Optical Isometry and Evolution

Life on Earth is based on the element carbon. This is not surprising, given that the element is capable of forming a vast number of different molecules to take up essential roles in the chemistry of life. One interesting aspect of these molecules is that almost all of them possess a property known as optical isomerism, which means they could in principle exist in two distinct forms which are mirror images of each other, though in nature only one form prevails. The subject of this essay is how the dominance of one optical isomer over another is driven by evolution.

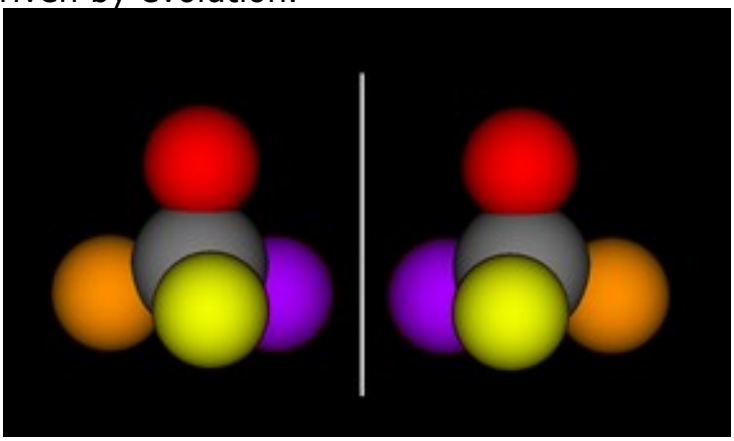

Figure 1: Enantiomers

Let us begin by describing optical isomerism with reference to a basic carbon molecule. In Figure 1 we have a diagram showing two possible structural configurations for four different types of atom (shown in different colours) surrounding a single carbon atom (shown in charcoal grey). The carbon atom in this instance is said to be in the SP^3 hybridised state, which means that it is bonded to four neighbouring atoms in a tetrahedral arrangement. The surrounding atoms need not be atoms of different elements - they could, for example, be carbon atoms that possess different substituents and therefore differ in chemical function (which is often the case). Such differences can be detected by subtle spectroscopic experiments.

The two molecules shown in Figure 1 appear to be the same, but close inspection shows that they are mirror images of each other. Such molecules are generally *stable*, though they may inter-convert, one into the other, as the result of chemical intervention. That these molecules are physically different can be shown by passing polarised light through a solution of each of them separately. This reveals that the plane of polarisation is rotated by each in a different direction. (This is what is meant by the term *optically active*.) Generally, mirror-image molecules are referred to as *enantiomeric forms*, or simply *enantiomers*, and for our discussion we shall use the terms Left (L) and Right (R) to distinguish them. Enantiomers also possess different chemical properties, which becomes apparent when they react with other optically active molecules. This observation turns out to be highly significant for the biochemistry of living cells.

It will be appreciated that *any* SP^3 bonded carbon atom in a molecule can potentially show this optical isomerism. All it requires is for the four atoms bonded to it to be chemically different. A molecule that has a single optically active carbon has two possible forms (L and R). Each additional optically active carbon in a molecule doubles the number of possible molecular forms. Thus a molecule with *N* optically active carbons can have 2^N distinct forms and there will be 2^{N-1} pairs of them that are mirror images (L and R) of each other. This is potentially a colossal number of different forms for the same molecule. For example a molecule with 40 optically active carbons has over 10^{12} or 1,000,000,000,000 forms. When we ponder such numbers we must inevitably come to consider what it means in terms of biological evolution.

When it comes to the chemical processes that occur in a living cell, we are aware of some extremely distinctive features which make them different from the non-biological processes that we are able to perform in a laboratory. Firstly, the number of possible chemical reactions in a cell is huge. Most laboratory or industrial processes involve just one reaction (with perhaps a small number of side reactions). Secondly, a great number of biochemical reactions take place concurrently (i.e. at the same time) in a living cell. Thirdly, these reactions do not appear to interfere with each other, except in some purposeful way, such as a branching off to produce additional useful products rather than stopping a primary reaction pathway. Fourthly, the reactions are highly specific: the required product is produced with high fidelity. Fifthly, the reactions are highly controlled, with sophisticated feedback mechanisms ensuring the rate of production of required molecules is commensurate with the demand. Lastly, these reactions are generally facilitated by catalysts (themselves usually large molecules of biological origin, called *enzymes*), which control the rate and specificity of the reactions. No doubt the reader can think of other attributes of cellular chemistry that are equally profound. When considering evolution however, the question is how is this degree of complexity and specificity to be explained?

One aspect of biological chemistry that is often remarked upon is the occurrence of a *handedness* in the molecules of life. If we consider both L or R forms of a molecule, only one of them will generally exist in nature. The opposite form is significantly absent. Yet it is easy to imagine a world in which life would thrive equally well if every molecule in a living cell took the mirror image form. This prevalence of one form over another often leads to the speculation that there is something inevitable about this: that there is some inherent asymmetry in the laws of physics that brings it about. However, this is not necessarily the case. The view taken here is that molecular handedness is an inevitable consequence of the principles of natural selection at work and there is no necessity to consider new physics. In short, molecular handedness is a valuable clue as to how natural selection enables the complexity and specificity of biological processes to emerge.

If we were to imagine a system that is the exact opposite of a living cell, what would it be like? Evidently the chemical reactions required to build useful

molecules, such as proteins, would no longer be specific. As revealed above, molecules that have many optically active carbon atoms could arise in a multitude of forms. If we imagined creating a dimeric molecule from two precursors molecules A and B, where each exists as pairs of enantiomers: $\{A^L, A^R\}$ and $\{B^L, B^R\}$, this could potentially produce four possible outcomes[1], which we may describe as the dimeric molecules $A^L B^L$, $A^L B^R$, $A^R B^L$, and $A^R B^R$. In this set of dimeric molecules we recognise that $\{A^L B^L, A^R B^R\}$ and $\{A^L B^R, A^R B^L\}$ are enantiomeric pairs.

Since the structures in all these dimers is different, we can also say that they all have different *shapes*. The significance of which is that molecular shape is known to be highly relevant to biological function, principally through the effect of steric hindrance, which influences how molecules interact with each other and therefore guides the chemical that may ensue. In a cell where all of these forms are produced it is very unlikely that all of them could have the same biological function. Proceeding on, if we consider the possibility that the reaction proceeds further to extend the dimer to a trimer by combining with a molecule C (represented by the enantiomeric pair $\{C^L, C^R\}$) we would obtain eight forms of the trimeric molecule ABC (*vis.* $A^L B^L C^L$, $A^L B^L C^R$, $A^L B^R C^L$, $A^L B^R C^R$, $A^R B^L C^L$, $A^R B^L C^R$, $A^R B^R C^L$, and $A^R B^R C^R$, which includes the enantiomeric pairs $\{A^L B^L C^L, A^R B^R C^R\}$, $\{A^L B^L C^R, A^R B^R C^L\}$, $\{A^L B^R C^L, A^R B^L C^R\}$ and $\{A^L B^R C^R, A^R B^L C^L\}$. It is therefore evident that, as a model for a metabolic pathway of the kind seen in living cells, such a system as this would rapidly become chaotic and disorganised.

Clearly this bears no resemblance to what we know occurs in a real living cell. Furthermore, if we suppose that the molecule ABC has potential for building structural tissue the improbability of all these different forms being able to pack together successfully to complete their supposed function is evident. Any organism that functioned in such an anarchic manner would be highly inefficient at producing and utilising molecular material to construct a functioning cell. If, on the contrary, we supposed that any given biological reaction produces a molecular product with only one specific structure, it can be seen how this may be efficiently incorporated into the cellular development. The same selectivity also implies a purity of product, uncontaminated by related but useless forms. Natural selection thus inevitably demands that all biomolecules exist in a singular form and that an enantiomer should exist at the expense of its alternative. Handedness in biomolecular system is thus a consequence of natural selection.

It follows that natural selection must proceed by the mechanism of chemical selectivity in the chemistry of living cells. This selectivity necessarily must apply at *every stage* of a metabolic pathway leading to a specific molecular product if a catastrophically disordered system is to be avoided. We are thus led to the principle: *natural selection implies that biochemical reactions necessarily produce specific isomeric forms of biochemical molecules.* This principle must also include the selection of specific enantiomeric forms, as is

1 In this we are assuming, for simplicity, that joining of the two molecules does not disturb the structure of any of the optical centres.

argued above, though at this juncture we have no mechanism to explain *how* this selection occurs.

The above account explains why natural selection favours the emergence of biological systems (cells) in which a single enantiomeric form of each molecule prevail, however this does not lead to any prediction of which enantiomer (L or R) would ultimately dominate. It is possible however, to postulate scenarios where such a preponderance of one one particular enantiomer can emerge. (And once established may subsequently bias the later production of derivative molecules with a similar handedness.) The following is a simple and appealing speculation on how the dominance of a specific enantiomer could arise in naturally in environment where no bias previously existed.

In the time before life emerged it is understood that ordinary organic molecules (the precursors of life) could exist in multiple isomeric forms, some of which, by virtue of their shape and reactivity, had the potential for biological function. It is impossible to say how abundant such molecules were, but in an environment that did not (yet) favour one kind of enantiomer over another, either enantiomer could conceivably have initiated the evolutionary chain and both could have evolved further given the right circumstances.

As mentioned above, one factor that assists the process of selectivity is steric hindrance. In the linking of two optically active molecules A and B, we showed how the dimerisation could potentially lead to four different product isomers which constitute two enantiomeric pairs. In the reaction products we may assume that the proportions of each enantiomer in a pair are equal, since they are physically equivalent and equally favoured thermodynamically. However we should not expect that one enantiomeric pair has the same abundance as the other. To be clear: we cannot assume that the pair $\{A^L B^L, A^R B^R\}$ is equally abundant with the pair $\{A^L B^R, A^R B^L\}$. As mentioned above, the dimers have different shapes, so the degree of steric crowding of the atoms in each is different. This means that one of the pairs of enantiomers is likely to be thermodynamically more favourable than the other. The least favoured may even be produced in a miniscule quantity. So even in this case we can see how some degree of molecular selectivity is obtained. Alone however, this is insufficient to explain selection between enantiomers.

To progress further, we must consider the effect of catalysis. We noted above that biochemical reactions are usually catalysed (by enzymes or their precursors) and that the catalysts are themselves molecules with a specific structure and shape. In the pre-life era, molecules possessing catalytic activity are likely to be relatively small (by current standards of living cells) and probably rather crude in effect. We must assume that such molecules arose from chance alone, by accidental contact between molecular precursors. It seems unlikely that the accidental emergence of a molecule capable of catalytic activity could miraculously appear at the same instant in both enantiomeric forms, particularly if the concentrations of the precursors was extremely low. Once formed however, the new catalyst would itself possess a degree of handedness that must impose some specificity on the reaction it

catalyses and thereby accelerate hugely the emergence of new molecules with a particular handedness. The acceleration of processes of particular handedness may even be sufficient to tilt the odds in favour of one enantiomeric form of product and initiate the natural selection of molecular handedness. Furthermore, the removal of one specific enantiomer (say of form L) from the system would upset the equilibrium between enantiomers and cause conversion of the opposite enantiomer R to the form L, thus reducing the abundance of R in the system. It is of note that this suggested mechanism does not require any asymmetry in the laws of physical science.

We exemplify the proposed mechanism in the following scheme.

Consider a racemic solution of enantiomers A^R and A^L which are in equilibrium:

$$A^R \Leftrightarrow A^L \tag{1}$$

Since the solution is in equilibrium, the two enantiomers may interconvert one into the other reversibly over time, while the relative proportions of each remains the same (i.e. 1:1).

We suppose that in this racemic mixture there are a very small number of additional molecules C and D, which exist as enantiomeric pairs $\{C^L, C^R\}$ and $\{D^L, D^R\}$ respectively. We also suppose that C and D can react together to form a dimeric species CD, for which we have four possible dimerisation reactions:

$$\begin{aligned} C^L + D^L &\rightarrow C^L D^L, \\ C^L + D^R &\rightarrow C^L D^R, \\ C^R + D^L &\rightarrow C^R D^L, \\ C^R + D^R &\rightarrow C^R D^R. \end{aligned} \tag{2}$$

These reactions are formally reversible, but we assume that, because of the low concentrations of C and D this is very slow compared with the rate of reaction (1). (The four reactions shown in (2) are not expected to have the same rates; in fact we expect that the four possible rate constants obey the relation: $k_{RL} = k_{LR} \neq k_{RR} \neq k_{LL}$, for hopefully self-evident reasons.)

We now suppose that the dimer CD has a catalytic capability, which accelerates a polymerisation reaction of molecule A and we expect that the chirality of all the different molecules in the system will have some influence in what occurs. Specifically we propose (though other scenarios are possible) that dimers $C^L D^L$ and $C^R D^R$ have no catalytic ability whatsoever, while for the dimers $C^L D^R$ and $C^R D^L$ we have

$$\{A^L\}_n + A^L \underset{[C^L D^R]}{\Rightarrow} \{A^L\}_{n+1} \tag{3}$$

and

$$\{A^R\}_n + A^R \underset{[C^R D^L]}{\Rightarrow} \{A^R\}_{n+1} \quad (4)$$

In other words, the dimer $C^L D^R$ catalyses the formation of the polymer $\{A^L\}_n$ while the dimer $C^R D^L$ catalyses the formation of the polymer $\{A^R\}_n$. (Note that for simplicity once again, we are additionally assuming that the catalysts have no effect on the alternative enantiomer.)

In this system, the question arises: which of the two polymer forms, if any, will dominate in the system? Clearly the domination of either is equally possible and for this reason we may expect a racemic mixture of both polymers as the final outcome. However, we must take account of the initial dilution of the species C and D. The probability of one of these molecules meeting the other in dilute solution is exceedingly small. But when this occurs a catalytic molecule is created in the concentrated racemic solution of species A, which rapidly sets about polymerising one selection of the enantiomers. As the concentration of the selected enantiomer is removed, the equilibrium of reaction (1) moves to replace the stock of the polymerising monomer. It is conceivable in these circumstances that all of the molecules A could be polymerised before the second form of catalyst spontaneously arises in system. Even if the production of one specific polymer is incomplete at this stage, the overall chemical environment of the system would be enantiomerically biased and therefore be able to influence the further chemical evolution of the system (and its consequent optical activity). It is via such reactions (if not this one specifically) that biological systems could arise with a super dominance of one enantiomer.

Another way of thinking about this mechanism for optical selectivity in biochemical reactions is from the point of view of evolutionary theory. Though the initial system has no inbuilt preference any particular enantiomer, once the catalytic species arises, the chemical environment immediately favours a specific enantiomeric form. The emergence of the dominant molecular product is therefore an instance of natural selection occurring at the molecular level.

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