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Chiral autocatalysis: where stereochemistry meets the origin of life

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This article summarizes a series of recent and simple experiments to produce optically active substances from achiral precursors. These symmetry-breaking processes include either autocatalytic crystallization or asymmetric autocatalysis, and provide new insights into the origin of biomolecular homochirality. In addition, support from an extraterrestrial origin of chiral molecules has also come from recent findings.

Introduction

The question of the origin of life on Earth is invariably linked to the origin of enantiomerically pure compounds, even if there are no definitive arguments embracing both premises.[1] Ever since Pasteur's time, scientists have been fascinated with trying to understand the origin and amplification of chirality. A preliminary argument is that perhaps life needed no external influence beyond chance to choose its handedness. However, many scientists believe chirality of one or another form was inevitable because homochirality would have been a pre-condition for life. Racemic molecules would have been too inefficient for achieving biological processes such as self-replication, protein synthesis, regulation, and ultimately gene expression. Likewise, polymerization reactions affording long-chain stereoregular polymers (*e.g.* all-L-polypeptides or all-D-oligosaccharides) will not proceed in racemic solution since addition of a wrong monomer tends to stop the process.[2]

In principle, a biochemistry made up of D-amino acids or L-sugars should be just as efficient as L-amino acids or D-sugars found in our terrestrial life. An argument that reinforces this hypothesis is the fact that alternatives to ribose or deoxyribose can be synthesized and tried out as the sugar components of nucleic acids or new bases can be substituted for those nature uses. Evolution has selected the best available solution and not necessarily the best possible solution.[3] Nevertheless, even though the initial molecules are achiral, the handedness of the building blocks or the appropriate helicity of the oligomers had to be determined at an early stage. In fact only a small enantiomeric excess (ee) is required because such a value could be amplified by a series of mechanisms related to the concept of nonlinear stereochemistry.[4] Thus, a partially resolved chiral catalyst or auxiliary could give a stereoselection higher than its own ee. The phenomenon may be ascribed to diastereomeric interactions in solution, but there are also profound kinetic implications involved,[5] including the possibility that the diastereomeric catalysts have very different reaction rates.[6] Unfortunately, most nonlinear effects have been observed with organometallic reagents and in organic solvents. It is unlikely that these reaction conditions could be found in the prebiotic scene. Anyway, as we shall see later these unusual mechanisms involving cooperativity among the molecules do provide food for thought.

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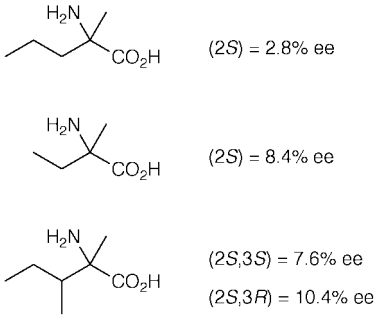
Cosmic chirality

Before we go any further, a few comments about the inherent handedness of matter are unavoidable. There are four forces in nature: electromagnetic, strong, gravitational and weak interactions, but only the latter is chiral. In other words, it can distinguish between right- and left-handedness in the spin polarization of elementary particles. Parity violation in the weak interactions was discovered in the late fifties as the radioactive decays of polarized ^{60}Co nuclei release more left-handed spinning electrons than right-handed spinning ones. Likewise, as far as we know there are no right-handed neutrinos: they are always left-handed.[7] The direct implication of these interactions is that there is a parity-violating energy difference between two enantiomers. Unfortunately, this energy shift is too small ($\sim 10^{-18}$ eV) to be measured with our current instruments, but theoretical calculations do confirm that the natural L-amino acids L-alanine, L-valine, L-serine and L-aspartate are more stable than their D-enantiomers by 10^{-17} kT, and D-glyceraldehyde was likewise found to be more stable than its unnatural counterpart by about 10^{-17} kT.[8] Although amplification mechanisms by factors of about 10^{17} could be suggested to explain the observed homochirality of molecules,[9] alternative hypotheses appear to be more plausible.

If the foundations of life are chiral cosmic forces operating at their origin, the finding of extraterrestrial chirality would provide a reasonable argument. In fact, we have learnt that circularly polarized light (CPL) or vortices may cause symmetry breaking, but even falsely chiral influences such as magnetic or gravitational fields, under kinetic conditions, might be sufficient.[10] The search for homochiral substances in the well-known Murchison meteorite reveals that L-enantiomers predominate slightly over D-enantiomers.[11] In particular, Cronin and Pizzarello have concentrated on branched α-amino acids,[11a] which are not present in terrestrial proteins, in order to exclude any sort of contamination from living systems. Although no appreciable ees were found for α-aminobutyric acid or norvaline, other ramified amino acids gave ees up to 10% (Scheme 1).

In an irony of fate, astronomers from the Anglo-Australian Laboratory reported that they had discovered high levels of CPL



Scheme 1 Enantiomeric excesses of α-ramified amino acids of extraterrestrial origin found in the Murchison meteorite.

(as much as 17%) in the constellation Orion.[12] Such radiation might have induced asymmetry in interstellar organic molecules, which could be delivered to the primitive Earth by comets or meteorites, a necessary surmise if one assumes that the distance from the solar system to the center of the nebula is estimated at about 1500 light-years!

One objection to this exciting work is that the authors observed only CPL in the infrared region, whereas UV light is required to deracemize chiral molecules. However, computations showed that circularly polarized ultraviolet light should also be present.[12,13]

Crystallization–induced resolution and autocatalysis

It would be interesting to devise a chemical system capable of producing a slight enantiomeric imbalance comparable with the levels of ees found in meteorites or achieved by CPL photolysis,[10a] which may be as low as 0.1%, but larger than those predicted by parity violation.

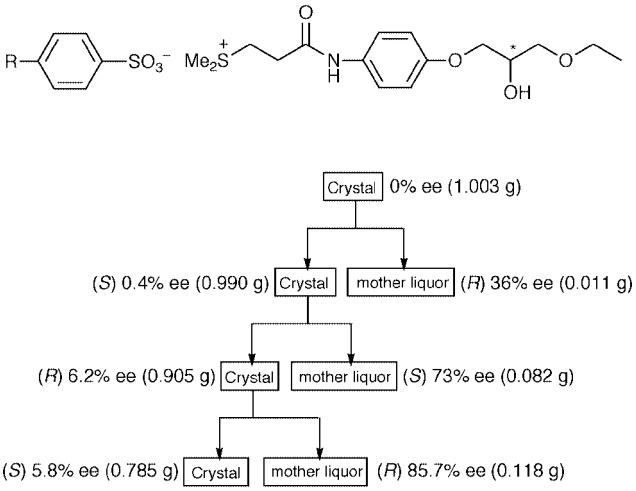
We must first overcome a common misconception taught at the freshman or even sophomore level: the assumption that racemates are made of *exactly equal* amounts of enantiomers. This belief goes against the logic of statistics, and in fact for n molecules in a racemate, the dominant component will have $(n/2) + n^{1/2}$ molecules.[14] As n becomes very large the ratio of the two enantiomers becomes very close to one. This does mean that the simple diffusional distance from 50:50 will result in a macroscopic observation (for instance through the examination of $[\alpha]_D$ values) of an optically inactive mixture.

Crystal growth is a good scenario that takes advantage of the statistical fluctuations in a system where crystallization of, let us say, a left-handed crystal acts as a seed and causes other crystals nearby to be left-handed also. This chiral primary nucleation is the origin of the known spontaneous resolutions, which will occur only if the racemate is a conglomerate in the solid state.[15]

An unusual enantiomeric resolution by recrystallization of a racemate has been recently disclosed by Japanese authors.[16] Compounds susceptible to this preferential enrichment were a series of racemic sulfonium sulfonates, and the flow diagram of Scheme 2 highlights its particular features. Thus, repeated recrystallization of the racemate results in an alternating enrichment of the two enantiomers in the mother liquors (up to 100% ee!) and at the same time when crystals with low ee are recrystallized, the deposited crystals have invariably the opposite handedness.

As might be expected, the authors were able to identify by X-ray diffraction analysis the presence of a racemic conglomerate composed of a regular packing of the *R* and *S* enantiomers in the crystal lattice, whereas compounds existing as disordered mixed crystals in which sites are occupied by the *R* and *S* enantiomers cannot be resolved.

Spontaneous resolution in fluid systems (*e.g.* liquid crystals) is rather unusual due to thermal fluctuations and molecular



Scheme 2 Preferential enrichment by recrystallization.

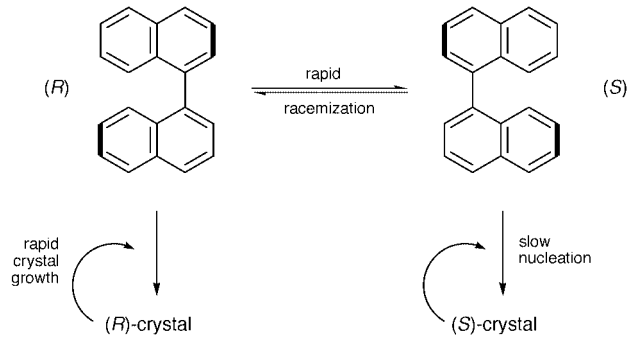
diffusion. Nevertheless, Mikami and his associates have described a spontaneous enantiomeric resolution in a fluid smectic phase of a racemate.[17] Similarly, a racemic liquid crystalline substance may be resolved on a crystalline graphite surface.[18]

Autocatalytic secondary nucleation

Chiral amplification by spontaneous nucleation may in practice be ineffective. Thus, sodium chlorate, which is an achiral molecule, may form left- and right-handed crystals by crystallization from a supersaturated solution. A statistically equal number of (+)- and (–)-$NaClO_3$ crystals are obtained from an unstirred solution, but if the solution is rapidly stirred, a large excess of either left- or right-handed crystals results.[19] It should be noted that the direction of stirring had no effect on the handedness of the crystals. The experiment was reproducible and could even be videotaped by McBride and Carter,[20] who noted that the process began with a single crystal and massive crystallization took place when the single crystal first contacted the stir bar. The overall process is called *secondary nucleation*, which involves the formation of new crystals by breaking up the dendritic structures that are constructed on the parent growing crystal. Presumably, stirring contributes to spread these secondary nuclei around the solution. Remarkably, the process is a chiral autocatalysis because the crystal nuclei generated have the same handedness as the mother crystal (compare with *primary nucleation* operating in the spontaneous resolutions mentioned above). In other words, all of the microcrystals were homochiral to the parent crystal. Both the stirring rate and the size of the nucleating crystal are critical parameters on the distribution of enantiomeric excess.[21]

The mechanism of secondary nucleation is not fully understood, even though a theory has been recently proposed.[22] Be that as it may, the phenomenon is thought-provoking, as natural crystals might have experienced this chiral nucleation under geological conditions.

Spontaneous resolution through stirring can be observed not only in solution but also in crystallization of a melt. When a large number of 0.20 g samples of 1,1′-binaphthyl are heated at 180 °C and the melt is then cooled from 180 to 150 °C and allowed to crystallize (mp is 158 °C) without any intervention, a statistically equal number of (*R*)-(−)- and (*S*)-(+)-crystals (*i.e.* a Gaussian-like distribution of optical activity centered around zero) are formed.[23] Alternatively, crystallization carried out with *constant stirring* gives rise to large ees (averaging 80%) in almost every crystallization,[24] though *R* or *S* enantiomers were randomly created (Scheme 3). Apparently, stirring suppresses the slow process of primary nucleation, thereby favoring the formation of secondary crystals with the same homochirality. In



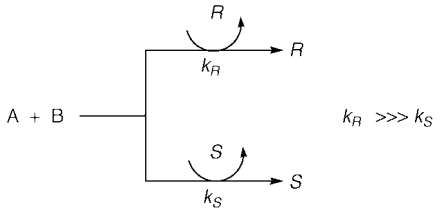
Scheme 3 Chirally autocatalytic spontaneous resolution.

addition, owing to stirring, the heat released will increase the temperature slightly, a factor that will also decrease the primary nucleation rate.

The authors have likewise studied the effect of seeding 1,1′-binaphthyl melts with (*R*)-(+)- or (*S*)-(−)-1,1′-bi-2-naphthol. Thus, a racemic sample of 1,1′-binaphthyl was cooled from 180 to 150 °C and a small amount of (*R*)-(+)- or (*S*)-(−)-1,1′-bi-2-naphthol was added, and the melt was stirred until all of it crystallized. There was a strong chiral influence of the added seed since (*R*)-(−)-1,1′-binaphthyl is isomorphous with (*R*)-(+)-1,1′-bi-2-naphthol. All of the samples seeded with (*R*)-(+)-1,1′-bi-2-naphthol presented a high value of optical rotation and close to 100% ee. Similarly, high ees were obtained for the samples seeded with (*S*)-(−)-1,1′-bi-2-naphthol.

Autocatalytic asymmetric reactions

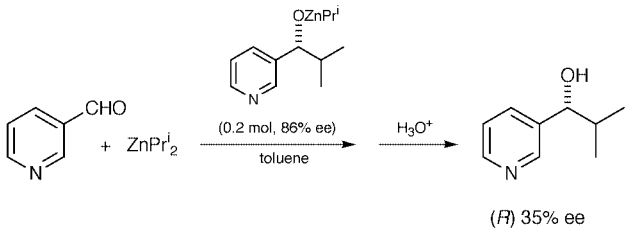
In the early fifties Frank proposed a mathematical model of chiral autocatalysis in which each enantiomer catalyzes its own formation and suppresses the production of the opposite enantiomer.[25] Owing to statistical fluctuations, a very small ee in an early stage can be amplified as the reaction proceeds (Scheme 4).



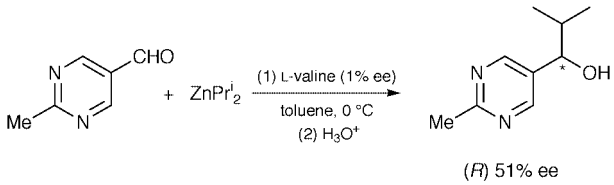
Scheme 4 Frank's hypothesis for chiral autocatalysis.

Autocatalysis implies the growth of the amount of catalyst, thereby modifying the initial *R/S* enantiomeric ratio. However, it can easily be demonstrated that an iterative autocatalytic process starting from a chiral catalyst with 100% ee and assuming a very high kinetic ratio k_R/k_S will inevitably end up with a lower ee unless nonclassical mechanisms such as a mutual inhibition of enantiomers are present.[4a] Furthermore, the use of catalysts of low optical purity may result in unpractical ees. Anyhow, a group of Japanese researchers led by Kenso Soai have found remarkable autocatalytic systems in the addition reactions of dialkylzincs to aromatic aldehydes.[26] Thus, a pyridyl alcohol of (*R*)-configuration with 86% ee catalyzes its own formation, although with a rather modest enantioselection (35% ee after subtracting the contribution of the catalyst, Scheme 5).

Better results were obtained by treating pyrimidine-5-carbaldehyde with diisopropylzinc in the presence of a pyrimidine alcohol with 2% ee, which gave the same chiral alcohol with up to 88% ee.[26d] In an extension of the latter autocatalysis, Soai *et al.* have recently reported that α-amino acids (*e.g.* leucine or valine) with 1–2% ee can serve as chiral initiators for the same addition reaction (Scheme 6). The configuration of the product



Scheme 5 Asymmetric autocatalysis in the reaction of pyridyl aldehydes with organozinc reagents.

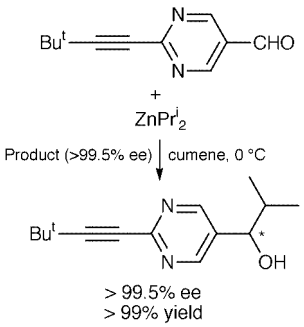


Scheme 6 Chiral autocatalysis promoted by nonracemic initiators.

is dependent on the configuration of chiral initiators. For example, L-leucine with 2% ee gives rise to an alcohol highly enriched in the *R* enantiomer, whereas addition of D-leucine causes the formation of the *S* alcohol in high ee.[27]

Improved results could be obtained with other chiral initiators such as (*R*)- or (*S*)-methyl mandelate and (*R*)- or (*S*)-butan-2-ol, even with 0.1% ee. The importance of this work lies in the fact that these initiators can be resolved by the action of CPL, thereby establishing a link between the influence of an external chiral force and autocatalysis. As mentioned, a process involving organometallic species in toluene is far from prebiotic conditions. Likewise, it would also be interesting if the same results could be obtained by irradiating with CPL the autocatalytic reaction in the presence of racemic initiators. In fact, this experiment will be attempted by these authors.[28]

An almost perfect asymmetric autocatalysis, in terms of enantioselectivity (> 99.5% ee), has been achieved in the addition of diisopropylzinc to 2-alkynylpyrimidine-5-carbaldehydes, albeit the autocatalytic alcohol had to be used with > 99.5% ee (Scheme 7).[29] The enantioselectivity was also

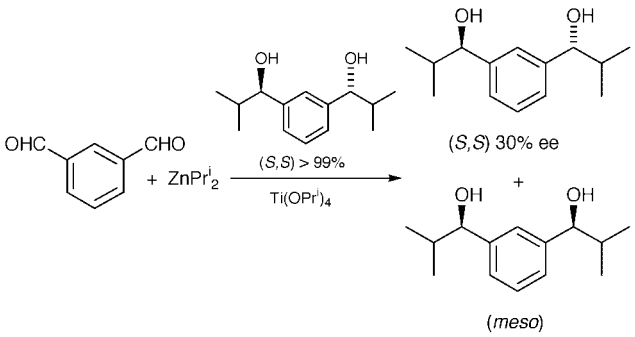


Scheme 7 Chiral self-replication of pyrimidyl alkanols.

dependent on both structural factors and reaction conditions. A rapid screening of 2-alkynylpyrimidyl alkanols revealed that a moderate electron-withdrawing alkynyl group along with a suitable bulkiness of the entire alkyne moiety are required. Accordingly, 1-(2-*tert*-butylethynyl-5-pyrimidyl)-2-methylpropan-1-ol was found to be an excellent autocatalyst. On the other hand, small differences in enantioselectivity were found when cumene was used instead of toluene, or better yet when a cumene solution of the organozinc reagent was used. It should be noted that either (*R*)- or (*S*)-pyrimidyl alkanols gave asymmetric autocatalysis with > 99.5% ee and in almost quantitative yields. If the reaction is performed consecutively with the product of one run serving as the autocatalytic reagent for the next entry, large multiplicative factors (10^3–10^7) are observed after a few rounds. An additional importance of these

chiral 5-pyrimidyl alkanols, which are obtained as single products, is their easy conversion into other important building blocks such as nonracemic α-hydroxycarboxylic acids.

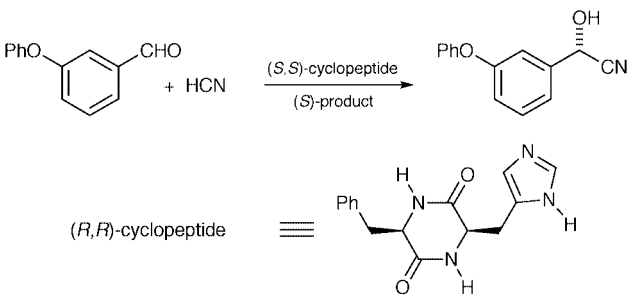
Besides asymmetric autocatalysis, a related process called *asymmetric autoinduction* may also amplify a small ee.[4] From a conceptual viewpoint, however, the term autoinduction implies a certain degree of interaction between the product and a chiral autocatalyst, which may be different or the same substance. There must be cooperativity between the two components through diastereomeric interactions, which anticipates any type of nonlinear effect. An enantioselective autoinduction has also been reported by Soai and his group in the addition of diisopropylzinc to aromatic dialdehydes.[30] The catalyst is a chiral titanium complex derived from $Ti(OPr^i)_4$ with the chiral diol (Scheme 8). This catalyst is different from



Scheme 8 Autoinductive addition of organometallic reagents to aromatic aldehydes.

the chiral zinc alkoxide which should be the actual intermediate, and this consideration justifies the term autoinduction rather than autocatalysis. Unfortunately, the product is obtained in only 30% ee along with a large amount of *meso* diol, starting from a catalytic diol with > 99% ee.

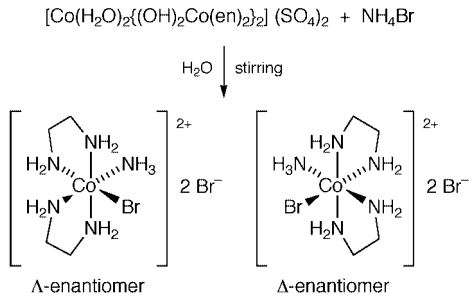
One of the most salient examples of chiral autoinduction has been reported by Danda *et al*. in the addition of HCN to aromatic aldehydes in the presence of small amounts of cyclopeptides.[31] The authors suggested that the catalyst arose from an *in situ* combination of the cyclic dipeptide with the resulting cyanohydrin. This hypothesis could be confirmed by adding a small amount of (*S*)-cyanohydrin with high ee to the cyclic dipeptide, either enantiopure or of low ee, at the beginning of the reaction (Scheme 9). Thus, catalyst with 2% ee



Scheme 9 Cyclopeptide-mediated asymmetric autoinduction.

gave product in 43% yield and 82% ee. Nevertheless, a catalyst prepared from the cyclic dipeptide in 67% ee plus (*S*)-cyanohydrin in 92% ee gave product in 89% yield and 96% ee, which is higher than the ee of both components of the catalyst. This does mean that the enantiomeric purity of cyanohydrin constitutes a key stereocontrolling factor on the catalytic cycle.

A very interesting autocatalytic reaction involving the formation of chiral coordination compounds in an aqueous environnement has been devised by Asakura and his associates.[32] The chiral octahedral cobalt complex *cis*-$[CoBr(NH_3)(en)_2]Br_2$ can be prepared by reaction of a diaquacobalt(II) complex, $[Co(H_2O)_2\{(OH)_2Co(en)_2\}_2](SO_4)_2$, with ammonium bromide in water. Despite the fact that all the reactants are optically inactive, when the reaction is stirred at room temperature for 1 min or at 50 °C for 5 min, crystalline optically active complexes are obtained in almost all runs. The ee, however, fluctuates randomly (Scheme 10).



Scheme 10 Autocatalytic nucleation of enantiomeric crystals of coordination compounds.

The chiral complex crystallizes as a conglomerate in which each crystal consists of either Λ- or Δ-enantiomers. In a stirring system, a crystal of a particular enantiomer can be self-replicated through secondary nucleation, thereby catalyzing its own formation. Again, the ee of the product was largely dependent on the stirring rate. In addition, when the stirred reactions were carried out in the presence of a tiny amount of crystals of one enantiomer, that enantiomer was preferentially produced. If an enantiomer is added in dissolution, such a preference is not observed. This does mean that an autocatalytic reaction operating *via* secondary nucleation *requires the presence of crystals* to induce symmetry breaking.

Prospects: symmetry breaking and evolution

If an aspect of chiral amplification dominates molecular evolution, it must surely be the formation of macromolecules, since enzymes, nucleic acids, and other biopolymers have acquired a definite handedness. More than four decades ago, Wald suggested that the regular secondary structure of peptides would have resulted from the helical sense preferred by the major enantiomeric amino acid whose handedness also permitted its own selection and growth.[33] Shortly afterwards, this hypothesis was verified on polypeptides derived from nearly an equal population of enantiomeric amino acids and on regularly isotactic vinyl polymers prepared by Ziegler–Natta polymerization.[21b,34]

Detailed studies and an in-depth interpretation of this so-called 'Majority Rule', which arises from the excess energy of the opposite helicity, has been recently carried out by Green, Selinger and their co-workers.[35,36] Thus, chiroptical measurements reveal that a polymer made of 98.4% achiral units and 1.6% chiral units, with an ee of only 2.8% among these chiral monomers, has the same optical activity as a polymer of just the chiral units with the same ee. Notably, the theory allows prediction of the helical sense ratio for any ee and, within certain limits, it is also possible to reduce the chiral component without affecting the optical purity.[36b,e,f] In the latter case, the circular dichroism (CD) spectrum does not show any variation until the composition of monomers reaches 99.2% achiral and 0.8% chiral.[36a] It seems that cooperative interactions in helical systems may lead to an important chiral amplification.[37]

Homochiral crystals of helical coordination polymers from achiral components have been obtained by Aoyama and his

group by treating an achiral pyrimidine derivative with cadmium nitrate in aqueous ethanol.[38] The achiral precursor itself, orthogonal 9-(5-pyrimidyl)anthracene, forms achiral $P2_1/n$ crystals with $Cd(NO_3)_2$ in methanol and without forming helical chains. However, the slow cooling (~ 6 h) of a hot (80 °C) ethanol–water solution of this compound and $Cd(NO_3)_2$ to room temperature afforded an adduct which crystallizes in chiral space group $P2_1$. The metal ion is hexacoordinated with two pyrimidine ligands, two nitrate ions, ethanol and water. The crystal structure contains an alternate arrangement of pyrimidine–metal helical layers and anthracene layers. The chirality results from a twist of the two pyrimidine rings and the overall helicity of the pyrimidine–metal array is maintained in the crystal by interstrand hydrogen bonding between the nitrate anions and water.

That the crystallization is homochiral is evidenced by the fact that all the crystals isolated from one crystallization show the same CD sign and hence the same helicity. Remarkably, chirality of this helical coordination polymer can be controlled by seeding. Thus, an achiral adduct can be converted into *P* or *M* helices at will, when the former is coground with a small amount of *P* or *M* adducts, respectively, and then exposed to vapors of ethanol.

In principle, the formation of chiral crystals from achiral building blocks is not surprising since achiral molecules can crystallize in chiral space groups.[15,39] However, these substances are obtained either as an in-crystal racemate or as a mixture of self-resolved enantiomeric chiral crystals.[40] The work by Aoyama and coworkers provides evidence for homochiral crystallization, by which achiral molecules afford spontaneously crystals with the same chirality, which can also be related to the concept of secondary nucleation mentioned above.

As long as a polymer can replicate, perhaps to perform a biological function, it could serve as the seed molecule. Its autocatalytic 'nucleation' would continue in an enantiomerically pure fashion. Thus, the number of copies of the selected homochiral polymer will become greater and greater while the number of competing stereoisomers will become fewer and fewer. The slight enantiomeric imbalance would have provided the driving force for such a selection, regardless of the appropriateness of structures or shapes.[3] Recent works by Eschenmoser *et al*. reinforce the idea that the choices of Nature were a question of availability. Pyranosyl-RNA has been found to be not only a stronger pairing system than furanosyl-RNA (and DNA as well), but also such a pairing is more selective and Watson–Crick purine–pyrimidine pairing in strictly antiparallel orientation was obtained.[41] Base sequences of pyranosyl-RNA can be copied with high regioselectivity and chiroselectivity. In general, the copying proceeds slower when one of the D-ribopyranosyl units of a homochiral tetramer-2′,3′-cyclophosphate is replaced by the corresponding L-unit.

Nevertheless, a general problem associated with the stereocontrol of self-assembly is the fact that the large number of random sequences from a mixture of right- and left-handed libraries will hinder the formation of regular cycles with specific-ordered sequences. At the molecular level effective self-replication may adopt the form of a hypercycle,[42] a type of nonlinear autocatalysis in which cross-catalysis superposes onto autocatalytic replication. These processes would have played a key role in the transition from inanimate to living systems, and hypercyclic peptide networks have been studied in detail. Thus, Reza Ghadiri and his associates have recently described two peptide autocatalysts that not only accelerate their own formation but also behave as cross-catalysts, each speeding up the production of the other more efficiently than its own duplication.[43]

At a discrete molecular level, only a few autocatalytic chemical systems contain vestiges of hypercylic organization.[44] Still, chiral hypercycles need to be disclosed and understood, but the above-mentioned transformations by Soai *et al*. constitute a good toehold for promising developments.

Conclusions

The ultimate origin of asymmetry in the universe is an unanswered question. During the last decade, however, a series of rather simple experiments have demonstrated the feasibility of producing optically active compounds from achiral materials. Crystallization processes, not involving spontaneous resolutions, and a few asymmetric reactions have established a direct linkage with the inherent handedness of prebiotic molecules and the biopolymers thereof. While we have seen the triumph of reductionism in explaining life in molecular terms, with stunning revelations of self-replication and regulation, still the large gap between molecular chirality and molecular evolution has become painfully clear. As noted by Avetisov and Goldanskii,[1d] this emerges from the lack of knowledge about the interrelations between the asymmetry of chemical processes involving simple organics and the chiral specificity of biological polymers. Accordingly, only a few assertions can be formulated about the role of symmetry breaking at the chemical stage of evolution, even though homochirality was forced by the initiation of enantiospecific functions in living systems. In any event, other recent studies, especially concerning oligonucleotide systems, suggest mirror symmetry breaking before replication.[39] This also supports the idea of autocatalytic processes capable of propagating the homochirality from an initial statistical mixture of chiral molecules. The interesting findings of enantiomeric excesses in extraterrestrial samples do not answer definitely the question of the generation of asymmetry, nor do they conflict with the statistical arguments.[14]

There will come a time, perhaps ten years from now, perhaps sooner, when we would not be able to discuss evolution at any finer level of detail without claiming the origin of enantiomeric homogeneity. That's what life is all about.

Acknowledgments

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Notes and references

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