ON BIOMOLECULAR HOMOCHIRALITY AS A QUASI-FOSSIL OF THE EVOLUTION OF LIFE

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CONTENTS

I. INTRODUCTION

Bereshit bara Elohim et ha-shamayim ve – et haáretz, ve- haáretz hayeta tohu -và bohu, ve choshech al penei tehom. The question of the origin of life has been discussed by mankind for thousands of years, at least. We review the question of homochirality as a quasi-fossil of the evolution of life. We discuss how this question is closely linked to fundamental symmetries of physics C, P, T, and their

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violation. There are several fundamentally different hypotheses for the origin of homochirality, but we do not know which one, if any, is correct. We show, which type of observation either in the laboratory or in astrobiological investigations would provide information. We summarize the current status of our investigations on molecular parity violation resulting in a small "parity-violating" energy difference between the enantiomers of chiral molecules. The theory for this phenomenon has been substantially revised by us in 1995 leading to about one to two orders of magnitude larger values than anticipated previously and is now well established. However, experimental confirmation (or refutation) is still missing, but we have made progress on this question. We conclude by a discussion of what the consequences of parity violation might be for future studies of the evolution of homochirality, as well as some cosmological speculations.

The question of the origin and evolution of life from "non-living" matter is one of the fundamental long-standing, but completely unsolved questions of the modern natural sciences. To some extent even the question of "what is life?" [1] is not yet answered in a completely satisfactory manner, although we shall take here the pragmatic point of view that we can distinguish in a fairly straightforward manner the "living" from the "non-living" world in most cases: A bacterium, a tree, or a cat belong to the world of the "living," whereas gaseous nitrogen, N_2, pure liquid water (H_2O), a block of iron or graphite belong to the non-living world and it is not our theme here to go into the finer details of this generally difficult distinction, although this would be worthy of an investigation in itself.

Based on solid evidence from isotope dating, we know that our planet Earth arose about 4.56 Gigayears ago (4.56×10^9 years) from the protoplanetary gas cloud generating our sun and the planets, and there seems to be good evidence that life appeared on Earth about 3.5 Gigayears ago, although this date is sometimes questioned, as the fossils remaining from this time have an uncertain interpretation. There remain no scientifically based doubts, however, that life on Earth is at least about 1 Gigayear old and has evolved substantially to a variety of forms recognizable in numerous well-established fossils.

An excellent survey of the broader aspects of the origin and evolution of life has been given in the paper by Sidney Leach at this meeting [2,3] as well as in a recent paper by Joshua Jortner [4], which we highly recommend for further reference. Also the papers and books by Al-Shamery [5], Eigen [6–10], Eschenmoser [11], Lehn [12,13], Luisi [14], and Miller and Orgel [15–17] can be consulted as a small selection from a truly vast literature on the topic.

Rather than addressing the very general question of the origins of life, we shall concentrate here on one particular aspect: the "biomolecular homochirality" which we find in the living species, that is, the essentially exclusive preference of L-amino acids and D-sugars in the biopolymers of life. Of the two possible enantiomers (Figure 1), only one type is preferred in all living species although the (nearly) symmetrically equivalent mirror image form also finds some specialized biochemical use in some cases and appears as equally abundant in non-living matter. After the recognition in the early 19th century that organic matter is

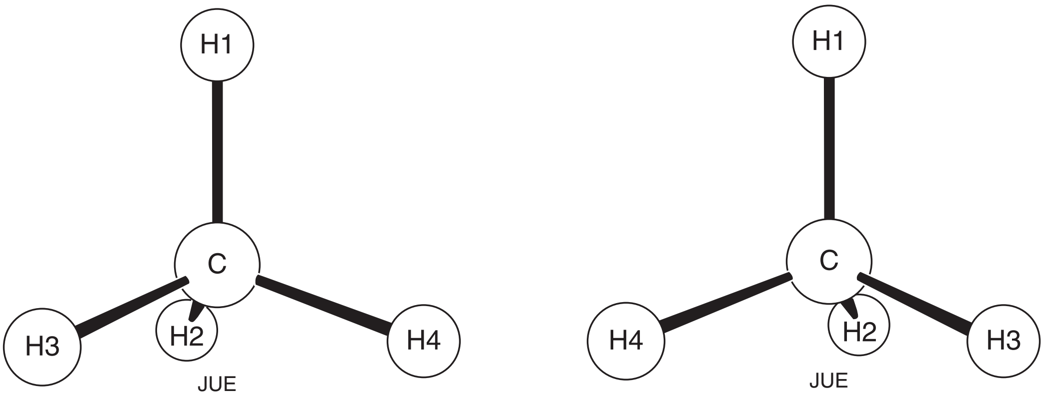

Figure 1. Chiral methane derivatives with four hydrogen isotopes (e.g., H, D, T, Mu). If one uses as substituents H, R, NH_2, COOH, one obtains the usual amino acids of proteins (with various R) of the D and L series (after References 18, 19).

not necessarily related to life phenomena, notably Louis Pasteur has suggested biomolecular homochirality as a possible simple "chemical signature of life" since 1848 and the question has been addressed more recently by Prelog [20] and Eigen [10] (see the detailed citations in a recent review [21, 22]).

Following a suggestion of Sidney Leach in correspondence prior to this meeting[1] we shall address the question why we can consider biomolecular homochirality as an important quasi-fossil of the chemical evolution in the origin of life. This particular quasi-fossil can be related to other quasi-fossils from the origins of our present universe (Section III) connected with to some strange asymmetries of physics. We refer to some of our earlier reviews on various aspects of the topic [18, 19, 21–29].

II. SOME FACTS OF LIFE

Before entering into more details on biomolecular homochirality, we shall summarize a few "facts of life" leading to very different possible views on the origin of life.

So far, we know only of one form of life in the Universe, the one on our Earth, which is all based on the same biochemical apparatus using the same type of biopolymers for sustaining, inheriting, and evolving life. From this observation, two very different conclusions have been drawn.

1. Life is extremely unlikely to evolve in the Universe, we are a singular event. This seems to be currently a minority opinion but with some prominent proponents [20, 30].

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[1] S. Leach (2012), Letter to M. Quack asking: "… (I would like you in your talk to persuade me)" … "as to why the biochemical chirality problem is a real issue in the origin of life and not simply a very interesting problem in chemical physics".

2. The alternative, appearing from many conversations (including also some votes by large audiences in public lectures) as a current majority opinion, states that life is very likely to emerge and evolve, given the appropriate physical–chemical conditions similar to the early Earth. With an increasing number of extrasolar planets being detected [31], there should be numerous planets in the Universe, where life exists (and it might exist on Mars, Titan, etc. in our solar system as well, although we have no good evidence for this).

A fair assessment of the two alternatives can only come to the conclusion that we do not know at present which one is correct. The question is open.

If the second alternative of “frequent life” turns out to be right, we can state again two alternative versions:

2.1. Life on the many appropriate planets and moons is always based on the same type of biochemistry, based on carbon-containing biopolymers, perhaps even always amino acids and nucleic acids.
2.2. Very different types of biochemistry occur in different life forms, using other elements (Silicon, etc.) and perhaps even “nonchemical” forms of life.

Again, a fair assessment must conclude that we do not know, what applies here, although the current majority seems to favor 2.1 (not too strongly, though).

If 2.2 were to apply, only speculation is possible. However, for 2.1, we can again formulate several opinions concerning homochirality.

2.1.1. All life forms are similar to ours, with only L-amino acids and D-sugars in the biopolymers of life.
2.1.2. The life forms choose one form of homochirality, but with about equal probability for separate evolutions, say only L-amino acids and D-sugars in one planetary system and D-amino acids and L-sugars in another, with a roughly random distribution among different planetary systems.
2.1.3. Some planets might be inhabited by life forms where the two enantiomeric forms of biopolymers coexist.

There seems to be a majority among currently active chemists and biochemists interested in the problem favoring the option 2.1.2., but again a fair assessment of our current knowledge must come to the conclusion that we do not know which of the three hypotheses is correct. Some might argue that 2.1.3. can be excluded, but the arguments for this are not truly compelling.

As a final remark on the option 2.1.2, we mention an early proposal we made more than two decades ago [32,33]. As we know only our current form of homochiral life, one approach toward a total synthesis of a new form of life would consist in analyzing a very simple species (say, a simple bacterium) quite completely in terms of DNA, proteins, indeed all of the biochemical properties and then resynthesize this whole apparatus as a complete mirror image with D-amino acids in the proteins and L-sugars in the DNA and so forth, as well as providing it with the appropriate mirror image food. Then again we have two hypotheses on the outcome of such an experiment.

2.1.2.1. This new mirror image species will essentially function like the original form, just as a complete chemical mirror image.
2.1.2.2. The new species will function very differently, perhaps not at all.

There seems to be a clear current majority favoring hypothesis 2.1.2.1, but a fair assessment must come to the conclusion that we simply do not know, which of these two hypothesis 2.1.2.1 or 2.1.2.2. is correct. It is at present also not clear, how far removed we are from a realization of such a project and no real project along these lines seems to be underway currently, more than two decades after the original proposal was made.

From our discussion, it seems obvious that there are many things in connection with the origin of life, of which we know that we do not know the proper answer. There are of course even more open questions (see the article by Jortner [4]). We shall now concentrate on the question of the role of biomolecular homochirality, which interestingly was nominated as number (1) open question by Jortner [4]. We shall discuss it here in relation to fundamental asymmetries of physics and chemistry. We shall see that homochirality may contain crucial clues to the origin of life. Figure 2 summarizes a survey of views as discussed in the present subsection. As a historical side remark I might mention that about 5 years ago I have lectured here in Chicago on this topic at the ACS Symposium on "Implications of Chirality in Physical Chemistry," March 2007, but there is no written record from this and we have made some progress since then.

III. SYMMETRIES AND ASYMMETRIES IN THE PRESENT WORLD

We summarize here briefly some observations on symmetries and their violations as observed in our present day world as a background for the discussion of biomolecular homochirality. More extensive discussions and explanations can be found in References 18, 19, 21, 22, 23–29, from which the discussion of this subsection is drawn.

A. Fundamental Symmetries of Physics and the Question of Left and Right

The following symmetry operations leave the molecular Hamiltonian operator generally invariant [18, 19, 21, 22, 23–29, 32–42]. (for limitations see below)

1. any translation in space
2. any translation in time

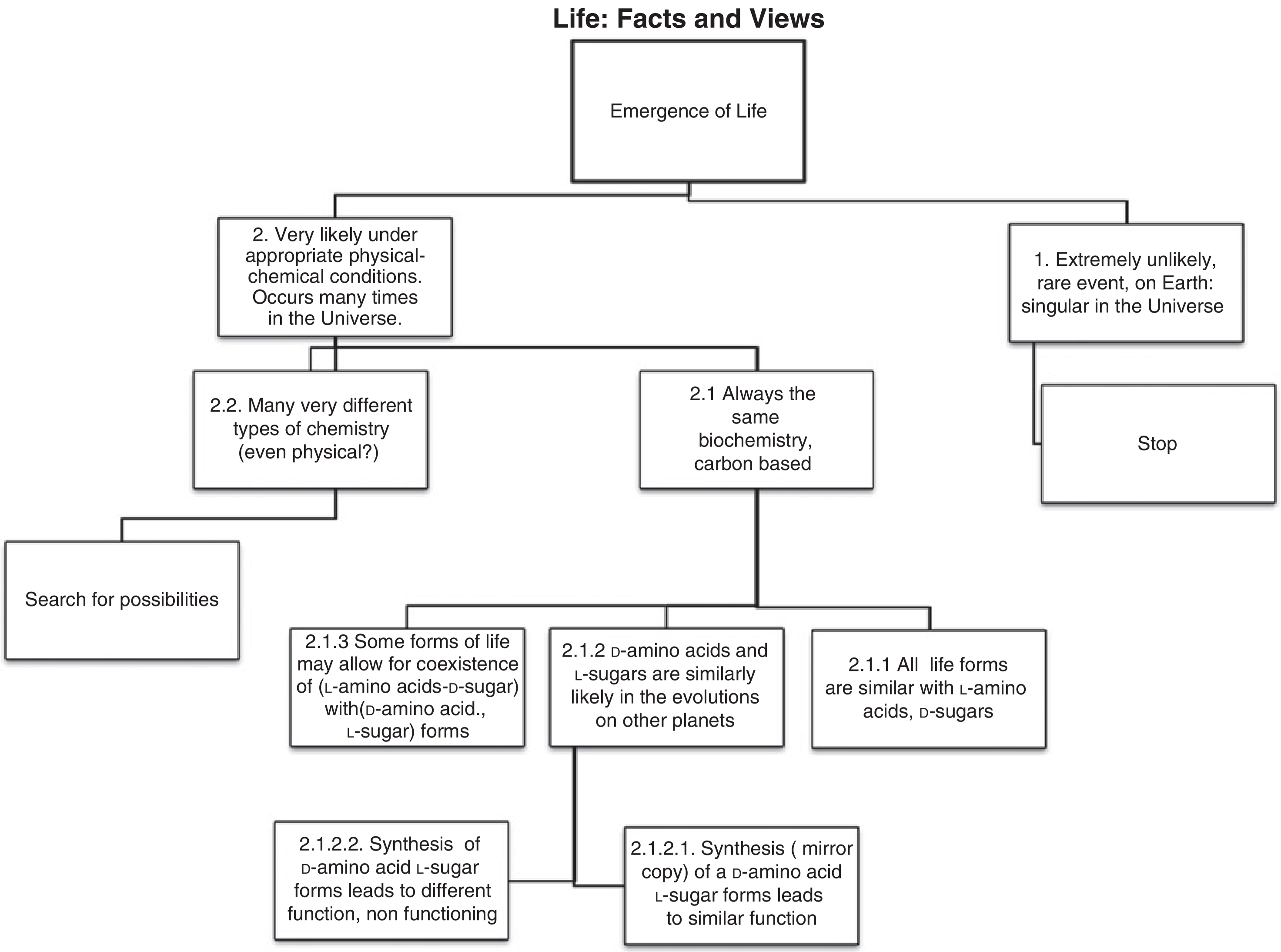

Figure 2. Summary of hypotheses on the origin of life and homochirality.

3. any rotation in space
4. reflection of the particle coordinates at the origin (parity operation P or E^*)
5. Time reversal or reversing momenta and spins of the particles (T for Tempus or time)
6. Every permutation of the indices of identical particles (the atomic nuclei, the nucleons, the electrons)
7. The replacement of all particles by their antiparticles of opposite charge (Charge conjugation C)

These symmetry operations form the symmetry group of the Hamiltonian operator. In correspondence with Emmy Noether's Theorem, each symmetry is associated with a conserved quantity. Even more interesting is the interpretation that a nonobservable quantity is associated with each exact symmetry [23, 29, 41]. The first three symmetries correspond to continuous operations with symmetry groups of infinite order, the four last discrete operations lead to groups of finite order. We shall concern ourselves here in detail only with these discrete symmetries. The symmetries P, C, T, and the combination CP are not exact: they have been found to be violated in some experiments, whereas their combination CPT is accepted as exact. It serves as a foundation of the entire modern theory of matter as summarized in the so-called standard model of particle physics (SMPP) and has to date not been disproven. The same holds true for the permutation symmetry (6) with N! symmetry operations for N identical particles, which leads to the generalized Pauli-principle [23, 29, 37, 38]. We have, however, already speculated earlier that possibly all discrete symmetries are violated [18, 19, 29, 34, 36, 39, 42]. It is important to define the terms symmetry violation and symmetry breaking more carefully, which we can do with the use of the geometrically easily understandable example of molecular chirality, which is connected with the parity operation or the right-left-symmetry.

Figure 3 illustrates the parity operation *P*. This is a reflection of the coordinates at the origin of a Cartesian coordinate system. It transforms a right-handed

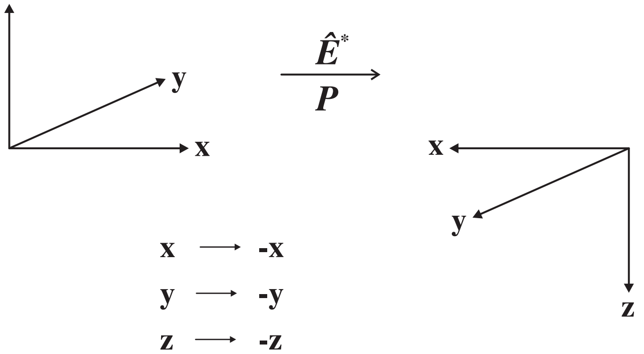

Figure 3. Reflection $\hat{E}^*$ or parity operation *P* (after Reference 25).

coordinate system into a left-handed coordinate system. If one then rotates the left-handed coordinate system in Figure 3 by an angle of 180° around the x axis, then the two coordinate systems shown here behave as the image and its mirror image in a normal plane mirror. Because the rotation by 180° is one of the infinitely many symmetry operations of rotation in space (see point 3 of the list above), the reflection in a mirror is in this sense also a symmetry of the molecular Hamilton operator. This type of reflection is mostly used in discussions of enantiomers of chiral molecules, which behave as image and mirror image of a handed system (see Figure 1, the word chiral comes from the Greek $\chi\epsilon\iota\rho$ = hand; the Greek word $\epsilon\nu\alpha\nu\tau\iota o\varsigma$ means "standing opposite" and $\mu\epsilon\rho o\varsigma$ is "a part of the whole," meaning that the definition of "enantiomer" is "consisting of parts which are so arranged that they stand opposite to each other as image and mirror image." The important common aspects of the two symmetries, of reflection from a plane mirror and reflection at the center of coordinates, is the transformation of a "left handed" into an equivalent "right-handed" system (molecule). The additional rotation, which differentiates the two symmetry operations, is not of importance for the freely moving isolated molecule in this context.

Interestingly, already Einstein had noted the "nonobservable" nature of the handedness of matter and space under the assumption of an exact inversion symmetry of space, which was at the time taken as self-evident and not questioned. In his words (from Reference 43 as cited and translated in Reference 29):

> There are thus two types of Cartesian coordinate systems, which are called "right-handed" and "left-handed" systems. The difference between the two is familiar to every physicist and engineer. It is interesting that an absolute geometric definition of the right or left handedness is impossible, only the relationship of opposition between the two can be defined.

This lack of an absolute geometric definition of handedness arising from a strict conservation law and rigorous symmetry is also sometimes expressed as the Ozma problem [44]: With the exact symmetry present, it would be impossible to communicate to a civilization in a distant galaxy that our proteins are made of L-amino acids by a coded message without sending a sample (see Reference 29). If the symmetry is violated *de lege* (see section III. B below), the Ozma problem disappears, one enantiomer would become more stable than the other and one could simply communicate that we are made of the more stable enantiomer (if so). The consequence of the inversion symmetry for the energetics of chiral molecules was also noted by van't Hoff [45, 46]. For the R and S enantiomers of chiral molecules, one would have exactly equal energies at a temperature $T = 0$ K and thus a reaction enthalpy $\Delta_R H_0^{\ominus}$ and Gibbs energy $\Delta_R G_0^{\ominus}$ exactly zero by symmetry (and also at all other T)

$$R = S; \quad \Delta_R H_0^{\ominus} = \Delta_R G_0^{\ominus} = 0 \text{ (exactly by symmetry).} \tag{1}$$

Van't Hoff writes in conclusion of the first chapter of his paper (originally in French, translated here by us):

"Such an equilibrium depends on the work ($\Delta_R G_0^{\ominus}$, van't Hoff writes E in old notation), which such a transformation can produce. This work must be zero in this case in view of the exact mechanical symmetry of the two isomers, following the concepts developed. It follows that the equilibrium constant K, which determines the relative proportion of the two compounds (enantiomers) is equal to unity because of the following equation:

$$\ln K = -\Delta_{\mathrm{R}} G^{\ominus}/(RT) \tag{2}$$

where T indicates the absolute temperature. It is thus clear that at equilibrium, the relative amounts of the two isomers (enantiomers) must be equal" (we have rewritten Eq. (2) in modern notation here).

If the symmetry is violated, then $\Delta_R H_0^{\ominus}$ can be different from zero, which is what current theory predicts, due to electroweak parity violation.

We have given here two citations of the basic question of "left" and "right" in the context of physics and chemistry (for more see Reference 29), and one might ask what is the first citation in the human literature. It seems that this is to be found in the book Jonah 4, 10-11: "Then the Lord said: You are concerned about the bush, for which you did not labor and which you did not grow; it came into being in a night and it perished in a night. And should I not be concerned about Nineveh, that great city, in which there are more than a **hundred and twenty thousand persons who do not know their right hand from their left** and also many animals?" We cite here from the "New revised Standard Version" (of 1989) and obviously some caution is in order with any translation. One might wonder what the writer of these lines wanted to say with reference to the persons who cannot distinguish their right hand from their left. I have heard numerous interpretations, the meaning of distinguishing right from wrong is one (but does not make much sense in this context). A more plausible interpretation might be, that some languages and cultures, perhaps Nineveh, did not have the concept of distinction between left and right handedness. As Hebrew has the distinction, it might be a reference to a lower cultural standard of Nineveh. In some old Egyptian paintings, one finds pictures where persons are drawn with two right hands, no distinction being made, which might be evidence in favor of such an interpretation (Figure 4). Another interpretation can be found in the "Zürich Bible" translation by the reformer Zwingli. It is translated with the meaning "who cannot **yet** distinguish between left and right" which might imply that the very young children of the town are meant. Luther does not add this "not yet" and neither in the original Hebrew text nor the ancient Greek "Septuaginta" one can find indication of "not yet." We have found an ultramodern translation in an American Bible that removes left and right altogether and writes "who live in utter spiritual darkness." Obviously, one can take some liberties in translation. Thus I also take some liberty and propose

Figure 4. Tomb wall depicting Queen Nefertari, the great royal wife of pharaoh Rameses II showing a person with two hands of the same handedness. (Wikimedia, public domain).

a new interpretation with a new super-ultramodern translation: "... who do not yet know about electroweak parity violation." With this note, which might not be taken too seriously, we turn now to symmetry breakings.

B. Symmetry Breakings: Spontaneous, *De Facto*, *De Lege*

When we observe the Universe today, we observe interesting actual asymmetries related to the three discrete symmetries C, P, T (see Table I): Matter dominates over antimatter, L-amino acids in proteins dominate over D-amino acids and time runs forward, not backward. The symmetries are broken, indeed, to a maximum degree, almost.

TABLE I
Asymmetries in the World as We Observe It (after Reference 21)

Observations		
	We live in a world:	Symmetry
1.	comprising matter (mainly), not antimatter	C, CP, CPT
2.	with biopolymers (proteins, DNA, RNA) out of L-amino acids and D-sugars (not D-amino acids and L-sugars) in usual life forms	P
3.	in which the time runs forward, not backward	T

The origin of these symmetry breakings is subtle and not understood in all aspects. They can be considered as quasi-fossils of the evolution of the universe.

We shall give here a brief summary with particular emphasis on biomolecular homochirality referring to the articles [21, 22, 23–25, 27–29] for much more extensive reviews and further references. For a systematic discussion, it is first necessary to identify three different types of symmetry breakings, spontaneous, *de facto* and *de lege*, which are frequently not so well distinguished (often all three or at least two of them (spontaneous and *de facto*) are mixed up and lumped together in terminology. As discussed in more detail in References 24 and 29 the three concepts are really to be distinguished. We shall illustrate this with the example of a chiral molecule with (almost) symmetrically equivalent enantiomers.

Figure 5 illustrates this with a potential function with two minima, each corresponding to one enantiomer, separated by a large potential maximum. With perfect space inversion (parity) symmetry the potential (in fact the Hamiltonian altogether) is strictly symmetrical and the classical mechanical state reflecting this symmetry would be at the intermediate maximum of the potential corresponding to the barrier, $V(q_c)$. This is a point of unstable equilibrium (see left hand part of Figure 5).

At lower energy, the state of the system will drop into one of the two minima, stable equilibria. In classical mechanics, only one state can be realized at a given time, either left at q_{L} or right at q_{R}. Neither state shows the symmetry of the potential or Hamiltonian. This corresponds to the phenomenon of spontaneous symmetry breaking, which is essentially a classical concept. It can be extended to the quantum mechanics of idealized systems with an infinite number of degrees of freedom, which we will not pursue here.

In molecular quantum mechanics, a new phenomenon arises, as discussed by F. Hund in 1927 [47, 48]: the superposition principle guarantees the existence of superpositions of states λ (localized left) and ρ (localized right). Indeed the energy eigenstates correspond to symmetrical and antisymmetrical superpositions of well-defined parity (positive, +, negative, –):

$$\chi_{+} = \frac{1}{\sqrt{2}}(\lambda + \rho) \tag{3}$$

$$-\chi_{-} = \frac{1}{\sqrt{2}}(\lambda - \rho). \tag{4}$$

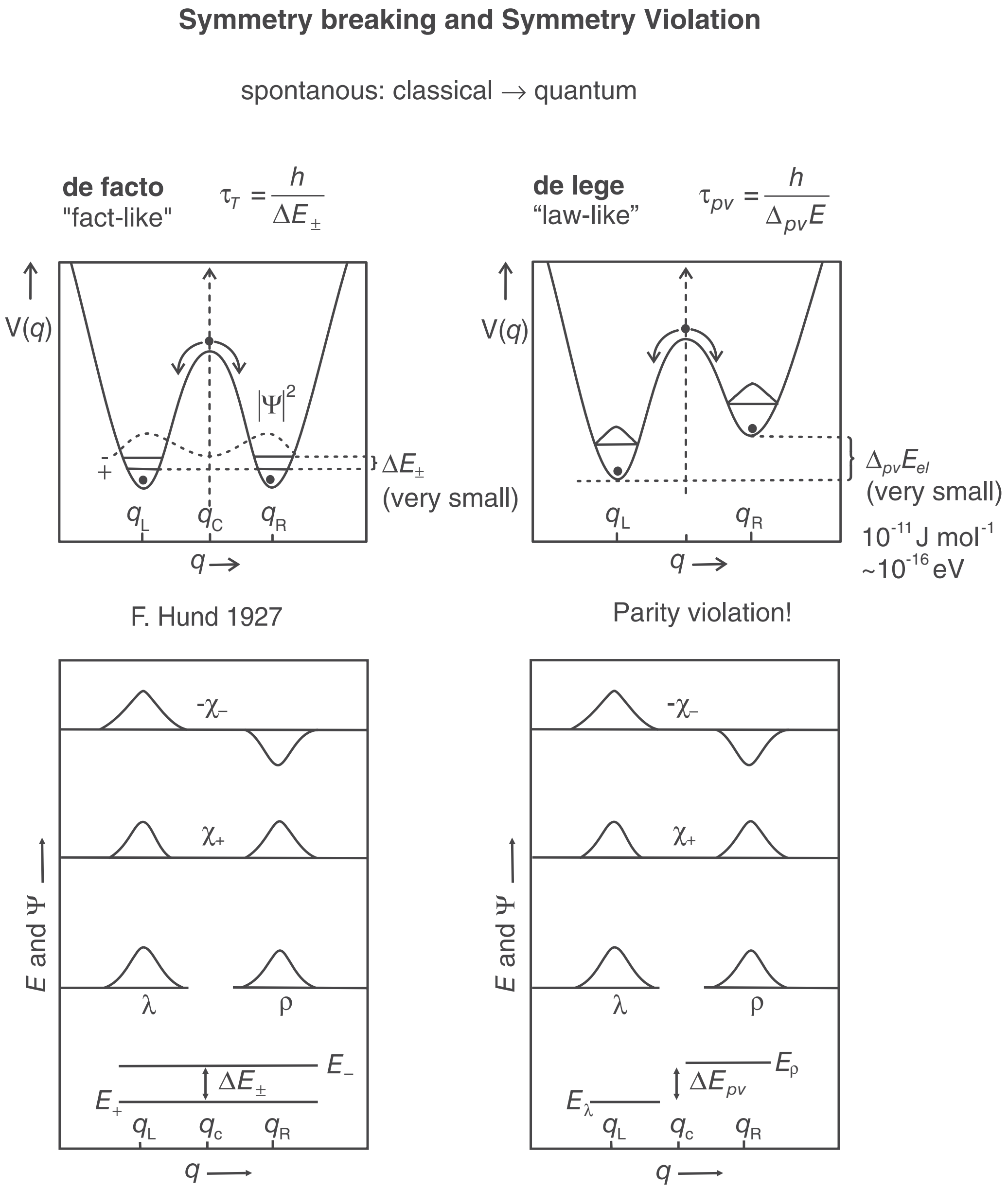

Figure 5. Illustration of symmetric and asymmetric double-well potentials for a chiral molecule (after Reference 28).

There is an energy difference $\Delta E_\pm = E_- - E_+$ between these two states and it is possible to generate the localized states as superpositions of the energy eigenstates:

$$\rho = \frac{1}{\sqrt{2}}(\chi_+ + \chi_-) \tag{5}$$

$$\lambda = \frac{1}{\sqrt{2}}(\chi_+ - \chi_-). \tag{6}$$

These states evolve with a period

$$\tau = \frac{h}{\Delta E_{\pm}} \tag{7}$$

and show a time for a transition from a localized state left to a localized state right, which is just the half period

$$\tau_{\lambda \to \rho} = \frac{h}{2\Delta E_{\pm}}. \tag{8}$$

This transfer happens at energies below the barrier separating the two minima and is thus classically forbidden. It provides an early reference to the tunnel effect in quantum mechanics [47,48], subsequent work being notably due to G. Gamow in treating α-decay.

As Hund pointed out, with small values of $\Delta E_{\pm}$, the state can remain for very long time localized on one side (say left), like the classical state, and this quantum phenomenon is called *de facto* symmetry breaking. Different from the classical spontaneous symmetry breaking, however, the delocalized states χ_+ and χ_- can be prepared at any time, as guaranteed by the superposition principle of molecular quantum mechanics, even if λ and ρ are extremely long lived due to the small splitting $\Delta E_{\pm}$. It should also be noted that the expectation values for the energies of λ and ρ are identical by symmetry, even if the energy is not sharply defined:

$$\langle E_\lambda \rangle = \langle E_\rho \rangle = (E_+ + E_-)/2 \tag{9}$$

Turning now to the phenomenon of *de lege* symmetry breaking, one arrives at the situation shown in the right hand part of Figure 5. The potential is no more symmetric, due to effects from electroweak parity violation [29], and the energy eigenstates are localized left with $E_\lambda^{(\mathrm{pv})}$ and right with $E_\rho^{(\mathrm{pv})}$ with a "parity-violating" energy difference

$$\Delta_{\mathrm{pv}} E = E_\rho^{(\mathrm{pv})} - E_\lambda^{(\mathrm{pv})}. \tag{10}$$

Now the eigenstates of parity evolve with a period

$$\tau_{\mathrm{pv}} = \frac{h}{\Delta_{\mathrm{pv}} E}. \tag{11}$$

With typical theoretical values of $\Delta_{\mathrm{pv}} E$, τ_{pv} is calculated to be on the order of seconds.

One might think now that given the generally proven effect of parity violation, the *de lege* symmetry breaking is the proper explanation for the origin of molecular

TABLE II
Communities of Belief Concerning Structural Hypotheses for Chiral Molecules (after Reference 24)

de facto	Spontanous	*de lege*
Hypothesis of Hund 1927	**"Classical" hypothesis"** – van't Hoff und le Bel 1874 – Cahn, Ingold, Prelog 1956/66) **"External perturbation" or "environmental" hypothesis** – Simonius 1978, Harris and Stodolsky 1981, Davies 1978/79 **Superselection rule hypothesis** – Pfeifer, Primas 1980 – A. Amann 1989f	**Electroweak interaction with parity violation** – Lee and Yang 1956, Wu et al. 1957 – Yamagata 1966 – Rein, Hegström and Sandars 1979, 1980 – Mason, Tranter, McDermott et al. 1983 ff (calculations) – Quack 1980/86 (proposed experiments on $\Delta_{\mathrm{pv}}E$, see also [26, 28, 29] for more recent theory)

chirality. This, however, cannot be guaranteed just by the mere existence of the effect, but it really depends on the results of a quantitative analysis. Indeed, *de facto* symmetry breaking provides essentially the correct treatment for the quantum dynamics of molecular chirality, if we have

$$\Delta E_{\pm} \gg \Delta_{\mathrm{pv}}E. \tag{12}$$

On the other hand, the *de lege* symmetry breaking prevails, whenever

$$\Delta_{\mathrm{pv}}E \gg \Delta E_{\pm}, \tag{13}$$

where in this last equation $\Delta E_{\pm}$ is to be understood as the tunneling splitting for the hypothetical symmetric potential.

From the numbers given above, we can conclude, that ordinary stable long lived chiral molecules with lifetimes of hours or years are dominated by the *de lege* parity violation [29], whereas molecules with short lived chirality such as H_2O_2, which shows tunneling on the ps timescale [49–51] are dominated by *de facto* symmetry breaking. Table II summarizes the current views of various types of symmetry breakings as relevant for molecular chirality as summarized in a careful analysis of the literature in 1989 [24]. As one can see there is quite a variety of explanations. The point we want to make here is that only a **quantitative analysis** for a particular case can provide the answer, which explanation is the correct one for this case. Without such an analysis, one does not know the answer. We shall encounter a similar situation for the different question of the evolution of biomolecular homochirality. We anticipate here our discussion in section IV and V, that for the quantum dynamics of molecular chirality, we can give a theoretically well-founded answer in many cases today (see Section IV). For the origin of biomolecular homochirality, the question remains open today (Section V).

IV. CURRENT STATUS OF THEORY AND EXPERIMENT FOR PARITY VIOLATION IN CHIRAL MOLECULES

Because of the possible importance of molecular parity violation for biomolecular homochirality, we give here a very brief review of the field, noting that more extensive recent reviews on the topic are available [21, 22, 28, 29, 33]. With the discovery of parity violation in nuclear and particle physics [52–55] and the subsequent development of electroweak theory in the framework of the SMPP [56–60], there were already early qualitative discussion of the role of molecular parity violation for chemistry including biomolecular homochirality [61,62]. Early suggestions and actual experimental attempts were made [63–67]. We know today that in the early experimental attempts about 10 orders of magnitude were missing in resolution or sensitivity.

Also, quantitative theory was developed for parity violation in atoms [68, 69] and molecules [70–76]. It turned out in a careful reinvestigation of the theoretical approach [77–85] that the early theoretical results were wrong, too small by about two orders of magnitude for the benchmark molecule H_2O_2 and other molecules, typically. These new developments after 1995 [77–85] were confirmed in numerous further independent approaches [86–91].

Figure 6 provides a graphical survey of the “big jump” in theory made around 1995. A brief summary of the current status of “electroweak quantum chemistry” (a term coined in Reference 77 and 78) can be that the new, much larger order

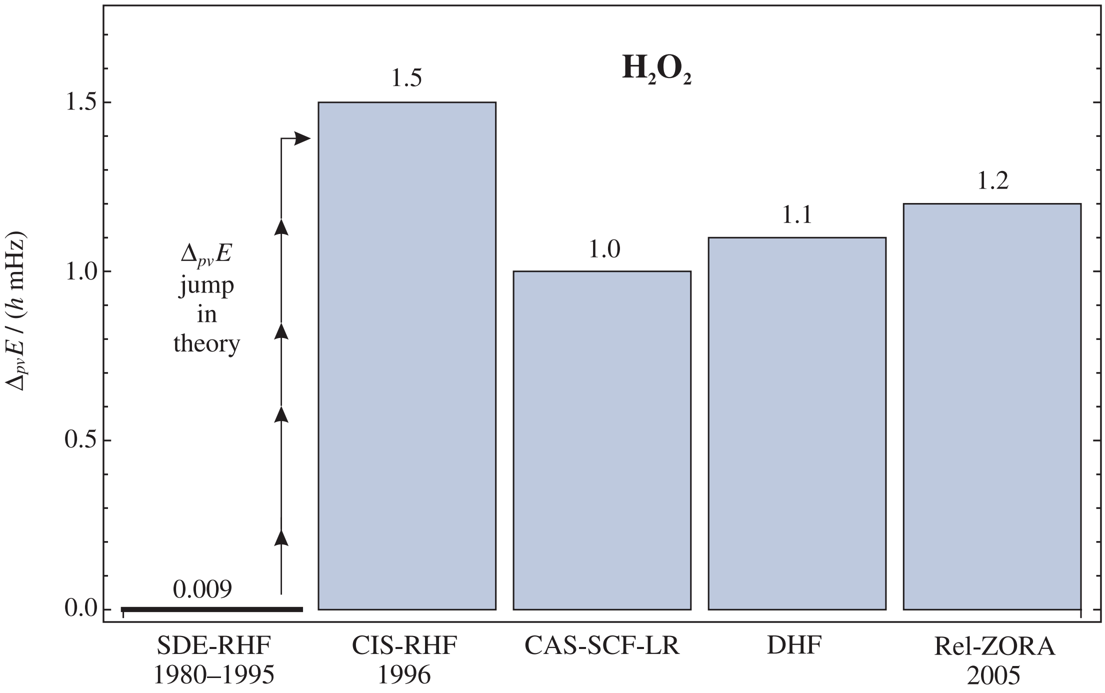

Figure 6. Graphical survey of the development of the theory of molecular parity violation with the “big jump” in 1995 (after Reference 33).

of magnitude is theoretically well established. Still, the values are very small, say about 10^{-11} Jmol^{-1} or 100 aeV for the prototypical molecules CHFClBr (or CDFClBr) [83,84] and ClSSCl [92], where tunneling splittings in the ground state are negligibly small, much smaller than the parity-violating energy differences [92].

For a detailed review, we refer in particular to the articles and reviews [27–29, 33, 78, 80, 84, 85, 93], as a detailed description of the theory would take too much space here. Nevertheless a brief discussion of the basic concepts may be in order.

The usual quantum chemical description of molecular quantum dynamics is based on the parity conserving electromagnetic force (see Reference 29 for a general survey in the framework of the SMPP). For visualization as well as for the practical approach one can use as a starting point the Born–Oppenheimer (or adiabatic) potential hypersurface $V(q_1, q_2, \ldots, q_S)$ as a function of the set of some generalized internal coordinates $\{q_1, q_2, q_3, \ldots, q_S\}$, where $S = 3N - 6$ is the relevant number of degrees of freedom of a chiral molecule with $N \geq 4$ being the number of nuclei (atoms) of the molecule. This potential is rigorously symmetric upon inversion of the coordinates at the center of mass (parity operation $\hat{P}$ or $\hat{E}^*$

$$\hat{E}^* V_R(q_1, q_2, q_3, \ldots, q_S) = V_S(\bar{q}_1, \bar{q}_2, \bar{q}_3, \ldots, \bar{q}_S) \tag{14}$$

with

$$V_{\mathrm{R}}(q_1, q_2, q_3, \ldots, q_S) - V_S(\bar{q}_1, \bar{q}_2, \bar{q}_3, \ldots, \bar{q}_S) = 0, \tag{15}$$

that is, exactly zero by symmetry. We have indicated by the index R and S that the inversion E^* transforms an enantiomeric configuration “R” into the corresponding enantiomeric “S” configuration, and the $\bar{q}_i$ indicates the coordinates with the inverted structure.

Of course, the symmetry of the Hamiltonian goes far beyond the Born–Oppenheimer, adiabatic or any other approximation, the exact molecular Hamiltonian $\hat{H}_{\mathrm{em}}$ in electromagnetic theory shows this symmetry. One notes that relevant molecular quantizations and potential energy differences in these potentials are on the order of 100 kJ mol^{-1} corresponding to about 1 eV (covering of course a range of a few orders of magnitude depending on the dynamical process considered).

On the other hand, in electroweak quantum chemistry, one calculates an additional effective “parity-violating” potential $V_{\mathrm{pv}}(q_1, q_2, q_3, \ldots, q_S)$, which is antisymmetric under the inversion operation.

$$\hat{E}^* V_{\mathrm{pvR}}(q_1, q_2, q_3, \ldots, q_S) = V_{\mathrm{pvS}}(\bar{q}_1, \bar{q}_2, \bar{q}_3, \ldots, \bar{q}_S) = -V_{\mathrm{pvR}}(q_1, q_2, q_3, \ldots, q_S) \tag{16}$$

Thus, one can define for every structure of the chiral molecule a parity-violating energy difference

$$\Delta_{\rm pv}\, E_{\rm el}(q_1, q_2, q_3, \ldots, q_S) = V_{\rm pvR}(q_1, q_2, q_3, \ldots, q_S) - V_{pvS}(\bar{q}_1, \bar{q}_2, \bar{q}_3, \ldots, \bar{q}_S). \tag{17}$$

These energy differences are typically very small, on the order of 100 aeV or 10^{-11} Jmol^{-1}. They vanish by symmetry for achiral geometries of the molecule. For chiral geometries, they satisfy the antisymmetry relation in Eq. (16). However, even within one set of enantiomeric geometries (say only for the R-isomer), the parity-violating potentials can change sign. Thus there can be, and indeed, there frequently are, vanishing parity violating potentials (and $\Delta_{\rm pv}E_{\rm el}$) also for **chiral** geometries. This property can be understood by the interpretation of the structure of the parity-violating potential as a trace of a tensor, thus the sum of three components of possibly different sign, but it does not depend on this interpretation [77–79]. While well understood, this property spoils any simplistic approach to estimate measurable parity-violating energy differences from theory. They can only be obtained from appropriate theoretical calculation of the parity-violating potential energy hypersurfaces in Eqs. (16), (17) for the relevant set of geometries. Although one can give some simple rules for estimating orders of magnitude of parity-violating potentials, such as the approximate Z^5 scaling with nuclear charge [28, 29, 33, 77–80], large deviations can occur for individual molecules, for instance, if the $V_{\rm pv}$ crosses zero near the chiral equilibrium geometry of the molecule. The chiral molecule 1,3-difluoroallene is such an example [94]. Another example is the amino acid alanine, where one has a zero crossing of $V_{\rm pv}$ as a function of a conformational change which is unrelated to enantiomeric structure [78, 81]. Thus, the actual calculation of the parity-violating potentials by the methods of quantitative electroweak quantum chemistry is necessary, if one wants to obtain accurate results. We do not discuss details here but refer to the careful descriptions in References 29, 77–97 as an incomplete survey of recent work of this kind.

The parity-violating potentials or parity-violating energy differences $\Delta_{\rm pv}E_{\rm el}$ in Eqs. (16) and (17) do not correspond to the directly measurable parity-violating energy difference $\Delta_{\rm pv}E$, for instance, in the ground state energy difference between the R and S enantiomers. This is calculated as an expectation value over $\Delta_{\rm pv}E_{\rm el}$ in the ground rotational–vibrational (perhaps also hyperfine) state. Thus, in practice, one uses

$$\hat{H} = \hat{T} + \hat{V}_R(q_1, q_2, q_3, \ldots, q_S) \tag{18}$$

obtaining ideally

$$\hat{H}\varphi_{\rm evr}^{\rm (k)} = E_{\rm evr}^{\rm (k)}\varphi_{\rm evr}^{\rm (k)} \tag{19}$$

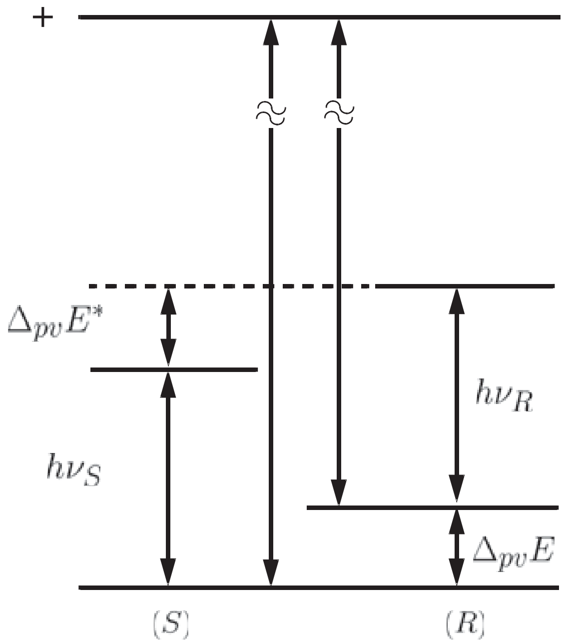

Figure 7. Energy level scheme for a chiral molecule including parity-violating energy differences $\Delta_{\mathrm{pv}}E$ and $\Delta_{\mathrm{pv}}E^*$ (after Reference 29).

by solving for the complete rovibronic wavefunctions $\varphi^{(\mathrm{k})}_{\mathrm{evr}}(q_1, q_2, q_3, \ldots, q_S)$ electronic ground state, and if needed including nonadiabatic and hyperfine structural effects. One obtains the desired parity-violating energy differences as expectation values

$$\Delta_{\mathrm{pv}}E^{(\mathrm{k})} = \left\langle \varphi^{(\mathrm{k})}_{\mathrm{evr}} \middle| \Delta_{\mathrm{pv}}E_{el} \middle|^{(\mathrm{k})}_{\mathrm{evr}} \right\rangle. \tag{20}$$

Calculations of this type have been presented at various levels of approximation in References 83 and 84, for instance. For the rovibrational ground state (($k = 0$), we simply use the symbol $\Delta_{\mathrm{pv}}E$ and for some excited states we use $\Delta_{\mathrm{pv}}E^*$. As a first approximation, one frequently takes $\Delta_{\mathrm{pv}}E_{\mathrm{el}}$ at the equilibrium geometry $(q_1^e, q_2^e, \ldots, q_S^e)$ in order to estimate $\Delta_{\mathrm{pv}}E$ in the ground state. We have shown, however, that the effects from calculating the correct average by means of Eq. (20) can be quite large [84].

Figure 7 illustrates the quantities discussed above in an energy level scheme for the two enantiomers. This scheme can also be used to discuss current experimental approaches. At present there are no successful experiments detecting parity violation in chiral molecules. However, there are three groups pursuing experiments attempting to prove effects from molecular parity violation by gas phase molecular spectroscopy (see Reference 33). These approaches follow two main experimental concepts, which can be illustrated schematically by Figure 7 (see also the recent discussion in Reference 98). One approach follows a proposal of Letokhov [63] to measure the difference between the frequencies in infrared absorption of corresponding lines in the R and S enantiomers. Apart from the early work on CHFClBr [64] and Camphor [65], there has been more recent work by our group using supersonic jet FTIR, diode laser, and FTMW spectroscopy [99, 100]. Under Doppler limited conditions in a supersonic jet of effective translational temperature T, the best possible relative resolution would be given by

$$\frac{\Delta\nu_{\mathrm{D}}}{\nu} \simeq 7 \cdot 10^{-7}\sqrt{\frac{T/K}{m/Da}}, \tag{21}$$

with mass m of the molecule.

Even at quite low T, this is still quite far removed from the necessary resolution to measure $\Delta_{\mathrm{pv}}E$, thus the results were used for detailed rovibrational and hyperfine analysis as ground work for a study at much higher resolution explicitly proposed in Reference 100. Such studies were subsequently carried out, reaching resolutions on the order $\Delta\nu/\nu \simeq 10^{-14}$ [101, 102], still quite far removed from the necessary values calculated to be below 10^{-16} for CHFClBr. For molecules with more highly charged "heavier" nuclei one might come close to the necessary resolution in the very near future but these have other severe disadvantages (see discussion in Reference 29). This approach has also been proposed to be combined with "cold molecule techniques" [103]. A general disadvantage of this approach is that a "difference of differences" is measured (see Figure 7):

$$\nu_{\mathrm{R}} - \nu_{\mathrm{S}} = (\Delta_{\mathrm{pv}}E^{*} - \Delta_{\mathrm{pv}}E)/h. \tag{22}$$

Thus, $\Delta_{\mathrm{pv}}E$ would not be directly accessible, although one could of course compare with theoretical values for $(\nu_{\mathrm{R}} - \nu_{\mathrm{S}})$.

The only realistic scheme to measure $\Delta_{\mathrm{pv}}E$ or $\Delta_{\mathrm{pv}}E^{*}$ separately and directly is currently pursued by the Zürich group following a scheme proposed in 1986 [104]. It relies on generating a superposition state of well-defined parity of the kind referred to in Eqs. (3) and (4).

This can be achieved by passing through an intermediate rovibrational state of well-defined parity. Such an intermediate state might be selected in an excited achiral electronic state of the chiral molecule, such as available, for instance, in 1,3 difluoroallene [94]. Such a situation is shown schematically in Figure 8.

One could, however, also use a highly vibrationally excited state in the electronic ground state by making use of "tunneling switching" [105]. We have recently identified such tunneling switching in the case of ortho-deuterophenol [106], an achiral molecule, though, where the small ground state energy difference arises from zero point energy effects, not from parity violation. Independently of which type of state is used, the experiment uses the time sequence of events shown in Figure 9. In the selection and preparation steps 1 and 2, one prepares the superposition "parity isomer," which has the line spectrum shown at the bottom of Figure 10 marked "–." In the evolution step, this evolves then into the spectrum above marked "+," in half a period of motion (Eq. 8). The time evolution of

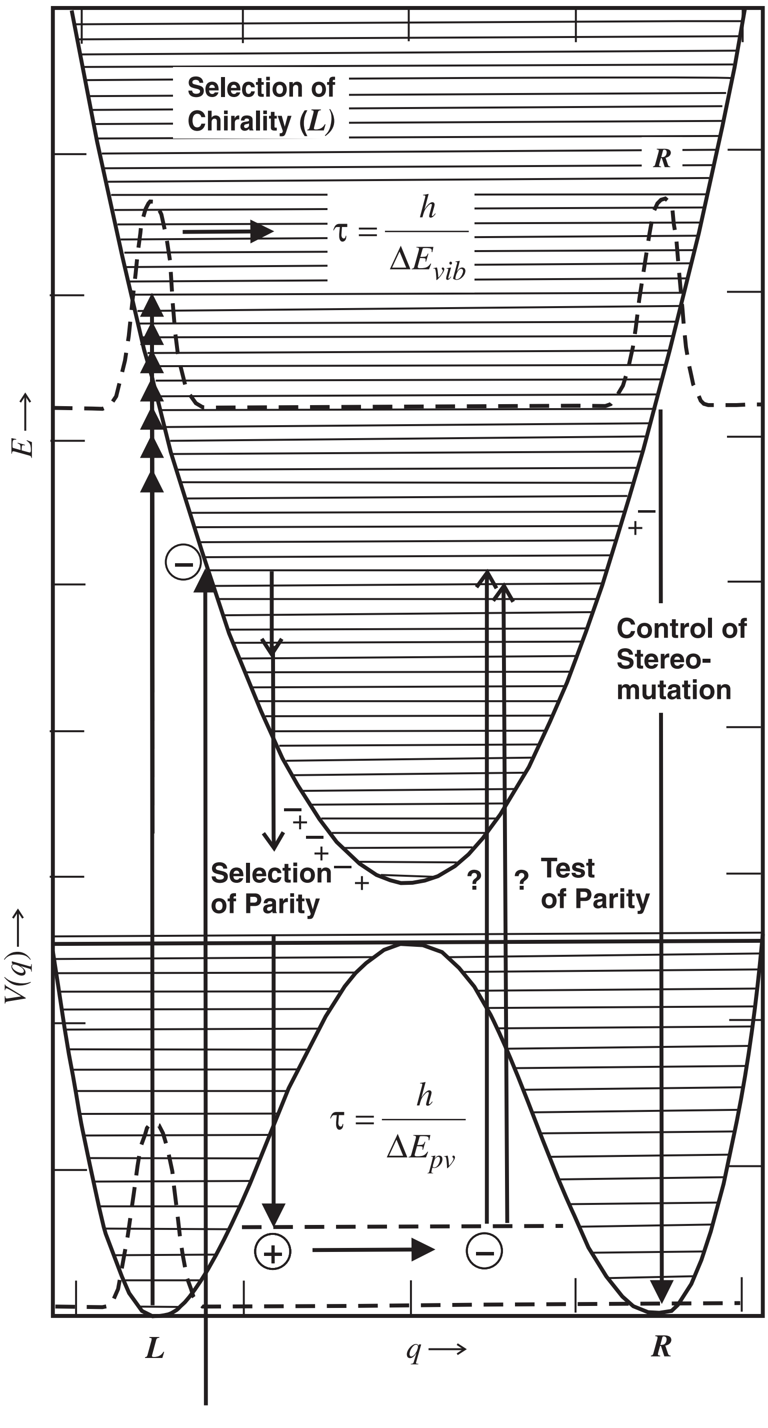

Figure 8. Experimental scheme to measure $\Delta_{\mathrm{pv}}E$ following the proposal of [104] (after Reference 23).

the initially "forbidden" lines (of the not prepared parity isomer π with initial population $y_\pi(t = 0) = 0$) follows the function

$$y_\pi = \sin^2(\pi t \Delta_{\mathrm{pv}}E/h) \tag{23a}$$

$$\simeq \pi^2 t^2 \Delta_{\mathrm{pv}}E^2/h^2 \text{ (at small } t) \tag{23b}$$

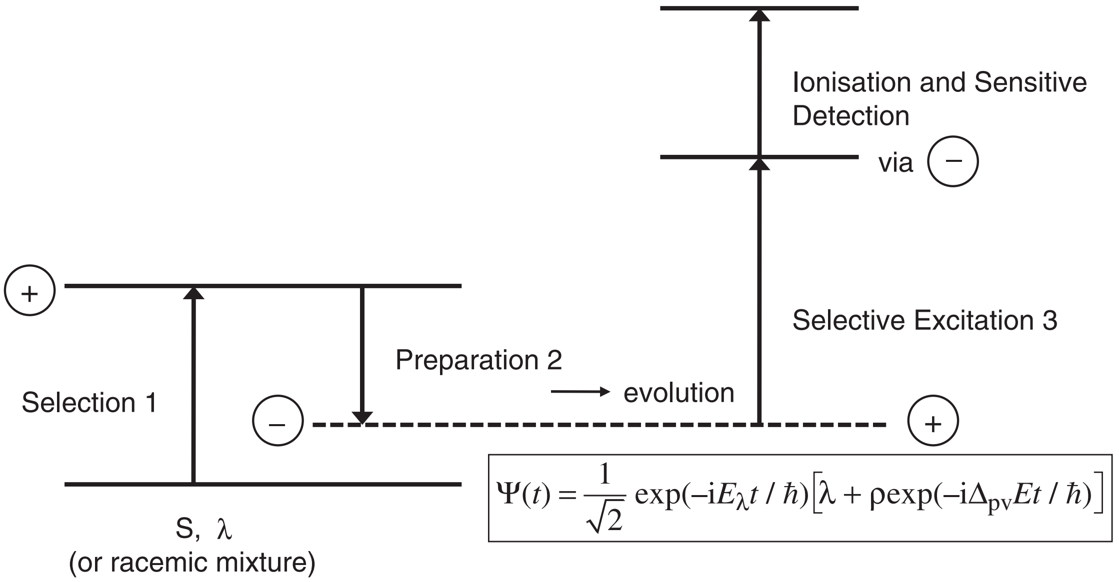

Figure 9. Sequence of steps in the experiment on molecular parity violation (after Reference 98).

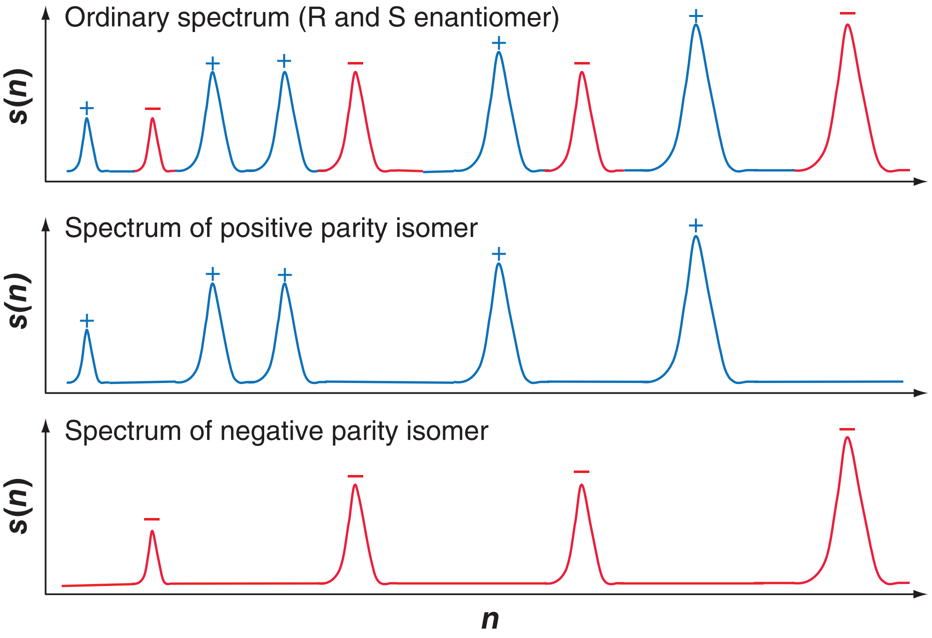

Figure 10. Schematic high-resolution line-resolved spectra of the parity isomers (positive shown in *blue* and negative shown in *red*). The normal line spectrum of a chiral molecule (either enantiomers or racemate) is the combination of two separate spectra from parity isomers. If one pure parity isomer is prepared, only its spectrum is observed initially, but as time proceeds the forbidden lines of the other isomer will appear because of parity violation. $n = \nu/\nu_0$ is a normalized frequency, and $s(n)$ is the spectral signal [29].

from which $\Delta_{pv}E$ can be obtained if y_π is determined experimentally in the selective excitation and detection step in the scheme of Figure 9.

In current experiments, we have already demonstrated this scheme to work on the simple achiral molecule NH_3 [107,108], but the realization for chiral molecules with more complex spectra and tunneling dynamics remains a task for the future. With this summary, we have a good description of the current status of theory and experiment, which looks bright for the near future, even though the experimental measurement of $\Delta_{pv}E$ remains still open. Once achieved one will gain knowledge on one hand on some fundamental aspects of the Standard Model (SMPP), but also on the comparison of experiment and theory on parity violation and possible consequences for the evolution of biomolecular homochirality to which we turn now. For much more detailed descriptions of both experiment and theory, we refer to References 21, 22, 28, 29, and 33.

Here, we can summarize the main breakthroughs leading to the current status of the field:

1. The theoretical breakthrough of the mid to late 1990s [77–81] showed the much larger (1 to 2) orders of magnitude of parity-violating energy differences compared to older theory, which thus became obsolete. This greatly increases the chances for successful experiments.
2. The experimental breakthrough of the mid to end 1990s led to the first quantum state resolved and analyzed spectra of chiral molecules in the "optical" (infrared range and to shorter wavelengths) domain [28, 29, 33, 99, 100]. This is an important and necessary step toward a spectroscopic detection of parity violation in ongoing efforts.
3. The current experimental work on molecular parity violation based on the advances made in steps 1 and 2 are based on different schemes and one can hope for success in the near future [28, 29, 98, 101–104, 107, 108].

Once experiment and theory on molecular parity violation lead to well established and converging results, we can envisage the study of realistic chemical reaction mechanisms leading to the evolution of biomolecular homochirality on the basis of the "*de lege*" parity violation.

V. THE ORIGIN AND SIGNIFICANCE OF BIOMOLECULAR HOMOCHIRALITY

There exists already a vast literature on this question (see e.g., References 21–25, 109 and references cited therein) and we have reviewed the topic ourselves repeatedly [21, 22, 23, 27]. Thus, we shall concentrate here on the main concepts, following in part [21, 22] and complement this by some additional considerations.

It may be surprising, but it is nevertheless a fact, that there are some basic observations related to the asymmetries summarized in Table I (Section III.B.), where we do not have a proper understanding, but where we have rather some scientific "communities of belief" [24], which have an explanation, which they accept, but where we have actually alternative explanations (and the corresponding "alternative communities of belief") and we do not know which of the alternative (and often several) explanations of the observed phenomenon is correct. Thus the lack of understanding does not result from a lack of explanations for the observed phenomena, but from the lack of experimental or theoretical evidence to decide which of the several hypotheses is correct. These questions thus remain open and we can phrase them in the form of questions such as,

What is . . .

1. the nature of molecular chirality?
2. the origin of biomolecular homochirality?
3. the origin of the very substantial excess of matter over antimatter in the presently observable Universe?
4. the origin of the irreversibility of physical–chemical processes, which can be related to our observation of a "direction of time," resulting in processes with a given direction from past to future, with the reverse processes not being observed?

From the discussion in Section IV, we can conclude that the first question can to some extent be answered by theory, although experimental confirmation remains still desirable. The other three questions remain open [21, 22] and we shall concentrate here on the second question of homochirality.

In the case of the evolution of homochirality, one can distinguish in principle two steps:

1. The initial generation of a (possibly small) excess of one enantiomer.
2. The reinforcement of this excess through various physical–chemical mechanisms, which can be abiotic as well as biotic.

Naturally both steps can be connected with each other. There are many mechanisms known, which in step 2 amplify the excess of one enantiomer, independent of how the original enantiomeric excess arose. Over the past few decades, a multitude of processes have been investigated and more or less well characterized. No limits seem to be set here for the creativity of chemists and we cannot refer to the very extensive literature here. We refer simply to the most important concepts, which are associated with the various "communities of belief" (see References 23–25 for details).

1. A stochastic "all or nothing" selection of an enantiomer (D or L) can take place as a result of a biochemical selection mechanism [6, 8, 110–114] or

also abiotically, for example, through crystallization and adsorption [115, 116]. According to this hypothesis, only one enantiomer is selected with every single evolution, but at the same time in many, separate evolution experiments D and L molecules are selected with equal probability or equal frequency on the average.

2. An accidental external chiral influence of a one-time evolutionary step selects in a preferred manner one enantiomer. Pasteur and later van't Hoff considered such possibilities, and since that time there have been innumerable different proposals of this type. As an example we mention the start of an evolution on a random chiral matrix, for example, a "left-quartz" (L-quartz) crystal [116]. When a favored enantiomer is formed, it could propagate itself and then remain dominant [117]. A currently popular possibility is the generation of an excess of one enantiomer in an interstellar gas cloud through polarized light. This excess could be then carried by meteorites to the early earth and would provide favorable starting conditions for one type of enantiomer. The observation of an excess of enantiomers of chiral biological precursor molecules in meteorites has persuaded many to favor this hypothesis [118].
3. A low temperature phase transition causes prebiotically (or, more generally, abiotically) a pure enantiomer on the basis of the parity-violating weak interaction. Enantiomerically pure or enriched organic starting material provides the foundations for a later biotic selection [119–121].
4. An enantiomer which is slightly favored, by virtue of thermodynamics or kinetics, by the parity-violating weak interaction gains an advantage through nonlinear kinetic mechanisms and in the end is then exclusively selected [61,62, 122–124] (see also References 25,27,77).

These four basic hypotheses can themselves, like the structural hypotheses of chirality, be grouped into *de facto* selection hypotheses (1) and (2), one could also use here the term "spontaneous," depending on whether one has a quantum or classical picture of the process, and the two *de lege* selection hypotheses (3) and (4).

The hypotheses also can be grouped into the two large categories "by chance" (hazard, Zufall) and "of necessity" (nécessité, Notwendigkeit) [30]. These categories of the evolution of homochirality can in principle be distinguished experimentally. If one repeats evolution following the mechanism of the category "chance," life based on L-amino acids will be generated in approximately 50% of the cases, and life based on D-amino acids will be generated in the other 50% of the cases. When a mechanism of the type "necessity" dominates, one would obtain as a result always (or mostly) our L-amino acid life form.

In principle, in order to distinguish the categories experimentally, one must repeat and understand the mechanisms of the origin of life and of evolution in the laboratory. At the moment we seem to be far removed from this, in any case further removed than we are from a measurement of parity violation in chiral molecules. The different hypotheses refer to the question of initial generation of enantiomeric excess. Before assessing the relevance of homochirality to the question of the origin of life a few observations are appropriate concerning the amplification of the excess and its propagation that is how it is passed on to future generations in living systems. We have today quite a good understanding in general terms of both of these, although we do not know, of course, the exact historical sequence of chemical and biological events in Earth history. That a given enantiomeric structure of DNA and proteins is inherited in life is clearly understood by all the molecular mechanisms of inheritance, which are understood reasonably well, at least in principle [6–10]. It is a little less clear, however, why the two enantiomeric forms of life should not coexist (see section II above).

The question of the amplification of an initial, possibly small, enantiomeric excess to obtain a macroscopic amount of just one enantiomer has been well investigated in recent years and there is now quite a large amount of evidence available that such an amplification is possible by several mechanisms, and, indeed, quite likely to occur.

Some early, indirect evidence can be seen in the mere observation that we do find even in the inorganic world such amplification toward a macroscopic (local) enantiomeric excess: We have known large crystals with the separate existence of L-Quartz and D-Quartz for a long time. Thus, locally we observe a macroscopic chiral environment. As far as there is adequate evidence, the statistics of L-Quartz and D-Quartz found on Earth indicate equal probability (i.e., "*de facto* selection" in these terms) [125].

Also, one has found total syntheses of chiral natural products from nonbiochemical (and achiral) starting materials, which lead to large enantiomeric excesses (essentially only one enantiomer) and not to the "expected" racemate. An interesting very early example of this kind has been reported in V. Prelog's autobiography [126], where he refers to a thesis work with this kind of result (and tragic outcome for the student).

Much recent work has concentrated on the spontaneous generation of large enantiomeric excesses by various crystallization mechanisms or by a variety of autocatalytic reaction mechanisms [127–141]. Thus, it seems plausible that some initial enantiomeric excess even in an abiotic environment can be amplified to generate an essentially locally homochiral environment.

It remains open, how this original enantiomeric excess arose. Many hypotheses concerning this have been proposed. Among them is polarized light in a localized astrophysical context. This could generate enantiomeric excesses even in primordial interstellar gas clouds. Enantiomeric excesses found in organic matter from meteorites have sometimes been reported and interpreted in these terms [142,143], but there remains considerable dispute on this problem.

The Frank mechanism allows for a local selection (but random) of one enantiomeric form even in the absence of any initial excess. Kondepudi and Nelson have proposed autocatalytic reaction mechanisms of selection, where the exclusive *de lege* selection of the enantiomer preferred by the extremely small enantiomeric excesses due to parity violation is possible in volumes of lakes and on geologically plausible timescales. At this point, we note that the theoretical claims [72–76], that L-amino acids and D-sugars are systematically stabilized by parity violation (compared to their enantiomers) cannot be maintained, as none of the early theoretical results can be maintained due to the erroneous orders of magnitude as discussed in [21–29, 77–82]. There were some debates, whether at least the sign of the early stabilization results might be correct, but there is no real theoretical basis for such a claim and it has been refuted in the case of alanine for instance [81]. Also, it should be clear, that such a "thermodynamic" stabilization is probably not a good approach anyway. In practice one would have to consider transition states for chemical reactions [82], for instance, in appropriate autocatalytic reaction mechanisms. While these statements might make us justly skeptical concerning the importance of molecular parity violation for biomolecular homochirality, this does not at all rule out a *possible importance* of parity violation in this context. The question remains open to be answered in the future [25].

Thus what summary can we derive from all these diverse observations concerning the question of the role of biomolecular homochirality in the evolution of life? The only form of life we know is homochiral. Thus, we may ask whether this is surprising. We can summarize in this respect as follows:

(i) It is *not difficult* to explain, how homochiral living systems pass on the information of homochirality to future generations.
(ii) We know also that an amplification of an initially small enantiomeric excess can be obtained by abiotic (prebiotic) mechanisms of physical chemistry.
(iii) That such an excess can originate from parity violation "*de lege*" has been demonstrated, in principle, but there are also many other possible "*de facto*" mechanisms.
(iv) The importance of parity violation for the quantum dynamics of stable chiral molecules can be considered as established.

Given these primary observations, we can draw some further conclusions: In terms of laboratory experiments for which we can now suggest a systematic approach:

(i) Select (guided by theory) molecules suitable for a spectroscopic measurement of $\Delta_{\mathrm{pv}}E$.
(ii) Synthesize these molecules and carry out high-resolution spectroscopy with them.
(iii) Prove molecular parity violation and measure $\Delta_{\mathrm{pv}}E$ quantitatively.
(iv) Compare experiment and theory and thereby test theory (to be amended if necessary).

(v) Use the thus established correct theory to study possible mechanisms of early prebiotic evolution of homochirality, if any.

(vi) Demonstrate evolution of life in the laboratory and investigate the corresponding mechanism for evolution of homochirality, if so.

(vii) In independent repeated evolution experiments test for the outcome for homochirality (in terms of *de lege* or *de facto* mechanisms).

While the first four steps might be achieved in the relatively near future, step (v) may be more difficult and steps (vi) and (vii) remain at present in the realm of speculation. However, we clearly can see the crucial role of homochirality in evolution.

Very different from the laboratory approach on Earth, we can also pursue an approach by astronomical and analytical, spectroscopic, and astrophysical observations. Here, biomolecular homochirality can play a key role as a chemical signature of life. If we find in our solar neighborhood (say Mars, Titan etc.) some form of life similar to ours, the observation of D-amino acids and L-sugars would be clear evidence for an independent origin and evolution of life. On the other hand, observing L-amino acids and D-sugars in the extraterrestrial biopolymers would be consistent with both the hypothesis of transport of life in the solar system and an independent evolution. If some previous life were extinct on extraterrestrial objects, we could still search for chemical fossils. However, usually the lifetime of biomolecular matter is considered short, less than a million years for DNA. For proteins from collagens in Dinosaurs survival times of about 80 million years have been claimed but the topic is subject to debate [144, 145].

Going beyond the solar system to the spectroscopy of extrasolar planets, often substances such as water (H_2O) or oxygen (O_2), even ozone (O_3) are taken as signatures for life. However, inorganic matter of this kind can at best be an indication for the *possibilities* for life to exist, not for life itself.

Also the frequent reference to the so-called “prebiotic” molecules [146] observed in the interstellar gas (and elsewhere in the Universe) should be really understood as synonymous with “organic molecules,” no evidence for life at all. By this we do not want to question the importance of understanding the chemical composition of interstellar matter [147–149], but it is not directly related to the quest for life in the Universe.

A fairly strong indicator for life would be the spectroscopy of chiral bioorganic molecules as they arise as emissions from woods etc. and a spectroscopic proof of a well-defined consistent homochirality of these compounds, say, by the spectroscopy of extra terrestrial or even extra solar planets or moons. While not a definitive proof for life, this would be very strong evidence in favor of life, as we know of no other mechanism of maintaining a biochemically consistent homochirality, although, of course, isolated enantiomeric excesses can be generated by other means [150]. These are just some examples on how homochirality can be used in conjunction with astrobiology and we shall return to this question below.

VI. DEAD OR ALIVE, DARK MATTER, COSMOLOGY AND THE WORLD GAME: CONCLUDING REMARKS AND SPECULATIONS

While up to this point, we have stayed on the solid ground of scientific facts or well-founded hypotheses, even if in many cases the answer had to state “ignoramus,” we shall leave this solid ground now and conclude with some remarks of speculation [21]. We refer here also to the “42 grand open questions” in Reference 33.

A. Homochirality of Matter and Cosmology

As is well known, even “nonliving elementary matter” shows a strange kind of homochirality which has led us before to some cosmological speculations [21, 22, 23, 29]. It is interestingly related to molecular chirality and fundamental symmetries.

Figure 11 provides an overview of chiral molecules in their four different enantiomeric forms being made of matter and antimatter. As we have discussed in Reference 39, spectroscopic investigations of these four “isomeric” molecules are well suited, in principle, for a very sensitive test of the underlying CPT symmetry of the combination of C, P, and T. Such experiments are certainly imaginable [34, 39] with sources of antimatter being in principle available today, however, they are not to be expected in the near future.

One can view the diagram in Figure 11 also in another fashion, highly speculative, and interpret it without a “solid” theoretical basis [29]. If one takes L as the normal, left-handed (strictly speaking, left helical) neutrino, then R* would correspond to the right-handed antineutrino (antimatter). The right-handed neutrino (R) made of normal matter has not been observed: the simplest assumption is that it does not exist. One can, however, imagine that it exists as a particle of very large mass, $\Delta_{\mathrm{pv}}E = mc^2$ would then be the parity-violating energy difference, for which one in complete absence of further information could assume values up to the GeV or TeV region. An interesting aspect of this speculation is the possibility of such

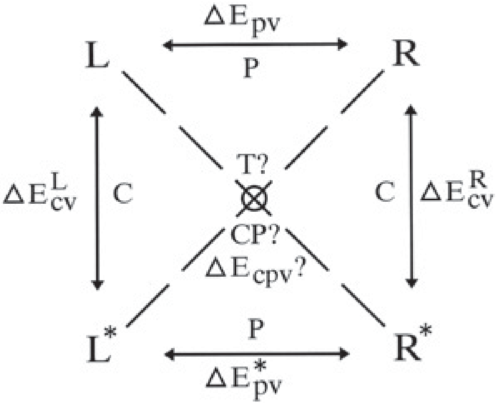

Figure 11. Diagram of enantiomeric molecules (L and R) made of matter and antimatter (L* and R*) with the notation “Left” and “Right,” used by physicists for the enantiomers instead of D/L or R/S. With CPT symmetry, the pair L and R* (L* and R) have the same energy. Thus $|\Delta E_{\mathrm{pv}}| = |\Delta E^{*}_{\mathrm{pv}}| = |\Delta E^{\mathrm{L}}_{\mathrm{cv}}| = |\Delta E^{\mathrm{R}}_{\mathrm{cv}}|$. The experiment proposed in Reference 39 could observe a departure from this relationship and a CPT symmetry violation with a relative precision of about $\Delta m/m = 10^{-30}$. If one interprets L and R* as neutrino and antineutrino, then R would be a possible heavy enantiomeric neutrino (see text, after References 29 and 39).

primordial heavy neutrinos being the cause of the so-called "dark matter," which has been proven by astrophysicists to exist because of its gravitational effects. Its effects dominate over those of the "visible" matter (mainly H and He). The nature of dark matter is unknown. So-called WIMPS (weakly interacting massive particles) are one possibility. Heavy neutrinos could be one kind of such WIMPS and contribute to the dark matter [29].[2]

One might address the question of how such dark matter might be observed in the laboratory, beyond indirect astronomical observation, which is subject to debate [151, 152]. Some experiments exist (all unsuccessful). We might note here that spectroscopy could provide a route [33]. The observation of a "heavy dark matter neutrino" (if any) is subject to similar problems as the observation of the "light dark matter neutrinos," which are required by current standard cosmology as remnants from the big bang (analogous to the 2.7 K blackbody background radiation, but with different timing and temperature, of course). These light neutrinos, which are expected to exist, contribute very little to dark matter and are very difficult to detect because of their low energy. They have not been detected, in contrast to the solar neutrinos of high energy. The suggestion for new experiments would be a two-step approach: One might build a "detector" which moves at high relativistic speed compared to the cosmological background neutrinos (one might use the chlorine experiment or something similar). Because of the high speed of the detector one could have similarly high collision energies as with the solar neutrinos, thus allowing detection by the same or similar means. Obviously the experiment must be modified [159], as it is not appropriate to accelerate tons of C_2Cl_4 to relativistic speeds. Once the "light dark matter" neutrinos are detected one could think of a similar experiment to find the "heavy dark matter" neutrinos. Obviously, some theory would be helpful to conceive an appropriate reaction partner for these. Clearly these things are something for the future, not for today or tomorrow.

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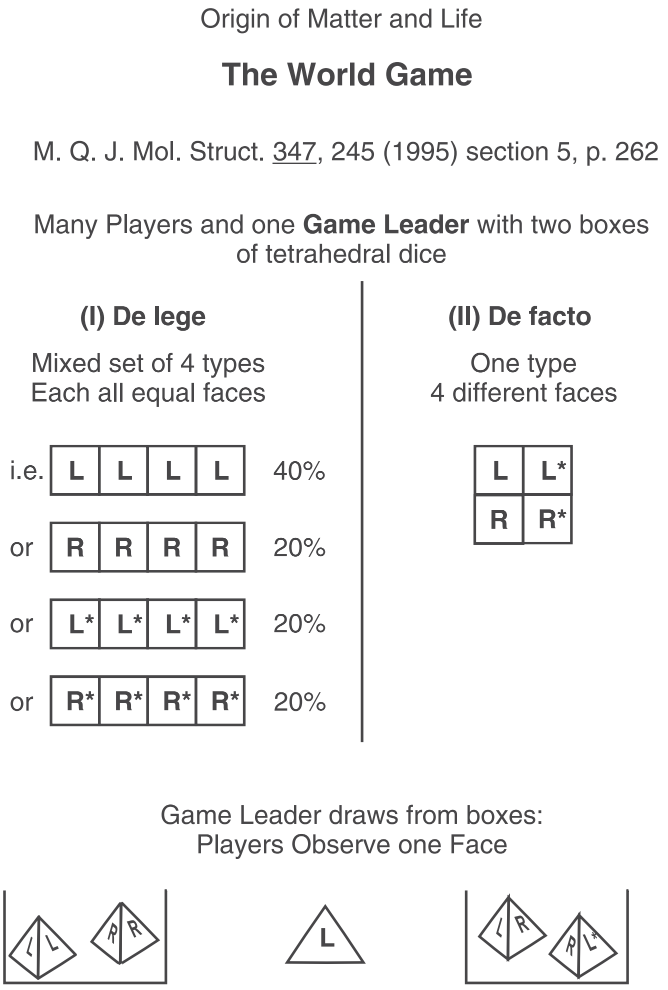
[2] The "dark matter" should be distinguished from the so-called dark energy which is discussed briefly by M. Eigen in [10]. The expression "dark energy" has been introduced as a result of cosmological considerations, the interpretation of which is still subject to large uncertainty. As opposed to this, the existence of "dark matter," through its gravitational effects in the dynamics of galaxies, is confirmed by many astronomical observations, and is thought of as certain. This was concluded by Fritz Zwicky decades ago and has been confirmed many times since then. These conclusions are just as well-founded as for example the earlier conclusions about the existence of the outer planets in our solar system, by observation of their gravitational effects on the courses of the inner planets which had previously been observed. The existence of the outer planets was then later confirmed through direct observation. The gravitational effect on the observed courses of the galaxies is also confirmed in the case of dark matter. An alternative interpretation would require a modification of the laws of classical mechanics and gravitation and this is thought to be very unlikely. The nature of dark matter is not known however. Speculations range from "difficult to see" normal matter (ionized interstellar hydrogen gas or a multitude of small planets are discussed here) up to new elementary particles, which display few interactions with normal matter, but obey gravitation in a normal fashion (so-called WIMPS).

B. The World Game

A further cosmological speculation also points to the importance of the symmetry violations. In References 34 and 35, we proposed a "world game," which is illustrated in Figure 12.

This was inspired by the book of Eigen and Winkler, which discusses various other types of "games" [111]. In our world game, there is a leader of the game, who draws tetrahedral dice of the type illustrated in Figure 12 out of one of two boxes (shown at the bottom of the figure). The sides of the dice L, L*, R, and R* correspond to the chiral molecules in the diagram in Figure 11. In the *de lege* box, one finds four different types of dice, in which each individual die shows one symbol on all four sides (e.g., L on all four sides, or L* on all four sides, etc.). In the *de facto* box, there are only identical dice, but these have four different sides L, L*, R, R*. The players (the scientists) are permitted to make one throw of one



Origin of Matter and Life

The World Game

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Many Players and one **Game Leader** with two boxes
of tetrahedral dice

(I) De lege

Mixed set of 4 types
Each all equal faces

i.e. L L L L 40%
or R R R R 20%
or L* L* L* L* 20%
or R* R* R* R* 20%

(II) De facto

One type
4 different faces

L L*
R R*

Game Leader draws from boxes:
Players Observe one Face

Figure 12. The world game. The different types of dice used in the game are shown schematically with their four tetrahedral faces and the *de lege* box (bottom left) and the *de facto* box (bottom right). In the middle we show the single face allowed for observation (after References 34 and 35).

die which the game leader has drawn, and are only permitted to observe one side of this die: the side facing them. They must then guess from which box the die has been drawn (*de facto* or *de lege*). Guessing correctly means winning.

If the *de lege* box has the same number of dice of each type, and the game leader is honest (statistical) when he draws the dice, there is only chance or luck as an overall strategy (therefore no real strategy). If, however, a player knows that the distribution in the *de lege* box is not uniform (symmetry violation, for example, 40% L and 20% each from the three others), then he will win if he guesses always that the dice are from the *de lege* box when he sees the L side of a die. Otherwise he will guess that the dice are from the *de facto* box. The analogy to the current situation of scientists, who observe an L amino acid world, is obvious [34, 35]. If one understood the mechanisms of symmetry violation and their consequences on the evolution of matter and life in detail, then "*de lege*" would have to be at the moment the correct and best possible answer.

Sometimes one finds a statement that because of our truly singular, isolated observation of an "L-amino acid–D-sugar world" no conclusion can be drawn on the mechanism of the early evolution of homochirality. As we have pointed out before [35, 39], this is not quite true. In terms of the world game we can draw from our present observation already the conclusion, that the mechanism *cannot* be a 100% bias in favor of selection a D-amino acid L-sugar world.

C. Life and Death in the Universe and the Question of Consciousness and Free Will

We have in this chapter addressed the question of "life" in terms of the general biological and biochemical mechanism of "living matter." There exists another question which is quite different in a subtle way: When is an individual alive and when is it dead? Following Erwin Schrödinger, let us consider a cat (Figure 13). It is not *a priori* obvious, what we mean by saying the cat is alive or dead, even though intuitively we think that we can decide in a given case. One must note, however, that even an alive cat, which might be old or sterilized, would not be able to contribute to propagation and evolution of "life," which would be required by some definitions of life (here we talk about "cat life"). On the other hand, a lot of life continues in the body of a dead cat (bacteria, worms, etc.), thus life as such has not ended in this cat, although "cat life" has ended. The question is then what we understand by the question of life and death of an individual. One way to express this in physical–chemical terms is related to symmetries and constants of the motion or conserved quantum numbers.

As long as the individual exists "alive," we can identify a conserved quantum number associated with his property, say "alive" = +1 (like positive parity). When the individual dies, the quantum number changes, say dead = –1 (like negative parity). Of course, the famous Schrödinger cat would be one, where we have a superposition state with both values of the quantum number at the same time. A

Figure 13. Schrödinger’s cat: dead and alive (communicated privately to us by R. N. Zare).

completely similar argument can be made by using the quantum numbers ρ and λ for the enantiomers of a chiral molecule.

The question remains, how exactly to measure the quantum number for “alive” or “dead.” This is not so clear and it might be that this is a limitation for the use of quantum dynamics in such cases (and a limitation for Schrödinger’s analogy).

In human beings, the concept of “alive” is sometimes associated with the concept of freedom of action and “free will.” Schrödinger’s book [1] has a chapter on this. We have shown in Reference 153 that our intuitive concept of freedom of will is inconsistent with molecular quantum mechanics, if decisions are made as a consequence of molecular processes in the brain. This interesting result is not widely appreciated.

D. SETI and Extraterrestrial Homochirality

The quest for extraterrestrial life and homochirality within our solar system is clearly technically feasible and may happen in the present century, if human civilization is maintained. To obtain definitive proof of life in extrasolar planetary systems, perhaps even other galaxies, might be very difficult, even though we have argued above that spectroscopic detection of a consistent homochirality would provide a very strong clue. This is possible in the future, even if very difficult.

There is another route to such a proof, which would be receiving and decoding messages from an extrasolar civilization. While an exchange of messages is difficult because of the timescales involved, understanding messages would be possible, in principle, if received from some civilization (if any). This is the well-known "Search for Extraterrestrial Intelligence" (SETI). Some science fiction stories start such messages with the sequence of prime numbers from which then a code could be derived to successively derive more complex messages (see also ref 160). Then this civilization could inform us about their biochemistry and homochirality. Given parity violation, they could inform us in an unambiguous way about their biomolecular homochirality (if any).

E. Search for Terrestrial Intelligence (STI)

One could argue that rather than addressing the very difficult project of a search for extraterrestrial intelligence, one should start with a "Search for Terrestrial Intelligence" (STI). Indeed, I have done personal researches in this direction. I have searched with political and religious leaders, scientists, university administrations, and so forth and was consistently disappointed. No terrestrial intelligence to be found anywhere. Then I was told to extend my search to Chicago with the hint that there was some being which just turned 240 years old with the label "SBJJSAR" and finally the STI was successful right here: Happy 240 Birthday!

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This paper is justly dedicated to Stephen Berry, Joshua Jortner, and Stuart Rice, who have been my teachers in many ways over many years. For S. B. and S. A. R., I can refer to Reference 154, which I have recommended to my students for decades, and to many conversations. Joshua Jortner has been in person a teacher of mine starting 40 years ago in the Swiss Jura (see Reference 153). Thanks to all of them.

The work reviewed here has obviously profited from the help of many coworkers as cited by the references. Special thanks go to Ruth Schüpbach for transforming my handwriting into proper manuscripts. Our work is supported financially by ETH Zürich, Schweizerischer Nationalfonds and the European Research Council. The research leading to these results has received funding from the European Research

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APPENDIX

On Nomenclature

In this review, we have not used a systematic nomenclature for enantiomers of chiral molecules. Rather, depending on the context, we have used either the "physical" notation for left and right (L and R or λ and ρ) or the old biochemical notation (D and L) which is still widely used in the biochemical and biological literature. Today, in principle, one should use the systematic nomenclature (R and S or P and M), which we have used as well. This should not lead to confusion (see also References [4, 155]; [156–159]).

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DISCUSSION

Session: IIIA
Speaker: Martin Quack

Mike Lipkin asked: If early Earth was anisotropic, rotation of the planet in the Solar Wind would provide a strong impetus for chirality. Are the energy levels for this mechanism appropriate for biochiral selection?

Reply of Martin Quack to Mike Lipkin: Yes, there are many possible external chiral influences that could, in principle, generate a chiral preference, and some of those similar to the ones you mention were already surmised by Louis Pasteur for possible causes of biomolecular homochirality (and many others thereafter). These are all of the "*de facto*" kind discussed by me. Parity violation "*de lege*" introduces a new element, but, of course, we do not at present know, what the actual cause for the selection of biomolecular homochirality was.

Session: IIIA
Speaker: Sydney Leach

Mike Lipkin asked: Do the extreme conditions of early Earth, that is, radioactivity, heat, etc. mean that exobiologial search should typically start with likewise extreme planets (or once extreme)?

Session: IIIA
Speaker: Martin Quack

Sydney Leach commented: It is possible that in very early times there existed both D-amino acid and L-amino acid biota and that the D-form was eliminated through some form of Darwinian conflict.

Reply of Martin Quack to the comment of Sydney Leach: Sydney Leach is perfectly correct that such a Darwinian selection of biomolecular homochirality could have happened, but we do not know, whether it happened this way or whether it started with a prebiotic selection.

Session: IIIA
Speaker: Sydney Leach/Martin Quack

Don Heller said: In trying to assess the likelihood of extraterrestrial life, we suffer from the basic problem of being unable to draw strong statistical inference from an $N = 1$ database.

That said, there are some considerations. Life on this planet (although perhaps not intelligent life) seems easy to come by. There is not only enormous biological diversity, but the observation that on a geological timescale, nearly as soon as the planet's temperature became low enough to support stable molecules (with ≈ 100 kcal mol^{-1} bond strengths) life began. This suggests that, once conditions are right to support it, life happens "spontaneously"—apparently, mechanism and free energy somehow favor the formation of life. One necessary condition appears to be constrained molecular mobility. Given that sufficient chemical constituents are proven to exist—perhaps this is all that is needed.

I point out that the lack of converse chirality (i.e., D-amino acids and L-sugars) in our biosystem is not the only surprise. Even within the L-amino acid family, DNA does not encode for every possibility. Apparently those omitted amino acids are just not necessary, but why should they be totally excluded in all DNA-based life forms? That is, since life seems to drive toward experimenting with (and generally increasing) diversity—why is this particular (molecular) diversity excluded? As to the issue of specific chirality, is this in any way related to the handedness of the double helix?

Martin Quack reply to Don Heller: Don Heller makes the point that the evolution of life appears likely under appropriate conditions. As I said in my contribution, this seems to be the majority view today, but there are prominent opponents to this (Jacques Monod and others). If one is honest about our current state of knowledge: We simply to not know for sure, which opinion on this matter is correct. And there are many open questions, as Don Heller correctly points out.