In Praise of Chirality*

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The phenomenon of chirality is surveyed from a point of view of a practicing chemist who considers the importance of chirality as being closely connected with diversity, be it diversity of possible structures, structural features or possible interactions. An attempt is made to discuss its impact on chemistry and also to point out some current problems. It is shown how recent developments that make parity violation a cornerstone of chirality can be instrumental in bringing about deeper understanding of *e.g.* the origin of homochirality on Earth and can put efforts to effect absolute asymmetric synthesis on a more rational basis (by using truly chiral physical influences, *e.g.* circularly polarized microwave radiation).

Step by step chemistry has been mastering the chirality phenomenon and, as shown by a recent citation analysis [1], chirality is ever more frequently found among the current chemical themes and in the vocabulary of contemporary, especially organic, chemistry. There are journals devoted to problems of chirality (CHIRALITY — published by Wiley—Liss, TETRAHEDRON:ASYMMETRY — by Pergamon Press, or a recent addition to the family — ENANTIOMER — published by Gordon and Breach), conferences on chirality and related topics (Chiral Europe — last in 94, Chiral USA — last in 95, International Symposia on Chiral Discrimination — the 7th was held in fall of 95 in Jerusalem, or Chiranal 97 — soon to be held in Olomouc, Czech Republic), and a rapidly growing demand for enantiopure compounds in research as well as industry.

Chiral phenomena have been also a part of the human experience. This has been, probably, contributing to the popularity of Lewis Carrol's Alice in "Through the Looking Glass" and may also explain the metaphorical power in the following stanza of Anna Akhmatova's poem " Song of the last ren-dez-vous" [2].

Helpless against blizzard's fury

Through the dark I quickly went

Put my left glove in a hurry

Unconsciously on t'right hand.

Chirality was introduced into the scientific terminology (*cf.* Ref. [3]) by a professor of natural philosophy at the university in Glasgow — William Thomson (who had become Lord Kelvin in 1892) — in a lecture [4] delivered to the Oxford University Junior Scientific Club on May 16, 1893 to define an attribute of "any geometrical figure, or any group of points if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself [5]"

The lecture was reprinted verbatim as Appendix H of Kelvin's "Baltimore Lectures" [5]. These Lectures were delivered in October 1884 but, as shown by a careful examination of the record [6], the term "chirality" was not used in any of them.

Thus, Lord Kelvin found a novel word (derived from Greek cheir, *gen.* cheiros, meaning a hand, a fist, a palm of the hand, or an arm [7]) to define something that, in the realm of molecules, had been forty-five years earlier called molecular dissymmetry [8] by Louis Pasteur (*une dissymétrie dans les molécules* — is written upon his mausoleum in Paris). In many respects, Lord Kelvin made a lucky move with this conception.

It has not only been a generalization, but also a way out of a conceptual confusion where "asymmetry" had been often used in place of "dissymmetry" It had started as early as the original Pasteur's lecture (*Recherches sur la Dissymétrie des Produit Organiques Naturels* [9]) from 1860 had been translated into English [10], continued with similar mistakes in translations into German (On May 24, 1912, a lecture was given in Société Chimique de France by *Alfred Werner* [11]: "*Sur les Composés Métalliques à Dissymétrie Moléculaire*" Into German this was translated [12] as: "*Über die Metallverbindungen mit molekularer Asymmetrie.*") and even found its way into some commemorative contributions to "one hundred years of chemistry in space" (*cf.* preface to Van't Hoff-Le Bel commemorative issues of *Tetrahedron* [13]).

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In the opinion of the author of these lines, chirality and dissymmetry are, at the current stage of understanding, not synonymous. This will be especially highlighted later on, when time will be considered as an important factor in dealing with chirality. The concept of dissymmetry characterizes a material object under scrutiny as to its symmetry – such an object is devoid of rotation-reflexion symmetry and is, consequently, not superimposable onto its mirror image. Chirality, on the other hand, is considered in a broader context as a property with also a physical meaning. In the molecular sciences chirality is the ability of an object or a system to support pseudoscalar properties (that can be expressed as a product of polar and axial vectors), in elementary particle physic chirality is given by the eigenvalue of the chirality operator (with values 1 and – 1 for fermions with pure "right" or "left" chirality, respectively).

A pseudoscalar quantity is a number which under space inversion, represented by the parity operator **P**, changes sign. In other words, a pseudoscalar is invariant under rotation of the coordinates but not under reflexion of all three coordinates at the origin. Parity operation (Fig. 1) is reflexion in any plane containing the coordinate origin, followed by rotation through 180°about an axis perpendicular to the reflexion plane. In quantum mechanics, only systems that exist in a state of mixed parity can behave in such a way, so that measurement on them can reveal observables with odd parity (pseudoscalar). Invariance under space inversion means also invariance under mirror reflexions. As shown by *Lee* [14], this implies that it is impossible to observe absolute right- or left-handedness (that absolute right- and left-chirality are non-observables). In situations where motion is not involved, there is no fundamental difference between chirality and dissymmetry.

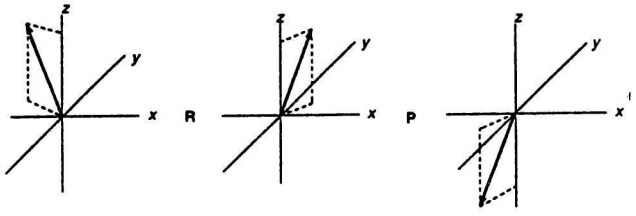


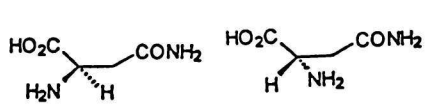
Fig. 1. The operation of reflexion (**R**) and parity (**P**).

Chirality and dissymmetry are concepts much more general than the concept of asymmetry itself — a subset of both. Chirality and dissymmetry are inextricably linked to the concept of enantiomorphism. There is, among structurally analogous chiral objects, a certain similarity, called homochirality (as evidenced by dactyloscopy, the chance that two identical right hands could be found is negligible; nevertheless, our eyes have little difficulty telling right from left hands), an inomissible feature of *e.g.* building-blocks of important biomacromolecules. Chemists have been continuously enlarging the content of the above-mentioned concepts with new examples (Fig. 2).

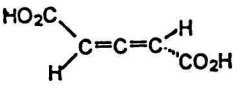
While the chirality of a geometrical model follows from its symmetry analysis, chirality of the real world comes to us through corresponding physical (*e.g.* interaction with electromagnetic radiation) or chemical phenomena (*e.g.* enantiodifferentiating course of a reaction or interaction). These have to be differentiated from the background noise and observed in a time interval corresponding to the Heisenberg uncertainty principle. Models have to respect that and have to correspond to the experimental conditions used, especially to the sensitivity and to the time-scale of the measurement. As more becomes known about topological chirality and the differences between topological and Euclidean chirality [20—24], as there are more and more novel types of chiral molecular structures [24], there is growing an awareness of how important it could be to quantify chirality [23], of how tempting it is and how rewarding it could be to look for hierarchy in chirality [25] and to find correlations between a "degree of chirality" of a molecular structure and its properties (*e.g.* effectivity of a chromatographic separation of enantiomers or its biological activity [23, 26]).

Until recently, much more attention has been paid to the study of symmetry than chirality and asymmetry. The concluding words of a famous book [27] state that "Symmetry is a vast subject, significant in art and nature. Mathematics lies at its root, and it would be hard to find a better one on which to demonstrate the working of mathematical intellect" and, no wonder, symmetry has been richly structured and its understanding has been based upon the appropriate apparatus of group theory. On the other hand, chirality and especially asymmetry presented itself as an amorphous undifferentiated whole. With realization that "symmetry is a requirement of stability and certainty, while asymmetry is the condition of unambiguous information storage and information transfer [28]" asymmetry (and chirality) are becoming the topic of interest.

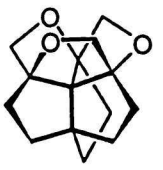
There are many obstacles, such as our deep-rooted dichotomous understanding of symmetry, and problems, perhaps insurmountable, in the search for a unified measure for both geometrical and physical chirality [29]. Since the 1960's, there have been efforts to formulate continuous measures of chirality and symmetry. They begun in a series of classic papers by *Ruch* [30] and have been continuing with increasing intensity [23, 31] as documented in an overview by *Weinberg* and *Mislow* [32]. There are two basically different approaches to quantification of chirality [23]. One aims at quantifying the difference between a chiral object and an achiral standard, while the other has as its goal quantification of the difference between enantiomers. The latter (where the chirality measure based on the Hausdorff distance [23] seems to be the best choice) is evidently more general as it covers also structures with topological chirality (such as *III*—*VI*, *cf.* Fig. 2) which have nonhomeotopic molecular graphs of the enantiomers and where it is therefore not possible to



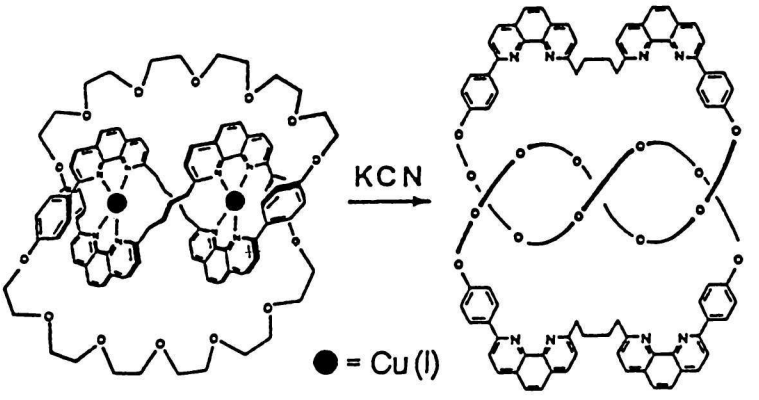
(*R*)-*I* (*S*)-*I*



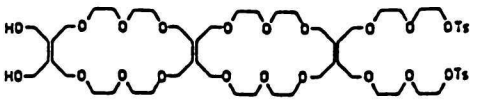
(*R*)-(-)-glutinic acid (*II*)



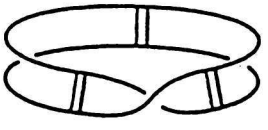
Simmons–Paquette [15,16]
K_5 propellane (*III*)



First synthesized and first resolved [17] trefoil knot (*IV*)

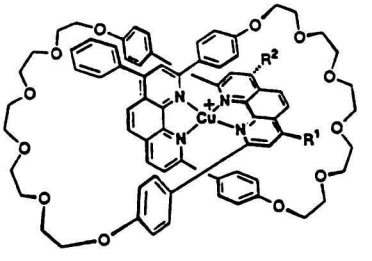


- 2 TsOH



Walba [18] first Möbius "ladder" $K_{3,3}$ molecule (*V*)

R^1, R^2 = H, Ph



Mitchell and *Sauvage* [19] first isolated topologically chiral catenate (*VI*)

Fig. 2. Examples of chiral molecular structures.

achieve their interconversion by a continuous deformation in three-dimensional space. The number of known interlocked and intertwined structures (catenanes, rotaxanes, and knots) [33] has grown tremendously in the last twenty years and, in the same time and at the same pace interest has been increasing in chemical and biochemical topology [3]. Knots [34] and catenanes [35] have been found in DNA; topoisomerases have been discovered — enzymes that help form and transiently break these DNA structures [36]; knots [37] and catenanes [38] have been found in protein structures; first rational syntheses were accomplished of topologically interesting "simple" molecules [15—19] and of knotted single-stranded DNA [39]. Topology of knots has been recognized as a rich source of intelectual and aesthetic experience for chemists and mathematicians [40] and their construction has been even declared the Holy Grail of stereochemistry [41].

Cheirality [41], amphicheirality, and nonamphicheirality [40], terms with an even more apparent bearing upon the Greek "cheir" than chirality itself have been rediscovered in connection with deeper understanding of topological chirality/achirality. Amphicheirality was introduced and defined by *Tait* [42] in his paper on knots in 1876, whereas the terms homo- and heterocheiral had been used first by *W. Thomson* [43] few years earlier. As the terms amphicheiral/nonamphicheiral apply only to knots and links, they are subsumed in the terms topologically achiral/chiral [40]. Cheirality has been used to describe chirality that refers to the knotting of molecules constructed from chiral components (like single-stranded DNA from D-nucleotides), regardless of the local backbone configuration [41].

In a general approach, *Barron* [44—47] has brought together several different fundamental symmetry considerations and has shown how the concept of chirality is rooted in sound principles of basic physics. Barron's contribution has, like Thomson's, come from where the river Kelvin flows through Glasgow and is important enough to justify a small digression.

The principal feature of symmetry of an object or of a process is its invariance under the corresponding operation. One speaks about C_2 rotation (continuous) symmetry of the molecular formula of the acid *II* as it is possible to convert it to itself by a continuous series of infinitesimal rotations that add up to 180° One speaks about mirror symmetry of molecular formulae (*R*)-*I* and (*S*)-*I* but the corresponding reflexion operation cannot be carried out continuously (without deformation); that is why reflexion symmetry and its corresponding symmetry operation are called discontinuous.

In physics, too, some of the basic symmetries are continuous (*e.g.* invariance under translation in space, in time, or rotation) and others discontinuous (invariance under space, time, or charge inversion). *Emma Noether* [48] has shown that the above-mentioned continuous symmetries are directly linked to basic conservation laws (of total momentum, total energy, and total angular momentum, respectively). It was long taken for granted that those discontinuous symmetries were also linked to the corresponding generally valid conservation laws. It was considered as true that the laws of nature were invariant under operation of parity (**P**) and charge (**C**) or time (**T**) inversion and that absolute chirality, absolute direction of time flow, and absolute sign of electric charge (as non-observables) would for ever remain a convention. (*Dirac* [49] suggested that, because reflexion was a discontinuous operation, there was no reason for physical laws to be invariant under it, whereas Pauli [50] held just the opposite view and was ready to support it by quite a sum of money.) Then, there came, in 1956, the turning point. A suggestion [51] had been made of how to prove that not all mirror-coupled processes occur with the same probability, experimental confirmation [52] had followed in the same year and in 1957 the Nobel prize for physics heralded to men of science that parity was not conserved in weak interactions. It is widely believed now that there exists invariance of laws of physical nature under combined operations of the mentioned discontinuous symmetries. The celebrated **CPT** theorem, derived from general considerations using relativistic quantum field theory [14], states that the Hamiltonian is invariant to the combined operations of **CPT** even if it is not invariant to one or more of those operations. Precision tests of **CPT** invariance have been performed, of which *e.g.* determination of the cyclotron frequencies of the proton and antiproton has shown that their mass-to-charge ratios are identical to within 1 part in 10^9 and, it has recently been stated that: "Although **C, CP,** and **T** symmetries may be violated individually, it is not possible to construct a Lorentz invariant, local field theory which is not invariant under **CPT**" [53]. Parity violation in electroweak interaction is related to weak charged currents (interacting by exchange of W^+ and W^- bosons) formed only by leptons with "left" chirality and to weak neutral currents (interacting by exchange of Z^0 bosons) formed differently for leptons with different chirality. Weak neutral current interactions between electrons and neutrons cause atoms to be chiral [54, 55]. Parity violation is also manifested in that there apparently are no neutrinos with "right" chirality and no antineutrinos with "left" chirality [52].

The theories of the weak interaction and the electromagnetic interaction have been unified into a single theory of a single "electroweak" interaction and so parity violation has been introduced into electromagnetism. There was no need to wait long for experimental confirmation — with some heavy metal vapours (Bi, Tl, Cs, Pb), predicted optical activity was found [56—59]. Thus, mirror-related processes mediated by electroweak interactions occur with different probabilities.

Chemistry, however, is governed by electroweak interactions and the consequences of parity violation should play a role. Here, however, our knowledge is insufficient yet. It seems that parity violation may force

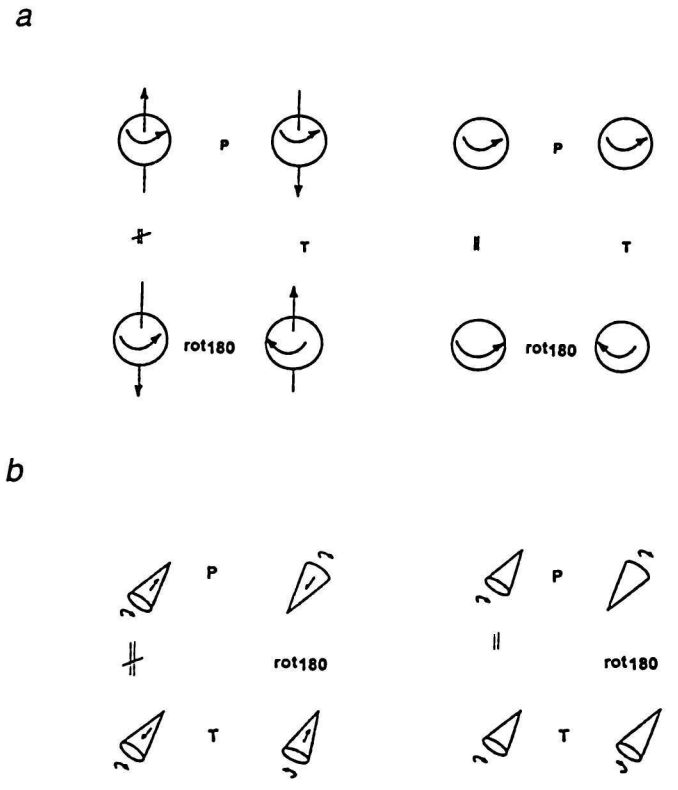


Fig. 3. Chirality as a time-invariant enantiomorphism.

us to abandon one of the cornerstones of stereochemistry and its point of friction with quantum mechanics — the concept of energetic degeneracy of enantiomorphic states. *Hund's* [60] quantum mechanical "paradox of enantiomers" can briefly be described as follows: In quantum mechanics enantiomers represent a system where interconversion takes place within a symmetrical potential energy profile. Degenerate states Φ_L and Φ_R of the system that are fully localized in one or the other potential minimum are not eigenfunctions of the Hamiltonian. Symmetry requirements are fulfilled by eigenfunctions $\Phi_{1,2} = (\Phi_L + \Phi_R)/\sqrt{2}$. It is considered paradoxical [60] that enantiomeric molecules are generally stable even though they do not represent the true stationary state. In another formulation [61], it is paradoxically often possible to get, from the stock room, pure enantiomers, whereas their coherent superposition is not available. Resolution of the paradox involves arguments that the typical inversion barriers are large enough to warrant virtually infinite lifetimes of the prepared enantiomers and that tunnelling is, with such systems, negligible [60], that there are stabilizing interactions with the surroundings [62, 63] or that parity violation removes symmetry of the potential energy profile [64] and, then, the Φ_L and Φ_R become eigenfunctions and the two enantiomeric states become the true stationary states. The problem is alive as evidenced by recent suggestions [65, 66] of how to prepare and monitor superposition of chiral wave functions by irradiating chiral molecules that are capable of photoracemization [67, 68] with femtosecond phase-locked light pulses. As a consequence of the **CPT** theorem, the molecule with the opposite absolute configuration will have exactly the same energy as the original only if it is composed of antiparticles. In the world of particles only, a chiral molecular structure and its nonsuperimposable mirror image are then diastereomers with the expected energy difference between them proportional to Z^5N (where Z is the atomic number and N the number of neutrons) [69]. This difference amounts [70, 71] to approx. 10^{-20} Hartree (10^{-14} kJ mol^{-1}) for small molecules and leads to an excess of approx. 10^6 molecules of the more stable enantiomer per mole of a racemic modification according to Boltzmann distribution for thermodynamic equilibrium at 300 K. Experimental confirmation has not yet been reported (even though experiments have been suggested, as discussed in detail by *Quack* [72]). Thus, current chemical understanding of chirality goes way beyond consideration of mere shape.

Let us now come back to *Barron* and the results of his analysis [44—47] of the chirality problem: Chirality is exhibited by systems that exist in two distinct enantiomeric states that are interconverted by space inversion, but not by time reversal combined with any spatial rotation (Fig. 3).

A sphere that is rotating and moving in the direction of the axis of rotation is a chiral object whereas a sphere that is only rotating is not (Fig. 3*a*). Two cones

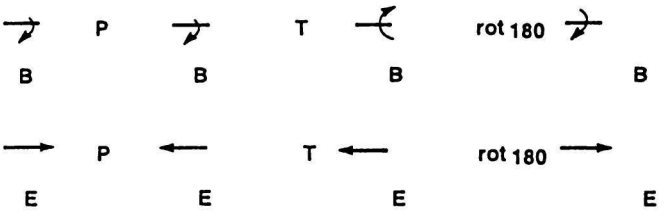


Fig. 4. Magnetic **B** and electric **E** fields and their transformation under the operation of parity (**P**), time inversion (**T**), and 180° rotation ($\mathbf{rot}_{180}$).

spinning in opposite directions around their symmetry axes (Fig. 3*b*) are enantiomorphous (Is this really adequately defined as a case of enantio***morphism*** ?) but, this enantiomorphism being time-noninvariant, is not, according to Barron, considered to represent chirality*, whereas when the spinning cones are also translating along the axis of spin, they each represent a chiral object. Chirality is thus a time-invariant enantiomorphism and chiral are systems that can support time-even pseudoscalar observables. This is of importance when chiral physical influences or chiral combinations of physical influences are sought that would, first in principle and then in reality, make possible absolute asymmetric syntheses.

How is it with a static magnetic field? Is it a chiral physical influence and would it be therefore possible to carry out enantioselective syntheses with its help? The year 1994 was also remarkable in that, in an influential journal, a positive answer was published [73] only to be presently withdrawn [74]. Static homogeneous magnetic field **B** can be represented as an axis with equivalent ends and defined sense of rotation. **B**, noninvariant under time inversion, is a time-odd axial vector, is achiral, and unable to cause chiral differentiation. As shown in Fig. 4, even combination of **B** with a homogeneous static electric field **E** (represented as a time-even polar vector), though dissymmetric, does not correspond to Barron's definition of chirality because it is not time-invariant. Using similar argument, it can be shown that there is a basic difference between optical activity in collections of chiral molecules and the Faraday effect, where optical activity is induced in an isotropic collection of achiral molecules by a static uniform magnetic field parallel to the light beam [45]. The magnetic optical rotation is a time-odd axial vector whereas the natural optical activity is a time-even pseudoscalar.

Detailed analyses are reserved for specialists but it has been undoubtedly important to include the time factor into discussion of chirality. Thus, chirality is exhibited by circularly polarized photons, by moving electrons, and also by combinations of physical fields [75, 76] that can be defined *a priori*. There is also a connection between chirality and relativity — at velocities smaller than that of light and with a particle with a definite chirality, its sense depends on whether an observer is moving towards or away from it. The very building-blocks of the universe are thus seen to be chiral which, in a remarkable way, gives right to *Pasteur*'s [77] anticipation of a general cosmic dissymmetry.

There is the *Neumann* principle [78, 79] (of which there is no rigorous proof, but no counter example is known to exist), stating that any type of symmetry exhibited by the point group of a system is possessed by every physical property of the system and there is its succinct restatement by *Currie* [80]: "C'est la dissymmétrie qui crée le phénoméne." But there also is a warning [81] that the Neumann's principle cannot be applied to a system in which entropy is changing. With systems that are away from thermodynamic equilibrium, as yet unspecified differences are to be expected.

From a certain standpoint, chemistry is the science that deals with formation, behaviour, and transformations of chiral molecules. (With monobromoalkanes $C_nH_{2n+1}Br$, for example [82], when $n = 5$, there are altogether eleven possible isomers out of which 6 are chiral; when $n = 8$ there are 176 chiral structures out of 199 structures possible and, with $n = 14$ the ratio of chiral to total structures is 109 864 to 110 500. With coordination number 4 and ligands different and achiral, there are two isomers, both chiral whereas, under the same conditions, there are 20 isomers, all chiral, with coordination number 5 in the form of a trigonal bipyramid [83, 84]. One finds a similar situation with knots, where out of total 12 965 knots with maximally 13 crossings, only 78 are topologically achiral (amphicheiral) [40]). The problem is, however, that in chemistry as we know it today, the chiral molecules usually come in racemic pairs and, as yet, no simple and general way is known of how to prepare them chirally pure, even though living organisms have successfully managed the process within their needs. Chirality spells a substantial, in some cases even total reduction of symmetry (of symmetry point groups that are of importance for description of static molecular

* Herein lies the bone of a serious contention. Let me quote Kurt Mislow, commenting on a draft of this manuscript: "How can a spinning cone be achiral? There is absolutely nothing "false" about the chirality of a spinning cone, even though this chirality is time-noninvariant. I therefore do not agree that chirality should be restricted to time-invariant enantiomorphism." In the eyes of the author (J. J.), it remains to be seen whether time-invariant enantiomorphism and time-noninvariant enantiomorphism have the same or different phenomenological consequences and to search accordingly.

structures, only the groups C_n, D_n, T, O, and I are chiral). Chirality is an all pervasive quality, affecting all parts of a chiral structure [85]. That is why there are only chirotopic parts in a chiral structure and there are no symmetrically equivalent atoms or bonds in an asymmetric structure [86]. The number of different arrangements that can thus be achieved for a given set of atoms is maximized and so is the number of possible interactions with the surroundings (supramolecular chemistry has supplied a nice example [87] showing how the number of ^{1}H NMR observable N—H groups in the complex hub$(M)_3$: barbital triples when the conformation with C_3 symmetry changes into the conformation with symmetry C_1).

In this connection, discussion might be relevant of whether large random objects and systems are always chiral, as explicitly stated in [88, 89]. *Mislow* and *Bickart*, considering a mole of argon gas at room temperature argue that: "At any instant in time, such an ensemble is bound to be chiral — indeed, asymmetric — since, *a priori*, any system is asymmetric unless constrained to be otherwise" [88]. Is it not so that, with increasing number of argon molecules, the probability will approach certainty, that there will be, at any instant of time, present a mirror image for any actual state of any argon molecule? In other words, always considering the given level of discrimination, is it not so, that the bigger the number of argon molecules, the higher the probability that the system is strictly racemic? The problem here probably stems from the way of modelling a time continuum as a series of static pictures which, to use an ancient paradox, does not let the arrow to reach its target.

In chemistry, chirality is an indispensable tool for preparations of pure enantiomers and differentiation of enantiomorphic structures as well as enantiotopic ligands and faces. Current understanding and experience have shown that, even though, generally speaking chirality can be generated by a spontaneous symmetry breaking which can occur in systems at thermodynamic equilibrium and in systems far from equilibrium [90, 91]*, specific chirality is only generated in the presence of definite chirality. It has therefore been of importance to look for ways that would lead to effective absolute asymmetric syntheses by using *e.g.* circularly polarized microwave radiation [93]. Besides fundamental epistemological problems of chirality and problems with generation of molecular chirality, phenomena are important for chemistry that result from interactions of a chiral structure with another chiral structure or chiral physical influences. The ones mentioned last are a source of important information about the structure under scrutiny (and to none have been accorded the degree of interest paid to chiroptical phenomena), the others (chiral or stereomeric discrimination) can lead to enantiomerically pure compounds or specific biological activity. Even in the highly important practical field of new nonlinear optical (NLO) materials, chirality has been an important tool.

Of the many NLO materials studied and used, most rely on molecular hyperpolarizability, a nonlinear effect of the second order that can only be found in suitable systems with a noncentrosymmetric structure or microstructure [94]. But, approx. 70 % of all achiral compounds form crystals which belong to centrosymmetric space groups [95] and that is why it is advantageous to use chiral compounds [96]. On the other hand, nonlinear optical activity (circular-difference response of second harmonic generation) has been shown to be a probe of biomolecular chirality with sensitivity several orders of magnitude higher than that of linear circular dichroism [97].

Chirality can be found at different levels in the realm of molecular structures — polysaccharides and polypeptides being the most common examples. There can be little doubt that there exists a direct connection between the kind, sense, and degree of chirality of the building-blocks and the secondary or higher structure of the polymer, the arrangement in the crystal or other supramolecular structures [98, 99]**

In spite of insufficient knowledge about mechanisms of self-assembly processes [102] and despite insufficient ability to distinguish manifestations of different chirality levels, it is already possible to design peptides and proteins *de novo* [103, 104]. To get a clear picture of the mentioned connections is important for the theory and has direct implications in practice. Crystallization of a compound potentially active in second harmonic generation (SHG) in an enantiomorphic space group (a process cogently called supramolecular asymmetric synthesis) has been a key step for manifestation of the SHG effect. While for polymeric molecules in solution realistic structures can be obtained routinely by mathematical modelling, first relationships have become known between chirality of a simple molecule and fine details of a supramolecular arrangement [105] and *e.g.* the chirality of deoxyribose and the sense of helicity in the corresponding DNA double helix [106], too little is known of how molecular symmetry is transferred into crystalline state [107].

* It seems probable that therein lies the origin of the microworld chirality and it has been noted that "the whole physical, chemical, and biological evolution seems to be regulated by the emergence of new symmetries and the breaking down of old ones" [92].

** Under proper conditions, higher types of structure are formed from polypeptide chains spontaneously, reproducibly, and in few seconds; considering the dimensions of the conformational space available, which for a polypeptide made of 50 amino acids has some 10^{50} conformational possibilities, the self-organization proceeds so quickly [100] that it has been termed the Levinthal paradox. As shown by the peptide antibiotics gramicidin A [101], the secondary structure of which rearranges reversibly from left-handed intertwined antiparallel helix to a single-stranded right-handed helix with a change of the solvent, the medium plays an inomissible role.

Kitaigorodskii's rules [108] of the closest packing lie at the root of the hazy relationships between molecular and crystal symmetry — the only element transferred usually into the crystal symmetry is the centre of symmetry as no packing effectivity is lost in such a way [108, 109].

There has been a continually increasing demand for efficient chiral catalysts or chiral auxiliaries to broaden the scope, enhance the yields, and enantiomeric excess of asymmetric [110], enantiodifferentiating [111], or enantioselective [112] syntheses. Nonlinear effects (departure from proportionality between the ee of the product and the ee of the chiral auxiliary or catalyst) were first described ten years ago [113] and are still studied [114]; autocatalytic modifications thereof could serve as a suitable model for the propagation of chirality on Earth [115—117].

Comparing the calculated CD and ORD curves with the experimental ones has become routine and there has been a renaissance of interest in CD for determination of absolute configuration. However, what has grown up in an amazingly short time among the chiroptical methods is vibrational optical activity (VOA), namely vibrational circular dichroism (VCD) and Raman optical activity (ROA). To use the words of Barron as cited in [118]: "VOA is an incisive probe of three-dimensional structure, especially in large biopolymers" and "for small chiral molecules, VCD or ROA spectrum coupled with an *ab initio* computation, is now the best way to determine absolute configuration" And not only configuration. The timescale of vibrational techniques, much shorter than that of NMR, is around 10^{-12} to 10^{-13} s and conformation dynamics can be studied with ROA in aqueous solutions [119].

The certainty with which we know that interactions between *e.g.* the molecules (*R*)-*I* and *II* will differ from interactions between (*S*)-*I* and *II*, and the only problem would be the extent of the difference, is based upon anisometry of (*R*)-*I* *II* with (*S*)-*I* *II* (impossibility of an interconversion that would save their shape and size). The mentioned differentiation of the enantiomers of *I* is called diastereomeric and, today, it is a textbook knowledge that, in principle, it is the same as *e.g.* differentiation of enantiomers by circularly polarized light. On the other hand, to understand why a liquid equimolar mixture of enantiomers crystallizes now as a racemic mixture and now as a racemate, enantiomeric differentiation has to be studied, *i.e.* the difference in interactions between *e.g.* (*R*)-*I* (*R*)-*I* and (*R*)-*I* ·(*S*)-*I*. Here, full understanding has still been lacking despite theoretical and practical importance of the problem, but there are studies under way [120].

Biological activity of chiral compounds [121] and the origin of homochirality in living systems [122] have been for decades, understandably, an active area of research and discussion.

From Pasteur experiments through *Fischer*'s concept of lock-and-key [123] to *Koshland*'s induced fit theory [124] on the one side and from *Pasteur*'s conjecture [77] to *Kondepudi* and *Nelson*'s model [125] on the other side, the effort has been enormous and has brought important results.

Differences in biological activity of enantiomers are numerous. As shown in Fig. 5, their spectrum is quite broad, from effects on taste to olfactory and pharmacological effects. The scope of this area can be gleaned from the following examples:

a) Among the racemate/enantiomer switches that successfully entered the market, the nonsteroidal anti-inflammatory (*S*)-ibuprofen (*XI*) is of special interest. With all the 2-arylpropionic acids ("profens") the anti-inflammatory activity arises from the inhibition of cyclooxygenase, the enzyme that converts arachidonic acid into prostaglandins and other mediators of the inflammatory response and resides exclusively with the (*S*)-enantiomers [131]. However, *in vivo*, there exists a mechanism, by which the (*R*)-enantiomer is inverted [132], so that when administering the racemic drug, the exact dose of the active species is virtually unknown.

b) There is often mentioned the difference in the activity of phthalidomide (*XII*) (Fig. 6) enantiomers and the tragic consequences that ensued from using racemic *XII* in prescriptions, especially in Germany. It can also often be heard, that tragedies could have been avoided [133] had pure (*S*)-(-)-*XII*, nonteratogenic, been used. That, however, seems not to be the case, as it was found that enantiomers of *XII* racemized by opening of the phthalimide ring in blood with a half-life of less than 10 min [134]. But, there is no doubt that the case has led to improved drug regulation [135] and further measures [136].

c) The dextrorotatory enantiomer of morphine, that was prepared [137] in 1957 and has not been found in nature, has shown no analgetic activity and D-(-)-ascorbic acid (*XIII*), enantiomer of vitamin C, not only shows no vitamin C activity, but seems to be its only known antagonist [138].

d) After rubredoxine [139] and HIV protease [140], 4-oxalocrotonate tautomerase (4OT) has been already the third biologically active protein that has been synthetically prepared in enantiomeric forms. 4OT is a hexamer of identical polypeptide chains, each made of 62 amino acids; enantiomeric D-4OT and L-4OT showed, as expected, the same activity towards an achiral substrate, 2-hydroxymuconate (*XIV*), attacking, however, its opposite, enantiotopic faces [141].

e) Sales of enantiomerically pure drugs amounted to US $ 35 billions in 1993 and there are estimates expecting them to reach more than US $ 60 billions in 1997 (*cf.* Ref. [142]).

f) Enantiomers of the potent antitumour antibiotic fredericamycin A, prepared by total synthesis

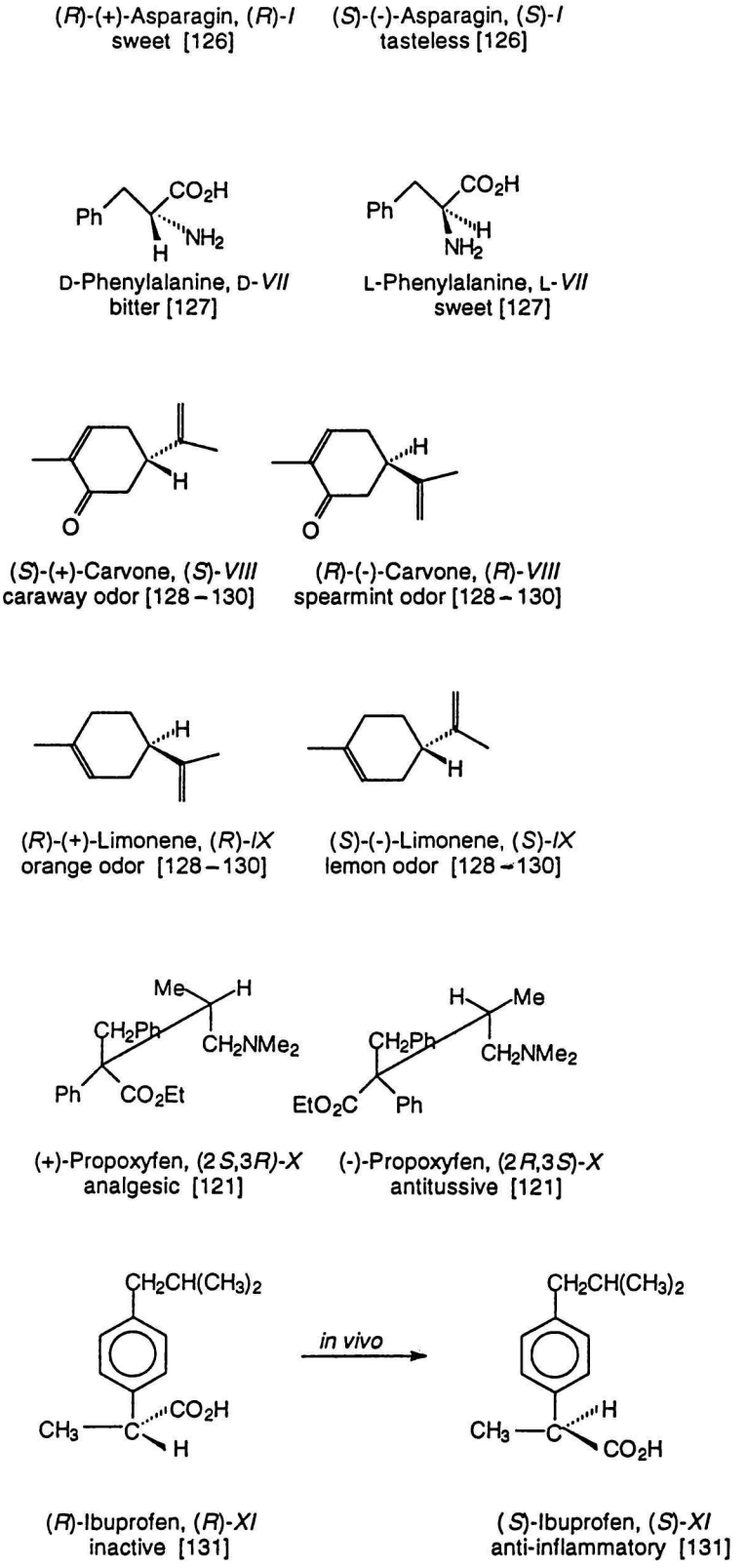


Fig. 5. Examples of different physiological activity of enantiomers.

have surprisingly shown comparable cytotoxic activity [143]; this might be of help in search for the active site and mechanism of its action.

In the realm of living systems (which store the genetic information in macromolecules built of only D-sugars, transfer it with help of enzymatic systems

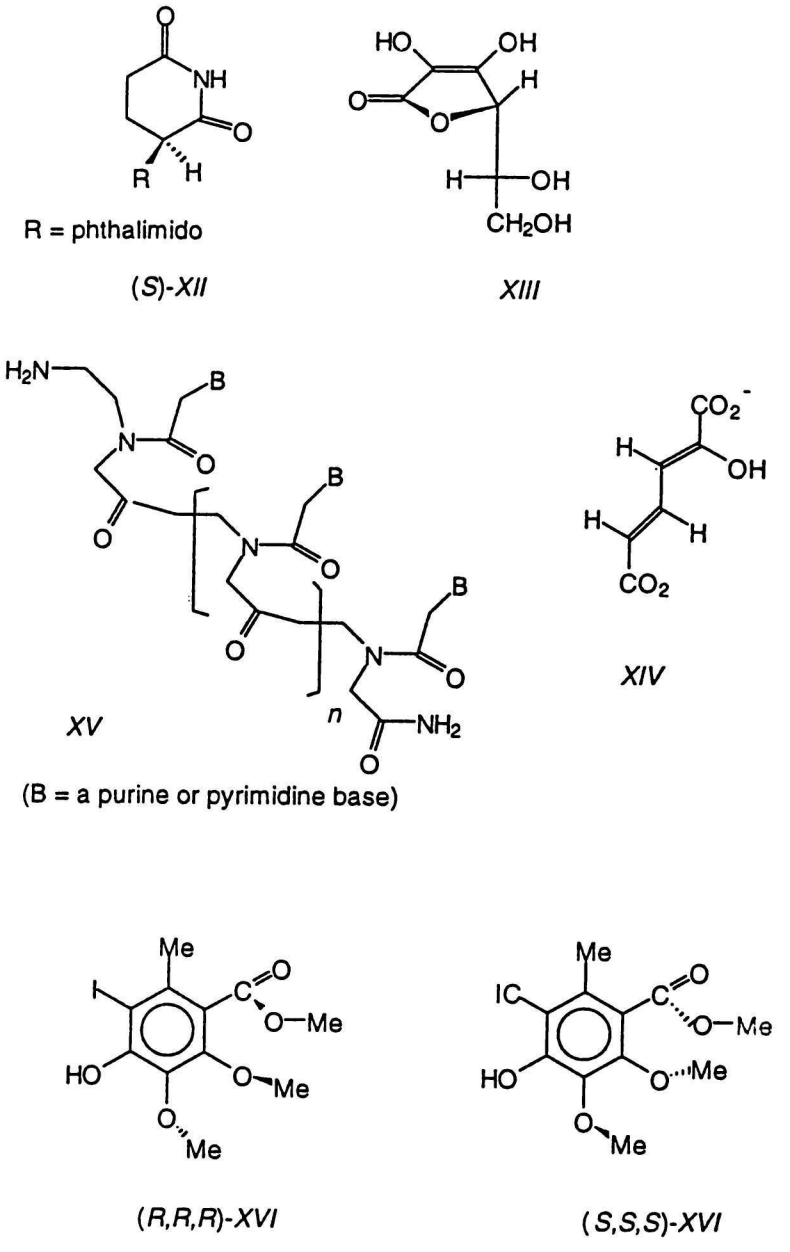


Fig. 6. Compounds *XII—XVI*.

composed of only L-amino acids, propagate [144] and defend [145] themselves with the aid of glycoproteins in which both building-blocks are incorporated) the chirality and homochirality is almost total. Why is chirality so indispensable for life and where has homochirality come from? Basically, the answer is known to the first part of the question.

It has become clear that, for instance, heterochiral proteins would not be able to function in the way homochiral proteins do (even simple homochiral peptides differ fundamentally from heterochiral ones [146]) and that life which would be based on heterochiral biopolymers would have to be governed by a stereoselectivity different from the one we know. And it seems that we know for sure that chemical reactions with such stereoselectivity would not ensure the functions needed for life to begin, continue, and evolve. Enantiomeric homogeneity of the monomers making up the critical biopolymers is not only essential for the existence of life, but self-replicating living matter would be impossible without such absolute enantiomeric purity [147]. Without homochirality, there would be no life.

Basically, there are abiotic or biotic hypotheses of the origin of homochirality in living systems [148, 149]. In the biotic hypotheses, life on Earth originated in a racemic environment and the origin of its homochirality is linked with the evolution of life itself. Homochirality is considered to be an inevitable consequence of the evolution of living matter. It is hardly ever possible to verify these hypotheses; they are speculative, some of them, however, have an appeal for the layman when competition is mentioned between

L- and D-systems on the primitive Earth [150, 151] or a "killer enzyme" (*e.g.* a D-peptidase) is invoked [152]. Fundamental criticism of the idea that life appeared first in a racemic environment on the primitive Earth was voiced by *Avetisov* [147] in 1985. Experiments [153], showing that formation of chirally pure polynucleotides in a template-directed nucleotide oligomerization is substantially dependent on the chiral purity of the monomer, support the conclusion [147] that living matter can only form and develop in a chirally pure medium. No general consensus has been reached yet, however, as shown by discussions at a recent conference [154], where, in a polyphony of views, biotic hypotheses were advocated again and even extraterrestrial origin of homochirality and life was championed anew [155, 156]. It seems that the first self-replicating molecules could hardly have been those of RNA, because the formation of ribonucleotides and their nonenzymatic replication is difficult under the conditions though to prevail in the prebiotic times [157]. Naturally, more simple and more easily formed molecules are considered to be the likely candidates, *e.g.* peptide nucleic acids [157—159] (PNA) (*XV*). PNA have achiral molecules as the monomer subunits (purine and pyrimidine bases are joined to the main poly(*N*-(2-aminoethyl)glycine) skeleton by —$COCH_2$— linkers). Their helical double-stranded macromolecules change helicity with time and can act as a template in oligomerization of activated nucleotides [159]. No wonder that PNA represent an interesting alternative of how to explain the origin of homochirality within a biotic hypothesis.

Abiotic scenarios presuppose that the living systems were preceded by a symmetry breaking in the racemic environment by either a chance or a determinate mechanism. In the first subcategory, let us first mention possibilities based upon statistical fluctuations.

As shown by *Mills* [160], the probability that an equal number of "right" and "left" molecules will be formed from an achiral precursor in a random process is practically zero. According to *Mills* [160], "When 10 000 000 dissymmetric molecules are produced under conditions which favour neither enantiomorph, there is an even chance that the product will contain an excess of more than 0.021 % of one enantiomorph or the other. It is practically impossible for the product to be absolutely optically inactive." Moreover, as the number of molecules increases, so does the statistical fluctuation, making the probability of obtaining a strictly racemic sample smaller even though the relative statistical fluctuation decreases. However, arguments can be found against a model wherein statistical fluctuations can be amplified into complete homochirality [161, 162].

There are other possibilities of spontaneous symmetry breaking which occurs whenever a "critical parameter" crosses a critical threshold. Spontaneous resolution by crystallization, made famous by Pasteur, is one possibility (an interesting recent example has been the spontaneous resolution [163] of enantiomers (*R,R,R*)-*XVI* and (*S,S,S*)-*XVI*, the aromatic part of calicheamycin-γ_1^I), crystallization of an achiral compound in a chiral symmetry group (as with sodium chlorate $NaClO_3$ which forms crystals in $P2_13$) is another one. Usually, the same amount of the enantiomorphic crystals is formed, but with $NaClO_3$, symmetry is broken easily and crystals are formed now of one enantiomorphic form and now of the other (parity is conserved). Here, the rate of stirring is the critical parameter [164].

There are other possibilities: catalysis by asymmetric surfaces of quartz and other common minerals like kaolinite and montmorillonite [165].

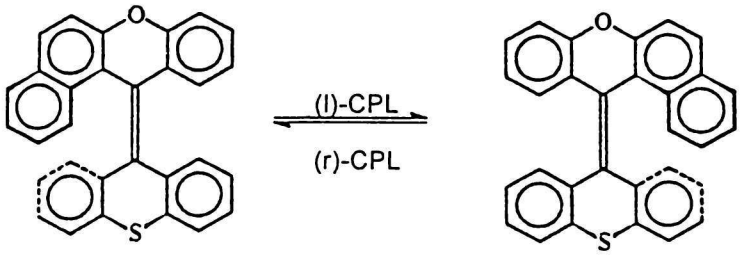
With the chance mechanisms, there is a common problem. How could the present state have developed from many sites formed by chance and with random chirality? Many convincing arguments [166, 167] have been published that cast doubt on any possibility of producing homochiral living systems by repetitive chance event on Earth, regardless of the enormous time available.

It is not surprising that news about extraterrestrial life are expected with impatience and excitement even by chemists as it would bring answer also to the question whether or not the homochirality of life as we know it on Earth reigns throughout the Universe. The resolution may come early next century. For 2003, NASA has plans to set down two modules onto the comet Wirtanen; one of them should be equipped to analyze for the presence of homochiral molecules [155].

Thus, our attention is naturally drawn to the abiotic determinate mechanisms of which many have been seriously considered in theory and supported by experiments. Among them, parity violation in electroweak interactions has been playing a leading role. The expected difference in energy between enantiomers which is called "parity-violating energy difference" (PVED), arises from the weak neutral currents, mediated by the Z^0 boson, between electrons and neutrons. Although extremely small, "the PVED affects all chiral molecules everywhere at all times, providing an ever present global chiral influence whose effect might eventually be amplified" [168].

Calculations [70, 71, 169, 170] show L-amino acids, D-glyceraldehyde, C_2-*endo* conformation of D-β-ribose, and D-deoxyribose to be, by approx. 10^{-17} kT, more stable than the corresponding enantiomers; also the right-hand sugar-phosphate backbone of DNA is PVED-stabilized by about 10^{-17} kT per sugar-phosphate unit. Sulfur modifications of right-hand helix DNA have even larger PVEDs; they range, depending upon where sulfur is located in the DNA structure, from 10^{-16} to 10^{-14} kT per unit [169].

Theoretical models have shown that, in a nonequilibrium system with suitable autocatalysis [171], even such tiny PVED can become an attractor and lead to total homochirality [172—174]. It has also been shown



(P)-*XVII* (M)- *XVII*

Fig. 7. Helicity switch between (P)-*XVII* and (M)-*XVII* upon irradiation with CPL light.

that even repeated crystallization can result in a substantial excess of the more stable enantiomer [175]. What a challenge for experimentalists. The *Kondepudi* catastrophic bifurcation mechanism [173] is based on an antagonism of enantiomers where the presence of one enantiomer catalyzes the production of itself but inhibits production of the other one. It is remarkable that 10^{-17} kT (the common PVED) seems to be a critical, turning point, value — PVED bigger than that is eventually amplified, with smaller PVED there is no amplification due to thermal fluctuations. The amplification time in the Kondepudi's scheme is 10 000 years for PVED of 10^{-17} kT; however, it is 1 year only for PVED of 10^{-16} kT. Moreover, as the figures are based on a reaction volume of 4×10^9 dm^3, concentrations of the order of 10^{-3} M, and a realistic reaction rate of 10^{-10} Ms^{-1}, amplification from PVED of 10^{-12} kT would take 1 year in 40 dm^3 — worth trying in a laboratory. Recently, however, *Bonner* made a strong case against the hypothesis that biological homochirality can be traced back to PVEDs between enantiomers [176].

Other hypotheses are based on an absolute asymmetric synthesis. Chiral physical influences or chiral combinations of physical influences have been considered, especially such as could have been active in the abiotic phase of Earth history. Most frequently mentioned are circularly polarized photons of different energy (*Vester*'s hypothesis [177], further developed by *Ulbricht* [178] and tested by both [179] and many others — *cf.* Refs.[148, 149]), polarized electrons [180] or a combination of photons with arbitrary polarization and a magnetic field parallel with the direction of their movement [181, 182]. Even though the hypotheses are in agreement with the current understanding of chirality, attempts to verify them experimentally have as yet failed to produce an enantiomeric excess of importance.

It has been reported [183] only recently that under irradiation with circularly polarized light (CPL), helicity is reversed of the 12-(9′*H*-thioxanthene-9′-ylidene)-12*H*-benzo[*a*]xanthene (*XVII*) (M) and (P) enantiomers, making this distorted double-bond system a successful molecular switch (Fig. 7). Moreover, CPL irradiation of the (MP) racemate resulted in deracemization, however, with an ee of only 0.07 %.

That is why homochirality of living matter on Earth is considered as having been formed in two stages. A small enantiomeric excess formed in the first stage was further amplified in the second stage. Likely candidates for the first stage are either the action of polarized light [184] or consequences of parity violation [168], for the second stage then amplification according to [171—175] (a successful preparation was reported [185] where, in an autocatalytical enantioselective addition of an organozinc compound to 5-pyrimidinecarbaldehyde, the initial ee of 5 % was in three cycles increased to 89 %) or amplification by quantum-mechanical tunnelling at 3 K, proposed recently by *Salam* [186]. Some experimental results [187] give support to an idea that implicates both of the secondary structures of proteins, α-helix and β-sheet. When polypeptide chains grow into the α-helices or β-sheets, a single enantiomer of the building-block is preferred.

The key questions about the origin of chirality on a macroscopic level and homochirality in life remain yet to be answered. On the other hand, there can be no doubt as to the importance of the chirality and homochirality phenomenon. But wherein does it lie? The heart of the matter may very well reside in the structural diversity it makes possible. Would the laws of nature require that molecules have always a symmetry higher than that of C_1, the number of possible molecular structures would decrease dramatically and living systems could, evidently, not have begun to

develop. In isomeric molecules, desymmetrization results in a decrease of the number of equivalent atoms, bonds, and groups, in an enlarged scale of possible intra- or intermolecular interactions, and in finer gradation of their energy thus increasing variability of molecular and supramolecular structures.

After all, is there any other way how to have "light" or "shadow", (+) or (-), life or death with the same methods, nearly the same means and practically the same input of energy?

Dear patient reader, there hardly is a more suitable epilogue than the words of *Chesterton* [188], used by *Mislow* and *Bickart* in their "Epistemological Note on Chirality" [88]: "The real trouble with this world of ours is not that it is an unreasonable world, nor even that it is a reasonable one. The commonest kind of trouble is that it is nearly reasonable, but not quite. It looks just a little more mathematical and regular than it is; its exactitude is obvious, but its inexactitude is hidden; its wildness lies in wait."

APPENDIX — Definitions of Chirality

1893 *"I call any geometrical figure, or any group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."* [5]

1975 *"An object is chiral if it cannot be brought into congruence with its mirror image by translation and rotation."* [189]

1986 *"True chirality is exhibited by systems that exist in two distinct enantiomeric states that are interconverted by space inversion, but not by time reversal combined with any proper spatial rotation."* [44—46]

1996 *"Chirality is the inability to make a structure coincide with a statistical realization of its mirror image; the probe-dependent measure of this inability is the chirality content of the structure."* [190] (The last definition has become a subject of discussion between the authors thereof [89] and *Barron* [191].)

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Translated by J. Jonas

Note added in proof

Recent analyses of DL-α-methylisoleucine and DL-α-methylalloisoleucine obtained from the 4.5 billion years old Murchinson meteorite show that the L enantiomer occurs in excess in both cases, thus indicating "an asymmetric influence on organic chemical evolution before the origin of life" [Cronin, J. R. and Pizzarello, S., *Science 275*, 951 (1997)].