Orig Life Evol Biosph (2015) 45:219–224
DOI 10.1007/s11084-015-9422-9

ORIGINS 2014

On the Biogenic Origins of Homochirality

Victor Sojo

Received: 26 November 2014 / Accepted: 27 November 2014 /
Published online: 14 March 2015

Abstract Homochirality, the single-handedness of optically asymmetric chemical structures, is present in all major biological macromolecules. Terrestrial life's preference for one isomer over its mirror image in D-sugars and L-amino acids has both fascinated and puzzled biochemists for over a century. But the contrasting case of the equally fundamental phospholipids has received less attention. Although the phospholipid glycerol headgroups of archaea and bacteria are both exclusively homochiral, the stereochemistries between the two domains are opposite. Here I argue that the reason for this "dual homochirality" was a simple evolutionary choice at the independent origin of the two synthesizing enzymes. More broadly, this points to a trivial biogenic cause for the evolution of homochirality: the enzymatic processes that produce chiral biomolecules are stereospecific in nature. Once an orientation has been favored, shifting to the opposite is both difficult and unnecessary. Homochirality is thus the simplest and most parsimonious evolutionary case.

Keywords Dual homochirality · Origins · Stereospecificity · Archaea · Bacteria · Lipid divide · Catalysis

Introduction

Homochirality, the exclusive prevalence of one chemical structure over its otherwise identical mirror image or *enantiomer*, is ubiquitous in biology. It is present in the monomers of all major groups of biological macromolecules. Prominently, the sugars of nucleic acids show the D configuration, whereas proteins are formed almost exclusively from L-amino acids (Fig. 1). The mirror L-sugars and D-amino acids do play relevant roles in some organisms, but their biochemical role is greatly restricted (Krebs 1935; Corrigan 1969). A conclusive explanation for the evolutionary origin and maintenance of homochirality is still lacking.

Paper presented at ORIGINS 2014, Nara Japan, July 6-11 2014.

V. Sojo
CoMPLEX, University College London, Gower Street, London WC1E 6BT, UK

V. Sojo (✉)
Department of Genetics, Evolution and Environment, University College London, Gower Street, London WC1E 6BT, UK
e-mail: v.sojo.11@ucl.ac.uk

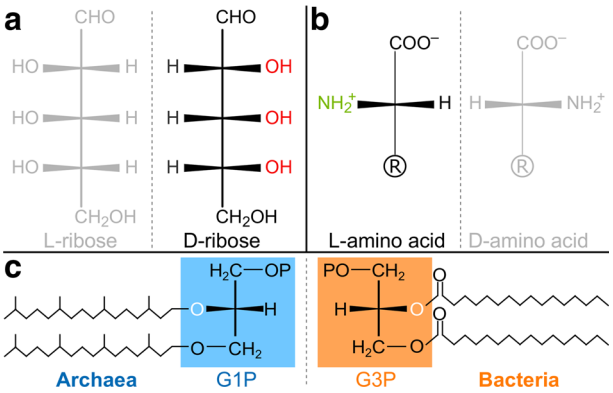

Fig. 1 Homochirality in sugars, amino acids and, dually, in lipids. **a** D-sugars exclusively form the backbone of DNA and RNA. **b** Although D-amino acids occur sparsely in certain organisms, proteins of all domains of life are formed almost entirely of L-amino acids. **c** Both archaea and bacteria have exclusively homochiral phospholipid headgroups. However, the geometry is inverted: all archaea use *sn*-glycerol-1-phosphate (G1P), while all bacteria use the enantiomer *sn*-glycerol-3-phosphate (G3P). Eukaryotes, not shown, were derived later and share their lipid biochemistry with bacteria. R: amino acid side chain. OP/PO: phosphate

In proteins, the advantage of a more stable secondary structure in the combination of twenty different amino acids may in itself account for the prevalence of one orientation over the other (Brack et al. 1979), and a higher stability of homochiral RNA has also been demonstrated (Urata et al. 2005). A slight bias towards biological-type enantiomers reported in the Murchison and Murray meteorites (Engel and Macko 1997; Pizzarello and Cronin 2000) has fuelled the search for intrinsic physical causes behind the origin of terrestrial homochirality. Parity violations in β-decay from electroweak nuclear interactions (Mason 1984; Kondepudi and Nelson 1985), spontaneous autocatalytic symmetry breaking (Blackmond 2004; Kawasaki et al. 2006), adsorption onto chiral surfaces (Karagounis and Coumoulos 1938; Bonner et al. 1975), and asymmetric photochemical reactions caused by polarized light from supernovae in the interstellar medium (Jorissen and Cerf 2002) have all been put forward as plausible physical forces behind a potential pre-biotic origin of homochirality in D-sugars and L-amino acids.

However, a case of *dual homochirality* is known in an equally fundamental group of biomolecules. The backbone of membrane phospholipids has opposite handedness in archaea and bacteria, the two basal domains of life. This crucial structure of cellular membranes consists of a glycerol-phosphate (GP) headgroup. Yet, intriguingly, all known archaea use *sn*-glycerol-1-phosphate (G1P), while all bacteria use exclusively the enantiomer *sn*-glycerol-3-phosphate (G3P) (Fig. 1). The synthesizing enzymes, *sn*-glycerol-1-phosphate dehydrogenase (G1PDH) and *sn*-glycerol-3-phosphate dehydrogenase (G3PDH), are unrelated (Koga et al. 1998). An explanation for this dichotomy may help elucidate some of the fundamental principles behind the origin and maintenance of homochirality.

The Dual Evolution of Homochirality in Lipids

A number of plausible scenarios for the *lipid divide* have been suggested. Most simply, it is possible that last universal common ancestor (LUCA) was not cellular in the modern sense and had no genes for specifying either type of lipid; not only the GP headgroups but the specific

enzymes required to synthesize all parts of the lipids evolved later, and independently, in archaea and bacteria (Martin and Russell 2003). However, the broad conservation of a number of membrane proteins, including the signal-recognition particle and the ATP synthase, would make a lipid-free scenario unlikely (Koonin and Martin 2005; Mulkidjanian et al. 2009). Early lipids may have been produced by abiotic means (Deamer et al. 2002; Martin and Russell 2003), and certain parts of the lipid-synthesizing machinery may have already been present in the common ancestor (Peretó et al. 2004), but the absence of the full machinery for lipid synthesis in LUCA would account for the vast differences between archaeal and bacterial membranes, chief of which is the opposing stereochemistries of G1P and G3P.

Another possibility is that both types of GP headgroup were present in LUCA, G3P being later favored at the divergence of bacteria, and G1P at the divergence of archaea (Wächtershäuser 2003). LUCA thus had a heterochiral membrane, either racemic or not (Peretó et al. 2004). In this scenario, it is likely that the ancestor of one of the two enzymes (G1PDH or G3PDH) evolved first. Since both G1P and G3P are well known to be viable and effective in a plethora of environments, it is difficult to see why a second enzyme would arise once the first one was in place, only to completely eradicate the other after the archaea-bacteria split.

Alternatively, a non-stereospecific ancestral enzyme existed first that produced a heterochiral mixture of the two GP headgroups. However, all known $NAD(P)^+$-dependent CH-OH dehydrogenases (E.C. number 1.1.1), are exclusively stereospecific in their hydrogen transfers (You et al. 1978; Benner 1982). Within this large supergroup to which both G1PDH and G3PDH belong, two classes exist. Class 1 dehydrogenases exclusively transfer the pro-*R* hydrogen of NAD(P)H, whereas Class 2 are stereospecific for the pro-*S* hydrogen. These redox reactions are intrinsically stereospecific both in their coenzymes and substrates (Fisher et al. 1953; Arnold et al. 1976).

The carbonyl center of dihydroxyacetone phosphate (DHAP), from which both G1P and G3P are formed, is prochiral: hydrogenation from one side of the double bond produces G1P, while reacting from the opposite side gives G3P. At the atomic level, the amino acids of the active site of G3PDH face the pro-*S* hydrogen of NADH, whereas the G1PDH active site has been recently reported to exhibit a pro-*R* geometry (Koga et al. 2014). The idea of a non-stereospecific GP-synthase is difficult to reconcile with biochemical knowledge of the enzymes that catalyze these reactions.

A simpler explanation is that LUCA, although cellular in nature, had neither of the two enzymes, and thus no glycerol headgroup (Sojo et al. 2014). Early membranes were a mixture of more rudimentary amphiphiles, most simply fatty acids. This would have made such membranes leaky to ions and other small molecules, and indeed may have been a necessity for the early evolution of membrane bioenergetics and free-living cells (Lane and Martin 2012; Sojo et al. 2014). In this scenario, G1PDH and G3PDH had independent origins after the divergence of archaea and bacteria.

In the evolution of the two novel enzymes, the stereochemistry of the respective ancestral proteins would be maintained (Hanson and Rose 1975). G1PDH was recruited from an ancestor of the alcohol-dehydrogenase/dehydroquinate-synthase/glycerol-dehydrogenase superfamily (Peretó et al. 2004). Like all extant members of this superfamily (You et al. 1978), this must have been a pro-*R* enzyme. Independently, G3PDH was derived from an ancestor of the UDP-glucose-6-dehydrogenase/3-hydroxyacyl-CoA-dehydrogenase superfamily (Peretó et al. 2004); analogously, like all members of this family (You et al. 1978), this would have been a pro-*S* enzyme. These two independent origins of DHAP reduction gave rise to the two opposing configurations of the glycerol-phosphate products, G1P and G3P. A non-stereospecific GP synthase was unlikely.

Homochirality as the Simplest Evolutionary Scenario

This dual origin of single-handedness in fundamental biological molecules provides a crucial insight into the evolution of homochirality in general. Whether or not pre-biotic molecules were enriched in one enantiomer, life itself would naturally choose one catalytic orientation over the other. This simply reflects the orientations that the ancestral enzymes had and their evolutionary availability for duplication, divergence, and neo-functionalization. The question, if any, lies in why nature went in one specific direction towards L-amino acids and D-sugars, rather than the opposite. Subtly, homochirality of a given molecule is in itself biologically trivial, while the specific orientation may or may not be.

The catalytic success of enzymes depends on their specific binding to substrates and cofactors, and these highly selective orientations largely account for the evolution of stereo-specificity in enzymes (Hanson 1972). Certain structures, such as cyclic molecules, are intrinsically obliged to react stereospecifically (Hanson 1972), so chiral exclusivity is a general principle of biochemical catalysis. The independent evolution of DHAP reduction by G1PDH and G3PDH sheds light on the prevalence of one orientation over the other. If the ancestral enzyme had an *R*-favoring orientation, the duplicated enzyme would have inherited this preference (Hanson and Rose 1975), and once an orientation had been favored, there would be no selective pressure to develop the opposite one. Such a process would not only be evolutionarily challenging, it would also provide little or no ecological advantage.

Implications at the Origin of Life

It is tempting to draw analogies between early biochemistry and classic non-biological synthetic chemistry. However, free-solution chemistry is not directly comparable to enzymatic catalysis, largely because of the highly specific binding of substrates, water, and cofactors to enzymes (Hanson and Rose 1975).

The overwhelming homochirality of terrestrial biochemistry makes it apparent that life itself could not have started in a racemic mixture (Cline 2005; Breslow 2011). However, recent findings of cross-chiral RNA-polymerizing ribozymes open the door for both D- and L-enantiomers potentially playing a key role in the origin of life (Sczepanski and Joyce 2014). In a plausible early system in which simple amino acids or short polypeptides were chelated to metals or larger mineral structures and started catalyzing reactions (Russell and Martin 2004), it is easy to envision a parsimonious explanation for a particular orientation being favored: the chirality of the amino acids themselves, or the peculiar arrangement of the primary sequence, would eventually but inevitably lead to stereospecific synthesis. Many reactions, indeed, might only occur stereospecifically or not at all (Hanson 1972), and it is far easier structurally for an efficient enzyme to catalyze a reaction stereospecifically than not, a simple implication of the lock-and-key principle of traditional biochemistry (Fischer 1894).

An early D-ribozyme that naturally started selecting for L- over D- amino acids would suffice as an explanation for L-homochirality in proteins (Sczepanski and Joyce 2014). If a ribozyme that synthesized D-proteins arose later, it would have been unable to compete against the earlier and by then more efficient L-selecting one. More broadly, an emerging fully functional proto-ribosome would have inexorably imposed its chiral preference across life and outcompeted all alternatives. On Earth, this triumphant proto-ribosome was itself D-homochiral and preferred L-amino acids. Any competing L-ribozymes and D-polypeptides were left behind as soon as the D-sugar/L-amino-acid association was established.

Conclusions

In the face of widespread lateral gene transfer between the two domains, it is remarkable that not a single case of G1P in bacterial phospholipids, or vice versa, has ever been observed. Both enantiomers are clearly viable, so no deeper explanation of this dual homochirality is necessary: independently derived enzymes catalyze stereochemically opposite reactions in archaea and bacteria, giving two molecules that perform the same job equally well. These enzymes, and all members of their evolutionary superfamilies, are stereospecific, and this is an intrinsic characteristic of enzymatic reactions.

Spontaneous enantioselection may have occurred pre-biotically, potentially clearing a path for natural selection to operate and favor one orientation over the other. However, homochirality would have arisen notwithstanding, as it is indeed the simplest solution in terms of both biochemistry and evolution: having a heterochiral product is not only structurally disadvantageous, it is biochemically cumbersome, ecologically unnecessary, and evolutionarily disfavored. In many cases, it is actually impossible. The origin and maintenance of homochirality may thus lie simply in the biochemical nature of enzymatic catalysis.

Acknowledgements This work was supported by funding from UCL-CoMPLEX and EPSRC (grant EP/F500351/1). Thanks are due to Nick Lane and Andrew Pomiankowski for valuable comments on the manuscript.

References

Arnold L, You K, Allison W, Kaplan N (1976) Determination of the hydride transfer stereospecificity of nicotinamide adenine dinucleotide linked oxidoreductases by proton magnetic resonance. Biochemistry

Benner S (1982) The stereoselectivity of alcohol dehydrogenases: A stereochemical imperative? Experientia 38: 633–637

Blackmond DG (2004) Asymmetric autocatalysis and its implications for the origin of homochirality. Proc Natl Acad Sci USA 101:5732–5736. doi:10.1073/pnas.0308363101

Bonner WA, Kavasmaneck PR, Martin FS, Flores JJ (1975) Asymmetric adsorption by quartz: A model for the prebiotic origin of optical activity. Orig Life 6:367–376. doi:10.1007/BF01130338

Brack A, Spach GG, Synthesis PI, Studies C (1979) *β*-structures of polypeptides with L- and D-residues. Part I. J Mol Evol 13:35–46. doi:10.1007/BF01732752

Breslow R (2011) The origin of homochirality in amino acids and sugars on prebiotic earth. Tetrahedron Lett 52: 4228–4232. doi:10.1016/j.tetlet.2011.06.002

Cline DB (2005) On the physical origin of the homochirality of life. Eur Rev 13:49–59. doi:10.1017/S1062798705000657

Corrigan JJ (1969) D-Amino Acids in Animals. Science 164:142–149. doi:10.1126/science.164.3876.142

Deamer D, Dworkin JP, Sandford SA et al (2002) The first cell membranes. Astrobiology 2:371–381

Engel M, Macko S (1997) Isotopic evidence for extraterrestrial non- racemic amino acids in the Murchison meteorite. Nature 389:265–268

Fischer E (1894) Einfluss der Configuration auf die Wirkung der Enzyme. Berichte der Dtsch Chem Gesellschaft 27:2985–2993. doi:10.1002/cber.18940270364

Fisher HF, Conn EE, Vennesland B, Westheimer FH (1953) The enzymatic transfer of hydrogen I. The reaction catalyzed by alcohol dehydrogenase. J Biol 202:687–697

Hanson K (1972) Enzyme symmetry and enzyme stereospecificity. Annu Rev Plant Physiol 23:335–366

Hanson K, Rose I (1975) Interpretations of Enzyme Reaction Stereospecificity. Acc Chem Res 8:1–10

Jorissen A, Cerf C (2002) Asymmetric photoreactions as the origin of biomolecular homochirality: a critical review. Orig Life Evol Biosph 32:129–142

Karagounis G, Coumoulos G (1938) A new method of resolving a racemic compound. Nature 141:917–918

Kawasaki T, Suzuki K, Shimizu M et al (2006) Spontaneous absolute asymmetric synthesis in the presence of achiral silica gel in conjunction with asymmetric autocatalysis. Chirality 18:479–482. doi:10.1002/chir.20273

Koga Y, Kyuragi T, Nishihara M, Sone N (1998) Did archaeal and bacterial cells arise independently from noncellular precursors? A hypothesis stating that the advent of membrane phospholipid with enantiomeric glycerophosphate backbones caused the separation of the two lines of descent. J Mol Evol 46:54–63

Koga Y, Sone N, Noguchi S, Morii H (2014) Transfer of Pro-*R* Hydrogen from NADH to Dihydroxyacetonephosphate by *sn*-Glycerol-1-phosphate Dehydrogenase from the Archaeon Methanothermobacter thermautotrophicus. Biosci Biotechnol Biochem 67:1605–1608. doi:10.1271/bbb.67.1605

Kondepudi DK, Nelson GW (1985) Weak neutral currents and the origin of biomolecular chirality. Nature 314:438–441. doi:10.1038/314438a0

Koonin EV, Martin W (2005) On the origin of genomes and cells within inorganic compartments. Trends Genet 21:647–654. doi:10.1016/j.tig.2005.09.006

Krebs HA (1935) Metabolism of amino-acids: Deamination of amino-acids. Biochem J 29:1620–1644

Lane N, Martin WF (2012) The origin of membrane bioenergetics. Cell 151:1406–1416

Martin W, Russell MJ (2003) On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry to chemoautotrophic prokaryotes, and from prokaryotes to nucleated cells. Phil Trans R Soc Lond B 358:59–83

Mason SF (1984) Origins of biomolecular handedness. Nature 311:19–23. doi:10.1038/311019a0

Mulkidjanian AY, Galperin MY, Koonin EV (2009) Co-evolution of primordial membranes and membrane proteins. Trends Biochem Sci 34:206–215

Peretó J, López-García P, Moreira D (2004) Ancestral lipid biosynthesis and early membrane evolution. Trends Biochem Sci 29:469–477. doi:10.1016/j.tibs.2004.07.002

Pizzarello S, Cronin J (2000) Non-racemic amino acids in the Murray and Murchison meteorites. Geochim Cosmochim Acta 64:329–338

Russell MJ, Martin W (2004) The rocky roots of the acetyl-CoA pathway. Trends Biochem Sci 29:358–363

Sczepanski JT, Joyce GF (2014) A cross-chiral RNA polymerase ribozyme. Nature 515:440–442. doi:10.1038/nature13900

Sojo V, Pomiankowski A, Lane N (2014) A bioenergetic basis for membrane divergence in archaea and bacteria. PLoS Biol 12:e1001926. doi:10.1371/journal.pbio.1001926

Urata H, Sasaki R, Morita H, et al. (2005) Kinetic analysis of hydrolytic reaction of homo- and heterochiral adenylyl(3'-5')adenosine isomers: breaking homochirality reduces hydrolytic stability of RNA. Chem Commun (Camb) 2578–25780. doi: 10.1039/b500673b

Wächtershäuser G (2003) From pre-cells to Eukarya – a tale of two lipids. Mol Microbiol 47:13–22

You K, Jr LA, Allison W, Kaplan N (1978) Enzyme stereospecificities for nicotinamide nucleotides. Trends Biochem Sci 3:265–268