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Non-stochastic spontaneous symmetry breaking: What kind of weak asymmetric forces is propelling?

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Abstract

We give a survey over recently published laboratory experiments on mirror-image chemical processes - inclusively new studies - that are mainly related to aggregation and crystallisation effects and have in common the observation of unexpected non-stochastic behaviour. While the outcome of these experiments should be rationally predicted as stochastic, *i.e.* to produce a statistically equal amount of left-handed and right-handed molecules or entities, the laboratory observations demonstrate in various cases exactly the contrary: one enantiomeric form arises persistently in significantly higher amounts than the other. These processes describe non-stochastic mirror-symmetry breaking and are related to far-from-equilibrium autocatalytic dynamics. The puzzling non-stochastic effects are often attributed to the presence of unknown chiral impurities mainly coming from the bio-organic environment. However, there is some indication that the impurity supposition not always holds, so that other influences such as the parity-violating energy difference (PVED) or other unspecified physical factors in combination with nonlinear kinetics should be additionally taken into account.

Key Words: chirality, mirror-symmetry breaking, non-stochastic behaviour, crystallisation

I INTRODUCTION

The word *chiral* was coined by Lord Kelvin in 1894. It is derived from the Greek word *kheir* that stands for *hand*. In chemistry, chirality is most often related to molecules bearing an asymmetric carbon atom. From the stereochemical point of view, if the four substituents of a carbon atom are all different, the corresponding structure is non-superimposable onto its mirror image, *i.e.* the molecule is chiral and occurs in two enantiomeric forms [Dutta and Gellman

(2017)]. As polarized light passes through a solution of chiral molecules, the rotation of the plane of polarization may be either clockwise (shifted to the right) or anticlockwise (shifted to the left) depending on which enantiomer, dextrorotatory (d) or levorotatory (l), is dominant. The enantiomeric excess (ee) reflects the degree of amount to which a sample contains one enantiomer over the other.

$$ee = (l - d) / (l + d) \quad (1)$$

For a racemic mixture $ee = 0$, while for an enantiomerically pure substance $ee = 1$.

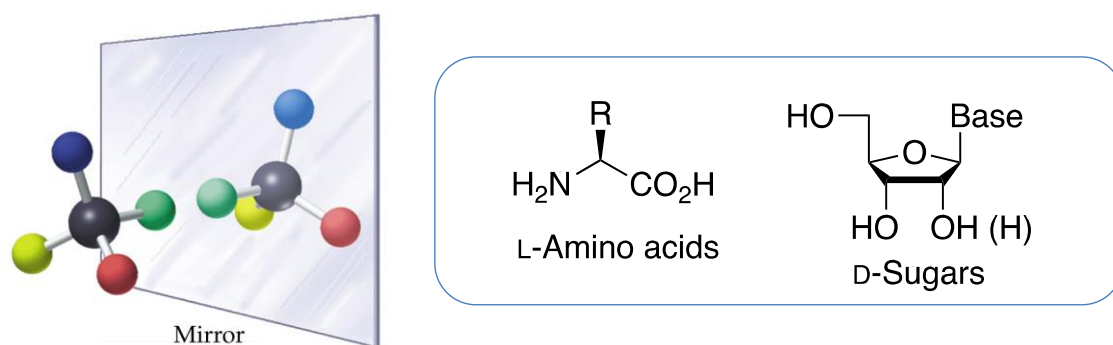


Figure 1. Molecule with an asymmetric carbon atom. The corresponding structure is non-superimposable onto its mirror image (left). Biopolymers are almost exclusively composed of L-amino acids (proteins) and D-sugars (nucleic acids) while their mirror images are missing in the natural world (right).

Most of the organic biomolecules such as amino acids and sugars are chiral and more interestingly, they are enantiomerically pure, occurring in only one of the two possible enantiomeric forms. Such a bias for a single handedness is viewed as among the most noteworthy natural features. Moreover, it is generally accepted that absolute chiral homogeneity was essential for the origin of life and that self-replication and biopolymerization would have been impossible without it [Bonner (1995); Siegel (1998); Podlech (2001); Cintas (2002); Weissbuch and Lahav (2011)].

The occurrence of biomolecules as only one of the two possible enantiomers, left-handed or right-handed, is an appealing example of mirror-symmetry breaking that has long captivated the scientific community. Mirror-symmetry breaking occurs when a non-equilibrium physico-chemical process such as crystallization, aggregation or chiral autocatalysis spontaneously generates a large excess of one enantiomer over the other [Viedma (2007)].

The origin of homochirality of the biomolecules is still a puzzling question. Abiotic theories consider both chance and determinate mechanisms. Among the determinate mechanisms, an energy difference between enantiomers has to be considered. This difference, also called parity-violating energy difference (PVED), is produced by the weak force, one of the four fundamental forces: electromagnetic, weak, strong, and gravity. Although extremely tiny (about $10^{-16}kT$), this force is universal and acting consistently in the same direction everywhere and continuously [MacDermott (2012)]. According to Kondepudi and Nelson (1985) such a difference could be sufficient to drive an amplification model system to homochirality, provided a sufficient waiting time during the amplification process. Moreover, some

correlations between the biological handedness and the sign of the PVED are supported by various gas-phase quantum calculations.

On the other hand, as it has been pointed-out by stochastic analysis [Lente (2006); Avalos *et al.* (2010)], random choice could be also a solution because as it is claimed, the indiscriminate fluctuations could be sufficient to wipe out any tiny bias. In this last case, we do not need PVED to account for the emergence of biological homochirality, the observed handedness of life is fortuitous.

Here, we report a series of recently published laboratory experiments, which seem to behave in a way similar to the biological homochirality: they give rise to spontaneous mirror-symmetry breaking, they exhibit a chiral sign selection and a particular handedness excess, in other words, they are unexpectedly non-stochastic.

Before going further in the analysis of these chiral bias, let us develop some classical elements related to chirality and chemistry.

II CHIRALITY and CHEMISTRY

2.1 Classical asymmetric synthesis

The preparation of enantiopure chiral compounds is highly desirable in the chemical industry, especially in the pharmaceutical sector. Enantiomers often smell and taste different and, moreover, can have dramatic differences in their biological action. The formation of a specific enantiomer is often performed by asymmetric synthesis.

In the early years, such synthesis was difficult to achieve, because left-handed and right-handed enantiomers tended to be produced in equal amounts if the process was not sufficiently directed, leading to a racemic mixture.

Enantioselective synthesis can be achieved by using chiral catalysts that favour the formation of one enantiomer over the opposite. Since the pioneering works of Noyori (2008), Knowles (2002), Sharpless (2002) and Kagan (2001), catalytic asymmetric synthesis has reached a mature age and high yields and high *ee* are nowadays more easily reached.

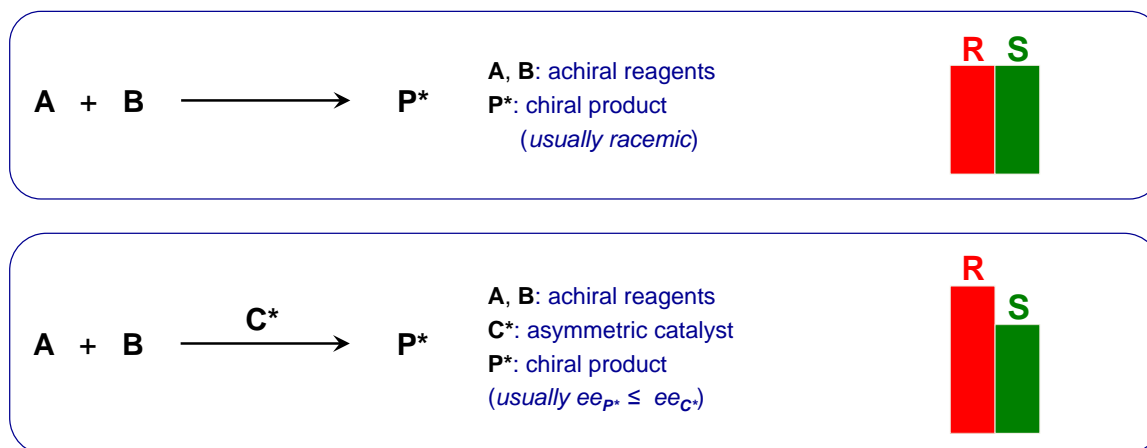


Figure 2. The generation of chiral molecules from non-chiral substrates usually leads to a racemic mixture of the chiral product (case 1, $R = S$). The use of a chiral catalyst with a certain enantiomeric excess (ee_C) can introduce an enantiomeric excess (ee_{P^*}) in the chiral product molecules (case 2, $R \neq S$).

On the other hand, general experimental expectancy and thermodynamic theory shows that when a chiral compound is formed from achiral precursors in the absence of enantiomerically pure chiral compounds or asymmetric physical fields, a racemic mixture is obtained [Barabas *et al.* (2007)]. While this statement applies to catalytic reactions, it does not still hold true when dealing with autocatalytic reactions. This is the case of so-called *spontaneous absolute asymmetric synthesis* where chiral asymmetry is generated through an autocatalytic process. Hence, spontaneous absolute asymmetric synthesis goes along with mirror-symmetry breaking.

2.2 Frank's mechanism

In 1953, Frank suggested a mechanism for spontaneous mirror-symmetry breaking [Frank (1953)]. The so-called Frank model is composed of an enantioselective quadratic autocatalysis, coupled to a mutual inhibition. An achiral reactant A turns into chiral products, R and S. The system is open such that the achiral reactant A is supplied from outside and its concentration is kept fixed.

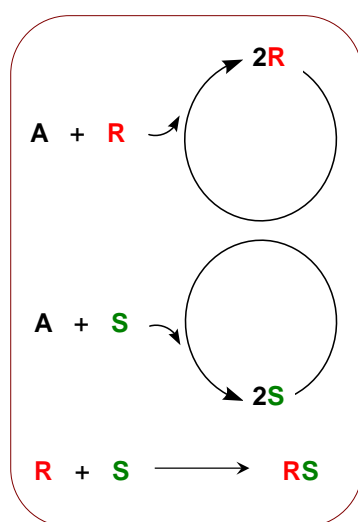


Figure 3. Principle of the Frank model where the achiral reactant A generates autocatalytically the product enantiomers R and S. Mutual inhibition leads to the formation of the heterochiral dimer RS.

The purpose of the mutual inhibition (racemate elimination) is to increase the *ee* [de Min *et al.* (1988)]. On the other side, the matter lost during the elimination is replenished by its own reproduction through the autocatalytic steps. These conditions lead to the dominance of the enantiomer originally in slight excess and in the disappearance of its antipode. Let us now develop briefly the mathematics of the Frank model [Saito and Hyuga (2013)]. The time evolution of the concentrations of the two enantiomers R and S is described by the following differential equations:

$$d[R]/dt = k_a[A][R] - k_i[R][S] \quad \text{and} \quad d[S]/dt = k_a[A][S] - k_i[S][R] \quad (2a \ \& \ 2b)$$

where k_a and k_i are the autocatalytic and the inhibition rate constants, respectively.

In an open system, [A] is kept constant since it is assumed that the achiral substrate A is supplied continuously. It can be simply seen that the steady state is racemic:

$$[R]_{ss} = [S]_{ss} = k_a[A]/k_i \quad (3)$$

However, this racemic steady state is unstable. From the rate equations it is easily demonstrated that the difference between the enantiomer concentrations, $[R] - [S]$, diverges exponentially:

$$d([R] - [S])/dt = k_a[A]([R] - [S]) \quad (4)$$

then

$$([R] - [S]) = ([R]_0 - [S]_0)\exp(k_a[A]t) = \alpha(t) \quad (5)$$

where $[R]_0$ and $[S]_0$ represent the initial concentrations of R and S, respectively.

If there is at the beginning a small chiral bias ($[R]_0 - [S]_0 \neq 0$), $([R] - [S])$ is amplified until the withdrawal of the minor enantiomer.

On the other side, from the same rate equations, the evolution of the enantiomeric ratio $[R]/[S]$ can also be reached in the following manner (from 2a and 2b):

$$(d[R]/[R] - d[S]/[S])/dt = k_i([R] - [S]) \quad (6)$$

then

$$d(\ln([R]/[S]))/dt = k_i([R] - [S]) \quad (7)$$

or

$$d(\ln([R]/[S]))/dt = k_i([R]_0 - [S]_0)\exp(k_a[A]t) \quad (8)$$

which can be integrated to:

$$[R]/[S] = ([R]_0/[S]_0)\exp\{(k_i/k_a)([R]_0 - [S]_0)[\exp(k_a[A]t) - 1]\} = \beta(t) \quad (9)$$

These two analytical functions $([R] - [S]) = \alpha(t)$ and $[R]/[S] = \beta(t)$ completely define the mode of evolution of the Frank model, which appears intrinsically unstable.

The enantiomeric excess is:

$$ee(t) = (\beta - 1)/(\beta + 1) \quad (10)$$

and the total chiral matter is:

$$([R] + [S]) = aee \quad (11)$$

When $t \rightarrow \infty$, $\alpha \rightarrow \infty$, $ee \rightarrow 1$.

Various comparable mathematical models, where autocatalytic loops with amplifying (autocatalytic) and inhibitory roles provide positive and negative feedback, were subsequently proposed [Decker (1974); Bonner (1995); Iwamoto (2002); Plasson *et al.* (2007); Crusats *et al.* (2009); Ribó *et al.* (2014); Stich *et al.* (2016)].

The theoretical Frank model has stimulated numerous organic chemists aiming at the discovery of the ultimate asymmetric synthesis [Stich *et al.* (2016)]. Until 1995, no chemical reaction has so far been invented or discovered to generate enantioenrichment according to that model [Avalos *et al.* (2010)].

2.3 Soai's reaction

The autocatalytic Soai reaction [Soai *et al.* (1995)] provided the first experimental proof-of-concept that amplification of enantiomeric excess could arise from a small initial imbalance via autocatalysis [Hein *et al.* (2013)]. The reaction consists of the asymmetric addition of diisopropylzinc to achiral alkynyl pyrimidine aldehydes in which the resulting chiral pyrimidyl zinc alkoxides serve as catalysts for their own formation.

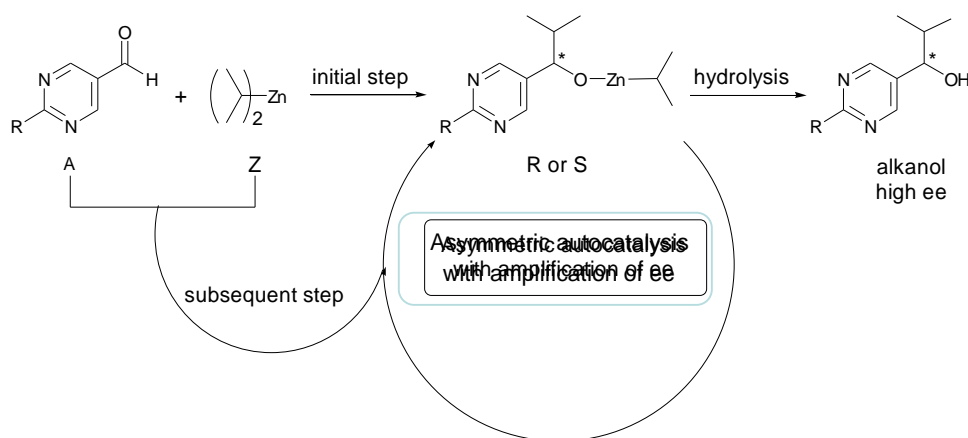


Figure 4. The autocatalytic Soai reaction featuring asymmetric amplification and spontaneous mirror-symmetry breaking.

The Soai group performed extensive studies on this reaction, revealing many appealing details and evidencing a sound *ee* amplification power. For instance, amplification can be reproducibly performed using a large variety of chiral sources such as organic or inorganic chiral crystals and even the subtle chiral effect provided by isotopic substitution [Soai *et al.* (2018)].

Virtually every described chiral additive becomes successful, thus providing *ee* amplification in conjunction with an almost quantitative yield. This extreme sensitivity originates from another extraordinary feature: namely, the Soai reaction is able to display spontaneous mirror-symmetry breaking by yielding enantiomerically enriched pyrimidyl alkanols even in the absence of any external chiral influence and starting with entirely achiral conditions. It then appears that the Soai reaction corresponds to a kinetically controlled absolute asymmetric synthesis that can be described within the framework of a Frank-like network [Ribo *et al.* (2014); Noble-Teran *et al.* (2018)].

This spontaneous symmetry breaking could be rationalized by the fact that in the beginning of the reaction the two enantiomeric products are submitted to small statistical fluctuations giving rise to a tiny *ee* [Mills (1932)]. Such small *ee* is then powerfully amplified by the asymmetric autocatalysis. Under these conditions a stochastic distribution of the R- and S-pyrimidyl alcohols, *i.e.* the product enantiomers, is expected.

To check this hypothesis, a systematic analysis of the Soai results has been carried-out by Barabas *et al.* (2007, 2015). Careful data analysis has been performed on the data of two independent articles by the Soai group. The first provides 37 experiments “without adding chiral substances” [Soai *et al.* (2003)] and the second reports 84 experiments “in the presence of achiral silica gel” [Kawasaki *et al.* (2006)], *i.e.* both series of experiments were performed

under achiral initial conditions. Although the first series of experiments shows some interesting tendencies, the authors could not arrive at conclusive statistical results. On the contrary, the second experimental series, affording 39 R- and 45 S-excesses, has been shown to represent two distinct and non-symmetric sets with different non-Gaussian distributions. In this case, a clear S preference was found with $ee_S = 73.4 \pm 23.6$ and $ee_R = 59.3 \pm 24.02$. Singleton and Vo (2002) and Gridnev *et al.* (2003) also reported an S-biased non-random distribution of enantiomers even without any chiral inductor added.

The reason for the observed S preference could be either chemical (chiral impurities of unknown origin) or physical (e.g. PVED or other chiral physical factors), without being able in the present time to draw the necessary conclusions from this analysis. Choosing between these two possibilities requires additional experimental and theoretical efforts. However, if the S-preference holds true, it would have a far-going significance [Barabas *et al.* (2015)] that could be identified in other areas, *i.e.* beyond the scope of pure molecular chemistry.

III CRYSTALLIZATIONS and AGGREGATIONS

A spontaneous resolution can occur during conglomerate crystallization. Roughly 10% of racemic chiral compounds crystallize as conglomerates when an enantiomer of a substance has a much greater affinity for the same enantiomer than for the opposite one. It results a mechanical mixture of enantiomerically pure crystals, for instance (RRR..) crystals and (SSS..) crystals. On the contrary, the 90% remaining substances crystallize mainly as racemates, for instance (RSRSR...) crystals or identically (SRSRS...) crystals.

A careful literature survey on conglomerate crystallization shows that, during spontaneous resolution, a number of researchers have observed anomalies in the behaviour of enantiomers [Shinitzky and Deamer (2008)]. They do not fit the expectation of stochastic (random or 50/50 coin tossing) distributions. In order to illustrate this idea, let us describe some representative examples.

3.1 the CuCl/triallylamine coordination system

When neat tri-allyl amine (taa) and CuCl were allowed to react without stirring at room temperature, monoclinic crystals of helical $[Cu_4Cl_4(taa)_4]$ were obtained by Vestergren *et al.* (2004). Out of five batches, three led to P-1 crystals and two M-1 crystals, indicating a stochastic behaviour. Conversely, when all CuCl was dissolved by heating before crystallization, only P-1 helices were obtained as it was demonstrated from the CD spectra of bulk samples.

The authors conclude that more experiments are obviously needed to confirm the reality of these non-stochastic homochiral crystallizations. On the other side, if they are aware that their reactions take place in a cryptochiral environment, they also recognize that if many compounds can be shown to exhibit the same behaviour, the observed chiral bias might have had something to do with a prebiotic mechanism linked to the origin of homochirality.

3.2 the cobalt thiophenic acid bipyridine coordination system

Another remarkable example has been found in the field of organometallic complexes. Namely a non-random distribution of chiral cobalt phosphonate from achiral precursors in the absence of chiral inducers has been described by Gao *et al.* (2016). The cobalt thiophenic acid bipyridine complex exhibits a 3D chiral metal phosphonate framework built from achiral ligands in the absence of any chiral source.

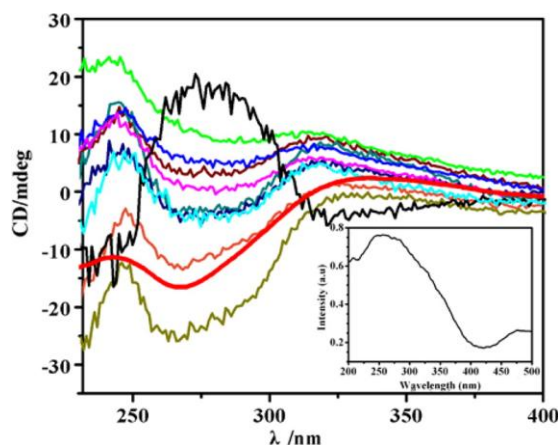


Figure 5. Solid-state CD spectra of 10 randomly selected crystals as well as the bulk sample (labeled in bold red). Note that there is only one (+) CD spectrum. [Published in: Chao-Ying Gao; Fei Wang; Hong-Rui Tian; Lei-Jiao Li; Jian Zhang; Zhong-Ming Sun; *Inorg. Chem.* **2016**, 55, 537-539. DOI: 10.1021/acs.inorgchem.5b02187. Copyright © 2015 American Chemical Society].

It is argued that both the Cotton effect displayed in the CD spectra and the structural refinements (Flack parameter) of randomly selected 26 crystals demonstrate that the chiral complex is enantioenriched with left-handed helical chains. It is explained that the handedness of the complex originates from the preferential conformation adopted by the thiophenic acid ligand. Therefore, the formation of left-handedness of bulk crystals over right-handedness, could be related to this preferential chiral conformation. It is assumed that such an unusual phenomenon is comparable to the biological homochirality, but it is recognized that it is the consequence of the combined action of many factors and its cause is still unidentified.

3.3 the 2-propyl-1H-benzimidazole system

Even more astonishing are the cases where one of the two possible enantiomorphic crystals was absent. The curious case of 2-propyl-1H-benzimidazole (2PrBzIm) in the solid state has been described by Quesada-Moreno *et al.* (2017). While this compound is achiral by fast rotation about the propyl single bond, it exhibits a conformational chirality and crystallizes as a conglomerate.

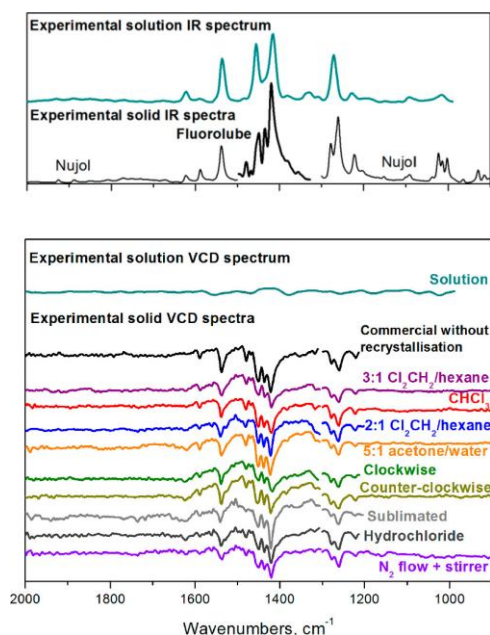


Figure 6. Recorded IR (upper) and VCD (lower) spectra for liquid and solid samples of 2PrBzIm. Note the persistent negative VCD signals. [Published in: María Mar Quesada-Moreno; Aurora J. Cruz-Cabeza; Juan Ramón Avilés-Moreno; Pilar Cabildo; Rosa M. Claramunt; Ibon Alkorta; José Elguero; Francisco J. Zúñiga; Juan Jesús López-González; *J. Phys. Chem. A* **2017**, 121, 5665-5674. DOI: 10.1021/acs.jpca.7b05220. Copyright © 2017 American Chemical Society].

The careful analysis of the solid state VCD spectra was supported by DFT computed structural models delivering wave number assignments. It was found that whatever the preparation method (commercial samples, synthesized samples, recrystallized from various solvents, produced by sublimation ...) all samples gave identical VCD spectra, validating the same handedness in all assessed crystals. Moreover, any attempt to get the opposite chirality, which was successful with some other similar imidazole, was always vain with 2PrBzIm.

The authors believe it is imperative to publish these questioning results even if they seem contrary to the 2nd law. They confess that they have not been able to identify any hidden cryptochiral environment.

3.4 the diprotonated tetrakis-(4-sulfonatophenyl) porphyrin system

It is recognized that aggregation, like crystallization, behaves as an experimental autocatalysis [Plasson *et al.* (2007)]. Being prominent in the field of chiral aggregation, the sign selection on the *J*-aggregates of diprotonated tetrakis-(4-sulfonatophenyl) porphyrin ($H_4TPPS_4^{2-}$) should also be mentioned [El Hachemi *et al.* (2009)]. When the *J*-aggregates of $H_4TPPS_4^{2-}$ are formed, they show circular dichroic spectra.

The unexpected result is that after several hundred independent experiments, the number of CD spectra corresponding to negative signals have appeared with a frequency approximately less than 0.4%. It is then assumed that the recurring formation of these chiral *J*-aggregates is the result of an unidentified biological contamination in the ultra-pure water used as a solvent and that the chiral contaminant exhibits some character of a cationic amphiphile. Therefore, chiral additives were used to confirm this hypothesis. The two additives enantiomers were *R*- and *S*- *N,N*-dimethyl-*N*-hexadecyl-*N*-(1-phenyl)ethylammonium bromide. Under the addition of the *R*- enantiomer, the same CD spectra as that of the blank but with higher dichroic values was observed. On the contrary, the addition of the enantiomer *S*- gave as expected an opposite CD spectrum. However, this effect only occurred above a critical concentration of the *S*-

enantiomer depending on the water quality. For the best quality, the limit can be estimated around 20nM (10ppb). In conclusion, there is a competitive effect of the *S*- and an additive effect of *R*- enantiomer with some chiral contaminant which is present even in the ultra-pure water. The chiral impurity probably consists of fragments of microorganism cell membranes or protein components. On the other hand, without taking into account the presence of such impurities, it has been shown that spontaneous symmetry breaking can be produced in an uncharged achiral porphyrin system by small temperature gradients that act as asymmetrical physical perturbations [Mineo *et al.* (2014, 2015)].

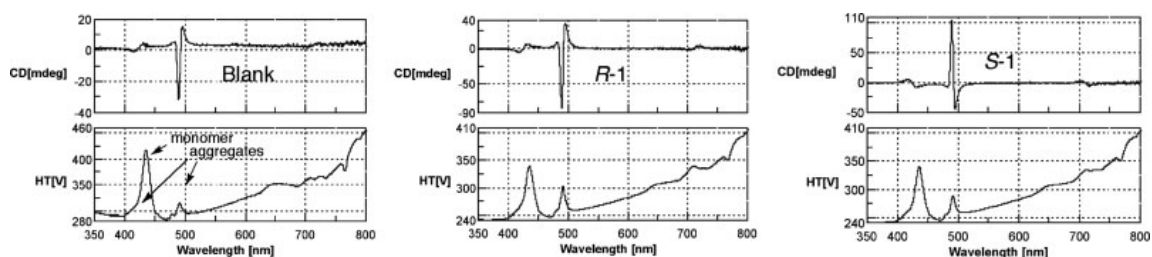


Figure 7. Characteristic CD spectra resulting from the competitive induction of *S*- and *R*-1 in the CD spectra of $H_4TPPS_4^{2-}$. [Published in: El Hachemi, Z., Escudero, C., Arteaga, O., Canillas, A., Crusats, J., Mancini, G., Purello, R., Sorrenti, A., D'Urso, A., Ribo, J.M. (2009). Chiral sign selection on the J-aggregates of diprotonated tetrakis-(4-sulfonatophenyl) porphyrin by traces of unidentified chiral contaminants present in the ultra-pure water used as solvent. *Chirality* 21 408-412.]

Conglomerate crystallisation or chiral *J*-aggregates formation is not limited to organic or organometallic complexes, some simple salts such as sodium chlorate undergo also conglomerate crystallisation.

3.5 the paradigmatic case of $NaClO_3$

The easy to handle sodium chlorate ($NaClO_3$) exists in solution as achiral dissociated ions or small clusters without any fixed chirality, but crystallises as two enantiomeric chiral crystals in the cubic space group $P2_13$ [Viedma (2005a)]. The stable chiral cubic unit includes four chlorate ions arranged in a helical architecture. Sodium chlorate is polymorphic as it can also exist transiently as an achiral metastable monoclinic phase [Ninomi *et al.* (2013)]. One may easily identify the handedness of individual $NaClO_3$ crystals between crossed polarizers by its rotation of linearly polarized light [McBride and Carter (1991)], where the two enantiomeric forms can be distinguished as dark and bright crystals.

Kipping and Pope (1898) measured the handedness of more than three thousands $NaClO_3$ crystals after quiescent crystallization and found that their D- vs L-crystal counting fell well within the statistical error of an unbiased 50/50 distribution as they have anticipated. Later, Kondepudi *et al.* (1990) confirmed these results.

On the contrary, when evaporating aqueous $NaClO_3$ solutions were subjected to left-handed electrons from an ^{90}Sr source, an asymmetric crystal distribution favouring D-crystals was obtained. Inversely, exposure to energetic right-handed positrons from an ^{22}Na source yielded mainly L-crystals. Without providing a more detailed mechanism, it was concluded that the spin polarized energetic particles are able to produce chiral nucleating sites and that the chirality of the radiation is correlated with the chirality of the created crystals [Mahurin *et al.* (2001); Pagni and Compton (2002)].

3.5.1 mirror symmetry breaking in stirred solutions

When the NaClO_3 solution is stirred during crystallization, spontaneous mirror-symmetry breaking occurs [Kondepudi *et al.* (1990)]. D-crystals predominated in 18 batches and L-crystals in 14. Mirror-symmetry breaking has been explained by the rapid production of secondary nuclei from a primary nucleus after its collision with the stirrer or by crystal-crystal collision. This process is autocatalytic as new-born small crystals play the role of seeds to promote the creation of more crystals of the same handedness [McBride and Carter (1991)].

3.5.2 Viedma ripening

The so-called Viedma deracemization is an undeniable improvement of the Kondepudi experiment since it has been demonstrated to be applicable to many other systems [Blackmond (2007); Noorduin (2008a, 2008b, 2010); Viedma *et al.* (2008); Hein *et al.* (2012); Spix *et al.* (2016a)]. Under Viedma's attrition-grinding process, the smaller NaClO_3 crystals dissolve faster than the larger ones because their surface-to-volume ratio is relatively high and thus their surface energy is high as well. The larger crystals grow by consuming smaller crystals via the saturated solution to give an Ostwald-like situation whose limit is the smallest possible surface-to-volume ratio. Repeated crystallization, grinding and dissolution where the chiral NaClO_3 crystals again transform into the achiral NaClO_3 solute, finally triggers an output of a homochiral crystal population [Amabilino and Kellogg (2011); Crusats *et al.* (2006)]. Because the suggested rationalization is related to the concept of Ostwald ripening [Noorduin *et al.* (2009)], this phenomenon has been referred to "Viedma ripening" [Viedma (2004, 2005a)].

In Viedma's NaClO_3 experiments [Viedma (2007)], the starting L- and D- crystals (racemic mixture) were the whole and "natural" population generated in a quiescent evaporation process. After attrition-grinding for 24h, Viedma found a clear-cut, non-stochastic predominance of D-crystals in repeated experiments. Again, such non-random chiral bias could be of chemical or physical origin. The author suspects the presence of optically active impurities that may either promote the formation of D-nuclei or disfavour the growth of L-crystals by selective surface adsorption. However, there is no indication about the possible nature of such impurity.

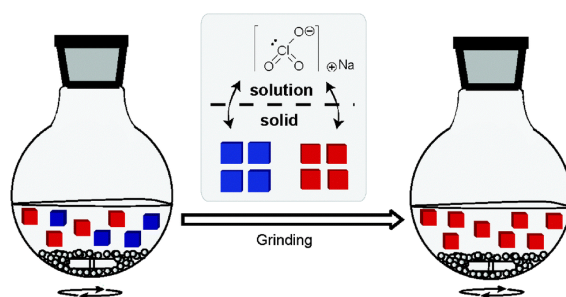


Figure 8. The principle of the Viedma ripening in the case of achiral NaClO_3 molecules that crystallise as a conglomerate. [Sögütöglu, L.C., Steendam, R.R.E., Meekes, H., Vlieg, E., Rutjes, F.P.J.T.; Viedma ripening: a reliable crystallisation method to reach single chirality. *Chem. Soc. Rev.* 2015, 44, 6723] - Published by The Royal Society of Chemistry.

Ultrasound-enhanced grinding has been successfully applied to the Viedma deracemization of NaClO_3 crystals. From 37 different crystallizations, 18 produced L-crystals and 19 were almost total D-crystals. A total of 19907 crystals were harvested. While 8473 were left-handed and 11434 right-handed, *i.e.* 15% more of D-crystals, it was concluded "as that reported

previously, in the absence of outside perturbations, statistically equal numbers of L- and D-crystals were obtained in each crystallization” [Song *et al.* (2008)].

3.5.3 Aerosol crystallization

In the same way, the asymmetric chiral growth of micron-size NaClO_3 crystals in water aerosols has been described by Osuna-Esteban *et al.* (2008). They have shown that similarly to the Viedma ripening or ultrasonic irradiation, their autocatalytic aerosol-liquid cycle is able to amplify any tiny initial imbalance up to total chiral purity in a single step process. Even in the absence of added catalysts, it was found that some undefined ambient contamination leads to preferential D-homochiral crystallizations in a ratio of 4 to 1. This ratio is more or less reversed (up to 1 to 2) by adding only 2 ppb of D-Phe. However, the effect of other additives (L-Phe and L- and D-Tyr) is less conclusive about the involvement of natural L-amino acids as chiral contaminants.

3.5.4 Petri dish experiments

On our side, we have carried out 16 series of Petri dish experiments, *i.e.* the slow evaporation of saturated quiescent NaClO_3 solutions in open vessels without any chiral additives, in which more than 10,000 crystals were counted. In these Petri dish experiments, primary nucleation occurs mainly at the air-water interface. Moreover, as stirring or mechanical crushing were excluded, the influence of secondary nucleation was negligible and large-sized crystals were generally obtained. After crystal counting, we recognized a persistent chiral bias towards D-crystals. We still do not know the cause of this chiral bias. However, it is interesting to note that the same D-shifted bias has been also acknowledged before in two different laboratories by two different experimental set-ups [Veintemillas-Verdaguer *et al.* (2007); Viedma (2007)].

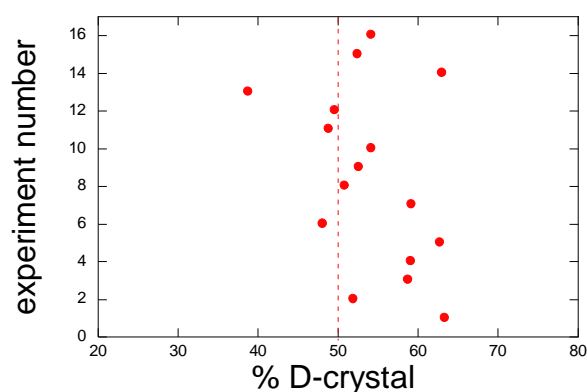


Figure 9. Counting of NaClO_3 crystals after 16 series of Petri dish experiments without chiral additives (more than 10,000 D- and L- crystals in total) showing a clear bias towards D-crystals.

Being fully aware that such bias is normally ascribed to the occurrence of heterogeneous nucleation on impurities present in the system and coming from the bio-organic world, we have undertaken a series of experiments by intentionally adding chiral "impurities". However, it was impossible to reallocate the D-bias even after careful addition of a number of chiral additives such as D-mannitol, D- and L-amino acids, D- and L-arabitol, D- and L-quartz,

fungal spores, lactobacillus, protein extracts or residues from microfilters that were used to clean the aqueous NaClO₃ solutions.

IV DISCUSSION

All autocatalytic chiral amplifications fit effectively the classical Frank nonlinear kinetic model where the major enantiomer catalyses its own production while it suppresses that of its mirror image [McBride and Tully (2008); Cintas and Viedma (2012)]. These far-from-equilibrium thermodynamics situations lead to a bifurcation in which chiral fluctuations at the bifurcation point impel the system stochastically to one or the other sign. However, under the influence of some chiral forces, it can be biased deterministically to one sign and not to the other [Crusats *et al.* (2006)]. The nature of such chiral forces is still matter of a hearty debate. Looking at the absolute asymmetric synthesis literature, several papers can be found, where the question of a possible existence of a chiral bias is addressed. Three main conclusions are encountered.

The first one, and the easier to defend interpretation, is to argue, that there will be finally a random distribution, *i.e.* the system tends to converge to a random distribution after a sufficiently large number of experiments [Pincock *et al.* (1971); Kondepudi *et al.* (1999, 2001)]. Also, two recent prominent papers can be cited [Kawasaki *et al.* (2015); Kaji *et al.* (2016)], they are both related to the spontaneous formation and asymmetric synthesis of enantioenriched α -amino acid precursors through preferential dynamic crystallisation of a conglomerate without the addition of any chiral substances. Both articles claim a quasi-stochastic distribution, *i.e.* that both enantiomers appeared randomly in each crystallization with almost the same probability.

Other recent papers asserting a “small bias” do not provide a sufficient number of experiments to be validated by robust statistical analysis [Ziach and Jurczak (2015); Steendam *et al.* (2015a)].

More profound analysis is demanded since there are many situations where seeding has been used for the purpose of mechanistic studies [Steendam *et al.* (2013); Gherase *et al.* (2014); Steendam *et al.* (2015b); Spix *et al.* (2016b)]. Additionally, the inability to control the handedness of the product motivates synthetic chemists to orientate the output chirality by seeding, therefore genuine absolute asymmetric synthesis is barely performed.

Much more interesting are the systems that exhibit a clear non-stochastic chiral outcome. Looking carefully at the literature, it appears that the few afore mentioned examples are not the only ones. In a number of chiral crystallization experiments, preferential symmetry breaking was observed. For instance, potassium silicododecatungstate seems to afford always dextro crystals exclusively [El Hachemi *et al.* (2009)]. Other older examples include the spontaneous formation of optically active methyl ethyl allyl anilinium iodide [Havinga (1954)] and the re-visitation of the sodium ammonium tartrate experiment by Thiemann and Wagener (1970).

Szabo-Nagy and Keszthelyi (1999) claimed the observation of the parity-violating energy difference between enantiomers, namely the spontaneous formation of a non-random distribution of tris(1,2-ethanediamine) cobalt(III) and tris(1,2-ethanediamine) iridium(III) crystals. Instead of organic compounds, these metal complexes were selected because the PVED increases in proportion to the sixth power of the atomic number Z of the element in the asymmetry center: C ($Z = 6$), Co ($Z = 27$) and Ir ($Z = 77$).

Few years later, Shinitzky *et al.* (2002) investigated the solubility of D- and L-tyrosine in water. Amazingly, D-tyrosine crystallised faster than L-tyrosine and the supernatant was enriched in L-tyrosine. However, the difference between the crystallization rates of the tyrosine enantiomers disappeared in D₂O. The authors concluded that these results seem to contravene the generally accepted consensus that there are no physical or chemical differences between enantiomers other than their well-known interaction with polarized light and that it could be the manifestation of the PVED.

It is not astonishing that such an unexpected discovery has been questioned and criticized. Lahav *et al.* (2006) have shown that commercial L-amino acids are generally contaminated by small amounts of other amino acids and that these impurities greatly shape the growth and dissolution of enantiomorphous crystals. They suggest to keep in mind the role played by impurities in the early stages of crystal nucleation because it is expected that such effects could be of several orders of magnitude larger than the awaited PVED.

After the influential warnings by Lahav, various authors became more cautious in their conclusions, invoking nearly always a “chiral impurity”, a “chiral substance” or a “cryptochiral environment” [Cheung *et al.* (2008); Steendam *et al.* (2014)].

Independently, Kojo *et al.* (2004) have shown that during the recrystallization of D,L-amino acid mixtures with excess D,L-asparagine, amino acids with the same configuration as asparagine (valine, arginine, aspartic acid, glutamine, histidine, leucine, methionine, phenylalanine, serine, tryptophane and tyrosine) were preferentially resolved. This result indicates that it is the nature of a mixture of racemic amino acids to produce a spontaneous high enantiomeric excess. Moreover, after consideration of the observed unexpected chiral bias, it was claimed that enantioselective crystallization of racemic amino acids induced by spontaneous resolution of D,L-asparagine assisted the selection of L-amino acids.

As already pointed-out by Wald (1957) many years ago, crystallization is a puzzling issue because it is very sensitive to seeding and external contamination. Almost in every laboratory exists the feeling that after a first time-consuming and tricky crystallization, the following will proceed much more easily. Any attempt to establish which kind of impurity is accountable for the initial symmetry breaking is challenging. To the best of our knowledge, this question has not yet been well addressed [Steendam *et al.* (2013)]. Regarding the wide variety of physicochemical situations where a chiral symmetry breaking is occurring (molecules, solvent, involvement of crystals or aggregates) makes the assumption of the involvement of a same impurity, for instance that of biological origin, unlikely. One must remember, for instance, that the S preference in the Soai reaction was also observed independently by Singleton and Vo (2002) and by Gridnev *et al.* (2003). The same situation also occurred for the D-preference in the NaClO₃ system observed by different research groups. It is also interesting to note that probably in all of these cases the research was not directed to discover such non-stochastic behaviour, in contrary, the puzzling results emerged as a "side effect" leaving the researcher with open questions to find and explain the possible causes.

On the other side, we must also be aware that, although very weak, the existence of a PVED between enantiomers is theoretically certain, although its experimental confirmation is still pending. According to Tranter (1985), the parity-violating energy difference has been calculated for a number of fundamental biomolecules. In each case, the natural enantiomer found in terrestrial biochemistry was shown to be stabilized over its unnatural enantiomer. If we apply the PVED, not to a unique molecule, but to a transition state in the framework of a kinetic approach, its tiny value appears now multiplied by “n”, the huge number of elementary units in a macroscopic crystal lattice. Such an assumption, associated with Kondepudi’s idea [Kondepudi and Nelson (1985)] that even in a randomly fluctuating environment a Frank-like

non-equilibrium mechanism can be shifted left or right by an infinitesimal chiral bias such as those occurring from the PVED, would revamp the chiral weak force hypothesis.

V CONCLUSION

In this survey, we have gathered a selection of articles about chiral symmetry breaking, *i.e.* related to all situations where an achiral input gives rise to a chirally asymmetric output. The common point of all these systems is the presence of an autocatalytic-like aggregation process coupled with a mutual inhibition step or perhaps with a higher-order autocatalytic process in which mutual inhibition becomes no longer essential.

A first key question arises: is the tiny *ee* emerging from parity violation sufficient or not to overcome stochastic fluctuations? Kondepudi and Nelson (1985) say “yes, but it will be lengthy”, Lente (2006) responds “no” on the basis of a stochastic analysis ignoring the amplification power of a Frank-like mechanism, while Cruz *et al.* (2008) underline the possible constructive role of noise for the enantioselection in the presence of tiny chiral influences.

The second key question is addressed to the experimentalists: Have you eliminated all obscure sources of dissymmetric influences? The unanimous answer is: it is a daunting if not insurmountable task because undetected chiral impurities may induce favourable nucleation of one of the enantiomers. Since unwanted impurities control the chiral outcome, some experimentalists artificially neutralize their effect by adding a known amount of a “neutralizing” chiral additive. For our part, we encourage the experimentalists to consider that the manifestation of PVED is an assumption that cannot be ruled-out without caution and to unveil their observations.

Beyond these fascinating but still speculative questions remain the importance of chirality. Chirality is now a top-class subject for academic research because it is related to the problem of origin of life and exobiology, but on a much more practical point of view, chirality is also very crucial for our everyday life. Nowadays, the access to pure enantiomers is a considerable scientific and economical issue. Most enantiomers of racemic drugs exhibit marked differences in biological activities. For instance, the pain reliever S-naproxen binds to the enzyme cyclooxygenase and inhibits its action in the synthesis of prostaglandins, while its enantiomer R-naproxen does not inhibit the cyclooxygenase and is toxic to the liver. Nowadays, many drugs are still used as racemates with their side effects. This problem is probably due not only to the synthetic or separation difficulty, but also to the production costs because asymmetric synthesis or resolution of racemic mixtures are generally expensive and may turn out to be tedious. If new chiral separation and synthesis methods will be developed with low cost, the number of racemic drugs could reduce drastically [Nguyen *et al.* (2006)]. Therefore, it is an imperative to promote the topic subject of chiral purity in scholar research as well as in the industry.

For instance, it is worth noting that the Viedma ripening technique [Viedma (2005b)] could be matured as an efficient separation/deracemization methodology in a pharmaceutical perspective. Moreover, mimicking Soai’s chiral autocatalysis, *i.e.* using the chiral product as part of the chiral catalyst, an enantioselective production of a key precursor to the HIV drug *Efavirenz* has been described allowing its manufacturing cost to be substantially reduced [Chinkov *et al.* (2011)].

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