the monomers. This leads to the conclusion (5) that only a chirally pure medium can sustain the existence and development of self-replicating systems, and that even the simplest of these can originate only in a medium already possessing a high degree of chiral purity. This means that the origin of self-replicating systems, on which life depends, could have occurred only *after* a previous "global" symmetry breaking in the racemic environment of the primitive Earth.

III. ABIOTIC THEORIES

Abiotic theories assume that the homochirality and stereospecific molecular interactions characteristic of the current biosphere could not have originated without some initial asymmetric bias (albeit small) in the primordial molecular environment, and accordingly seek to find abiotic mechanisms whereby such small asymmetries might have been engendered by external or internal factors in the racemic milieu, and then have been subsequently amplified to magnitudes useful for biotic evolution. In such a scenario, life at its origin *already had available* chiral molecules possessing an enantiomeric homogeneity sufficient to allow their stereoselective evolution into the chirally pure higher structures characteristic of our present biota. Abiotic theories have been the subject of intensive theoretical and experimental investigations over the past two decades, investigations which have produced a number of definitive answers regarding the mechanisms studied.

A. Chance Mechanisms

Abiotic theories, in turn, fall into two subcategories, *chance* and *determinate* mechanisms. Chance mechanisms presuppose physical processes for symmetry breaking at the molecular level (i.e., processes capable of producing a net enantiomeric excess) which have an equal probability of affording either enantiomer (D or L) from the racemic or prochiral environment. In any given molecular event initiated by the process, either D or L is selected randomly. Determinate mechanisms, assume that some intrinsic internal or environmentally external *chiral physical force* acts on the racemic or prochiral primordial molecular milieu in such a way as to cause production of a preponderance of one of the enantiomers (i.e., causing $[D] \neq [L]$). In either

case, the randomly or deterministically selected small enantiomeric excess may then be amplified to a biotically useful magnitude by subsequent stereoselective mechanisms which we shall consider later. At this point we examine recent developments regarding both chance and determinate mechanisms.

1. Spontaneous Symmetry Breaking Models

If we flip a coin, it has a 50:50 chance of coming up heads (or tails). If we flip the coin 100 times, however, it does not necessarily come up 50 times heads and 50 times tails. It may be 54 heads and 46 tails, vice versa, or any other combination of positive numbers totaling 100. The deviation between the observed number of heads and that expected from chance is thought of as a "statistical fluctuation." When the number of flips is N, the expected number of heads will be $0.5 \times N$. As N becomes larger the statistical fluctuation becomes larger also, but the percentage fluctuation, that of (say) heads, relative to the expected, or the "relative statistical fluctuation," becomes smaller. Conversely, the smaller the number of flips, the larger will be the relative statistical fluctuation. The same is true of the random synthesis of D and L molecules from a prochiral precursor, or of allowing an exactly racemic mixture of D and L molecules to randomize by racemization. In all such cases we get a mixture that deviates from the "theoretical" 50:50 by a statistical fluctuation whose magnitude depends on the number of molecules (i.e., the number of "flips"). In 1932 Mills (17) calculated the mathematical probability of enantiomeric excesses arising by such statistical fluctuations. He showed that if 10^7 chiral molecules ($\approx 10^{-16}$ mol) were produced under random conditions, there was an even chance that the product would contain an excess of at least 0.021% of either enantiomer, and thus that it would be "practically impossible" to achieve a completely racemic product. Statistical fluctuations thus produce small and random enantiomeric excesses (defined as $([D] - [L])/([D] + [L])$, or %D − %L in the mixture). Spontaneous symmetry breaking models, mathematical and experimental, owe their existence to these random enantiomeric excesses arising from statistical fluctuations.

In 1953 Frank (18) first proposed a "life model" consisting of a chemical substance that was a catalyst for its own production and an anticatalyst for production of its enantiomer. Developing the kinetic equations for growth of such mutually antagonistic self-reproducing systems, he showed that they were fundamentally unstable and led eventually to the dominance of one enantiomer. Sixteen years later and apparently unaware of Frank's work, Calvin (19) introduced the concept of "stereospecific autocatalysis" and showed diagrammatically (Figure 1) that chirally pure materials result inevitably in such systems. In Calvin's scheme we have two rapidly equili-
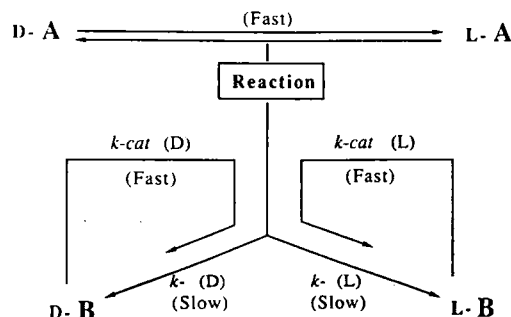
Figure 1. Stereospecific autocatalysis.

brating D and L enantiomers of reactant **A**, each of which is converted by some reaction into the corresponding enantiomers of product **B** at rates $k(D)$ and $k(L)$, which are slow. Product D-**B** can then act as a stereospecific autocatalyst for the formation of more D-**B** from D-**A**, and product L-**B** similarly catalyzes the formation of more L-**B**, each catalytic reaction proceeding at a much faster rate than the noncatalytic reaction (i.e., $k\text{-}cat(D$ or $L) \gg k(D$ or $L)$). Owing to statistical fluctuations, however, the enantiomeric reactants D-**A** and L-**A** will not be present in exactly equal amounts at the outset. If D-**A** is in slight excess, for example, it will form a slight excess of its product D-**B**, which will rapidly catalyze formation of more D-**B**. Because of the rapid equilibration of the reactants D-**A** and L-**A** and the slowness of the uncatalyzed reaction rates, the system will thus rapidly become entirely product D-**B**. In 1971 Seelig (20), unaware of either Frank's or Calvin's ideas, independently proposed a third system including autocatalytic reactions with similar feedback loops, and showed by a computer simulation that tiny asymmetries in the initial concentrations of reactants will flip the entire system into one enantiomeric state.

Following the publications of Frank, Calvin, and Seelig, a number of papers have appeared by several authors who have developed a variety of additional stochastic models for spontaneous symmetry breaking and evolution into chirally homogeneous states (21–24, 273). These mathematical models, essentially more sophisticated versions of the ideas presented above, are generally based on the kinetic behavior of hypothetical racemic systems that are inherently unstable and undergo symmetry breaking at some random "bifurcation point," then rush inevitably into a state of chiral purity. None of these models rests on any experimental basis (except possibly those

suggesting spontaneous resolution by crystallization, discussed below), and very few of the authors even suggest experiments which might test or support their models. The papers are generally replete with sophisticated kinetic equations and tend to be mathematically formidable for the nonspecialist, except for the lucid hydrodynamic analog of Buvet (25), which was developed because of this. It might be pointed out that the biotic theories discussed in Sect. II are additional examples of such symmetry breaking hypotheses, with spontaneous bifurcation occurring, however, only after life began.

Several authors recently presented convincing arguments against models wherein a small initial asymmetry resulting from statistical fluctuations is amplified into an eventual enantiomeric predominance. Czege and Fajszi (26) have developed a model, again assuming plausible starting conditions, in which small initial asymmetries in the system not only fail to amplify, but actually vanish. That two similar mathematical models with slightly different assumptions should lead to totally contradictory conclusions thus makes it questionable whether the earlier models have any relevance whatsoever for the origin of enantiomeric homogeneity. However, a number of actual experimental models for spontaneous symmetry breaking do in fact afford enantiomerically homogeneous chiral systems. They are examined in the following sections.

2. Spontaneous Symmetry Breaking on Crystallization

Racemic solids may crystallize from supersaturated solutions either as *racemic compounds* or as *conglomerates*. The more common racemic compounds contain an equal number of molecules of each enantiomer in the lattice of each crystal. The less common conglomerates consist of a mixture of crystals, which has an equal number of separate crystals of each enantiomer. The optical resolution of racemic compounds requires diastereomeric interactions, such as the use of resolving agents or chromatography on chiral phases. The resolution of conglomerates is more interesting both practically and prebiotically, since it can occur spontaneously during simple crystallization. If the resulting crystals are hemihedral and show left- and right-handed morphological characteristics, they are visually distinguishable and can be separated manually. This rare phenomenon allowed Pasteur in 1848 to perform the first optical resolution, that of racemic sodium ammonium tartrate, which crystallizes as a conglomerate below, and as a racemic compound above, a transition temperature of 27.2°C. The separate crystals of most conglomerates, however, are usually morphologically indistinguishable.

When a supersaturated solution of a racemic conglomerate is allowed to stand, it frequently deposits crystals of only one of its enantiomers. These can be separated carefully from the mother liquors, and an optical resolution thus

achieved. The process is a random one, however, and in a duplicate experiment the other enantiomer may equally well be deposited (3). However, the crystallization of one desired enantiomer from a conglomerate solution may usually be guaranteed by consciously "seeding" the solution with a crystal of the desired enantiomer. This technique has proved important for resolving a number of optically active compounds commercially (27, 28), and many ingenious experimental modifications of the seeding technique have been developed to augment the efficiency of the process (28).

Though rare compared to racemic compounds, which comprise over 90% of all racemates (29), the number of known conglomerates is nevertheless impressive. By 1981 Jacques et al. (30) had compiled an inventory of nearly 250 conglomerates, conveniently listing their melting points, structural formulas, the means by which they were characterized, and literature citations. The list includes random organic racemates containing from 1 to 38 carbon atoms (71%), salts and complexes of amino acids and their derivatives (18%), miscellaneous salts of organic acids and bases (6%), and organometallic or inorganic complexes (5%). Their thorough and scholarly treatise (30) should be consulted for information on all pertinent theoretical, experimental, and practical aspects of phenomena involving racemates and their means of resolution. Since completion of this inventory several additional examples of spontaneous resolution have been reported (31), including many new octahedral complexes of cobalt with bidentate ligands (32).

Spontaneous resolution by crystallization was early championed (3) as a likely mechanism for the origin of optical activity in nature, and such suggestions are still current (33). It remains today without question the most effective means of chiral symmetry breaking, and is the most economical route for preparing pure enantiomers on scales ranging from a few grams to tons (30).

3. "Total" Spontaneous Resolution

Spontaneous resolution during the crystallization of certain conglomerates, as discussed above, produces in a single operation at best less than 50% of the total material in the original racemate. However, if the uncrystallized enantiomers remaining in solution could rapidly equilibrate while the slower crystallization of one enantiomer was occurring, the *entire* racemate would obviously crystallize eventually as a single enantiomer. Such a process, recently called "total spontaneous resolution" (28), would clearly provide an example of Calvin's "stereospecific autocatalysis" model (19) for complete chiral symmetry breaking. Several such "total" spontaneous resolutions have been observed experimentally.
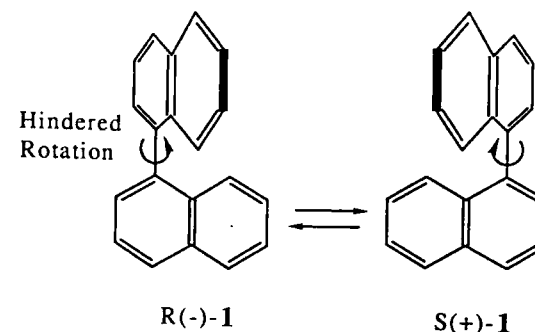

Figure 2. Enantiomers of 1,1'-binaphthyl (1).

Because of steric hindrance, 1,1'-binaphthyl (1) is subject to moderately restricted intramolecular rotation about its 1,1'-bond, and accordingly can exist as two enantiomers (Figure 2). These have specific rotations of $(\pm)$-245°, and half-lives for racemization in solution of *ca.* 15 min at 50°C. Racemic 1 may exist as a metastable low-melting (145°C) polymorph or a stable high-melting (159°C) polymorph. In 1971 Pincock and Wilson (34) discovered that racemic 1 underwent spontaneous resolution under three sets of conditions: (1) on allowing its supercooled melt to crystallize as the high-melting form; (2) on slowly heating the low-melting form to 145°C, where it melts to a metastable liquid which crystallizes as the high-melting form; and (3) on slowly heating the low-melting form to almost 145°C, where it undergoes a solid-state transformation to the stable high-melting form. In each case the high-melting form obtained was optically active, showing variable (+) and (−) optical rotations, and the analogy to Calvin's autocatalysis model was pointed out (34, 35).

A statistical study was then made (35) of the incidence and magnitude of the spontaneous optical activity produced. In 200 samples of spontaneously resolved 1 the specific rotations ranged from −218 to +206°, with the largest number having low rotations (± 2 to $\pm 48°$). The observed rotations fitted a Gaussian distribution curve, with a mean of $+0.18 \pm 86.4°$. Thus nucleation of the enantiomers of 1 was a random process, giving a symmetrical distribution of (+) and (−) rotations and a mean of $\approx 0.0°$. Subsequent studies were conducted (35, 36) to assess the effect of optically active impurities on the random nucleation of pure 1. Some 18 different contaminants (including D and L pairs) were studied at various concentrations up to 30% by weight. Some impurities showed no effect, while others imparted an asymmetric bias to the spontaneous resolution of 1. D- and L-mandelic acid gave comparable

opposite effects, while other D and L pairs gave the same effect, suggesting that unknown contaminants of overriding power might be present and influencing the results. Pincock and co-workers later investigated the solid-state resolution of **1** mechanistically (37), as well as the spontaneous resolution of 4,4'-dimethyl-1,1'-binaphthyl (38) and the solid-state resolution and racemization of 4,4'-diamino-1,1'-binaphthyl (39). Earlier examples of "total" spontaneous resolutions are those of N-methyl-N-ethyl-N-allylanilinium iodide (3) and tri-o-thymotide (3, 40). Each is obtained in optically active form by slow crystallization from a solution which remains virtually racemic.

4. Lattice-Controlled Reactions in Chiral Crystals

The first instance of a chiral crystal lattice directing an asymmetric synthesis to yield an optically active product was reported by Farina and co-workers in 1967 (41). All-*trans* perhydrotriphenylene (**2**) has no alternating axis of symmetry, and can be resolved into its enantiomers. Racemic **2** forms an inclusion compound with *trans*-1,3-pentadiene (**3**), which on irradiation in the solid state with γ rays affords an isotactic polymer of *trans*-1,3-pentadiene (**4**). When an inclusion compound was prepared from **3** and $R(-)$-**2**, then irradiated, the polymer **4** showed an unambiguous (+) optical rotation, opposite to that of $R(-)$-**2**. An opposite effect was obtained using $S(+)$-**2**. Thus optical activity was produced under "rather primitive and scarcely

2

3

4
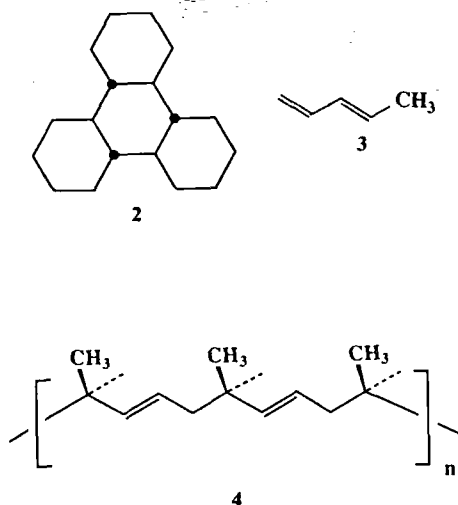
selective conditions." Similar results were obtained on γ irradiation of inclusion compounds of *cis*- or *trans*-**3** with deoxycholic acid (41).

Shortly thereafter, Penzien and Schmidt (42) provided a second example of a lattice-controlled solid state asymmetric synthesis. 4,4'-Dimethylchalcone (**5**) crystallizes as enantiomeric crystals. When individual monocrystals were exposed to bromine vapor, an optically active dibromo product (**6**) was obtained having a maximum, $[\alpha]_D^{28} = +9.8°$, corresponding to an optical yield of 6%. Products of either sign of rotation were noted.

5

6
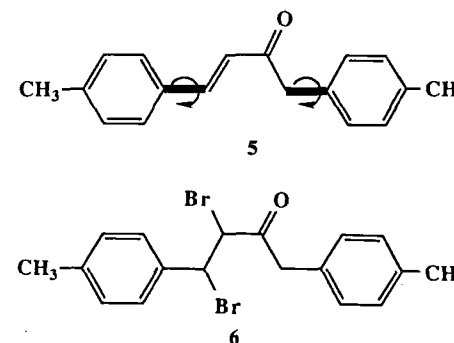
In 1974 Green and Heller (43) reinvestigated the bromination of **5**. In solution or in the melt, rotation about the emphasized single bonds in **5** cause rapid interconversion between right- and left-handed enantiomeric conformations. In the crystals, however, the conformations are frozen, and cannot interconvert. Also, in the chiral crystals of **5**, all molecules in any single crystal have the same conformation. Since polycrystalline samples of **5** contain both crystal chiralities in random proportions, the optical rotation of dibromide **6** was found to vary randomly in both sign and magnitude. However, when **5** was crystallized along with 3.97 mol % of optically active dibromide (+)-**6**, bromination of the mixture afforded only the (−)-**6** product. Opposite results were noted using 3.97 mol % (−)-**6**, only the (+)-**6** product now being obtained. Thus a small amount of the chiral product **6** induced crystallization of **5** in such a way as to produce exclusively **6** of the opposite chirality sense. Ignoring this observed "inversion effect" (Sect. IV-C), the authors then proposed the following autocatalytic mechanism for the origin of homochirality. A racemic material whose enantiomers interconvert in the liquid state crystallizes into a chiral crystal structure, which undergoes a solid-state

reaction to give a chiral product. The product, nonracemizable in the liquid state, then induces further crystallization of the reactant into that crystal chirality which yields more product of the same chirality.

Another novel lattice-controlled asymmetric synthesis involves a $[2\pi + 2\pi]$ photocycloaddition reaction within a two-component single crystal made up of two 1,4-diarylbutadienes (44). The 1,4-diaryl-1,3-butadienes 7 and 8 undergo solid-state photocycloadditions to form the dimers 9 and 10, respectively (Figure 3). Compounds 7 and 8 are isomorphous, and when their

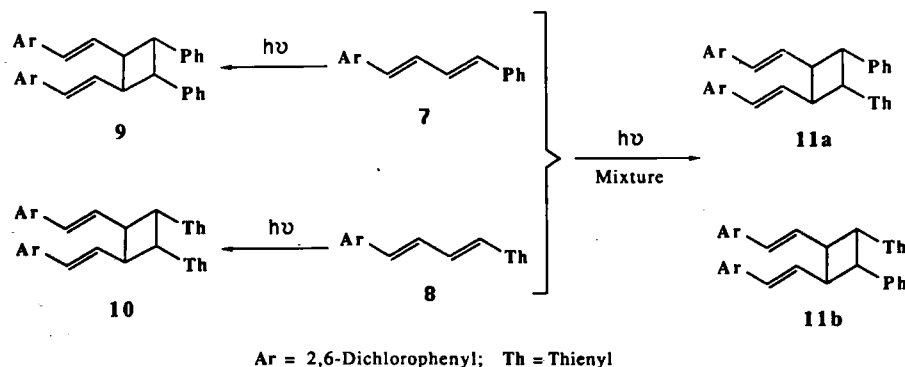Ar = 2,6-Dichlorophenyl; Th = Thienyl

Figure 3. Asymmetric photodimerization of 1,4-diarylbutadienes.

1:1 mixture is cooled from a melt or crystallized from ethanol, mixed crystals are formed. On irradiating a polycrystalline sample of such mixed crystals (using appropriate filters such that the formation of the homodimers 9 and 10 are minimized), the racemic mixed dimer 11a,b results. A large *single* mixed crystal containing 85% 7 and 15% 8 was then prepared, powdered, and irradiated. The resulting dimer 11 was consistently optically active, with $[\alpha]_D$ randomly $\sim \pm 1.0°$.

In 1975 Addadi and co-workers, again using $[2\pi + 2\pi]$ topochemical photocycloadditions, reported (45) the first asymmetric synthesis of chiral dimers and polymers by a lattice-controlled reaction in a *one-component* chiral crystal, and the first such synthesis in a crystal of racemic composition. An optically pure polycrystalline sample of the divinyl monomer 12, having a chiral s-butyl group in one of its vinyl sidechains, was irradiated ($\lambda > 300$ nm) to give a dimer plus low- and higher-molecular-weight polymers (13) which were separable by chromatography (Figure 4). The dimer and low-molecular-weight polymer were optically active, with rotations *opposite* in sign to that of the starting monomer 12. That this asymmetric synthesis was not due to the chirality of the s-butyl groups in the monomer was shown as follows.

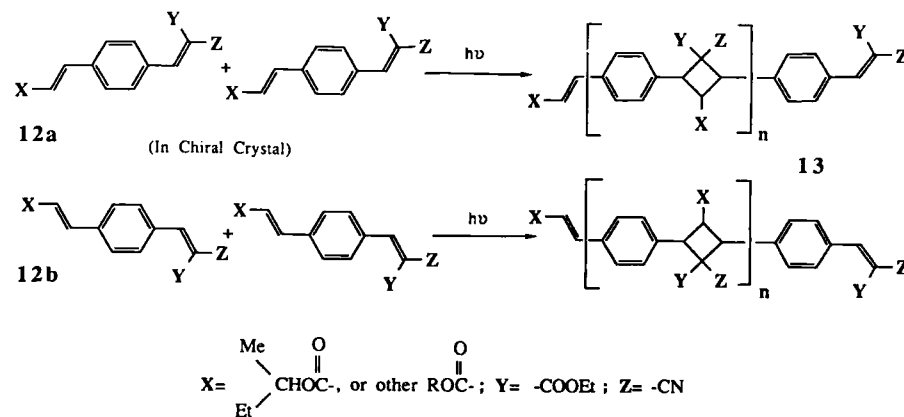Figure 4. Asymmetric polymerization in enantiomeric monomer crystals.

Racemic 12 does not spontaneously resolve on crystallization, but gives a solid solution of the two enantiomers. With its chiral handles (X) randomly arranged, each enantiomeric single crystal of racemic 12 has equal numbers of Xs of opposite chirality, and each enantiomer has an equal probability of crystallizing. A large crystal of racemic 12, which was optically inactive in solution, gave on irradiation a mixture of products having $[\alpha]_D^{25} = -24°$. Thus the dimer and polymer products owed their optical activity to the backbone configuration of the crystal lattice of the racemic monomer. It was subsequently shown that the irradiation of optically pure (S)-(+)-12 or (R)-(−)-12 crystals also led to chiral dimers, trimers, and oligomers in quantitative (>97%) enantiomeric yield (46). Extension of such studies to include *achiral* monomers similar to 12 (X=i-Pr, 3-pentyl) again led to polymers of high optical purity (47). Solid-state photodimerization reactions have also been used ingeniously for the enantiomeric purification of several 1-arylethanols (48). The principles behind such topochemical reactions in the crystalline state have been reviewed extensively (49). Later attempts by Addadi and co-workers to use their photodimerization–polymerization reactions in an autocatalysis scheme which might be a model for the origin of chirality are described in Sect. IV-C.

5. Reactions in Cholesteric Phases

In 1975 Saeva and co-workers (51) first described a "lattice-controlled" reaction using, instead of chiral crystals, the *anisotropic* ordering of a solute in a liquid crystal mesophase, which then directed an asymmetric synthesis not

possible in an isotropic medium. In a cholesteric mesophase there exists a "superchiral" environment, with a macroscopic helical structure formed by the chiral organization of "nematic-like" layers having uniaxial molecular rearrangement within the layers. It was expected that this ordering might induce an achiral solute in the mesophase to react asymmetrically. The authors conducted a Claisen rearrangement of γ-methallyl-*p*-tolyl ether (**14**) at 200°C in a mesophase formed from a mixture of 5% **14** in 95% cholesteryl *p*-nitrobenzoate. The 2-(α-methallyl)-4-methylphenol product (**15**) was shown

14   **15**
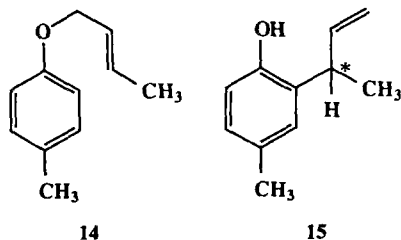
by its circular dichroism to be optically active, but no optical yield was reported. The effect was not observed with 30% of **14** in the mixture, indicating that the chirality of the cholesteryl *p*-nitrobenzoate itself was not responsible for the asymmetric effect observed.

A second example was provided 3 years later by Nakazaki and co-workers (52), who irradiated a mixture of 1% by weight of 2-styrylbenzo[c]phenanthrene (**16**) and a trace of iodine in a mesophase consisting of a 3:2 mixture of cholesteryl nonanoate and cholesteryl chloride, using ultraviolet light at


16   **17**
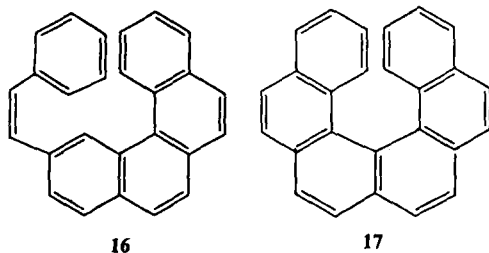
23°C. The hexahelicene (**17**) product obtained had $[\alpha]_D^{23}$ +40°, corresponding to an optical yield of 1.1%. When the photocyclization was conducted at 55–60°C, slightly above the cholesteric–isotropic liquid transition temperature, the product was optically inactive, suggesting that the macrostructural

chirality of the mesophase was responsible for the asymmetric synthesis. Similar results were obtained with a cholesteryl benzoate liquid crystal at 145–150°C, and with other cholesteric mesophases (212).

Several additional examples of asymmetric transformations occurring in cholesteric liquid crystals were subsequently reported. These include the decarboxylation of ethylphenylmalonic acid (**18**) in cholesteryl benzoate at 160°C to obtain *R*(−)-2-phenylbutanoic acid (**19**) ($[\alpha]_D^{27} = -14.2°$; 18% e.e.) (53), the transformation of a racemic mixture of sulfoxide enantiomers into mixtures with one enantiomer in up to 9.2% excess (54), and the Hofmann elimination pyrolysis of trimethylcyclooctylammonium hydroxide (**20**) in several new mesophases, to yield *R*(−)-*trans*-cyclooctene (**21**) in up to 7.2% e.e. (55).

18   **19**

20   **21**
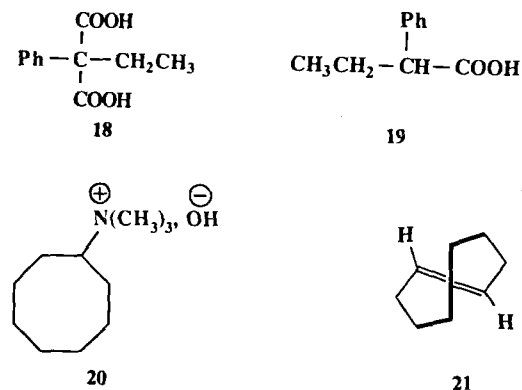
In 1979 Eskenazi et al. (56) attempted the photocyclizations of α-(*N*-methylanilino)styrene (**22**) to *N*-methyl-2-phenylindoline (**23**) and of the nitrone **24** to the oxaziridine **25** in a number of cholesteric mesophases. Since the products **23** and **25** proved to be optically inactive, an attempt was made

22   **23**

24   **25**
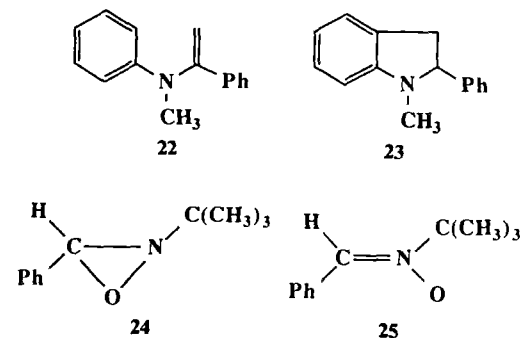
to duplicate the earlier claims of successful asymmetric conversions involving **14** (51), sulfoxides (54), and **18** (53). In no case was any significant optical activity observed in the products obtained. The authors concluded that the previously reported high optical rotations in these experiments were probably due to contamination of the isolated products with residual cholesteric material, and that "the effect of mesomorphic anisotropic ordering on asymmetric induction remains to be clearly established."

6. Asymmetric Adsorption on Quartz

The silica mineral quartz is frequently found in nature in well-defined crystals having either a right- or left-handed morphological handedness, and an optical rotation of $(\pm)21.72°$ mm^{-1} along the optical axis for 589-nm light. As early as 1938, Karagounis and Coumoulos, after reporting the partial resolution of a racemic chromium complex by adsorption on optically active quartz crystals, suggested that such adsorption of racemates by chiral inorganic minerals might have constituted a mechanism for the origin of optical activity in nature, a view later championed by Bernal (3). In 1938, however, Amariglio and co-workers were completely unsuccessful in their attempts to repeat the dozen or so earlier reports in the literature describing resolutions on chiral quartz crystals, and accordingly concluded that the earlier positive findings were erroneous and due to one or more of several artifacts involving the polarimetric observation techniques employed (57). Thus in the early 1970s the validity of the phenomenon of asymmetric adsorption on chiral minerals was an open question, as was its possible relevance in primordial chiral symmetry breaking.

This ambiguity was addressed in 1974 by Bonner and co-workers (58), who used a method not relying on the polarimetric observation of optical rotation to assess the possible occurrence of asymmetric adsorption. The alternative technique, which involved the use of radioisotopically labeled substrates, was designed to circumvent the artifacts enumerated by Amariglio (57). The radioactivities of very dilute (2×10^{-5} M) solutions of ^{14}C- and ^{3}H-labelled D- and L-alanine hydrochlorides in anhydrous dimethylformamide were measured before and after equilibration with finely powdered d- and l-quartz under scrupulously anhydrous conditions. The difference in radioactivity count before and after equilibration then gave a direct measure of the total amount of labeled alanine adsorbed, and the difference in the fraction of D- and L-alanine adsorbed gave an indication of the asymmetric bias in the adsorption process. In 10 independent replicate experiments, the total adsorption of alanine by the quartz was some 20–30%, and l-quartz preferentially adsorbed L-alanine and d-quartz D-alanine, the "differential adsorption" ranging from 1.0 to 1.8%. These observations were later confir-

Table 1
Asymmetric Adsorption of DL-Alanine Hydrochloride by d- and l-Quartz

	Labeled Enantiomer in Racemate	
	D	L
1. Stock solution (counts)	82570	172626
2. Supernatant over l-quartz (counts)	64976	133185
3. Supernatant over d-quartz (counts)	60250	146477
4. % Adsorbed by l-quartz[a]	21.3	22.8
5. % Adsorbed by d-quartz[b]	27.0	15.1
6. Total racemate adsorbed (%)[c]	48.3	37.9
7. Differential adsorption (%)[d]	−11.8	20.3

[a] $100 \times$ (No. 1–No. 2)/No. 1.
[b] $100 \times$ (No. 1–No. 3)/No. 1.
[c] No. 4 + No. 5.
[d] $100 \times$ No. 4/No. 6 − $100 \times$ No. 5/No. 6.

med using an artificially prepared D,L-alanine hydrochloride sample, with a ^{14}C label on the D- and a ^{3}H label on the L-alanine enantiomer, which could be counted separately. As illustrated in Table 1, the total DL-alanine adsorbed in these experiments was 38–48%, and the differential adsorption [defined as (% adsorbed on d-quartz − % adsorbed on l-quartz)/total adsorbed] was 11.8–20.3%. Moisture in the system led to a lack of adsorption or to nonreproducible results. The studies described above constituted the first unambiguous demonstration that d- and l-quartz actually do show asymmetric adsorption, and in fact do so with a "prebiotically realistic" substrate.

Kavasmaneck and Bonner (59) later investigated the quartz asymmetric adsorption phenomenon for its mechanistic details, using other amino acids and other amino acid derivatives. The isopropyl ester (**26**), the N-trifluoroacetyl (N-TFA) derivative (**27**), and the N-TFA isopropyl ester derivative (**28**) of

$$CH_3-CH-COOCH(CH_3)_2$$
with NH$_2$ on the CH
26

$$CH_3-CH-COOH$$
with NHCOCF$_3$ on the CH
27

$$CH_3-CH-COOCH(CH_3)_2$$
with NHCOCF$_3$ on the CH
28