

What is the Origin of Homochirality in Nature?

Chirality denotes the handedness of a molecule, where two structures called enantiomers are mirror images of each other and thus not superimposable (Blackmond, 2011). Homochirality occurs when only one of the chiral structures is present. For example, all chiral amino acids are L-chiral (left-handed), and all sugars are D-chiral (right-handed) (Weller, 2024). The origin of this preference, especially the mechanism, is the subject of debate. Current hypotheses include propositions of outer space meteorites, the asymmetric influence of other physical agents, or simply by chance (Blackmond, 2020; Pavlov & Klabunovskii, 2015). One physical agent that stands out is spin-polarized electrons in an effect called Chiral-Induced Spin Selectivity (CISS) (Naaman et al., 2020; Stefani et al., 2024). As electrons have two spin configurations, the mechanism proposes a strong coupling between the direction of spin and the chiral configuration of a molecule. Enantiomers have different energies, so will prefer and react faster with electrons with a specific spin. If there are more electrons of a certain spin, one enantiomer would react faster and lead to an imbalance that is amplified into homochirality. In prebiotic nature, magnetite (iron ore) deposits could act as the source of spin-polarized electrons. Thus, the current most probable origin of homochirality in nature is the CISS effect arising from magnetite deposits due to the plausibility of the mechanism itself and prebiotic possibility.

To begin, the mechanism of the CISS effect should be considered. Enantiomeric excess (ee) is a measure of how much of each enantiomer is in a mixture (Hansen, 2023). 0% represents a racemic (equal) mixture and 100% represents homochirality; it is a common measure in determining the bias towards a particular chiral structure. Thus, a viable mechanism must be able to induce ee consistently and to a high degree. The CISS effect revolves around the strong correlation between spin-polarized electrons and the chirality of a molecule. Göhler et al. (2011) demonstrated this relationship by noticing spin-polarization of photoelectrons shot from a UV laser through a monolayer of DNA. Researchers then proposed that the mechanism should also be able to work in reverse; spin of electrons should be able to favour an enantiomer. Rosenberg (2015) showed a higher yield of the dissociation for one enantiomer when on top of a monolayer of chiral DNA; they attribute this result to the spin-polarized

electrons that arise from being filtered by the DNA. Their experimentation shows the relationship between electron spin and chirality goes both ways. Ozturk et al. (2022) builds upon this idea, proposing a proper mechanism for the origin of homochirality in nature called CISS-driven reduction chemistry (CDRC). The theory states that if there is more of one spin of electron, one enantiomer will react faster on average. Ozturk et al. (2023) published an experiment demonstrating the concept using ribo-aminooxazoline (RAO). They were able to successfully demonstrate CDRC and self-amplification in achieving homochirality from a racemic mixture, highlighting the applicability of the mechanism.

The proposed theory is prebiotically reasonable considering the geochemical environment at the time. The environment in prebiotic nature greatly differs from the modern era, but the exact conditions and state are unknown. However, it is generally agreed upon that primitive Earth had abundant water, an oxygen-free atmosphere, intense UV radiation, and the existence of simple molecules containing carbon, hydrogen, nitrogen and oxygen (Dondi, 2007). It is also suggested that minerals, like the iron ore magnetite, were present; the Gale crater on Mars is analogous to aqueous lakes in prebiotic Earth and shows evidence of magnetite (Ozturk & Sassellov, 2022). Additionally, magnetite has a low work function, meaning it can easily emit electrons when exposed to UV light which was abundant and intense in the anorexic conditions of prebiotic Earth. Its highly magnetic property also creates a local magnetic field that can strongly affect the spin of electrons. It is suggested that magnetite served as the source of spin-polarized electrons. UV light from the sun could irradiate the magnetite, causing the release of spin-polarized photoelectrons. Given the presence of magnetite, the mechanism can occur in prebiotic conditions. Furthermore, this proposal of CDRC utilizes synthesis rather than dissociation of enantiomers to induce ee. This is important as the reaction yield is not diminished in multistep reaction networks, but instead, reaction yield increases to approach homochirality. This mechanism can be proposed as the origin of homochirality in the cyanosulfidic network, as electrons are required in one of the initial steps of synthesis. Even considering the bulk of the electrons being non-helical, the presence of some spin-filtered electrons may induce ee and be amplified to a significant degree. It should be noted that this is

only a proposed application, as no experimentation has been completed on the cyanosulfide network yet.

Due to the ambiguity still surrounding the topic of the origin of homochirality, many other mechanisms have been proposed. Opponents of CDRC may turn to other mechanisms like autocatalysis and mutual inhibition, stating it is a better model for the evolution of homochirality due to having better established mechanism workings and pointing out the lack of conclusive evidence in the CISS effect mechanism theory. Autocatalysis refers to a substance being the catalyst to its own reaction and mutual inhibition is the suppression of its enantiomer's reaction (Blackmond, 2011). When combined, this mechanism can easily amplify the imbalance of enantiomers. Soai (2019) first experimentally proved the feasibility of the mechanism in 1995, using autocatalytic alkylation of pyramidal aldehydes with dialkyl zincs. He was able to report up to 85% ee. When applying the theory to prebiotic chemistry, the catalysts used in Soai's reaction would not exist in the prebiotic world (Blackmond, 2020), thus Blackmond (2001) demonstrated that any small initial bias towards an enantiomer is enough for the mechanism to amplify and reach homochirality. This research suggests that the only requirement is an initial bias for an autocatalytic set, making it a viable theory for the origin of homochirality. Furthermore, a simulation experiment demonstrated that the autocatalytic set was most strongly able to break mirror symmetry and induce ee, increasing the strength of this proposed mechanism (Gagnon & Hochberg, 2023). There are also many limitations existing within the CISS theory itself, as a big proportion of it is only theorized and an idealized process; there is no testing on the cyanosulfide networks that the mechanism is best applied to. The RAO experiment required researchers to increase the strength of the magnetic field compared to Earth, thus also weakening its applicability to prebiotic conditions. Opponents may use this lack of physical evidence and data to state CISS is not a sure mechanism in the origin of homochirality.

However, autocatalytic sets are rare and thus are less applicable to the prebiotic world. There is also a lack of definity around autocatalysis being the key condition that propagates ee. While the CISS effect is a newer theory with less experimentation, the coupling between electron spin and chiral molecules has been established and its plausibility in prebiotic

chemistry ultimately makes it the more viable theory. Firstly, the same simulation determined that while autocatalytic sets are best at breaking symmetry, it is not necessary or sufficient by itself as a condition for inducing *ee* (Gagnon & Hochberg, 2023). The simulation demonstrates that not all autocatalytic set configurations could break mirror symmetry and other catalyzed reactions could achieve mirror symmetry breaking without being autocatalytic. Autocatalytic sets of enantiomers are also rare; it is difficult to find a set of enantiomers that will accelerate its own reaction while inhibiting its enantiomer. This issue becomes even more difficult when limiting the molecules to those that are prebiotically possible. Soai's mechanism is the only documentation of spontaneous asymmetric synthesis but cannot occur in an aqueous prebiotic environment and complex reactants that likely did not exist (Blackmond, 2020). While the search continues for more autocatalytic networks, the inability to find more sets that demonstrate this mechanism without the constraint of prebiotic conditions suggests that there is a very low chance that it could be the origin of homochirality in nature. Although opponents try to explain the idea of a small bias being amplified, it still begs the question why one enantiomer is favoured to the other, as it is hard to conceive areas all over the Earth favoured the same enantiomer by chance. Ultimately, the autocatalysis and mutual inhibition is too complex of a mechanism to explain homochirality in prebiotic terms.

When comparing to the CISS-effect, CDRC is much more viable. While the example of cyanosulfide network is hypothetical, it should be noted that spin electrons can induce a spin bias in cyanosulfides, but rather, the efficiency and significance is unknown due to a lack of knowledge about the yield limiting step of the reaction (Ozturk & Sasselov, 2022). The issue has already been addressed by proposing various methods to determine the yield-limiting step through electrochemical experimentation. Additionally, an experiment using RAO has proven the viability of the mechanism (Ozturk et al., 2023). Although the magnetic field was adjusted, the conditions of prebiotic Earth are also under contention, thus is not enough of a reason to dismiss the theory. CDRC was also used in generating homochirality in RAO (Ozturk et al., 2023). This is significant as RAO is a precursor to RNA and plays a critical role in synthesizing ribonucleotides. The chirality of RAO will determine the chirality of the RNA, thus influencing the chirality of the amino acids encoded for on the RNA. RAO is a central molecule for prebiotic

synthetic networks. The generation of homochiral RAO using CDRC furthers the idea that this mechanism is plausible for prebiotic conditions. If homochirality can be achieved in RAO, it suggests that other prebiotic molecules enantiomers could have been selected in the same way. While opponents may point out the need to adjust the strength of the magnetic field in the experiment to produce the results, it should be noted that it is still early in the development of this theory; thus, other reaction pathways may be proposed to reduce the need for such a strong magnetic field to spin-polarize electrons. The primary function of the magnetic field is to polarize the electrons, however, there are several other ways, like UV irradiation, that may achieve the same effect. Ultimately, CDRC is the most promising theory in explaining the origin of homochirality in nature, showing higher plausibility in mechanism occurrence and prebiotic viability compared to other theories like autocatalysis.

CISS effect is the strong coupling between electrons spin and chiral molecules. Due to this relationship, a proposed mechanism of the origin of homochirality in nature is CISS-driven reduction chemistry (CDRC) where spin-polarized electrons freed from magnetite by UV radiation can lead to the favouring of one enantiomer. The amplification of this initial *ee* bias can lead to homochirality, as seen in the experiment with RAO. While other theories like autocatalysis coupled with mutual inhibition are also viable mechanisms, ultimately CDRC is the most plausible current theory due to its conceivability and applicability of its mechanism and considering prebiotic conditions.

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