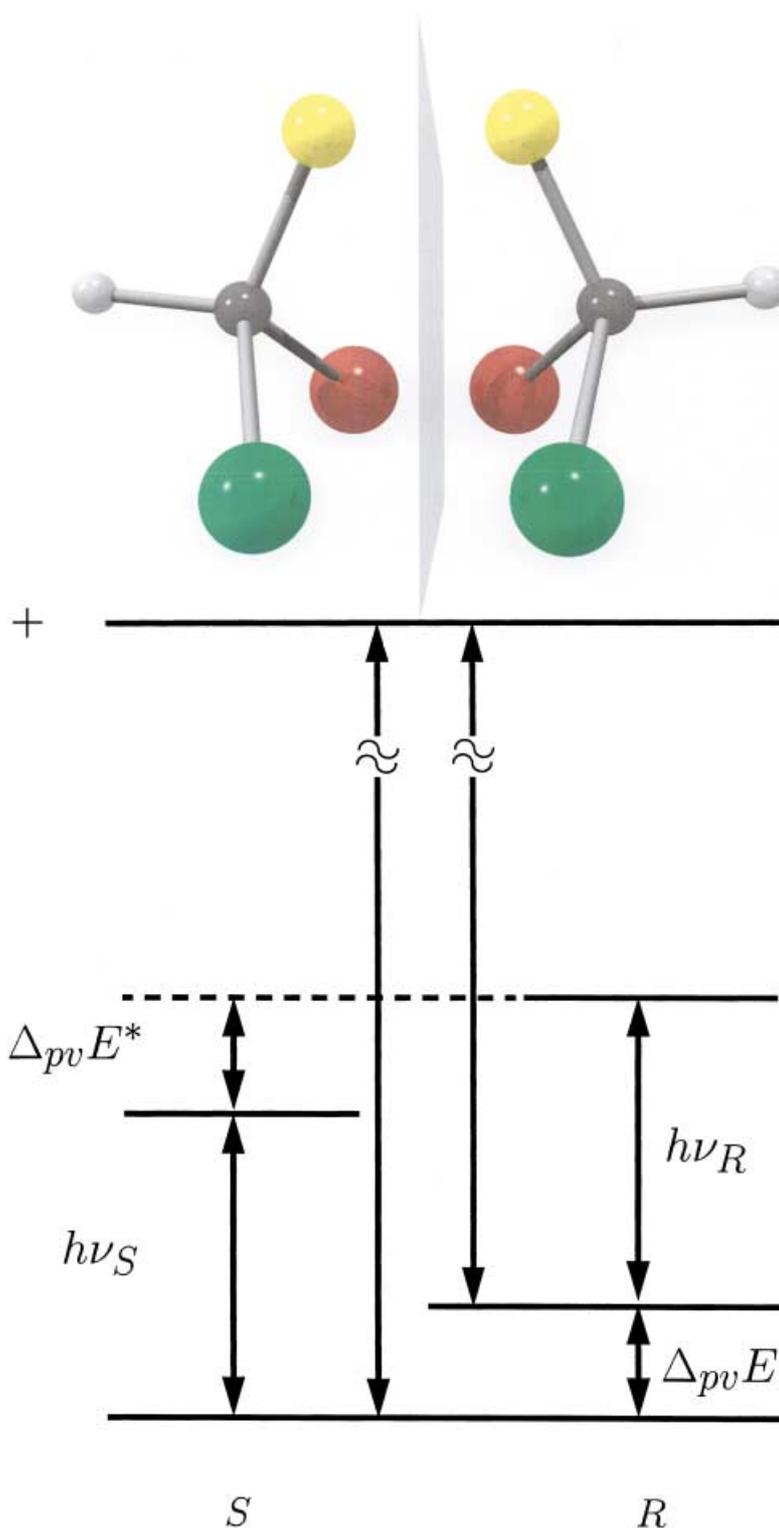


The energies of enantiomers are different because of a symmetry violation.



The energy difference $|N_A \Delta_{pv}E| = |\Delta_{pv}H_0^\circ|$ for the reaction $S \rightleftharpoons R$ might be measured following the spectroscopic scheme shown. It is predicted to be about $10^{-11} \text{ J mol}^{-1}$. How important would this tiny difference be for chemistry? What are the consequences for physics and biology?

How Important is Parity Violation for Molecular and Biomolecular Chirality?

Martin Quack*

Dedicated to Professor Hans H. Günthard on the occasion of his 85th birthday

Parity violation leads to energy differences $\Delta_{pv}H_0^\circ = N_A\Delta_{pv}E$ of enantiomers in the femtojoule to picojoule per mole range. Recently introduced methods of electroweak quantum chemistry predict such energy differences to be one to two orders of magnitude larger than

previously accepted—but still very small. How can such small energies be measured and what are the consequences for our understanding of molecular chirality, biomolecular homochirality, and perhaps fundamental physics? The review gives some tenta-

tive answers to these questions. We discuss the current status of theory and some of the current experimental approaches.

Keywords: biological homochirality • chirality • parity violation • symmetries

1. Introduction: Chirality and Fundamental Symmetries

The short introductory answer to the question in the title of this review might be: Parity violation is much more important—even by orders of magnitude—than believed on the basis of calculations commonly accepted until recently.^[1, 2] The history of this striking development will briefly be reviewed and an outlook presented on possible consequences for our understanding of the two big open questions on chirality discussed by us in a review a little more than a decade ago.^[1]

1. What is the origin of chirality in molecular physics and thus the “nature” or intrinsic structural feature of a chiral molecule or a chiral structure?
2. What is the origin of (homo)chirality in molecular biology, that is, the *chiral bias* that favors some enantiomers over others (in the chemistry of life as we know it)?
At the end of this review we shall complement this with a tentative answer to a third question:
3. Can a new experimental and theoretical understanding of molecular chirality contribute to our understanding of the fundamental laws of physics?

It should be made clear at the outset, that the purpose of this short review cannot be a complete and encyclopedic,

technically detailed review of the current status of the field, which is best dealt with separately. Rather we intend here to highlight briefly the development of the main concepts (and some controversies) with an outlook also towards ongoing research. Most current efforts of chemists in the field of chirality pertain to the enantioselective syntheses of chiral compounds and their industrial applications. Such work has been repeatedly honored, recently with the Nobel prizes conferred upon W. S. Knowles, R. Noyori, and K. B. Sharpless in 2001.^[3] Other important questions in chemistry concern the analysis of the structure and composition of complex chiral compounds—for instance by crystallographic or spectroscopic techniques or else simply tricky problems in the description of and the nomenclature for chiral compounds (see ref. [4, 5] for examples). Indeed, chirality-related research plays a substantial role in many chemistry departments worldwide, and the ETH-chemistry department is but one example among many (nicely summarized in ref. [6])

In addition to such classical “chemical” questions, however, molecular chirality is also important in relation to fundamental physics, in particular in relation to the underlying symmetries of physical laws. This relationship was already addressed in very general terms by the discoverer of molecular chirality, Louis Pasteur, 150 years ago.^[7]

More specifically, in an early review of the stereochemical concepts introduced in parallel by J. A. Le Bel and himself^[8] van't Hoff explicitly uses the “exact mechanical symmetry” between enantiomers to argue (rewritten and shown here in modern notation) that the standard Gibbs energy $\Delta_R G^\circ$, the enthalpy $\Delta_R H^\circ$ and the entropy $\Delta_R S^\circ$ of an isomerization reaction between the *R* and *S* enantiomers of a chiral

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molecule must all be exactly zero at all temperatures [Eq. (1) and (2)]; including 0 K with $\Delta_R H_0^\circ$] and thus the equilibrium constant K must equal exactly 1 because of Equation (3)

$$R \rightleftharpoons S \quad \Delta_R H_0^\circ \quad (1)$$

$$\Delta_R G^\circ = \Delta_R H^\circ - T\Delta_R S^\circ \quad (2)$$

$$K = \exp(-\Delta_R G^\circ/RT) \quad (3)$$

This is a clear reasoning that leads from a fundamental physical symmetry to a chemical result: $K=1$. In modern words, he refers to the invariance of the mechanical laws that govern molecular motion under the space inversion operation leading from a left-handed to a right-handed coordinate system (i.e. replacement of all particle coordinates following $x \rightarrow -x$, $y \rightarrow -y$, $z \rightarrow -z$; see Figure 1). Such a symmetry (and thus in chemistry the equilibria (1)–(3)) is related in a most fundamental way to our understanding of nature, what is “observable” and “not observable”. If the exact symmetry is present, then the absolute handedness is not observable (only

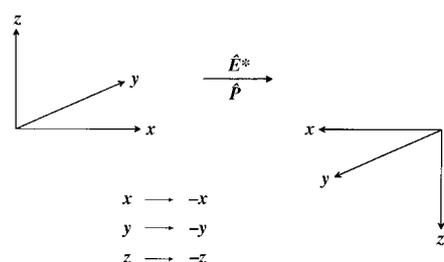


Figure 1. The symmetry operation of space inversion \hat{E}^* or \hat{P} transforms a right-handed coordinate system (left) into a left-handed system (right). In electroweak quantum chemistry, the symmetry with respect to space inversion is not valid. By rotating the coordinate system on the right by 180° around the x -axis, one can show the equivalent standard “mirror-image” relationship of these coordinate systems as enantiomeric structures.

the relative handedness of enantiomeric objects can be observed). In the words of Einstein^[9] “There are thus two types of cartesian coordinate systems which are called “right-handed” or “left-handed” systems. The difference between the two is familiar to every physicist and engineer. Interestingly, an absolute geometric definition of the right or left handedness is impossible, only the relationship of opposition between the two can be defined.”

Chemists could test whether that symmetry actually applies, for instance by measuring the equilibrium constant to very high precision. If K were found to be systematically different from 1 within high experimental confidence, the symmetry would be proven by experiment to be absent and thus the absolute handedness would become observable. It should perhaps be pointed out here that the determination of a conventional “absolute configuration” in the chemist’s sense is not a determination of absolute handedness of space, the latter being on a more fundamental level. The symmetry reasoning is valid within both classical and quantum mechanics. However, in single measurements there will be statistical deviations from the value $K=1$.

2. Hund’s Quantum-Mechanical Treatment of the Stereomutation of Chiral Molecules by the Tunnel Effect with Parity Conservation (1927)

In 1927 F. Hund^[10] noted in the framework of quantum mechanics that with the invariance of the molecular Hamiltonian operator \hat{H} under space inversion \hat{P} , as expressed by the commutation relation (4), the energy eigenstates χ_+ and

$$\hat{P}\hat{H} = \hat{H}\hat{P} \quad (4)$$

χ_- of chiral molecules will have a well-defined positive or negative parity π (the eigenvalues of \hat{P} are $\pi \pm 1$). They will

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thus be delocalized over both enantiomeric structures. This quantum number parity is conserved as a constant of motion related to the fundamental symmetry (parity conservation). Hund explained the observation of stable *R* and *S* enantiomers of chiral molecules by noting that one can generate localized wavefunctions by the superposition of parity eigenstates [Eq. (5) and (6)]. These localized wavefunctions reside

$$\sigma = (\chi_+ - \chi_-) / \sqrt{2} \quad (5)$$

$$\rho = (\chi_+ + \chi_-) / \sqrt{2} \quad (6)$$

at low energies in the wells of the lowest potential, which is drawn schematically in the upper part of Figure 2. The wavefunctions move periodically from one well to the other,

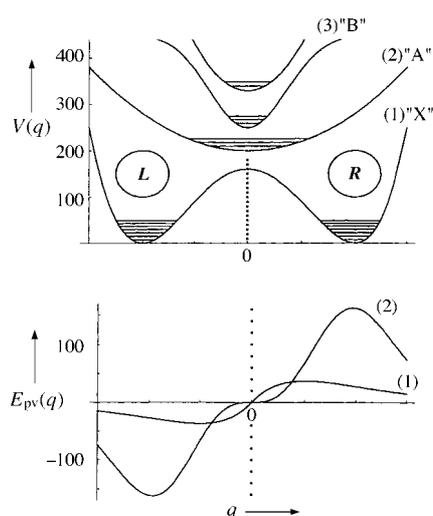


Figure 2. General illustration for parity-conserving and parity-violating molecular potentials (from ref. [2]). Upper: Born–Oppenheimer-type or possibly more general ground and excited-state effective potentials ($V(q)$ in kJ mol^{-1}) which are exactly inversion symmetric (i.e. symmetric under $q \rightarrow -q$), and separate this space into a left-handed (L) and right-handed (R) section; in this example with a general notation (standard conventions might associate L with *S* and R with *R* enantiomers or L with *M* and R with *P* enantiomers with helical chirality here, but this is quite arbitrary). The ground-state potential has a chiral equilibrium geometry and the excited states have achiral equilibrium geometries in this example. Lower: Small parity-violating effective potentials for the two lower states (schematic; $E_{pv}(q)$ in fJ mol^{-1}). These should not be interpreted naively as additions to a Born–Oppenheimer potential, but instead as effective potentials of a different symmetry (antisymmetric under $q \rightarrow -q$) and of a very different, very small order of magnitude. Recent work in electroweak quantum chemistry has shown that these antisymmetric potentials are orders of magnitude larger than previously accepted.^[1, 2]

that is, from *R* to *S* structures and the reverse, even at a low energy that is well below the top of the barrier to stereomutation in this potential, in a time corresponding to the half period of motion [Eq. (7)], where $\Delta E_{\pm} = E_- - E_+$ is the energy difference between the energy eigenstates of well-defined parity. The possibility of such a process in quantum mechanics was figuratively said to be caused by a “tunneling process”.

$$\tau_{RS} = h / (2\Delta E_{\pm}) \quad (7)$$

Hund’s treatment of chiral molecules seems in fact to be the historical discovery and first application of the important tunnel effect in chemistry and physics, just one year after Schrödinger’s famous papers on wave mechanics in 1926 and not even two years after Heisenberg’s formulation of quantum mechanics. Thus a careful treatment of a stereochemical problem within the framework of the then new quantum mechanics led to the discovery of this important physical phenomenon. Its 75th anniversary can be dated 28 May 2002. Physics textbooks frequently attribute the discovery of the tunnel effect to a later paper by Gamow on nuclear α decay.^[11]

For typical tetrahedral van’t Hoff structures of chiral molecules, Hund estimated tunneling times of millions of years, which readily explains the stability of enantiomers (for a critical discussion of these quantitative estimates see ref. [12]). The qualitative conceptual understanding of chirality again appeared complete within this picture, with retention of space inversion symmetry. At that time the firm belief was expressed that the underlying physical laws for all of chemistry were known.^[13] This turned out to be in error with respect to chirality. While thus, in this round, molecular chirality in chemistry was fruitful in introducing a fundamental physical concept, which was later to be used in nuclear and high energy physics and elsewhere, the next important development came about another three decades later from atomic and nuclear physics.

3. The Discovery of Parity Violation and its Relationship to Molecular Chirality

In 1956, Lee and Yang pointed out in a discussion of the experiments available at the time that there was actually no good evidence for parity conservation and thus for the underlying space inversion symmetry in nuclear β decay.^[14] Subsequent experimental tests, indeed, quickly led to the confirmation of parity violation.^[15] Many physicists were highly reluctant to accept the removal of this symmetry from their theories and Wolfgang Pauli is said to have bet large amounts of champagne against it when the suggestion of parity violation first appeared. Similarly, as reported in the December 2001 news of the American Physical Society, Richard Feynman considered at the time the notion of parity violation to be “unlikely, but possible, and a very exciting possibility”, and he made a 50 dollar bet with a friend that parity would not be violated. However, Feynman lost that bet and experimental proof of parity violation was swift and complete.

The concept was rather quickly transferred to molecular chirality. While one can find a few early, scattered remarks about the importance of parity violation for molecular chirality (for instance by Wigner and others), it was Yamagata in 1966 who clearly formulated the possible consequences both for molecular chirality and biomolecular homochirality.^[16] He pointed out that, because of parity violation, there will be a small difference in energy between enantiomers and thus in Equation (8) we have a parity-violating energy

$$\Delta_R H_0^e = \Delta_{pv} H_0^e = N_A \Delta_{pv} E \quad (8)$$

difference. He also discussed, in a simple kinetic model, the possible kinetic consequences of generating homochirality in the formation of biopolymers with monomeric units from different families of monomeric enantiomers (*R* and *S*). In the concluding sentence, he correctly points out the qualitative conceptual consequences for the hypotheses of the appearance of homochirality in the biochemistry of life with the famous phrase of “chance and necessity”.^[17]

Yamagata's extremely rough quantitative estimates were, however, somewhat overoptimistic, and in fact were flawed. One can cautiously interpret Yamagata's proposal with a value of $\Delta_{pv}H^\circ \simeq 10^{-6} RT (\simeq 10^{-3} \text{ J mol}^{-1}$ below room temperature), which is many orders of magnitude too large according to present knowledge.^[2] Also, his selection mechanism is problematic because in the limiting case in which the parameters of the model allow for substantial selection of one enantiomeric form, no appreciable product would ever be formed.^[18] Other mechanisms are needed to explain selection of homochirality on this basis (see ref. [12] and Section 6). Nevertheless, Yamagata's contribution had great merit, in that it kept interest alive in the quantitative question of molecular parity violation and introduced the distinct issue of biological evolution into the discussion.

In the 1970s and early 1980s, several papers addressed the estimation of $\Delta_{pv}H^\circ$, providing more adequate estimates,^[19–24] which were still qualitative and covered quite a range of values. By 1980 this corresponded to about $\Delta_{pv}H_0^\circ \simeq 10^{-10} \text{ J mol}^{-1}$, with acknowledged uncertainties of more than five orders of magnitude that arose mostly from the nature of the molecular electronic wavefunction, which was not properly calculated in any of these estimates. It should be mentioned that some of the progress in these estimates was certainly stimulated by parallel work on atomic parity violation and optical activity, a field which we cannot cover here (see ref. [25] for reviews). These estimates of the order of magnitude of $\Delta_{pv}H^\circ$, although still extremely crude, were already sufficient to predict qualitatively that parity violation actually dominated over tunneling, given the extremely long tunneling times of millions of years already predicted by Hund (really even much longer^[12]). These times would correspond to tunneling energies of about $10^{-25} \text{ J mol}^{-1}$; much smaller than any acceptable estimate for $\Delta_{pv}H^\circ$ at that time. This situation, in which the parity-violating energy difference in principle becomes a measurable difference between the zero-point levels of enantiomers was in fact predicted by all authors from 1966 to 1977.^[16–21] It was thus clear that, in spite of its small magnitude, parity violation had a real stereochemical significance in molecules such as CHFClBr [in terms of a real, nonvanishing $\Delta_R H_0^\circ$ in Eq. (1)].

Another limiting case with large tunneling splitting and effective parity conservation was routinely observed in the high resolution spectroscopy of molecules such as the textbook example NH_3 ^[26] (“chiral” NHD has not been studied, to my knowledge) or $\text{C}_6\text{H}_5\text{-NHD}$,^[27–29] which is chiral in its equilibrium geometry but not in its energy eigenstates (for the older available theories of tunneling in symmetrical and asymmetrical potentials see for example ref. [30]).

There were also attempts to measure infrared line shifts caused by parity violation^[20] on CHFClBr^[31] and camphor.^[32]

With a best relative uncertainty of $\Delta\tilde{\nu}/\tilde{\nu} = 10^{-8}$ in these experiments, there was no hope of seeing an effect (and none was seen); we know today that at least about 10^{-16} is needed. Another interesting point was raised by Harris and Stodolsky in 1978:^[22] If the barrier to stereomutation were such that the tunneling splittings and parity-violation energies were about equal, one might experimentally observe a time-dependent oscillation of optical activity with an amplitude significantly different from Hund's prediction for a symmetrical potential. In such cases, one could indirectly derive the parity-violating coupling-matrix element, from this amplitude of optical activity, by reference to the tunneling splitting. Because optical activity is difficult to observe at the high dilutions in a molecular beam needed for such an experiment, and because the class of suitable molecules is very special, this remained only a theoretical possibility. For the usual case of stable chiral molecules with negligible tunneling, dominated by parity violation, the time dependence of optical activity is practically indistinguishable whether or not there is parity violation. This time dependence would change from millions or billions of years in Hund's traditional theory to infinite time with parity violation, a change which is not suitable for laboratory observations on isolated molecules.

In 1980 and the following years, another experimental concept that should give direct access to the measurement of $\Delta_{pv}H_0^\circ$ for the realistic case of dominant parity violation was proposed by the present author and reported at several meetings. It is based on generating a new form of strange, unstable superposition isomers of well-defined parity for chiral molecules and observing the time evolution caused by parity violation. Because initially the technical difficulties seemed insurmountable, the details were published only in 1986^[33] and we shall return to this point below when discussing experiments that are currently pursued (Section 5). Around 1980 all experiments on molecular parity violation seemed far removed from successful realization.

From the theoretical side we may summarize the also somewhat unsatisfactory situation until about 1980 as follows: The estimates of $\Delta_{pv}H_0^\circ$ were uncertain by about five orders of absolute magnitude and there was no knowledge about the sign (whether *R* or *S* would be more stable for a given pair).

4. The Quantitative Theory of Molecular Parity Violation

Quantitative calculations of molecular parity violation were seriously attempted around 1980 in the work of Hegström, Rein, and Sanders, who formulated a theory based on the single determinant excitations—restricted Hartree–Fock approach (SDE–RHF).^[34, 35] This theoretical approach was widely used for the following decade (refs. [36–38] and references cited therein), leading to highly publicized results for biochemically relevant molecules such as amino acids and sugars.^[36–40] While alternatives were considered,^[41] the results of the SDE–RHF approach were generally believed to be firm and reliable for more than a decade (see also the review in ref. [1]).

It thus came as a surprise that the calculated parity-violating energy differences increased by one to two orders of magnitude when our group introduced the new CIS–RHF (CIS = configuration interaction singles) approach to *electroweak quantum chemistry* in 1995^[2, 42, 43] (this is where the latter term was coined), and later the more efficient and powerful multiconfiguration linear-response approaches (MC-LR).^[44] The starting point for this discovery was by no means spectacular. When rederiving all the basic equations again from scratch (see ref. [2] for the full account) and taking a closer look at the perturbation expressions for the parity violating potentials, it appeared that the SDE–RHF wavefunctions were really not very suitable for the description of the excited states appearing in the perturbation expressions for the parity violating potentials. Thus, we tried practically the simplest possible improvement of the theory (which is CIS–RHF), which immediately yielded the very large changes mentioned above. At the same time we showed that the parity-violation potentials E_{pv} appear as the trace of a tensor, $E_{pv} = E_{pv}^{xx} + E_{pv}^{yy} + E_{pv}^{zz}$, where the individual elements may have different signs and evolve independently in the calculations. This result implies that none of the calculations of sign and magnitude of $\Delta_{pv}E$ in polyatomic molecules prior to 1995 can be relied upon with any degree of certainty. Although changes of the order of magnitude and of the sign for a calculated heat of reaction ($\Delta_R H^\circ \equiv N_A \Delta E_{pv}$) are certainly spectacular, it must be remembered that the absolute values remain exceedingly small.

Our new approaches have been applied to various problems in different molecules such as H_2O_2 , H_2S_2 , ethylene torsion (all these having been investigated already in the earlier work, but with very different results)^[35–37] distorted CH_4 and C_2H_2 , N_2O_4 , $CHBrClF$, $CDBrClF$, fluorooxirane, S_2Cl_2 , and alanine in both the gas phase and solution.^[2, 42–51] For many of these molecules, significant coordinate-dependent parity-violating potentials such as shown in Figure 2 could be calculated, giving the magnitude, the sign, and the antisymmetry of these effective potentials. Careful convergence checks indicated that, with appropriate computational expense, convergence can be reached.^[44] Some of these new results were also confirmed by independent calculations in other research groups.^[52–56]

Table 1 provides a short survey of results for H_2O_2 , H_2S_2 , and S_2Cl_2 , which indicates that, in recent work, the order of magnitude obtained increases as well as demonstrating the good convergence of recent results from different groups. In this context in particular the approach by Schwerdtfeger and co-workers is noteworthy,^[54–56] because it uses quite a different quantum chemical framework within Dirac–Fock theory, but agrees nevertheless very well with the results of our group. One may thus hope that the recent theoretical approaches give quantitatively accurate results within the limits of basis sets and methodological convergence, which results in remaining uncertainties of perhaps 30% in $|\Delta_{pv}E|$, depending on the molecule. With appropriate care (and cost) even more accurate results should be accessible using our methods. Very recently a density-functional theory approach to molecular parity violation has also been published.^[57]

Table 1. Parity-violating energy differences $\Delta_{pv}H_0^\circ = \Delta_i H_0^\circ(M) - \Delta_i H_0^\circ(P)$ for H_2O_2 , H_2S_2 , and Cl_2S_2 at the geometries of the P and M enantiomers indicated (close to but not exactly equilibrium geometries, chosen for intercomparison of different results). The geometry parameters used were: $r_{OO} = 149$ pm, $r_{OH} = 97$ pm, $\alpha_{OOH} = 100^\circ$, $\tau_{HOOH} = 90^\circ$ for H_2O_2 , $r_{SS} = 205.5$ pm, $r_{SH} = 135.2$ pm, $\alpha_{SSH} = 92^\circ$, $\tau_{HSSH} = 92^\circ$ for H_2S_2 , and $r_{SS} = 194.7$ pm, $r_{SCl} = 205.2$ pm, $\alpha_{SSCl} = 107.55^\circ$, $\tau_{ClSSCl} = 85.12^\circ$ for Cl_2S_2 .

Molecule	Method	References	$\Delta_{pv}H_0^\circ$ [10 ⁻¹² J mol ⁻¹]
H_2O_2	SDE-RHF 6-31G	[36]	– 0.0036
	CIS-RHF 6-31G	[2, 42, 43]	– 0.60
	TDA 6-31G	[52]	– 0.84
	DHF	[54]	– 0.44
	CASSF-LR/cc-pVTZ	[44]	– 0.41
H_2S_2	SDE-RHF 6-31G	[36]	0.24
	TDA 4.31G	[52] (scaled 75% ^[43])	14.4
	CIS-RHF 6-31G**	[2, 43]	22.5
	MC-LR RPA/aug-cc-pVTZ	[48]	22.4
Cl_2S_2	DHF	[54]	33.5
	MC-LR RPA/aug-cc-pVTZ-A	[47]	– 15.4

A more complete critical review of the “technical” question of which theoretical approaches are most suitable for the calculation of molecular parity violation in a given instance is best dealt with separately.^[18] From a formal point of view, a relativistic theory of molecular parity violation is the most logical starting point (see ref. [2, 41, 54]). However, this does not imply that direct relativistic approaches at a given computational expense (for instance the maximum possible expense with current resources) will also provide the most accurate description of molecular parity violation. Indeed, physically, molecular parity violation arises as a contactlike interaction between electron and nucleons (in practice the nucleus) because of the short range of the weak nuclear interaction mediated by the massive Z boson as a field particle. This can be related to the gradient of the wavefunction of the electron at the position of the nucleus,^[46] which is somewhat comparable (but not identical!) to the Fermi contact interaction which is responsible for the hyperfine structure in ESR spectra or the J -coupling constants in NMR spectra. It is thus important that the theory provides an accurate electronic wavefunction at the position of all the nuclei. For very accurate calculations on small molecules with light nuclei, the best strategy may well be to use as a starting point a very high-level standard nonrelativistic quantum-chemical approach and introduce relativistic corrections by perturbation theory, as necessary.^[2] Because of the very high computational expense, the direct relativistic (Dirac–Fock-type) approaches^[54] may not allow for a sufficiently high-level treatment at the same (maximum) computational expense. On the other hand, for large polyatomic molecules the most efficient, and thus relatively most accurate, approach may be the application of density-functional theory,^[57] although it suffers from the notorious lack of systematic improvement to convergence. Finally, for molecules involving heavy, highly charged (high Z) nuclei, direct relativistic approaches may provide the most efficient starting point. However, it would be misleading to state that the direct relativistic approaches are always numerically the most accurate.^[53] All approaches should give similar and approximately correct results at the

appropriate level of theory. We exclude here the ever-present possibility of some fundamental omission that might be common to all current theories. This possibility could be tested by experiment.^[33]

5. Experimental Approaches towards Detecting Molecular Parity Violation

Experimental approaches towards molecular parity violation have been suggested repeatedly, but to date no experiment has been successful in confirming the effect. Very broadly one may distinguish here between spectroscopic measurements on isolated molecules in the gas phase and experiments on macroscopic condensed-phase samples. The latter have led to a number of claims of success, but not to adequate proof, in our opinion. Recent crystallization experiments^[58] may be mentioned here, among several examples. The main problem of all macroscopic approaches can be summarized as follows: Even if reproducible effects are found, how can one guarantee that their origin is intrinsically from parity violation and not from some parasitic effects arising from intermolecular interactions in the macroscopic experiments? Minor impurities could play major roles because we are talking about energetic effects of the order of 1 in 10^{12} – 10^{15} (at ordinary temperatures) and thus interactions with impurities (and differences in impurities) of that order might become important. How can one guarantee the absence of effects of this type and of other parasitic effects in a macroscopic experiment? The other difficulty is to relate quantitatively the macroscopic observations to the theory of parity violation. This seems to be extremely difficult at present.

We think that definitive and useful experiments will come from the spectroscopy of isolated molecules in the gas phase. Figure 3 summarizes the type of experiments which have been proposed and are under current study in our laboratory, as well as in a few others worldwide.^[1, 20, 31–33, 46, 59–67] The energy-level diagram for the enantiomers of a chiral molecule is shown here—not to scale at all, with the parity-violating value $\Delta_{pv}E$ greatly overemphasized (by ten orders of magnitude or more). Different concepts for spectroscopic experiments on parity violation can be distinguished by the nature of the transitions observed in Figure 3 (see also the review in ref. [59]).

Historically, the first concept relies on the measurement of separate spectroscopic transitions in *R* and *S* enantiomers (originally in the IR region).^[20, 31, 32] Because of parity violation, the corresponding transition energies $h\nu_S$ and $h\nu_R$ will be slightly different. The realization of such experiments has been discussed for the radiofrequency range in NMR spectroscopy^[60, 61] and the microwave range, where for CHFClBr a modest Doppler-restricted limit with $\Delta\nu_D/\nu \simeq 7 \times 10^{-7} \sqrt{(T/K)/(m/u)}$ was reported in supersonic jet spectra at low effective temperatures *T* for the absence of parity-violating splittings.^[62]

At the same time a first, full rotational analysis was given for an infrared band accessible to CO₂ laser line coincidences and thus ultrahigh-resolution sub-Doppler spectroscopy was suggested.^[62, 63] Such experiments were subsequently reported

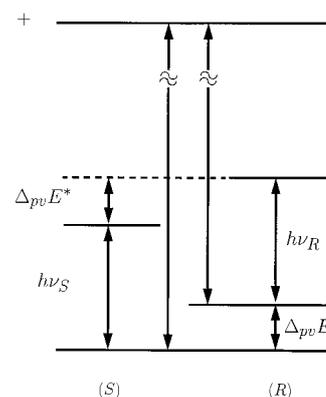


Figure 3. Energy level diagram for *R* and *S* enantiomers of a chiral molecule (from ref. [46]). Experimental (spectroscopic) schemes to observe effects from parity violation can measure differences in spectral transitions $h\nu_S$ and $h\nu_R$ in the separate enantiomers. These yield differences $|\Delta_{pv}E^* - \Delta_{pv}E|$ in parity-violating energy differences (ν_S and ν_R can correspond to NMR, microwave, IR, UV/Vis, or γ ray spectroscopy). Alternatively one can observe transitions to an achiral excited (vibrational or electronic) state with well-defined parity (here positive, +). Such a state can combine allowed transitions to both enantiomers and thus the differences of the two spectral lines in the middle provide $\Delta_{pv}E = \Delta_{pv}H_0^*/N_A$ directly. This approach can be realized with time-independent and time-dependent spectroscopic approaches.^[1, 33] Vertical lines between full horizontal lines correspond to allowed spectroscopic transitions, whereas connections to the dashed horizontal line or transitions labeled by $\Delta_{pv}E$ are forbidden and illustrate only energy differences.

by the Paris group of Bordé and Chardonnet, and show a null effect with an very small estimated relative experimental uncertainty of $\Delta\nu/\nu \simeq 4 \times 10^{-13}$.^[64, 65] Calculations in our group both prior to and after those experiments predicted that the actual effect would be three to four orders of magnitude smaller^[45, 46] as confirmed in further calculations^[55] (for a more complete history of the CHFClBr experiments and theory see ref. [59]). We had, however, anticipated that, for chiral molecules with two or more heavier atoms, the parity-violating frequency shift might become observable in infrared spectra in the relatively near future, although the quantitative theoretical analysis of the effect is difficult for such heavy molecules.

The highest frequency range considered for this experimental concept is Mössbauer (γ ray) spectroscopy.^[66] NMR and Mössbauer spectra of condensed phases may have extra problems of interpretation because of intermolecular interactions, even if the nuclei at the origin of those spectra may be considered to be relatively well-shielded. In any case, this whole experimental concept is unable to provide direct access to the parity-violating energy difference $\Delta_{pv}E = \Delta_{pv}H_0^*/N_A$, as can be seen from Figure 3. Rather, differences $|\Delta_{pv}E^* - \Delta_{pv}E|$ of parity-violating energy differences are measured (this point has been misrepresented in several of the relevant publications).

The second proposal, historically, for experiments in which parity violation in molecules could be detected concerned the measurement of time-dependent optical activity in chiral molecules, in which the parity-violating potentials and stereomutation tunneling splittings are of about the same magnitude.^[22] This experiment can be discussed in relation to Figure 3, if we reinterpret and rename some quantities in the level scheme. In the case of tunneling without parity violation,

the splitting between the two lowest levels is caused only by pure tunneling and corresponds to two delocalized energy states [ΔE_{\pm} in Eq. (7)]. This difference is unrelated to parity violation and no information on parity violation can be drawn from observation of the time-dependent oscillation expressed by Eq. (7), for instance as a time-dependent optical activity of period $2\tau_{RS}$. Indeed, this observation of time-dependent optical activity would be the tunneling variant of the first quantitative kinetic experiment carried out by Wilhelmy in 1850 on the “inversion” of sucrose, which is, however, not an elementary reaction (see the short review in ref. [71] for a discussion and citation of the original literature).

If parity violation becomes important compared to hypothetical tunneling ΔE_{\pm} in the symmetric case, then the amplitude of the oscillation of optical activity will decrease and from this decrease one can derive the parity-violating coupling V_{pv} as compared to the tunneling splitting, as pointed out by Harris and Stodolsky.^[22] A significant observation in the ground level is possible only for a very special class of molecules, in which the tunneling splitting ΔE_{\pm} and V_{pv} are fairly similar, a rare exception. The generalization of this concept to excited states is discussed in ref. [1]. In the limiting case, in which parity violation becomes dominant, and the splitting between the lowest levels is $\Delta_{pv}E$ (see Figure 3) the time dependence of the optical activity vanishes and thus $\Delta_{pv}E$ cannot be directly measured by this technique. Indeed, this experimental approach is best adapted to a direct measurement of tunneling stereomutation τ_{RS} without parity violation, while parity violation appears as a perturbation of this process, whenever it becomes important. We note in concluding the discussion of this experimental concept that with the identification of an “intermediate tunneling” molecule,^[48] the proposal of measuring the rate and amplitude of time-dependent optical activity^[22–24] for such a rather special case has also gained some practical, experimental credibility, although such experiments will surely be very difficult. The use of excited (vibrational or electronic) states with proper tunneling splittings has also been suggested in connection with this idea.^[1] This would also solve the problem of state preparation (by optical transition from a chiral ground state) not addressed in ref. [22], but it might introduce other problems.

It has also been discussed^[1] that for such intermediate tunneling molecules, as well as for ordinary achiral molecules such as “achiral” methane or methane derivatives, one might measure the time-independent optical activity, because with the inclusion of parity violation even “achiral” molecules become chiral and optically active. This could be considered to be a separate experimental concept similar to the optical activity of atoms.^[1, 25]

The first experimental concept that allows a direct measurement of $\Delta_{pv}E$ in the effective absence of tunneling relies on the key idea of using an intermediate spectroscopic level of well-defined parity (denoted by “+” for the example of positive parity in Figure 3).^[33] Such intermediate levels can arise from excited electronic states with achiral equilibrium geometry, as schematically shown in Figure 2 for the excited electronic potentials (as predicted for amines,^[27] methane derivatives,^[67] and allenes^[1, 33, 119]), or else they can arise from excited vibrational states with large tunneling splittings. These

intermediate levels possess allowed spectroscopic transitions to both the *R* and *S* enantiomers. As seen in Figure 3, the measurement of the difference of frequencies, either directly or by a beat frequency of two stabilized lasers,^[1] would provide us with the desired value $\Delta_{pv}E$. We note that theoretically $\Delta_{pv}E$ shown in Figure 3 and $\Delta_{pv}H_0^{\circ}$ has important anharmonic vibrational zero-point corrections as recently shown^[59, 121]

A particularly interesting variant of this approach utilizes the “synthesis” of the strange, unstable achiral “parity isomers” which are superpositions of normally stable *R* and *S* enantiomers. These strange achiral isomers have different line spectra at rotational resolution, which combine together to give the ordinary rotational–vibrational spectrum of the enantiomers or racemates. The situation is somewhat similar to nuclear-spin isomers such as *ortho* and *para*-hydrogen or the more interesting case of H_3^+ ,^[68, 69] in which the nuclear-spin isomers also have complementary spectra, although the analogy should not be overemphasized. Indeed, such unstable parity isomers have to date not yet been prepared, but if this were to succeed, for instance by the method of ref. [33] they would be unstable with respect to collisions and parity violation. In the absence of collisions and other external perturbations, the time evolution would initially be quadratic in time. If at $t=0$ the π isomer (positive parity isomer) is populated, we find the relationships (9) and (10),^[33] where c_{μ} is the concentration of the negative parity isomer (μ). We previously suggested calling these P (plus) and M (minus) isomers, but because of the quite different use of the P and M nomenclature for axially (helically) chiral molecules, the Greek letters π and μ are now preferred. Such exotic isomers will not be harmed by an exotic, that is Greek, nomenclature.^[70]

$$\pi \rightarrow \mu \quad (9)$$

$$c_{\mu} \propto (\pi \Delta_{pv} E t / \hbar)^2 \quad (\text{for } c_{\mu} \ll c_{\pi}) \quad (10)$$

The preparation of such exotic isomers following ref. [33] could, in a sense, introduce a new kind of chemistry into molecular chirality, an important application of which would be to measure $\Delta_{pv}E$ by c_{μ} , following Equation (10). However, as discussed in ref. [1] the experiment in ref. [33] would also be able to also test other hypotheses of molecular chirality such as the superselection-rule hypothesis of Pfeiffer and Primas^[72] or the collision hypothesis of Harris and Stodolsky,^[24] as well as other fundamental concepts.

The same fundamental scheme as described in ref. [33] can also be used to measure excited-state parity violation by exchanging the role of lower and upper states (also in the Figures 2 and 3). This was pointed out at an early stage and the idea has been revived recently.^[73] There have also been proposals of numerous further variations on the different schemes to measure parity violation including level-crossing experiments^[67] and other possibilities, but it is not the aim here to provide a complete listing.

To summarize our discussion of the main experimental (spectroscopic) concepts, these comprise three fundamentally different approaches:

1. Measurement of small differences of spectral line frequencies between enantiomers of ordinary, stable chiral mole-

- cules (in spectra ranging from the radiofrequency over infrared to the γ range).^[20, 31, 32]
- Measurement of time-dependent optical activity in a very special class of molecules, in which tunneling splittings and parity-violating potentials are of similar magnitude.^[22–24]
 - Direct spectroscopic measurement of the parity-violating energy difference $\Delta_{pv}E$ between enantiomers by means of a spectroscopic combination difference or by means of the time dependence of the quantum number “parity”, which corresponds to an isomerization between the unusual “parity isomers” of chiral molecules.^[33]

Only the third of these three approaches is able directly to provide the reaction enthalpy $\Delta_R H_0^e(1) = \Delta_{pv} H_0^e = N_A \Delta_{pv} E$. A nonzero value of $\Delta_R H_0^e(1)$ also introduces a new viewpoint for this isomerization process: It becomes more similar to a simple isomerization of, for example, *cis* and *trans* isomers in achiral molecules, as the exact symmetry relationship between *R* and *S* isomers is removed: These isomers are now predicted to differ slightly in their scalar properties such as ground-state energies, in NMR, microwave, or infrared spectra, structures, and other properties. There is also a new concept here concerning the predicted existence of unstable^[11] “achiral” parity isomers^[33] with lifetimes of the order of seconds in addition to the ordinary, stable “chiral” enantiomers. To our knowledge, currently active experimental programs exist only along the lines of concepts 1.^[62, 64–66] and 3.^[33, 47, 49, 59]

The advantage of all spectroscopic experiments on isolated molecules resides in the possibility of a quantitative theoretical analysis by electroweak quantum chemistry.^[42–49] We shall return to this point in the concluding remarks.

6. Parity Violation and Biomolecular Homochirality

The origin of biomolecular homochirality has certainly been the most extensively discussed and most controversial issue in relation to molecular parity violation. It concerns the nearly exclusive selection of *L* amino acids and *D* monosaccharides exhibited by terrestrial biopolymers and indicates the central role chirality plays in life as we know it. In contrast to the other topics discussed in this essay, this particular topic has received extensive and even excessive attention in numerous papers and reviews. With apologies to many other authors not cited we may cite here refs. [1, 12, 16, 38, 42, 50, 51, 56, 58, 74–90]. This subject has been the specific theme of a recent review^[91] and Highlights.^[92] We thus will be brief here, and follow essentially the line of thinking expressed in ref. [93] The whole field related to this question is characterized by the existence of “communities of belief” on how biomolecular homochirality has arisen on earth rather than any safe empirical or theoretical knowledge. The beliefs can be broadly classified according to the old phrases of selection by “chance” or by “necessity”,^[16, 17] or in more technical terms caused by symmetry breaking *de facto* (factlike) or *de lege* (lawlike)^[1] in the selection process. Each of these fundamental hypotheses can be further subdivided into further subsections as follows:

- One may have a stochastic “all or nothing” selection in a biochemical selection mechanism^[74–76] or an abiotic mechanism, for instance by crystallization.^[77, 78] According to this hypothesis, each selection will lead uniquely to either “*D*” or “*L*” life evolution, but on average over many independent evolutionary processes to equally frequent *D* and *L* (referring to amino acids, for example).
- One may have an accidental external chiral influence in evolution, such as a locally existing chiral quartz crystal,^[79, 80] a local existence of circularly polarized light,^[81] or the local influence of external magnetic fields.^[83–85] This local influence could be reversed in another environment with equal probability; this is then also a “chance” (*de facto*) mechanism. The influence of circularly polarized γ rays or polarized β radioactivity might appear under the *de facto* or—in view of parity violation—the *de lege* mechanisms.^[82]
- It has been suggested that a low-temperature phase transition under the influence of parity violation might provide a prebiotic mechanism for enantiomer enrichment,^[86–88] and if so, this would be a *de lege* (“necessity”) selection.
- Finally, in a nonlinear kinetic scheme, even the very small selection advantage arising from parity violation might be sufficient to provide selection of one and always the same kind of enantiomer—for example, *L* amino acids.^[38, 89, 90]

These four basic hypotheses may appear as numerous variants. Indeed, each time some new effect for some perhaps possible mechanism in chiral selection comes up in the literature, this is quickly praised as the “solution to the problem” (sometimes with cautious remarks in very small print) in the popular science press. There was a considerable amount of speculation in relation to the early findings of the stabilization of *L* amino acids and *D* sugars by parity violation.^[36–40] These results were, however, refuted by recent theory^[2, 42, 50, 51, 56] and it was argued that, in any case, the calculation of transition states, precursors, or intermediates in biochemical mechanisms would be more relevant.^[50, 51, 120] We think that no clear answer to the question of the origin of biochemical homochirality exists at present or is to be expected in the near future.^[93] Minimal conditions for such an answer would be that 1) in each possible mechanism for a desired selection all possible control experiments for proving the opposite outcome must be carried out and 2) the precise mechanism by which the effect leads to a selection of homochirality must be theoretically understood. To our knowledge none of the numerous suggestions existing today come even close to satisfying these minimal requirements. Even the observed data are frequently suspect, as is, for instance, the case for the alleged extraterrestrial enantiomeric enrichments.^[94, 95] The alleged excess of *L* amino acids found in meteorites is a fairly typical case with “proof” and “refutation” being repeated more than once.

The question is not definitely settled for this and related examples. With these skeptical remarks we do not imply that the fundamental question is only “philosophical” or pure speculation. On the contrary, the problem of either *de lege* (“necessity”) or *de facto* (“chance”) selection of homochirality is a clear scientific question with a clear answer, in principle. For instance, if some day we were able to repeat

evolution of life in the test tube, the *de lege* mechanism would always generate (or predominantly) one form (e.g. L amino acid life) in repeated experiments, whereas the *de facto* (“chance”) hypothesis would predict equal probability for both forms (averaged over many separate experiments, even if each single experiment gave only one form). Also there might be observational evidence. If we were to find some day remnants of D amino acid life on Mars, this would clearly contradict the strong forms of the *de lege* hypotheses (the reverse would not be true, though). We even have some very limited observational evidence already. The mere fact that we observe L amino acid life today on earth excludes at least the strong form of the *de lege* hypothesis in favor of the D amino acid life forms. By means of a game analogy (the “world game”)^[96] it can be argued that if an appropriate bias of principle caused by parity violation can be proven, then *the best guess* (in a statistical sense) could be in favor of the *de lege* hypothesis. It would be a very weak guess, though, which might be easily overthrown by contrary observed evidence. The only thing that can be said at present is that, given the recent prediction of substantially increased energetic effects from parity violation in molecules, the chances of the *de lege* hypothesis being correct have improved, but they are still very close to 50%.

A remark on common misunderstandings that can be found in either camp (“chance” or “necessity”) might be appropriate. The *de lege* (parity violation) community often expresses the belief that, because we know for certain that there is *some* preference at the molecular level that is caused by parity violation, there must “somehow” be a connection to the evolution of biomolecular homochirality at the next higher level of organization. Such an argument can be easily refuted because, at the still higher level of organization, human biosystems may choose left or right-handed traffic rules, or screws, or left or right-side partings of the hair. Both choices are in fact made clearly unrelated to the fact that all human beings are made up preferentially of L amino acids. On the other hand—and this opposes a common belief of the “*de facto*” camp—this kind of argument does not rule out that at the lower levels of molecular and biomolecular organization a fundamental connection to parity violation might exist. We just do not know at present.

7. Conclusion

In the conclusion of this review, we return to the three questions raised at its beginning. Clearly, these questions have been around for a while, but our recent discovery of the order of magnitude increases of parity-violating energies in chiral molecules^[42] has triggered substantial recent work—both theoretical and experimental—with the objective of demonstrating the importance of parity violation. Thus, of the five existing basic hypotheses on molecular chirality identified in ref. [1] (see also ref. [93]), the fundamental hypothesis number 5 has received a special status from the recent theoretical findings.^[97] Except for a still possible (but less likely) fundamental omission, quantitative theory shows that parity violation is as a rule quantitatively important, or even

essential in answering the first question about the physical–chemical nature of chirality, certainly in relation to the traditional hypotheses (numbers 1 and 2^[1,97]). While this result was qualitatively anticipated as early as 1966,^[16] current theoretical results are distinguished by their quantitative nature. Experimental confirmation (or rejection) of this quantitative theory can be expected in the near future. It should be pointed out that one proposed type of experiment^[33] would also allow for testing the remaining alternative superselection rule hypothesis^[72] (no. 3^[1,97]) or collisional and related “environmental” hypotheses^[24, 97, 98] (no. 4 in ref. [1, 97]).

The second question on the origin of biomolecular homochirality in evolution is both subtle and complex, and a definitive answer is hardly impending.^[93] Current quantitative theories of molecular parity violation^[42–56] can be combined with kinetic models of evolution^[12, 74, 75, 89] to provide a *starting point* for a theoretical understanding of the possible role of *de lege* symmetry breaking in evolution. A conclusive *answer*, which implies the exclusion (or confirmation) of alternative explanations by experiment and theory, is in our opinion only expected in the more distant future, and one should refrain from the premature claims that are all too abundant. A substantial research effort is still needed in this area. Systematic biochemical efforts on enantioselective enzymes^[99] or other types of chiral amplification in polymers^[115] in relation to theoretical calculation of parity violation and later—why not?—investigation by resynthesis of bacteria with opposing chirality could provide experimental routes.^[100]

The third question on the role of molecular parity violation for fundamental physics leads us to further motivation for a sustained experimental and theoretical research effort in this field. A combination of accurate experiments with accurate calculations of the expected effects can be used as a testing ground for the “standard model”,^[102] which is really a theory which comprises the current understanding of the fundamental microscopic physics of all known matter. This has been pointed out in accounts of experiments and theories of atomic parity violation^[25, 101, 116] as well as molecular parity violation.^[2, 42, 43] It is a particular feature of the standard model that, while providing a complete theoretical framework, it contains parameters that can only be determined by experiment. Each time such parameters are newly determined with higher accuracy (or by providing tighter bounds on parameter ranges), some new fundamental insights arise. The determination of the mass and lifetime (2.6×10^{-25} s = 0.26 ys) of the Z boson (which led to a determination of the allowed number of fundamental-particle families) in 1983 is a “historic” example.^[103] The current search for the Higgs particle and its mass in billion dollar (or euro) projects in huge accelerators is a current example.

It may be that the investigations of much lower cost on molecular parity violation may provide crucial information in the future.^[33, 42, 43] For this to happen, first accurate theory and second accurate measurement are needed, for instance of $\Delta_{\nu} H_0^{\circ}$. We think that our recent theoretical advances have essentially provided the first part of the necessary input, or at least provided a neatly paved route towards this. With the first

analyses of rotational-vibrationally resolved spectra of chiral molecules^[49, 62–65] the second, experimental part for the answer will also approach its completion. In this context it should be pointed out that, for *chiral molecules*, experiments should be feasible that involve only light elements, and thus exclude the uncertainties that necessarily arise from relativistic theory and complex, poorly known nuclear structure when heavy elements are involved. Heavy elements are unfortunately a requirement in all currently feasible experiments on atomic parity violation.^[25, 101, 117] While the statistical uncertainty in the atomic approaches has been sometimes quoted to be smaller than 1%, the systematic experimental and theoretical uncertainties are presumably larger. A high precision in atomic experiments and calculations does not necessarily imply high accuracy.

Finally, chiral molecules could be important in even more fundamental tests of the symmetries of physics. If pairs of chiral molecules and their counterparts made of antimatter are considered,^[104–108] then an experiment similar to the one proposed in ref. [33] can be devised^[109, 110] that would lead to a fundamental test of CPT (charge, parity, and time reversal) symmetry^[118] at a relative resolution $\Delta m/m$ or $\Delta E/E$ of about 10^{-30} , about 20 orders of magnitude better than achieved today in proton–antiproton experiments and about 10 orders of magnitude better than what is currently available (K meson or electron–positron pair experiments) or even proposed in still-hypothetical experiments on antihydrogen.^[111] This would render not only the handedness of space “observable”, but even the absolute direction of time and, in combination with this, the definition of what is matter versus antimatter (see ref. [93] for a review). It should be clear, however, that such an experiment is at present entirely hypothetical, although it could become a reality in the more distant future. It would relate to fundamental aspects of our understanding of the world beyond elementary particle physics and molecular physics and biology.^[93, 112–114]

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have much of a winning strategy against other players. If one player knows, however, that the de lege box contains a bias towards one type of die (say 40% *S* and 20% each of the others), he will win with the strategy of guessing “de lege” if he sees an “*S*” in the single throw and “de facto” if he sees any of the other faces. In fact, however small the known bias is, in the long run he will always win over those who don’t know the bias and that is, why it is important to know the bias, also in the analogous physical situation. In our world we observe living matter to be made of *S* amino acids, and of ordinary matter, not of antimatter, where in the general notation *S* and *R* indicate the type of enantiomer and the star indicates antimatter as opposed to ordinary matter (without star). One obvious conclusion concerning the physical situation in biochemical evolution can be drawn from the single observation of an *S* amino acid world: The bias cannot be 100% in favor of any combination of *R**, *R*, *S**.

- [97] The five competing fundamental hypotheses of chirality that were identified by the time of writing the review^[1] are: 1. the classical hypothesis of macroscopic molecular models (basically van’t Hoff’s description of spontaneous symmetry breaking); 2. the quantum-mechanical hypothesis of de facto symmetry breaking with parity conservation, originally from Hund; 3. the superselection-role hypothesis of Pfeiffer and Primas with spontaneous symmetry breaking caused by the influence of the radiation field; 4. the “environmental” or collision hypothesis of Simonius, Harris, and Stodolsky that induces de facto symmetry breaking in chiral molecules because of interactions with an external medium; 5. the hypothesis of de lege symmetry breaking in chiral molecules because of parity violation. A detailed discussion of these hypotheses can be found in sections 2.1 to 2.5 of ref. [1], where it is also shown how one might distinguish experimentally which hypothesis might be applicable, mostly by using the scheme in Lit. [33].
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