3 Chirality and the Origin of Homochirality

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3.1 Chirality: Basic Concepts

> "I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself".

This definition of chirality was given by Kelvin in May 1893, at the time of a conference of the Oxford University Junior Scientific Club (Kelvin, 1904). The definition was illustrated by the following comment:

> "Two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally similar or allochirally similar (but heterochirally is better). These are also called "enantiomorphs", after a usage introduced, I believe, by German writers".

The hand as metaphor is deeply rooted in the history of stereochemistry. (The term chiral derives from the Greek *cheir*, hand.) As Mislow (1996) has pointed out, Kelvin's geometric definition of chirality is equivalent to that given many years later by Vladimir Prelog in his 1975 Nobel Prize lecture:

> "an object is chiral if it cannot be brought into congruence with its mirror image by translation or rotation."

This is now the commonly accepted definition of chirality.

Every object must be either chiral or achiral and, if it is chiral, it can exist a priori in two non-superposable mirror image, i.e., enantiomorphic/enantiomeric forms. Symmetry group theory provides a mathematical criterion by which it can be unequivocally determined whether an object is chiral or achiral. The criterion is expressed as follows: an object is achiral if, and only if, it possesses an improper axis of rotation of the order n. The symmetry operation associated with this element of symmetry corresponds to a rotation of $360°/n$ around the axis, accompanied by reflection in a plane perpendicular to the axis (see Fig. 3.1).

Here S_1 corresponds to a plane of symmetry (σ) and S_2 corresponds to a center of inversion (i). On the other hand, S_4 does not have an equivalent notation. Occasionally one still finds in the chemical literature the formal criterion stated incorrectly by referring only to the absence of a center and plane of symmetry.

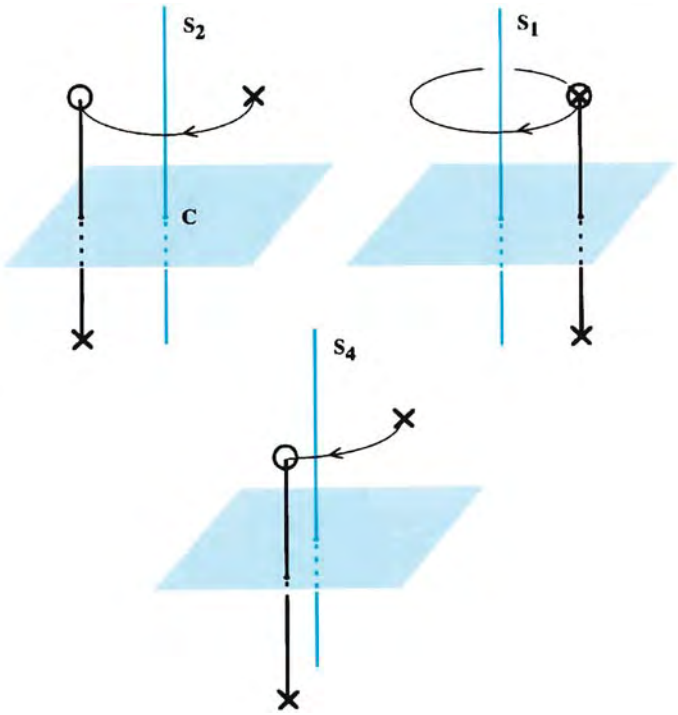

Fig. 3.1. The operations S_1, S_2, and S_4 performed on a material point, X, i.e., rotation about an angle $360°/n$ ($n = 1$ for S_1, $n = 2$ for S_2 and $n = 4$ for S_4) accompanied by reflection in a plane perpendicular to the axis

Nevertheless, it is true that molecular chirality is most commonly due to the absence of a center and (or) planes of symmetry.

A tetrahedron whose four vertices are rendered different, for example by numbering as in Fig. 3.2, is a chiral object of particular interest in chemistry. Indeed, if the center of the tetrahedron is occupied by an atom, for example a carbon atom, and the vertices correspond to different atoms or different groups of atoms bonded to the central atom, the central atom is said to be *asymmetric*. The exchange of two atoms or groups generates the enantiomer, i.e., the nonsuperposable mirror image structure. This is the significant property of the asymmetric tetrahedron from the chirality point of view. The chirality of the molecules found in living things is due to the fact that they contain one, or sometimes many, four-bonded carbon atoms that are asymmetric in this way.

Geometrical chirality can be discussed in spaces of any dimension. The chemist is generally interested in three-dimensional space (E^3) although work of the Mislow group at Princeton has also been directed to quantification of the geometrical chirality of two-dimensional objects such as triangles (Auf Der Heyde et al., 1991; Buda and Mislow, 1991; Buda et al., 1992; Mislow, 1997).

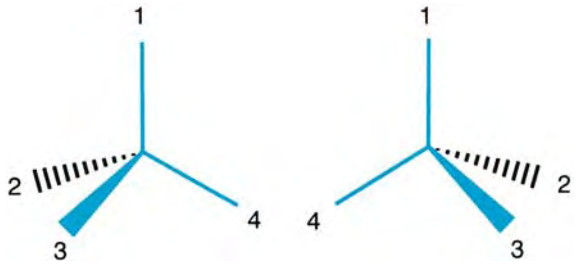

Fig. 3.2. An asymmetric tetrahedron: a chiral object of particular importance in chemistry

Very recently, the problem of the most chiral triangle has been considered by Rassat and Fowler (2003) using a very elegant approach based on quantum mechanics (calculation of eigenfunctions of the Schrödinger equation for the particle confined to an equilateral triangular box).

Two-dimensional space is also of interest because one must often represent a three-dimensional object as a two-dimensional picture, for example, on a page (see Fig. 3.3). Certain rules for handling these representations are imposed by the fact that two enantiomeric objects in two-dimensional space can become congruent (superposable) after passage through three-dimensional space.

Thus it is necessary to be careful in the use of the two-dimensional Fisher projection. For example, if one wishes to determine whether two Fisher projections correspond to the same molecule or, instead, represent two enantiomers, one must test their congruence by translations and rotations only within the plane in which they are represented and not move one or the other through the third dimension.

When the object is a molecule, the Kelvin–Prelog definition remains valid even though molecular objects have some unique properties relating to their dynamics (Mislow, 1997).

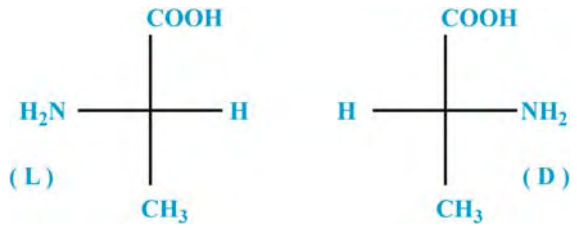

Fig. 3.3. Fisher projection of the two enantiomers of alanine. By convention, the two atoms or groups of atoms (here H and NH_2) at the ends of the *horizontal line* (*bonds*) are viewed as being in front of the plane of the page and the two groups of atoms at the ends of the *vertical line* (here COOH and CH_3) are viewed as being behind the plane of the page. The asymmetric carbon atom is not explicitly shown but is understood to be located at the intersection of the lines

For example, the methane molecule (CH_4) is commonly described as a tetrahedral structure. However, it is sometimes necessary to consider the variations from this ideal structure that can result from motions of the C–H bonds. In reality, the regular tetrahedron is a model that describes the average structure of a great number of methane molecules at any moment (or the average structure of a particular methane molecule taken over time). However, if one were able to photograph, using an infinitely short exposure time, a collection of methane molecules, one would see that only a very small number of them are regular tetrahedrons. The majority of the molecules would be seen to have atomic configurations that are chiral. Of course, one would see among them, in equal numbers, the enantiomeric configurations as well.

An equimolar mixture of enantiomers (molecules that differ only because they are of opposite chiralities) is called a racemic mixture. The term "racemic" was first used by Gay-Lussac to designate an organic acid that lacked optical activity but was of identical composition to optically active tartaric acid (Racemic comes from the Latin, *racemus*, bunch of grapes). Pasteur later showed racemic acid to be composed of equal amounts of the two enantiomers of tartaric acid (see Sect. 3.3) and the term racemic subsequently came to be used as a descriptive term for any such equimolar mixture of enantiomers. This definition is subject to some qualification on the basis of statistical variation, a subject that will be discussed further in Sects. 3.7 and 3.10.

It is important to note that some molecules do not contain asymmetric atoms and owe their chirality to an overall structure that is helical and thereby asymmetric. Although the homochiral molecules isolated from living things owe their chirality primarily to the presence of one or several asymmetric carbon atoms, some biopolymers (proteins, polysaccharides, and DNA) that have asymmetric carbon atoms in their monomeric units (amino acids, sugars, and deoxynucleotides, respectively) also adopt helical conformations. Interestingly enough, at the macromolecular level a hypothetical right helix and a hypothetical left helix made of the same chiral subunits would not be enantiomers but diastereoisomers.

The chirality we have been concerned with up to this point is observed in objects for which the formal interconversion of one enantiomeric form to the other can be carried out by an inversion of space (denoted P), compared to a fixed arbitrary origin. The effect of this inversion is identical to a reflection in a plane mirror. This geometrical chirality does not depend on the overall motion of the object; however, there is another type of chirality associated with movement. An example is a half-cone rotating around its axis. In this case, the inversion of time (operation T), which consists of replacing "t" by "$-t$" and reversing the direction of the movement, transforms the dynamic chiral object into its image. On this basis, Barron (1982) introduced a distinction between "true" chirality and "false" chirality. "False" chirality is associated with objects, like the half-cone example, for which the object-image interconversion can be carried out, not only by inversion of space, but also by inversion of time (followed eventually by rotation in space). Within the framework of this chapter we shall

deal only with "true" chirality; however, we must point out that true chirality can be associated with movement (and thus time), for example, in the case of circularly polarized radiation. Indeed, using a wave description, the electric field vector (just like the magnetic field vector) of circularly polarized radiation describes a helix. This helix is palindromic, i.e., the horizontally oriented helix is identical whether traversed left to right or right to left. Thus the inversion of time (which corresponds to the inversion of the direction of the propagation of the light) does not modify the sign of the helicity. On the other hand, the inversion of space transforms right-circularly polarized radiation into left-circularly polarized radiation, i.e., radiation opposite in the sign of its helicity. Thus, one can conclude that circularly polarized radiation possesses true chirality.

In this context, linearly polarized radiation can be described, figuratively, as "racemic" radiation since it is composed of both right-circularly polarized and left-circularly polarized radiation. When such racemic radiation traverses a chiral medium, one of the circularly polarized components is propagated less rapidly than the other and the plane of the polarized light beam is rotated; this phenomenon is called optical rotation (or optical rotatory dispersion when the optical rotation is measured as a function of wavelength). In addition, if the medium is chromophoric, one of the two circularly polarized components is absorbed more than the other, which results in the phenomenon of circular dichroism. The individual enantiomers of chiral compounds differ only with respect to the signs associated with these optical phenomena and have otherwise identical physical and chemical properties except, of course if they interact or react with other homochiral molecules (see Sect. 3.2).

Before ending this section, it may be useful to describe the ways in which enantiomers are specified. In the past, it was usual to designate them with (+) and (−) symbols or with the letters *d* (dextrorotatory) and *l* (levorotatory) preceeding the name of the chiral compound. The former was simply the sign of the optical rotation measured with light of the wavelength of the sodium D-line emission. According to a suggestion of Fisher, the D and L nomenclature was based on the relationship between the asymmetric centers of the enantiomers in question and that of a chiral reference compound, the glyceraldehyde of (+) optical rotation (at the D-line wavelength of Na), which Fisher designated D-glyceraldehyde. This assignment depends on the ability to chemically transform the enantiomer into glyceraldehyde. For example, the amino acid serine can be converted to glyceraldehyde by a series of reactions that does not affect the configuration of the groups attached to its asymmetric carbon atom. The product was found to be (−)glyceraldehyde, the levorotatory enantiomer, and thus natural serine is designated L-serine (see Fig. 3.4). The D/L nomenclature is well established for the sugars and amino acids and their derivatives and will be used in this chapter. In Fig. 3.3 the enantiomers of alanine are designated in this way.

In 1950, it was shown by X-ray diffraction carried out by the Bijvoet group that the configuration arbitrarily assigned by Fisher to D-glyceraldehyde was correct (there was a 50% chance!) and since then the D/L nomenclature also

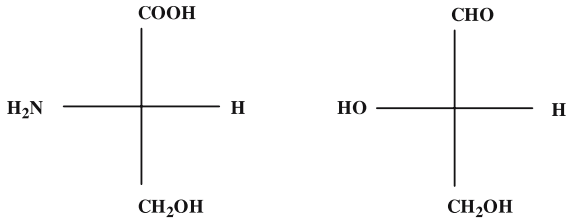

Fig. 3.4. Fisher projection of L-serine and L-glyceraldehyde

correctly denotes absolute configuration. Today, the configurations of chiral molecules are most commonly described by the Cahn–Ingold–Prelog (CIP) system recommended by the IUPAC (International Union of Pure and Applied Chemistry). This nomenclature, which is independent of any measurement of optical rotation, absolutely defines the configuration of every asymmetric center (stereocenter) in a molecule and designates each one as S or R (sinister or rectus).

The reader interested in a concise introduction to stereochemistry and molecular chirality is referred to Mislow (1965). One will find an exhaustive treatment of these subjects in Eliel and Wilen (1994).

3.2 Reactivity of Chiral Molecules

The behavior of chiral molecules when they are not alone is an important consideration. Chemists and biochemists are frequently interested in molecules when they interact (or react) with other identical or different molecules and models are necessary that allow the properties of such sets of interacting molecules to be described. A molecule that is achiral when it is alone can become chiral when it interacts with a chiral molecule. An extreme case is the "chiralisation" of xenon atoms trapped in a chiral molecular cage (Bartik et al., 2000, 2001).

Neglecting for the moment the very small differences in energy due to violation of parity (discussed in Sect. 3.8), two enantiomers have the same internal energy and are characterized by identical reactivity if the second reactant is achiral. What is true for a covalent bond making/breaking chemical reactions is also true for weaker intermolecular interactions if the interaction is with an achiral material. However, for the same reason that a right foot slides easily into a right shoe and with some difficulty into a left shoe, the reaction/interaction will occur at different rates for enantiomers if the molecule with which it reacts/interacts is itself an enantiomer. Enantiomers D1 and L1 will react with reactant D2 with different rates. The interacting pairs (D1–D2) and L1–D2), whether they are dissociable complexes, reaction transition states, or stable molecules, are called *diastereomers*, meaning that they are stereoisomers (but not enantiomers) and therefore have different internal energies and different properties. The symbols

1 and 2 are not necessarily meant to indicate different molecules: they may be the same or they may be different.

The work of Blount and Idelson (1956) presents an interesting example. They observed that the polymerization of a glutamic acid derivative occurs 20 times faster starting with molecules of the same chirality (only D–D or L–L reactions) rather than with a racemic mixture (D–L and L–D reactions can occur). Matsuura et al. (1965) found that the partial polymerization of a reactive derivative of alanine having a small enantiomeric excess led to an increased enantiomeric excess in the polypeptide products, i.e., they showed that these differences in reactivity could be used to enhance the enantiomeric excess in the product. This is an example of a kinetic resolution (Kagan et al., 1988). The term "resolution" in this context means a process allowing the separation of enantiomers. The possible importance of such processes to the origin of homochirality will be examined in Sect. 3.10. Molecular-recognition processes, which are of enormous importance in biology, are frequently highly chirospecific when both the ligand and the binding molecule are chiral. They represent examples of diastereomeric interactions in which one is generally unfavorable to the point of insignificance. For example, the transport of D-glucose through the membrane of the red cell is facilitated by a chiral transport molecule, a protein.

L-glucose is essentially not recognized by this protein and thus its only mode of penetration into the red blood cell is by unfacilitated diffusion, a much slower process (Rawn, 1989).

3.3 Pasteur and the Discovery of Molecular Chirality

The crystallization of chiral compounds provides many interesting examples of the interaction of homochiral or heterochiral molecules. In fact, it was Pasteur's careful studies of crystals of sodium-ammonium paratartrate that led to the discovery of molecular chirality. Tartaric acid obtained from wine was known to have optical rotation, whereas paratartaric acid lacked optical activity but seemed identical to tartaric acid in all other respects.

In Pasteur's notebooks (Valléry-Radot, 1968), one finds this description of his separation of the enantiomorphic crystals he obtained by crystallization of the sodium-ammonium salt of paratartaric acid.

> "The happy idea came to me to just orient my crystals in a plane perpendicular to the observer, and then I saw that in this confused mass of crystals of paratartrate there were two kinds of them with respect to the distribution of the asymmetric facets. In the one case, the facet of asymmetry close to me was inclined on my line, relative to the plane of orientation of which I spoke, while the others, the asymmetric facet was inclined to my left. In other words, the paratartrate presented itself as formed of two kinds of crystals, one asymmetric to the right, the other one asymmetric to the left. A new idea, very naturally, soon came

to me. The crystals, asymmetric to the right, that I could manually separate from the others, were absolutely identical in form to those of right tartrate".

Pasteur had made a simple discovery with profound implications. He had found that paratartaric acid was a racemic mixture of D- and L-tartaric acids (see Fig. 3.5) but, more importantly, he had shown for the first time that a single organic compound can exist in two forms that differ in the sign of optical rotation and, underlying this, in their molecular asymmetry. The exact nature of this asymmetry was unknown at the time although, according to Mislow (1996), Pasteur explicitly considered that it might be due to an asymmetric tetrahedral arrangement of atoms. It was left to van't Hoff and Le Bel to fully develop the idea that tetrahedral carbon atoms bounded to four different proups are the basis for the chirality of organic molecules such as the tartaric acids and their salts.

The structures of D- and L-tartaric acid are shown in Fig. 3.5. It can be seen that tartaric acid has two asymmetric carbon atoms and, because of this, its stereoisomerism is a little more complicated than we have seen thus far. In the D- and L-tartaric acids, the two asymmetric carbon atoms are of the same configuration (two "right hands" in one case, two "left hands" in the other); however, there exists another form, known as mesotartaric acid, in which the two asymmetric carbon atoms have opposite configurations (one "left hand" and one "right hand"). Consequently mesotartaric acid is optically inactive as a result of internal compensation, that is, the chirality associated with one asymmet-

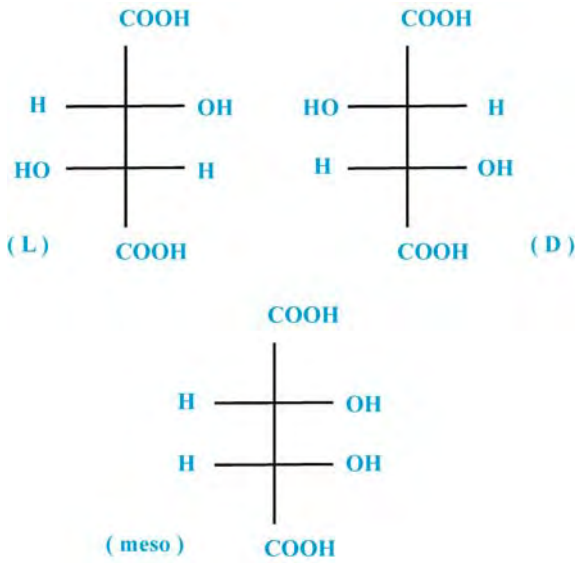

Fig. 3.5. L- and D-tartaric acid and mesotartaric acid in Fisher projection (mesotartaric acid is achiral and is not represented as a mirror image since it is identical)

ric carbon atom is exactly compensated intramolecularly by the chirality of the other asymmetric carbon atom. One might think of mesotartaric acid as being analogous to a right hand and a left hand coupled palm against palm. In contrast to the internal compensation observed in these meso compounds, one can consider a racemic mixture, such as paratartaric acid, as optically inactive due to "external" compensation since the compensation results from the presence of opposed chiralities in different molecules present in equal numbers.

Readers who are interested in the respective roles of Pasteur, van't Hoff, and Le Bel in establishing the foundations of stereochemistry will read with interest the special review volume of Tetrahedron published in 1974 on the occasion of the 100th anniversary of the publication of the work of van't Hoff and Le Bel. The preface to this volume (Robinson, 1974) and an article by Mason (2002) make apparent the pioneering role that Pasteur played in 1860. An article by Lardner et al. (1967) also furnishes information on historical aspects of the chemistry of tetrahedral carbon.

3.4 Crystals and Crystallization

Pasteur's discovery resulted from a combination of exceptional scientific ability and a stroke of good luck. Indeed, the crystallization of a racemic mixture is not always accompanied by enantiomer segregation into enantiomorphic crystals, a process that is unfavorable from the entropic point of view. Generally, molecules of opposite chiralities crystallize together to give a single type of crystal, i.e., a crystal racemate that does not allow separation of the right- and left-handed molecules. Also, the temperature of crystallization is a sensitive factor in determining the type of crystals obtained and this is particularly true in the case of the crystals studied by Pasteur.

Mason (1982), Jacques et al. (1981), Collet (1980), and Collet (1990) thoroughly discuss the question of crystallization of mixtures of enantiomers, the phase diagrams of these mixtures, and the reasons why the crystallization of a racemic mixture more frequently gives crystals of the racemate rather than a conglomerate of crystals composed individually of only one enantiomer. According to Collet (1990), only approximately 10% of racemic mixtures crystallize in the form of conglomerates.

While considering the crystallization of chiral molecules, it is important to note that some achiral molecules can form chiral crystals, which can exist as enantiomorphs. A well-known example is quartz, in which the macroscopic chirality of the crystals arises from the helical arrangement of the achiral SiO_2 units of which they are composed (see Fig. 3.6). On a global basis quartz is racemic, a conclusion based on examination of 27,053 quartz crystals (Frondel, 1978).

There are several examples (see Bonner, 1996) of achiral substances that, on crystallization, give enantiomorphic conglomerates. For example, sodium chlorate ($NaClO_3$), when crystallized from supersaturated solutions without agitation, always gives a conglomerate in which there are equal numbers of right and

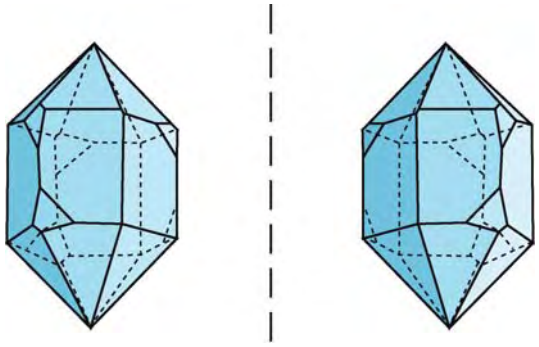

Fig. 3.6. Enantiomorphic crystals of quartz

left crystals. On the other hand, when crystallization is brought about with agitation, sometimes right crystals predominate and sometimes left crystals (Kondepudi et al., 1999). In this case, each experiment gives a spontaneous symmetry breaking, a spectacular phenomenon in which an achiral solution yields a crystalline solid in which the crystals are homochiral! The interpretation of these observations is straightforward: primary nucleation leads to formation of the first chiral crystal and this crystal is then broken by agitation. The fragments, dispersed in the liquid phase, serve as crystallization nuclei and induce secondary crystallization leading, by a cascade effect, to a symmetry breaking (McBride and Carter, 1991). As in the case of quartz, sodium chlorate has been the subject of many studies aimed at showing statistically that the number of right crystals is equal to the number of left crystals. Such crystal counts might at first seem trivial but, as we will see in Sect. 3.8, this is not the case. They aim at eventually obtaining evidence, at the macroscopic level, of an important physical phenomenon called violation of parity.

There are also substances that, in the molten state or in solution, are known to exist as a rapid equilibrium between enantiomers (that is, there is rapid interconversion or racemization) and that, upon crystallization, give homochiral crystals (Havinga, 1954; Kondepudi et al., 1999). In this case there is again a cascade effect in which the separation of the first crystals provides nuclei for further crystallization, effectively displacing the equilibrium toward the first enantiomer to crystallize. These examples of symmetry breaking illustrate the amplification of an initially very slight enantiomeric excess represented here by the first crystal formed. In Sect. 3.10 we shall return to the general problem of the amplification of enantiomeric excesses.

3.5 Homochirality and Life

The importance of Pasteur's discovery to biology was immediately apparent to him. At the time, it was already well known that optical rotation was a property

of natural liquids such as turpentine, oil of lemon, and oil of laurel, and therefore must be a property of the molecules, per se. Optical rotation was also known to be a property of solutions of sugars, camphor, tartaric acid and, as we have seen, tartrates. Pasteur's work gave a deeper meaning to these observations by making it clear that molecules, as well as crystals, could exist as asymmetric pairs. Because the direction of optical rotation correlated with a particular asymmetry, and because optical rotation had been observed in so many biological materials, it became clear that the use of molecules of a particular asymmetry was a fundamental property of life. Then the question of the origin of homochirality could be asked for the first time, i.e., how did life choose between the two enantiomeric possibilities with which it was almost always presented? Against the advice of his mentors, the young Pasteur set about attempting to answer this question.

It is ironic that in the second half of the 19th century molecular chirality came to provide one of the last bastions for vitalism, which Pasteur's later research effectively discredited (see Mason, 1982). According to the advocates of this theory, the matter of living things is qualitatively different from that of inanimate matter and one of the differences is that the chiral molecules extracted from living things are always homochiral, whereas, when the chemist synthesizes these same compounds in the laboratory, a mixture of enantiomers in equal amounts, that is, a racemic mixture, is always obtained.

Although Pasteur was unable to answer the fundamental question of the origin of homochirality, he did clearly perceive why chemists were unable to prepare homochiral molecules. At a conference in 1883, he declared:

> "Indeed whenever the chemist in his laboratory combines elements or products born of the elements, he brings into play only nonasymmetric forces. For this reason the syntheses which he carries out never show asymmetry.... I would try asymmetric combinations of elements.... I would make them react under the influence of magnets, solenoids, elliptically polarized light – finally, under the influence of everything which I could imagine to exert asymmetric actions." (Vallery-Radot, 1968)

This statement is similar to, but earlier than, the more general one of Curie, which is now called the symmetry principle:

> "When certain causes produce certain effects, the elements of symmetry of the causes must be found in the produced effects. When certain effects reveal a certain asymmetry, this asymmetry must be found in the causes which gave them birth" (Curie, 1894).

Pasteur made additional comments that are quite interesting in an origin of life context

> "If the immediate principles of life are asymmetric, it is because, in their development, they are governed by asymmetric cosmic forces; therein, in my opinion, is a link between life on the surface of the Earth

and the cosmos, i.e., the entirety of forces spread throughout the universe".

It is remarkable that more than a century ago Pasteur, because of his need to discover "asymmetric forces" that could bring about the symmetry breaking necessary for the homochirality of biomolecules, came to view life on Earth in a cosmic context. In fact, most of the questions that arise today in connection with the origin of the homochirality of life have roots in the work of the 19th century scientists, Pasteur, van't Hoff, and Le Bel.

3.6 The Why and When of Homochirality

Chiral molecules dominate organic chemistry. For example, if we consider the acyclic saturated aliphatic α-amino acids, we see that glycine, the only two-carbon member of the series, is achiral; however, alanine, the C_3 member of the series, is chiral; one of the two C_4 isomers is chiral; all of the three C_5 isomers (including valine) are chiral; and six of the seven C_6 isomers (including leucine and isoleucine) are chiral. In general, the more atoms there are in molecules, the more isomers there are and the larger the number of isomers that are chiral. Clearly, chirality must be a fact of life unless life is somehow constrained to use only the very simplest molecules.

Given that organic chemistry is dominated by chiral molecules, why is biochemistry so rigorously homochiral? The answer to this question lies in understanding the importance of biopolymer structure. Life is based essentially on polymers of two fundamental types, proteins and nucleic acids (DNA and various RNAs). Both of these biopolymers result from the polymerization of chiral monomers and the biological function of both is strongly dependent on their existence in precisely defined three-dimensional structures (conformations). The right-handed double-helical structure of DNA and the unique globular structures of enzymes provide vivid examples of these functionally essential three-dimensional structures.

In the case of proteins, the monomeric units are 19 L-amino acids (to which we could add two very rare L-amino-acids units) plus the achiral amino acid, glycine. In the biosynthesis of a particular protein these amino acids are polymerized to give a chain (polypeptide) having a unique length and amino-acid sequence determined by a particular gene. The resulting polypeptide folds, spontaneously in many cases, to assume the conformation necessary for its biological function. If the amino acids were incorporated in the correct sequence but could vary randomly with respect to their chirality, an enormous number of diastereomeric polypeptides would result (2^{100} for a 100-amino-acid polypeptide). Only a very small fraction of these might be expected to fold correctly to give the exact three-dimensional structure (conformation) required for proper function. Therefore, specification of a particular amino acid as well as its chirality is essential at each step in the biosynthesis of a polypeptide chain in order to insure that all of

the products assume the correct three-dimensional structure. The homochirality of amino acids simply precludes chiral variation by providing amino acids of only one configuration (L) for protein synthesis. Of course, this homochirality is now reinforced by the strict chiral specificity displayed by the enzymes of contemporary organisms. The great majority of these enzymes are themselves proteins.

A priori, proteins could have been composed of D-amino acids. If this were the case, the chiralities of all the other constituents of cells would also be of the opposite chirality. This is illustrated by observations made on the enzyme HIV-1 protease when chemically synthesized from D-amino acids. This synthetic enzyme exhibits catalytic activity identical to that of the natural enzyme except that it is specific for the enantiomer of the natural substrate (Milton et al., 1992).

The question has been raised whether molecular homochirality is an absolute requirement for life and many believe that it is. For example, Bonner (1996) finds heterochiral life to be inconceivable. Nevertheless, if, as we have argued above, it is biosynthetic reproducibility of protein structure that life requires, in principle, this does not demand amino-acid homochirality. One can imagine an alternative life form that is both similar and different from terrestrial life: similar in having a triplet nucleotide genetic code, but different in that it specifies both the D and L enantiomers of the 19 chiral amino acids. Its polypeptides could then contain, in precisely ordered sequence, both D and L enantiomers of the chiral amino acids. Each polypeptide would fold and assume a unique three-dimensional structure and would have an active site and display a particular activity just as a homochiral polypeptide does. Such a requirement for both enantiomers of amino acids would, of course, lead to some metabolic duplication of effort. If both D- and L-amino acids were required, it would be necessary, inter alia, to have dual sets of t-RNAs and amino acyl t-RNA synthetases, proteases specific for D–X and L–X peptide bonds, a chirally nonspecific peptidyl transferase, and racemases in order to ensure a balanced supply of both sets of enantiomers.

In the case of the nucleic acids, random heterochirality of the deoxyribonucleotide and ribonucleotide monomeric units of DNA and RNA, respectively, would be just as disastrous for the function of the nucleic acids as is random amino-acid heterochirality for proteins. It would make the regular double-helical structure of DNA impossible as well as the replication and transcription of DNA, during which an extensive regular double-stranded structure is formed transiently (Gol'danski and Kuz'min, 1988). However, in this case, specified heterochirality as suggested for the amino acids of proteins would be equally disastrous because it would also preclude formation of the unique higher-order structure, the antiparallel double helix, that is required for function. Consequently, homochirality is a necessity for a ribose/deoxyribose-nucleotide-based genetic system.

On the other hand, achirality is a possibility for nucleic-acid-like molecules. Achiral nucleic-acid analogues have been synthesized, for example, the pep-

tide nucleic acid (PNA) of Nielsen (1993; 1996). This nucleic-acid analogue, which is completely devoid of asymmetric centers, has a linear array of bases, i.e., the essential feature necessary for encoding and translating information, and can take on the double-helical structure necessary for function (Miller, 1997). If such an informational macromolecule were to provide the genetic memory necessary to reproduce protein amino-acid sequence and, if it specified the use of both D- and L-amino acids, a PNA-protein biochemistry is conceivable in which overall homochirality would not be a necessity. If terrestrial life began on such an achiral-heterochiral basis, the strict homochirality that characterizes life now must have been an outcome of very early evolution and been achieved before the appearance of the Last Universal Common Ancestor (LUCA).

Thus, it is possible to imagine life that is at least partially heterochiral if, but only if, the chiralitry of each amino-acid subunit were fully specified. But how likely is the origin of life on such a basis? If life originated as a PNA-world, catalytic molecules, the analogues of ribozymes, would have been necessary and these would have been asymmetric in their folded forms. Their active sites would have been asymmetric and those that catalyzed key steps, e.g., transamination, in the formation of amino acids would have had a strong tendency to be enantioselective. Therefore, amino-acid heterochirality would have been unlikely. On the other hand, if proteins were necessary for the origin of life, it is difficult to see how the necessary reproducibility of three-dimensional structure could have been achieved without homochirality first having been achieved abiotically. Consequently, we conclude that, although partially heterochiral life is conceivable, its origin and/or evolution on this basis seems unlikely.

The alternative to an evolutionary origin of homochirality is that it was achieved prior to the origin of life. In this case, complex molecules could have been used from the beginning since the problem of chiral variations in monomer sequences that would complicate the production of reproducible biopolymers would have been solved. In the following sections we shall consider some plausible prebiotic processes that might have (a) created a symmetry breaking in chiral molecules and (b) brought about amplification of the possibly small initial enantiomeric excesses that might have resulted.

3.7 Origin of Homochirality and Spontaneous Symmetry Breaking

Many hypotheses have been put forward to explain how homochirality, or at least a significant imbalance in the amounts of enantiomers, might have appeared on the prebiotic Earth as a result of a spontaneous symmetry breaking. For example, a symmetry breaking can occur by the spontaneous separation of a racemic mixture into its constituent enantiomers during crystallization if there is the formation of a conglomerate or a unique L or D crystal (see Sect. 3.4). However,

it should be noted that the permissive conditions are tightly constrained and would have a low probability of being met on the primitive Earth. For example, the crystallization of a racemic mixture as a conglomerate followed by separation of the enantiomorphic crystals requires both a high concentration (saturation) as well as the correct temperature for crystallization as a conglomerate and not a racemate. Also, the initial mixture of enantiomers must be relatively pure because the formation of crystals requires that the compound not be a minor constituent of a complex mixture. Finally, some process must be available by which the crystals, once formed, can be spontaneously separated, i.e., an abiotic equivalent of Pasteur's human intervention.

Another possibility is presented by enantiomers in rapid equilibrium in the liquid state that can crystallize as a conglomerate. Here, again, total conversion of the mixture to one enantiomorphic crystal type can be achieved through secondary crystallization caused by strong agitation. Very demanding conditions, even more than in the previous case, must be met in order to observe this behavior. Asakura et al. (2002) continued the work of Kondepudi et al. (1999) in this area. The temperature of crystallization has a narrow range and the excesses of one homochiral crystalline form in comparison with the other varies by an order of magnitude! We concur with the opinion expressed by Bonner in his 1994 review that spontaneous resolution under racemizing conditions, of which there are numerous laboratory examples, probably does not constitute a mechanism of importance for the natural appearance of homochiralty.

Another spontaneous symmetry-breaking scenario is the selective adsorption of one enantiomer from a racemic mixture at the surface of a chiral crystal. As noted in Sect. 3.4, quartz crystals are asymmetric as a consequence of the right- or left-handed helical arrangement of the SiO_2 units and d-quartz and l-quartz selectively adsorb the enantiomers of amino acids. This enantioselective behavior was observed as early as 1935, a role for it in the origin of homochirality suggested by 1938, and the observations more recently confirmed (Bonner, 1996). In verifying this work, Bonner found that the phenomenon required carefully controlled anhydrous conditions, conditions quite unlikely to have been met on the primitive Earth. Furthermore, a survey of terrestrial quartz crystals has shown them to be racemic and, consequently, incapable of giving rise to an overall enantiomeric excess, that is, beyond what might be produced by a single crystal. This limitation to an extremely small locale is a general criticism that can be raised of the hypotheses for the origin of homochirality based on enantioselective adsorption by minerals/crystals. Nevertheless, such hypotheses continue to be suggested as the cause for homochirality on the primitive Earth.

The locality limitation is particularly severe when the adsorptive enantiomorphic surfaces are on the same crystal. For example, enantioselective adsorption has been observed with monoclinic, centrosymmetric and therefore achiral glycine crystals (Weissbuch et al., 1984). Although glycine is achiral, the crystals present enantiotopic faces, that is, their two-dimensional faces are nonsuperposable mirror images of each other. If such crystals float on the surface of a solu-

tion containing a racemic mixture of an amino acid and, if only one of the two enantiotopic faces is immersed in the solution, that face can act as a specific adsorbant and enantioselective adsorption approaching 100% can be obtained. More recently, Hazen et al. (2001) have carried out enantioselective adsorption experiments using one of the asymmetric faces of single calcite crystals and gone on to develop a rather comprehensive hypotesis for the origin of self-replicating homochiral peptides.

Clay minerals have been of interest as possible prebiotic catalysts for many years. Many are achiral and thus incapable of playing a role in the origin of homochirality. Others, for example kaolin, are, in principle, chiral, although it has not been possible as yet to demonstrate the chirality of single crystals. Many years ago it appeared that the chirality of kaolin might have been the basis for observations of enantiospecific adsorption and polymerization of amino acids (Jackson, 1971); however, in a careful subsequent study neither effect could be reproduced (Bonner and Flores, 1975). The possibility of such a role for kaolin was later resurrected in a theoretical study that assumed the existence of asymmetric crystals as a result of parity violation (see Sect. 3.8) and showed that enantiospecific amino-acid adsorption is possible (Julg, 1989; Julg et al., 1989).

Following Mills (1932), Dunitz (1996) and Siegel (1998) have suggested that homochirality could have arisen from statistical fluctuations from the equimolar condition that defines the racemic state. As these authors point out, it is incorrect to consider a racemic mixture as consisting of exactly the same number of enantiomeric molecules. If the synthesis of an enantiomeric mixture from achiral starting materials is repeated many times, the products obtained will have different enantiomeric compositions. A plot of frequency vs. enantiomeric composition will give a bell-curve centered on the exactly equimolar composition and with a width proportional to the square root of the variance. The statistics that apply to this situation are the same as those that apply to tossing a coin, that is, an independent event with a binary outcome having a probability $p = 0.5$ for each outcome repeated n times and under the same conditions (Droesbeke, 2001). In this case one obtains a binomial distribution of outcomes with variance proportional to n. If n is equal to 10^{24}, the distribution width will therefore be 10^{12}. According to these authors, a spontaneous symmetry breaking due to statistical fluctuation, followed by its amplification, can be the basis for the origin of homochirality. Mills (1932) explicitly states

> "we might account on the basis of the laws of probability for the existence of an initial minute bias towards one optical system or the other; and this would then, if the principles which I have endeavoured to explain are justified, eventually lead to the complete optical activity of the molecularly dissymmetric components of all living matter."

Furthermore, he stresses the importance of such fluctuations for microscopic prebiotic systems containing, for example, 10^6–10^8 molecules in which the statistical enantiomeric excess, although small in absolute value, can be large relative to the total number of molecules.

In dealing with evolution, Monod (1970) famously employed the dichotomy of chance versus necessity, distinctions that are useful in discussing the origin of homochirality. In the cases described above it is clear that, whatever the cause of the symmetry breaking, the probabilities of formation of both enantiomers are exactly the same and whichever one becomes predominant is a matter of chance. In the section that follows, we will consider an aspect of atomic physics that necessarily gives one particular enantiomer a slight advantage, that is, to use coin tossing as a metaphor, a situation in which the two faces of the coin do not have equal probabilities.

3.8 Origin of Homochirality and Parity Violation

If the homochirality of terrestrial life was a "necessity" and not a matter of "chance" selection, one must ask in what way the biological amino acids of the L-series and monosaccharides of the D-series could have been advantaged. An answer has been suggested by the recognition of a basic asymmetry of matter, the violation of parity that was previously alluded to in regard to the enumeration of quartz crystal enantiomorphs and studies of the handedness of sodium chlorate crystals. This parity violation constitutes a symmetry breaking at the level of the basic laws of atomic physics (Zee, 1999).

Until the 1950s, it was believed that quantum-mechanical operators, wave functions, and the observables that derive from them, preserved parity (P) and were thus independent of the operations of symmetry, that is, inversion with respect to a point or reflection with respect to a plane. In 1956, two young physicists, Tsung-Dao Lee and Chen Ning Yang, suggested that this conservation of parity applied only to quantum systems in which the controlling forces are the intranuclear strong interactions and the electromagnetic interactions. On the other hand, according to Lee and Yang, systems controlled by the weak intranuclear interactions were likely to undergo transformations that did not preserve parity.

Nonconservation of parity was soon experimentally demonstrated in the β-decay of ^{60}Co by Wu and collaborators in 1957. In their experiments, carried out at a temperature close to 0 K and in a static magnetic field in order to create a privileged direction of space, the dissociation of a neutron to a proton, an electron, and an antineutrino was observed. The fact that the intensity of the emission of electrons was not the same parallel and antiparallel with respect to the orientation of the magnetic field constituted proof that the angular momentum of the electrons was preferentially directed antiparallel with respect to the moment associated with the linear movement, i.e., that the electron spin preferentially describes a left-handed helix.

In 1974 Vester reported the first attempts to experimentally induce chirality through the interaction of an achiral reactant with β-radiation from various radioactive sources. He carried out numerous experiments but obtained only false

positive and artifactual results. This fruitless work used β-radiation but also the associated circularly polarized light (bremsstrahlung). Bonner (1996) describes later work, including some by his own group. He carried out β-irradiations (exceeding ten years in some cases) using β-radiation from various elements (^{32}P, ^{14}C) and also bremsstrahlung in the hope of obtaining an enantioselective degradation of racemic amino acids but was unable to observe a significant effect.

In addition to the chirality of β-radiation, there is another consequence of the violation of parity that originates in the so-called electroweak interactions that result from unification of the intranuclear weak interactions and electromagnetic interactions. The resulting z force interacts with both the nucleus and electrons and, because of its parity-violating character, distinguishes between left and right. Yamagata (1966) pointed out that because of this coupling, enantiomers cannot have the same energy and that this fact could have relevance to the origin of biological homochirality. The energy difference between enantiomers is called the parity-violating energy difference (PVED). It results from the CPT theorem that states that physics is invariant if, simultaneously, one inverts space (operation P), replaces the elementary particles by their antiparticles (operation C for "loads conjugation") and inverts time, that is, the direction of movement (operation T). To explain the existence of the PVED between enantiomeric molecules, it suffices to take only CP into consideration since in this case time does not play a role.

The apparently equal amounts of enantiomers present in racemic mixtures (i.e., equilibrium mixtures) indicate that K_{eq} must be extremely close to 1.0 and the PVED therefore exceedingly small. To date, it has not been possible to experimentally measure its value; however, there are experimental approaches, in principle, and it may be possible to accomplish this in the future (Quack, 2002). In the meantime, it has been necessary to rely on theoretical methods for determination of PVED. Yamagata's early attempt at such a calculation overestimated its value by several orders of magnitude but, over the last 20 years, increasingly sophisticated ab initio quantum-mechanical calculations have been applied to the problem (reviewed by Quack, 2002). These calculations have generally given PVED values of about $10^{-14}\,\mathrm{J\,mol^{-1}}$ corresponding to enantiomeric excesses of about 10^{-15}%, although more recent calculations have given larger values for PVED by about one to two orders of magnitude (Quack, 2002).

In addition to the magnitude of the PVED, the question of whether it favors the L- or D-enantiomer of the amino acids and monosaccharides has been of great interest with respect to the origin of terrestrial homochirality. Recent calculations for the amino acids, alanine, valine, serine, and aspartate, and the simplest of the monosaccharides, glyceraldehyde, have shown the PVED to have the "correct" sign, i.e., to favor the biological enantiomers (Zanasi et al., 1999; Mac Dermott, 2002). However, such results are controversial, as their outcome is dependent on both the conformation assumed for the molecule in question as well as the particular calculation method that is used (Buschmann et al., 2000). Bonner

(2000), after a careful recent review of the literature in this area, is unconvinced of a causal link between parity violation and biological homochirality.

3.9 Origin of Homochirality and Photochemistry

As noted in Sect. 3.5, Pasteur included elliptically polarized light among the "asymmetric forces" that he suggested might be capable of inducing enantioselectivity. Nevertheless, it was necessary to wait almost 70 years for an experimental demonstration of this phenomenon. In 1929 Kuhn and Braun showed that partial photolysis of a racemic mixture by irradiation with UV circularly polarized light (UVCPL) gave rise to an enantiomeric excess in the residue. In 1974, Balavoine et al. provided a theoretical treatment of this process that allows calculation of the enantiomeric excess obtained as a function of the degree of photolysis and the differences in the extinction coefficients of the enantiomers for UVCPL. Both Norden (1977) and Flores et al. (1977) demonstrated that aminoacids are subject to enantioselective photolysis by UVCPL. Flores et al. obtained enantiomeric excesses of 1.98% and 2.50% in originally racemic leucine solutions when photolysed to the extent of 59% and 75%, respectively. In this case, the difference between the extinction coefficients relative to their average value (g factor) is about 2%. Recently, Nishino et al. (2001) studied the reaction mechanism and found that acidic conditions are required and that glycine is one of the products of the reaction. Bonner and Bean (2000) have shown that enantioselective photolysis of racemic leucine can also be observed with elliptically polarized light. A role for UVCPL in the origin of the homochirality of terrestrial amino acids has been discussed by Norden (1977; 1978), Rubenstein and Bonner (1983) and by Bonner and Rubenstein (1987). Greenberg (1996) showed that partial UVCPL photolysis of a racemic mixture of the amino acid tryptophan in his laboratory model of low-temperature interstellar-grain chemistry gave an enantiomeric excess in the residue.

Circularly polarized light can also be used to effectuate enantioselective syntheses starting with an achiral reactant. In this case, CPL is the only chiral element. The first example of this was published by Kagan et al. in 1971 and concerned the synthesis of helicene (see also articles by Buchardt (1974), Mason (1982), Rau (1983), and Inoue (1992) which furnish other examples of enantioselective photosyntheses). In Sect. 3.11, we shall discuss the possible role of UV circularly or elliptically polarized light in the formation of the enantiomeric excesses found in the amino acids extracted from certain meteorites.

The results of these experiments are consistent with the Curie principle in that circularly or elliptically polarized light has true chirality and, therefore, a photolysis or a photosynthesis induced by such light must lead to nonracemic products. A recent paper by Rikken and Raupbach (2000; see also the commentary of Barron (2000)) shows that nonpolarized laser light can also lead to enantioselectivity during a photochemical reaction if the irradiated system is

placed in a magnetic field and the field is not orthogonal to the propagation direction of the light. Indeed, the combination of a magnetic field B and a wave vector $\boldsymbol{k}$ (along the propagation direction of the light) is endowed with true chirality in so far as $\boldsymbol{k}$ and B are not orthogonal. Reflection in a mirror inverts the propagation direction of the light and therefore the orientation of $\boldsymbol{k}$ but leaves B unchanged since it is an axial vector. The theory of the dielectric constant of an isotropic environment, with or without an external magnetic field, allows quantification of the response of the material environment to the electric field of the electromagnetic radiation. The theoretical expression that follows from this treatment (Jorissen and Cerf, 2002) shows the dielectric constant as an expansion into a series. If one assumes the response of the environment to be linear, one notes that there are four terms that depend on the static magnetic field B in which the sample is placed. These four terms correspond, respectively, to the magnetic rotatory dispersion, the magnetic circular dichroism, the magnetochiral dispersion and the *magnetochiral dichroism*. The results obtained by Rikken and Raupbach (2000) point to the same phenomenon as the one that is responsible for magnetochiral dichroism. There appears a factor $g{\cdot}B$ that measures the difference between the extinction coefficients of the unpolarized light by the two enantiomers if these are placed in a field B. If B is zero (absence of external field), $g{\cdot}B$ is therefore also zero and enantioselective photochemistry is not observed. According to Wagnière and Meier (1983), g, in the case of the magnetochiral effect, is several orders of magnitude less than the g characterizing the different response of the two enantiomers to circularly polarized light. This means that to obtain significant enantioselectivity, B must be increased, typically by a few Tesla. (For comparison, the Earth's magnetic field at the surface of the planet is about 10^{-4} Tesla.) Could there exist, at the heart of a protosolar cloud, environments where such large magnetic fields prevailed and where, at the same time, photochemical syntheses produced molecules of biological interest? This remains an open question: the surroundings of a neutron star could be a favorable place in the sense that an enormous magnetic field exists there as well as synchrotron emission of electromagnetic radiation. This light can also be circularly polarized (see Sect. 3.11) but in this case CPL is not necessary for enantioselective syntheses.

Although UVCPL and magnetochiral photochemistry are usually considered to be extrasolar effects, it is necessary to consider the possibility of photosyntheses or enantioselective photolyses on the primitive Earth. In fact, the solar light incident on the Earth is circularly polarized as a result of scattering from atmospheric aerosols (Wolstencroft, 1985; Jorissen and Cerf, 2002). Nevertheless, this effect is canceled, on average, on a daily basis and it is necessary to imagine special topographies such that photosynthesis cannot occur during a part of the day or to invoke light-intensity differences between the morning and evening. The weak circular polarization of the scattered light along with the very constrained conditions that must be satisfied suggests that enantioselective photosynthesis in the atmosphere of the early Earth would not be a very likely occurrence.

3.10 Amplification of Enantiomeric Excesses

3.10.1 Introduction

Thus far we have dealt with several ways in which the symmetry, that is, the perfect enantiomeric equivalence, of racemic compounds can be broken. These symmetry breaking can be nearly quantitative, as in the case of crystallization, or can be minuscule, for example, as predicted for the PVED or allowed by natural statistical deviation from the equivalence of the racemic state. In this section we shall consider mechanisms by which enantiomeric excesses might be amplified, even to homochirality. Bonner's reviews (1991; 1996) critically discuss many of these mechanisms.

3.10.2 Kinetic Resolution

Kinetic resolution (Kagan and Fiaud, 1988), which takes advantage of the different reaction rates of diastereomeric transition states, is particularly pertinent in the case of amino-acid polymerization, a reaction that is commonly assumed to have occurred under prebiotic conditions. As noted previously (Sect. 3.2), transition states for the coupling of chiral amino acids can be diastereomeric (e.g., L L vs. L D) and, as a result, they have different energies and their reactions occur at different rates. Consequently, a homochiral amino-acid pair might react more rapidly than a heterochiral pair. Likewise, the transition states for the next addition can differ similarly (e.g., L L–L vs. D L–L) and their polymerization rates will differ (end-group diasteroisomerism effect).

When about eight amino acids have been joined in this way, the resulting peptide can begin to assume secondary structure, for example, a helical twist. Helixes are themselves chiral and their handedness can be dependent on the chirality of the constituent amino acids. The chirality of such helical coils can reinforce the effect of end-group diasteroisomerism in promoting the preferential addition of a particular amino acid enantiomer (helix effect). The unexpectedly large increase (20×) in the rate of polymerization for derivatives of D- or L-benzyl glutamate compared with that of racemic DL-benzyl glutamate suggested that the helicity of the product might be playing a significant role (Blout and Idelson, 1956). This led Wald (1957) to suggest that the α-helical structure of polypeptides might favor the further addition of amino acids of the same chirality as those that determined the handedness of the helix and that this could have been of significance in the origin of the homochirality of biological amino acids. Later, Spach (1974) demonstrated that the enantioselective effect observed in the polymerization of the benzyl glutamates arises mainly from the helical structure of the product. However, a positive helix effect is not observed with all amino acids. Blair and Bonner (1980) found substantial increases in enantiomeric excess in the polypeptide product when a derivative of leucine was polymerized but enantiomeric decreases with the corresponding valine derivative. Brack and Spach (1981) have pointed out that formation of another type of

secondary structure assumed by some polypeptides, that is, the β-pleated sheet, can also give rise to enantiomeric enrichments.

A third effect, the greater stability to hydrolysis of the helical polymer in comparison with the corresponding random coil (stability effect), can further enhance the enantiomeric excesses achieved by polymerization. An example of the amplification that can be achieved by amino-acid polymerization combined with partial hydrolysis has been given by Blair et al. (1981). They found that partial polymerization of a leucine derivative having a 31% L-enantiomeric excess gave polypeptide products with an enantiomeric excess of 45% and that after partial hydrolysis of this material the enantiomeric excess in the surviving residue was 55%. Blair et al. (1981) suggested that repeated wet–dry cycles on the prebiotic Earth might have led to partial polymerization of amino acids followed by partial hydrolysis of the polypeptide products and thus similarly enhanced any initially small enantiomeric excesses.

The work of Eschenmoser et al. (Bolli, 1997) gives an example of what the authors describe as a deracemization process that possibly could occur during polymerization. Activated tetramers of ribonucleotides containing ribose as a pyranose ring were involved in further polymerizations. 8-mers (octamers), 12-mers and even 16-mers are obtained. A strong chiroselectivity was observed and the presence of tetramers containing L-ribose instead of D-ribose had no major influence on the polymerization rates. If we consider one mole of a 50-mer based on 4 different but homochiral ribonucleotides it is impossible to form all the possible sequences because 4^{50} is much larger than the Avogadro number. Following Eschenmoser et al. the final mixture of polymers must necessarily be nonracemic leading therefore to a deracemization process without any chiral external influence. Siegel (1998) also has pointed out the practical impossibility of generating all possible enantiomers in a mixture of polymers with a high (or even moderate) degree of polymerization by starting from racemic mixtures of 20 different monomers.

Recently, Zepik et al. (2002) have given an interesting example of amplification of an enantiomeric excess by polymerization in the two-dimensional environment provided by a water/air interface. The activated monomers of amino acids (lysine and glutamic acid) were functionalized with long-chain hydrocarbons to make them amphiphilic. As a result, they accumulate at the water/air interface where they associate in crystalline two-dimensional aggregates. When the starting mixture was enantiomerically unbalanced, they observed the formation of a racemate along with an enantiomorphic phase that polymerizes, yielding homochiral oligopeptides. In this case intermolecular packing at the interface provides structural order analogous to the helix effect described in the preceding paragraph for homogeneous polymerization. A mechanism for separation of the enantiomeric and racemic phases was not suggested by the authors. Although this phenomenon could be of prebiotic interest with respect to hypothetical chiral amphiphilic compounds it should be noted that amino acids and

monosaccharides are quite water soluble and, unless chemically modified, do not accumulate at a water/air interface.

Takats et al. (2003) have shown that clustering of serine molecules is a efficient process for chirality amplification as well as for chirality tranfer to other amino acids or sugars. Although this is not polymerization in the strict sence, it does provide an example of an amino acid based suparmolecular system with possible relevance to prebiotic chemitry.

3.10.3 Chiral Catalysis

Chiral catalysis allows the transfer of chirality from a catalyst to the reaction product and, in many cases, impressive enantiomeric excesses are achieved in the product when the catalyst is enantiomerically pure. Sometimes very significant nonlinear effects are also observed in such catalytic reactions, that is, when the catalyst is not enantiomerically pure, a greater or lesser enantiomeric excess than that of the catalyst may appear in the product (Girard and Kagan, 1998). In the former case, this amounts to an amplification of chirality.

The work of Feringa et al. (1995) describes a physical system in which a small amount of an enantiomer stimulates a large effect. Here an achiral mesophase (achiral liquid crystals), when seeded with a very small quantity of a chiral additive, gives a transition phase leading to a chiral environment at the macroscopic level (transition between an achiral nematic phase and a cholesteric chiral phase). The chiral additive in this case is a photoisomerizable dopant that allows, according to the wavelength of irradiation, the induction of a cholesteric phase of either right or left helicity (chiroptical switching). Of course, the presence of achiral or chiral mesophases on the primitive Earth is an area of sheer speculation.

3.10.4 Asymmetric Autocatalysis: Theoretical Models

Asymmetric autocatalysis can be considered to be a special case of chiral catalysis in which a chiral reaction product acts as the catalyst. Franck (1953) proposed an early theoretical model for such a process, that is, for the amplification of an enantiomeric excess by means of a chemical reaction in which the product is a chiral compound and one enantiomer (for example, the L-enantiomer) catalyzes its own formation while inhibiting the formation of the other enantiomer (the D-enantiomer). The crystallization from solution of an enantiomeric mixture in rapid equilibrium is an example of such a process. In this case, a very slight initial excess of one enantiomer due to a random fluctuation in the racemic mixture can trigger a crystallization cascade that carries the system far from equilibrium, i.e., toward a large enantiomeric excess of the randomly favored enantiomer (see Sect. 3.4).

Following Franck, Decker (1974) systematically studied four different chemical systems all characterized by the presence of autocatalytic feedback. He

showed that such systems show bifurcation phenomena that manifest themselves by the sudden amplification of a very small initial enantiomeric excess. Decker explicitly placed this work in the context of the Brussels school of the thermodynamics of open systems far from equilibrium. Kondepudi, based on previous work by Prigogine and Nicolis, has published several papers (Kondepudi and Nelson, 1984; 1985; Kondepudi, 1996; Prigogine and Kondepudi, 1999) devoted to an in-depth study of a system composed of five interdependent chemical reactions likely to show bifurcation phenomena. The system, also a modification of the autocatalytic model of Franck, is as follows:

$$\begin{aligned}
&A + B \rightarrow X(L)\\
&A + B \rightarrow X(D)\\
&X(L) + A + B \rightarrow 2X(L)\\
&X(D) + A + B \rightarrow 2X(D)\\
&X(L) + X(D) \rightarrow Y
\end{aligned}$$

The scheme has two autocatalytic steps and an irreversible mutual destruction step, features that appear to be essential in systems that show symmetry breaking. The system is open, that is, A and B, the chiral reactants, are maintained at constant concentrations throughout the simulation experiment and the product Y is eliminated, thereby rendering the reverse reaction impossible and making the evolution of the system irreversible.

Kondepudi et al. are interested in the magnitude of X(L)–X(D), the enantiomeric concentration difference, in relation to the concentration of the perfect racemic mixture (X(L)–X(D) = 0). They carried out several simulations corresponding to different values of the molar concentrations product $A \cdot B$ and observe that there exists a critical value of product $A \cdot B$ beyond which the symmetrical solution X(L) = X(D) becomes unstable. This means that a random statistical fluctuation can provoke bifurcation of the system toward a state in which X(L) is no longer equal to X(D) and that corresponds to a spontaneous symmetry breaking. However, if at the start there is a chiral perturbation of the system, for example by the presence of a very small excess of X(D) or of X(L), a bifurcation will be observed when the critical value is attained leading to an amplification of the initial enantiomeric excess (Fig 3.7).

According to Kondepudi et al., this mechanism will allow amplification of initial excesses as small as those that are predicted by the violation of parity (PVED) (see Sect. 3.8) if the accumulation of A and of B can continue in a very large volume (typically a lake of some km^2) for long time periods (typically tens of thousands of years), in this way reaching the critical value of the concentration product $A \cdot B$. Kondepudi and Nelson (1984) note that in their simulations they cannot account for the effect of chance chiral impurities in the environment that would affect the kinetics of the system. They conclude that

> "When one finds a real chemical system that breaks chiral symmetry, in order to preserve the effects of weak-neutral current interactions, the

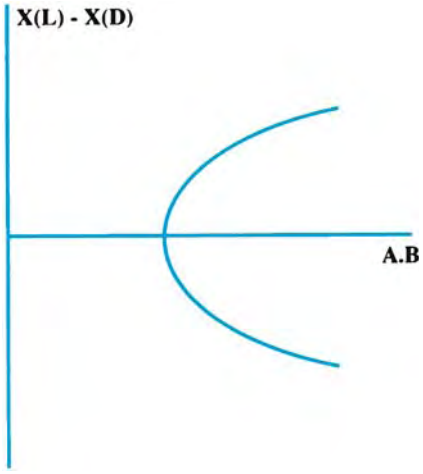

Fig. 3.7. Example of bifurcation predicted by the theoretical model of Kondepudi. A and B are the molar concentrations of the achiral reactants A and B while X(D) and X(L) are the molar concentrations of the chiral products X(L) and X(D) (see text for discussion)

system must be prepared with sufficient purity that the selection occurs due to this interaction and not due to the presence of a chiral impurity."

These condition and constraints raise serious questions as to the significance of such a theoretical model in the context of prebiotic chemistry. However, as will be seen in what follows, the general point is quite significant in evaluating experimental systems of this type.

3.10.5 Asymmetric Autocatalysis: Experimental Data

Recently, asymmetric autocatalysis has been experimentally shown by the group of Soai to give spectacular amplifications (Soai et al., 1995; 2000; Shibata et al., 1998). Soai and his coworkers have studied in detail the addition of an achiral organozinc derivative to an achiral aromatic aldehyde (Soai reaction). The reaction ultimately yields a mixture of enantiomeric alcohols. These alcohols then act as catalysts of their own synthesis. If the reaction is carried out in the presence of a chiral initiator such as leucine with 2% L-enantiomeric excess, the mixture of alcohols obtained at the end of the reaction shows an enantiomeric excess of 21% in one of the enantiomers. If the initiator is enriched in D-leucine, at the end of the reaction the mixture of alcohols is enriched in the other enantiomer and the enantiomeric excess is 23%. The interpretation of these results is as follows. The presence of the chiral initiator leads to very small enantiomeric excess in the first alcohols formed. These then act as the asymmetric catalyst. Since the alcohol is catalyzing its own synthesis an autocatalytic system is operating

that amplifies the enantiomeric excess. Soai et al. have observed that an initiator with an enantiomeric excess of only 0.1% can give a mixture of alcohols with an enantiomeric excess greater than 80%! The authors point out that the enantiomeric excess in the leucine used as the initiator is similar to those that can be obtained by enantioselective photodecomposition of a racemic mixture of leucine using UVCPL (Sect. 3.9). They conclude that autocatalysis in the presence of a chiral initiator could have played a role in the appearance of terrestrial homochirality. Furthermore, these researchers (Soai, 1999) have observed that homochiral quartz crystals are also able to play the role of initiator and, starting with the same achiral reactants, give enantiomeric excesses of greater than 80% in the product alcohol. Depending on whether the quartz crystals are l or d, a preponderance of one or the other alcohol is observed.

Subsequently, Singleton and Vo (2002) attempted to use the Soai reaction to test whether the statistically allowed enantiomeric excesses that occur in "racemic" mixtures might be sufficient to initiate the formation of products with a substantial enantiomeric excess. They were unable to demonstrate this for an unexpected reason: the chiral impurities present in even purified solvents are capable of initiating the amplification process in this autocatalytic system and effectively overwhelm any weaker effects. Thus, as Kondepudi and Nelson pointed out (see above), the ubiquity of homochiral molecules in terrestrial environments poses a severe experimental problem for those who would hope to attribute chiral effects to minute enantiomeric excesses such as the statistically allowed variations of racemic mixtures or those that might arise from PVEDs.

Very recently, Soai et al. (2003) appear to have accomplished the amplification of enantiomeric excesses having only a statistical origin. They carried out the synthesis of the chiral pyrimidyl alcohol from only the achiral reagents (the pyrimidyl aldehyde and diisopropyl zinc) in pure solvents and obtained enantiomeric excesses ranging from 29–91% with each enantiomer predominating in approximately half of the cases (18*R*, 19*S*). As Mislow (2003) points out in an interesting commentary on this work, this is an example of absolute asymmetric synthesis, i.e., the formation of enantiomerically enriched products without the influence of any pre-existing chirality. Apparently, the random statistical fluctuations in the chirality of the initially formed catalytic zinc complex are amplified and determine the asymmetric outcome of the overall reaction. To be consistent with Curie's symmetry principle "this [product] asymmetry must be found in the causes that gave them birth" and in this case no causal asymmetric influence appears to be available other than random statistical fluctuation.

These results are of obvious importance in the context of the origin of homochirality problem although, as Avalos et al. (2000) have pointed out, the particular reaction studied by the Soai group does not readily proceed under prebiotic conditions. Organometallic chemistry requires rather restrictive nonaqueous conditions but it is hoped that in the near future similar autocatalytic reactions will be discovered that are more compatible with the constraints imposed by prebiotic chemistry. If such are found, it will be possible to agree with

Siegel (2002) when he states that "*in the prebiotic world examples of dominant molecular handedness were already likely to be abundant.*"

3.10.6 On the Possibility to Amplifying Enantiomeric Excesses due to Parity Violation

Kinetic resolution and other related processes associated particularly with phase changes like crystallization can lead to amplification only when starting with mixtures having initial enantiomeric excesses that are very much greater (many orders of magnitude) than those that might be provided by the PVED. (see Sect. 3.8.) Consequently, amplification of these extremely small enantiomeric excesses is a subject that has received considerable attention and is treated separately here although, as discussed below, it has much in common with the problem of amplifying statistical excesses in racemic mixtures.

Yamagata (1966), who recognized very early the possible implications of parity violation for the origin of homochirality, also speculated as to how such small enantiomeric excesses might be amplified. He proposed an "Accumulation Principle," that is, the amplification of a very small enantiomeric bias when it is repeatedly multiplied by itself, for example, when it affects each step in a linear reaction sequence composed of a very large number of discrete steps. According to Yamagata, this principle would be applicable to either polymerization or crystallization phenomena. However, the application to polymerization considers only the possibility of formation of two completely homochiral polymers (enantiomers) and fails to consider the inevitable formation of numerous heterochiral polymers (diastereomers). Likewise, the proposal of irreversible consecutive steps is an oversimplification of crystallization. An excess of the l enantiomorph in natural quartz has been cited as possible evidence for the influence of PVED on crystallization (Tranter, 1985); however, as noted in Sect. 3.4, more recent evaluation of the data has failed to confirm a significant enantiomorphic excess (Frondel, 1978). Bonner (1999) has recently evaluated the Accumulation Principle and found it to be incapable of producing amplification by either polymerization or crystallization (see also Avalos, 2000).

Work by Szabo-Nagy et al. (1999) is purported to be the first experimental demonstration of the PVED. The authors prepared a racemic mixture of the *tris*(1,2-ethanediamine) complexes of Co^{3+} and Ir^{3+} by mixing the enantiomers to zero circular dichroism (CD). They then crystallized numerous samples and measured the CD of their solutions. A distribution of CD values was obtained, which, in the case of the metallocomplexes, was shifted from zero. On this basis, the authors claim that undetectably small enantiomeric excesses due to the PVED were amplified by crystallization. The observation of an effect only with the metallocomplexes and not with the racemic mixture of tartaric acids was attributed to the higher atomic number of the atom at the asymmetric center and the resulting larger PVED. The results are controversial (Avalos, 2000). It is not clear that the amplification is attributable to the PVED rather than

deviations from the exactly racemic state and/or the effect of chiral impurities on the crystallization process. Circular dichroism is not sufficiently sensitive to detect small enantiomeric exess, even ones much larger than expected taking into account parity violation or statistical fluctuations.

Salam (1993) has proposed another mechanism by which the minuscule enantiomeric excesses due to PVEDs might be amplified. Salam, who received the Nobel Prize for his work on unification of the weak interactions and electromagnetic interactions, envisages an interconversion of the less stable enantiomer to the more stable one in the crystalline phase below some critical temperature. This cooperative effect would occur by a second-order phase transition and is similar to the transition observed when an electrical conducting material becomes a supraconductor. Figureau et al. (1995) attempted to observe a configurational change in racemic cystine over the temperature range 0.6–77K but failed to obtain a positive result. More recently, Wang et al. (2000) published results that are presented as a partial experimental confirmation of the Salam hypothesis. These authors claim to have observed a phase transition at 270 K by measuring the difference between the specific heats of D- and L-alanine in the solid crystalline phase. Measurements of magnetic susceptibility and by Raman spectroscopy also appear to show unique behavior at this temperature. Wang et al. also found that the specific heat of D-alanine is greater than that of L-alanine. These results are interesting but also surprising, notably because of the high transition temperature reported. One hopes that further studies along these lines will be carried out in order to confirm these results and exclude the possibility of artifacts.

The results of Soai et al. (2003) on the amplification of the enantiomeric excesses that occur in racemic materials as a result of random statistical variation require a rethinking of the possible role of enantiomeric excesses due to the PVED. In the Soai reaction initially 0.1 mMole of the chiral zinc complex was formed and it can easily be calculated that the statistically allowed enantiomeric excess in even this relatively large amount of material would be of the order of 10^{-8}%. Since random enantiomeric excesses of this magnitude will always exist and can, as Soai and his coworkers have demonstrated, be amplified in an autocatalytic reaction to as much as 90%, the presence of much smaller enantiomeric excesses of the order 10^{-15} to 10^{-13}% attributable to the PVED would have no significance.

In summary, it is apparent from this brief review that amplification processes are not lacking and many have been subjected to thorough laboratory testing, in part because of the importance of obtaining pure enantiomers for the pharmaceutical industry (Triggle, 1997). It has also become clear that experimental studies concerning the amplification of extremely small enantiomeric excesses can be subject to misinterpretation due to the presence of chiral contaminants. Finally, it should also be stressed that in the context of research on the origin of the homochiralty of life, amplification mechanisms that require pure crystals, enantiomer solutions near saturation, anhydrous conditions, or reactors on the

scale of a lake that are free of chiral impurities for time periods measured in centuries or millenia, are unrealistic.

3.11 Exogenous Origin of Homochirality

The exogenous delivery of organic matter to the primitive Earth is now widely acknowledged to have been an important aspect of its prebiotic chemistry (Chyba and Sagan, 1992). There is little doubt that organic matter of meteoritic, micrometeoritic, and cometary origin accumulated in the hydrosphere of the primitive Earth (for reviews see the chapters by D. Despois, by F. Robert and by A. Morbidelli and D. Benest in Gargaud et al., 2001). Therefore it is understandable that the question of chiral organic matter in meteorites, particularly in carbonaceous chondrites has interested researchers for several decades (see reviews of Mullie and Reisse, 1987; Reisse and Mullie, 1993; Cronin and Pizzarello, 2000). In this regard, it is important to recognize that contamination of meteoritic matter by terrestrial compounds is almost unavoidable and that this can easily give artifacts. The work carried out by Meischein et al. (1966) on optical activity was pioneering in this respect. A meticulous analysis of an extract of the Homestead meteorite led these authors to the conclusion that the optical activity observed in meteoritic extracts by earlier workers was a result of contamination. However, more recently some of the amino acids detected in the Murchison and Murray meteorites have been found to be nonracemic (Cronin and Pizzarello 1997; Engel and Macko, 1997; Pizzarello and Cronin, 1998; 2000; Pizzarello et al., 2003), a discovery of considerable interest with respect to the origin of homochirality. It should be noted that the method of analysis used is no longer measurement of optical rotation or rotatory dispersion but rather gas chromatography (GC) on chiral supports coupled to mass spectrometry (MS) or isotope ratio mass spectrometry (IRMS), more sensitive and specific methods than those that were available in 1966.

There remains a great risk of contamination in the analysis of those meteoritic amino acids that are also present in the biosphere and this cannot be neglected regardless of the analytical methods used. In order to reduce this risk, Cronin and Pizzarello (1997) studied α-methyl amino acids that are either unknown or rarely found in the biosphere. These authors initially reported significant enantiomeric excesses (1 to 9% depending on the amino acid) in favor of the L-enantiomers and more extensive later analyses of isovaline have shown even larger enantiomeric excesses (Pizzarello et al., 2003).

On the basis of these results, it seems very probable that certain of the amino acids present on the primitive Earth had enantiomeric excesses and that these excesses were large enough to be susceptible to amplification by the processes discussed previously, notably by polymerization. It is necessary to add that the α-methyl amino acids, which are relatively abundant in carbonaceous chondrites, are particularly good candidates for amplification by polymerization.

As discussed in Sect. 3.10, the formation of secondary structures of the alpha-helical or beta-pleated-sheet type enhances amplification by polymerization and it has been shown (Altman et al., 1988; Formaggio et al., 1995) that the α-methyl amino acids give polyp eptides with very stable secondary structure of a helical type.

The origin of the enantiomeric excesses found in meteoritic amino acids is an important question. These amino acids have general characteristics that clearly indicate their production by abiotic processes (Kvenvolden et al., 1970; Cronin and Chang, 1993). They are nearly racemic, structurally diverse, with all possible isomeric forms represented, and are found in amounts that decrease exponentially within homologous series. Furthermore, they are isotopically distinct from their terrestrial counterparts, being substantially enriched in the heavier stable isotopes of C, H, and N (Epstein et al., 1987; Engel et al., 1990; Pizzarello et al., 1991; 2003; Engel and Macko, 1997). The isotopic enrichment, particularly in deuterium, is suggestive of chemistry at very low temperature, e.g., the ion–molecule reactions that occur in cold interstellar clouds (Wannier, 1980; Penzias, 1980). Thus, it is possible that meteoritic amino acids are of presolar origin (Epstein et al., 1987), although it is has been suggested that appropriate low-temperature conditions may have also existed within the solar nebula (Aikawa and Herbst, 2001).

As discussed previously (Sect. 3.9) UV circularly polarized light (UVCPL), when absorbed by a racemic organic compound, leads to photolysis with preferential survival of increasing amounts of one enantiomer as the photolysis proceeds. According to Rubenstein et al. (1983) and Bonner and Rubenstein (1987), a neutron star can produce UVCPL as synchrotron radiation resulting from the circulation of an electron plasma in the equatorial plane of the star. In addition, circular polarization has been observed within interstellar clouds and attributed to Mie scattering of light by aligned interstellar grains (Bailey et al., 1998). Bonner and Rubenstein go on to suggest that the UVCPL generated in these ways might affect the organic matter of interstellar clouds or the organic matter at or near the surface of a primitive planet thus giving rise to enantiomeric excesses in its chiral components. This hypothesis was adopted as a possible explanation for the asymmetry observed in meteoritic amino acids (Cronin and Pizzarello, 1997; Engel and Macko, 1997). Greenberg (1996) determined that it is probable that interstellar grains were, at some point in their existence, subjected to circularly or elliptically polarized radiation emitted by a neutron star and therefore concluded that a "*significant fraction of Solar Systems started off with significant enantiomeric excesses*." The possibility of obtaining UVCPL from a neutron star has been questioned by Roberts (1984), and Mason (1997) has expressed doubt, based on the Kuhn–Condon effect, whether the broad band UVCPL emitted by a neutron star could achieve preferential photolysis. The latter objection has been effectively countered by Bonner et al. (1999). Mie scattering is not subject to these objections and a strong case can be made for its greater significance as a source of interstellar UVCPL (Bailey, 2001). Cerf and Jorissen (2000) and

Jorissen and Cerf (2002) have also discussed the pros and cons of a UVCPL scenario for the origin of enantiomeric excesses.

It is also necessary to consider quantitative aspects of the UVCPL photolysis hypothesis in evaluating its relevance to the origin of the enantiomeric excesses observed in meteorites. L-enantiomeric excesses up to 9% were initially observed in the isovaline from the Murchison meteorite and an excess as high as 15% has been measured for this amino acid more recently (Pizzarello et al., 2003). Although not impossible, enantiomeric excesses of this magnitude are difficult to achieve by UVCPL photolysis. The extinction coefficients of the enantiomers of aliphatic amino acids for UVCPL are not very different ($g \cong 0.02$), both enantiomers are subject to photolysis, and substantial enantiomeric excesses are achieved only as the reaction approaches completion. For example, it can be seen from the theoretical treatment of Balavoine et al. (1974) that a practical limit for *ee* of about 9% is reached for a fixed population of aliphatic amino acid molecules subjected to irradiation with UVCPL. (For $g \cong 0.02$, $ee = 9.2\%$ at 99.99% decomposition.) It seems likely that in any natural setting UVCPL irradiation would occur under conditions inferior to the optimized conditions used in laboratory studies and, consequently, that enantiomeric excesses values smaller than maximal, perhaps much smaller, would be observed if asymmetric photolysis of a racemate were the operative mechanism. From this perspective, some of the L-excesses measured for the meteoritic amino acids seem quite large, which raises doubt about UVCPL as the cause if the process is conceived of in terms of the laboratory model, i.e., a single exposure of a fixed population of molecules. In principle, UVCPL can effect an enantiomeric excess in an amino acid not only by the asymmetric photolysis of its racemate but also by synthesis; however, such photosyntheses are also limited to enantiomeric excess values governed by the g-value, i.e., approximately 2%.

However, two possibilities envisioned by Balavoine et al. (1974) seem worth considering in this context. If a mechanism existed whereby the residual fraction of photolyzed amino acids could accumulate from a large volume and experience a second exposure to UVCPL, this time starting with the small enantiomeric excess achieved previously, a further enhancement in the excess could be attained, although again at the expense of the total amount of amino acid surviving. Such a process of accumulation and re-exposure is conceivable as an interstellar cloud collapses in the process of nebula formation. The second possibility is the secondary formation of amino acids by an asymmetric catalyst. In this case one must imagine the formation of an asymmetric catalyst by the preferential photolysis of a racemic compound and this enantiomerically enriched catalyst then acting to promote the formation of amino acids with substantial enantiomeric excesses. As described in Sect. 3.10.5, in some autocatalytic reactions even small enantiomeric excesses in a chiral initiator can have dramatic nonlinear effects on the chirality of the reaction products.

Magnetochiral photochemistry (Rikken and Raupbach, 2000), which was discussed in Sect. 3.9, is possibly another explanation for the enantiomeric excesses

observed in meteoritic amino acids. In this case, photochemistry with unpolarized light propagated parallel to a magnetic field would have been the asymmetric agent that influenced the organic chemistry of the interstellar medium in a region that contributed to meteoritic matter. The enantiomeric excesses achieved would have depended on the magnetic field strength. Presumably, magnetic fields of widely varying field strength exist near stars embedded in interstellar clouds.

3.12 Hypothesis and Summary

As we have seen, life on Earth is inextricably linked to homochirality and the origin of the latter remains a key unanswered question within the larger origin of life problem. In the foregoing sections we have attempted to provide the reader with a basic understanding of chirality as it pertains to organic compounds and then to review some of the more significant ideas that have been put forward with respect to the origin of the homochirality of life. In this section we describe a scenario based on our own evaluation of the many mechanisms that have been suggested. We assume that homochirality was achieved by prebiotic chemistry, i.e., by purely physical/chemical processes operating before the origin of life. We include within "prebiotic chemistry", chemistry that took place in the presolar cloud, as well as chemistry that might have unfolded from it within the solar nebula and on the early Earth. This may encompass reactions of molecules that eventually, in the course of evolution, completely or largely disappeared, for example, the α-methyl amino acids. In evaluating the suggested mechanisms we have considered whether they seem to have a reasonable chance of having operated within the constraints set by the conditions, to the extent that we can know them, that obtained on the prebiotic Earth. We have also been guided by Occam's Razor, the dictum that the best hypothesis is the one that minimizes the number of required assumptions.

Hypothesis: Terrestrial homochirality is a consequence of the postaccretional provision of organic compounds, particularly nonracemic amino acids, by the fall of meteorites, micrometeorites, and possibly comets on the primitive Earth. The enantiomeric excesses that initially characterized the amino acids were amplified at the time of pre-biotic polymerizations alternating with partial hydrolyses. The resulting polypeptides (not necessarily constituted of the contemporary protein amino acids) were necessarily asymmetric and some were endowed with catalytic properties. These polypeptides (protoenzymes) influenced the chirality of the products formed in their catalytic reactions by either the production of a specific enantiomer from achiral reactants or by the selection of a particular enantiomer in the case of chiral reactants.

This hypothesis is based on the following observations and experimental results described in more detail previously:

– Enantiomeric excesses ranging up to 15% are observed in α-methyl-α-amino acids isolated from carbonaceous chondrites impacting the Earth now. Such

amino acids were very likely present and probably more abundant on the primitive Earth when meteoritic, micrometeoritic and cometary infalls were more intense than they are today.
- Partial polymerization of amino acids coupled with partial hydrolysis is an effective amplification mechanism of small enantiomeric excesses. Polymerization reactions are a necessary feature of prebiotic chemistry.
- The α-methyl amino acids form unusually stable helical structures and are thus particularly subject to amplification of their initial enantiomeric excesses by polymerization. Furthermore, they do not readily racemize and the gains achieved in their enantiomeric purity are not susceptible to loss as in the case of their α-hydrogenated counterparts.
- Random polypeptides are sometimes endowed with catalytic activity (Fox and Krampitz, 1964).
- Folded helical polypeptide conformations are inherently asymmetric and the binding of chiral substrates will necessarily be chirospecific and lead to pervasive chiral specificity and eventual homochirality.

The symmetry breaking postulated in this hypothesis is presumed to be due to irradiation of the organic matter of the presolar cloud by UVCPL produced by either a stellar source or by scattering. In this respect, the hypothesis is a more specific version of the one suggested by Pasteur more than a century ago, according to which terrestrial homochirality could be the consequence of *"des actions dissymétriques dont nous pressentons l'existence enveloppante et cosmique"* (Valéry-Radot, 1968). The production of enantiomeric excesses in amino acids by UVCPL is well documented by laboratory studies carried out even under low-temperature interstellar-grain conditions. In this case, the terrestrial preference for L-amino acids rather than D-amino acids would have been a matter of chance and life on extrasolar planets could have the same or the opposite chirality with equal probability as nothing requires that circularly polarized light have the same helicity in all protostellar clouds. The magnetochiral effect is also an attractive possibility; however, it has been subject to laboratory verification only with respect to the displacement of an equilibrium mixture and has not, as yet, been shown to affect stable enantiomers, i.e., enantiomers like those of amino acids that are not ordinarily in rapid equilibrium.

The hypothesis proposes the prebiotic amplification of the small initial enantiomeric excesses by polymerization. Insofar as polymerization leads to even weakly catalytic polypeptides, it also has the potential for providing, at the culmination of the prebiotic period, not only homochiral amino acids, but also a more extensive organic milieu with not only chiral specificity but also specificity with respect to the compounds represented. This latter specificity would arise as a consequence of the statistical impossibility of the formation of all polypeptide sequences, i.e., all catalytic activities, as well as the improbability of the formation of their enantiomeric forms. Although this hypothesis provides an explanation for the origin of both chiral and molecular specificity, it should

be noted that it is silent with respect to the vexing problem of how certain catalytic polypeptides, formed at first by chance, could be reproduced, that is, in regard to the essential event that marked the transition from a prebiotic to a biotic world.

The possibility that the small enantiomeric excesses in the amino acids present on the early Earth acted as chiral initiators in Soai-type autocatalytic reactions is an attractive idea. In this way, large enantiomeric excesses could conceivably have been rapidly achieved. We expect that further research in this area will lead to the demonstration of similar effects in prebiotically more realistic aqueous phase reactions but, unless/until this is achieved, Occam's Razor causes us to favor the well-established polymerization–hydrolysis amplification mechanism.

Insofar as this hypothesis postulates "polypeptides first" with respect to the establishment of homochirality as well as early catalytic activities, it is incompatible with an exclusively RNA world, although it would not be incompatible with an RNA world in which, once homochirality was established, polypeptides played a subsidiary role. One might imagine that polypeptides in which α-methyl amino acids were important had, for reasons unknown, a limited future and that the rise of the more familiar nucleic acid-protein world awaited the exclusive use of the more easily (bio)synthesized α-hydrogen amino acids for protein synthesis. As a corollary to this hypothesis, one might postulate that an early catalytic polypeptide had the ability to polymerize formaldehyde to D-ribose and thus solved one of the two chirality problems that must be dealt with on the way to an RNA-world.

With regard to other possible symmetry-breaking mechanisms, we would note that hypotheses invoking specific adsorption on natural mineral surfaces to break symmetry suffer from the fact that, insofar as is known, the enantiomorphic forms of minerals occur equally; thus, unless the origin of homochirality was spatially confined to a very small area/volume, any enantiomeric excess achieved would be countered by a nearby equal and opposite excess. As discussed previously, symmetry breaking by crystallization effects requires a concentration and degree of purity that seem unrealistic under prebiotic conditions.

The violation of parity is difficult to dismiss because of the intuition that such fundamental asymmetry might have far-reaching consequences. However, enantiomeric excesses in chiral molecules deriving from parity violation have not been demonstrated. Furthermore, it is not possible to see how such very small excesses could have emerged from the "noise" of random statistical fluctuation to a degree that would allow their amplification. The possibility that this "noise" itself, i.e., the statistically allowed excursions away from the perfect racemic state, provided the symmetry breaking for the origin of homochirality is an interesting possibility made more plausible by the demonstration of their apparent amplification in the "Soai reaction." If a similar reaction can be shown to occur under aqueous, prebiotic conditions a statistical symmetry breaking must be seriously considered for the origin of homochirality.

3.13 Homochirality Analyses in the Solar System and Beyond

Exobiologists have taken an interest in homochirality as a signature of life and attention has been given to the analysis of chirality (or, more precisely, enantiomeric excesses) beyond the terrestrial environment by the SETH (search for extraterrestrial homochirality) project. SETH could be accomplished remotely on various Solar System bodies by landers equipped with detectors of enantiomeric excesses such as miniaturized polarimeters (Mac Dermott, 1996) or chromatographs with chiral support materials (Meierhenrich et al., 1999). The Rosetta mission to the Churyumov-Gerasimenko comet which was launched in February 2004 and that will reach the comet in November 2014 involves a SETH. SETH also encompasses the broader goal of finding the remains of life and could, for example, contribute to the validation of chemical fossils on other bodies of the Solar System such as Mars. However, diagenesis is accompanied by partial and ultimately complete racemization of chiral molecules and this poses a problem for the use of chirality as a signature of past life. This record is written with ink that inevitably fades with the passage of time. It inevitably fades in terrestrial sediments and must in all sediments (Bada and Miller, 1987; Bada and McDonald, 1995). SETH assumes the necessity of homochirality for life and as long as we know only one form of life it is not possible to know with certainty whether homochirality is an absolute requirement for life although it seems highly probable that it is. The enantiomeric excesses found in meteoritic amino acids add another complication as they are of abiotic origin and widely distributed. It seems clear that drawing the correct inferences from extraterrestrial chirality measurements will require their interpretation within a broad chemical, morphological, and geological context. It is also necessary to remember that, if extant or extinct life on Mars were discovered to have the same molecular homochirality as that of terrestrial life, the meaning of this discovery would not be unambiguous. Transfers of matter between Mars and the Earth are relatively frequent on a time scale of the age of these planets and such transfers may allow the insemination of one planet by the other (Mileikowsky, 2000).

The study of homochirality outside the Solar System, *SEXSOH* (search for extrasolar homochirality) will probably be a goal of future missions but at present, it is too early to predict when (and even how) observations might be carried out.

Dedication

This chapter is dedicated to Kurt Mislow in recognition of his 80th birthday and with appreciation for his many experimental and theoretical contributions to the modern understanding of chirality and stereochemistry in general.

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