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From parity to chirality: chemical implications revisited†

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Abstract

Parity violation represents an essential property of particle and atomic handedness used to cope with the complex phenomenon of asymmetry in the universe. At the molecular level, however, numerous experiments suggest that parity-violating energy differences have not determined the amplification and propagation of homochirality. Asymmetric transformations conducted under far-from-equilibrium conditions reveal the existence of non-linear autocatalysis which is stochastic in nature. In any event and, globally considered, chirality appears as a unifying characteristic of our visible environment with evolutionary implications, thereby suggesting areas for productive research.

Contents

1. Introduction

Life, at least as we know it, is invariably linked to homochirality. Living organisms on the early Earth would have selected biomolecules of a certain handedness, often accompanied by a

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† Dedicated to the memory of André Collet (1945–1999).

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conformational bias, to carry out specific functions such as regulation or replication. A traditional belief has held that the preponderance of the D- or L-configuration in biomolecules was the result of a better choice leading to structures which had the ability to copy themselves and so to replicate or to recognize a complementary site. This is not likely to be true, since a mirror world would have been equally efficient, and in fact the opposite enantiomeric forms (e.g. D-amino acids) have survived in primitive or simpler organisms. This anti-Darwinian vision would more likely be consistent with a question of availability. The enantiomeric homogeneity could be the consequence of a statistical imbalance that was further propagated by any sort of amplification mechanism, which will be discussed later.

While the possible role of chirality as a key element for the origin of life has been confined to specific surveys, it is surprising that recent books[1–5] and reviews[6] dealing with the chemical basis of the origin of life pay little or no attention to the subject. It is also astonishing that major biochemical references do not discuss the topic in detail, with the sole exception of the classical Ogston's three-point theory, a model accounting for the stereospecificity of enzymes.[7,8] An early and interesting book by Miller and Orgel,[9] discussed, among other questions, why all amino acids in proteins have the L-configuration and why all sugars, and hence nucleotides, have the D-configuration. These authors compared the structure of DNA with a spiral staircase. The DNA composed of D-nucleotides affords a regular right-handed double helix, while a left-handed arrangement would result if the double helix were synthesized from L-nucleotides. Nevertheless, a DNA consisting of both D- and L-nucleotides could not give a truly helical structure because its handedness would be changing.

However, the search for molecular chirality focused on biopolymers offers a complicated situation, since their handedness had to be selected at an early stage of evolution. Two immediate and interlocked questions about the emergence of the chiral substances that once formed the basis for life have been repeatedly addressed:[10] (a) what is the physical origin of chirality beyond a three-dimensional arrangement of atoms or groups; and (b) what is the origin of biochirality; in other words, the reason favoring one enantiomer over the other. Neither of them has been completely solved, but it is clear that a solution to the physical origin could provide reasonable theories as to where the energy for molecular discrimination came from. The discovery of nonparity conservation in weak interactions suggested that this natural force could have a series of fundamental implications. The further electroweak unification also led to the fact that certain particles and atoms can be denoted as chiral entities. Thus, asymmetry appears as the unifying property of matter: the universe is inherently asymmetric (or chiral in the language of chemists), even though we do not know why. Unfortunately, interpretations based on the theoretical background of quantum mechanics are extremely complicated, requiring a mathematical formalism beyond the scope of this review. However, most chemists, including the practitioners of asymmetric reactions, are aware of the fundamental discovery of parity violation which has been invoked as the source of the chiral bias at a macroscopic molecular level. It is not our purpose to explain this topic to an audience of organic chemists as other specialized articles have tried to fill this gap.[11–13] We shall briefly discuss what parity violation means, its energetic consequences on enantiodiscrimination, and the attempts to induce asymmetric transformation with elementary particles and radiation sources.

The subsequent topics involve other central issues in the discussion of the origin of biochirality on Earth, and by implication on Earthlike planets elsewhere if they exist, such as influence of the external fields, extraterrestrial chirality, and naturally-occurring amplification mechanisms. The latter issues have also been covered in detail, and separately, in recent revisions.[14–18] The information provided here is not comprehensive, but the aim is to offer a fair, balanced, and if possible, unified presentation of topics. In so doing, chiral evolution will be appreciated as a particular domain of prebiotic chemistry which should stimulate, it is hoped, future developments.

2. Parity violation

"*The more extraordinary the claim, the more extraordinarily well-tested the evidence must be. The person making the extraordinary claim has the burden of proving to the experts at large that his or her belief has more validity than the one almost everyone else accepts*" Carl Sagan

Before going on, it is convenient to recall the four fundamental forces present in the universe: strong and weak interactions, electromagnetism, and gravity. The former is the binding force of the nucleus that holds together the strong interacting particles. The weak force was indirectly known following the discovery of radioactivity.

Since the early 1930s, it had been assumed that the basic forces of nature cannot distinguish between left and right. This conservation of parity had long been known in the basic laws that describe the structure and interactions of macroscopic objects, but it was now extended into subatomic particle interactions. This does mean that nature would equally be effective in either of two enantiomorphic ways. Nevertheless, as noted by Gardner in his well-acclaimed assay 'The ambidextrous universe',[19] such a conservation does not mean that a particular handedness cannot be perceived in the universe. For instance, the planets of our solar system move through the galaxy in such a way that all of them trace orbits of the same handedness. Here, we can denote explicitly our solar system as 'asymmetric'.[20] But there is no doubt that other planets in a different galaxy will trace orbits of opposite handedness. In other words, the universe would be ambidextrous.

Fortunately, perhaps, the laws of nature are not completely blind to the equivalence under mirror symmetry. In 1956 two Chinese-born physicists, Tsung-Dao Lee and Chen Ning Yang, proposed that parity is not always conserved. Their classical paper 'Question of parity conservation in weak interactions'[21] analyzed numerous cases of strong and weak interactions and showed that the evidence for parity conservation applies only to the first interaction and not to the weak one. From a historical perspective, it is pertinent to mention here that the discovery of Yang and Lee runs parallel to that of van't Hoff and LeBel. Like the proponents of tetrahedral carbon, these physicists were then young (Lee 30, Yang 34) and unknown within the scientific community. Moreover, they were not the first in suggesting that parity could be violated. Other charismatic physicists, such as Richard Feynman, did consider this choice, but they also thought the idea very unlikely.[22] This time Yang and Lee were fortunate because no 'Kolbes' appeared on the horizon refuting their theory, and they won the Nobel prize in physics in 1957.

What is astonishing in this story is the fact that Yang and Lee were not skillful in the lab (Lee had never had any experience), but they proposed that weak interactions should show some measure of built-in right- or left-handedness that might be experimentally verified. This hypothesis was conclusively proven the following year (1957) by C.-S. Wu and her associates, who demonstrated that the electrons ejected together with antineutrinos from unstable cobalt nuclei (^{60}Co) in the process of β-decay are predominantly left-handed.[23,24] The spin vector of such electrons is opposite to their direction of travel; that is, their spin rotation is that of a left-handed screw. Likewise, the β-decay of ^{58}Co to ^{58}Fe occurs with the emission of a positron and the corresponding neutrino.[25] In this case the positron possesses an inherent right-handedness and are preferentially projected in the antiparallel direction to the spin axis vector of the antiparticle (Fig. 1).[26]

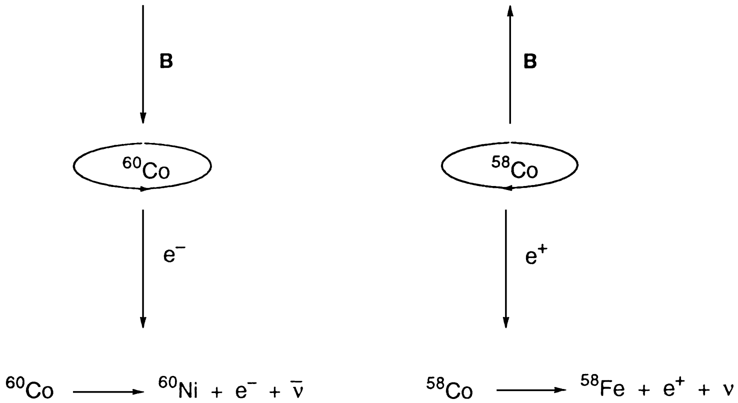


Figure 1. Parity non-conservation in the weak interaction

Although many readers have heard of this classical experiment, most chemists are equally unaware of its importance or how it was designed. The team led by Wu found an initial and relevant technical problem. ^{60}Co is a radioactive isotope that regularly emits electrons. If one assumes for these atoms a spherical model, the electrons of a nucleus of ^{60}Co will be projected in all directions. Nevertheless, when a strong magnetic field (**B**) is applied to cobalt nuclei, which are also cooled to temperatures near absolute zero (liquid helium) to reduce the motion caused by heat, these atoms will be aligned and the β-decay emission will occur in two directions: parallel or antiparallel to the field axis. Colloquially, electrons will be ejected toward the north or the south ends of the magnetic field. If the β-decay is a symmetric process, an equal number of electrons should be emitted in either direction. On the contrary, a larger number of electrons ejected in one direction does denote a particular handedness.

In the nucleus, the weak interactions are mediated by charged and neutral massive W and Z particles. Nevertheless, the weak charged currents have a minor importance for the asymmetry of the nuclei. In fact, as we shall discuss later, enantiodiscrimination of racemates by radionuclides or polarized electrons is not completely conclusive. In the late 1960s a group of researchers was able to unify the weak and electromagnetic forces as two closely related parts of the so-called electroweak theory.[27,28]

From a chemical viewpoint, the main consequences of the electroweak interaction are firstly, the fact that all atoms are inherently chiral due to parity violation in the compound nucleus, in other words, *a universal optical activity*. Secondly, because of the inherent handedness of the electron, the right-handed and left-handed enantiomers in the world of matter do not have the same energy. Only an enantiomer composed of electrons and other particles will have a 'true enantiomer', with identical energy, made up of positrons and other antiparticles in a parallel universe of antimatter.[29,30] As pointed out by Barron "*the ordinary enantiomers found in stereochemistry are not strictly degenerate*".

The optical activity resulting from the electroweak interaction which is proportional to Z^6, Z being the atomic number, is only important for the heavier atoms. Tiny optical rotations and ORD (optical rotatory dispersion) measurements have been observed in vapors of heavy metals (Tl, Pb, Bi, Cs).[31] The atomic electroweak optical activity for lighter atoms (C, N, O) is almost negligible and, in any event, smaller by a factor of 10^{-9} to 10^{-12} than the molecular optical activity predicted by the electromagnetic theory for two enantiomers composed of such atoms (e.g. a chiral carbogenic organic compound). If one considers the overall optical activity as the sum of the electroweak and electromagnetic contributions, two enantiomers will have values which are opposite in sign, but not the same magnitude for each enantiomer, which is a manifestation of parity violation in free atoms.[32]

Also, in a chemical context, the immediate consequence of parity violation (or more precisely, of the electroweak interaction) in chiral molecules is the existence of a parity-violating shift of the electronic binding energy, E_{pv}, which is positive for one enantiomer and negative, and of equal magnitude ($-E_{pv}$), for its mirror image.

Accordingly, there is a parity-violating energy difference, hereafter denoted as PVED, between two enantiomers (Eq. (1)):

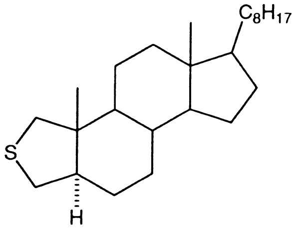
$$\mathrm{PVED} = \Delta E_{pv} = E_{pv} - (-E_{pv}) = 2\ E_{pv} \tag{1}$$

This difference results in a small enantiomeric excess (ε)[33] given by Eq. (2) for two chiral states *R* and *S*:

$$(R-S)/(R+S) = \Delta E_{pv}/2kT = E_{pv}/Kt = \varepsilon \tag{2}$$

Like optical activity, the energy shift E_{pv} depends on the configuration and the average molecular conformation. Furthermore, the PVED could be observed for a molecule with a given handedness or for any transient chiral state, such as transition structures. Since the two enantiomers of a chiral molecule are not energetically equivalent, the transition states of an enantioselective reaction, either thermal or photochemical, are in fact diastereomeric structures.

The absolute magnitudes of such PVEDs are too small to be measured experimentally by our current instruments available, but they can be evaluated by theoretical calculations. Thus, in the thiacholestane derivative **1** containing a thioether linkage,[34] the study considered this triatomic chromophore in the chiral field of the other atoms of the steroid skeleton. Bearing in mind the Z^6 dependence of the E_{pv}, a heavy sulfur atom should give an enhanced PVED. Nevertheless, the parity-violating energy shift (E_{pv}) is only -2×10^{-22} au (atomic units).



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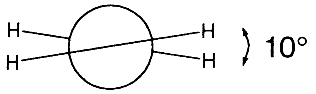

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The energy shift E_{pv} can also be estimated for chiral conformations[35] such as the enantiomers of the chiral ethylene **2**, viewed through Newman projection, with a dihedral symmetry (D_2) owing to a 10° torsion of the two methylene groups around the carbon–carbon bond.[34] Ab initio calculations give a E_{pv} value of $+2\times10^{-20}$ au for the (*R*)-isomer of the D_2 ethylene, and in this case, the (*S*)-counterpart will become stabilized by the PVED of -4×10^{-20} au. Compared with **1**, this result suggests that an inherent asymmetry provided, for instance by a conformational bias, may be more important than a symmetric unit (C–S–C linkage) within an asymmetric environment, despite the dependence on the atomic number.

There is no doubt, however, that the most important results, and perhaps conclusions, should be attained for typical biomolecules such as amino acids or sugars which constitute two basic pillars of the terrestrial homochiral biochemistry. The natural L-α-amino acids are stabilized by

PVEDs in the order of $\sim 10^{-20}$ to 10^{-17} hartrees,[36–39] equivalent to 10^{-17} to 10^{-14} kT at room temperature.[40] Likewise, ab initio calculations for the two main regular arrangements of the polypeptides (the α-helix and the β-sheet), indicate that the polymers constructed on the naturally-occurring L-amino acids are stabilized over the D-counterparts by a similar difference.

D-Glyceraldehyde and D-deoxyribose are equally PVED-stabilized by some 10^{-20} hartrees,[41] and the right-handed helical DNA is stabilized by about 10^{-20} hartrees per monomer.[42] It is noteworthy that larger PVEDs, 10^{-17} hartrees, corresponding to 10^{-14} kT, have been found in thiosubstituted DNA analogs,[43] thereby highlighting the amplification effects of heavy atoms. The natural phosphate link ($O–PO_2–O$) is replaced by sulfur atoms ($O–PS_2–O$, $S–S–CH_2$, and S–S–S) with the natural right-handed helix being also the more stable arrangement.

The absolute magnitudes of the PVED between enantiomers (10^{-17}–10^{-14} kT), taken as a free energy difference, indicate that an enantiomeric excess $\varepsilon = \Delta E_{pv}/kT = 10^{-17}–10^{-14}$ would be expected. In molecular terms, that imbalance corresponds to an enantiomeric excess of some 10^6–10^9 molecules of one enantiomer per mol of the corresponding racemate at ambient temperature and under thermodynamic equilibrium. This very small, almost negligible excess ($\sim 10^{-13}$–10^{-16}%, note the value of the Avogadro number!) would need to be dramatically amplified to give values consistent with the homochirality observed in living systems.

The hypothesis that β-decay could be the origin of biological chirality was in fact launched shortly after the discovery of parity violation.[44,45] The mechanism proposed by Vester and Ulbricht (the V–U hypothesis) suggests that during the passage of longitudinally polarized β-decay electrons through a compound, the electrons slow down with the concomitant emission of γ-rays (the so-called 'bremsstrahlung' phenomenon). Since the γ-radiation would be circularly polarized, the resulting photochemical reaction might lead to an enantiomeric excess (vide infra). Garay reported that separate β-irradiations of D- and L-tyrosine solutions by ^{90}Sr resulted in a greater decomposition of the D-enantiomer, although the enantiomeric composition of the samples was not explicitly tested, but only the reduction in the intensity of UV absorption by the amino acids.[46] Positive results were also obtained by interaction of positrons and spin-polarized electrons,[47] although the small values of enantiodiscrimination are no more large than the experimental error. Theoretical estimations suggest that the probability of β-particle absorption is different for amino acid enantiomers.[48] Further studies with high energy β-particles generated from radioactive ^{32}P nuclei in solutions containing (*R*)- or (*S*)-butyric acid derivatives show a relative increase in radiolysis of one of the enantiomers,[49] but the origin of enantioselection is uncertain.

We wonder why would nature choose a parity violation-based configurational bias which would take an extremely long time. In other words, what would have happened if the parity conservation had not fallen? Then, either a physical force characteristic of matter would have caused the enantiomeric bias in nature or there was a mechanism during evolution leading to homochirality.[11–15,50–52]

An appropriate scenario to detect PVEDs can be chiral crystals because they contain a large number of molecules. It is well known that the naturally-occurring quartz consists of chiral crystals (Section 4.1.2), namely L-(–)-quartz and D-(+)-quartz. An early report described a slight excess (~1%) of the former over the latter, the excess being found in all localities sampled over the world.[53] However, a further study reviewed a much larger number of samples (27059 compared with 16807 samples described in Ref. 53), noting that there is an insignificant 0.3% excess of the opposite D-(+)-quartz.[54] Since the terrestrial distribution of quartz crystals is not wholly racemic, the question now is whether that statistical deviation could be determined by parity violation. Theoretical calculations[43,55,56] show that L-quartz is PVED-stabilized by $\sim 10^{-17}$ kT per SiO_2 unit. Again, the value is practically negligible, although it might be amplified on a realistic time scale.

Even though the enantiomeric excess of quartz crystals is within the statistical error, it has been proved that dextrorotatory α-quartz preferentially adsorbs D-alanine hydrochloride, whereas the levorotatory quartz adsorbs the L-enantiomer from a racemic mixture with ~1% selectivity.[57] If one combines this enantioselection with ~1% *ee* of L-quartz, then it would give rise to an overall electroweak enantioselectivity of $\sim 10^{-4}$, considerably larger than the PVED observed for individual molecules.[38] In fact, the difference between the adsorption energies of the two enantiomers of alanine lie in the range 0.13–0.17 kJ/mol, data corroborated by recent calculations.[58] For the positive ion, the energy difference on α-quartz is found to be 0.3 kJ/mol. The study has also been extended to the adsorption of L- and D-alanine on kaolinite, a clay mineral capable of existing in two chiral enantiomorphous arrangements denoted A and B.[59] Adsorption of the L-enantiomer on the structure of kaolinite A is favored by 0.03 and 0.01 kcal/mol (0.14 and 0.04 kJ/mol) for the positive ion and the zwitterion, respectively. Obviously, on the structure of kaolinite B, the D-amino acid is preferentially adsorbed with respect to the L-form. It should also be pointed out that kaolinite A is PVED-stabilized with respect to structure B.

As before, the exponential dependence of ΔE_{pv} on Z suggests that crystallization of a labile racemate containing a heavy atom might afford a shift in the enantiomeric distribution. Together with quartz, it has been reported that crystallization of potassium dodecatungstosilicate in aqueous solutions gives preferentially dextrorotatory crystals, and likewise potassium dodecamolybdenosilicate crystallizes with a small enantiomeric excess.[36] Crystallization of allyl ethyl methylanilinium iodide gives predominantly dextrorotatory crystals,[60] and a salt containing a heavy actinide, sodium uranyl acetate, also crystallizes in the (cubic) space group $P2_13$,[61] one of the groups possible for chiral molecules.[62]

A very recent study by Hungarian authors claims that the enantiomeric excess found in the crystallization of transition element-containing salts has its origin in the contribution of the parity-violating weak interaction.[63] The authors chose racemic mixtures of (+)- and (–)-sodium ammonium tartrate, tris(1,2-ethanediamine)cobalt(III), and tris(1,2-ethanediamine)iridium(III). No appreciable enantiomeric selection could be detected in the case of tartrate, whereas enantiomeric excesses appeared in the crystallization of the cobalt and iridium complexes as evidenced by the distribution of the circular dichroism (CD) spectra. Thus, crystallizations of racemic sodium ammonium tartrate fitted a symmetric Gaussian curve around zero with no significant CD shift. However, in the case of the cobalt or iridium complexes, the distribution of the CD signals for the crystalline materials gave asymmetric Gaussian curves, shifted from the zero value and broadened relative to the distribution for the initial racemate and for triply-distilled water. Through a statistical analysis, the authors also calculated the value of $\varepsilon = \mathrm{PVED}/kT$ and found the expected magnitude of 1×10^{-17} for tartrate, but 8.3×10^{-14} and 4.5×10^{-11} for cobalt and iridium complexes, respectively, thereby evidencing how PVEDs grow with the atomic number Z. Still such values are very small and other authors have demonstrated that the theoretical values of PVEDs are strongly dependent on the quality of methods.[64,65]

The above-mentioned work by Szabó-Nagy and Keszthelyi has been the subject of considerably controversy and it is difficult to ascertain whether PVED does effectively play any role. The authors used racemic material in the first place for their experiments by mixing (+)- and (–)-molecules to produce racemic solutions with CD values of zero within the experimental error. This is in fact questionable assuming the statistical fluctuations of racemates. A further statistical analysis found that the Ir(III) data are *statistically* significantly asymmetric, in other words, they deviate insignificantly from an asymmetric Gaussian distribution. No significant conclusion, however, could be extracted from the tartrate and Co(III) data.[66] Accordingly, the results are not conclusive, albeit in the case of Ir(III) the enantioselection might be supported by the PVED. Moreover, it is likely that any enantiomeric excess observed in crystals may not reflect the PVED, but rather a chiral nucleation, a topic that will be discussed below in connection with amplification mechanisms.

The last word, still tantalizing result, about the effect of the electroweak force operating within the nuclei of atoms, has been released in a report in *Science*.[67] The authors claim that crystallization of sodium chlorate from a solution irradiated by anti-parallel spin electrons from radioactive strontium resulted in an excess of right-handed crystals, while crystallization exposed to parallel spin positrons gave preferentially left-handed crystals.

3. Absolute asymmetric synthesis

"*I'll tell you all my ideas about looking-glass house. The books are something like our books, only the words go the wrong way. Perhaps looking-glass milk is not good to drink*" Lewis Carroll

Deracemization processes capable of producing a breaking of mirror symmetry could have occurred only if there exists an external force countering effectively the tendency to restore the racemic state. The influence of such chiral fields is denoted *absolute asymmetric synthesis* which has recently been reviewed by us and others,[12,15,16] and consequently a repetition of fundamentals will not be included here. The basic question one should address to understand the effect of an external field on racemization is which field is inherently chiral. Then, an interaction with chiral molecules would lead to a diastereomeric relationship, a concept familiar to most chemists. The main problem is that, in the case of a field one must provide a dynamic component, particularly the direction of motion, which is not included in the classical concept of chirality.[68] A reasonable answer was suggested by Barron in terms of *true and false chirality*.[69,70] True chirality is exhibited by systems capable of existing in two enantiomeric states that are interconverted by space inversion (equivalent to mirror reflection), but not by time reversal (*T*, which corresponds to reverting the motions of all the points in the object) combined with spatial rotation. As noted previously,[12,15] it is not the aim to add much ado about semantics, as the words *true* and *false* do not necessarily mean *possible* or *impossible* absolute asymmetric syntheses, especially under non-equilibrium conditions. Such concepts have demonstrated a great predictive power, thereby establishing why irradiation with circularly polarized light (CPL) may lead to an enantiomeric excess from a racemate, whereas a magnetic field alone will be ineffective for this purpose. Furthermore, it has been theoretically demonstrated that the circularly polarized field can stabilize chiral molecules.[71]

The chirality of translating spinning particles, such as electrons or photons in a circularly polarized light beam, appears evident by inspection of Fig. 2. Let us consider a particle translating with its spin projection parallel or antiparallel to the propagation direction. Parity interconverts right- and left-spin polarized enantiomers propagating in opposite directions, but *T* does not. Nor can the results of *P* and *T* operations be interconverted by any proper spatial rotation.

Now we should turn our attention to the situation of a spinning cone. Fig. 3 describes the application of *P* and *T* to this system. Space inversion gives rise to a mirror image that is not superimposed on the original. However, this is a falsely chiral system since *T* combined with a rotation through 180° perpendicular to the symmetry axis gives the same spinning cone as space inversion. Absolute asymmetric synthesis should not be expected, under equilibrium conditions, by means of this type of devices. Some irreproducible results have been reported, which were attributed to artifacts.[15]

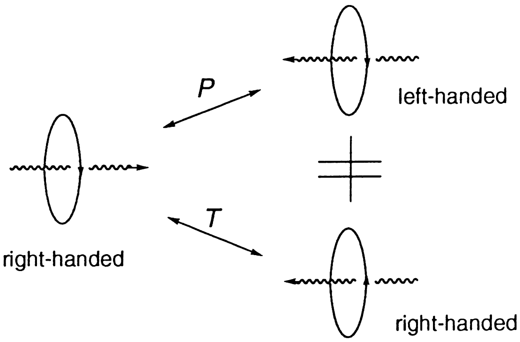


Figure 2. The effects of parity (*P*) and time reversal (*T*) on the motion of a translating spinning particle.

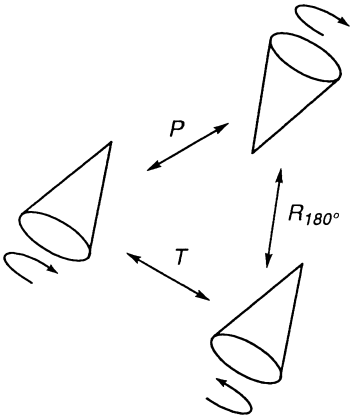


Figure 3.

But if the rotating cone is also translating along the axis of spin, the operation of time reversal followed by the 180° rotation generates a system that does not match that generated by space inversion. This is the situation of a vortex, which is in fact a chiral object (Fig. 4).

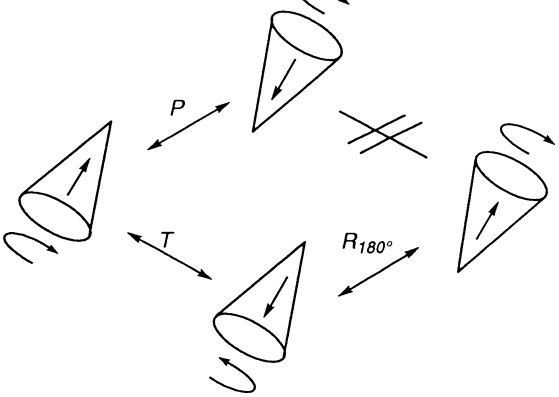


Figure 4.

4. Chiral evolution

"*The method of testing in the experimental sciences is characterized, not by inductive inference, but by deducing empirically testable claims from proposed theories*" Sir Karl R. Popper

Even if the matter is intrinsically chiral owing to the asymmetric electroweak interaction, one should assume that the chirality observed in the living systems would have moved from the negligible domain of parity violation to, in most cases, the experimentally obtainable 100% *ee*. Essentially this represents an amplification of chirality. On the scale of time, the question as to how long has amplification been occurring in the universe could go back to the origin of the universe itself. However, while all of the above discussion still remains at the roots of molecular physics, what we now call evolution did begin with the formation of our solar system and the primitive Earth. This fact reduces considerably the number and nature of hypotheses developed to account for this amplification,[11,14–16,72–80] albeit the putative effects of parity violation should also be considered.[13,80] Unfortunately, in an area in which the experimental verification can be extremely difficult and assuming that there is not yet a unifying mechanism, the most basic ideas referring to the homochirality of biological systems were already expressed over three decades ago.[81] It seems that "*the progress does come in circles or spirals, not linearly*".[82] Nevertheless, some hypotheses have been revealed to be unpractical based on statistical arguments, whereas exogeneous theories which claim an extraterrestrial origin of homochirality and life have been reinforced and enjoy a renaissance supported by recent observations and analyses of distant stars.

4.1. Biotic and abiotic processes

In general, the mechanisms proposed to explain the origin of homochirality can be divided into biotic and abiotic.[14,83] Biotic theories, also called *selection theories*, suppose that life emerged in a racemic environment and, the primitive organisms in an early stage of biochemical evolution, would have gradually selected one enantiomer (L-amino acids or D-sugars) as being more efficient to survive than the other enantiomer. Conversely, other competing life forms could have selected the opposite enantiomer, having a certain evolutionary advantage, by interaction with other non-racemic building blocks. These assumptions are evident by considering that proteins composed of D-amino acids are present in bacterial cells, numerous eukaryotes, and even in vertebrate brains.[84–88]

One of the most exotic biotic theories was proposed by Ageno in the early 1970s.[89] In a very early stage of biological evolution, living and sexually reproducing organisms composed of heterochiral (e.g. D/L) or homochiral molecules (D/D or L/L) could have developed from a mixed population of both enantiomers. However, individuals of opposite symmetries would have been sterile, thereby disfavoring the survival of chiral hybrids.

An immediate conclusion of biotic theories is that enantiomeric homogeneity is not a prerequisite or imperative for the origin of life. Under such conditions, it is senseless to speak about an energy difference between optically active molecules. It is consistent with biotic hypotheses that once the symmetry is broken, the initial selection of one enantiomer fixes the chirality of the resulting biochemical pathways via diastereomeric interactions. There is no doubt that our terrestrial life, based essentially on L-amino acids and D-sugars, and its mirror image counterpart should be equally efficient. The main drawback of biotic theories is that they are probably impossible to be tested experimentally. On the other hand, experiments[90] and a theoretical model[91] reveal that self-replication of homochiral macromolecules does not occur in a racemic medium.

In contrast, abiotic theories, which have now become preferred, suggest that life required an initial enantiomeric excess. In other words, the formation and evolution of primitive biomolecules (DNA, RNA, peptides or any kind of biological chimeras) would have been impossible without the establishment of an enantiomeric imbalance. Such an inhomogeneity could have occurred by chance or in a determinate way.

Chance or *random mechanisms* interpret that there was equal probability of forming either enantiomer. These include the spontaneous crystallization of conglomerates, enantioselective adsorption on quartz or clay minerals, or chemical reactions in chiral crystals or chiral phases (e.g. cholesteric liquid crystals). Then, one enantiomer by means of an autocatalytic process propagates the replication of the same handedness but inhibits the opposite one.[92]

Alternatively, *determinate mechanisms* suggest that some chiral physical interaction acting on racemates would have caused an initial, very small, enantiomeric excess which could subsequently be amplified. Examples of such chiral fields are circularly polarized light,[93] crystal-to-crystal photoreactions,[94] or photochemical reactions on the surface of a liquid crystal[95] or zeolites.[96]

Although one should expect mirror symmetry breaking in the case of a truly chiral influence such as polarized photons, achiral forces such as magnetic or gravitational fields under kinetic conditions might suffice.[15,97] The Earth magnetic field might have been a possible source of chirality,[98] and within this context the hypothesis suggested by Gilat[99] for the origin of homochirality has received a certain consideration. Gilat's idea is based on the asymmetric interaction between the magnetic moment, induced by currents in amino acids, and the terrestrial magnetic field (Fig. 5). If one considers amino acids such as tryptophan, valine, leucine, or phenylalanine having a hydrophobic side chain located at a water–air interface, the hydrophobic residue is attached to the liquid layer pointing towards the air while the polar groups are located in the aqueous phase. In the latter, charges move from the amino group to the carboxylate function, thereby originating an induced magnetic dipole (μ) with opposite directions for L- and D-amino acids. The interaction with the Earth's magnetic field (**B**) causes a small difference in the population of the two enantiomers at the interface given by Eq. (3):

$$\Delta n/n = 2\mu \times \mathbf{B}/kT \tag{3}$$

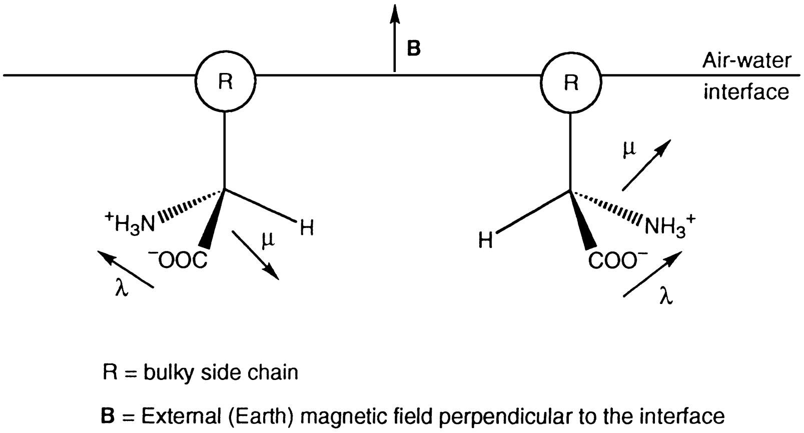


Figure 5. Gilat's hypothesis for enantiodiscrimination of amino acids induced by the terrestrial magnetic field. λ is the electric dipole moment and μ the induced magnetic dipole moment

A few comments about Gilat's work are necessary within the context of absolute asymmetric synthesis. The overall interaction constitutes an example of false chirality because electric and magnetic fields are involved. This means it could only operate under nonequilibrium conditions. Moreover, Equation (3) derives from the Boltzmann distribution, which only applies to a system at equilibrium. Then, at equilibrium, chiral enantiomers will always be degenerate in the presence of a magnetic field, even it they are aligned as on a surface (in Gilat's hypothesis), or in an electric field. Therefore, the Boltzmann distribution will give equal populations of the two enantiomers.[15]

Whatever, this hypothesis should be treated with caution because there are other practical difficulties such as the reversed directions of the Earth's magnetic field in the two hemispheres and the fact that the orientation has changed many times,[100] as well as possible inhomogeneities.

4.1.1. *Cosmic homochirality*

Determinate mechanisms, however, constitute a direct connection between terrestrial and extraterrestrial chirality since such forces, especially of gravitational or electromagnetic nature, are also operating in the universe. Assuming that a considerable amount of organic matter, chiefly in the form of interstellar dust, is delivered to Earth,[101] chiral biogenic compounds in our planet might have had an extraterrestrial origin. This represents a crucial issue in the discussion of the origin of homochirality on Earth, and presumably it will be a futuristic research area since the international space agencies are planning missions to visit comets and neighboring planets.[102–104]

In principle, there are two classes of celestial bodies that might deliver organic matter from space: comets and asteroids, which are different in both their composition and dynamics.[4] The latter objects are essentially rocky bodies and their fragments can be collected as meteorites, which are known to contain carbonaceous prebiotics such as amino acids. Recent analyses on the well-known Murchison meteorite indicate, after excluding terrestrial contamination, a slight enantiomeric excess of branched L-amino acids.[105]

In stark contrast, a comet is thought to be composed essentially of ice, along with organic matter and silicates in the form of dust. Such organics may be delivered to Earth or another planet when the comet passes through the solar system and close to the planet, or perhaps by an ancient impact with the Earth itself. It is by now quite accepted that organic molecules must have existed as nebular grains before the formation of comets and incorporated into the nuclei of comets during their formation.[106,107] Then, comets would have delivered organic dust and volatile matter on Earth and on the lunar surface.[108–110] Under these premises and likewise considering the rapid transport of optically active substances (comets have very high speeds when they reach the solar system, ~80 km/s), these objects are suitable places in the search for extraterrestrial homochirality.[104,111]

A reasonable objection, however, to the role of comets is the fact that they have extremely elliptical, nearly parabolic orbits. Asteroids co-orbit with the major planets in the solar system and have low eccentricities and inclinations. Asteroidal fragments approaching the Earth will have much lower speeds (~15–30 km/s) than comets and accordingly, the probability that their organic or volatile contents remain intact after penetrating the Earth's atmosphere will therefore be much higher.[112]

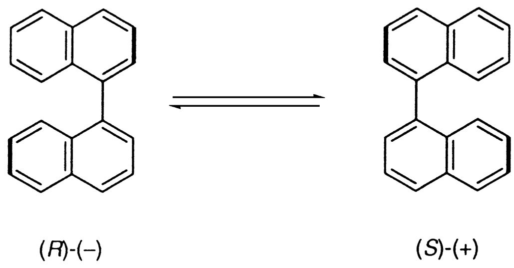
Even though comets and asteroids may account for the transport and delivery of chiral prebiotics, determinate mechanisms operating in the farthest reaches of the solar system or in distant galaxies and nebulae, and involving external chiral radiation such as circularly polarized light would have produced significant enantiomeric excesses from racemates or prochiral molecules. A hypothesis pioneered by Bonner and Rubenstein suggests that synchroton radiation from a rapidly rotating neutron star, which stems from a supernova explosion, will be circularly polarized (both in the UV and visible regions), and capable of interacting with interstellar organic matter.[113] Arguments validating this cosmic origin of chirality were pointed out by Bailey and co-workers, who found high levels of infrared CPL in the constellation Orion, arguing that such a radiation might have induced asymmetry in interstellar organic molecules.[114] Although infrared polarized light is of insufficient intensity to deracemize chiral molecules, spectral calculations suggest that radiation in the UV region is also present. CPL-mediated photochemical reactions should be considered one of the most plausible determinate mechanisms for the origin of enantiomeric excesses in the universe. Recent observations have also evidenced the presence of UV light in old and distant galaxies. With an exquisite resolution, the NASA Hubble space telescope has allowed, for the first time, the existence of hot blue stars deep inside an elliptical galaxy located at about 2.5 million light-years away in the constellation Andromeda. Hubble data indicate that the UV light arises from hot helium-burning stars at a late period of their lifetimes.[115]

4.1.2. Asymmetric autocatalysis

Studies in crystallization and polymerization are especially relevant since such large molecular entities—crystals and polymers—may be composed of achiral precursors, but their arrangement has a sense of handedness. The spontaneous resolution of racemates can be achieved by formation of individual crystals, each containing only one of the two enantiomorphic forms of the molecule. Here the optical activity resides in the chirality of the molecule like in Pasteur's experiment with racemic sodium ammonium tartrate, which crystallizes in hemihedral prisms. However, it is also known that certain achiral substances are able to form chiral crystals which are characterized by one of the 22 chiral space groups, actually as 11 pairs of enantiomeric space groups.[116] Among these substances are trigonal quartz having a helical arrangement of SiO_2 units, cinnabar (the red form of mercuric sulfide), or cubic sodium chlorate.

Like quartz, when a solution of $NaClO_3$ is allowed to evaporate, the resulting crystallization affords a statistically equal number of left- and right-handed crystals. Moreover, a large number of crystallizations of $NaClO_3$ evidences that there is no statistical excess of a particular enantiomer as one might expect from a process governed by parity violation. Nevertheless, Kondepudi and his associates demonstrated that, whereas crystallization from unstirred solutions gives rise to a statistical equal number of (+)- and (–)-$NaClO_3$ crystals, stirring does favor the formation of a large excess of one hand.[117] A similar result has recently been found in crystallizations of 1,1′-binaphthyl melts, under stirring too.[118] This substance racemizes rapidly at a temperature as high as 180°C (Scheme 1). When the melt is cooled from 180°C (to ensure that the starting material is not optically active) to 150°C and allowed to crystallize, a statistically equal number of (*R*)-(–)- and (*S*)-(+)-crystals results. The conglomerate has a melting point of 158°C, while the racemate melts at 145°C.

When the same crystallization is performed with constant stirring, large enantiomeric excesses (~80%) are produced in most crystallizations, albeit there is a random distribution of *R* or *S* enantiomers, in other words, the process is stochastic in nature. The overall crystallization is an *autocatalytic secondary nucleation* in which stirring causes the formation of new crystal nuclei by breaking up the structure of the parent growing crystal. Stirring also contributes to spread such secondary nuclei around the solution. Then, crystals which grow into daughter crystals have the same homochirality as the mother crystal.[119] This feature differentiates s*econdary nucleation* from the *primary nucleation* observed in the spontaneous resolution of conglomerates.[120] Apparently,



T_{rac} = 180 °C

M.p.(conglomerate) = 158 °C

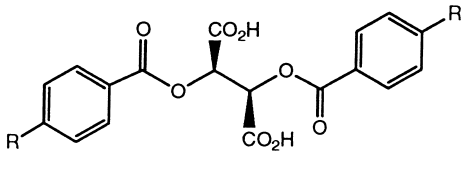
Scheme 1. Rapid racemization of 1,1′-binaphthyl

secondary nuclei are generated from a crystal only when its size exceeds a certain threshold size. The latter together with the influence of other parameters have been gathered in a kinetic model that reproduces well the experiment.[121]

The autocatalytic nucleation has been videotaped,[122] and SEM (scanning electron micrography) studies reveal that secondary nuclei may arise from growth and detachment of irregularities on the surface of parent crystals.[123]

In an interesting extension to amino acid chemistry, Kondepudi and co-workers have shown the chiral interactions in the stirred crystallization of glutamic acid and lysine.[124] The crystallization of (*S*)-glutamic acid is influenced by the presence of (*S*)-lysine, but not (*R*)-lysine. Moreover, the effect is a nonlinear function of the lysine concentration.[125] The importance of this work lies in the fact that a chiral impurity may inhibit the crystallization of one of the enantiomers, thereby crystallizing the opposite enantiomer through a rapid secondary nucleation. This process competes with the classical resolution of conglomerates in which crystallization occurs under low supersaturation and little or no stirring.

Within this context, it is noteworthy that an impurity will have a major influence on the crystallization process of a given compound if there is structural similarity between both substances.[126] As an elegant illustration of this key concept, one of the most recent and novel resolution of racemates, invented by Dutch chemists, is the so-called 'family approach'.[127] In this experiment the family of resolving agents is made from an enantiomer of tartaric acid acylated with benzoyl, *p*-toluoyl, or *p*-anisoyl groups. Thus, the members of a family bear generally strong structural similarity and are stereochemically homogeneous (Fig. 6). However, a mixture composed of tartaric, malic, and lactic acids does not constitute a family. Compared with a classical resolution that uses one chiral resolving agent, the Dutch team add an equimolar mixture of the three



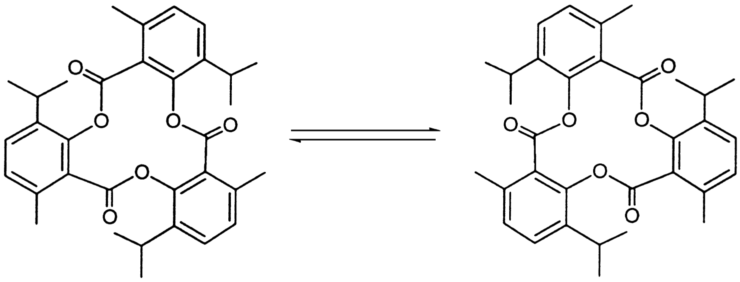
3 R = H **4** R = CH_3 **5** R = OCH_3

Figure 6. Family of resolving agents

acylated tartaric acids to a solution of a racemic phenethylamine. The mixture was screened like a library in the hope that the least soluble salt would crystallize out. Surprisingly, most resolutions employing this strategy were a success. The crystallization was faster and the enantiomeric excess of the phenethylamine higher than that obtained with any one of the three tartaric acids. Remarkably, the salt that crystallizes is not any single one of the three tartrates, but rather a mixture of the three salts in a ratio 20:5:1 that could not be modified by recrystallization.

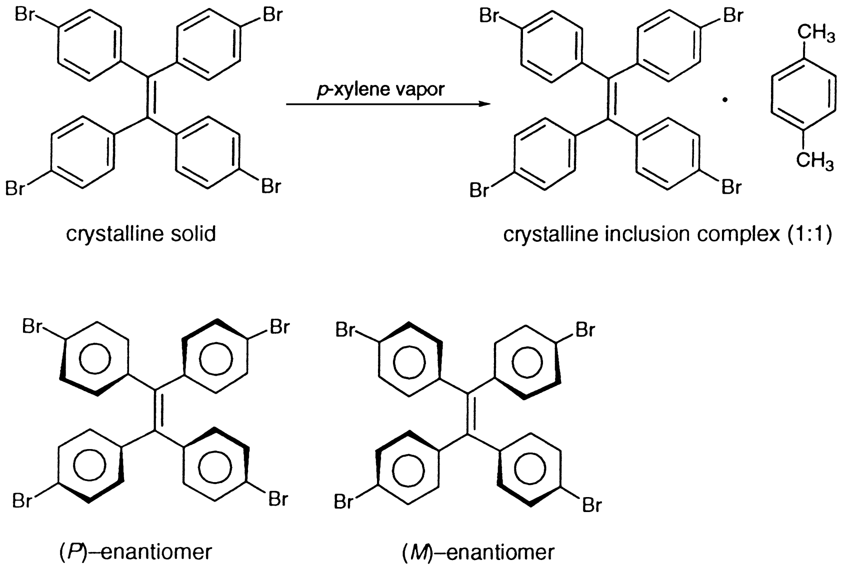
The above-mentioned spontaneous resolution of 1,1′-binaphthyl is based on the fact that both enantiomers are stable at room temperature owing to steric hindrance of the two naphthalene rings. At higher temperatures the barrier to rotation is overcome, thereby favoring interconversion. In fact, the crystallization of 1,1′-binaphthyl from the molten state had been previously studied by Pincock and co-workers, who obtained a Gaussian-like distribution centered around zero.[128]

Spontaneous resolution by formation of host–guest complexes also evidences that the absence of *secondary nucleation* gives equal probabilities of right- and left-handed crystals. A well-studied case is the formation of crystalline clathrates with tri-*o*-thymotide, a cyclic lactone capable of encapsulating small molecules and solvents. Like in the equilibration of 1,1′-binaphthyl, the chiral clathrate exhibits restricted rotation of single bonds at ambient temperature, but after dissociation into its two components (thymotide and guest), the cyclic host racemizes rapidly (Scheme 2).[129] Thus, when tri-*o*-thymotide was dissolved in hot benzene, allowed to cool, and the resulting benzene clathrates analyzed polarimetrically, the enantiomeric composition was again a Gaussian distribution centered around zero. This random process also discards an imbalance favored by PVED.



Scheme 2. Interconversion of thymotide enantiomers

Host–guest chemistry also offers the possibility of chiral crystallization of achiral molecules, which could be utilized for resolving racemic compounds. A salient example is the transformation of racemic crystalline tetra(*p*-bromophenyl)ethylene into chiral inclusion crystals by treatment with solvent vapors.[130] Whereas the formation of chiral crystals during recrystallization of achiral substrates from their solutions is well documented, this is probably the first example in which such chiral inclusion crystals are obtained through solid–gas reactions. Thus, this tetraarylethylene forms both racemic and chiral inclusion complexes by recrystallization from different solvents. With *p*-xylene, a chiral 1:1 inclusion complex is obtained by this procedure and notably, by simple exposure to *p*-xylene vapors at room temperature (Scheme 3). While the *rac*-crystal of the starting material contains independent molecules of the right-handed *P*-enantiomer and the left-handed *M*-enantiomer in the unit cell (space group: P_{ccn}), the molecules in the inclusion compound occupied the chiral space group $P2_12_12_1$. Apparently, the chiral crystalline lattice is stabilized by Br···Br interactions among the achiral hosts. It should also be mentioned that the inclusion crystals of the tetraaryl derivative with THF and β-picoline obtained by solid–gas



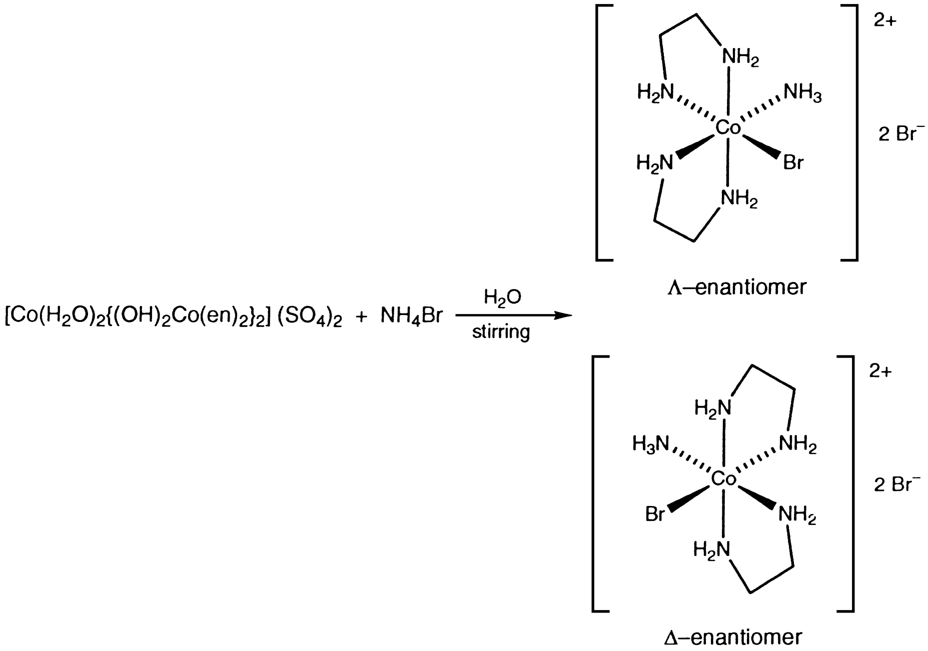
Scheme 3. Chiral inclusion complexes by solid–gas reaction

reactions were chiral, while the recrystallization technique afforded racemic crystals. In any event, the mechanism of generation of chirality in such crystals is still unclear.

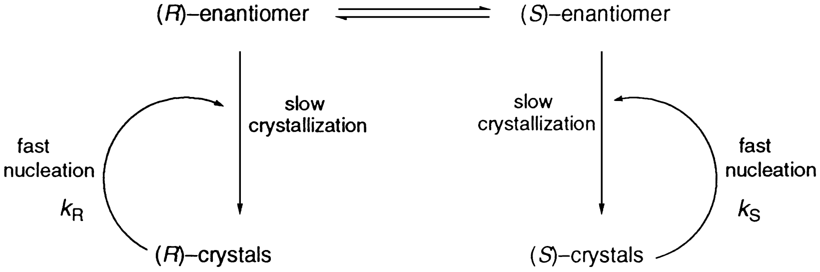
Crystallization of labile coordination compounds may be accomplished by ligand exchange reactions. This may lead to chiral metal complexes such as *cis*-$[CoBr(NH_3)(en)_2]Br_2$ which crystallizes as a conglomerate, each crystal containing molecules of either Δ- or Λ-enantiomer (Scheme 4). While the reaction conducted without stirring yielded a statistically equal number of both enantiomers, the introduction of mechanical agitation gave rise to crystalline optically active complexes in most runs.[131] Here a crystal of a given enantiomer catalyzes its own formation through secondary nucleation. As expected the distribution of enantiomers fluctuates randomly, though if the stirred reaction is performed in the presence of crystals of one enantiomer, the latter is selectively produced.

As predicted before (Section 3), vortices may be a source of chirality, although special caution should be taken to avoid artifacts and misinterpretations. Thus, even though a gravitational field constitutes a falsely chiral influence,[15] small *ee*s were reported in an asymmetric epoxidation conducted in a rotating vessel, either clockwise or anticlockwise about an axis perpendicular to the Earth's surface.[132] Experiments claiming the separation of enantiomorphic crystals in a fluid under rotation,[133] or by rotation in a drum filled with a nonsolvent liquid, less dense than the crystals,[134] have been described. The latter hydrodynamic resolution was applied to crystals of tartaric acid and lysine, although no *ee*s were reported. A further study also revealed that directional stirring in a similar rotating system had no effect on the fractional crystallization of *rac*-sodium ammonium tartrate.[135]

Leaving apart the situation of asymmetric crystallizations, the topic of autocatalytic mechanisms dates back to the early 1950s when Frank proposed a highly cited model to explain the amplification of small enantiomeric excesses originated by random fluctuations in the enantiomeric composition of a racemic mixture.[92] A similar amplification mechanism was described later by Calvin (Scheme 5).[136] This model involves the rapid equilibration of two enantiomers which may



Scheme 4. Autocatalytic formation of chiral octahedral cobalt complexes

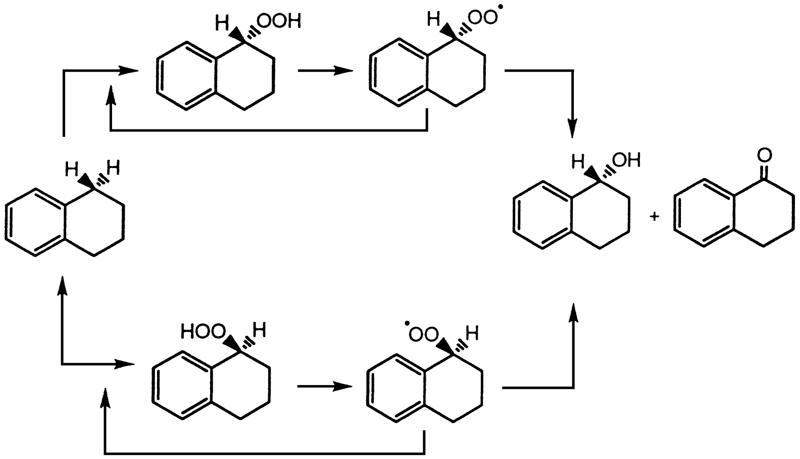


Scheme 5. Autocatalytic amplification

also undergo different reactions (including for instance, their separate crystallization) to afford nonequilibrating products. If there is an initial excess of one of the products, the latter might catalyze its autocatalytic production from its own enantiomer. Such a process causes the corresponding equilibrium shift to the favored enantiomer, which would ultimately result in the conversion of the racemate into an enantiomerically pure substance.

Since these early reports on chiral autocatalysis, other authors have likewise considered nonlinear mechanisms to account for amplification.[137–140] Again, such models are based on an open flow system in which a small enantiomeric imbalance generated by physical forces or stochastic fluctuations is strongly amplified. They also take into account the concepts of self-organization and dissipative structures established by Prigogine for systems far from equilibrium.[141] Of particular interest is the situation of autocatalysis or autoinhibition in which one or more reaction products affect the overall rate through a positive or negative feedback, respectively.

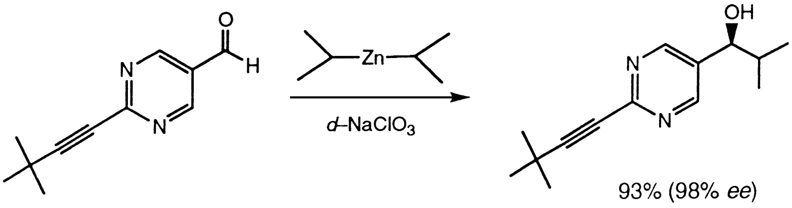
A stereospecific autocatalysis, not involving crystallization processes, has been devised by Thiemann and his associates for the radical liquid-phase autooxidation of tetralin.[142] Here, an achiral hydrocarbon is oxidized by oxygen in liquid phase to afford tetralin hydroperoxide which itself is chiral and which is decomposed to give peroxy radicals, which are equally chiral and react with the parent hydrocarbon leading again to the formation of more chiral intermediates along with the final products: tetralol and tetralone (Scheme 6). The transformation is suggested to be catalyzed by tetralol which accumulates autocatalytically during the radical chain oxidation. Computer simulations predict a strong amplification of enantiomeric excess.



Scheme 6. Autocatalytic oxidation of tetralin

It should be emphasized that the autocatalytic amplification must involve some sort of nonlinear effect or cooperativity, otherwise the classical Frank hypothesis leads inevitably to a gradual erosion of enantiomeric excess which is especially noticeable after a large number of catalytic cycles.[143,144] So far, excellent levels of chiral amplification have been obtained in the addition of dialkylzinc reagents to pyrimidyl aldehydes catalyzed by the resulting pyrimidyl alcohols, a process extensively studied by Soai and his associates.[145] These results are, however, of scant importance in the context of the origin of homochirality because organometallic species would have not survived under prebiotic conditions. Anyway, this research provides a starting point for future developments. It is also remarkable that such enantioselective autocatalyses have been conducted in the presence of (+)-quartz and (–)-quartz, the former favoring a product possessing (*S*)-configuration, while levorotatory quartz produces the (*R*)-enantiomer in high *ee*.[146] In a subsequent study, the same team has used enantiomorphic crystals of sodium chlorate.[147] Addition of crystals of dextrorotatory $NaClO_3$ to a solution of a functionalized pyrimidine-5-carboxaldehyde, followed by addition of diisopropylzinc, resulted in the formation of the (*S*)-isopropylpyrimidinylcarbinol in 93% yield and 98% *ee* (Scheme 7). It has been suggested that chiral crystals initiate the formation of the (*S*)-configurated alcohol, and as that isomer accumulates it autocatalyzes production of more molecules with the same configuration.

The induction of bioorganic homochirality by surface-mediated reactions on chiral minerals has been proposed as an organic economy process during the prebiotic period. Optical resolutions



Scheme 7. Asymmetric autocatalysis mediated by sodium chlorate

and asymmetric synthesis have been performed by adsorption on layered aluminosilicates related to the chiral kaolinites.[148]

It is noteworthy that nonlinear effects, and the concomitant optical enrichment of the product with respect to the *ee* of the starting substrate had already been reported as early as 1936 by Langenbeck and Triem,[149] who reacted L-menthol with oxalyl chloride. The chiral terpene was varied from racemic to optically pure and the authors determined the optical rotation of the product mixture which consisted of the optically active ester together with the *meso* bis-menthyl oxalate. A positive deviation of the *ee*s of the product with respect to all other *ee*s of L-menthol was observed, which is otherwise characteristic of a nonlinear effect.[143,144]

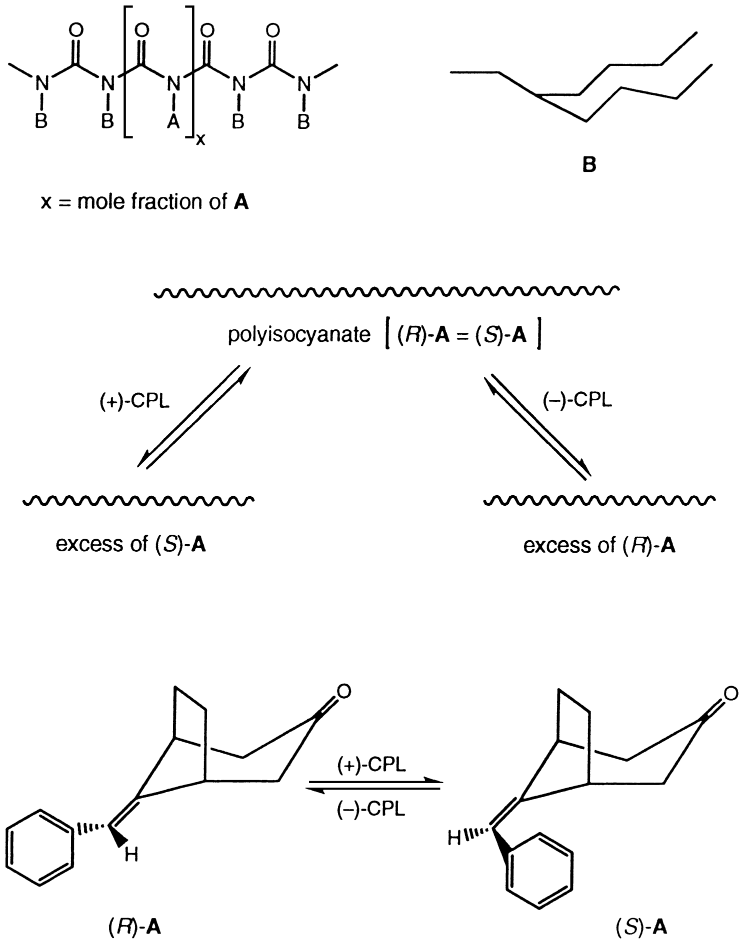
The formation of stereoregular polymers and discrete oligomers constitute the other scenario in which self-replication of achiral units may provide chiral structures. Chiral amplification in polymer chemistry is a complex subject and cooperative interactions largely determine the helicity of these systems.[150] The stereochemical outcome of the polymerization appears to be dictated at a large extent by the secondary structure of the growing polymer. Thus, a stable α-helix is only possible for a homochiral sequence of amino acids as noted, among others, by Wald in the late 1950s.[151] It should also be pointed out that the helical handedness of a polymer may be influenced by external fields. A series of recent and insightful examples illustrate the aforementioned concepts. Thus, the macromolecular helicity can be induced in a polymer by an optically active amine. This helicity can be 'memorized' when the chiral amine is replaced by various achiral amines. Even if the helicity is now imperfect, it can repair itself over time.[152]

Achiral bisureido derivatives undergo spontaneous self-assembly to give chiral aggregates with a high degree of helical twisting, both left- and right-handed helices.[153] These substances form gels which are stable for several months, but are disrupted by mechanical stirring. Anyway, gel formation is thermoreversible as the macromolecular structure can be restored after heating above the melting point followed by cooling at ambient temperature. In this case the helical sense characteristics have been attributed to the existence of small distortions and a strong anisotropic growth. Helical ordering of molecules can also be formed by spin-coating solutions of non-polymeric dicholesteryl esters.[154]

Polymerization of a mixture of D- and L-lactic acid dimers, even in the presence of a racemic catalyst, affords a crystalline polylactic acid resin having superior physical properties to those of unordered configurations. Although the resin is a mixture of all-D and all-L chains, such isotactic chains cocrystallize to give a stereoregular polymer with high crystallinity. Any kind of cooperativity should be present as the (+)-catalyst promotes polymerization of the L-lactide, whereas the (–)-catalyst polymerizes only the D-lactide.[155] This strategy represents one more step forward in the creation of stereoregular polymers from racemic starting materials, instead of single-isomer ones. In addition, it competes with the common protocol to obtain an isotactic polylactic acid that requires polymerization of optically active L-lactic acid.

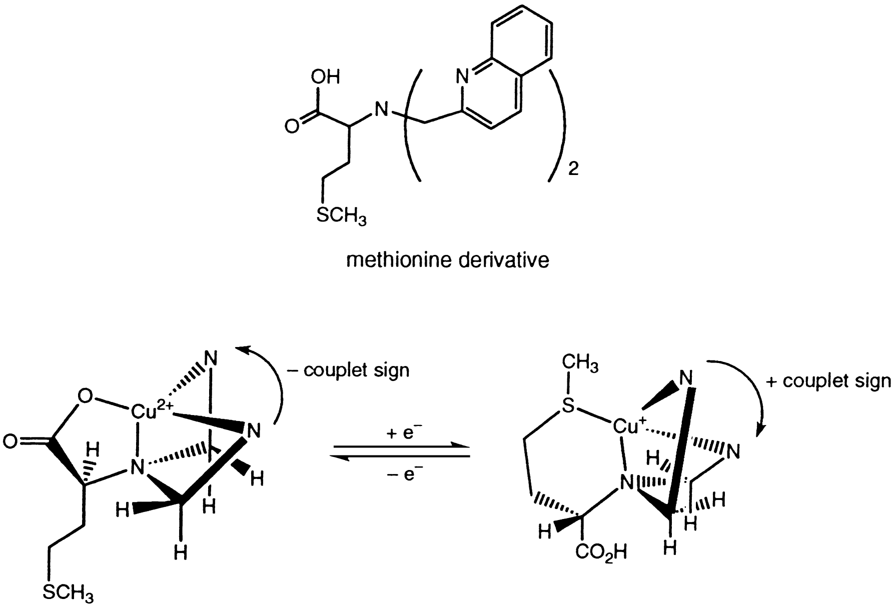
Homochiral crystallization whereby achiral molecules yield crystals with the same chirality, a fact related to secondary nucleation, has been observed in the copolymerization of a pyrimidine-substituted anthracene with $Cd(NO_3)_2$.[156] The strategy involves heating of both achiral precursors in aqueous ethanol followed by slow cooling at room temperature. The resulting helical aggregate crystallizes in the chiral space group $P2_1$.

As mentioned, reversible inversion of helical chirality has not only a major importance in connection with life's homochirality, but also in the development of chiral molecular devices. Polyisocyanates, which exist as equally populated interconverting right- and left-handed helical backbones were functionalized with a racemic mixture of a photoresolvable ketone. Irradiation with CPL yields measurable CD signals in the polymer helix, which changes sign depending on the handedness of CPL (Scheme 8).[157] This reveals that the small enantiomeric excess obtained by irradiation in the ketone's chromophore can be amplified to a significant excess of one helical sense. Furthermore, the latter result is a valuable contribution about the enantiodiscrimating role of CPL, which has been observed in asymmetric photosynthesis of hexahelicenes[158] or in the photoinduced interconversion of *P* (right-handed) and *M* (left-handed) helices of sterically overcrowded chiral alkenes.[159]



Scheme 8. CPL-induced switching of mirror images in a polymer

Helical polymers also reverse their handedness at a selected temperature.[160] At the discrete level of small molecules, the effects of temperature and solvents have been observed in the photoresolution of racemic mixtures.[161] A very interesting result is the inversion of helicity upon oxidation or reduction, as observed in copper complexes of *N*,*N*-dialkylmethionines (Scheme 9).[162] In the Cu(II) oxidation state, the coordination of groups around the metal centre gives rise to a clockwise propeller that displays a negative Cotton effect. After reduction, the Cu(I) complex affords a nearly mirror image CD spectrum.



Scheme 9. Inversion of helical chirality induced electrochemically

4.2. *Amplification of parity violation: facts and fictions*

Many experimental results at the level of biomolecules clearly suggest that homochirality is not determined by PVED. Anyhow, if there are plausible mechanisms capable of supporting the enormous amplification required, the contribution of parity violation cannot be excluded, albeit it must be taken with serious caution within the geological time scale. The key question here *is not how to demonstrate the formation of chiral substances from achiral precursors, but how to explain the amplification itself* from the stage of parity violation. Although there are several hypotheses, three basic mechanisms have been identified, which are the subject of current discussion and controversy. These models are the Yamagata cumulative mechanism or the accumulation principle,[163] the Kondepudi chiral amplification mechanism, also called the Kondepudi catastrophic mechanism,[164] and the Salam mechanism or the phase transition homochirality.[165]

The accumulation principle was initially proposed to explain the chiral amplification during crystallizations or polymerizations of chiral monomers. Thus, let us consider the formation of an *n*-unit polypeptide, both the natural all-L form and its unnatural all-D counterpart (Eqs. (4) and (5)):

$$L_n{-}1{+}L \rightarrow L_n \tag{4}$$

$$D_n{-}1{+}D \rightarrow D_n \tag{5}$$

During polymer growth a monomer may add onto a growing oligomer of either handedness. For each step the ratio of the amounts of D- and L-polymers (N_L and N_D) will be determined by the ratio of the reaction rates (p). However, owing to parity violation, or more precisely PVED, such a ratio will be different from unity, and at the final stage the quantities encountered for each polymer verify that:

$$N_L/N_D = p^n = (1{+}\mathrm{PVED})^n \tag{6}$$

The small rate difference at each of N stages of polymerization results in a fractional excess, which, after an iterative process, leads to an enantiomeric excess of one handedness. This also means that the corresponding free energies changes will be unequal for both polymers and, under kinetically controlled reactions, a similar amplification effect will occur due to differences in activation energies.

With this rather naive perspective, numerical estimations for the Yamagata mechanism do predict large amplifications, in terms of N_L/N_D rates, provided that PVED $>10^{-10}$. Unfortunately, this theory has never been supported by experimental evidences, notwithstanding it has largely been mentioned in the literature. Starting from racemic amino acid monomers (ee = 0%), their homogeneous polymerization gives very small *ee*s ($\sim 10^{-4}$).[166] Amplification may, however, be observed at the beginning but it gradually decreases as the polymerization progresses.[167] On the other hand, all attempts to correlate the very small *ee*s during the fractional crystallization of racemates with PVED are certainly speculative (vide supra). In a recent and superb survey, Bonner has analyzed in detail the accumulation principle refuting its statements with a series of considerations and numerical figures.[78]

A preliminary consideration is the fact that this theory presupposes that the polymerization is homochirally stereospecific, e.g. PVED dictates the formation of all-L polymers versus all-D polymers. This is in practice unrealistic since heterochiral oligomers can be formed. Starting from an initial stage of dimer formation to a fourth stage of pentamer formation, Bonner has shown that the mole fraction of the L-amino acid-containing polymer rapidly decreases through the process, since there is a considerable number of diastereomeric possibilities.

The overall crystallization appears to be a complex physical process that cannot be explained by the accumulation principle as a simple multiplication of PVED. The final remark by Bonner states, with realistic arguments, perhaps in a lapidary form, that this hypothesis "should no longer be cited as a viable mechanism for the amplification of small *ee*s."[78]

The Kondepudi amplification mechanism,[164] which should not be confused with the above-mentioned experiments developed by Kondepudi and his group, is based on a kinetic model that involves autocatalysis and chiral antagonism, i.e. an enantiomer catalyzes its own formation but inhibits replication of its mirror image; a theory reminiscent of the classical Frank theory of autocatalysis.[92] By means of nonequilibrium statistical thermodynamics, Kondepudi showed that amplification could occcur starting from relatively large PVED ($>10^{-17}$ kT), whereas for smaller values the amplification effect would be cancelled by thermal fluctuations.

The Kondepudi hypothesis predicts an amplification time of 10^4 years for a PVED of 10^{-17} kT, although a large reaction volume is required: 4×10^9 l, equivalent to the volume of a small lake. Both the time and volume can be considerably reduced by increasing the magnitude of PVED. If the latter increases by one order of magnitude, the amplification period decreases by four orders of magnitude, and thus for $\text{PVED}=10^{-16}$ kT it takes only one year.

This mechanism also considers slow racemization rates, though for small PVED the racemization half-lives might be smaller than the time required for amplification. Thus, the racemization lifetimes of amino acids under wet conditions have been estimated in only about 10^4 to 10^6 years, but they can greatly be enhanced in dry or frozen conditions from 10^{13} to 10^{27} years.[168] It has been suggested that, even if life would have become extinct on other planets, homochirality could have been preserved in fossilized organisms as long as they cooled more quickly than Earth. It has also been speculated that the extremely dry, cold, and low pressure conditions of Mars, especially in the Martian polar regions, would have enabled the survival of chiral molecules over long geological periods.[169] In connection with the latter argument, a recent survey has critically examined the held assertion that life had been discovered during the Viking mission to Mars and found to be implausible. Previous hypotheses were based on the fact that labeled released data were similar to those obtained with terrestrial samples.[170]

Although the catastrophic mechanism provides reasonable figures within an evolutionary timescale, again there is no experiments supporting a direct relationship between the magnitude of PVED and the autocatalytic amplification. Furthermore, a serious drawback also occurs with autocatalytic polymerization as a stereospecific process is not guaranteed. There is a large number of random sequences from a mixture of right- and left-handed monomers, and their diastereomeric interactions, ignored in this model, will impede the formation of regular cycles with a specific sequence.

There is still a third mechanism, postulated by the Nobel Prize winner Abdus Salam, stating that below a certain critical temperature (T_c), tunneling to the more stable enantiomer might occur by a phase transition effect.[165] This mechanism could work at low temperatures such as those of the interstellar space, and where the Kondepudi mechanism[164] would proceed very slowly. The key idea is that condensation phenomena may give rise to second-order phase transition below T_c, thereby favoring the transformation to the enantiomer of lower energy dictated by the PVED. Attempts to verify experimentally this hypothesis have been unsuccessful.[171–173] Thus, racemic cystine crystals cooled at very low temperatures, in the hope that the presence of a heavy sulfur atom would increase PVED, gave no optical rotation.[173] However, this and similar experiments at a few K or mK do not rule out that such transitions may effectively occur in the cosmos.

Although the observation of chirality below a cryogenic critical temperature may be experimentally problematic, symmetry breaking could occur in condensed media in which a large number of particles can cooperate to produce a sharp transition between symmetric and asymmetric states of the sample. For instance, in a ferroelectric crystal below its phase transition temperature, the field for each molecular dipole holds the others in the same direction. However, at the phase transition temperature, there is a sufficient number of dipoles reversed and the system converts into a state where opposite signs for each dipole take place with the same probability.[174,175]

Although without apparent connection with the Salam hypothesis, because experiments are conducted at much higher temperatures, phase transition effects may be important for chiral discrimination. Thus, it has been described as the spontaneous resolution of the left- and right-handed molecules in two-dimensional crystallites at an interface, such as in 2D-Langmuir films or thin-layered nanostructures.[176–178] Here the role of the interface is crucial. Achiral molecules in the gas phase when adsorbed on a surface may lead to a chiral packing causing the formation of enantiomorphic structures. Deposition of 1-nitronaphthalene on Au(111) surface from the vapor phase gives a 2D chiral structure. The resulting clusters which are one layer thick display shapes of opposite chirality (denoted as *L*/*R*-enantiomers). Remarkably, these discrete clusters (mostly decamers) could be removed from the gold surface without being altered and then separated into enantiomers.[179]

A marginal, but notable phase effect, was observed by Liu and Orgel who described the oligomerization of β-amino acids at –20°C mediated by a water-soluble carbodiimide.[180] If the solutes are insoluble in ice, they are concentrated in the liquid phase when the solution is partially frozen. β-Glutamic acid and the condensing agent at 25 or 0°C gave no significant formation of peptides, but at –20°C the rate of polymerization was increased to give yields greater than 50%. However, in this case the effect should be attributed to concentration rather than temperature. Thus, addition of a concentrated solution of sodium chloride, to prevent the separation of ice, suppressed the polymerization reaction even at –20°C.

5. Concluding remarks

> "*We shall not cease from exploration and the end of all our exploring will be to arrive where we started and know the place for the first time*" Thomas S. Eliot

The great poet was right as we are at the start again. Through this account we have attempted to provide a general perspective of the exciting topic of chirality which embraces physics, chemistry, as well as the structure and function of biological molecules in our modest Earth. Presumably, both achiral and chiral molecules had the ability of self-replication to afford sequences that contained information. In contrast to the situation of cells or microorganisms which contain millions of chiral molecules assembled in stereoregular structures, at the beginning there could be a few chiral molecules within a racemic world. Copolymerization of such components could give discrete structures with the ability to self-organization and replication. These regular arrangements were capable of creating chiral perturbations with vicinal molecules. In the presence of external forces and under nonequilibrium conditions, the molecular system may not obey the classical thermodynamic principles.

Perhaps chiral molecules would have become established on Earth with notable rapidity once conditions were conducive to its survival, i.e. avoiding racemization. If this view is correct, the origin of homochirality and hence the origin of life was facile, perhaps inevitable, with implications for its appearance elsewhere.[4,181] The abiotic endurability of chirality may be appreciated not only in the remarkable formation of chiral crystals, but also in tests of artificial in vitro evolution of enantioselectivity.[182] On the other hand, and as previously mentioned, the stereoregularity of biological macromolecules is largely governed by the homochirality of their components.

It is by now difficult to demonstrate that these chemical and biological reactions are parity violation-driven processes. Perhaps the violation of the elemental symmetries is important in the evolution of the universe, but not in the unique and isolated event of terrestrial evolution. The experimental evidences collected so far indicate that parity violation in biopolymers and other molecular structures, characterized by a single homochirality, is in no way the consequence of parity violation at the level of elementary particles.[80]

It is dubious that science will someday discover the ultimate origin of the asymmetry in our universe because we know only one, and the perfect right–left symmetry could only be observable in a higher space-time. Why should we be dismayed because the enantiomorphous of an object does not exist?[183] The great physicist and Nobel laureate Richard Feynman once said: "[We might] think that the true explanation of the near symmetry of nature is this: that God made the laws only nearly symmetrical so that we should not be jealous of His perfection".[184] Then almost nothing needs to be said here.

Note added in proof. After completing this manuscript a dazzling article on magnetochiral photochemistry has appeared[185] (see also Ref. 186). This contribution is particularly noticeable since it clarifies the correct thinking about magnetic fields after 150 years of confusion and misinterpretation. Rikken and Raupach have now shown experimentally that magnetochiral anisotropy can give rise to an enantiomeric excess in a photochemical reaction conducted with unpolarized light in a parallel magnetic field.[185] In other words, a magnetic field parallel or antiparallel to an unpolarized light beam is a truly chiral system that has the same status as circularly polarized light in being able to induce absolute enantioselection under all circumstances (equilibrium or nonequilibrium conditions). This might have been important in the origin of the homochirality of life.

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