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Absolute Asymmetric Synthesis under Physical Fields: Facts and Fictions

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I. Introduction

One of the most fascinating endeavors of chemical research is to discover the origin of molecular handedness. Few topics as the search for the enantiomeric homogeneity of nature have surpassed the purely chemical threshold, interlocking the physical and life sciences and attracting the interest of their scientists over generations.[1] Absolute asymmetric synthesis involves the use of an external physical influence to produce an enantiomeric excess (ee) in what would otherwise be a racemic product of a prochiral chemical reaction.[2] From a conceptual viewpoint, the terms asymmetric synthesis and asymmetric induction are often misused as equivalents. The latter is a broader term: it refers to the extent of excess of one enantiomer over the other achieved in an asymmetric synthesis.[3] The study of these reactions is of wide interest because they occur spontaneously and are central to discussions about the origin of chirality in nature. So far chemists have recognized that crystal-to-crystal solid-state photoexcited reactions, which have been extensively reviewed,[4] as well as asymmetric photochemical reactions in solution,[5] constitute suitable methodologies for inducing molecular asymmetry. The latter reactions were comprehensively reviewed by Inoue in 1992 and involve either direct asymmetric reactions with CPL or diastereoselective photoreactions, in which the asymmetric induction is provided by a chiral substituent, a chiral complexing agent, or a chiral solvent.

In sharp contrast to light, the interaction of molecules with other external influences, mostly electric and magnetic fields, as a source of “absolute” asymmetric induction has not extensively been explored. This is simply because photochemical reactions can be more easily conducted than other types of perturbed reactions in a reproducible fashion, and for the traditional belief that influences other than light cannot effect measurable enantiodifferentiation of racemates. Jaeger's dictum, namely that the necessary conditions will be that the externally applied forces are a *conditio sine qua non* for the initiation of the reaction which would be impossible without them,[6] together with the results of numerous experiments, appear to justify this belief. However, the earth's crust in the prebiotic era was in a stage of great upheaval, so that the contribution of huge electromagnetic fields and other types of radiations under such conditions to the abiotic synthesis of optically active molecules cannot be so easily dismissed. Since this topic has been of intense interest and controversy over the past decade, it is timely to discuss critically these facts in the light of a broader concept of chirality in physical systems.

This review will focus on the use of external fields to induce absolute asymmetric synthesis, combining

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theory and experiment. We will discuss particularly the potential chirality of magnetic, electric, and gravitational fields. Likewise, asymmetric photochemistries with polarized photons, especially CPL, or translating spin-polarized electrons which as we shall see constitute truly chiral influences, will be treated as well.

II. The Abiotic Origin of Chirality

Biotic and abiotic theories have been proposed to account for the origin of chiral molecules.[1] Biotic theories suggest that if life originated at an advanced stage of chemical diversity in the presence of racemic building blocks, the competing living systems would have gradually selected one enantiomer as being more efficient to survival than their mirror images. The enantiodifferentiation could be a consequence of the interaction of symmetrical molecules with an asymmetrically substituted pattern. The analogy of the animal with two identical horns, which is familiar to many biologists, provides a clue as to how chance mechanisms could be operative. In most collisions with other animals, it will be as likely to damage its right horn as its left. But in encounters with humans, who are asymmetrically armed with clubs in their right hands, it is more likely to damage its left horn. This is also reminiscent of the classical Ogston's three-point attachment to a chiral surface in which two identical groups might be distinguished.[7] A central tenet of biotic theories is that enantiomeric homogeneity is not a requirement for the origin of life. Yet by their own nature, these biotic processes cannot be experimentally tested in a definitive manner.[1d]

On the contrary, abiotic theories suggest that life developed after the appearance of a certain, even very small, enantiomeric excess of the molecules that characterize the life processes, such as the primitive forms of RNA, DNA, or peptide backbones. Furthermore, according to De Duve's argument, life processes would have occurred as a consequence of the laws of chemistry, and therefore as a cosmic phenomenon which is not restricted to our solar system.[8] Assuming such physicochemical constraints, it should be expected that prebiotic life had to arise with the same basic chemical reactions it has today.[9,10] One of the most attractive theories, close to the interpretation by De Duve, claims an extraterrestrial origin of the organic molecular building blocks of life, brought to the surface of the earth by meteorites, cometlike objects, or a continuous accumulation of extraterrestrial matter in the form of interstellar dust.[1h,11,12] Whether or not this cosmic rain of organic molecules is racemic, or is homochiral due to chiral influences such as parity violation, etc., is a topic of much current debate.[1]

The analysis of the Murchison meteorite containing, among the carbonaceous fragments, numerous amino acids common in living systems and, remarkably, some of them in nonracemic form (L enantiomers predominated slightly over D enantiomers),[13−15] reinforces the idea that chiral purity was achieved at the stage of prebiotic evolution and was presumably a requisite for the subsequent processes of self-replication. Nevertheless, a vision of extraterrestrial chiral molecules invading earth is somewhat speculative and meets reasonable objections. However, the objection that deracemization could be caused by terrestrial contamination appears to have been met by the latest study which focused on nonterrestrial amino acids, e.g., α-methylisoleucine, α-methylnorvaline, etc.[15] Finally, the left-handed amino acids in the Murchison meteorite have now been confirmed to be of extraterrestrial origin: Engel and Macko find that the amino acids are enriched in ^{15}N, which is characteristic of extraterrestrial matter.[16a] In a recent paper, however, Pizzarello and Cronin have pointed out that incomplete chromatographic resolution of L-alanine and other meteoritic amino acids may have affected both the enantiomer excess and the ^{15}N determination of Engel and Macko.[16b] The resolution could have occurred by low-temperature diagenetic reactions in space. In this context, Goldanskii's cold prehistory of life scenario[1h] takes place at ~20 K on interstellar dust grains where the chirality of a molecule might be stabilized by interaction with the low-temperature medium,[17−19] not on the primitive earth which would be much too hot.

Scientists have concentrated their efforts for more than 50 years on abiotic mechanisms accounting for the establishment of chirality by chance, such as the spontaneous crystallization of conglomerates of racemates or the diastereomeric interactions of enantiomers in nonideal solutions.[20] The alternative abiotic mechanism, where chirality is established via absolute asymmetric synthesis induced by external fields or forces,[1g,21] constitutes the focus of the present review and represents an unifying aspect of terrestrial and extraterrestrial chirality because of the ubiquity of electromagnetic and gravitational fields. This issue bears upon philosophical problems about the nature of space and time, causality, and laws of nature. It is not the aim to address these implications critically, which lie beyond the scope of this review. The discussions that follow are merely a detailed examination of experiments, which can be analyzed in the light of a more precise interpretation of chirality, thereby providing a clue about the validity of such experiments.

III. False and True Chiral Systems

In chemistry, chirality is usually taken as a purely geometric property associated with the nonidentity of an object with its mirror image. Both objects are said to be enantiomorphous and, of course, they should be isometric in a three-dimensional Euclidean space. The existence of enantiomorphic molecules, enantiomers, is associated with the lack of certain symmetry elements such as a center, a plane, or an improper axis of symmetry.[22] While this definition guarantees chirality in a stationary object, it cannot be admitted for systems in which motion is involved. Furthermore, if chirality arises from the interaction of matter with intrinsically chiral radiation, which is otherwise defined by space- and time-dependent magnitudes, chirality should also be denoted under the same physical variables. Some years ago, one of us coined the concept of true and false chirality in an attempt to provide a more satisfactory and broader vision of molecular chirality.[23−25] This new definition of chirality states that "true chirality is shown by systems existing in two distinct enantiomeric states that are interconverted by space inversion, but not by time reversal combined with any proper spatial rotation". The essential feature of a chiral system is that it can generate time-even pseudoscalar observables, meaning numbers which change sign under space inversion but not under time reversal. In other words, the enantiomorphism of chiral systems is time-invariant, while the time-noninvariant enantiomorphism is quite different and characteristic of false chirality. Strictly speaking, the term "enantiomorph" is usually reserved for a macroscopic object such as a crystal, and "enantiomer", for a molecule, but because of the ambiguity of scale in the case of general physical systems these two terms are used as synonyms in this article.

The advantages of this definition will become evident through the rest of the discussion. If we consider a stationary object, say a molecule, space inversion associated with the parity operator *P* corresponds to inverting the positions of all the particles in the object through an arbitrary fixed origin. The overall process is equivalent to the traditional mirror reflection followed by a rotation through 180° about an axis perpendicular to the mirror plane. Time reversal, associated with the operator *T*, corresponds classically to reversing the motions of all the particles in the system (in quantum mechanics it is more complicated). Time reversal is of course irrelevant for a stationary object, but is essential if motion is involved in the source of chirality.

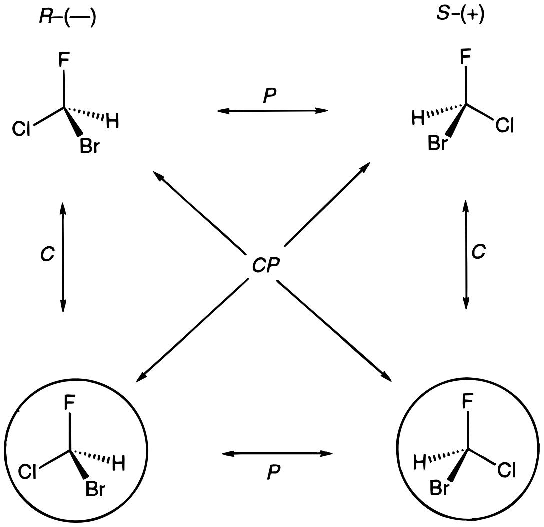


Figure 1. Interconversion of true enantiomers (strictly degenerate) under the combined *CP* symmetry operation. The structures within the circles are antimolecules built from the antiparticle versions of the constituents of the original molecules.

The quintessential truly chiral influence is the parity-violating weak neutral current interaction which lifts the degeneracy of the enantiomers of a chiral molecule.[26] But for most chemical purposes these parity-violating energy differences are extremely small and below the current levels of detection. Strictly speaking, however, the existence of a parity violating energy difference between conventional *P* enantiomers means that the true enantiomer of a chiral molecule is that with the opposite absolute configuration but composed of antiparticles, since this will have exactly the same energy.[21,27] Figure 1 highlights this exotic but conceptually important aspect of enantiomorphism, exemplified by CHFClBr whose absolute configuration has recently been found using Raman optical activity.[28] The two pairs of true enantiomers (strictly degenerate) of this chiral molecule with a stereogenic center are interconverted by the combined *CP* operation since *P* violation in the weak interactions is accompanied by a "compensating" *C* violation. The strict degeneracy of *CP* enantiomers is maintained even if *CP* is violated provided *CPT* invariance holds overall.[27] An experimental comparison between *CP* enantiomers is not possible to date, since it requires the inaccessible antiparticle-containing mirror images. *Parity violation provides a cornerstone for the identification of true chirality since it only lifts the degeneracy of the P enantiomers of a truly chiral system; the P enantiomers of a falsely* *chiral system remain strictly degenerate*.[25]

In a recent analysis of the chirality of large random supramolecular structures, an extended definition of chirality was proposed to accommodate the problem that the exact enantiomer of such an object can never be formed in the laboratory.[29] However, one problem with this definition in the present context is that it invokes a statistical realization of the mirror-image object and so abandons the "gold standard" of the precise quantum-mechanical degeneracy of enantiomers[30,31] upon which instructive concepts such as those developed above depend. Since its implications (if any) for absolute asymmetric synthesis are not yet clear, we shall not consider it further.

In two recent papers, Jonas has also analyzed the different definitions of chirality, especially those that accommodate the consequences of parity nonconservation, and discussing these concepts in a practical chemical context.[32]

There are several questions of crucial importance to both theoretical and synthetic chemists devoted to fundamental aspects of stereochemistry and asymmetric synthesis: What kind of physical influence does induce absolute asymmetric synthesis? Under what circumstances? What kind of influence is chiral? Although a physical system might be able to exist in two distinct mirror-image states, it is necessary to establish unequivocally whether the enantiomorphism is time-invariant or time-noninvariant since the associated physics will be quite different. The distinction between true and false chirality is a useful criterion for determining the potentiality of physical agents for inducing absolute asymmetric synthesis. In short, only a truly chiral influence can induce absolute asymmetric synthesis in an isotropic reaction system which has been allowed to reach thermodynamic equilibrium, while for processes controlled kinetically a falsely chiral influence might suffice to induce molecular chirality.[33]

A. Magnetic and Electric Fields

It is known that a magnetic field may induce a series of chemical and physical effects, thereby altering reaction rates and mechanisms. This exciting topic was comprehensively reviewed for *Chemical Reviews* in 1989 by Steiner and Ulrich.[34] Recently, Grissom has also outlined the importance of magnetic effects in biology.[35]

Can a magnetic field induce absolute asymmetric synthesis? This question has risen to prominence during this decade.[36−40] It was Pasteur, more than 100 years ago, who first tried to answer the question in an attempt to connect what he called dissymmetry (chirality) with external physical forces, which might be responsible for such a phenomenom in nature.[41] Since a magnetic field can induce optical rotation, the so-called Faraday effect, Pasteur thought that a magnetic field has the same kind of asymmetry as an optically active molecule, and used magnetic fields in unsuccessful experiments to induce chirality. This erroneous idea has caused much confusion right up to the present time. It is possible that Lord Kelvin had Pasteur in mind when he said "...even to the present day we frequently find the chiral rotation and the magnetic rotation classed together in a manner against which Faraday's original description of his discovery contains ample warning".[42]

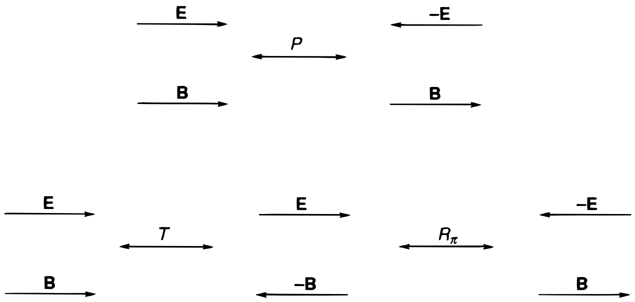


Figure 2. Transformation of electric and magnetic fields under the operations of parity *P* and time reversal *T*.

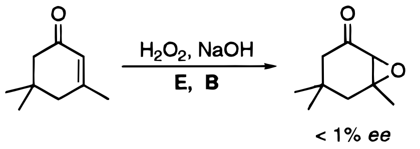
A deeper analysis suggests that the quantum states of molecules that can support natural optical rotation are different from those supporting magnetic optical rotation. Thus, the natural optical rotation observable for an isotropic collection of chiral molecules is a time-even pseudoscalar, while conversely the magnetic optical rotation associated with a collection of achiral molecules is a time-odd axial vector. The former requires quantum states of mixed parity but definite reversality; the latter definite parity but mixed reversality.[24]

Coming back to the nature of electric and magnetic fields, it is clear that neither a static uniform electric or magnetic field in isolation represent a truly chiral influence according to the above definition. A static uniform electric field **E** is a time-even polar vector so that its direction is reversed by *P* but not by *T*; a static uniform magnetic field **B** is a time-odd axial vector and its direction is reversed by *T* but not by *P*; however, rotations R_π through 180° restore the original sense in both cases. Similarly, time-dependent uniform electric and magnetic fields are not truly chiral. Nevertheless, if the electric or magnetic fields are nonuniform, true chirality may exist for certain configurations.[33] These arguments lead to the practical conclusion that a *homogeneous* magnetic field provided, for instance, by a permanent magnet, electromagnet, cryomagnet, or an NMR spectrometer cannot effect enantiodifferentiation in a reacting system under thermodynamic control that is isotropic in the absence of the field, and ee's of zero should therefore be expected. But under nonequilibrium conditions additional possibilities arise which complicate the arguments (vide infra).

Toward the end of the last century, Pierre Curie suggested that the parallel or antiparallel combination of a static uniform electric and a static uniform magnetic field could constitute a chiral system.[43] However, such a combination is a case of false chirality, a fact recognized later by Zocher and Török.[44] Parallel and antiparallel electric and magnetic fields produce enantiomorphism because they are interconverted by space inversion and are not superimposable. But they are also interconverted by time reversal in combination with a rotation through 180° (Figure 2). Notice that a static uniform electric or magnetic field in isolation is not even falsely chiral since there is no associated enantiomorphism.

Gerike claimed to have achieved absolute asymmetric synthesis by performing a series of reactions such as the base-catalyzed epoxidation of isophorone (Scheme 1), oligomerization of alkenes, bromination of carbon−carbon double bonds, and the alkylation of prochiral ketones with Grignard reagents to form secondary alcohols, by applying simultaneous electric and magnetic fields.[45] His conclusions were based on the observation of nonzero, though very small ($<$1% ee), optical rotations in the reaction mixtures for both static and time-dependent uniform fields, and without preference for either *R* or *S* enantiomers. Likewise, the author carefully indicated that fields might not have been uniform nor constant. The same reactions conducted in the absence of the fields, or in the presence of only an electric field or only a magnetic field, gave no optical activity.

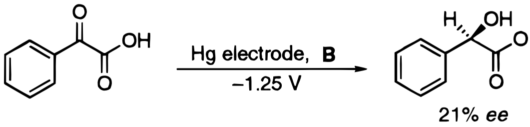
Scheme 1. Epoxidation of Isophorone in the Simultaneous Presence of Electric and Magnetic Fields



At first sight it would appear that whatever the origin of the optical rotations, they cannot have arisen from the effects of the uniform applied fields. Thus a few years earlier, De Gennes demonstrated theoretically the impossibility of asymmetric synthesis in the presence of static electric and magnetic fields, on the basis of the invariance of the molecular Hamiltonian under space inversion and time reversal.[46] Gerike's work was also criticized by Mead and co-workers who ruled out the physical fields as the source of chirality, since the application of the symmetry operators *P* and *T* leads to an isoenergetic correspondence between both enantiomers even in the presence of **E** and **B**.[47] An important advance was made by Rhodes and Dougherty who pointed out that the asymmetric synthesis is not possible only if the reacting systems have reached complete thermodynamic equilibrium.[48] In their discussion, these authors suggested that, in principle, it is possible for uniform collinear electric and magnetic fields to modify the kinetics of a prochiral reaction to allow asymmetric synthesis. In addition, they calculated the kinetic effect for transition states having electric and magnetic moments for a series of fixed parameters. However, the evaluation of the ratio of rate constants corresponds to an ee as low as 3×10^{-5}% which should be achievable with magnetic flux densities of up to 10^4 G (1.0 T) and an electric field strength of 10^3 V/cm. Although De Gennes[49] found merit in the idea of these kinetic effects, they were considered unconvincing by other authors based not only on time reversal invariance but also on the condition of detailed balancing.[50] We have however indicated the validity of the argument by Rhodes and Dougherty by showing that a falsely chiral influence might induce an enantiomeric excess under kinetic conditions.[1g,21,40,51]

Another recent case of enantioselective synthesis involving electrical and magnetic fields is the electrochemical reduction of α-keto acids (Scheme 2).[52]

Scheme 2. Electrochemical Reduction of α-Keto Acids in the Presence of a Magnetic Field

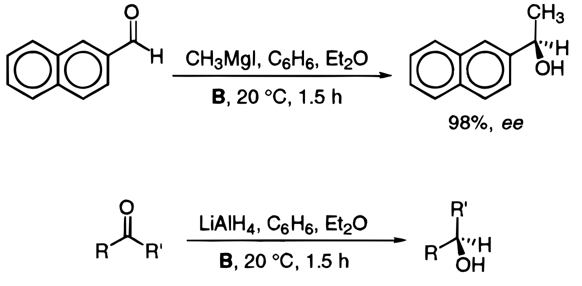


Thus, Takahashi and co-workers reported that the electrolytic reduction of phenylglyoxylic or piruvic acid, in the presence of magnetic fields of 980−1680 G, resulted in the formation of dextrorotatory mandelic or lactic acids, respectively. The asymmetric reductions were carried out with parallel or antiparallel arrangements of the magnetic field to the normal of the surface of the Hg electrode, and the optical yield increased proportionally to the magnetic flux density. No optical rotation was found when the magnetic flux was orthogonal to the electrode, i.e., directed horizontally to the normal of the surface. In the case of the asymmetric reduction of phenylglyoxylic acid, the ee amounted to at most 21% at 1680 G and a controlled potential of −1.25 V (vs SCE). Apparently, there are no obvious flaws, but the electrochemical reduction is a heterogeneous process occurring at the electrode interface where mass transport phenomena play an important role. Again, this might suggest a role for kinetic effects under the influence of collinear uniform electric and magnetic fields. Nevertheless, attempts to reproduce these results failed.[1e]

If Gerike's paper was the subject of a fruitful discussion, a recent paper by German authors reporting enantioselective reactions in a 1.2-T static magnetic field was quite disturbing to the scientific community.[36] They described ee's as high as 98% of methyl-α-naphthylcarbinol from reaction of α-naphthaldehyde with methylmagnesium iodide (Scheme 3). The enantioselective reduction of acetophenone with lithium aluminum hydride gave α-phenethyl alcohol in 67% ee. These results could not be reproduced by other researchers who obtained ee's of zero.[37,38] Moreover, Kaupp and Marquardt suggested again that the ee's could not have had their origins in the magnetic field and any facial selectivity of the prochiral carbonyls would have to occur prior to the precipitation of products.[38] Finally, the original paper was withdrawn.[39]

Despite these facts, the discussion about the possible influence of magnetic fields on asymmetric induction is not yet over. Thus consider a unimolecular reaction in which an achiral molecule A can be converted either into a chiral molecule *R* or its enantiomer *S*. In the absence of an external truly chiral influence, both enantiomers will be isoenergetic and no ee will be generated assuming that the reaction is allowed to reach thermodynamic equilibrium.[33,48] This is also true under a falsely chiral influence since the chiral enantiomers will remain degenerate and no ee can exist at equilibrium. Only with a truly chiral influence will the energy of an

Scheme 3. Enantioselective Reactions in a Static Magnetic Field



R	R'	*B* (Tesla)	*ee* (%)
C_6H_5	CH_3	1.2	67
2-naphthyl	CH_3	0.4	68
C_6H_5	C_2H_5	2.1	55
C_2H_5	CH_3	2.1	11

enantiomer be different from that of its mirror image and an asymmetric induction can now exist at equilibrium. The validity of such considerations, however, should be questioned for reactions under kinetic control because the enantiomeric transition states might have different energies (vide infra).

How can a falsely chiral influence affect chemical reactions? An instructive example arises in the realm of elementary particle physics where a breakdown of microscopic reversibility associated with *CP* violation is observed in particle–antiparticle processes involving the neutral *K* meson.[53,54] An examination of this process suggests that a falsely chiral influence such as collinear electric and magnetic fields, because it breaks *P* and *T* separately but is *PT*-invariant overall, might induce a difference in the rates for the production of the *P* enantiomers *R* and *S*, thereby leading to an absolute asymmetric synthesis in a chemical reaction far from equilibrium.[1g,21,40,51] Besides elementary particle processes, there is at least a "macroscopic" phenomenom in which the breakdown of microscopic reversibility has been recognized: reflective optical activity from chiral media.[55]

The conventional principle of microscopic reversibility may be conceptualized as the same potential energy barrier for the forward and backward reactions, based on the invariance of the scattering amplitude under time reversal. As shown in Figure 3 the breakdown of microscopic reversibility in the chemical process is then visualized as different potential energy profiles for the direct and reverse reactions involving a given enantiomer in the presence of a time-noninvariant enantiomorphous (falsely chiral) influence. Symmetry is recovered in the time-reversed enantiomeric process (i.e., the process generated by *PT* rather than *T* alone), leading to the concept of enantiomeric microscopic reversibility. Accordingly, a falsely chiral influence might be viewed as a chiral catalyst because it alters potential energy profiles to change relative rates of formation of enantiomers but without affecting the equilibrium thermodynamics.[1g,27,40] The overall effect is to introduce a ratchetlike mechanism into rate processes involving chiral molecules. A simple example of how this might come about is provided by the conrotatory interconversion of a butadiene with a chiral cyclobutene in which transient magnetic moments of equal magnitude but opposite sign are generated by the two possible senses of conrotatory motion associated with formation of the two enantiomers.[51]

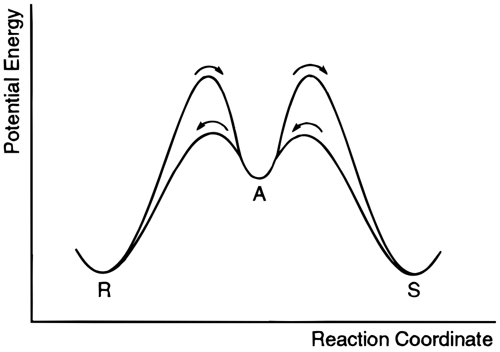


Figure 3. Potential energy profiles for unimolecular reactions of an achiral molecule A producing a chiral molecule *R* or its enantiomer *S* in the presence of a falsely chiral influence such as collinear electric and magnetic fields. The arrows illustrate the principle of enantiomeric microscopic reversibility in that the potential energy profile for the process A → *R* is the same as that for the time-reversed enantiomeric process *S* → A, and similarly for A → *S* and *R* → A.

Notice that the ratchetlike mechanism considered here, in which the effective barrier heights are different for the forward and backward reactions, is not the same as that recently discussed by Kelly et al.[56-58] in the context of triptycene-substituted helicenes which function as molecular ratchets since in these molecules the barrier heights (but not the slopes) are the same for forward and backward motion. As expected from thermodynamic considerations,[58] experiments showed that these ratchetlike molecules do not in fact show unidirectional behavior.[56,57] However, in view of the remarks in the previous paragraph, it might be interesting to reanalyze the microscopic aspects of these findings in terms of unitarity, rather than microscopic reversibility as used so far.[58]

More accurately, Figure 3 should be taken as the potential energy profile for a particular interconversion pathway between specific quantum states of *R* and *S*. If the system is racemic and in thermal equilibrium, equivalent enantiomeric states are equally populated. Then invoking the unitarity of the scattering matrix (which corresponds to the fact that the sum of the transition probabilities from a given state to all possible final states is unity) it is possible to show that no excess of one enantiomer over the other can develop at thermal equilibrium even when the presence of a falsely chiral influence destroys the equality between rates for specific enantiomeric transitions.[51] Put more simply, although one interconversion pathway might favor production of *R* over *S*, another might favor *S* over *R*, so when all possible pathways have equilibrated (as at true thermodynamic equilibrium), unitarity guarantees exact cancellation of any enantiomeric excess. This is consistent with the fact, not widely appreciated, that Boltzmann's H-theorem and hence the second law of thermodynamics in fact depend on unitarity, and not microscopic reversibility as often used in textbook derivations,[59] and so still hold even when microscopic reversibility breaks down.[60−62]

Although the breakdown of microscopic reversibility has only been observed to date in elementary particle processes and possibly in reflective optical activity, this possibility cannot be excluded in chemical reactions. Furthermore, very small ee's could largely be amplified by a chiral autocatalytic process.[63] These reactions which occur under nonequilibrium conditions can amplify in a few cycles small initial ee's.

Very recently, Hegstrom and Kondepudi have demonstrated theoretically that a static magnetic field can enhance the ee generated by chiral autocatalytic radical-pair reactions.[64] The hallmark of the process is the ability of the magnetic field to alter the rate of the key step or elementary steps in the kinetic reaction mechanism. If the reaction proceeds, at least partially, by a radical pathway, then the simplest stage should involve a singlet state radical pair or biradical. The presence of a magnetic field indeed favors spin evolution into the triplet state.[34] Once in this state, the reactant species owing to spin selection rules cannot give rise to products which are spin singlets. The overall result is the slowing down of the reaction step which enables extra time for clusters of chiral catalyst product molecules to reach a certain critical threshold concentration. The enhancement of the ee depends on the rate constants, the applied magnetic field, and the reaction mechanism itself. By means of computer simulation, these authors showed that the rate constant can be reduced as much as 50% by a magnetic field of a few tesla, thereby increasing the ee. Still an experimental challenge, the importance of this study is that it provides general conditions to be satisfied to produce enantioselection in kinetic reactions by applying a magnetic field. The model also introduces parameters that can be calculated or determined experimentally. Furthermore, it suggests the intermediacy of radical species in autocatalytic reactions, which could eventually be detected by spectroscopic techniques. Hegstrom and Kondepudi's analysis is based entirely on conventional kinetic arguments: the consequences of incorporating the extra ingredient of a breakdown in microscopic reversibility have yet to be explored.

The breakdown of microscopic reversibility goes also against the classical interpretation of chemical kinetics stating the same potential energy barrier for the forward and reverse reactions. Nevertheless, Onsager had already recognized that the principle of microscopic reversibility does not apply in the presence of an external magnetic field.[65] However, Onsager's prescription of reversing the magnetic field along with the motions of the particles does not restore microscopic reversibility when the field is a component of a falsely chiral influence. Even then, the consequences will be observable only if the particles are chiral. On the contrary, if the particles are achiral, the P enantiomers are indistinguishable from the original (in other words $R = S$) and the right and left energy barriers in Figure 3 must coalesce, so the forward and reverse barriers for an enantiomer are identical.

We have not yet experimental evidence for a breakdown of microscopic reversibility in chemical reactions. But if reproducible ee's may be obtained for reactions under kinetic control with collinear electric and magnetic fields, or any other type of falsely chiral influence, the fact would clearly prove such a breakdown. The function of the electric field is to partially align the dipolar molecules in the fluid so that one sense of circular motion of charge in a plane perpendicular to the magnetic field direction is preferred over the other for a particular enantiomer as the chiral reaction intermediate evolves.[51] Thus a magnetic field alone might induce asymmetric synthesis if the molecules are already aligned, as in a crystal, on a surface or at an interface (or indeed if some preferential alignment develops in an autocatalytic reaction) and the reaction is far from equilibrium.

Before leaving the controversial subject of magnetic fields, we should mention that Gilat[66] has suggested that a magnetic field will disturb the equilibrium of enantiomers aligned at the surface of a bulk racemic solution so that one particular enantiomer will tend to concentrate at the surface. However, this idea conflicts with the above analysis which requires aligned enantiomers to remain strictly degenerate at equilibrium in a magnetic field: nonequilibrium conditions as in reaction, transport or phase transition processes are necessary to achieve enantiomeric separation.

B. Magneto-Chiral Fields

As shown above, a static magnetic field is not a chirally asymmetric influence. Under thermodynamic conditions, absolute asymmetric synthesis will only occur with the superposition of additional directional fields capable of giving rise to truly chiral field systems. Two collinear vectorial fields, one polar the other axial, can generate true chirality *if both of them* are either time-even or time-odd. Thus a uniform magnetic field $\mathbf{B}$ collinear with the propagation vector $\mathbf{k}$ of a light beam of arbitrary polarization constitutes a truly chiral influence, which is responsible for interesting effects such as magneto-chiral dichroism and birefringence.[67,68] Wagnière and Meier indicated that a static magnetic field parallel to the direction of propagation of an unpolarized light beam can produce a small shift in the value of the absorption coefficient (ϵ) of a chiral substance.[67] The shift changes sign either on replacing the chiral substance by its enantiomer, or on reversing the relative directions of $\mathbf{B}$ and $\mathbf{k}$. Parallel or antiparallel arrangements of both vectors are now chiral enantiomers because they cannot be interconverted by time reversal since $\mathbf{B}$ and $\mathbf{k}$ are both time-odd. Magneto-chiral dichroism has recently been observed for the first time: dissymmetry factors of $\sim 10^{-3}$ were induced in chiral europium complexes with a magnetic field of 0.9 T.[69] The first observations of magneto-chiral birefringence were reported shortly afterward with values for the differential refractive index in a camphor derivative and in carvone of $\sim 10^{-7}$ with a magnetic field of 5 T.[70]

A simple argument allows us to understand that magneto-chiral dichroism does not violate parity and time reversal symmetry. Since **B** and **k** are axial and polar vectors, respectively, *P* reverses their relative directions so the dichroism (in terms of the absorption coefficient) will change sign. But space inversion also replaces the chiral molecules by their enantiomers. Parity is thereby conserved because both the initial and the space-inverted situation are distinct and realizable. Under time reversal the collection of chiral molecules remains unaffected and, since both **B** and **k** are time-odd, *T* does not change their relative directions and hence will not change the sign of the dichroism.

Initially, the effect was formulated in terms of a linear perturbation by the external static magnetic field of the interference terms between electric dipole and magnetic dipole interactions, and electric dipole and electric quadrupole interactions.[67] Later, Barron and Vrbancich extended the discussion of these magneto-chiral phenomena within the unified context of effects generated by the time-odd parts of the complex optical activity tensors.[68] In further work, Evans discussed the molecular dynamical origin of magneto-chiral dichroism in terms of a correlation function between the linear and angular rates of a diffusing chiral or achiral molecule.[71]

As a truly chiral influence, the combination of an unpolarized light beam collinear with a static magnetic field can induce absolute asymmetric synthesis under thermodynamic control. Thus optically active spirans, with very small ee's, were claimed to be produced when the reactions were conducted in a vessel placed between the poles of a powerful magnet and with a high-intensity beam of polarized light passing through the vessel.[72] However, the results of other experiments have been unsuccessful.[72,73] Nonetheless, magneto-chiral dichroism certainly constitutes a source of true chirality and this mechanism could be operative in molecular evolution as a way of promoting absolute asymmetric synthesis in prochiral substrates.[71,74]

C. Gravitational Fields and Vortex Motion

The gravitational effect should always be taken into account when considering an asymmetric transformation. Achiral molecules can crystallize in any of the 65 chiral space groups from the 230 distinct space groups. In solid-state asymmetric synthesis, the chirality is clearly introduced in the crystallization step; the chemical reaction then converts the chirality of the crystal into that of the product.[4] In this context, it should be pointed out that there are two types of asymmetric transformations, i.e., the transformation of a mixture of stereoisomers (usually 50:50) into a single stereoisomer, or into an enantiomerically enriched mixture, by an equilibrium process.[75] Asymmetric transformations of the *first kind* involve equilibration without concomitant separation; and in the case of enantiomers the enrichment requires a chiral medium (e.g., a chiral, nonracemic solvent) or other chiral influence. However, in an asymmetric transformation of the *second kind*, following equilibration, one stereoisomer crystallizes from solution and may be obtained enantiomerically or diastereomerically pure. Likewise, an additional consideration in relation with the optical activity in the solid state is the fact that certain achiral compounds can crystallize in enantiomorphic space groups or in chiral conformations.[76]

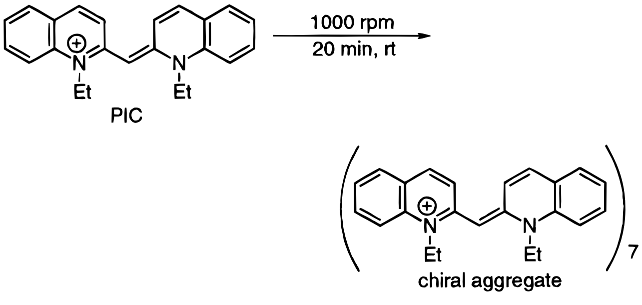
In solution, however, the molecules that may eventually precipitate in crystalline form must first be generated chemically. In other words the enantiofacial selectivity will take place prior to crystallization. At this stage, a truly chiral influence might produce the selective precipitation of chiral molecules from a homogeneous solution in what would otherwise be a racemic mixture in the absence of the external influence.

A gravitational field might have an influence in the case of a rapidly rotating vessel with the axis of rotation perpendicular to the earth's surface. We have the time-odd axial angular momentum vector of the spinning vessel either in a parallel or antiparallel arrangement to the earth's gravitational field, which is a time-even polar vector. We have therefore an analogous situation to collinear electric and magnetic fields, so that the complete system constitutes a falsely chiral influence.

Dougherty and co-workers reported absolute asymmetric synthesis of isophorone oxide by epoxidation of isophorone in a rapidly rotating vessel at 6000−14000 rpm.[77,78] They attained opposite optical rotations when the vessel rotated clockwise or anticlockwise about an axis perpendicular to the earth's surface, but rotation about an axis parallel to the earth's surface gave no optical rotation. This claim of asymmetric synthesis was criticized by some authors on the basis of the invariance of the Hamiltonian.[50,79] The argument appears to be consistent because no enantioselectivity was found in the polymerization of amino acids in solution with a similar rotating system.[80] Likewise, directional stirring had no effect on fractional crystallization of racemic sodium ammonium tartrate.[80]

A related result was reported by Honda and Hada in the asymmetric synthesis of a polymer derived from the dye 1,1′-diethyl-2,2′-cyanine chloride (pseudocyanine, PIC) (Scheme 4).[81] This substance is mono-

Scheme 4. Synthesis of a Circularly Dichroic Cyanine Dye Polymer: Its Apparent Induced CD Could Be Due to Linear Dichroism of Oriented Molecules



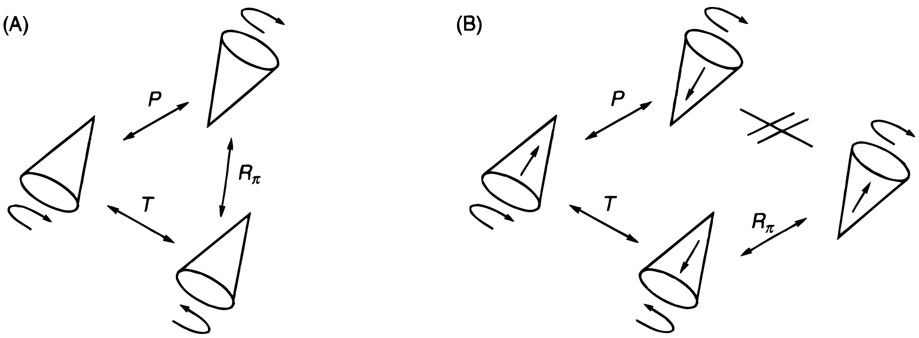


Figure 4. The effects of parity, time reversal, and spatial rotation on (A) a stationary and (B) a translating spinning cone.

meric in ethanol but in water at concentrations above 10^{-3} M forms a fluorescent polymer, often referred to as the Jelley-Scheibe polymer or J-aggregate, characterized by a very sharp absorption band at a longer wavelength (572 nm) than the monomer (524 nm). It is believed that the J-aggregate contains at least seven monomer units. While the CD of this polymer has been induced by chiral substances such as α-helical poly-L-glutamic acid or potassium tartrate, the Japanese authors observed that the Cotton effect can be induced by swirling the solution in a porcelain crucible without any chiral additives (swirling solution at about 1000 rpm at room temperature for 20 min gave a reaction mixture of monomers, dimers, and J-aggregates in equilibrium). Clockwise and anticlockwise stirring produced CD spectra with opposite signs of ellipticity. The CD disappeared after standing for 24 h. They also observed optical activity in J-aggregates of similar cyanine dyes by regular stirring.

These results could not be reproduced by other authors, who suggested that the observation might have been an artifact due to linear dichroism from accidentally oriented material.[82,83] In a further study, Nordén suggested that the possibility of optical activity induced by vortex motion cannot be eliminated, but experiments involving formation of J-aggregates on passing a solution through a conical flow cell did not induce any CD.[84] Nordén also pointed out that diffusion differences in an asymmetric flow would in principle provide a way to separate enantiomers, that asymmetric strain (twisting in one direction) could perturb conformer equilibria asymmetrically to give optical activity, and that preferential degradation could also give rise to optical activity.[84]

At this point, it should be noted that Italian authors found optically induced dichroism and birefringence in a fluorescein-doped glass, again evidencing the favorable effect of a rigidly held dye molecule.[85] It is worth also mentioning that the chirality associated with cholesteric liquid crystals is due to their highly oriented structures. These substances exhibit high values of optical rotation, a valuable property that can be harnessed to detect or to amplify very small optical rotations, which is the basis of a chiroptical test referred to as “chirality amplification”.[86]

Be that as it may, a simple swirling action in two dimensions does not even have false chirality, whereas vortex motion possesses true chirality since it comprises rotation plus translation as illustrated in Figure 4. In a cone spinning about its symmetry axis, space inversion *P* generates an image that is not superimposable on the original. The apparent chirality however is false, because the operation of time reversal *T* followed by a rotation through 180° generates the same system as space inversion (Figure 4A). But when the spinning cone is also translating along the axis of spin, time reversal followed by the 180° rotation generates a different system to that formed by space inversion (Figure 4B). Moreover, the translating spinning object does not have to be necessarily a cone, and the argument can be valid for other objects as well (see the next section).[33]

D. Polarized Photons, Electrons, and Neutrons

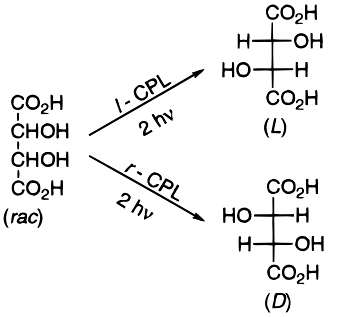
The potential use of either right- or left-CPL (r- or l-CPL) in enantiodifferentiating photoreactions of racemic mixtures was recognized by the end of the 19th century by van’t Hoff and Le Bel. In addition, Inoue has reviewed in detail[5] the asymmetric photochemistry in solution with CPL as mentioned in the introductory remarks.

The importance of CPL lies in the possibility of enantiomeric enrichment from a racemate, a methodology much easier than the absolute asymmetric synthesis of a specific enantiomer. When a racemic mixture of molecules with sufficiently small excited electronic state barriers to enantiomer inversion is irradiated with CPL at a wavelength of significant CD, the initial equality of the enantiomers in the ground state will change. The concentration of the more strongly absorbing enantiomer will decrease, and that of the other will increase resulting in an ee. Interestingly, this particular photochemistry can be exploited in chemical kinetics. The induced optical rotation after irradiation enables one to measure the temporality of the inversion process, both the rate constants of the photoresolution and the subsequent racemization.[87]

From a mechanistic viewpoint, photochemical induction of optical activity with CPL may occur via different pathways such as (i) the preferential decomposition of one enantiomer of a racemic mixture, (ii) asymmetric photosynthesis, or (iii) photointerconversion of the enantiomers of a racemate. The differential features of these methodologies have been discussed in earlier synthetic reviews,[5,88] and for the purpose of this review we employ the wider concept of deracemization, without mechanistic implications, illustrating the concept of chirality exposed through the discussion.

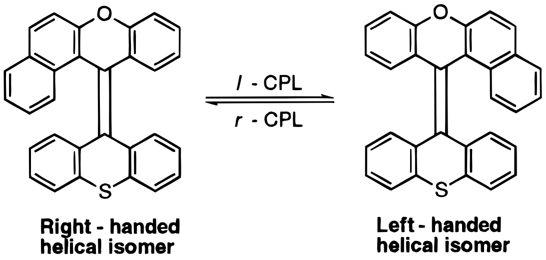
In general the only drawback of direct photochemistry with CPL is that the ee's can be extremely low, even values of zero, unless a high-intensity source is utilized. With the advent of laser technology, it is now possible to perform multiphoton absorption processes, giving products in appreciable ee's.[89−92] Thus, in a remarkable example provided by Bonner and his associates, racemic leucine not only can be photolyzed with r- and l-CPL, but also r-CPL preferentially decomposes the (*R*)-leucine enantiomer and l-CPL the (*S*)-leucine enantiomer of the racemate, yielding ee's of 1.98 and 2.50%, respectively.[89] Similar results were found recently by Japanese researchers in an enantioselective synthesis of D-tartaric acid with a highly intense CPL from a XeF 351-nm excimer laser.[91,92] Irradiation of the racemate with r-CPL decreased the concentration of the L form with increasing adsorbed energy. However, the concentration of the D form remains almost constant giving the product with a maximum 7.5% ee. Conversely, irradiation with l-CPL resulted in enrichment of the L enantiomer through a decrease of the D form. Thus, the switching of the sense of circularity in CPL produces an inversion in the enantioselectivity (Scheme 5).[92] The attractiveness of these and other experiments is that they provide the basis of dynamic processes in which the sense of asymmetric induction can be controlled at will.

Scheme 5. Selective Enantioenrichment of Tartaric Acids by Circularly Polarized Light



A related and interesting result has been recently reported by a team of Dutch chemists. This group made a chiral molecule consisting of two related polycyclic fragments connected by a carbon−carbon double bond. This alkene would tend to lie flat, but steric hindrance between the two bulky units gives it a slight twist. In fact, the chirality of the molecules depends on steric repulsion causing nonplanarity. Two opposite helicities, which are mirror-image isomers, can exist, and when exposed to polarized light, they can interconvert through an excited state.[93] Again, the helical molecule twists from left to right by changing the handedness of light shining on it (Scheme 6). When a solution of the racemic mixture is irradiated with l-CPL at 313 nm, a tiny fraction of the right-handed helicene isomerizes to the left-handed one, but the ee is extremely low, 0.07%. Likewise, when the solution is irradiated with r-CPL of the same wavelength, the same ee of the right-handed helicene is produced. Even though the ee obtained is not practical, the importance of this work lies in the fact that when added to a liquid crystal film, helical molecules serve as a light-activated trigger to switch the film organization from racemic to chiral. Many scientists know that a nematic liquid crystal can be transformed into a cholesteric phase, which is inherently chiral, by addition of a small amount of an optically active molecule (vide supra).[86] However, instead of using a single enantiomer as the additive, the Dutch group added 20 wt % of the racemic polycyclic molecule to a nematic liquid crystal. When a film of this doped phase was irradiated with l-CPL for 90 min, the helicene became enriched in the left-handed enantiomer and a left-handed cholesteric phase resulted. The process is reversible and thus, when the cholesteric phase was exposed to unpolarized or plane-polarized light, the nematic phase returned.[93]

Scheme 6. CPL-Induced Chirality Switching between Liquid Crystal Phases



In a recent paper discussing control of molecular chirality in chemical reactions by CPL, Shao and Hänggi formulated a theory of absolute asymmetric synthesis within the framework of quantum-mechanical perturbation theory.[94] Numerical estimates showed any ee to be far too small from a practical point of view. However, for unstable chiral molecules, it was found that enantioselective reaction may be achieved via destruction of quantum coherence by the electric field of the CPL wave. From their key result, these authors also claimed to have established a dynamic proof of the De Gennes theorem,[46] stating the impossibility of absolute asymmetric synthesis in a static electric and/or magnetic field (even though De Gennes himself allowed this possibility in reactions under kinetic control).[49] However, the situation considered by these authors is not directly relevant to the case of collinear electric and magnetic fields discussed above because both **E** and **B** in a light wave are perpendicular, and because only freely rotating molecules were considered, whereas the function of the static electric field is to partially align the molecules. Furthermore, De Gennes[49] suggested that the source of absolute asymmetric synthesis in collinear electric and magnetic fields should be sought in differences in the preexponencial factors in the rate expressions for formation of the two enantiomeric activated complexes, rather than in the differences in the two activation energies (which are equal).

There is no question here that the physical influence provided by CPL is truly chiral because resolutions and absolute asymmetric syntheses have been

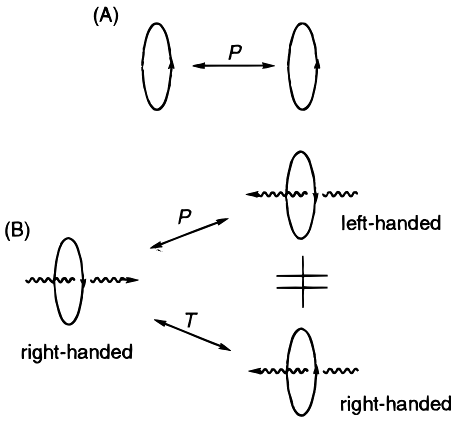


Figure 5. The effects of parity and time reversal on (A) a stationary spinning particle and (B) a translating spinning particle.

successfully achieved. It is also quite plausible that CPL had a role in the abiotic synthesis of optically active molecules.[1]

The true chirality of polarized photons can be easily demonstrated anew by considering the effects of P and T on the system in question (Figure 5). The photons in a beam of circularly polarized radiation propagating as a plane wave are in spin angular momentum states with a spin quantum number $s = 1$ and quantum numbers $m_s = \pm 1$, which correspond to projections of the spin angular momentum vector parallel or antiparallel to the propagation direction. There are no states with $m_s = 0$ because, unlike electrons, photons are massless so they have no rest frame and consequently always move at the velocity of light, which means that there is no symmetry with respect to the complete group of rotations in three dimensions but only axial symmetry about the direction of propagation (the usual $2j + 1$ projections for a general angular momentum vector are defined in the rest of frame).[95] A circularly polarized photon shows true chirality since P interconverts the right- and left-circularly polarized forms which are nonsuperimposable mirror images, but T does not (Figure 5B).

An analogous reasoning can be utilized in the case of spinning electrons. Electrons, however, have rest mass and are characterized by a spin quantum number $s = {}^1/_2$ with $m_s = \pm {}^1/_2$. A stationary spinning electron is not a chiral object because space inversion P does not reverse the spin sense and, therefore, does not generate a distinguishable enantiomer (Figure 5A). However like photons, translating spin-polarized electrons do exhibit true chirality (Figure 5B).

In sharp contrast to the readily available CPL as a current strategy that can give rise to enantiodifferentiating reactions, the use of spin-polarized electrons as a source of chiral field has been scarcely employed in chemical reactions, even though this radiation might have also played an important role in the origin of molecular chirality.[1d,96] Spin-polarized electrons can be generated as a result of parity violation in nuclear β-decay products.[97−102] A chiral molecule and its enantiomer will be ionized at different rates by longitudinally spin-polarized electrons; the effect can be enhanced for molecules containing heavy atoms.[101] Radiolysis of racemates and optically active samples, particularly amino acid derivatives, have been performed with a β-radiation source and the asymmetric effects analyzed by chiroptical methods and gas chromatography.[97−100] In the case of racemic leucine, norleucine, norvaline, and proline as solid samples, and of leucine and tyrosine in solution, no appreciable optical rotation could be measured. However, radiolysis of nonracemic samples of D-leucine and L-leucine resulted in small differences, although the ee's are close to the experimental error.[98,99] In further studies, it was demonstrated that left-handed electrons degrade D-leucine more extensively than L-leucine on irradiation of racemic D,L-leucine, while right-handed electrons decompose asymmetrically D,L-leucine in exactly the opposite sense.[100] Anyhow the results seem to validate mechanisms for the abiotic generation of optical activity with this truly chiral influence.

Neutrons can also be a source of chirality. In this respect neutrons, being spin-${}^1/_2$ particles with mass, are more akin to electrons than photons. It has been demonstrated theoretically that there is a very small, but nonzero, optical activity of a beam of polarized neutrons owing to its magnetic interaction with the electrons in a chiral molecule.[103] Translating spin-polarized neutrons might then be a source of chirality, analogous to a beam of spin-polarized electrons, but smaller effects should be expected.

It should also be noted the situation with particles (atoms, nuclei) of spin ≥ 1. The interaction of such particles with matter produces a phenomenon similar to light birefringence in optically anisotropic crystals.[104]

E. Other Types of Radiation

An interesting type of partial photoderacemization of fluids involving circularly polarized radio frequency radiation was proposed by Baranova and Zel'dovich.[105] If the molecules are dipolar, an electric field will partially orient them so that the rotating electric field of the circularly polarized radio frequency radiation will induce angular motion in the molecules, which in turn will induce translation of the two enantiomers in opposite directions on account of the hydrodynamic "propeller effect". However the radio frequency field is not acting here as a truly chiral influence since only the circular, but not the linear, component of its motion is responsible for the discrimination. If the rotation axis of the electric field coincides with the axis of a tube filled with a racemic solution of chiral molecules, these authors calculated that a stationary concentration gradient might be established with opposite enantiomers tending to congregate at opposite ends. This situation does not conflict with the concepts outlined in this paper since it would correspond to a transport process in a steady state, driven by free energy input from the external radio frequency field, rather than at thermodynamic equilibrium. In other words, the rotating electric field vector is supplying free energy to the system so it is not at equilibrium. Although this propeller effect might be considered somewhat exotic, it is intriguing that the Baranova/Zel'dovich experiment falls within the topic of molecular (Brownian) motors.[106] Thus, external fluctuations or a chemical reaction far from equilibrium can bias the Brownian motion of a particle if the medium is anisotropic. Directed motion is possible even in an isothermal system, without gravitational force or a macroscopic electric field. Such mechanism by which chemical energy can drive the motion of particles or macromolecules may find application in separations and the design of molecular pumps. See also De Gennes[49] for a discussion of the inverse version of this experiment in which chiral enantiomers are separated by the rotating fluid within a horizontal cyclinder rotating about its axis: if the molecules are constrained not to rotate with the fluid, the enantiomers in a racemic mixture will “screw” toward opposite ends of the cylinder. While on the subject of inverse experiments, it should be mentioned that, as pointed out by Peres,[79] a reaction vessel rotating in static electric and magnetic fields mutually perpendicular to each other and to the axis of rotation might induce absolute asymmetric synthesis. In this case the influence would be truly chiral because, from the point of view of the molecules rotating with the vessel, the symmetry characteristics of the influence are the same as for stationary molecules in CPL. The same is also true for **E** and **B** replaced by mutually perpendicular components of the earth's natural gravitational and magnetic fields.

In this context, it is also interesting to mention the work by Space et al. on the feasibility of using a laser-induced photophoresis experiment to create a concentration gradient of solvated molecules.[107] The molecules are dissolved in a solvent that is not appreciably absorbing at the applied radiation frequency. The anisotropic, propeller-shaped molecule has a transition dipole capable of driving ro-vibrational motion. The polarization of the laser can be taken as rotating slowly with the molecules, thereby establishing a net flow in a finite cell. In a further simulation of molecular propellers, Vacek and Michl have designed a chiral octahedral complex with two ligands derived from *o*-phenanthroline having opposite charges, which was exposed to a flow of a rare gas from a supersonic source. The gas flow caused the dipolar propeller to rotate in the expected sense and to reach a steady state.[108]

From a practical viewpoint, the chirality of other available types of radiation should also be considered, in particular microwaves and ultrasounds, two nonconventional tools that have gained considerable interest among chemists during the past decade.[109] The rapid heating produced by microwave irradiation is provided by a source that is electromagnetic in nature, and hence no absolute asymmetric synthesis will be induced in isotropic systems that have been allowed to reach thermodynamic equilibrium, unless the microwaves are circularly polarized.

The case of ultrasound is somewhat different because the sonic energy, unlike the electromagnetic one, is a nonquantum radiation and there is still a controversy about its exact nature. Most chemical and physical effects of ultrasound derive from cavitation, i.e., the rapid growth and collapse of microbubbles in a fluid thereby generating high pressures and temperatures in a few microseconds.[110] This releases enormous kinetic energy that drives the chemical process. Even if thermal and pressure effects are prevalent, any type of electromagnetic field cannot be ruled out.[111] Although the local temperatures and pressures in the cavities behave as time-even scalars, the associated gradients ∇T and ∇P will be time-even polar vectors and could supplement any local electromagnetic fields as components of falsely chiral influences. Hence cavitation, taking place far from equilibrium, could be a source of local false chirality which might give a boost to any chiral autocatalysis. So far no enantioselectivity has been found under the influence of an ultrasonic field alone, but it is known that ultrasound may largely improve the diastereoselectivities of some asymmetric reactions occurring by single electron transfers.[112]

IV. Conclusions

Through this review we have demonstrated how the concept of true and false chirality provides a useful criterion to evaluate the interaction between an external physical field and matter which may result in absolute asymmetric synthesis. A detailed analysis of past and present literature confirms explicitly the usefulness of this approach which is based on the basic symmetry operations of parity P and time reversal T. This alternative vision is often simpler and more intuitive than the invariance properties of the Hamiltonian of a molecule in the presence of the external influence, as well as considerations based on the conventional detailed balancing which may not be valid for reactions involving chiral molecules, especially under a falsely chiral influence.[1g,21,51]

While parity violation, and symmetry violation in general, constitutes one of the most striking ingredients of modern physics, it is generally thought to be irrelevant for chemistry. However, we have indicated that parity violation provides a criterion for the identification of true chirality. Moreover, there have been some discussions about the role of CP and T violations in processes with chiral molecules, which could be relevant for understanding the selective formation of naturally occurring enantiomers.[113−115] In the context of the origin of biomolecular homochirality, it is noteworthy that all ab initio calculations of the parity-violating energy difference predict that the naturally occurring left-handed amino acids are indeed more stable than their enantiomers, as are some key D-sugars and right-hand helical DNA.[116] Even though symmetry violation cannot be unequivocally proved, the effects of external fields may be an opportunity to mimic it.

Only a truly chiral influence (time-invariant enantiomorphism) is capable of inducing absolute asymmetric synthesis in reactions which are isotropic in the absence of the external field, and which have been allowed to reach thermodynamic equilibrium.[33] This has been exemplified in reactions with polarized photons and electrons, in particular in the selective reactions with CPL.

In sharp contrast to the unquestionable success of enantiodifferentiating photoreactions, the claims of absolute asymmetric synthesis under falsely chiral influences have attracted much controversy which we hope this article has helped to clarify. Special caution should be taken against the traditional belief that absolute asymmetric synthesis requires that the influence be truly chiral. The positive results reported by Dougherty et al.,[77,78] and, perhaps, those of Gerike's experiment[45] could however be genuine and further work on absolute asymmetric synthesis induced by falsely chiral influences would be valuable. Kinetic conditions circumvent the theoretical barrier necessary for the existence of true chiral enantiomorphism. Even if a time-noninvariant enantiomorphic influence was extremely weak, an enhancement of the ee may occur through autocatalysis in conjunction with the "ratchet effect" of the associated breakdown in microscopic reversibility. Finally, if a breakdown of microscopic reversibility can indeed be clearly demonstrated experimentally, this would in addition change our current interpretation of transport and phase transition processes of chiral molecules.[1g,40] Perhaps unexpectedly, the forthcoming years will witness the potential use of falsely chiral influences, thereby confirming the predictions of this theory.

V. Abbreviations

The following abbreviations have been utilized through this review:

C	symmetry operation of *charge conjugation* (particle−antiparticle exchange), associated with the absolute sign of electric charge
P	symmetry operation of *parity* (space inversion), associated with the absolute chirality, left- or right-handedness
T	symmetry operation of *time reversal*, associated with the absolute direction of motion
CPT	combined symmetry operation that is always thought to be conserved for all processes
CD	circular dichroism
CPL	circularly polarized light
ee	enantiomeric excess

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