New Developments in the Origins of the Homochirality of Biologically Relevant Molecules**

Helmut Buschmann, Richard Thede, and Detlef Heller*

In numerous review articles models have been compiled to explain why the essential molecular building blocks for life, proteinogenic amino acids and the ribose or deoxyribose units in nucleic acids, both have the same chiral sense.[1] Competing autocatalysis, asymmetric adsorption, and the symmetry fractures during crystallization belong to the "abiotic" explanations, which describe the occurrence of homochirality in biomolecules as accidental. The basic concept of the alternative "determined mechanism" is an external physical interaction, which is able to produce an enantiomerically enhanced product from an optically inactive starting material, or which utilizes chirality already intrinsic to the molecule. Typical examples of this are photochemistry with circularly polarized light—either as asymmetric destruction, as photo deracemization, or as asymmetric synthesis—and the energy differences between molecules which can usually be regarded as enantiomers. The latter originates from the parity violation of the electroweak interaction. Herein we will present new results on the energy difference between enantiomers and on asymmetric autocatalysis as an amplification model.

Since the prediction and the experimental confirmation that the weak interaction (responsible for the β-decay of atomic nuclei) is, in contrast to the other fundamental physical forces (gravitation, electromagnetism, and the strong interaction), parity violating,[2] the intrinsic "handedness" of certain elementary particles has been known.[3] In the universe presently accessible there are only left-handed neutrinos and only right-handed anti-neutrinos. A unified discussion of the electromagnetic and the weak interaction leads to the parity violating electroweak interaction. The resulting z force interacts between the electrons and the atomic nucleus and is able to differentiate between right and left because of its parity violating character. Quantum mechanical calculations which consider the z force show that an energy difference between enantiomers exists. This energy difference is called *p*arity *v*iolating *e*nergy *d*ifference (PVED).[4] However, so far it has not been possible to measure the PVED values of enantiomers although possible experiments have been suggested for several years.[5]

Since the beginning of the 1980s ab initio calculations have been available, particularly from Mason and Tranter,[6] that show the energy difference between enantiomers resulting from parity violation is in the order of 10^{-14} J mol^{-1} and leads to an energetic stabilization of the L-amino acids and the D-sugar, these are the isomers that we find in nature. For peptides consisting of the achiral amino acid glycine an energetic advantage for the naturally occurring secondary structures, the α-helix as well as the β-pleated sheet, was calculated.[6b,d] Results for ribose show how sensitive the PVED value is to conformational changes (C_2-*endo* compared to C_3-*endo*),[6g] with the known consequences in the α-helix. Also noteworthy is that considerably larger stabilization-energy values are to be expected [6i] for sulfur-substituted DNA analogues.

To the question of whether these types of energy differences, corresponding to a value of approximately 10^{-15} % *ee*, are the reason for the homochirality found in relevant biomolecules there are contradictory answers, even when assuming highly effective amplification mechanisms. While there are estimations that a period of 10 000 years should be sufficient for enantiomeric purity to be reached in a lake of 4 million m^3 by an autocatalytic process (Kondepudi – Nelson scenario)[7], many other authors, however, dismiss this process as being too inefficient.

Recently published ab initio results from Quack et al. showed for the first time, that with improved methods PVED values could be obtained which are one order of magnitude larger than previously thought.[8] Results, from another research group, concerning biologically relevant molecules such as alanine, valine, serine, asparate, and glyceraldehyde, confirm larger PVED values between enantiomers and again indicate an energetic preference for the L-amino acids and the D-sugar.[9] However, it must be pointed out that for the example of alanine Quack et al. and also Schwerdtfeger et al.

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have questioned the energetic preference for the L-enantiomer.[8b,e] Besides the differences in calculation techniques applied, which lead to systematic deviations extensively discussed in ref [8d], the various possible conformations of biologically relevant molecules complicate the unequivocal interpretation of results. Interestingly, the results for glyceraldehyde in the hydrated form always lead to an energetic stabilization of the D-enantiomer, regardless of the torsion angles (PVED values between $0.5-2.6\times 10^{-13}$ J mol^{-1}).[9a,b]

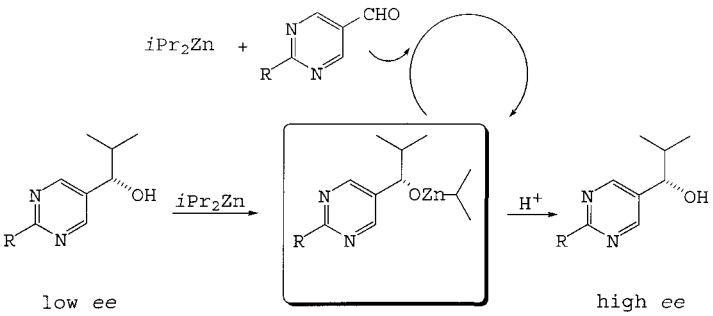
In spite of the unanswered questions, it remains undisputed that the PVED values calculated with the improved methods are clearly larger than those previously accepted. Today it seems increasingly more likely that the cause for the homochirality of biologically relevant molecules can be assigned to the intrinsic chirality present at the elementary particle level. The higher PVED values also lead to an increase of the characteristic critical temperature in the model suggested by Salam which describes the development of homochirality of amino acids on the basis of the Bose–Einstein condensation.[10]

Recent reports concerning the possible demonstration of parity violation during the crystallization of racemates of tris(ethylenediamine)cobalt(III) and analogues of iridium complexes are described in ref [11].

An essential element in the chain of logic to relevant homochiral biological molecules is (after successful symmetry fractures) the amplification of the very small, according to most models, enantiomeric excess. Nonlinear effects in asymmetric synthesis, the result of which is diastereomeric interactions, offer an interesting potential to considerably increase the small enantiomeric excess of a catalyst. This topic was reviewed very recently by Kagan et al.[12] Analogous amplification phenomena also result when optically enriched initial materials react ("meso-effect").[13]

A process is described as autocatalytic[14] if the product and the catalyst are identical. In an asymmetric synthesis the chiral auxiliary is normally structurally different from the chiral target material. The advantages of an asymmetric autocatalyic reaction are clear; the chiral product and the chiral catalyst do not have to be separated, they are identical. In addition no chiral source, other than the product, is necessary. The kinetics of asymmetric autocatalysis were formally described in 1953 by Frank as a model for the generation of homochirality.[15] Assuming the conditions of a "specific mutual antagonism" for the enantiomers formed autocatalytically, the system is in an unstable racemic state. A slight disturbance of the racemic composition—for example by a statistical fluctuation or because of the energy difference between the enantiomers[7]—moves the system into one of the enatiomerically pure states.[16]

An autocatalysis that amplifies the enantioselectivity was first reported by Soai et al (Scheme 1).[17] The alkylzinc complex reacts first with the optically enriched chiral alcohol. The optically active isopropylzinc alkoxide formed in situ clearly catalyzes its own formation by an enantioselective addition of iPr$_2$Zn to the aldehyde. Subsequent hydrolysis leads finally to the initial chiral alcohol, but with an increased enantiomeric excess.



Scheme 1. Amplifying asymmetric autocatalysis according to Soai et al.;[17a,b] the asymmetric autocatalyst is shown in the middle.

Today these first results do not seen overwhelming, but they could be enhanced effectively by the consequent optimization of the system to ideality.[18] Using, for example, 1-(3,3-dimethyl-1-butinyl-5-pyrimidyl)-2-methyl-1-propanol (R in Scheme 1: Me$_3$C–C≡C) leads under optimal conditions to yields of >99% and to enantioselectivities of >99.5% *ee*. When the alcohol formed is used as starting material in a subsequent cycle an amplification factor of 6×10^7 is achieved![18c]

Other "chiral initiators" can also be used, however, it is no longer an asymmetric autocatalysis in the strictest sense. Thus the conversion of the achiral compound 2-methylpyrimidine-5-carbaldehyde (R in Scheme 1: Me) with iPr$_2$Zn in the presence of L-leucine with an enantiomeric excess of only 2% (molar ratio: 1.0:2.4:0.02) produces the respective 1-propanol derivative in a yield of 82% and with an *ee*-value of 21%.[19] The alcohol produced can be "replicated" by an amplifying autocatalysis as described above. Even enantiomeric excesses as small as 0.1% in a chiral initiator ((*S*)-2-butanol) yield positive results. Racemates, naturally, only produce the racemic pyrimidyl alcohol.

Recently, enantiomorphic inorganic crystals,[20] (*d*)- and (*l*)-quartz (see Figure 1),[21a] and (*d*)- and (*l*)-$NaClO_3$,[21b]—were used very successfully as initiators for the first time by Soai et al. Yields >90% and enantioselectivities ranging from 93–98% *ee* could be attained in the known (3,3-dimethyl-1-butyl)pyrimidine-5-carbaldehyde/iPr$_2$Zn system by adding portions of the components in the presence of enantiomorphic

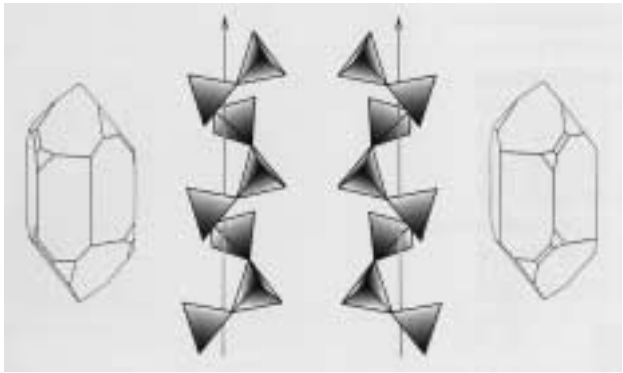


Figure 1. Macroscopic (outer) and microscopic (inner) views of the two enantiomers of quartz, (*l*)-quartz (left) and (*d*)-quartz (right). Reprinted from *Rechts oder links In der Natur und anderswo*, Wiley-VCH, Weinheim, **1999**, p. 170.

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quartz or $NaClO_3$ crystals. The chirality of the enantiomorphic crystals determines reproducibly the chirality of the alcohol generated. Mixtures from (*d*)- and (*l*)-quartz (80 % *ee*) are employed with equal success. These results are significant in two respects. First, these findings clearly demonstrate that an amplified asymmetric synthesis has occurred and that it is comparable with the example quoted in ref [12]. Second, this result is also significant for the question concerning the origin of homochirality; a possible connection between the energy difference of enantiomers from parity violation and the naturally occurring excess of (*l*)-quartz is discussed in ref [22], but ref [23] should also be studied. Whatever the contradictory opinions might be about a global excess of one quartz enantiomer,[24] it is acknowledged that there are local excesses of one of the quartz enantiomers. A discussion of the preliminary results[25] anticipates that further highly interesting relationships between crystallization and parity violation can be expected in the near future.

The subject of chirality amplification, as described above, has developed rapidly during the last few years.[26] That the newly calculated energy differences between the enantiomers of relevant biomolecules is about one order of magnitude larger than previously assumed increases the probability that the homochirality of relevant biomolecules, and consequently the origin of our existence, might be determined by an intrinsic chirality at the elementary particle level.[27]

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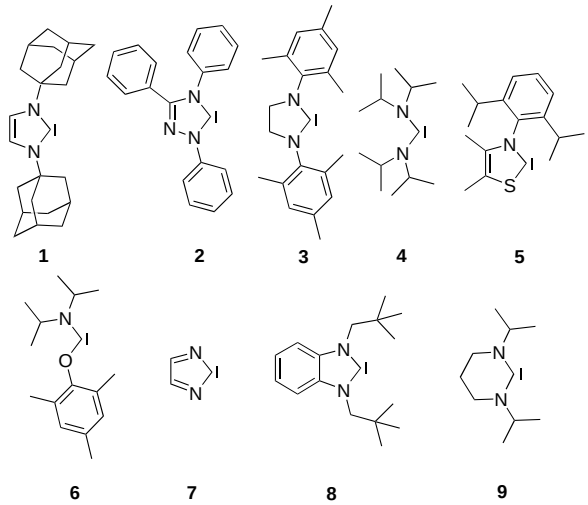
The "Wanzlick Equilibrium"**

Volker P. W. Böhm and Wolfgang A. Herrmann*

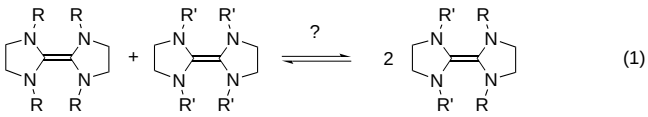
Dedicated to Professor Manfred Regitz on the occasion of his 65th birthday

Carbenes have attracted considerable attention in both organic and inorganic preparative literature due to their unique properties as reagents and reaction intermediates.[1] The isolation of a stable carbene was pursued for a long time until 1,3-bis(1'-adamantyl)imidazolin-2-ylidene (**1**) was prepared in 1991.[2] In the following years, related carbenes, such as **2** – **9**, were characterized.[3–9] Among these, imidazolidin-2-ylidenes like **3**,[2f, 10] had been postulated by H.-W. Wanzlick in 1960 as intermediates in the formation of electron-rich tetraaminoethylenes.[11] At that time, Wanzlick already suspected these carbenes to be rather stable, although they could only be identified by characteristic trapping reactions.[12] Wanzlick's assumption of an equilibrium between the carbene and the olefin [Eq. (1)] was based on simple molecular weight measurements.[11]



1 **2** **3** **4** **5**

6 **7** **8** **9**



10a **10b** **10c** (1)

Before their isolation, carbenes were seen stable only as ligands in metal complexes. The first two complexes of N-heterocyclic carbenes of type **1** were isolated independently by Wanzlick in Berlin and by Öfele in Munich in 1968.[13, 14] In the meantime, the coordination chemistry of these ligands has attracted attention: A broad scope of synthetic routes to their metal complexes was established.[15] N-heterocyclic carbenes (NHCs) were also used as ligands in the catalytic hydrosilylation.[16] It was shown that asymmetric induction is also possible with NHC ligands in catalysis.[17] However, major interest in catalysts that bear NHC ligands started when applications in ruthenium-catalyzed olefin metathesis[18–20]

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