Chirality in Abiogenesis

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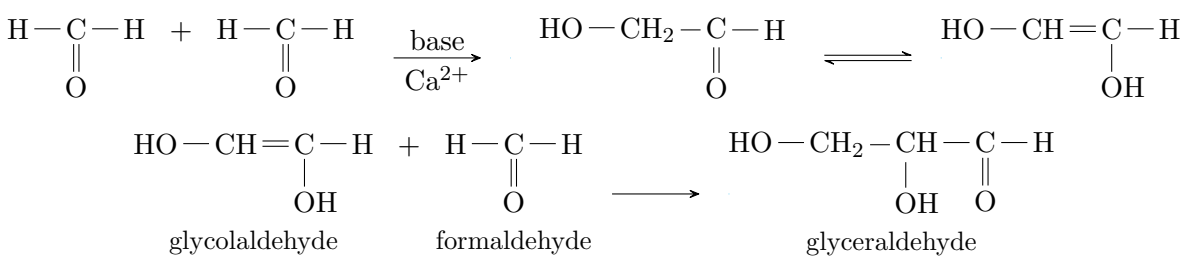
The most perenially interesting problems in science are the origin problems such as *How did the universe begin?* or *How did mankind arise from the primates?* In between these two particular questions of course is the fundamental problem of abiogenesis - how a completely lifeless planet changed into one filled with myriad living organisms. Abiogenesis is different from other "big" questions because it can be discussed with relatively simple chemistry - no quantum mechanics, relativity theory or genomics required. Of course there are theological answers to origin questions, but from a scientific standpoint it is perhaps best to frame the problem in the form *Does our present understanding of scientific laws allow us to explain this event?* While not rejecting divine intervention as a hypothesis, we simply remove it from the present discussion to focus on what may be missing from our current understanding of the material world. This is the approach I take here to discuss briefly how life may have arisen from simple chemical beginnings. Any serious student of the topic is well aware that we are very far from a convincing explanation, and some of the proposed routes from initial state to cellular life reflect almost desperation. Francis Crick famously supported panspermia, microorganisms from space, on the grounds that there was simply insufficient time (a thousand million years or so) for life to spring from chemical soup on a primitive Earth. Darwin's "warm little pond" may have been necessary, but it hardly seems sufficient, which is why everything from volcanic vents, clay deposits, radiation-scarred minerals and even just ice have all been put forward as the crucial missing ingredient.

Living organisms do several things very well that are essential for their continued existence; they channel energy in useful directions and they store and employ genetic information with remarkable fidelity. The first steps towards life must have been far simpler, perhaps involving some chemical entity duplicating itself from available materials using thermal and radiation energy. Observation of the common elements of present-day living cells shows that ribonucleotides are crucial conserved elements involved in both energy storage (in the form of ATP) and information processing. RNA is capable of catalysing chemical reactions, and provides the crucial active site at the heart of every ribosome. Does this present day role reflect an RNA world, that existed long before DNA proved a more chemically robust molecule for making genomes? The hypothesis is not without difficulties but, in any case, it seems that ribonucleotides must have arisen early, and this step alone highlights problems. Although Miller-Urey type experiments (employing electrical discharges to trigger reactions in a simple model early atmosphere) can produce bases such as uracil, cytosine, guanine and adenine, there is no simple way to add ribose to these bases, since the reaction is kinetically and thermodynamically disfavoured. The problem inspired Sutherland and co-workers to find a possible way past this block, avoiding ribose as an intermediate. They produced pyrimidine ribonucleotides directly instead, from cyanamide, cyanoacetylene, glycoaldehyde, glyceraldehyde and inorganic phosphate. Although an important result, the authors themselves noted that glycoaldehyde and glyceraldehyde must be supplied separately in different steps to avoid messy chemistry with a mix of products, and there is as yet no obvious scenario for such controlled addition of substrates in a prebiotic environment.

Scheme 1: Formose reaction - from formaldehyde to sugars



This problem is familiar from the Formose reaction, shown in Scheme 1, which has been known for about 150 years. Under certain conditions, such as high pH in the presence of metal ions, formaldehyde can

be converted into sugars. After the initial combination of two formaldehyde molecules into glycolaldehyde the reaction becomes autocatalytic. This shows that sugar-like molecules can arise from simple starting molecules, but reactions like this offer no control over product formation. Glyceraldehyde is chiral, and each additional carbon atom generates a new stereocentre in the growing chain. Without some form of control there is no reason to favour one chirality over another. Ribose is only one five-carbon sugar, without any obvious advantage of stability over its diastereomers xylose, arabinose and lyxose. The closed-ring (furanose) form of ribose in fact has four chiral centres (shown in Figure 1). In β-D-ribose the C3 hydroxyl group is oriented away from C5, so that extended chains can form through these atoms; at the same time the hydroxyl at C1 in the β anomer can hold another group such as a base without steric clashes. L-lyxose has the wrong chirality at C4 to form long chains easily. It is in fact perfectly possible to build nucleic acid chains with α-D-ribose, and these can adopt quite different geometry from natural DNA, even forming parallel chains instead of anti-parallel ones. The selection of ribose in extended chains is therefore understandable *post factum*, but we are a long way from understanding how chirality first arose. Sutherland's group, it should be noted, employed racemic glyceraldehyde in their synthesis, and found that the xylose and lyxose forms gave lower yields among the mixture of products. Even so, the authors were forced to suggest that perhaps selective crystallisation gave final enrichment of ribose amino-oxazoline over the arabinose form. The ring closure reaction may well favour the natural β anomer in the final product, but the handedness problem (D-ribose *vs.* L-ribose) is unresolved.

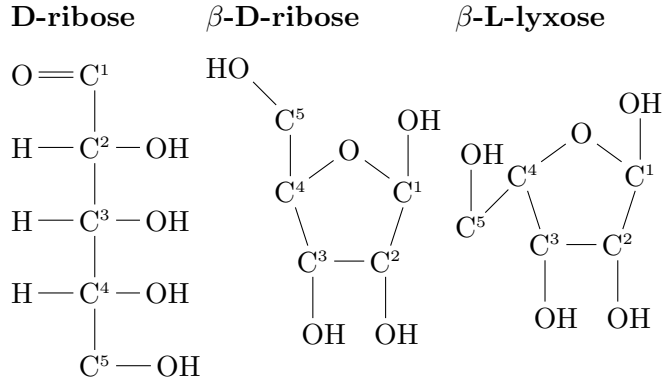
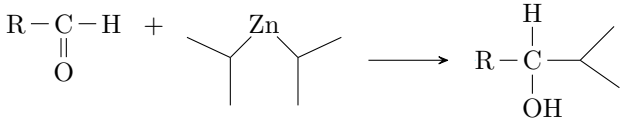


Figure 1: Comparison of open-chain D-ribose (shown as a Fischer projection) with the cyclic form and L-lyxose. Carbon numbering is shown as superscripts. Carbon atoms C2, C3 and C4 are chiral in the open form. C1 is also chiral in the furanose form. Hydrogens attached to carbon are omitted for clarity in the two furanose structures.

Chirality remains a fundamental problem for abiogenesis because all the building blocks of biological polymers (except the amino acid glycine) are chiral. As we have seen, each ribose group in nucleic acid has four chiral centres, and there is no particular reason why L-ribose, the mirror image of the molecule we find in nature, should not function equally well in a "looking-glass world". Crystallisation is one effective way to separate a racemic mixture into its component parts, and Pasteur first made his name by demonstrating this with tartaric acid. To invoke crystallisation as a spontaneous purification method is somewhat stretched, however, since (for example) rehydrating mixed D- and L-form crystals to allow further chemistry will produce a racemic solution again. Pasteur, remember, required a microscope and tweezers to make the separation permanent. (Nor can successive dessication/crystallisation cycles be invoked with much confidence if a prebiotic synthetic scheme otherwise requires chemical feedstocks and ambient conditions provided by a volcanic vent 200 metres below sea-level).

Scheme 2: Soai reaction adding iso-propyl groups to an achiral aldehyde



The most promising lead we have at present for cracking the chirality problem is the Soai reaction, shown in Scheme 2. First described over 30 years ago, this reaction shows that extremely small enantiomeric excesses in a chemical feedstock can, in some cases, yield highly pure chiral products. The process works by autocatalysis, when a chiral product promotes formation of more molecules of its own handedness. Other chiral molecules in the reaction mixture can also initiate the selectivity. The chemistry (alkylation of an aldehyde by diisopropyl-zinc) is highly specific, however, and generally performed in strictly anhydrous ice-cold toluene. Understandably, the reaction has not yet become a general model for prebiotic chemistry, even though the R group in the classic Soai reaction is a pyrimidine. Nevertheless,

the discovery that chirality can arise spontaneously is a major step forward, and perhaps suggests how selection may have occurred from a mixed pool of substrates created by messy chemistry. The Soai reaction seems to work because the product molecules bind to the zinc, aggregating into homo-chiral clusters that make better catalysts than hetero-chiral ones.

The problem, however, is that even decades after its discovery the Soai reaction remains very unusual. Similar results have been obtained by working with similar reagents, but no-one has reported anything like the same level of chiral selectivity in an aqueous reaction, possibly because of the role of aggregation. Perhaps the Soai reaction is, rather like ribose itself, not a step towards abiogenesis but a clue about where to look. Perhaps the minimally complex system capable of generating chirality in water involves more than one reaction. Many ideas on the subject remain speculative. Bernal first suggested in the 1940s that prebiotic organic molecules could attach to clays, and similar ideas have been proposed since to enhance the stability and concentration of reactants, enabling their condensation into larger molecules. The idea has triggered numerous experimental studies. A good deal of work has also been done on Formose-style reactions with different amines present, but this is largely focused on control of product distribution rather than chirality. Autocatalytic cycles are another popular field, related to feedback loops and complexity, but work on enantio-enrichment is largely neither water-based nor obviously related to plausible prebiotic chemistry. Aggregates of sugar-like molecules are difficult to form at low concentrations in water, so perhaps we need to look more widely at minerals or salts at high enough concentration to reduce water activity appreciably. That in itself would favour condensation reactions.

My suggestion is to work with aqueous systems near the solubility limit of the chosen reactant. Hydrocarbons may well have been abundant on the primitive Earth, but there is little to suggest biochemistry began in such a medium. Water is crucial to life, and seems to be the best solvent to start with. If self-aggregation can help the Soai reaction produce large enantiomeric excesses, then large, rather hydrophobic groups attached to a starting molecule might help. If this molecule can undergo some sort of addition reaction creating a stereocentre, then it is possible that control of aggregation could produce different relative yields of the enantiomers. Working with sugars is also possible, but it has yet to be shown that any molecule likely to have been present in the prebiotic environment could influence the Formose reaction to produce selected chiral products. My preferred starting molecules would be closer to achiral purines and pyrimidines, perhaps a Soai-like aldehyde. Cytosine is highly soluble in water, adenine less so, thymine even less, and guanine is poorly soluble. Guanine forms hydrogen bonded aggregates (and even ordered tetrameric ones) but can be solubilised with high pH or warming. It's a very long shot, but perhaps under the right conditions a guanine-like aldehyde could combine features of the Formose and Soai reactions, and produce an interesting result.

The question of abiogenesis has progressed substantially since the discussions by Oparin in the first half of the 20th century, but the breakthrough has yet to be found to offer a solid clue to the chirality problem. It can be explained to a 12 year old in minutes, but we still don't have a working model system that looks as though it actually happened on a prebiotic Earth. Life seems to have started only once, so we should not imagine it to have been easy. Given chiral building blocks of one biological polymer then others may follow, but at present we still need to keep looking for that initial step that breaks the molecular looking-glass.

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