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Review Article

On the Physical Basis of Asymmetry and Homochirality

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ABSTRACT Mirror symmetry breaking is ubiquitous in our visible universe taking place in elementary particles, atoms, and molecules. Molecular chirality is not biogenic in itself, although its detection is often considered a biosignature, a conjecture inferred from the fact that we do not know life devoid of homochirality. The question of whether there is a connection between the cosmic preference for one enantiomer, as imposed by the weak force, and the single chirality displayed on Earth is vividly debated. This article gives a glimpse on the origin of asymmetry from a cosmological perspective and on physical transformations that lead to an enantiomeric imbalance, leaving chemical reactions essentially aside. These processes are more plausible as sources of prebiotic chirality than asymmetric amplifications requiring unnatural substrates and conditions and fighting against racemization. The latter may actually be a friend, not foe, and a driving force for enantioselection. *Chirality 24:894–908, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: cosmic asymmetry; physical homochirality; phase transitions; attrition-enhanced deracemization; crystallization; sublimation; environmental conditions

INTRODUCTION

> *If Nature in her lifeless beginnings had not been fundamentally stereometric, would we have acquired from her an incalculable and immeasurable life?*
>
> Johann W. Goethe

Goethe (1749–1832), the renowned German poet and dramatist, was of course unaware of stereochemistry, although as a true polymath, he realized that morphology was a distinctive feature of living organisms (stereometry deals with forms and dimensions of solids). Goethe's reflections were certainly inspiration for some 19th century vitalists claiming the inorganic basis of biological forms.[1,2]

It was not until the late 19th century that chemists recognized the stereometric nature of molecules, with the central idea of tetrahedral carbon, thereby unveiling the existence of stereoisomers. Nature's selectivity in discriminating between enantiomeric forms of biomolecules has intrigued and puzzled scientists for generations and will continue for years to come. Within the emerging field of systems chemistry, some scholars engaged in the origin of life contend that one of the potential powers of replication in autocatalytic cycles (either genetic or metabolic) is expected to be the achievement of system homochirality.[3] Accordingly, a high degree of enantiopurity of the starting reactants might have been helpful but not necessarily a prerequisite for self-organization. Unfortunately, the question of how a chiral bias would have been incorporated into prebiotic reactions cannot easily be answered. The transformations that could have occurred in primeval stages give rise to complex mixtures and low yields of individual products. On the other hand, the vast repertoire of bench-invented asymmetric protocols or the remarkable Soai autocatalysis, capable of amplifying dramatically a low enantiomeric excess (*ee*) of the initial catalyst, would hardly be compatible with environmentally credible scenarios. Said that, asymmetric reactions certainly provide an invaluable help in understanding how the amplification process surely occurs, paving the way to biomimetic transformations.

The allure of amplification mechanisms relies on some intrinsic features of the racemic state, which can be described at the molecular level by a binomial distribution having the standard deviation $\sigma = \sqrt{N}/2$. A simple statistical analysis reveals that we have rarely true racemic mixtures and there is a tiny stochastic imbalance between enantiomeric molecules.[4] Racemization is, of course, the sword of Damocles in asymmetric autocatalysis, but it can move from foe to friend in scenarios requiring enantiomer interconversion for further selection to occur. Such models constitute a paradigmatic shift that overcomes the necessity of a stereoselective reaction. On the contrary, physical scenarios involving the coexistence of both enantiomers and

This paper is dedicated to the memory of Ronald Bentley, who passed away on 6 June 2011. His correspondence and advice were always a gift.

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controlled by thermodynamic and/or kinetic factors may ultimately lead to a single-chirality (*unichirality*)[5] state.*

This review summarizes some symmetry-breaking mechanisms in atoms and molecules within a physical, and occasionally physico-chemical perspective, that help us understand the origin of chirality on Earth and elsewhere. The asymmetry of matter at atomic and subatomic levels is a subject that deserves a comprehensive and separate treatment. However, a bit of background is introduced herein not only because it shows the cosmic significance of chirality but also because of the influence of physical fields on deracemization, which is particularly noticeable in photochirogenesis.

COSMIC ASYMMETRY AND CHIRAL INFLUENCES

The most seductive explanation of molecular chirality argues that life selected an enantiomeric bias, such as the left-handed form of proteinogenic amino acids on the basis of the fundamental asymmetry exhibited by the weak neutral force and present in interstellar light, such as circularly polarized light in the ultraviolet region (UV-CPL). Although this has not yet been established unambiguously, it is attractive enough in terms of unification between life and cosmos.

Cosmologists assume that matter and antimatter were created during the primeval explosion from pure energy with a perfect symmetry and with the unification of the four forces, including gravity (although the latter might have been an a posteriori event that fueled spatio-temporal patterns). It is believed that a few nanoseconds after the Big Bang, the electroweak interaction separated and the early universe would be in a plasma-like state. As suggested by Sakharov,[6] the abundance of matter over antimatter could be attributed to the charge-parity (*CP*) violation. This symmetry breaking resulting from the left-handedness of the weak force implies that some elementary particles and their antiparticles decay at slightly different rates.

The violation of *CP* and *T* (time reversal) symmetries constitutes a distinctive property of our universe. Only *CPT* is a true symmetry: the Hamiltonian is invariant to *CPT* even though it is not invariant to one or more of these operations. It is not by chance that since 1957, when Yang and Lee showed clear evidences on parity violation, several Nobel prizes have been awarded for shedding light into spontaneous symmetry breaking in particle physics.[7] Significant hallmarks were the prediction of the electroweak interaction (1979) or the discovery of W and Z particles (1984), which serve as commutators of weak interaction. The last prize awarded so far (2008) to Nambu, Kobayashi, and Maskawa recognizes further efforts to unveil the mechanism of chiral symmetry breaking, which is related to quark mixing.[8–10] Like leptons (electrons or muons for instance), quarks come in different flavors, and only a model with an extended family of quarks accounts for broken symmetry. Although the Standard Model of elementary particles can be familiar to a wide audience of scientists, these aspects lie obviously beyond the scope of this article. In the present territory and as we shall see in the following text, it suffices to consider *CP* violation and its implications at the molecular level.

At this stage is also convenient a break on the proper use of language regarding the terms *chiral symmetry* and *chiral symmetry breaking*, which are widely and regrettably employed in chemistry and biosciences. Both are misleading because chirality is not a symmetry at all in molecular terms. Chiral symmetry looks an oxymoron. In stark contrast, chirality denotes some types of reduced spatial symmetry that enables an object or molecule to exist in two nonsurposable mirror-image forms. Hence, *mirror symmetry breaking* is more appropriate.[11,12] However, the term chiral symmetry breaking makes sense in elementary particle physics because chiral symmetry is an internal symmetry of massless particles and has therefore no geometrical connotation. The idea that chirality may be fundamentally fuzzy deviates from its classical definition formulated by Kelvin more than one century ago. Rather, fuzziness arises from the, perhaps historically unfortunate, association of chiral with distinct states that are interconverted by fundamental symmetry operations.[13]

The existence of parity violation tells us that nature makes an absolute distinction between left-handed and right-handed spin-polarized particles, and as a result, parity (*P*) is not a true symmetry. Only parity plus charge conjugation (*CP*) interconverts a particle (or atom) and its antiparticle (or antiatom) showing equal and opposite energy values. The energy shift (E_{PV}) and hence the enantiomeric imbalance caused by parity violation in chiral molecules are extremely small (in the range from 10^{-18} to 10^{-14} J/mol at 300 K for molecules composed of the lighter elements), even far below the statistical imbalance present in a conventional racemic mixture. Parity violation also depends on several parameters, especially the nuclear charge (it is roughly proportional to Z^5), and accordingly, large differences can be computed and measured for heavy-element-containing molecules. As a typical example, the (*M*)-enantiomer of Cl_2S_2 (twisted around the S-S bond) has a E_{PV} ~10^3 times higher than that calculated for the second-row analog (*M*)-H_2O_2 (twisted around the O-O bond).[14] More importantly, the marriage between computation and experiment has come true via high-resolution laser spectroscopy capable of measuring E_{PV} for molecules containing late transition metals or heavy *p*-block elements.[15,16]

Parity-violating energy differences are likewise sensitive to structural parameters such as torsion angles, and accurate calculations have been reported recently for amino acids and *N*-methyl amino acids.[17,18] In general, gas-phase calculations predict that neutral L-configured structures are stabilized with respect to D-enantiomers; however, this trend cannot be unambiguously established in solution where zwitterionic structures are prevalent. Certainly, the level of theory plays a crucial role on ascertaining the sign and magnitude of E_{PV}, and significant differences will occur with larger molecules such as proteins or polynucleotides. The key lesson is that the tiny *ee* emerging from parity violation should not be

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[*] This manuscript uses the terms homochiral and homochirality as quoted in the original sources, although, unfortunately, the literature is often confused on the meaning and usage of such terms. Strictly, homochiral refers to a comparison of individual chiral molecules (or objects) having the same sense of chirality (i.e., L-alanine, L-cysteine, and L-serine are homochiral). The term should not be used to denote the enantiomer homogeneity of a sample (even though in some cases, there is no problem if the context is adequately placed: e.g., D-glucose isolated from plants is necessarily a homochiral substance). However, consider the improper and puzzling usage when one alludes to a homochiral peptide. In the original sense, the peptide is composed of all-D-amino or all-L-amino acid residues, but some authors allude to homochiral in the enantiopure sense, that is, to mean, for example, that the sample is enantiopure even if the peptide contains both D-amino and L-amino acids. For the sake of clarity, other terms have been introduced, and *unichiral* represents a good and valuable surrogate (see Ref. 5 for an extended analysis). The term clearly denotes substances that are single enantiomers.

neglected as source of molecular biochirality, although this conjecture needs to be verified experimentally through a realistic amplification mechanism.

The symmetry operations of *P* and *T* can be advantageously employed to recognize the chirality of objects in a given Euclidean space, especially when motion is involved. This is one of the most elegant conceptual contributions of Laurence Barron, which provides a rationale for the chirality of physical fields such as circularly polarized photons or polarized electrons.[19] There are two types of enantiomorphism for which the terms *true* and *false chirality* have been coined. The former breaks parity but not time reversal and is therefore a *time-invariant enantiomorphism*. In other words, two distinct enantiomorphous states are interconverted by *P* but not by *T* combined with any spatial rotation. This enantiomorphism is characteristic of chiral influences capable of inducing absolute asymmetric transformations (i.e., lifting degeneracy of enantiomers) in all circumstances. Conversely, a *time-noninvariant enantiomorphism* breaks both *P* and *T* separately but is *PT* invariant. Two enantiomorphous states can be distinguished, but now they are interconverted by both *P* and *T*. This sort of enantiomorphism cannot induce absolute enantioselection in a system at equilibrium, although enantiodiscrimination might be eventually observed under kinetic conditions.

As pointed out by Barron, there is a useful analogy between the quintessential ingredient of cosmic chirality (*CP* violation) and asymmetric catalysis.[19] Thus, *CP* violation lacks *CP* and *T* invariance separately, though it is *CPT*-invariant. The same occurs in falsely chiral influences that lack *P* and *T* invariance separately. Such chiral influences play the role of a chiral catalyst by modifying the energy barriers that change the rates of formation of enantiomeric products. A falsely chiral influence does not affect the equilibrium thermodynamics. Likewise, in *CP* or *T* violation involving particles and antiparticles, only the kinetics, but not the thermodynamics, is affected.

Scheme 1 summarizes the aforementioned ideas and highlights the physical effects that may actually lift enantiomer degeneracy at equilibrium, in particular, circularly polarized light (CPL; next section), vortex motion, and the combination of a magnetic field with light of arbitrary polarization (magnetochirality).

Chirality from stirring vortices has been investigated by some groups, especially by Ribó and associates who have demonstrated the importance of hydrodynamic gradients and shear forces to induce enantioselection in some supramolecular aggregates.[20,21] It is interesting to note that whereas chaotic flows lead to a racemic mixture of supramolecular species, vertical flows lead instead to scalemic mixtures. The action of vortices involves rotation plus translation and constitutes a time-invariant enantiomorphism. Bear in mind that a stationary spinning electron is not a chiral object. However, it becomes truly chiral if translating with its spin projection parallel or antiparallel to the propagation direction. The enantiomorphous states cannot be interconverted by *P* and *T* following any spatial rotation (Fig. 1).[19] This is the situation of a translating electron and a circularly polarized photon, which is always truly chiral because photons move at the velocity of light.

A magnetochiral phenomenon is cosmically plausible as well and might have contributed to small *ees* of chiral molecules on Earth and the outer space. The effect using a static magnetic field parallel or antiparallel to the propagation direction of an unpolarized light beam was proven experimentally by Rikken and Raupach in 2000 on metal coordination compounds.[22] More recently, magnetochiral dichroism has been observed for organic compounds such as porphyrin *J*-aggregates, whose enantiomers were prepared by addition of either L-tartaric or D-tartaric acid as chirality-directing agents.[23]

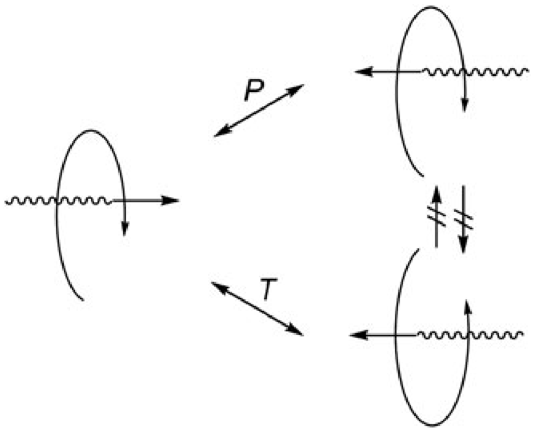
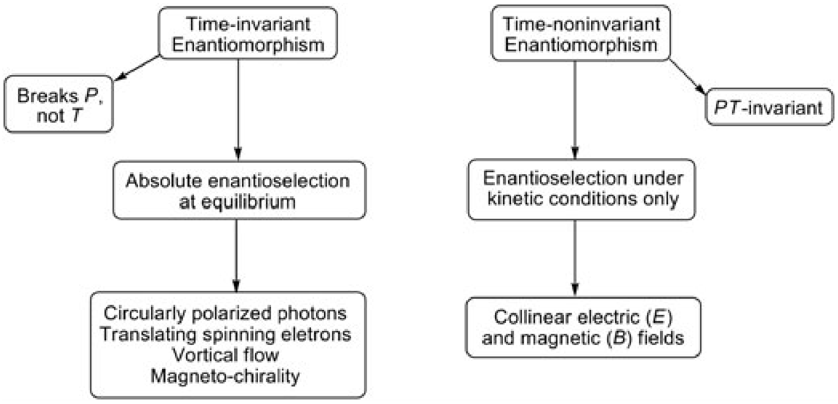


Fig. 1. Chirality of circularly polarized photons: right-handed and left-handed circularly polarized photons are interconverted by *P* but not by *T* with a further spatial rotation.



Scheme 1. Enantiomorphisms and physical fields.

A smart demonstration of enantioselective destruction of 2-butanol enantiomers by spin-polarized electrons, thus leading to a small enantiomeric imbalance (along with photolyzed side products), was reported by Rosenberg and coworkers.[24] Low-energy secondary electrons were generated by ionizing radiation (X-ray source) interacting with the organic substrate adsorbed on a magnetized Fe–Ni alloy (Scheme 2). The direction of the spin was determined by the relative orientation of the magnetic field (magnetization vector) with respect to the propagation direction of the light beam (either parallel or antiparallel). This mechanism harnessing the spin polarization of secondary electrons only requires a magnetic substrate and a source of ionizing radiation. Although it is dubious the role of this effect in astrophysical chirogenesis, the technology can also be valuable en route to enantioenriched magnetic materials.

Absolute asymmetric synthesis can be achieved by means of three independent physical fields, none being chiral in itself, such as electric fields (time-even vector) and a flat surface. This combination simply imparts directionality and may provide macroscopic chirality.[25] Although the whole effect will be negligible for organic molecules in solution, directionality can be accomplished by attaching such molecules to surfaces and interfaces.[26] Notably, soft matter as exemplified by liquid crystals can be easily aligned in electric (as well as magnetic) fields. Application of an electric field is sufficient to drive the formation of conglomerate domains from an initially homogeneous liquid–crystal racemate (smectic C phase) composed of rod-shaped molecules.[27]

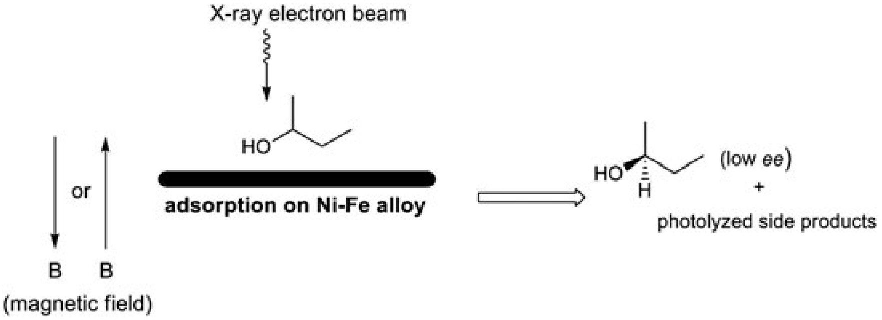
PHOTOCHIROGENESIS: THE AMINO ACID PUZZLE

Having established that CPL constitutes a truly chiral influence leading to absolute enantioselection, there have been numerous studies aimed at elucidating the different mechanisms. These results have also profound implications on how life might have occurred and how proteinogenic amino acids in particular acquired their left-handed form.

In this way, asymmetric photochemistry involving UV-CPL may be responsible for the enrichment of L-amino acids in stellar bodies, especially carbonaceous chondrites.[28] Although the physical source of CPL has long been debated, ranging from pulsars to supernovas and neutron stars, the most compelling evidence was reported nearly two decades ago by Bailey and associates from the Anglo-Australian observatory on the basis of the observation of circularly polarized infrared light in the Orion nebula, a star-forming region.[29,30] CPL is most likely produced by scattering phenomena, and unfortunately, its detection in the UV range could not be achieved. Only model calculations suggest that twisted light in the most energetic UV region, which is otherwise required to carry out asymmetric photoreactions, should also be present in the nebula.[31] Accordingly, the interaction of UV-CPL with chiral organic molecules would have afforded enantioenriched products. The existence of organic matter in space has been confirmed in recent astronomical observations and simulated interstellar/circumstellar conditions. Thus, amino acids can be photochemically generated in interstellar ice analogs by irradiating mixtures of H_2O, NH_3, CO, CO_2, and CH_3OH condensed at temperatures between 10 and 80 K.[32,33] Direct observation of molecules such as H_2O, HCN, C_2H_2, or CO_2 in regions of planet-forming disks around a young star indicates the existence of chemical precursors of life.[34]

The asymmetric formation of amino acids in space can be rationalized in terms of enantioselective photolysis by UV-CPL as well as by enantioselective photosynthesis from a mixture of achiral precursors, both processes based on circular dichroic (CD) transitions of amino acids at specific wavelengths.[35,36] Asymmetric photolysis of proteinogenic amino acids in the solid state using vacuum UV-CPL is of interest because these experiments are closer to interstellar conditions than studies in solution. Strong CD transitions have been observed between 140 and 190 nm. A few α-H-amino acids (alanine, valine, leucine, serine, and aminobutyric acid) showed the same CD magnitude and the same sign. Conversely, the CD spectra of α-methylated amino acids L-isovaline and L-α-methyl valine showed CD signals opposite to those of the α-H-amino acids, which can be attributed to conformational features that alter the corresponding electronic transitions.[37] These results suggest that twisted CPL may indeed induce a small enantiomeric imbalance in proteinogenic amino acids (Fig. 2).

Because amino acids can also be generated by vacuum UV irradiation of a mixture of small achiral molecules of prebiotic and interstellar interest, a further reasoning suggests that CPL with a twist (either left or right handed) might likewise lead to enantioenriched amino acid samples. Some successful experiments have been carried out, although they do not always simulate a real astrophysical scenario.[38] To this end, a recent and accurate investigation has shown the enantioselective formation of alanine from a condensed mixture of H_2O, NH_3, and $^{13}CH_3OH$ at 80 K and high vacuum (10^{-7} mbar) using UV-circularly polarized synchrotron radiation (Scheme 3).[39] ^{13}C-labeled methanol was employed to exclude any terrestrial contamination. Although the *ees*



Scheme 2. Enantioenrichment obtained by spin-polarized electrons and a magnetic substrate.

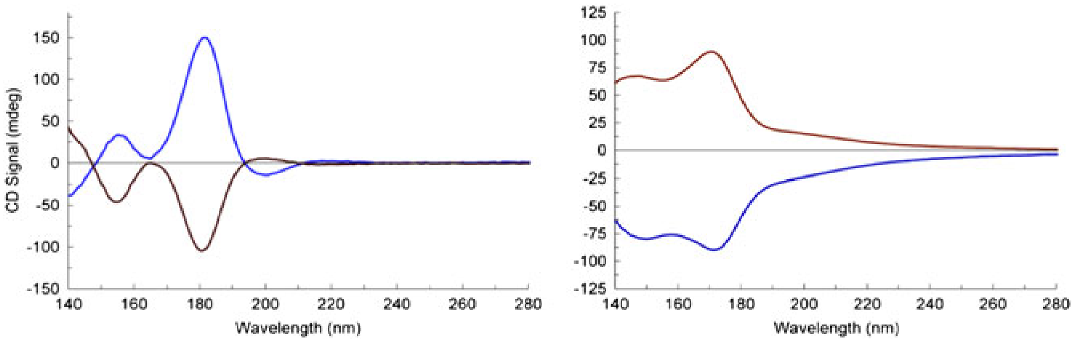
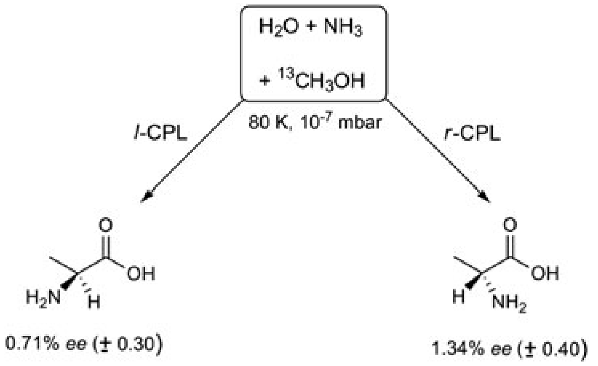


Fig. 2. Solid-state circular dichroic transitions observed for some amino acids in the vacuum UV range (between 140 and 190 nm). Left: L-alanine (top line), D-alanine (bottom line); Right: D-isovaline (top line), L-isovaline (bottom line). Reproduced with permission from Ref. 35. Copyright 2011 by Elsevier B.V.



Scheme 3. Enantioselective photosynthesis of alanine with CPL of a given helicity (left or right handed).

were certainly very small, the team confirmed that such imbalances arose from UV-polarized light as an alternative experiment with linearly polarized synchrotron radiation gave an *ee* close to zero.

Moreover, according to a recent study, peptide bonds can also be generated in the gas phase by using vacuum UV radiation at 157 nm. Such photoexcitation leads to water elimination and formation of long amino acid chains.[40] Although this approach may provide insight into astrochemical processes, gas-phase collisions are indeed rare in space, and as discussed throughout this section, photoirradiation on ice analogs and condensed phases appears to be more realistic.

Interstellar and circumstellar asymmetries are attractive enough in the context of *panspermia hypotheses*, that is, extraterrestrial delivery, particularly through meteorites and comets, as well as impacts by asteroids, which would have provided organic matter susceptible of triggering life on early Earth. Carbonaceous meteorites contain a rich variety of organic molecules, including amino acids (both proteinogenic and nonproteinogenic), and it is plausible to conjecture that the small *ees* present in such bodies would have been amplified by autocatalytic transformations after landing. This issue has long been controversial since the initial reports describing nonracemic amino acids in the Murchison and Murray meteorites.[28,41,42] Given the minute *ees* found in meteoritic samples, even up-to-date analytical techniques will not allow to establish unequivocally their indigenous provenance. Thus, the current understanding is that although L-*ee* of valine and alanine (as well as leucine, serine, threonine, and glutamic and aspartic acids) are seen in meteorite falls all the time, their extent follows the terrestrial weathering of the stones and can even be regarded as a gauge of terrestrial contamination.[43]

Does this mean that amino acids do not display very small *ees* in meteorites or that even larger ones were not there before and racemized subsequently? The point is uncertain, but the behavior of the isoleucine diastereomers in pristine meteorites would actually seem to suggest a positive answer.[44] Along with this case of diastereomeric alloisoleucine and isoleucine, collected in a carbonaceous meteorite in Antarctica, which largely escaped from terrestrial contamination, the other genuine result comes from isovaline. The *ees* found for this nonproteinogenic amino acid in meteorites are unusually high (about 15% in the Orgueil meteorite and up to 18.5% in the Murchison chondrite) and beyond the limits of UV-CPL (both terrestrial and extraterrestrial) as the only source of asymmetry. It is now assumed that aqueous transformation in the parent meteorites might have not only caused racemization of α-H-amino acids but also increased the *ees* of the α-methylated derivatives such as isovaline.[35,45,46]

Even though the extraterrestrial origin of organic matter in space objects may be indisputable, decomposition reactions before delivery would also alter the initial composition. With quantum yields of vacuum UV light, solid L-alanine deposited on the surface of a meteorite would have a half-life of about 50 days, even when only considering the energy from solar photons.[47]

Together with meteorites and interstellar dust, comets could have seeded the abiotic chemistry prior to life. This idea flourished several decades ago and has been since a recurring theme in astrochemical research.[48–50] Recent computational studies also suggest that comet shockwaves after impact could promote oligomerization reactions giving rise to higher peptides. This does mean that temperatures and pressures would be lower than once thought, and therefore, amino acids (either present on the comet or early Earth) might survive.[51]

Finally, whether the detection of only L-enriched amino acids in space samples point to a universal cosmic force that ultimately determined life's handedness, the argument remains elusive. A conclusive statement would require the detection of the same bias in other zones of our galaxy and hopefully elsewhere.[52]

DOWN TO EARTH: CRYSTALLIZATION AND ENANTIODISCRIMINATION

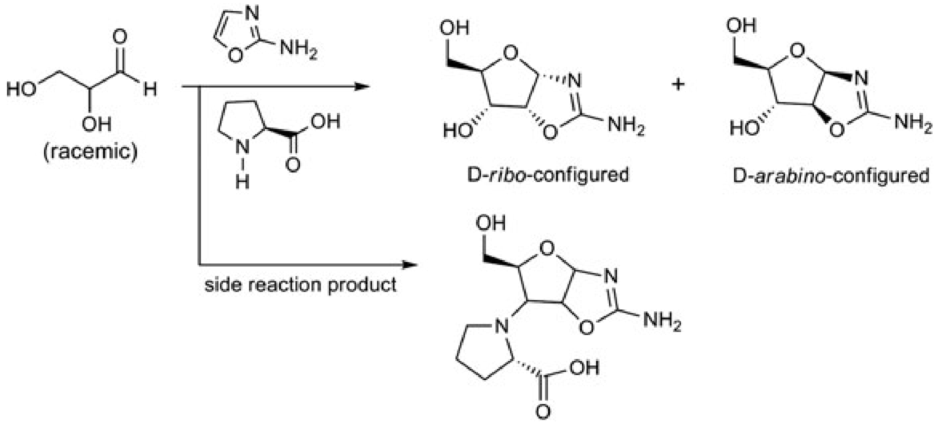
As far as we know, only living organisms have acquired a thermodynamically stable state of unichirality in their biomolecules. In fact, the extent of racemization represents a signature of death and a useful paleobiological clock for dating fossils.[53] A racemic mixture is entropically favored by a value of free energy equivalent to $k_BT\ln 2$, being k_B the Boltzmann constant and T the temperature. At a temperature of 300 K, the latter amounts to approximately 4×10^{-21} J or expressed in molar terms $RT\ln 2 = 1.7$ kJ/mole. It seems obvious that deracemization methods, being either a physical field or chemical reaction, have to supply at least several k_BT worth of energy per molecule to cause effective enantioseparation. Furthermore, entropic effects and solvent considerations are important on assessing spontaneous resolution by crystallization as any thermodynamic drive is indeed small.[54]

Enantiomer discrimination is guided by the distinctive properties of stereoisomers (racemates versus enantiomerically pure compounds). An initial enantiomeric disproportionation may eventually be amplified through a physical change involving for instance evaporation, crystallization, or sublimation because the interactions responsible for discrimination between a racemate and either enantiomer are diastereomeric in nature.[55,56] In this context, Morowitz highlighted a simple, yet thoughtful, argument in the late 1960s: "In cases where the pure isomers are more soluble than the mixture an evaporative process will serve to selectively concentrate an isomer which exists in a slightly higher concentration."[57] Thus, starting from scalemic mixtures of chiral molecules for which the racemic compound exhibits a lower solubility than their enantiomers, the solution at equilibrium will have a composition (eutectic value) incorporating the major enantiomer. Breslow and coworkers have reported significant enantioenrichment of amino acids and ribonucleosides that show a higher solubility of the enantiomer crystal.[58,59] Application of this naive strategy to key molecules such as nucleosides is remarkable, and uridine, adenosine, and cytidine can be obtained in high *ee* of the D-enantiomer. Guanosine crystallizes, however, as conglomerate and cannot be enriched in this way (the racemate is actually more soluble than the enantiomers). L-amino acids might have acted as catalysts in prebiotic reactions such as the formose condensation, thus causing a slight alteration in the D/L-glyceraldehyde ratio, which would further be amplified by slow evaporation of water that forces the racemic crystals to precipitate.[60]

Blackmond and coworkers have shown that the organocatalytic ability of some amino acids (notably proline) correlates well with the *ees* of their eutectic compositions.[61] In an independent and separate study, Hayashi *et al.* carried out dissolution and crystallization experiments with powdered L-proline (or D-proline) and DL-proline. Starting from a solid of only 10% *ee*, the resulting solutions had large *ees* (85%–99%).[62] Racemic DL-proline (but not a conglomerate) precipitates preferentially from a mixture of enantiomers in solution. Racemic crystals are considerably less soluble than the pure enantiomers as the heterochiral structure exhibits two energetically favored hydrogen bonds between adjacent proline molecules along a columnar arrangement, as inferred from X-ray diffraction analysis.[62] Likewise, a salient finding is that serine, which forms a racemic compound, has a eutectic composition of 99% *ee*. Therefore, an almost enantiopure solution will result by dissolving a nearly racemic sample of D-serine and L-serine under solid–liquid equilibrium conditions.[61] Note that this behavior of serine has nothing to do with the ability of this amino acid in forming homochiral clusters (usually octamers), which have been detected under ionizing conditions only (mass spectrometry experiments)[63] and do not exist in solution.[64]

The case of aspartic acid, a proteinogenic amino acid, is also unusual in the fact that the solution phase may afford either conglomerate crystals or a racemic compound.[65] Conversion of the former to racemic aspartic acid is dependent on both temperature and time, although the process can be inhibited with some additives. Spontaneous resolution of L-aspartic acid from the conglomerate has then been proposed as an ancestor of left-handed molecules.[66]

A clever approach that combines both chemical and physical enrichments has been shown recently by Blackmond and her group en route to RNA precursors from racemic glyceraldehyde and 2-amino-oxazole in the presence of L-proline with a small enantiomeric imbalance of 1% *ee*.[67] As depicted in Scheme 4, a side three-component reaction involving the amino acid sequesters the unnatural L-glyceraldehyde (actually a kinetic resolution), whereas the natural D-isomer reacts with 2-amino-oxazole to afford D-configured *ribo*-amino-oxazoline and *arabino*-amino-oxazoline. Crystals of enantiopure *ribo*-amino-oxazoline could be obtained from this mixture. To rule out amplification because of cryptochiral impurities, enantiopure crystals of the opposite handedness (i.e., L-*ribo*-amino-oxazoline) were produced similarly from racemic glyceraldehyde and using 1% *ee* of the unnatural D-proline. This stereoselective transformation was also carried out with other proteinogenic amino acids, although affording less enantioenriched products than proline. This protocol



Scheme 4. Chemical synthesis and physical separation by crystallization of ribonucleotide precursors.

simulating a prebiotic pool of relatively simple molecules, including amino acids with low *ees*, harnesses both a chemical amplification and enantiosegregation via crystallization. The study also represents a step forward with respect to previous efforts targeting the selective synthesis of ribonucleotides[68] or plausible routes capable of sequestering D-ribose from other sugars.[69]

Mirror symmetry breaking by spontaneous crystallization is rather unusual, but it has long been known and employed in chemical synthesis and isolation of bioactive components, and such processes involving naturally occurring molecules are indeed prebiotically relevant.[55,70,71] Autocatalytic amplification in close resemblance of the classical Frank model (each enantiomer catalyzes its own production while suppressing that of its mirror image)[72] is provided by the paradigmatic cases of $NaClO_3$ and $NaBrO_3$, which crystallize in the form of conglomerates, that is, enantiomorphous crystals of opposite handedness even if such molecules are achiral.[73] The seminal finding that stirring may lead randomly to $NaClO_3$ crystals of the same handedness convinced us that symmetry breaking takes place via secondary nuclei from a single mother crystal.[74,75] Such an efficient resolution can be applied to chiral molecules in solution or from the melt.[76] Stirring drives the system far from the equilibrium, a situation that can also be attained under other forms of agitation such as an ultrasonic field. In a recent study by Mastai *et al*., amplification experiments were conducted from supersaturated solutions of DL-threonine (an amino acid that crystallizes as conglomerate) when exposed to pulsed ultrasound irradiation.[77] This field is clearly a falsely chiral influence,[78,79] although it largely accelerates the crystallization and reduces the average crystal size. Starting from slightly enriched solutions of threonine (2.5%–5% *ee* of the L-enantiomer or D-enantiomer), a significant amplification (up to 87% *ee*) could be detected under ultrasonic irradiation.[77]

Crystal surfaces may also be the sites for enantioselective reactions, and such processes are likewise of prebiotic significance.[80] Adsorption on mineral surfaces such as calcite or quartz is plausible, and some stereoselection has been observed, although enantioselectivity is critically dependent on morphological features such as the existence of kinked structures and terraces.[81–83] Achiral crystals, in particular those belonging to the monoclinic, triclinic, and tetragonal systems, are decorated by pairs of two-dimensional homochiral surfaces of opposite handedness (i.e., enantiotopic faces). If during crystal nucleation and growth, one of these faces becomes eventually blocked by the environment (e.g., at the air–water interface), thereby leaving the opposite enantiotopic face to interact selectively with additive molecules in solution, there may be a real enantioseparation. Such enantioselective interactions also lead to morphological changes in the centrosymmetric crystals induced by the additives. With these premises, spontaneous resolution of all the racemic amino acids, with the exception of proline, was reported by Lahav and associates through enantioselective occlusion within α-glycine crystals grown at the air–water interface (Fig. 3).[84]

This process exhibits actually two basic ingredients of autocatalytic models: (1) self-recognition and (2) enantiomeric cross-inhibition. Hydrophilic and hydrophobic α-amino acids in solution inhibit enantioselectively growth of one enantiomorph only. As shown in Figure 3 when one single crystal of glycine floats and exposes its (010) face toward the solution, the enantioselective adsorption of (*R*)-amino acids will lead to a small imbalance of the (*S*)-enantiomers in solution. As a consequence, crystal growth will continue by orienting that (010) face to the solution. A similar enantiodiscrimination is observed when α-glycine exposes the other enantiotopic face to the solution, which causes adsorption of the (*S*)-enantiomers leaving an enantioenrichment of (*R*)-configured molecules in solution.

There are numerous examples describing topotactic transformations on both achiral and chiral crystals, and the reader is referred to the recent and comprehensive survey

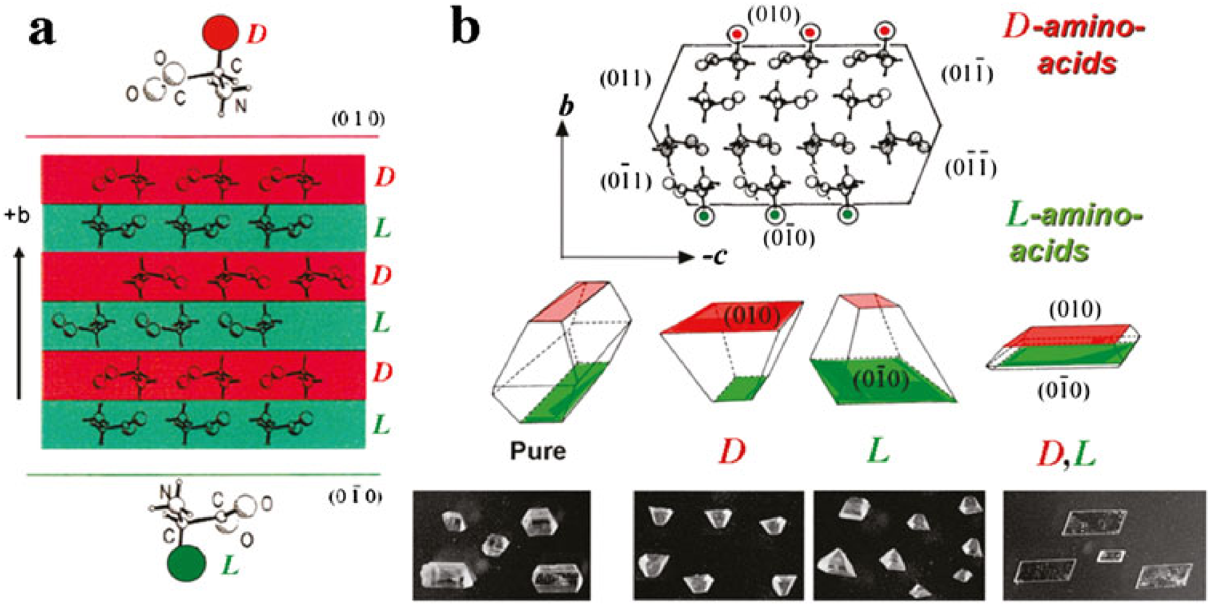


Fig. 3. (**a**) Packing arrangement of α-glycine crystals showing enantiotopic faces. (**b**) Morphologies of α-glycine crystals pure and grown in the presence of D-α-amino, L-α-amino, and DL-α-amino acids. D-amino and L-amino acids are adsorbed enantioselectively on enantiotopic faces. Reproduced with permission from Ref. 80. Copyright 2011 by the American Chemical Society.

by Weissbuch and Lahav.[80] Because this review excludes deliberately asymmetric reactions to a large extent, one might still highlight an elegant and purely physical transformation that involves a phase transition of single crystals of centrosymmetric cytosine monohydrate (achiral crystal: $P2_1/c$) into the corresponding enantiomorphous crystals of anhydrous cytosine (chiral crystal: $P2_12_12_1$).[85] The handedness of each enantiomorph is controlled by heating one enantiotopic face as detected by the solid-state CD signal (Fig. 4). Because cytosine is not chiral, the enantiomorphism arises from a helical molecular arrangement of the dehydrated crystal, which should also be dictated by the reactant crystal lattice.

DERACEMIZATION BY ATTRITION

Unlike the aforementioned cases of symmetry breaking by spontaneous crystallization, a different mechanism can also work to resolve completely a mixture of enantiomorphous crystals. A few years ago, one of us casts doubt on the necessity of a mother crystal, a question also motivated by the fact that under realistic conditions, both enantiomers of chiral molecules (or enantiomorphous crystals of opposite handedness) would have coexisted in natural systems. However, a racemic mixture of crystals at equilibrium seems to be the end of an otherwise entropically favored situation without any further evolution. In this context, the discovery of attrition-enhanced deracemization was a matter of serendipity.[86] When mixtures containing equal amounts of *dextro*-$NaClO_3$ and *levo*-$NaClO_3$ crystals are stirred with a magnetic bar, the result is invariably a racemic conglomerate, just like at the beginning of the experiments. By chance, one flask contained a magnetic bar with a ridge (pivot ring) around the center instead of a smooth stirrer bar. Surprisingly, this experiment led to one enantiomorph of arbitrary handedness. The pivot ring leaves a small space between the bar and the base, and as a result, the agitation can actually crush the crystals below the bar (Fig. 5).

Two major contributions account for this phenomenon: (1) the Gibbs–Thomson rule (small crystallites generated by fragmentation dissolve faster than the larger ones) and (2) the so-called Ostwald ripening favoring the growth of large crystals as molecules from solution will have only the choice of accreting on an existing crystal irrespective of its initial chirality. This dynamic dissolution–crystallization process can be considerably accelerated when the slurry of crystals is ground with glass beads.

The cases of $NaClO_3$ or $NaBrO_3$ crystals[86,87] can be extended to other achiral molecules forming chiral crystals such as ethylenediammonium sulfate affording enantiomorphous crystals of single handedness under grinding.[88] For the latter, the presence of additives such as amino acids may favor a particular handedness of the resulting crystals.[89] Provided that the corresponding enantiomers racemize in solution (Fig. 6), this particular deracemization of conglomerate crystals has been successfully translated into the practical scenario of chiral molecules. Examples include amino acid derivatives and other substances of pharmaceutical interest (Fig. 7).[90] It is noteworthy the application of this approach to an unprotected proteinogenic amino acid, aspartic acid.[91]

The operational protocol can be executed under different variations; especially, the presence of a catalyst is often required to promote the solution-phase racemization. It should also be mentioned that recent examples also include enantioenriched products from chemical reactions such as reversible aldol or Mannich reactions with racemic or achiral catalysts.[92,93] Such results illustrate the potentiality of this methodology; however, they introduce further complications. For instance, fast deracemization of a Mannich-type product has been observed, even though the racemization half-life time in the homogeneous solution takes long. This apparent paradox has been overcome assuming that racemization occurs quickly and predominantly at or near the solution–crystal interface, rather than in solution as commonly thought.[94]

In an elegant contribution that combines a truly chiral influence with grinding, Noorduin *et al.* have shown that CPL radiation induces symmetry breaking in a phenylglycine derivative and the resulting small *ee* can then be amplified under attrition.[95] The amino acid is, of course, a

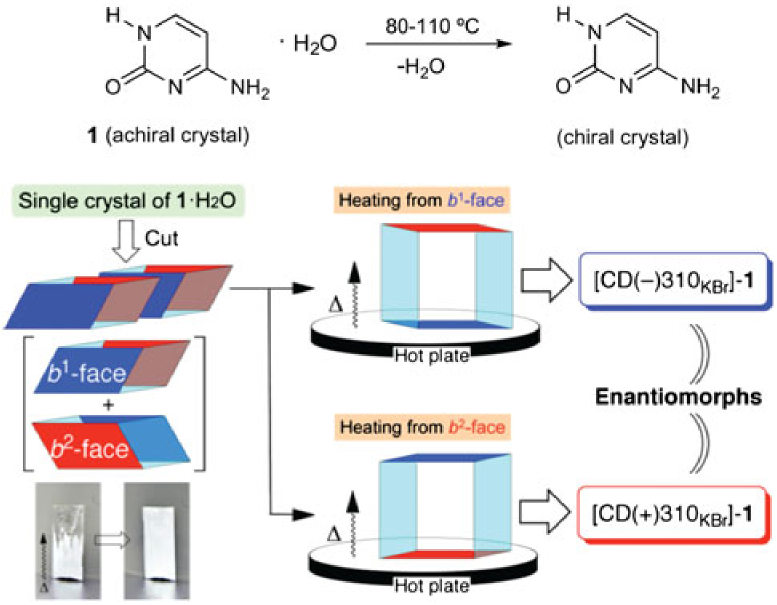


Fig. 4. Conversion of achiral cytosine monohydrate crystal into chiral cytosine crystals. The bottom figure is reproduced with permission from Ref. 85. Copyright 2010 by the American Chemical Society.

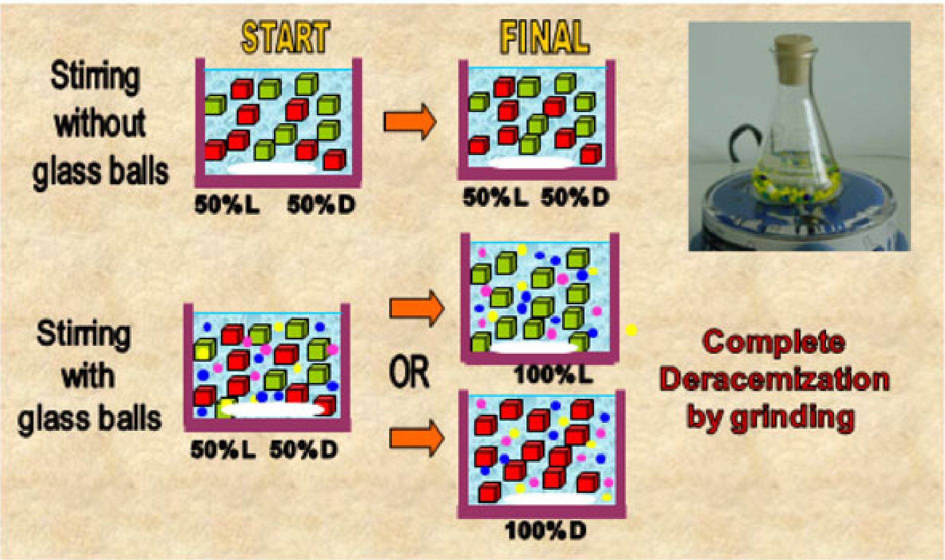


Fig. 5. Complete deracemization of $NaClO_3$ crystals by grinding.

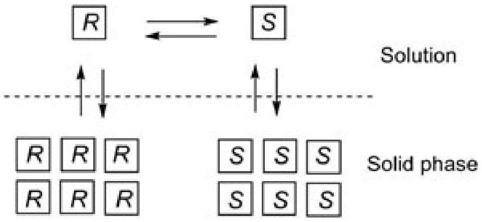


Fig. 6. Solution-phase racemization of a chiral molecule in equilibrium with solid conglomerate crystals of each enantiomer.

conglomerate that can be easily racemized in solution. The final configuration is determined by the twist of the incident radiation: *r*-CPL yields an (*R*)-configured product, whereas *l*-CPL results in the (*S*)-enantiomer. It seems that CPL generates a chiral and nonracemizable photoproduct that acts as an enantioselective crystal growth inhibitor. Thus, selective irradiation (e.g., by *l*-CPL) of a solution containing (*R*)-enantiomer and (*S*)-enantiomer in equilibrium with the corresponding solid phases leads to an (*R*)-configured inhibitor that hampers the growth of (*R*)-crystals, and as a consequence, the solid phase becomes enriched in the opposite enantiomer.

The success of the aforementioned deracemizations is dependent on the existence of conglomerates. This racemate phase can be investigated by numerous techniques, including the classical phase diagrams, which also unveil the limitations and pitfalls of preferential crystallization.[96] A recent and more innovative technique explores the advantages of second harmonic generation and its interaction with crystalline materials as demonstrated by Coquerel and his group.[97]

The search for an accurate rationale of the attrition-enhanced deracemization has been challenging from the onset. Although a satisfactory mechanism capable of explaining the whole picture has not yet been provided, it is clear that secondary nucleation cannot by itself account for the enantioselection. There are, in addition, other distinctive features relative to the classical Ostwald ripening (*vide infra*). Preliminary mechanistic studies have concentrated on modeling and kinetic understanding of simple systems such as that of $NaClO_3$ crystallization. As rightly pointed out by Skrdla

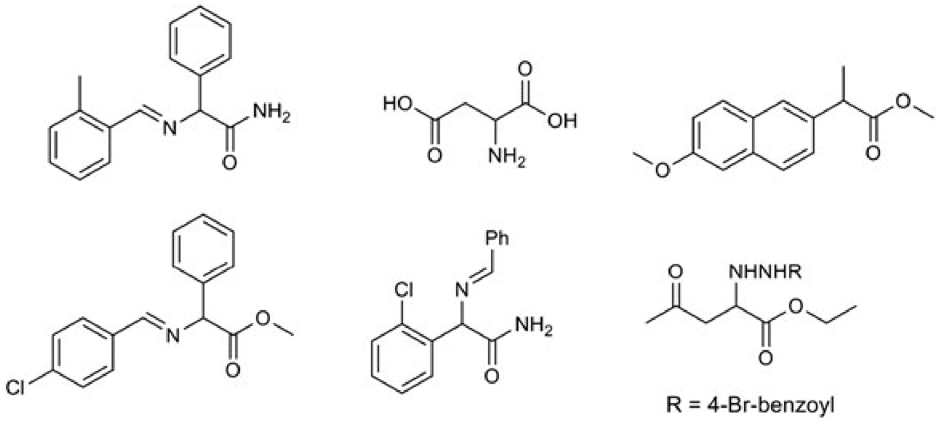


Fig. 7. Chiral molecules deracemized under abrasive grinding.

recently,[98] the literature shows that several mechanisms are possible because by altering the experimental conditions, the kinetic profiles are largely affected. The efficiency of attrition depends on parameters such as solubility, crystal size, and temperature. The system complexity also discourages a direct comparison between the results (and hence conclusions) of isothermal and nonisothermal processes as different rate-limiting mechanisms can generate a single-chirality state. Grinding accelerates the conversion of the racemic mixture into a unichiral phase as crystal breaking facilitates dissolution, thereby increasing the solution concentration (of the minor enantiomer fraction). Ostwald ripening will concomitantly produce an increase of larger crystals of the handedness in excess, and a higher surface area will also increase the possibility of secondary nucleation.

Alternatively, Uwaha and Katsuno have suggested that subcritical clusters can convey their specific chirality prior to nucleation.[99–101] This argument had been previously introduced by Addadi and Lahav, although in a different scenario involving photoirradiation of chiral crystals,[102] as well as Viedma in the preliminary experiment on grinding.[86] The model has been extended by others through the incorporation of an autocatalytic step that explains the exponential enantioenrichment.[103] Further experiments point to recognition among subcritical clusters, even though secondary nucleation and ripening may also provide a synergic effect.[104]

A different model proposed by Saito and Hyuga focuses on deracemization occurring at the surface of growing crystals.[105] Vlieg *et al.* have investigated in detail the attrition mechanism on an amino acid derivative and found a phenomenon of reverse dilution, which would represent the thermodynamic driving foce leading to a nonequilibrium crystal size distribution, unlike the equilibration process of Ostwald ripening (the authors suggest the term *Viedma ripening* instead). Thus, addition of solvent to a slurry under grinding increases the concentration in the solution of the minor enantiomer in the solid phase. After racemization, the solution drives molecules towards the chirality of the major enantiomer in the solid phase. These results, at least in that case, contradict the hypothesis of an enhanced surface racemization as the *ee* of the solution would be zero without racemization. However, this team also suggests that surface-assisted racemization might play a certain role with the incorporation of clusters forming the basis of the deracemization mechanism.[106] Recently, Saito and Hyuga have moved to the idea of cluster growth based on Monte Carlo simulations.[107,108]

A mathematical analysis has scrutinized the $NaClO_3$ situation where chiral clusters compete for achiral material through aggregation and fragmentation and without any interaction between clusters of opposite handedness.[109] The smallest clusters leading to a chiral state might be tetramers, although a racemic state would also result in long-time limits. Truncation at hexamers would instead lead to a final steady state with one handedness dominating the reaction mixture. The model also extrapolates the experimental and temporal conditions of the seminal article[86] to prebiotic conditions, thus, estimating that symmetry breaking might be accomplished within a time scale of about 10 million years. The study does not take into account the time required to obtain a small *ee* (5% in Viedma's experiment), which could emerge from stochastic fluctuations or amplification from parity violation. On assuming such requisites, the process would still be credible within a geological scale.

Recently, a kinetic study shows that attrition of conglomerate crystals follows a sigmoidal conversion rather than a first-order (simple exponential) mechanism.[98] This modeling supports that nucleation is the rate-limiting step in Viedma-type deracemizations and such a nucleation should be secondary, not primary. Unlike the equilibrium provided by the classical Ostwald ripening, it is clear that attrition leads to a nonequilibrium situation involving formation of secondary nuclei and/or chiral clusters as the critical steps of the deracemization process. Moreover, grinding supplies a continuous energy input for crystal disintegration, which also facilitates dissolution and further growth by Ostwald ripening.

The last theoretical study released so far evidences that Viedma's ripening is a complex issue, and all the mechanisms might have an effect.[110] However, both size-dependent solubility and agglomeration are necessary conditions for deracemization to occur. Attrition in itself is not necessary but does significantly increase the deracemization rate. The latter point was indeed exemplified by the deracemization of aspartic acid under heating, which proceeded as efficiently as that with glass bead-assisted attrition.[91] The evolution of the *ee* without grinding was not exponential with isothermal heating to 105 °C. In that case, there should be less than exponential growth of the major isomer's crystal surface, while the thermal acceleration in the presence of glass beads should be ascribed to the activation of the solution-phase racemization.

SUBLIMATION: THE OVERLOOKED PATHWAY

Sublimation is a *Cinderella* process in our planet because under standard conditions, only a relatively small number of molecules are volatile enough to undergo sublimation. Furthermore, chemistry and physics on the terrestrial biosphere are dominated by water and aqueous reactions, and as a result, sublimation effects are difficult to distinguish from those of melting. However, on frozen planets under vacuum or low atmospheric pressure, sublimation is of primary importance in the understanding of landforms and certain textures observed on the surface.[111] Thus, ice sublimation is ubiquitous in the solar system, whereas CO_2 sublimation would only be possible in the coldest locations. Sublimation of other condensed gases such as SO_2 is also thermodyanically possible, although SO_2 is indeed a rare material in the solar system (e.g., the Jovian moon Io).

Sublimation of extraterrestrial organics does likewise constitute an astrophysically relevant process, much more plausible than crystallization.[46] Amino acids can be isolated from natural samples by sublimation under partial vacuum, even at elevated temperatures without appreciable racemization or decomposition.[112] Examples of enrichment after sublimation were gathered in the classical book of Jacques, Collet, and Wilen, although some data and interpretations are confusing.[113] Recent investigations illustrate the scope and potentiality of the technique to obtain enantioenriched molecules.[114] For instance, Soloshonok and associates reported the isolation of almost enantiopure samples after sublimation of (*S*)-α-(trifluoromethyl)lactic acid of lower *ee*. It is interesting to note that the racemate sublimed prior to either enantiomers, which can be rationalized in terms of crystal packing and density.[115] In a subsequent study dealing with amino acids, Feringa and coworkers obtained significant *ees* after sublimation; leucine with an initial 2% *ee* (an imbalance otherwise available via CPL photolysis) could be enriched up to 40% *ee*.[116] In most cases the results correlate well with the *ee* of the eutectic composition,[114,117,118] although this interpretation is not a general rule and depends on both the substrate and experimental conditions.[118,119] Moreover, there is an interplay of thermodynamic (energy or stability of crystals) and kinetic features (e.g., crystal shape), at least with some fluorinated derivatives.[120]

Although the term "resolution by sublimation" has been invoked,[113] it is obvious that separation of enantiomers cannot be achieved by sublimation; rather as correctly stated by Soloshonok, the process implies separation (or self-disproportionation) from *the excess enantiomer* by sublimation.[120] In this context, and as strange as there may be, the preceding examples do not amplify the *ee* at all; they represent cases of fractional sublimation or stereoisomer disproportionation because of the differences in vapor pressure between the racemate and the enantiomerically pure compound.[55] The preferential vaporization of an enantiomer relative to that of the racemate was demonstrated in the early 1970s by mass spectrometry with differential isotopic labeling of the two enantiomers.[121] Furthermore, another drawback of the examples reported so far is that only a small amount of starting material is scrutinized to assess either enhancement or depletion of the *ee*.

What if one were able to sublime the whole mass and not only a small fraction? After examining sublimation of various amino acids at high temperature, surprises came with valine. This substance, which crystallizes as a racemic compound, converts into a conglomerate phase by sublimation.[122] This behavior is unprecedented in amino acids, although such a conversion has been apparently reported for a norbornenol derivative.[123] Because a conglomerate is required for spontaneous resolution, the sublimed alcohol had indeed nonzero optical rotations consistent with a partial enantioenrichment. Unfortunately, the nature of the starting racemate was unclear, thus, hampering a conclusive statement;[55] it was just claimed that the nonsublimed material exhibited no optical rotation.[123]

In stark contrast, the situation of valine is unambiguous, and X-ray powder diffraction witnesses the conversion into a conglomerate under such a thermal treatment. More importantly, when started from scalemic mixtures (with an initial 40% *ee*), the conglomerate undergoes further enantioenrichment, which is particularly relevant in the front line (Fig. 8, left). This amplification also takes place in open flasks (with less enrichment nevertheless), a fact that disagrees with a rationale based on the eutectic behavior. Mechanistic studies are under way, and like in attrition-enhanced deracemization, the intermediacy of subcritical clusters and flask surface-mediated enantiomerization cannot be excluded.[122]

IS THERE ANY OTHER PHYSICAL ENANTIOSEPARATION AT THE BOTTOM?

One should invariably ask the pioneers regarding the possibility that other purely physical processes or phase transitions can change an initial enantiomeric composition, which might also be plausible under environmental conditions.[55,56] Together with crystallization or sublimation, distillation would represent the next choice. However, early examples reported insignificant variations, and it was concluded that an enantiomerically enriched mixture will remain unaffected by distillation.[124] Recent research conducted on certain substrates, especially fluorinated compounds, clearly contradicts this assumption.[125–127] Thus, distillations of (*S*)-isopropyl 3,3,3-trifluoro-2-hydroxypropanoate, its racemate, and scalemic mixtures of varied *ee* have been explored and show that resolution is indeed possible. A sample having 20% *ee* has a boiling point of 115 °C, which is markedly different from those of the racemate (93 °C) and the pure enantiomer (136 °C).[126] The authors suggest that enantiodiscrimination by distillation in the case of trifluorolactates can be ascribed to a hydrogen-bonding network in the liquid state.[127]

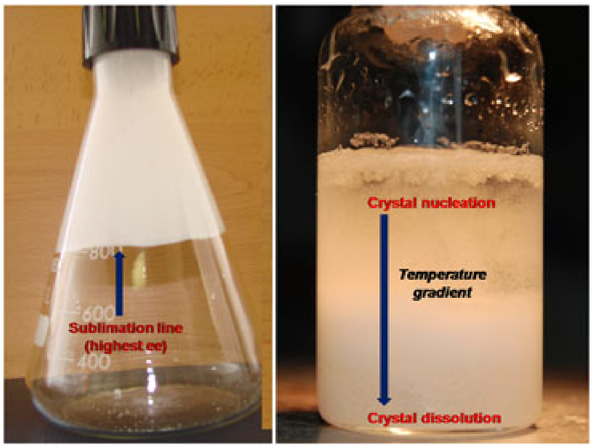


Fig. 8. Two distinctive and complementary physical processes; left: high-temperature sublimation of valine crystals in a capped flask. A racemic compound undergoes conversion to the conglomerate phase. Further amplification of *ees* occurs when the process begins with an enantioenriched sample (excess of either L-valine or D-valine). Right: deracemization of $NaClO_3$ crystals in a boiling mixture because of a temperature gradient that promotes continuous dissolution and crystal nucleation.

A final unichiral state can also be attained during crystallization of $NaClO_3$ from boiling solutions.[128] This constitutes a Kondepudi-type experiment where stirring has been replaced by a thermal gradient that leads to a system far from equilibrium. We wondered whether, like in abrasive grinding, a racemic mixture of enantiomorphous crystals could coexist in a boiling solution. Using again the rewarding $NaClO_3$ model, we have shown that equal populations of *dextro*-$NaClO_3$ and *levo*-$NaClO_3$ crystals evolve randomly to a solid phase of single handedness provided that a temperature gradient along the flask is warranted.[129] The latter induces a dynamic cycle of dissolution and crystal growth (Fig. 8, right). At first sight, one might envisage a certain abrasive effect in a heterogeneous mixture at reflux, thus, being a variation of the glass bead-assisted attrition. However, it was explicitly verified that agitation had a detrimental effect as the thermal gradient vanished, thereby avoiding crystal recycling. As a result, the mixture remains racemic. Moreover, it was also feasible to stir the boiling mixture without any noticeable grinding, which led newly to a racemic system of large enantiomorphous crystals. Clearly, neither a temperature gradient nor the subsequent nucleation could be accomplished under such conditions.

Although differences may be negligible, any property capable of distinguishing a racemic compound from the corresponding pure enantiomers can be potentially employed for enantioenrichment. According to Wallach's rule (not general in any case), solid-state racemic compounds are on average denser than their enantiomers. By bearing this idea in mind, separation of racemate from excess enantiomer has been reported in the case of alanine (20% *ee*) using density gradient ultracentrifugation.[130]

Finally, the effect of pressure on phase equilibria remains largely underestimated, albeit as predicted again by Jacques, Collet, and Wilen,[56] and an increase in pressure should affect the inequality of the specific volume between the racemic compound and the pure enantiomers. With thermodynamic arguments, a research team has shown recently that enantiomer resolution of mandelic acid would be possible at approximately 0.64 GPa and 460 K (at such conditions, the conglomerate becomes more stable than the racemic compound), which should be technically feasible.[131] However, pressure does not necessarily change the racemate structure. In an attempt to increase the density under pressure and validate the Wallach rule, the crystallization of racemic *trans*-1,2-diaminocyclohexane (a useful ligand in catalysis) has been studied under pressure.[132] Up to 2.04 GPa, this substance crystallizes as an enantiomer conglomerate, thus, contradicting the general rule that racemic compounds tend to be denser. The preferential conglomerate crystallization occurs at ambient pressure because of molecular arrangements in the crystal lattice, and high pressure enhances the close packing still further.

CONCLUSIONS

Symmetry breaking appears to be a constant and universal feature embedded in the intimate nature of matter. Through purely physical processes that involve interaction of radiations with interstellar or circumstellar organic matter, enantiomeric imbalances are generated and could have survived via meteorites or comets. We cannot assume that biochirality in our modest and small planet is rooted in such a tiny asymmetry of cosmic origin, although this point constitutes a sound and plausible hypothesis that deserves restless attention. A satisfactory conclusion will likely remain a long way off. Like in space, we have learned that physical transformations involving phase transitions and harnessing stereoisomer discrimination can lead to substances of single chirality.[133–135] Of particular importance is the idea that racemization may actually be the driving force for enantioseparation. One could reasonably conceive a scenario where such processes took place and evolved prior to the existence of biochemical reactions. In addition, these protocols simplify enormously the production of enantiomerically pure substances and can be adapted to the pharmaceutical industry to obtain unichiral drugs. Perhaps, life cannot be anything but chiral; a physical touch may help a lot.

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